



Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease



Matthieu F. Bastide^{a,b,1}, Wassilios G. Meissner^{a,b,c,1}, Barbara Picconi^{d,1}, Stefania Fasano^{e,1}, Pierre-Olivier Fernagut^{a,b,1}, Michael Feyder^{f,1}, Veronica Francardo^{g,1}, Cristina Alcacer^{g,1}, Yunmin Ding^{h,1}, Riccardo Brambilla^e, Gilberto Fisone^f, A. Jon Stoesslⁱ, Mathieu Bourdenx^{a,b}, Michel Engeln^{a,b}, Sylvia Navailles^{a,b}, Philippe De Deurwaerdère^{a,b}, Wai Kin D. Ko^{a,b}, Nicola Simola^j, Micaela Morelli^j, Laurent Groc^{k,l}, Maria-Cruz Rodriguez^m, Eugenia V. Gurevichⁿ, Maryka Quik^o, Michele Morari^p, Manuela Mellone^q, Fabrizio Gardoni^q, Elisabetta Tronci^r, Dominique Guehl^{a,b}, François Tison^{a,b,c}, Alan R. Crossman^s, Un Jung Kang^g, Kathy Steece-Collier^t, Susan Fox^u, Manolo Carta^r, M. Angela Cenci^g, Erwan Bézard^{a,b,s,*}

^a Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 33000 Bordeaux, France

^b CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 33000 Bordeaux, France

^c Department of Neurology, University Hospital Bordeaux, France

^d Laboratory of Neurophysiology, Fondazione Santa Lucia, IRCCS, Rome, Italy

^e Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, 20132 Milan, Italy

^f Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

^g Basal Ganglia Pathophysiology Unit, Department of Experimental Medical Science, Lund University, Lund, Sweden

^h Department of Neurology, Columbia University, New York, USA

ⁱ Pacific Parkinson's Research Centre and National Parkinson Foundation Centre of Excellence, University of British Columbia, Vancouver, Canada

^j Department of Biomedical Sciences, Section of Neuropsychopharmacology, Cagliari University, 09124 Cagliari, Italy

^k Univ. de Bordeaux, Institut Interdisciplinaire de neurosciences, UMR 5297, 33000 Bordeaux, France

^l CNRS, Institut Interdisciplinaire de neurosciences, UMR 5297, 33000 Bordeaux, France

^m Department of Neurology, Hospital Universitario Donostia and Neuroscience Unit, Bio Donostia Research Institute, San Sebastian, Spain

ⁿ Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^o Center for Health Sciences, SRI International, CA 94025, USA

^p Department of Medical Sciences, Section of Pharmacology, University of Ferrara, Ferrara, Italy

^q Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, 20133 Milano, Italy

^r Department of Biomedical Sciences, Physiology Section, Cagliari University, Cagliari, Italy

^s Motac Neuroscience Ltd, Manchester, UK

^t Michigan State University, College of Human Medicine, Department of Translational Science and Molecular Medicine & The Udall Center of Excellence in Parkinson's Disease Research, 333 Bostwick Ave NE, Grand Rapids, MI 49503, USA

^u Morton & Gloria Shulman Movement Disorders Center, Toronto Western Hospital, Toronto, Ontario M4T 2S8, Canada

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ABSTRACT

Involuntary movements, or dyskinesia, represent a debilitating complication of levodopa (L-dopa) therapy for Parkinson's disease (PD). L-dopa-induced dyskinesia (LID) are ultimately experienced by the vast majority of patients. In addition, psychiatric conditions often manifested as compulsive behaviours, are emerging as a serious problem in the management of L-dopa therapy. The present review attempts to provide an overview of our current understanding of dyskinesia and other L-dopa-induced dysfunctions, a field that dramatically evolved in the past twenty years. In view of the extensive literature on LID, there appeared a critical need to re-frame the concepts, to highlight the most suitable models, to review the central nervous system (CNS) circuitry that may be involved, and to propose a pathophysiological framework was timely and necessary. An updated review to clarify our understanding of LID and other

* Corresponding author at: Institut des Maladies Neurodégénératives, Université de Bordeaux, Bât 3B 1er étage, 146 rue Léo Saignat, 33076 Bordeaux cedex, France.

E-mail address: erwan.bezard@u-bordeaux.fr (E. Bézard).

¹ These authors are co-first authors.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1% of the population over 65, the mean age at which the disease is first diagnosed. PD was first described by James Parkinson (Parkinson, 1817, 2002) and consists of a syndrome including bradykinesia/akinesia, rigidity, postural abnormalities and tremor. The principal pathological characteristic of PD is the progressive death of the pigmented neurons of the Substantia Nigra pars compacta (SNc) (Hassler, 1938). The discovery, in 1960, that degeneration of the dopamine (DA) supplying neurons of the SNc causes parkinsonism (Ehringer and Hornykiewicz, 1960) opened the way for the development of pharmacological therapies for PD that act to enhance synaptic DA transmission using the DA precursor L-_{3,4}-dihydroxyphenylalanine (L-dopa) (Birkmayer and Hornykiewicz, 1961, 1962; Lees, 1994; Yahr et al., 1968).

The initial enthusiasm surrounding the positive effects of L-dopa in PD soon gave way to the recognition that long-term L-dopa therapy is complicated by the development of adverse events related to fluctuations in motor response. Motor fluctuations include ON–OFF fluctuations, sudden and unpredictable changes in mobility, and the wearing-off phenomenon, a decrease in the duration of L-dopa action (Quinn, 1998). However, the most debilitating class of motor fluctuation is involuntary movements known as L-dopa-induced dyskinesia (LID). These abnormal involuntary movements (AIMs) have been noted from the first introduction of L-dopa in the late 1960s (e.g. after 6 months of treatment over half of patients had developed dyskinesia) (Duvoisin, 1974). Long term experience has continued to report that the majority of L-dopa-treated patients experience dyskinesia, with up to 80% of patients having LID within 5 years of treatment (DeJong et al., 1987; Lees and Stern, 1983; Lesser et al., 1979; Marsden et al., 1982; Rajput et al., 1984). Eighty to ninety per cent of PD patients suffer from LID after 10 years of DA replacement therapy (Ahlskog and Muentner, 2001; Hauser et al., 2007), a condition affecting their quality of life (Hechtner et al., 2014). It should be noted that treatment-related dyskinesia are not solely a problem of L-dopa but DA receptor agonists are also capable of eliciting dyskinesia. Therefore, within this review, the term LID will be used to describe dopaminergic (DAergic) treatment-related dyskinesia generally. In the past 20 years, the understanding of the neural mechanisms underlying LID in PD has strongly advanced (Bezard et al., 2001a; Cenci et al., 1998; Fasano et al., 2010; Fiebinger et al., 2014b; Fisone and Bezard, 2011; Jenner, 2008; Picconi et al., 2003). Dyskinesia has been associated with a sequence of events that include pulsatile stimulation of DA receptors, downstream changes in proteins and genes, abnormalities in non-DAergic transmitter systems all of which combine to produce alterations in the neuronal firing patterns that signal between the basal ganglia and the cortex.

In this review, we aim at focusing on the changes affecting both DAergic and non-DAergic transmission, and particularly focus on

changes observed at the peak-dose of L-dopa plasma concentrations, that is when dyskinesia are more commonly expressed, so called – ON dyskinesia, as opposed to OFF dyskinesia where the pathophysiology relates to low levels of DA. We also review other L-dopa-induced side-effects and highlight their pathophysiology as well as possible links to pathophysiology of LID. This overview has the goal to advance our understanding of LID, which might contribute to the development of novel therapeutic strategies aimed at preventing dyskinetic symptoms.

2. Spectrum of LID and other L-dopa-induced side effects

2.1. Clinical presentation

LID can be classified into peak-dose dyskinesia (involuntary movements that coincide with the peak-action of levodopa and thus period of best anti-parkinsonian action), diphasic dyskinesia (involuntary movements that emerge just before the DA replacement therapy turns the patient ON and that reappear at the end of the therapeutic benefit) and OFF period dystonia. The movement disorders most commonly associated with peak-dose LID are chorea, dystonia and ballism.

Chorea is characterized by involuntary, irregular, purposeless, non-rhythmic, abrupt and rapid movements that seem to flow from one part of body to the other. Choreic or larger amplitude choreo-athetotic movements are the most common forms of LID. They are most commonly associated with peak-dose dyskinesia. Chorea usually manifests first on the side of the body that is predominantly affected by PD. The severity of choreic movements varies from minor (involuntary movements may not be recognized by patients) to major (involuntary movements may significantly interfere with activities of daily living). Neck and limbs are most commonly affected.

Dystonia is the second most common form of LID. It is characterized by sustained contractions of agonist and antagonist muscles that may involve focal/segmental muscle groups. Dystonia as part of LID can be observed as peak-dose dyskinesia, diphasic dystonia or “OFF” dystonia. Diphasic dystonia usually presents as involuntary leg kicking movements. “OFF” period dystonia symptoms is most commonly seen as painful early morning dystonia of one foot or toes.

Ballism is characterized by very large amplitude unilateral or bilateral choreic movements of the proximal parts of the limbs. Ballistic movements are usually part of severe choreoathetosis rather than being isolated.

2.2. DA replacement therapy in PD

More than 50 years after its introduction (Cotzias et al., 1967), L-dopa remains the most effective and best tolerated treatment for PD motor symptoms (Fox et al., 2011; Goetz et al., 2005). DA agonists have also proven their efficacy in large randomized trials

as monotherapy in early PD and as adjunct therapy in advanced disease stages (Fox et al., 2011; Goetz et al., 2005). The main purpose of prescribing DA agonists to younger PD patients was to delay the onset of motor complications, such as wearing off and dyskinesia (Hubble, 2002). However, long term follow up of short term randomized controlled studies comparing early DA agonist versus L-dopa administration shows that such delays are only short lived and once L-dopa is introduced, LID will occur regardless of early use of DA agonist or not (Hauser et al., 2007; Katzenschlager et al., 2008). Such view is counter-balanced by a recent meta-analysis suggesting that initial DA agonist treatment encompasses a lower risk for dyskinesia even after the unavoidable introduction of L-dopa that increases the risk for dyskinesia in a dose-related manner (Chondrogiorgi et al., 2014).

Other treatments are available adjunct to L-dopa to extend ON time, such as inhibitors of the DA degrading enzymes catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). The efficacy of the COMT inhibitors tocicapone and entacapone have been extensively studied in PD patients with motor fluctuations (Adler et al., 1998; Myllyla et al., 2001; Olanow et al., 2004; Poewe et al., 2002; Rajput et al., 1997; Shoulson et al., 2002; Waters et al., 1997). In clinical trials, new or worsening of dyskinesia was more frequently reported as side effect in patients receiving COMT inhibitors. However, dyskinesia generally subsided after L-dopa dose reduction and no differences were observed at study end between COMT inhibitors and placebo. Rasagiline, an inhibitor of monoamine oxidase (MAO)-B, is also used as monotherapy in early PD and add-on in more advanced disease stages (Parkinson Study, 2002; Parkinson Study Group, 2005). However, in clinic practice, both COMT and MAO-B inhibitors can worsen or induce dyskinesia.

2.3. Genetics of LID

The expanding field of genetics has also involved the search for factors that may result in greater susceptibility in developing LID. For instance, the autosomal recessive parkinsonism genes, PARK2 (*parkin*), PARK6 (*pink-1*) and PARK7 (*DJ-1*) are all associated with young-onset PD and often frequent appearance of dyskinesia suggesting the involvement of genetic factors related to parkinsonism (Dekker et al., 2003). However genetic parkinsonism tends to affect individuals at a younger age, and age itself is known to be a risk factor for developing LID. However, observations suggest that subjects with *parkin*-related parkinsonism may have a delayed onset of dyskinesia, probably due to a lower daily L-dopa dose (Lohmann et al., 2009). Patients with autosomal dominant LRRK2 gene mutations (PARK8) had a higher rate of dyskinesia compared to genetically undefined patients in two studies (Lesage et al., 2008; Nishioka et al., 2010), while this difference was not observed in Israeli LRRK2 patients with parkinsonism and the cohort of the International LRRK2 Consortium (Healy et al., 2008; Yahalom et al., 2012). Noteworthy, the time to LID onset was longer in patients with mutations in LRRK2 than in patients with idiopathic PD in the cohort of the International LRRK2 Consortium but not in Israeli LRRK2 patients. It remains therefore unclear if these genetic abnormalities have a direct effect on the risk of developing LID or if other mechanisms play a role.

Besides these genetic forms of PD, more classic loci of possible factors linked to dyskinesia have been investigated. Various studies have investigated genetic associations of DA and non-DA receptors implicated in basal ganglia function with LID, as well as DA transporters and enzymes involved in the metabolism of DA. Accordingly, polymorphisms of DA D₂ receptors (D₂R) but not of D₁ receptors (D₁R) seem to reduce the risk of developing LID (Oliveri et al., 1999; Rieck et al., 2012), a result not confirmed in more recent studies (Kaplan et al., 2014). By contrast, the TaqIA polymorphism located in the gene encoding the D₂R was shown to increase the risk

of developing motor fluctuations in PD patients (Wang et al., 2001). This observation was not confirmed by others (Lee et al., 2011; Rieck et al., 2012). In a study investigating genetic susceptibility factors of diphasic and peak-dose LID, diphasic dyskinesia was associated with the DA D₃R p.S9G variant. Carrying the AA genotype was likely to shorten the onset of diphasic dyskinesia, while the presence of peak-dose LID was not associated with any of the genetic variants studied (Lee et al., 2011). One recent study found that a polymorphism in the SLC6A3 gene encoding for the DA transporter extends the time to LID onset (Kaplan et al., 2014). Finally, a COMT Val158Met polymorphism is associated to an increased risk of developing dyskinesia (de Lau et al., 2012).

Opioid receptors have also been implicated in the genetics of LID. In this view, carrying the G-allele of the A118G single nucleotide coding region polymorphism of the μ opioid receptor is associated with an increased risk of earlier onset of dyskinesia (Strong et al., 2006).

The role of brain derived neurotrophic factor (BDNF) in LID has also been investigated. PD patients with the Val(66)Met allele of BDNF have a significantly higher risk of developing dyskinesia earlier in the course of their disease (Foltynie et al., 2009). However, more recent studies did not observe an association between seven polymorphisms of the BDNF gene and LID onset (Cheshire et al., 2014; Kaplan et al., 2014).

Many of those studies are however in need of replications, thereby requiring that readers pay attention to their limits. While one polymorphism seems not enough to clearly enhance the risk for LID, the possibility that combined polymorphisms affecting more than 2 genes is a possible factor in determining an individual's lifetime L-dopa exposure warrants further investigation (Cheshire et al., 2014). Taken together, the contribution of the genetic factors in the overall risk of developing LID needs further investigation or could be considered as of modest impact upon the propensity of patients to develop LID. New findings may however have implications for helping predict individual PD patients at risk of developing LID.

2.4. Current management of LID in PD patients

2.4.1. Amantadine

Currently the only evidence-based medicine review recommended add-on anti-dyskinetic agent is amantadine, a multi-target drug with antagonistic activity at the N-methyl-D-aspartate receptor (NMDA) receptor (Fox et al., 2011). The efficacy of amantadine at reducing dyskinesia severity was first assessed during an acute intravenous L-dopa infusion in a small placebo-controlled cross-over study in 18 PD patients with motor fluctuations and peak-dose dyskinesia (Verhagen Metman et al., 1998b). Amantadine reduced peak-dose dyskinesia severity without modifying PD motor symptoms. The level of dyskinesia reduction was related to plasma amantadine levels. The same patients were assessed 1 year later in a placebo-controlled follow-up paradigm while still receiving amantadine (Metman et al., 1999). The magnitude of the anti-dyskinetic effect was similar suggesting a sustained effect of amantadine on peak-dose dyskinesia. Another randomized placebo-controlled study tested the effectiveness of amantadine in subsequent 18 consecutive PD patients with motor fluctuations and peak-dose dyskinesia (da Silva-Junior et al., 2005). After three weeks of treatment, Unified Parkinson's Disease Rating Scale (UPDRS) scores were improved while CDRS scores were unchanged and not different from placebo. The effect of acute intravenous amantadine infusion was tested in 9 PD patients with motor fluctuations and peak-dose dyskinesia in a placebo-controlled cross-over study (Del Dotto et al., 2001). Intravenous amantadine infusion reduced AIMs scores by 50% compared to placebo.

The observation of a benefit of amantadine treatment lasting for less than 8 months in a randomized, placebo-controlled study including 40 PD patients with motor fluctuations and peak-dose dyskinesia questioned the usefulness of this drug for treating dyskinesia in the long run (Thomas et al., 2004). Withdrawal of the drug at study end induced a transient rebound with increase of LID in 11 patients.

The results of the trial by Thomas et al. (Thomas et al., 2004) were challenged by two randomized placebo-controlled parallel-group studies that assessed the long-term anti-dyskinetic effect of amantadine in 32 and 57 PD patients, respectively (Ory-Magne et al., 2014; Wolf et al., 2010). In the first study, patients who received amantadine for LID for at least one year were switched in a double blind manner to amantadine or placebo. Dyskinesia scores worsened significantly in patients receiving placebo but not in those pursuing amantadine. In the second trial, patients were switched to either amantadine or placebo after at least six months of stable treatment with amantadine (Ory-Magne et al., 2014). Similar to the study by Wolf and colleagues (Wolf et al., 2010), dyskinesia scores were significantly higher in the placebo group compared to patients pursuing amantadine. Moreover, dropouts for LID worsening and higher AIMs scores were observed in the discontinuing group.

Taken together, these results of both recent trials argue for long-term anti-dyskinetic effects of amantadine in PD patients with LID. The ongoing PREMANDYSK trial assesses the efficacy of amantadine in delaying the onset of LID in PD patients without motor complications (NCT01538329). Of note, the extended release formulation soon to be available (Pahwa et al., 2015).

2.4.2. Deep brain stimulation (DBS)

Within the last two decades, deep brain stimulation (DBS) of the Subthalamic Nucleus (STN) and the internal part of the Globus Pallidus (GPI) have become routine surgical methods for treating well selected PD patients with severe motor fluctuations and LID (Deuschl et al., 2006; Follett et al., 2010; Krack et al., 2003; Moro et al., 2010; Volkmann, 2004; Weaver et al., 2012).

DBS of the postero-ventral part of the GPI is particularly effective to treat LID. Accordingly, a reduction of 76% of LID severity was observed after surgery (Rodrigues et al., 2007). Longer follow-up studies confirmed marked and sustained improvement of dyskinesia (75% in duration and 64–100% in severity) over 5–6 years of pallidal stimulation (Moro et al., 2010; Volkmann, 2004). The efficacy of pallidal stimulation is independent of the type of LID and also includes respiratory dyskinesia (Oyama et al., 2011). Although the underlying mechanisms remain unclear some evidences suggest that the reduction of LID could be related to the stimulation of inhibitory afferents coming from the striatum, the external part of the Globus Pallidus (GPe) or collaterals of GPI neurons to the posterior ventral pallidum (Boraud et al., 1996; Wu et al., 2001). Alternatively, GPI-DBS could reverse the abnormal pattern of neuronal activity that is induced by DA replacement treatment in the basal ganglia-cortex network (Guridi et al., 2008; Wu et al., 2001).

STN-DBS is the commonest target for advanced PD patients due to an excellent benefit on all PD symptoms and improvement in LID. Historically, lesioning of STN induced dyskinesia in normal subjects (Beurrier et al., 1997) and so concerns arose as to the effects in PD subjects. During STN-DBS surgery, dyskinesia can occur due to a lesional effect of the implanted electrode but the occurrence of choreic or ballistic movements in the operating room is considered as an indication for the accurate placement of the stimulation leads within the sensorimotor part of the STN. STN-DBS-induced involuntary movements are frequent during the first month following surgery (Zheng et al., 2010). Rarely such movements persist and make additional GPI-DBS necessary (Reese et al., 2011). In

most cases, the duration and severity of LID decrease over time and patients experience a very good improvement in quality of life (Deuschl et al., 2006; Follett et al., 2010; Krack et al., 2003; Simonin et al., 2009). The shift from 130 Hz to 80 Hz may be helpful in patients with residual LID (Merola et al., 2013). STN-DBS improves the entire spectrum of LID including peak-dose, biphasic and OFF period dyskinesia (Fraix et al., 2010; Katayama et al., 2006; Krack et al., 1999). The mechanisms involved in the reduction of LID after STN-DBS remain unclear but the concomitant decrease in DA replacement therapy is frequently incriminated. Indeed, STN-DBS reduces LID by 46–85%, which is paralleled by a concomitant reduction of the equivalent daily L-dopa dose by 50% (Breit et al., 2004; Guridi et al., 2008). The delayed decrease in LID further suggests that the desensitization to LID requires several months of drug withdrawal (Russmann et al., 2004). However, some authors have suggested direct effects of DBS on STN neurons and the structures in the vicinity of this nucleus. Accordingly, DBS dorsal to the STN (zona incerta, lenticulus fascicularis) seems to be able to directly suppress LID independently of changes in DAergic medication (Alterman et al., 2004; Herzog et al., 2003). DBS of this region may improve LID through a disruption of the pallido-thalamic connection or a modification of the activity pattern of STN neurons (Garcia et al., 2003; Katayama et al., 2006; Meissner et al., 2005; Obeso et al., 2000; Sankar and Lozano, 2011). Others have hypothesized that STN-DBS induces overall stabilization of the basal ganglia network and striatal synaptic function (Simonin et al., 2009).

DBS of the thalamic centromedian and parafascicular complex (CM/PF) seems also effective in reducing LID severity in PD patients, but current evidence for the usefulness of this target remains weak (Caparros-Lefebvre et al., 1999).

Taken together, DBS of GPI or STN are effective treatments of LID in PD patients suffering from motor fluctuations. To date, there is no study that has demonstrated a significant difference in efficacy against either LID or motor symptoms between both targets (Follett et al., 2010; Lukins et al., 2014; Odekerken et al., 2013; Sako et al., 2014). Thus, the choice of the target must be determined in a patient-by-patient fashion, with side effect profile such as cognitive and speech deficits taken into consideration.

2.5. Beyond LID: impulse control disorders and DA dysregulation syndrome

In addition to the wide array of non-motor symptoms occurring in PD, DA replacement therapy can induce non-motor side-effects. Among them, addiction-like disorders have been described with a growing interest since the early 2000s (Cilia et al., 2014; Giovannoni et al., 2000; Lawrence et al., 2003; Weintraub and Nirenberg, 2013; Weintraub et al., 2013; Weintraub and Potenza, 2006). They mainly encompass impulse control disorders (ICD), which can be seen as behavioural addictions and DA dysregulation syndrome (DDS), corresponding to compulsive medication use. While they mainly have a non-motor expression, their link with LID has been questioned (Voon et al., 2009).

2.5.1. Impulse control disorders (ICDs)

ICDs are behavioural affections during which individuals fail to resist to internal or external stimuli, leading them to act inconsiderately. These impulsive behaviours generate anxiety and can result in dramatic alterations of the social or professional functioning (Pontone et al., 2006). The clinical spectrum of ICD has been extensively described elsewhere (Voon et al., 2009, 2007a). Briefly, different types of ICD are reported.

2.5.1.1. Pathological gambling. Pathological gambling is the most common ICD and is found in 5–6% of PD patients (Avanzi et al., 2006; Weintraub et al., 2010). Parkinsonian gamblers are mainly

interested in games providing immediate reward such as scratch cards, bets, casinos or internet gambling games (Voon et al., 2009). Pathological gambling can have dramatic consequences on patient's life due to important monetary losses, with an average financial loss of US\$10,000 (Voon et al., 2006). Noteworthy, in the latest Diagnostic and Statistical Manual of Mental Disorders (i.e. the DSM V) (American-Psychiatric-Association, 2013), gambling disorders left the 'Impulse Control Disorders' category to be classified as 'Substance-related and addictive disorders', thus emphasizing its 'Behavioural addiction' aspect (Weintraub et al., 2015).

2.5.1.2. Compulsive shopping. Compulsive shopping is defined by continuous thoughts towards buying behaviour and results in high anxiety (Black, 2007). In PD, compulsive shopping is observed in 5.7% of patients (Weintraub et al., 2010) but such troubles may be difficult to detect and necessitate the use of defined diagnostic criteria (McElroy et al., 1994). The purchases are usually useless, very expensive, time-consuming and anxiogenic and should be observed aside from any manic episode. Compulsive shopping seems to be more commonly observed in women than in men (7.8% versus 4.5%; Weintraub et al., 2010).

2.5.1.3. Hypersexuality. Hypersexuality has been defined by the presence of maladaptive preoccupation with sexual thoughts with the occurrence of intrusive paraphiliac ideations preventing the focusing on daily tasks. Orgasms are described as not satisfying and lead to the need of repeated sexual intercourses (Kaplan, 1994). Its prevalence is difficult to estimate but might reach 3.5% (Weintraub et al., 2010) and diagnostic criteria have been proposed (Voon et al., 2006). Hypersexuality appears to occur more frequently in men than in women (5.2% versus 0.5%; Weintraub et al., 2010). Compulsive sexual behaviours are difficultly tolerated by PD patients and are often associated with depression (Klos et al., 2005; Voon et al., 2006). In addition to the discomfort felt by the patients, these behaviours can have disastrous consequences on the spouse or a third person (Muller et al., 2014).

2.5.1.4. Compulsive eating. Compulsive eating refers to an irresistible need of food intake far beyond satiety (Nirenberg and Waters, 2006). Its occurrence in PD is estimated to 4.3% (Weintraub et al., 2010). Unlike the majority of parkinsonian patients who are losing weight, an abnormal weight increase is usually a red flag (Nirenberg and Waters, 2006). Diagnostic criteria follow the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) items and include: the occurrence of binge eating along with a loss of control, rapid eating, feeling uncomfortably full, eating large amounts when not hungry, eating alone because of embarrassment of amounts, feeling disgusted or guilty after overeating, in the presence of visible distress. Such behaviours should be present during at least 2 days/week over 6 months in absence of compensatory behaviours, or during anorexia or bulimia nervosa (American-Psychiatric-Association, 2000).

2.5.1.5. Punding. Punding is not considered as an ICD per se but frequently follows the same classification because of its compulsive nature. Initially described in amphetamine and cocaine users (Rylander, 1972; Schiorring, 1981), punding can be defined as an intense fascination for repetitive tasks, which can be simple such as gathering, manipulating, sorting objects or more complex such as painting or gardening (Voon et al., 2009). Other repetitive behaviours such as hobbyism and walkabout follow the same classification (Evans et al., 2004; Giovannoni et al., 2000). Punding is often misevaluated in PD because of the lack of precise diagnostic criteria, but studies reported a prevalence between 1.4 and 14% (Evans et al., 2004; Miyasaki et al., 2007). Punding is mainly observed with apomorphine and DA D₂R/D₃R agonists.

Attempts are pursued to reduce punding in patients, such as repetitive transcranial magnetic stimulation that brings a transient beneficial effect, similar to that reported in PD patients with LID (Nardone et al., 2014).

Finally, the spectrum of DA replacement therapy-induced ICD can be extended to various other behaviours such as excessive hoarding, kleptomania or reckless generosity (Bonfanti and Gatto, 2010; O'Sullivan et al., 2010a, 2010b).

Clinical studies reported the occurrence of ICD within 24 months following the beginning of the treatment and a cessation of the troubles when DA replacement therapy is tapered or stopped (Dodd et al., 2005). They are preferentially observed with DA D₂R/D₃R agonists (Gallagher et al., 2007), which might increase by 2–3.3-fold the risk of developing such troubles (Weintraub et al., 2010). A cross-sectional study conducted in the United States and Canada identified the occurrence of at least one ICD in 13.6% of PD patients (Weintraub et al., 2010). Interestingly, this study highlighted that an adjunctive L-dopa therapy increases the odds of an ICD by 50% compared to DA agonists alone. A younger age at disease onset, past experiences of illegal drug use or cigarette smoking might constitute risk factors (Bastiaens et al., 2013; Weintraub et al., 2010). A novelty seeking (Voon et al., 2007b) or a sensation seeking (Djamshidian et al., 2011a) personality have also been reported and are suspected to be important factors in the development of ICD.

2.5.2. Dopamine dysregulation syndrome (DDS)

DDS refers to a pathological overconsumption of the DAergic medication. Its occurrence is estimated between 3 and 4% of PD patients (Giovannoni et al., 2000; Pezzella et al., 2005), it is mainly found in patients with younger age at disease onset and it is associated with past legal or illegal drug use (Cilia et al., 2014; Evans et al., 2005; Giovannoni et al., 2000; Lawrence et al., 2003). In addition, most DDS cases are reported in patients taking fast-acting drugs such as subcutaneous apomorphine or L-dopa as opposed to long acting drugs (Giovannoni et al., 2000). Despite appropriate treatment of motor symptoms, DDS patients feel under-medicated and start to increase their DA replacement therapy intake (Lawrence et al., 2003). This is associated with a distorted perception of the motor status, and patients only feel 'on' when highly dyskinetic (Giovannoni et al., 2000; Lawrence et al., 2003). Moreover, a sensation of pleasure, well-being and a psychostimulant effect are reported (Castrìoto et al., 2013; Tellez et al., 2006). A core feature of DDS is an increased intake of DA replacement therapy, which will necessitate multiple providers (multiple physicians, internet purchases) or drug hoarding (Lawrence et al., 2003; Tellez et al., 2006). Thus, DDS has been associated to a 'hedonistic homeostatic dysregulation' (Giovannoni et al., 2000) where the motivation to retrieve the pleasant feelings procured by the drug is driven by the unpleasant sensation of withdrawal (Koob and Le Moal, 1997; Solomon and Corbit, 1973). DDS is associated with the presence of LID and ICD (Catalan et al., 2013; Giovannoni et al., 2000).

The DDS diagnosis follows DSM-IV criteria for substance dependence (American-Psychiatric-Association, 2000) but its use has been discussed in the specific context of PD (Bearn et al., 2004). Indeed, the excessive DA replacement therapy intake occurs in the context of a neurologic disease, which needs drug intake to relieve motor symptoms (Giovannoni et al., 2000). Therefore, an alternative classification has been proposed. Mainly following the DSM-IV criteria, it considers the specificities of PD and proposes the diagnostic of a DDS when symptoms vary from a 'classical' parkinsonian syndrome (Giovannoni et al., 2000).

2.5.3. DA replacement therapy withdrawal syndrome

In patients presenting DDS, tapering or stopping L-dopa or apomorphine may result in withdrawal signs including dysphoria,

depression, irritability and anxiety (Giovannoni et al., 2000; Lawrence et al., 2003). These negative sensations are different from those classically occurring for end-of-dose fluctuations and have been considered as core features for the diagnosis of DDS. Withdrawal signs have also been observed in up to 19% of PD patients specifically treated with DA agonists (Rabinak and Nirenberg, 2010). They are similarly characterized by psychostimulant-like withdrawal symptoms such as anxiety, irritability, orthostatic hypotension and panic attack when the treatment is reduced and have been named DA agonist withdrawal syndrome (DAWS). Wearing-off symptoms refractory to L-dopa and psychiatric manifestation resistant to antidepressant or anxiolytic are specific features of DAWS. Interestingly, DAWS has exclusively been observed in patients presenting ICD (Pondal et al., 2013; Rabinak and Nirenberg, 2010), suggesting a generalized dysfunction of reward systems (Nirenberg, 2013).

2.5.4. Dyskinesia and compulsive behaviours

The repetitive movements of LID and the compulsive behaviours of punding have been proposed to share common mechanisms (Voon et al., 2009). An altered functioning of the basal ganglia network is associated with deficits in inhibiting competing behaviours (Mink, 1996). Clinical studies showed that PD patients with severe motor symptoms have deficits in on-line suppression of impulsive responses (Wylie et al., 2010). Moreover, parkinsonian patients presenting punding behaviours exhibit more severe dyskinesia than other patients and punding severity correlates with LID severity (Silveira-Moriyama et al., 2006). Finally, LID and compulsive DA replacement therapy use might share similar presynaptic mechanisms. Studies using [¹¹C]raclopride (a DA D₂R/D₃R ligand) binding revealed increased DA levels in the dorsal striatum after L-dopa intake in dyskinetic patients (de la Fuente-Fernandez et al., 2004) whereas an increased DA release in the ventral striatum after L-dopa intake is observed in DDS patients (Evans et al., 2006). Altogether, it appears that both LID and compulsive DA replacement therapy intake are two aspects resulting from abnormal DAergic stimulation. A better understanding of their common mechanisms will be crucial for their treatment.

2.6. Other adverse effects of L-dopa

In addition to the motor and neurobehavioral complications of DA replacement therapy, several other side effects have been reported. These include autonomic symptoms (nausea, orthostatic hypotension), excessive daytime sleepiness and psychiatric complications (hallucinations, delusions). However, some of these autonomic and psychiatric manifestations are also inherent to the disease and their link with L-dopa is thus not as straightforward as it is the case with LID and compulsive behaviours triggered by DA replacement therapy.

L-dopa (as well as DA receptor agonists) can induce nausea and vomiting, side-effects that were considered due to the stimulation of DA receptors of the area postrema (Duvoisin, 1972), which is devoid of blood–brain barrier. Hence, nausea and vomiting are significantly reduced since the use of peripheral aromatic L-amino acid decarboxylase (AADC) inhibitors which have allowed to dramatically decrease the daily dose of L-dopa (Lieberman et al., 1975). In the same way, those side effects were commonly treated with domperidone, a peripheral DA receptor antagonist.

Orthostatic hypotension is a well-identified autonomic symptom of PD related to the involvement of the sympathetic nervous system early in the disease process (Fereshtehnejad and Lökk, 2014). Several lines of evidence indicate that L-dopa can have cardiovascular side-effects, including worsening of orthostatic hypotension (Senard et al., 1997), as well as a decrease in blood pressure and heart rate (Bouhaddi et al., 2004).

Altered vigilance, including excessive daytime sleepiness and sudden-onset sleep attacks is frequent in PD patients. Several studies have demonstrated an association between L-dopa equivalent dosage and excessive daytime sleepiness (Brodsky et al., 2003; Ghorayeb et al., 2007; Ondo et al., 2001). Intake of L-dopa has also been associated with increased risk of sleep attacks (Brodsky et al., 2003) and L-dopa can also induce drowsiness in healthy subjects (Micallef-Roll et al., 2001).

Hallucinations in PD have been historically described prior to the introduction of L-dopa (Fenelon et al., 2006) and may affect up to 40% of PD patients (Fenelon et al., 2000). Several studies have contributed to highlight a multifactorial origin of hallucinations in PD and have consistently identified several risk factors such as advanced age, duration of the disease and cognitive status (Biglan et al., 2007; Fenelon et al., 2000; Zhu et al., 2013). Although some studies have found links between L-dopa dosage and the occurrence of hallucinations (Zhu et al., 2013), others failed to report a significant association with L-dopa intake (Merims et al., 2004; Williams and Lees, 2005). Even though DAergic treatments as a whole can be considered as one of many risk factors for hallucinations in PD, there is no definite evidence incriminating L-dopa rather than other anti-parkinsonian therapies.

3. Animal models of LID and other L-dopa-induced abnormal behaviours

Understanding the pathophysiology of LID as a basis for therapeutic solutions has fuelled the search for valid, translational experimental models of the L-dopa-induced side effects in animals.

3.1. Hyperlocomotion in the reserpine-treated rat model of PD

The reserpine model was the first animal model of PD. Carlsson and co-workers in 1957 showed for the first time that the central action of reserpine induced a sharp decrease in motor activity with resultant hypokinesia, akinesia and even catalepsy in several species (Carlsson et al., 1957). Animals also presented other symptoms, which resemble those observed in human PD, the most frequent being rigidity of skeletal muscles, tremor and postural flexion. In the reserpine-treated rat model, administration of a high dose of L-dopa (150 mg/kg) produced a hyperkinetic state characterized by an increase in horizontal and vertical motor activity, which were later proposed to represent correlates of anti-parkinsonian and prodyskinetic activity, respectively (Johnston et al., 2005). Numerous studies have been conducted to investigate the potential of various agents to reduce LID-like hyperlocomotion. Some drugs that have retrospectively been found to reduce LID in parkinsonian primates and PD patients without compromising the anti-parkinsonian efficacy of L-dopa selectively and dose-dependently reduced vertical components of activity when co-administered with L-dopa in reserpine-treated rats (e.g. amantadine and idazoxan). Others, such as haloperidol (1 mg/kg), an agent blocking most effect of L-dopa, reduced both horizontal and vertical activity. The reserpine model, heavily used in the past, is no more included in the mainstream translational chain of models for validating either a putative therapeutic target or a therapeutic strategy for LID.

3.2. Behavioural sensitization in the 6-OHDA-lesioned rat

Behavioural sensitization to dopaminomimetic drugs (i.e. L-dopa, DA agonists or DA-releasing agents) was first described by Ungerstedt in a rodent model of PD (Ungerstedt, 1971b). The model consists of rats in which ascending DA nigrostriatal neurons are unilaterally destroyed by an intracerebral injection of 6-hydroxydopamine (6-OHDA), usually into the medial forebrain bundle (MFB). In this model, systemic administration of DAergic drugs

results in turning (rotation) of the animal towards the side opposite to the lesion (contralateral turning) whereas DA-releasing agents (e.g. amphetamine) cause ipsilateral turning (Ungerstedt, 1971b). Such rotational behaviour is thought to result from the supersensitivity of DA receptors on the denervated side and requires an extensive denervation (>95%) to occur. The response is routinely used for confirming the extent of DA depletion prior to behavioural pharmacological studies (Schwartz and Huston, 1996a, 1996b).

3.3. Abnormal involuntary movements in 6-OHDA-lesioned rodents

3.3.1. Rat model

For decades, the Ungerstedt model (Ungerstedt, 1971b) has constituted the gold standard rodent model in PD until the behavioural repertoire of 6-OHDA-lesioned rodents has been more closely analyzed, looking for parallels with human PD and LID (for review, see Cenci et al., 2002).

In the late 1990s, Cenci and co-workers developed a scheme of rating AIMs in the L-dopa-treated, 6-OHDA-lesioned rat (Cenci et al., 1998). They observed that rats were not simply displaying a sensitized rotational behaviour but also a series of complex behaviours that resembled LID (Cenci et al., 2002). In addition to the well-characterized contralateral circling behaviour, AIMs affected the forelimb contralateral to the lesion (limb dyskinesia), the trunk with twisting movements (axial dyskinesia) and the orofacial musculature (orofacial dyskinesia) (e.g. Cenci et al., 1998; Lee et al., 2000a; Lundblad et al., 2002; Winkler et al., 2002). These AIMs are quantified on the basis of their topographical distribution, amplitude and duration (e.g. Cenci et al., 1998; Lee et al., 2000a; Lundblad et al., 2002; Winkler et al., 2002), as is done in the clinic for rating human LID. The first rodent dyskinesia rating method was based on the proportion of observation time during which each AIM subtype was present, in a scale from 0 to 4 (Cenci et al., 1998; Lundblad et al., 2002). A variant of this method combined the time-based scores with descriptive categories regarding the severity of the movements (Lee et al., 2000a). Further methodological refinements were afforded by combining the original time-based rating scale of Cenci et al. (Cenci et al., 1998) with an additional scale that is based on the amplitude of the dyskinetic movements (Mela et al., 2007; Rylander et al., 2010a; Winkler et al., 2002). A validation study has established that combining time- and amplitude-based scores affords greater sensitivity in detecting effects of anti-dyskinetic interventions in the rat (Breger et al., 2013). AIMs appear with therapeutic doses of L-dopa, only when >80% of striatal DA terminals or nigral DA neurons are lost, and dyskinetic movements of maximal severity only occur when the extent of DA denervation exceeds 90% (Winkler et al., 2002).

Importantly, the Cenci's group established that rotometry in L-dopa-treated 6-OHDA rat cannot discriminate between dyskinetic and anti-akinetic effects of anti-parkinsonian treatments (Lundblad et al., 2002), a finding often replicated (Sgroi et al., 2014). In other words, the rotational behaviour is not, in this model, a reliable analogue of dyskinesia while AIMs are. L-dopa-induced AIMs share several features with human LID, such as: (i) their time course resembles peak-dose LID; (ii) they disrupt normal motor activities when they are severe (Lundblad et al., 2002; Winkler et al., 2002); (iii) their incidence and severity are conditional on the dose of L-dopa (Lindgren et al., 2007; Picconi et al., 2008; Putterman et al., 2007); (iv) they are improved by drugs proven to be effective in dyskinetic patients, such as amantadine, and clozapine (Dekundy et al., 2007; Lundblad et al., 2002); and (v) they are not induced to any significant extent by DA receptor agonists having low dyskinesigenic potential in PD (Dekundy et al., 2007; Lundblad et al., 2002), unless rats are previously primed with L-dopa or apomorphine.

Because of the distinct anatomical features and less articulate behavioural repertoire of rodents, the AIMs seen in these species

are not obviously translatable to the chorea and dystonia seen in patients (Cenci et al., 1998; Henry et al., 1999). However, Steece-Collier and collaborators have defined rating methods to distinguish between dystonic, stereotypic, and hyperkinetic components of rodent dyskinesia (Maries et al., 2006; Steece-Collier et al., 2003). These methods have been validated by other research groups (Breger et al., 2013).

3.3.2. Mouse model

Since the systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, although commonly used to produce degeneration of DA neurons, fails to produce consistent and stable symptoms of parkinsonism (Bezard et al., 1998), the model is not in use for the study of LID. The 6-OHDA model has, therefore, been used from the mid 2000s in a few studies to produce stable, unilateral DA lesions in mice (Akerud et al., 2001; Fredduzzi et al., 2002). Cenci and co-workers have fully characterized this lesion procedure in mice sustaining injections of 6-OHDA either in the MFB or in the sensorimotor part of the striatum (Francardo et al., 2011; Lundblad et al., 2004). Both types of lesion produced a similar degree of forelimb akinesia on the contralateral side. The lowest dose of L-dopa that significantly relieved this akinetic deficit (i.e. 6 mg/kg) did not differ between MFB and intrastriatal lesions (Francardo et al., 2011; Lundblad et al., 2004). However, the L-dopa threshold dose for the induction of dyskinesia did differ between the two lesion types, requiring a daily dose of 6 mg/kg for MFB-lesioned mice in contrast to 18 mg/kg in the striatally lesioned animals to develop abnormal movements affecting orofacial, trunk, and forelimb muscles on the side contralateral to the lesion (Lundblad et al., 2004). Dose is currently much lower for inducing AIMs in the MFB-lesioned mice with doses as low as 1–3 mg/kg for a fixed 12.5 mg/kg of benserazide (Won et al., 2014). Later studies showed that LID could be induced in striatally lesioned mice even with lower doses of L-dopa (e.g. 10 mg/kg) (Santini et al., 2012, 2009b). However, with lower doses of L-dopa, some mice with intrastriatal 6-OHDA lesions will not display dyskinetic behaviours (Francardo et al., 2011). In the mouse model, L-dopa-induced AIMs were not expressed by animals treated with ropinirole or KW-6002 at doses that improved forelimb akinesia, and were significantly reduced by the acute administration of compounds that have been shown to alleviate LID both in parkinsonian patients and in rat and monkey models of PD (e.g. amantadine, bupropion, riluzole) (Lundblad et al., 2005).

The AIM mouse model, although laborious and behaviourally less articulate than its rat equivalent, offers the advantage of enabling molecular studies in genetically modified mice. Consequently, a large number of ground-breaking papers relied upon this model (Ahmed et al., 2010; Alcaccer et al., 2012; Cenci and Lundblad, 2007; Cerovic et al., 2015; Crittenden et al., 2009; Fasano et al., 2010; Fieblinger et al., 2014b; Francardo and Cenci, 2014; Francardo et al., 2011; Marti et al., 2012; Pavon et al., 2006; Santini et al., 2009a, 2012, 2009b, 2010b, 2007). It is, however, at the expense of intense animal care to control mortality rate. Indeed, at odds with the unilateral MFB rat model, unilateral lesion of the MFB in the mouse causes a rapid loss of body weight and body temperature. MFB-lesioned mice therefore need intense care in the 2–3 weeks post-surgery, including rehydration, a sugar-rich diet, and housing conditions affording a warmer atmosphere (Fasano et al., 2010; Francardo et al., 2011).

3.4. Hyperlocomotion in the DA-deficient DA transporter knock-out mice

Historically developed after the AIM models but conceptually closer to the reserpine model, the hyperlocomotive behaviour induced by L-dopa administered to DA transporter-knock out mice

treated with α -methyl-p-tyrosine (DA deficient DAT-knock-out: DDD mice) (Manago et al., 2012; Sotnikova et al., 2005) has recently been proposed as a model of LID (Urs et al., 2015). DA transporter knock-out mice display increased DA release and extracellular content (with only 5% of tyrosine hydroxylase (TH) expression) associated with hyperlocomotion (Giros et al., 1996). After α -methyl-p-tyrosine treatment (250 mg/kg, i.p.), a potent irreversible inhibitor of TH, the mutant mice become akinetic due to DA deficiency (Costa et al., 2006; Sotnikova et al., 2005). As expected, L-dopa treatment reverses this phenotype and induces an increased activity proportionally to the dose of the drug (Manago et al., 2012). The chronic hyperdopaminergia induced by the genetic deletion of DA transporter is likely responsible for the hypersensitization of these animals once DA depleted and stimulated by L-dopa. The DDD mouse model can be used as a screening tool before testing the strategy in the AIM rodent model (Urs et al., 2015).

3.5. Genetic mouse models of bilateral dopamine deficit

The aphakia mice selectively lose dopamine neurons in the midbrain, especially in the SNc early in development as a consequence of a naturally occurring deletion of the promoter region and the noncoding exon 1 of the *Pitx3* gene (Hwang et al., 2003; Nunes et al., 2003; Smidt et al., 2003; van den Munckhof et al., 2003). Consistent with the loss of DA neurons in the SN, there is significant DA denervation in the dorsal striatum, which results in motor deficits that can be ameliorated by dopaminergic agents (Beeler et al., 2010; Hwang et al., 2005; van den Munckhof et al., 2006). Aphakia mice also show AIMs that increase with repeated L-dopa exposure consistent with the characteristics of LID (Ding et al., 2007; Li and Zhou, 2013). Furthermore, pharmacological responses to amantadine and differential effects of D₁R versus D₂R agonists are also similar to those of other traditional LID models in rodents (Section 3.3.1) (Ding et al., 2007; Li and Zhou, 2013) and in PD patients. In addition, biochemical changes such as FosB and prodynorphin expression are similar to other rodent models of LID (Ding et al., 2007; Li and Zhou, 2013; Solis et al., 2015). Although the underlying neurobiological changes associated with LID are similar in aphakia mice and unilateral PD models, as a bilateral lesion model, the dyskinetic behaviour in aphakia mice is quite different from that seen in unilateral PD rodents (Ding et al., 2007; Li and Zhou, 2013). There is no typical limb, axial and orolingual dyskinesia in aphakia mice treated with L-dopa. Rather, the animals adopt a vertical position next to the cage or testing chamber wall with their front paws sliding along the vertical surface, behaviour termed front-paw dyskinesia. With higher doses and/or longer L-dopa treatment, LID becomes more severe with additional involvement of one of the hind paws. In the most severe cases, dyskinetic aphakia mice can show four-paw dyskinesia with body weight supported by the tail. The dyskinetic behaviours typically seen in aphakia mice are also observed in other bilateral dopamine deficient models. For example, wild type mice treated with MPTP show similar behavioural response to a high dose of L-dopa (Nicholas, 2007), as do wild type mice with bilateral 6-OHDA-induced lesion in the dorsal striatum (Li et al., 2015). Of note, there is a need for replication in these neurotoxin-based models. Dopamine deficient (DD) mice with selective knock-out of TH in DA neurons show similar vertical movements upon repetitive L-dopa exposure (Chartoff et al., 2001; Henschen et al., 2013) with three-paw dyskinesia (Urs et al., 2015). These observations illustrate the common behavioural phenotype of LID in bilaterally DA-deficient models produced either by biochemical loss or by the degeneration of the nigrostriatal projection.

The aphakia mouse provides a unique model of PD in several ways: (i) DA depletion occurs predominantly in nigrostriatal system. (ii) Unlike the hemi-parkinsonian rodents, the denervation

of striatal DA is bilateral. (iii) The loss of nigrostriatal system occurs very early in development, which may facilitate compensatory mechanisms that may underlie the generation of dyskinesia. Similar to aphakia mice, early-onset PD patients are more likely to develop LID than late-onset PD. (iv) Aphakia mouse represents a more consistent and less heterogeneous model of nigrostriatal DA depletion which would facilitate molecular and biochemical analysis of mechanisms underlying LID and provide a test model for therapeutic approaches. However, the early loss of nigrostriatal projection may bring about other developmental changes, such as a deficit in midbrain GABAergic neuron migration (Vasudevan et al., 2012). As with any animal models of human disease, the limitations of the model in recapitulating the specific aspects of human LID should be carefully considered, but aphakia mouse and other genetic models that produce bilateral nigrostriatal deficits present complementary models to traditional toxic lesion models.

3.6. Non-human primate models of LID

3.6.1. History

Modelling LID in non-human primates became possible because of the development of the now gold-standard model of parkinsonism obtained by exposure to the toxin MPTP. MPTP is a neurotoxin that induces a form of parkinsonism in humans which is indistinguishable from idiopathic PD (Langston et al., 1983). Primates exposed to MPTP show all of the motor problems typically encountered with L-dopa therapy, including wearing-off and peak-dose dyskinesia (but not on-off fluctuations) (Langston and Ballard, 1984). MPTP-lesioned non-human primates chronically treated with L-dopa display all of the human symptoms of LID (Clarke et al., 1987; Crossman, 1987; Crossman et al., 1987). They are moreover sensitive to the main risk factors for LID, such as the loss of nigrostriatal DA projections (Guigoni et al., 2005b), the dosage of L-dopa (Huot et al., 2012b, 2013; Porras et al., 2014) and an increase incidence of dyskinesia with chronic L-dopa treatment (Bezard et al., 2001a; Iderberg et al., 2012).

The significance of MPTP emerged from the discovery that a group of young drug addicts were found to display a clinical profile almost indistinguishable from PD after the self-administration of a synthetic heroin analogue contaminated by MPTP. The symptoms were so close to PD that, soon after, MPTP was administered to experimental animals, including non-human primates, in which it reproduced most of the clinical and pathological hallmarks of PD (Chiueh et al., 1984; Crossman et al., 1985; Doudet et al., 1985; Langston et al., 1984b). The discovery of MPTP as a cause of parkinsonism has led to the development of valuable experimental models of PD in non-human primates (Bédard et al., 1992; Bezard et al., 1998; Langston et al., 2000). Intracarotid or systemic MPTP intoxication induces a degeneration of the DAergic neurons residing in the SNc, leading to a DA depletion in the caudate-putamen similarly to PD (Bezard et al., 2001c; Burns et al., 1983; Engeln et al., 2014b; Guigoni et al., 2005c; Jan et al., 2003; Jenner et al., 1984; Leenders et al., 1988). Lesions of the serotonergic and noradrenergic systems occur as in PD (Engeln et al., 2014b; Mitchell et al., 1985; Pifl et al., 1991; Rylander et al., 2010b). MPTP intoxication produces a parkinsonian syndrome in primates that is remarkably similar to PD (Benazzouz et al., 1992; Bezard et al., 1998; Clarke et al., 1987; Crossman, 1987; Crossman et al., 1987). The animals display bradykinesia, rigidity and postural abnormalities (e.g. Bédard et al., 1992; Benazzouz et al., 1992; Bezard and Przedborski, 2011; Langston et al., 1984a, 2000; Schultz et al., 1985) and in some cases/species resting tremor (François et al., 1998). Those symptoms respond positively to the medications available in the clinic (Cenci et al., 2002; Fox and Brotchie, 2010). A number of DAergic (Iderberg et al., 2012; Meissner et al., 2011) or surgical (Aziz et al., 1991; Benazzouz et al., 1993; Jarraya et al.,

2009; Kordower et al., 2006; Tass et al., 2012) therapies have been investigated in MPTP-treated primates and subsequently successfully transferred into clinical practice. So far, effects observed in MPTP-treated primates have proven to be predictive of symptomatic efficacy in human, provided the magnitude of the effects in this model was large enough for overcoming the inherent disease and human variability. L-dopa treatment to such MPTP-lesioned primates causes dyskinetic motor manifestations that are remarkably similar to those displayed by patients; chorea and dystonia are easily distinguished and clearly equivalent to their human counterparts (for review, see Fox et al., 2012; Langston et al., 2000).

Four species have been regularly used, namely the macaque monkeys (*Macaca mulatta* and *Macaca fascicularis*), the common marmoset (*Callithrix jacchus*) and the squirrel (*Saimiri sciureus*) monkeys, while other species might appear in the literature such as baboon monkeys (*Papio anubis*) and African green monkeys (*Cercopithecus aethiops*). The vast majority of pathophysiological studies have however been conducted in the macaque monkeys.

3.6.2. Macaque models

The cynomolgus (*Macaca fascicularis*), rhesus (*Macaca mulatta*) and Japanese (*Macaca fuscata*) macaques display the human-like symptoms of PD and LID and are currently the species of choice to study LID (Bezard et al., 2001a; Iderberg et al., 2012; Johnston et al., 2010a, 2013; Koprich et al., 2013; Langston et al., 2000; Morin et al., 2013, 2014; Porras et al., 2012b). Dyskinetic MPTP-intoxicated macaques exhibit various combinations of choreic-athetoid (i.e. characterized by constant writhing and jerking motions), dystonic and even ballistic movements (i.e. large-amplitude flinging, flailing movements), although less frequently for those latter (Ahmed et al., 2010; Bezard et al., 2001a, 2003; Iderberg et al., 2012; Johnston et al., 2010a, 2013; Koprich et al., 2011, 2013; Langston et al., 2000; Morin et al., 2013, 2014; Porras et al., 2012b). Both the repertoire and severity of dyskinesia are not distinguishable from LID occurring in PD patients (Bezard et al., 2003; Fox et al., 2012).

Several rating scales exist to quantify LID in non-human primates and were reviewed and criticized, with a focus on macaques (Fox et al., 2012). Fox and co-workers proposed a revised LID rating scale in monkeys as well as guidelines for their observation: the Non Human Primate Dyskinesia Rating Scale (NHPDysR), based on the Dyskinesia Disability Rating Scale (Fox et al., 2012). For each AIMs, the monkeys are scored from a score of 0–4: 0 = no AIMs, 1 = mild LID: transient and intermittent AIMs present of less than 30% of the scoring time, 2 = moderate LID: monkeys display AIMs for more than 30% of the observation period and are still able to perform all motor tasks, 3 = marked LID: AIMs are present less than 70% of the scoring period and the monkeys are unable to eat with significant decrease in motor tasks, 4 = severe LID: AIMs are continuous and present for more than 70% of the observation period. LID interfere with the ability to do any motor task (Fox et al., 2012). The anti-parkinsonian effect of L-dopa therapy is quantified using rating scales based on the UPDRS (Imbert et al., 2000).

Once parkinsonism is stable, macaques are then treated with daily administration of L-dopa (L-dopa/carbidopa, ratio 4:1) for 4–5 months at an individually tailored dose designed to produce a full reversal of the parkinsonian condition, i.e. in a clinically relevant approach. Over this period, animals develop consistent and reproducible dyskinesia (Iderberg et al., 2012). Moreover, even if the L-dopa treatment is stopped for months, only one L-dopa administration will be sufficient to induce the same AIMs scores as observed before (Ahmed et al., 2010; Bezard et al., 2003, 2004; Fasano et al., 2010; Gold et al., 2007; Iderberg et al., 2012; Porras et al., 2012b; Rylander et al., 2010a), i.e. a profile of response observed in humans as well who do not benefit from drug holidays. Although L-dopa doses are individually tailored, the benefit of the

L-dopa therapy is invariable and consistent for each MPTP macaque, which mimics the treatment adaptation to parkinsonian patients performed in the clinic and underlies how this model is relevant before undergoing clinical trials.

Even if the similarity to human symptoms makes the MPTP macaque relevant on a clinical level for LID, this model is expensive, sizable (weighing up to 7–10 kg) and need specialized infrastructures with highly qualified personnel to handle the animals (Iderberg et al., 2012; Morin et al., 2013, 2014). Moreover, neither the extent nor the pattern of nigrostriatal lesioning are sufficient to explain the occurrence of dyskinesia in the MPTP-treated macaque model of LID (Fernagut et al., 2010; Guigoni et al., 2005b). In addition, chronic administration of high dose L-dopa (80 mg/kg) for several months can provoke dyskinesia in normal macaque (Pearce et al., 2001). Based upon these data, it is necessary to include in future investigations normal animals treated with L-dopa as control, in addition to another essential control group, L-dopa treated animals with nigral lesion that do not develop dyskinesia (Engeln et al., 2014b; Fernagut et al., 2010; Porras et al., 2012a; Santini et al., 2010a).

3.6.3. Marmoset model

Common marmosets (*Callithrix jacchus*) were used because of their small size and their convenience in housing and handling compared to macaques. They feature a cerebral conserved structural organization.

Parkinsonian marmoset models can be induced by either systemic MPTP intoxication (Jenner et al., 1984) or by unilateral (Annett et al., 1992) or bilateral (Mitchell and Carroll, 1997; Mitchell et al., 1995) repeated intracerebral injections of 6-OHDA in the nigrostriatal bundle. Very few studies used the 6-OHDA-lesioned marmosets to analyze LID pathophysiology (Pirker et al., 2001; Svenningsson et al., 2002). Most studies relied upon the MPTP-treated marmoset that displays a parkinsonian state that reverses after administration of L-dopa and other DA agonists (Jenner et al., 1984). Following L-dopa administration, MPTP-treated marmosets display dyskinetic-like abnormal involuntary behaviours including chorea-like (i.e. picking/flicking movements), dystonic-like (i.e. sustained posturing) and repetitive purposeless movements (Pearce et al., 1995) as well as L-dopa-induced hyperlocomotion (Ando et al., 2014). MPTP-intoxicated marmosets chronically treated with L-dopa are often restless and show consistent and continuous hyperkinetic behaviour at the L-dopa peak-time of action (Iderberg et al., 2012; Morin et al., 2013, 2014; Pearce et al., 1995). Moreover, the marked hyperkinesia of dyskinetic marmoset highly complexities the distinct assessment of choreic-like and dystonic-like abnormal movements, which clearly differs from clinical observation of dyskinetic patients (Fox and Brotchie, 2010).

Kuoppamäki and co-workers reported on the relationship between L-dopa dose and the duration and severity of dyskinesia in MPTP-treated marmoset with marked nigral degeneration mimicking late stage of PD (Kuoppamäki et al., 2007). With increasing doses of L-dopa, locomotor activity increased and motor disability declined. The duration of dyskinesia following L-dopa administration dose-dependently increased and showed a linear correlation with total locomotor activity (Kuoppamäki et al., 2007). In contrast, severity of dyskinesia showed a nonlinear correlation with total locomotor activity, low doses of L-dopa eliciting severe dyskinesia for short periods of time (Kuoppamäki et al., 2007).

The use of the MPTP-treated marmoset model to study novel therapies for LID was facilitated by its property to respond with a strong motor activity to L-dopa therapy (Iderberg et al., 2012), allowing to easily quantify the anti-parkinsonian state and the prototypical development of LID in response to a given test item (Hill et al., 2003, 2004a, 2004b; Huot et al., 2011, 2014; Johnston

et al., 2011; Kobylecki et al., 2011; Maratos et al., 2001; Nash et al., 2004; Pearce et al., 1998; Silverdale et al., 2005). Such de novo protocol remains an asset of the model (Nash et al., 2000) as the kinetics of LID appearance in this model is far less variable than in macaque (unless macaques are left without DAergic therapy for months before starting such de novo protocol). However, the difficulties in distinguishing choreic-like movements from dystonic-like ones during LID is not representative of the human LID pattern of expression and represent a drawback for this model to understand LID pathophysiology (Ilderberg et al., 2012; Morin et al., 2013, 2014). Finally, while the marmoset model has been heavily used in the 1990s, the development of experimental research in macaques, making them relatively easily available, has led the field away from this species, as attested by the decreasing number of papers relying on this species in the past 5 years.

3.6.4. Squirrel monkey model

As for the common marmoset, squirrel monkeys (*S. sciureus*) were employed for their convenience in handling and housing because of their small size. Squirrel monkeys intoxicated by MPTP develop parkinsonian-like syndromes as akinesia, rigidity and bradykinesia (Langston et al., 1984a). MPTP-lesioned squirrel monkeys treated with L-dopa display dyskinetic-like movements including a choreic and dystonic component (Boyce et al., 1990b; Di Monte et al., 2000). However, chorea is always most prevalent at the L-dopa peak-time of effect while dystonia is barely noticeable (Boyce et al., 1990b). The ability of squirrel monkeys to display dyskinesia allowed several investigations on LID pathophysiology using this model (Boyce et al., 1990a, 1990b; Di Monte et al., 2000; Hsu et al., 2004; Neale et al., 1984; Stephenson et al., 2005) with a pronounced focus on the opioid (Chen et al., 2005; Cox et al., 2007; Quik et al., 2002a) and nicotinic system (Quik et al., 2003, 2007, 2013c, 2002b, 2005; Zhang et al., 2013a). In addition, Togasaki and co-workers demonstrated that normal squirrel monkeys (i.e. unlesioned) treated twice daily with a therapeutically relevant dose of L-dopa (15 mg/kg with carbidopa, *per os*) for 15 days can develop LID (Togasaki et al., 2005, 2001). These data are coherent with previous reports showing that L-dopa, at very high doses and after very long treatment, can induce dyskinesia in the absence of nigrostriatal damage in normal primates (Pearce, 1999; Pearce et al., 2001; Sassini et al., 1972). Normal squirrel monkeys however do develop LID after receiving clinically relevant doses of L-dopa and over few days (Togasaki et al., 2005, 2001). Clinical findings might suggest it also does in non-parkinsonian patients (Goodwin et al., 1970; Lieberman et al., 1972) although such report has not been made since the 1970s and only in patients being responsive to L-dopa, for instance in TH deficient patients (Pons et al., 2013) or in dopa-responsive dystonic patients in whom the nigrostriatal projections are also spared (Hwang et al., 2001).

Even if this finding limits the translational value of the MPTP-intoxicated squirrel monkey in LID, it should be very interesting to understand the physiological and the molecular basis on how L-dopa can induce dyskinesia without any nigrostriatal denervation.

3.6.5. Other species

Other non-human primate species are used to investigate PD and LID pathophysiology such as the baboons (*P. anubis*) or the African green monkeys (*C. aethiops*).

African green monkeys can be qualified as mid-sized non-human primate weighing around 3–7 kg at adulthood requiring specific infrastructure, just like macaques. MPTP intoxication of African green monkeys is able to induce parkinsonian-like symptoms including akinesia, bradykinesia, rigidity and tremor (Elsworth et al., 1987, 1990; Taylor et al., 1994, 1997; Wichmann et al., 1999). Therefore, since macaques seldom present tremor once lesioned, African green monkeys have been used to study

parkinsonian tremor besides other aspects of PD pathophysiology (Bergman et al., 1998; Boulet et al., 2008; Guehl et al., 2003; Mounayar et al., 2007; Pessiglione et al., 2003; Rosin et al., 2011; Wichmann et al., 1999). Only a few studies focused on LID pathophysiology (Heimer et al., 2002, 2006) or risk for developing LID in response to transplantation of foetal DAergic neurons treatment (Redmond et al., 2008).

Baboons are sizable non-human primates weighing up to 40 kg at adulthood and require particularly suitable infrastructure and highly qualified personnel to handle the animals. Only few research teams still work with them in the world. MPTP-intoxicated baboons develop PD symptoms such as hypokinesia, bradykinesia, postural impairments, rigidity and resting tremor (Hantraye et al., 1993; Varastet et al., 1994). They were used to mostly investigate PD pathophysiology and innovative surgical therapeutic approaches because of their brain size (Chen et al., 2008; Drouot et al., 2004; Ferrante et al., 1999; Hantraye et al., 1996; Kishima et al., 2004; Todd et al., 1996). Although not directly used for the pathophysiology of LID as chronic oral treatment in such animals is far too risky, they are physiologically capable of displaying AIMs. Baboons were indeed used to model Huntington's disease (Hantraye et al., 1990; Isacson et al., 1989; Palfi et al., 1996). For instance, excitotoxic striatal lesions with 3-nitropropionic acid induces dyskinetic-like abnormal movements following apomorphine injection (Palfi et al., 1997).

3.7. Models of DDS/ICD

Increased awareness about the dramatic consequences of DDS and ICD for PD patients (Giovannoni et al., 2000; Lawrence et al., 2003; Voon et al., 2011b; Weintraub et al., 2010), prompted to investigate their underlying mechanisms. Imaging studies (Evans et al., 2006; Thobois et al., 2010; van Eimeren et al., 2010) as well as impulsivity evaluation (Djamshidian et al., 2011a; van Eimeren et al., 2009; Voon et al., 2007b) have provided insights into some of the alterations underlying these troubles and regarding associated risk factors. However, these studies being mainly conducted in PD patients already under DAergic treatments and usually with documented DDS or ICD histories, it is virtually impossible to decipher the respective contributions of the degenerative process, DA replacement therapy, and individual vulnerability factors.

The progressive DAergic loss occurring in both nigrostriatal and mesolimbic pathways and the subsequent action of DA replacement therapy on these altered pathways have been proposed to disrupt the reward system (Ambermoon et al., 2011; Giovannoni et al., 2000; Lawrence et al., 2003). Indeed, in many aspects DDS as well as ICD remind addiction to drug of abuse and behaviours associated with the abuse of psychostimulants. Multiple works thus proposed that, in addition to the data coming from experiments on basal ganglia dysfunction in PD, the addiction framework might help to understand and to study these non-motor side-effects (Ambermoon et al., 2012, 2011; Bearn et al., 2004; Giovannoni et al., 2000; Lawrence et al., 2003). The study of ICD and DDS might thus take advantage of works conducted in both the PD and the addiction fields. While there is a great diversity of experiments to test addiction theories in animals, there are currently no distinct DDS or ICD animal models as for LID. However, multiple aspects involved in the emergence of DDS or ICD can be reproduced in animal models and give information on their triggering factors that might not be directly assessed in patients.

3.7.1. The role of the DAergic medication

An action of DA replacement therapy on reward pathways has been proposed to disturb reward processing (Evans et al., 2010). To measure the effectiveness of DA replacement therapy to act on

these pathways, experiments conducted in rodents aimed to evaluate both reward processing disruption and reinforcing properties of DA replacement therapy. The D₂R/D₃R agonists have been mainly incriminated in ICD in humans (Gallagher et al., 2007; Weintraub et al., 2010). Using various operant conditioning paradigms, experiments on rats evaluated the impact of Pramipexole (PPX) on impulsive behaviours and revealed that naïve rats dose-dependently do more impulsive choices under PPX, preferring smaller-sooner over larger-later rewards (Koffarnus et al., 2011; Madden et al., 2010). Such results are consistent with reports of parkinsonian patients doing more impulsive choices and being more sensitive to delay under DA agonists (Voon et al., 2010). Other works evaluating the effect of PPX on risk taking in rats using operant tasks allowing the choice between a safe option providing a small reward and a more hazardous option offering a larger reward showed that under PPX, animals dose-dependently increase their choice towards the most risky option (Johnson et al., 2011, 2012). These results are reminiscent of the described desensitization to punishment and increased risk taking of PD patients with pathological gambling under DA agonists (Djamshidian et al., 2010; Voon et al., 2011a, 2007b). Finally, some studies evaluated the ability of D₂/D₃ agonists to act on the reward pathway as hypothesized for ICD (Gschwandtner et al., 2001; Schott et al., 2007). In self-administration procedure, D₂/D₃ agonists have been shown to dose-dependently maintain responding to stimuli previously paired with cocaine (substitution), but also to induce responding for stimuli associated with cocaine (Collins et al., 2012; Collins and Woods, 2007). Later studies further revealed that naïve, as well as parkinsonian rats display conditioned place preference (Riddle et al., 2012) or can self-administer PPX (Engeln et al., 2012), demonstrating the rewarding properties of D₂R/D₃R agonists. Experiments evaluating the ability of DAergic treatments to trigger ICD- or DDS-like features on naïve (e.g. non DA lesioned) animals might however bring incomplete insight on the nature of these troubles. Indeed, despite the fact that ICD are also reported in non DA-depleted individuals (Davie, 2007; Holman, 2009; Ondo and Lai, 2008), the neurodegenerative process occurring in PD has been questioned in the development of impairments in reward processing in both ICD and DDS (Lawrence et al., 2003; Schott et al., 2007).

3.7.2. The role of the DAergic lesion

The onset of ICD or DDS with the emergence of PD raised questions on the contribution of both nigrostriatal and mesolimbic DAergic degeneration in the emergence of these side-effects of DA replacement therapy (Lawrence et al., 2003; Thobois et al., 2010). While unilateral lesioning of mesencephalic DAergic systems is well-suited for the study of LID, owing to a marked DAergic asymmetry facilitating the quantification of abnormal motor behaviours, such models are not adapted for studying non-motor aspects of DA replacement therapy as drug-induced rotations will bias operant behaviours. Obtaining a viable bilateral lesion model is however uneasy (Dunnett and Lelos, 2010; Ungerstedt, 1971a) and might in part contribute to the relatively small number of work conducted so far in rodent models of PD. Using different bilateral lesioning strategies, several studies have investigated how the DAergic lesion may affect behavioural dimensions relevant to ICD and DDS. Lesion studies in rats first highlighted that a bilateral nigrostriatal lesion using 6-OHDA could reduce motivation in rats in various paradigms such as place preference, instrumental responding or food consumption test (Drui et al., 2014; Faure et al., 2005; Pioli et al., 2008). Bilateral lesions of the nigrostriatal pathway obtained by injecting 6-OHDA in the dorsal striatum showed that the establishment of a conditioned place preference for PPX necessitated a greater dose in sham than in lesioned rats (Riddle et al., 2012). Moreover, risk-taking evaluation showed that

PPX increased intracranial self-stimulation-mediated probabilistic discounting in both sham and lesioned rats (Rokosik and Napier, 2012). Mixed bilateral nigrostriatal and mesolimbic lesions achieved with intracerebroventricular 6-OHDA infusion however resulted in similar reinforcing properties, comparable motivation and equally low drug-seeking for PPX between sham and lesioned rats using intravenous self-administration procedures (Engeln et al., 2012). Conditioned place preference experiments in animals injected with small 6-OHDA doses in the MFB showed that high doses of bromocriptine (D₂R agonist) might have rewarding properties, but failed to report such results for supraliminal (50–200 mg/kg) doses of L-dopa (Zengin-Toktas et al., 2013). Recently, bilateral nigrostriatal lesions were obtained by using viral-mediated α -synuclein overexpression in the SNc (Engeln et al., 2013). This latter model is promising as it reproduces many of the cellular and molecular features of PD, including early synaptic dysfunction as well as accumulation and aggregation of α -synuclein (Decressac et al., 2012a, 2012b). In these animals, a moderate lesion of the SN was necessary and sufficient to reveal psychostimulant-like properties of L-dopa. Indeed, clinically relevant doses of L-dopa (12 mg/kg) elicited a conditioned place preference as well as a decreased interest for a non-drug reward exclusively in lesioned rats (Engeln et al., 2013). These latter findings provided significant details on how L-dopa might act on altered DAergic pathway to result in reward dysfunction as observed in DDS.

In human, the role of the DAergic loss is difficult to evaluate, as it would require large prospective studies comparing patients before and after the diagnosis of PD. To date, only one study conducted in α -synuclein duplication carriers compared pre-symptomatic and symptomatic stages, showing reward impairments solely after the establishment of significant neurodegeneration (Szamosi et al., 2013).

It is interesting to notice that in rodents, DA agonists may trigger addiction-like behaviour in both control and lesioned rats, while L-dopa is rewarding only in lesioned animals. Such observations are in agreement with clinical reports of low mood elevation effects of L-dopa in normal individuals (Liggins et al., 2012). Thus, after evaluating the potential for DAergic treatments to act on the reward pathway of lesioned animals, studies are now evaluating their ability to affect impulsive behaviours.

Finally, clinical studies have suggested that individual risk factors could contribute to the emergence of both ICD and DDS (Djamshidian et al., 2011b; Evans et al., 2005; Voon et al., 2007b). A family history of gambling, a higher alcohol consumption or previous use of legal or illegal drugs is associated with both increased DDS and ICD incidence (Evans et al., 2005; Weintraub et al., 2010). Similarly, personality traits such as sensation seeking, impulsiveness or risk taking might be triggering elements (Voon et al., 2011b). These traits might be present before PD's motor symptoms and could also evolve with the progression of the disease process. While a study suggested that unmedicated de novo PD patients have no increased risk to develop ICD compared to the general population (Weintraub et al., 2013), it is unknown if the ongoing degenerative process may affect impulsiveness in these patients. Experimental models will help to solve this question.

3.7.3. The role of individual risk factors

The most difficult aspect of ICD and DDS to investigate in human is the influence of the DAergic depletion on personality traits. Information on premorbid 'baseline' impulsive behaviours obtained retrospectively by interviewing patients or their family might be biased and misleading. Surprisingly, there is currently no animal study providing a longitudinal measurement of impulsive behaviours before and after DAergic depletion. A prelesional

screening of impulsiveness might yet be crucial in the understanding of ICD pathophysiology. Behavioural tests such as delay discounting tasks, evaluation of impulsive choice and action, risk taking measures are available in rodents and could provide important information on the evolution of the personality trait over the course of the disease. Thus, prelesional versus postlesional inhibitory control assessment would help to elucidate if and how the DAergic denervation may affect these individual traits. Moreover, the differential impact of DA replacement therapy on behavioural inhibition according to specific behavioural traits would help to assess individual responses to the treatment of PD. Future experiments in this direction will be mandatory as individual vulnerability appears to be a critical factor in the propensity to develop non-motor side effects of DA replacement therapy.

Rodent models of ICD and DDS offer the possibility to measure cellular and molecular changes occurring after lesion, drug exposure and behavioural tasks. Again, only few data are currently available regarding these factors. Experiments evaluating the reinforcing properties of DA D_2R/D_3R agonists in rats revealed that PPX induces striatal Δ FosB accumulation (Engeln et al., 2012). Moreover, motivation for PPX was correlated with the density of Δ FosB-positive cells in different striatal compartments in sham and lesioned rats, suggesting the involvement of different cortico-subcortical loops in DA depleted animals. Interestingly, an increased Δ FosB expression was found in the dorsal striatum of lesioned rats, a region mainly described for its role in dyskinesia (Cenci et al., 1999). In psychostimulant addiction, drug seeking (Yin et al., 2005) and habit learning (Yin et al., 2004) are known to involve dorsal regions of the striatum. Δ FosB accumulation is well known for its role in addiction (Nestler et al., 2001), specifically in striatal subregions after various drug exposures (Lobo et al., 2013). Altogether, these observations suggest that common mechanisms may operate in motor and non-motor side-effects of DA replacement therapy where specific molecular modifications underlie both motor and reward dysfunctions. Indeed, similarities between the repetitive movements of dyskinesia and the stereotyped behaviours of punding are observed. It has been proposed that both dyskinesia and ICD or DDS might be part of the same continuum (Voon et al., 2009). In rats, procedures used to induce stereotypies are comparable to those used to induce dyskinesia, and these two behaviours induce similar striatal molecular adaptations (Graybiel et al., 2000). Moreover, according to the striosome/matrix organization of striatal functioning, while stereotypies induce molecular changes (including Δ FosB accumulation) in the matrix of the medial striatum, LID induce modifications in the matrix of the lateral striatum. In susceptible individuals, the activation of striosomes at the interface between the 'limbic' medial striatum and the 'motor' lateral striatum might underlie compulsive behaviours such as punding (Graybiel et al., 2000). Studies conducted in DA-depleted rats further showed that an increase in the DAergic tone leads to a global involvement of the striatum and could jointly activate neuronal networks which were previously distinct (Saka et al., 1999). It is thus possible that compulsive/addiction-like behaviours and dyskinesia may share similar neuronal circuits. Considering the limbic and motor interfaces of the striato-nigro-striatal spiralling pathways (Haber et al., 2000), a molecular sensitization of the connectivity between the ventral and the dorsal striatum might operate both in motor and non-motor side-effects of DA replacement therapy. Studies investigating the possible common pathways of both LID and compulsive behaviours might provide new opportunities to approach broad basal ganglia modification linked with DA replacement therapy.

In summary, experimental modelling of DDS and ICD is still in its infancy and there is currently no validated animal model

replicating the clinical features of these non-motor side effects of DA replacement therapy. However, works conducted in rodents already provided precious information on the respective and combined roles of the DA replacement therapy and the DAergic depletion in triggering ICD- and DDS-like features. Further studies are now required to understand the role and the evolution of personality traits over the course of the lesional process. Upcoming studies will also need to provide information regarding the cellular and molecular changes occurring in these troubles. It has to be noticed however that animal studies might carry some limitations. While LID may affect virtually all PD patients over chronic exposure, DDS occur in 1–4% and ICD are reported in 6–14% of PD patients (Giovannoni et al., 2000; Weintraub et al., 2010). Assuming that such prevalence would be reproduced in animals, large numbers of subjects will be required. Screenings of susceptible animals (Deroche-Gamonet et al., 2004; Lenoir et al., 2013) might however help to overcome these limitations. Dimensions of ICD and DDS, such as financial loss, are difficult to model in rodents and could participate to experimental limitations. The use of primate models would be of great interest to study higher cognitive processes.

3.8. Modelling other L-dopa-induced side-effects

Autonomic and psychiatric side-effects of L-dopa have received very little attention in experimental models of PD. Even though several models recapitulate some of the cardiovascular features of PD, including depletion of norepinephrine and reduced meta-iodobenzylguanidine uptake (for review, see Fleming, 2011), the effects of L-dopa on cardiac function have not been examined in experimental models. There is however evidence in normal rats that L-dopa can affect the baroreflex and, interestingly, such effect may be related to a direct action of L-dopa in the nucleus of the solitary tract (Kubo et al., 1992; Misu et al., 1995; Yue et al., 1994).

The effects of L-dopa on vigilance (excessive daytime sleepiness, sleep attacks) in experimental models of PD remain poorly understood. In MPTP-treated monkeys, L-dopa does not affect rest-activity rhythms (Vezoli et al., 2011). On the other hand, a high-dose of L-dopa (50 mg/kg) increases wakefulness and decreases slow wave sleep and paradoxical sleep in MPTP-treated mice (Laloux et al., 2008).

Few studies have investigated supposed "psychosis-like" behaviours in experimental models of PD and have assessed the effects of DA replacement therapy, including L-dopa (Johnston et al., 2011; Visanji et al., 2006a). Whether the observed behaviours (stereotypies, agitation/hyperactivity, repetitive grooming, staring or tracking an apparent non-stimulus) may represent adequate correlates of psychotic behaviours occurring in PD patients remain hypothetical. Indeed "psychosis-like" behaviours systematically occur in L-dopa-treated animals (Johnston et al., 2011; Visanji et al., 2006a), while such behaviours are only observed in a subset of PD patients. Given the multifactorial nature of psychosis in PD, including the occurrence of hallucinations and other psychotic behaviours unrelated to L-dopa treatment (Fenelon et al., 2006), the relevance of experimental models to this aspect of PD remains difficult to ascertain.

4. Pathophysiology of peak of dose LID

In the present review, we aimed at focusing on changes observed at the peak-dose of L-dopa plasma concentrations. Indeed, in the literature, LID pathophysiology refers to various states. In several papers, animals chronically exposed to L-dopa were considered as "dyskinetic" even when they were actually terminated OFF L-dopa (i.e. more than 3 h after their last L-dopa injection). While the OFF state is very interesting and informative

on the neuronal plasticity induced by chronic treatment, it cannot be considered as the ON LID state. Indeed, the ON LID state reflects the neuronal pathological events occurring at the peak effect produced by the treatment, at which LID are the most strongly expressed, and allows a correlation between the progressive motor response induced by L-dopa and the cellular alterations. We will therefore structure this part by clearly distinguishing: naïve animals (i.e. never exposed to dopamimetics), the ON state (i.e. peak of dose of L-dopa plasma concentrations, best anti-parkinsonian effect) with or without LID, and the OFF state (i.e. animals otherwise dyskinetic when challenged).

4.1. Pharmacokinetics and pharmacodynamics

Chronic L-dopa administration remains the best treatment for PD since its introduction in the 60s (Birkmayer and Hornykiewicz, 1961, 1962; Cotzias et al., 1967; Lees, 1994; Yahr et al., 1968). However, L-dopa therapy faces several challenges resulting from the complex interactions between the pharmacokinetics of L-dopa itself (LeWitt, 2015) and the progressive neuronal alterations induced by the neurodegeneration in PD. L-dopa displays particular peripheral characteristics (Contin and Martinelli, 2010; Contin et al., 1993). First, it is highly metabolized into DA by peripheral AADC expressed in the gut allowing only 30% of L-dopa to reach the systemic circulation (Contin and Martinelli, 2010). This issue was overcome by concomitant administration of AADC peripheral inhibitors (AADCi) with L-dopa. Nowadays, two main AADCi are used: carbidopa at a L-dopa/carbidopa dose ratio of 4/1 or 10/1 and benserazide (L-dopa/benserazide ratio of 4/1) (Contin and Martinelli, 2010). The use of AADCi allowed to almost triple L-dopa oral bioavailability, strongly reducing the required L-dopa therapeutic dose (Contin and Martinelli, 2010; LeWitt, 2015). Interestingly, concomitant administration of L-dopa and AADCi induce a plasmatic peak in patients at 1.1 ± 0.2 h (Okereke et al., 2004) and in non-human primates, like macaques, at 1.6 ± 0.3 h (Huot et al., 2012b) associated with a brain C_{max} which correlates with the peak of LID severity, around 60–90 min *post* oral administration (Huot et al., 2012b) and 20 min *post* intravenous administration (Porrás et al., 2014) of L-dopa in macaques. Note that Huot et al. measured L-dopa in cerebrospinal fluid (Huot et al., 2012b) while Porrás et al. did access to extracellular levels in the striatum itself using microdialysis (Porrás et al., 2014). In addition, intravenous (2.5 mg/kg) or oral (20 mg/kg) administrations give rise to comparable increase in extracellular striatal L-dopa levels (Porrás et al., 2014). Even though the oral doses of L-dopa administered to MPTP-lesioned macaques are higher than the doses frequently administered in idiopathic PD, the macaque plasma exposures are consistent with those achieved in clinical settings with acute challenges of 200 mg (Huot et al., 2012b). The experimental data provide pharmacokinetic validation, to support the existing pharmacological validation, of the MPTP-lesioned macaque model of PD as a platform from which novel therapeutics, including those modulating L-dopa actions, might be developed.

L-dopa shares some similarities with neutral amino acids, notably in term of intestinal absorption and transport at the blood brain barrier (Nutt and Fellman, 1984). Indeed, L-dopa competes with the transport system of neutral amino acids during their absorption in the intestinal mucosa and at the blood brain barrier (Contin and Martinelli, 2010; Contin et al., 1993). L-dopa transport from the plasma to the brain depends on the same system (Contin and Martinelli, 2010). The intake of high protein meals doubles the plasmatic concentration of neutral amino acids, which then interferes with the transport of L-dopa to the brain thereby decreasing its therapeutic efficacy (Nutt et al., 1984). Consequently, L-dopa administration timing needs to be adapted to mealtime to optimize the therapeutic effect of L-dopa (Juncos et al., 1987).

Parkinsonism, however, does not seem to modulate the L-dopa cerebral bioavailability. The plasma and cerebrospinal fluid bioavailability of L-dopa was found comparable in healthy and MPTP-treated macaques (Thiollier and Bezard, Unpublished observations). Pharmacokinetics and pharmacodynamics experiments of drugs addressing PD might thus be performed in healthy animals unless the drugs are known to interact with the organic cation transporter (Thiollier and Bezard, Unpublished observations).

4.2. Imaging

4.2.1. Studies of the DA system

Neuroimaging studies have provided *in vivo* support for the role of pulsatile stimulation of DA receptors in the emergence of LID (Stoessl, 2015). DAergic function can be assessed using positron emission tomography (PET) with ligands that bind to the vesicular monoamine transporter type 2 (VMAT2), the plasmalemmal DAT (Au et al., 2005; Brooks et al., 2003) and postsynaptic DA D₁R and D₂R receptors. Additionally, the fluorinated analogue of L-dopa, 6-[¹⁸F]fluoro-L-dopa (6FD) can be used to assess uptake and decarboxylation of L-dopa to DA, as well as storage of DA in synaptic vesicles and, when prolonged scans (4 h, rather than the usual 90–120 min) are performed, DA turnover (Sossi et al., 2001).

Dyskinesia tend to occur in more advanced PD. One might therefore anticipate a loose relationship between markers of presynaptic DAergic integrity and LID. With the possible exception of dyskinesia that emerge following foetal mesencephalic transplantation (see below), there is little evidence for this in the literature, apart from a report by Linazasoro and colleagues, who found an inverse relationship between 6FD uptake and dyskinesia (Linazasoro et al., 2004) and a more recent study using [¹⁸F]-FP-CIT PET showing that presynaptic dopaminergic denervation in PD plays a crucial role in the development of LID (Hong et al., 2014). Fluctuations in motor function, which commonly occur together with dyskinesia, are associated with reduced 6FD uptake (de la Fuente-Fernandez et al., 2000; Stoessl, 2015), but there is substantial overlap between patients with and without motor fluctuations, suggesting that other factors play an important role.

Traditional measures of presynaptic DAergic integrity give only a rough estimate of striatal DA nerve terminal density. As discussed elsewhere in this review, a critical factor in the emergence of motor complications is the pattern of DA receptor stimulation. Thus, assessment of the central pharmacokinetics of L-dopa action may provide greater insight. As previously described in this review, [¹¹C]raclopride labels D₂R and D₃R with relatively low affinity and its binding is subject to competition with endogenous DA (Breier et al., 1997; Seeman et al., 1989). Thus, interventions such as L-dopa therapy that result in increased synaptic DA concentrations will result in reduced [¹¹C]raclopride binding as assessed by PET (Tedroff et al., 1996). De la Fuente-Fernandez et al. found a greater magnitude but less sustained decline in [¹¹C]raclopride binding in PD patients who had a stable response to L-dopa at the time of the PET study but who went on to develop motor fluctuations within 3 years compared to those subjects who had stable response to medication 3 years later (de la Fuente-Fernandez et al., 2001). In a follow-up study, these authors found that the relative decrease in [¹¹C]raclopride binding 1 h after oral L-dopa increases with disease duration and even after correction for this factor, is higher in subjects with LID compared to those with a stable response, while there is no difference between dyskinetic and non-dyskinetic subjects 4 h after L-dopa (de la Fuente-Fernandez et al., 2004). This is compatible with a more pulsatile pattern of L-dopa-induced DA release in subjects with motor complications (Stoessl, 2015). Similar findings have been reported by other groups (Pavese et al., 2006).

These findings are reminiscent of the sensitization of DA release that is associated with drug addiction as previously discussed in

this review. In contrast to the motor complications, which are associated with sensitized DA release in the putamen (i.e. motor striatum), PD patients with DDS have sensitized DA release restricted to the ventral striatum as assessed by change in [¹¹C]raclopride binding in response to L-dopa (Evans et al., 2006). As is the case for ventral striatal release of DA induced by amphetamine in healthy control subjects (Leyton et al., 2002), the change in [¹¹C]raclopride binding correlated with 'drug-wanting' rather than the subjective pleasure or 'liking' of drug.

Another way of looking at the kinetics of DA release and metabolism is to estimate DA turnover using prolonged scans with 6FD. While uptake measured over the standard 90–120 min scan reflects uptake, decarboxylation to fluoroDA and trapping of fluoroDA in synaptic vesicles, prolonged scans also reflect the egress and subsequent metabolism of this trapped radioactivity. The model used to analyze the acquired radioactivity data thus shifts from one that assumes unidirectional transport of tracer (i.e. the radioactivity is trapped) to a reversible model. The effective distribution volume that is derived from this reversible tracer model correlates well with the inverse of the ratio of tracer loss to tracer uptake constants (Sossi et al., 2001), which in turn correlates with classical neurochemical measures of DA turnover (Doudet et al., 1998). DA turnover measured using this approach is increased early in PD (Sossi et al., 2002) and further increases occur with disease progression (Sossi et al., 2004). Furthermore, even when one accounts for disease severity, the magnitude of the abnormality in DA turnover is greater in PD patients with younger disease onset than the abnormality of 6FD uptake (Sossi et al., 2006). This suggests that comparable degrees of denervation result in greater increases in DA turnover in younger individuals and is in keeping with the fact that such individuals are more prone to dyskinesia (Golbe, 1991; Grandas et al., 1999; Quinn et al., 1987; Kumar et al., 2005).

The determinants of DA turnover are not fully understood. However, it appears that in patients with PD, downregulation of the DAT results in increased turnover, again even after correcting for disease severity (Sossi et al., 2007). One would therefore predict that downregulation of DAT beyond the degree expected based on disease severity (i.e. loss of DA nerve terminals) would be an independent predictor of the development of LID and this indeed appears to be the case (Troiano et al., 2006). Thus, while downregulation of the DAT may serve a useful function in early disease in order to conserve levels of DA in the synapse (Calne and Zigmond, 1991; Lee et al., 2000b), in the long run such a compensatory mechanism may prove deleterious. As discussed in the next section, increased DA turnover may result when exogenous L-dopa is converted to DA in surviving serotonergic neurons, which are unable to regulate the release and reuptake of DA.

Dyskinesia that occur following foetal mesencephalic transplantation may represent a special example, as they may occur either as an exaggerated form of LID or, in some patients, may occur off medication (Freed et al., 2001; Olanow et al., 2003). Ma and colleagues reported post-operative increases in 6FD uptake in the left posterodorsal putamen and left ventral striatum of patients who developed post-transplant dyskinesia (Ma et al., 2002). In contrast, using a combination of 6FD and [¹¹C]raclopride, Piccini et al. found no evidence for increased graft-derived DA release in subjects with dyskinesia (Piccini et al., 2005).

4.2.2. Studies of non-DAergic mechanisms

As reviewed elsewhere in this manuscript, there is extensive evidence from animal models of alterations downstream to striatal DA receptors following chronic DAergic stimulation, thought to contribute to LID. These include upregulation of immediate early genes and of several neuropeptides, including enkephalin and

dynorphin. There is very limited evidence available in the imaging literature, largely reflecting the paucity of tools. Piccini and colleagues demonstrated reduced striatal binding of the opioid ligand [¹¹C]diprenorphine in PD patients with LID, presumably reflecting occupancy of striatal opioid receptors due to increased opioid levels (Piccini et al., 1997). Whone and colleagues demonstrated in a preliminary study a reduction in thalamic NK1 neurokinin receptor binding in PD patients with LID (Whone et al., 2002). Whether this represents a loss of NK1 receptors or increased receptor occupancy reflecting increased availability of endogenous substance P is unclear. Studies have demonstrated increased adenosine A₂ binding in PD patients with dyskinesias compared to those without (Mishina et al., 2011). Using a marker of activated NMDA channels, Ahmed et al. (2011) demonstrated increased striatal responsiveness to L-dopa in PD patients with LID.

Studies of cerebral blood flow have been mainly used to infer changes in patterns of neuronal activity within the basal ganglia and its connections, although the two parameters may be independently regulated by certain pharmacological treatments. Hershey and colleagues used PET with [¹⁵]H₂O to study the haemodynamic responses to L-dopa in PD patients with and without LID. They found increased cerebral blood flow following drug administration in the thalamus of dyskinetic patients, associated with reduced blood flow in primary motor cortex (Hershey et al., 1998). As regional cerebral blood flow (rCBF) predominantly reflects synaptic activity, this finding is compatible with a sensitized response to L-dopa in the GPi and while it is not easily explained by standard "box and arrow" models of the basal ganglia (Albin et al., 1989; Calabresi et al., 2014), it is very much in keeping with the reduction in LID that is consistently reported following pallidotomy (Fine et al., 2000). Sanchez-Pernaute and colleagues have studied the haemodynamic response to a selective DA D3 receptor agonist using functional magnetic resonance imaging (fMRI) and found that the response was increased in rodent and non-human primates with LID (Sanchez-Pernaute et al., 2007), in keeping with in vitro and behavioural evidence (Bezard et al., 2003; Bordet et al., 1997; van Kampen and Stoessl, 2003).

As to the regulation of cerebral blood flow in LID, an intriguing phenomenon has been discovered by Eidelberg and collaborators using a multimodal PET approach to image both blood flow and glucose metabolism in the same scanning session (Hirano et al., 2008). While regional glucose metabolism and rCBF were well-matched in PD patients during the 'off' medication state, the administration of L-dopa greatly enhanced rCBF but not glucose metabolism in a brain network that includes putamen, pallidum, and midbrain-pons (Hirano et al., 2008). In these regions, the dissociation between flow and metabolism was particularly striking in patients affected by LID (Hirano et al., 2008). Because the cerebral metabolic rate for glucose is mainly dictated by synaptic activity, these findings suggest that L-dopa exerts haemodynamic effects that are independent of its modulation of neuronal metabolism. A similar phenomenon occurs in the rat model of LID, which features a large increase in rCBF 'ON' L-dopa in many parts of the basal ganglia, usually in the absence of large concomitant changes in glucose metabolism (Ohlin et al., 2012). The flow-metabolism dissociation response is particularly intriguing because it points to a previously unappreciated effect of L-dopa on vessel-associated cells controlling the blood flow to the striatum and the midbrain (Choi et al., 2006). The underlying mechanisms have not yet been resolved. On-going studies are addressing the hypothesis that an increased capillary density in the striatum and the midbrain (Faucheux et al., 1999; Ohlin et al., 2011) may drive more blood flow to these regions under conditions of high DAergic tone (note that DA can modulate cerebral blood flow by acting directly on brain arterioles and microvessel-associated cells, cf. Choi et al., 2006).

4.2.3. Potential future applications

With the few exceptions noted above, most studies performed to date have focused either on DAergic mechanisms or on patterns of cerebral activation in response to medication. Within the DA system, study of the D₃R may be of particular interest, but investigation has been hampered by the lack of selective positron-emitting tracers. Other neurotransmitters of interest with respect to their role in LID include serotonin (5-HT – 5-hydroxytryptamine), adenosine, excitatory amino acids, and GABA. There were however no relevant studies, in part reflecting the paucity of informative radioligands, until the studies of Politis et al. investigating the serotonergic mechanisms responsible for LID in PD patients (Politis et al., 2010, 2014; Smith et al., 2015). These authors first demonstrated that dyskinesias in patients who had undergone foetal nigral transplants were associated with serotonergic hyperinnervation and that the dyskinesias responded to administration of a 5-HT_{1A} agonist, presumably reflecting activation of 5-HT somatodendritic autoreceptors (Politis et al., 2010). Identical L-dopa doses induced markedly higher striatal synaptic DA concentrations in PD patients with LID compared with PD patients with stable responses to levodopa, confirming earlier studies. While patients with LID presented relative preservation of serotonergic terminals, oral administration of the 5-HT_{1A} receptor agonist bupirone prior to L-dopa reduced L-dopa-evoked striatal synaptic DA increases and attenuated LIDs (Politis et al., 2014), supporting the model based on studies in animals (Carta et al., 2007) that striatal serotonergic terminals contribute to LID pathophysiology via aberrant processing of exogenous L-dopa and release of DA as false neurotransmitter in the denervated striatum of PD patients with LID. In more recent work, Politis and colleagues have suggested that 5-HT innervation and aberrant DA release in the globus pallidus may play a role in LID (Smith et al., 2015). While bupirone (Buspar) has a high affinity as a 5-HT_{1A} receptor partial agonist (IC₅₀ = 35 nM), this drug also potently antagonizes D₂R at nanomolar concentrations (IC₅₀ = 250 nM) (Taylor, 1988) (resulting in potentially anti-dyskinetic effect;

Shin et al., 2012a, 2014) and is metabolized to the potent alpha₂-adrenergic receptor antagonist, 1-(2-pyrimidinyl-piperazine) (Caccia et al., 1986; Engberg, 1989; Gobert et al., 1997).

4.3. Electrophysiology

4.3.1. In vivo extracellular recordings

Studies of neuronal activity of the basal ganglia in LID, both in animal models of parkinsonism and in PD patients, have been conducted using mainly two different approaches, single cell and local field potential recordings (Fig. 1). In this review, human, non-human primate and rodent studies will be summarized.

4.3.1.1. In vivo single cell recordings. Single cell recording is obtained using microelectrodes and provides information about the frequency and the pattern of discharge of single neurons. The classical model of basal ganglia function considered that LID result from over-decreased neuronal firing rates in the GPi (Albin et al., 1989; DeLong, 1990), the main output structure of the primate basal ganglia, leading to increased activity of thalamocortical motor circuits (Fig. 1). Accordingly, micro-recording of the neuronal activity in MPTP-treated monkeys with DAergic-related dyskinesia showed a reduction of the firing frequency in the GPi in comparison with the OFF state (Boraud et al., 2001; Filion et al., 1991; Heimer et al., 2006; Papa et al., 1999) and with the ON state without dyskinesia (Boraud et al., 2001; Heimer et al., 2006; Papa et al., 1999). There was also a change in the firing pattern concomitant with the onset of dyskinesia (Boraud et al., 2001; Heimer et al., 2006). A reduction in the fraction of oscillatory cells and in the oscillatory correlations among neurons was observed in the GPi during the ON state, which was higher when LID were present (Heimer et al., 2006).

Although firing rate in GPi neurons was increased in the ON state respect to the OFF state (Boraud et al., 2001; Heimer et al., 2006), no differences either in the firing frequency or pattern of neuronal discharge were encountered between the dyskinetic and

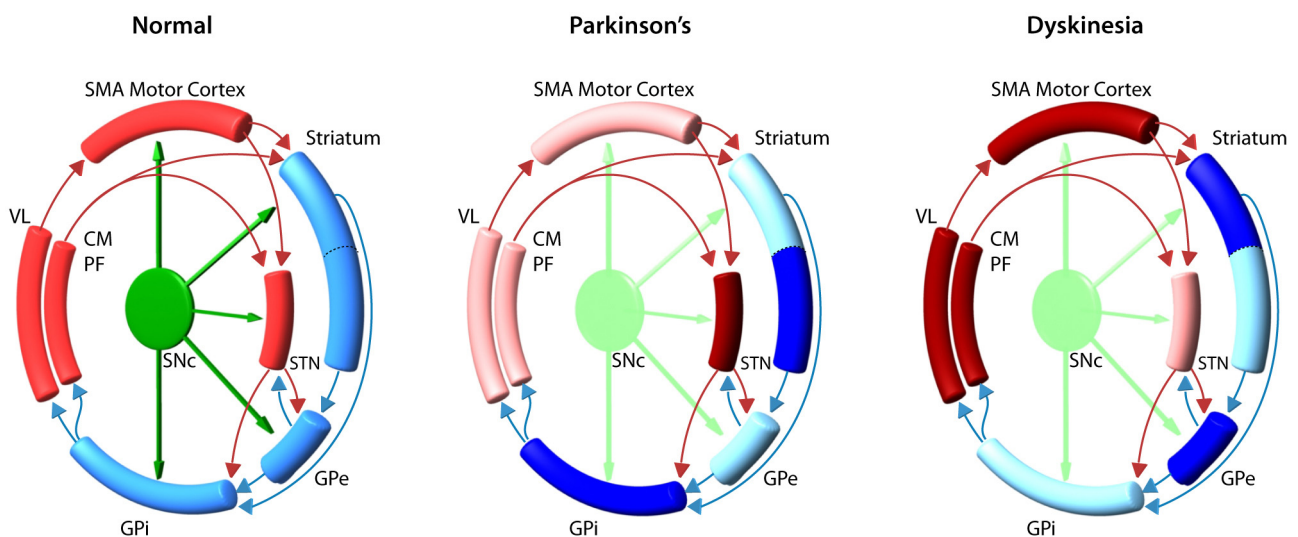


Fig. 1. Anatomic-functional organization of the basal ganglia brain regions classically involved in Parkinson's disease (PD) and L-dopa induced dyskinesia (LID) pathophysiology. Red corresponds to excitatory glutamate pathways, blue corresponds to inhibitory GABA (γ -aminobutyric acid)-releasing pathway, and green corresponds to the dopamine projections from the substantia nigra pars compacta (SNc). Changes in colour intensity indicate the level of activity of individual projection systems. The upper half of the striatum that is directly connected to the internal part of the Globus Pallidus (GPi)/SNr corresponds to the medium spiny neurons that bear D1 dopamine receptors (direct pathway). The lower half, which is indirectly connected to GPi/SNr through the external part of the Globus Pallidus (GPe) and Subthalamic Nucleus (STN), corresponds to medium spiny neurons that bear D2 dopamine receptors (indirect pathway). In PD, degeneration of SNc neurons (paler green) breaks the striatal dopamine homeostasis, inducing hyperactivity of the GPi (darker blue), which brakes neuronal activity in the supplementary motor area (SMA, paler red). In LID, exogenous supply of levodopa and/or dopamine receptor agonists might act at structures previously innervated by dopamine neurons. The net result would be hypoactivity of the GPi (paler blue), leading to a hyperactivity of SMA neurons (darker red). VL: Ventral lateral thalamus. CM/PF: centromedian (CM) and parafascicular (PF) complex of the thalamus.

non-dyskinetic states (Boraud et al., 2001). In contrast, Heimer et al., 2006 observed a reduction in the fraction of oscillatory cells only when LID were present (Heimer et al., 2006). In addition, they observed that the ratio of the mean firing rate of the GPe/GPi increased during the LID recording respect to the ON state with optimal recovery of parkinsonism without dyskinesia (Heimer et al., 2006).

Thus, single cell studies in the MPTP monkey indicated that LID would take place when frequency is excessively decreased in the GPi (i.e. lower than in the normal situation), and the firing pattern suffers a change in the oscillatory activity with a reduction in the fraction of oscillatory cells.

In human studies, dyskinesia induced intra-operatively by administration of apomorphine to patients with PD were associated with a reduction of the GPi firing rate respect to the OFF state (Lee et al., 2007; Levy et al., 2001; Merello et al., 1999a), while differences between ON state with and without dyskinesia were not clearly observed (Lee et al., 2007; Levy et al., 2001). The firing pattern was also altered during ON state with dyskinesia respect to the OFF state with an increment in the burst-like (Levy et al., 2001; Merello et al., 1999a) or irregular (Lee et al., 2007) discharges. In contrast, the mean firing rate of the neurons of the STN was not reduced during the ON state without dyskinesia respect to the OFF state while it was significantly reduced when LID were present (Levy et al., 2001). LID were also associated with an increment in the proportion of spikes in burst in the STN, which was not observed during the ON state without dyskinesia (Levy et al., 2001). Of note, there was a high variability in the effect of apomorphine upon the firing rate of single STN and GPi neurons (Levy et al., 2001). Regarding the GPe, just a few neurons have been studied, which had an increment in the firing rate by 50–90% (Lozano et al., 2000).

Thus, in PD patients, LID are associated with reduced firing rate and change in the pattern of GPi neuronal discharges with respect to the parkinsonian state, while the major difference between the states ON with and without dyskinesia seems to be the firing pattern (Fig. 1). In the STN, a reduction in the firing rate marked the presence of LID along with a more bursty or irregular firing pattern. Findings in the GPe are less consistent and further studies are needed to elucidate its role in LID.

4.3.1.2. *In vivo local field potentials.* The implantation of electrodes for DBS in the STN and GPi of patients with PD has allowed recording local field potentials (LFP) and recognizing specific patterns of activity according to the motor states. Thus, information about oscillatory activity of neuronal populations in the basal ganglia of PD patients with dyskinesia has become available more recently.

In the STN, peak-dose LID is associated with an increment in the power of the theta-alpha (4–10 Hz) band with a mean frequency at 8.38 Hz (Alonso-Frech et al., 2006; Foffani et al., 2005), a finding very much in line with recordings performed in substantia nigra pars reticulata (SNr) of dyskinetic 6-OHDA rats (Meissner et al., 2006) and GPi of dyskinetic MPTP-treated macaques (Bezard, unpublished). The specificity of this relationship is confirmed by different facts. Firstly, the increment of the power in the theta-alpha band is only recorded when patients are exhibiting dyskinesia and not during the ON periods without such abnormal movements (Alonso-Frech et al., 2006). Secondly, in patients with unilateral dyskinesia, this oscillatory activity was only recorded in the STN contralateral to the hemi-body where LID was present. In patients in whom LID starts in one hemi-body and then spreads to the other side, a gain of power of the theta-alpha activity is firstly recorded in the STN contralateral to the hemi-body where LID starts and then, time-locked with the beginning of LID, it starts in the other STN (Alonso-Frech et al., 2006). In addition, patients who

suffered diphasic dyskinesia, which are a subtype of LID that appear typically at the onset and end of L-dopa anti-parkinsonian action, exhibit a similar theta-alpha activity (mean frequency 7.38 Hz) during this involuntary movement (Alegre et al., 2012).

The theta-alpha activity associated with peak-dose dyskinesia was mainly recorded through the dorsal contacts of the electrode, which were located in the dorsal portion of the STN, therefore indicating that this oscillatory activity was generated in the motor region of the STN (Rodriguez-Oroz et al., 2011).

In the GPi, a study conducted in 2 patients found a negative correlation between LFP power in the band comprised between 8 and 40 Hz and EMG recordings in the contralateral limb with LID (Silberstein et al., 2005). In contrast to studies in the STN, this correlation was peaking in the 8–12 Hz in one case and the 21–30 Hz in the other case, but in both cases there was a strong negative correlation in the beta band. Beta oscillatory activity is typically observed in the parkinsonian state and correlates with rigidity and bradykinesia (Little et al., 2012; Lopez-Azcarate et al., 2010). The lowering of the power in this band during LID could be interpreted as an over-reduction of these motor signs during the abnormal excessive movements. For instance, a clinical observation is that rigidity is usually abolished in dyskinetic limbs. In addition, the suppression of the “antikinetic” activity of the beta band could also lead to the release of unwanted motor programmes. On the other hand, the discrepancy between GPi and STN activity associated with LID could be due in part to methodological aspects (i.e. GPi recording have been conducted in two patients, electromyogram recorded only in one muscle). On this regard, in one patient with unilateral LID induced by a lesion-like effect of the electrode implanted for DBS in the STN, enhanced STN-GPi coherence at low frequencies (10 Hz) was recorded in the nuclei contralateral to the dyskinetic hemi-body suggesting that an oscillatory activity in the theta-alpha band is probably present along the basal ganglia circuit during LID (Foffani et al., 2005). Although there is no similar record in PD patients with LID, this might also be a feature of this state.

Recording the SNr has proven helpful as well for understanding pathological plasticity induced by L-dopa. Per-operative recordings of the GPi and SNr in patients showed that patients with less severe dyskinesia underwent greater depotentiation following low frequency stimulation than patients with more severe dyskinesia (Prescott et al., 2014). This demonstration of impaired depotentiation in basal ganglia output nuclei in PD patients with dyskinesia is an important validation of animal models of LID (see below the *in vivo* section). Loss of the ability to depotentiate at the output nuclei may underlie, or contribute to the cellular basis of dyskinetic movements.

In summary, the classical model of the basal ganglia explained LID as the consequence of a striatal DAergic overstimulation that eventually causes an inhibition of the GPi. However, the fact that lesions of the GPi not only improved parkinsonism but abolished or greatly ameliorated LID proved this concept to be incorrect (Calabresi et al., 2014). Interestingly, although in MPTP-lesioned monkeys studies the firing rate of the GPi was lower during the ON state with or without dyskinesia, this has not been demonstrated in PD patients as the neuronal firing rate was similar when patients were in ON state both with or without LID. In contrast, a more irregular and bursty pattern of discharge has been encountered in all single cells studies undertaken in primates and in humans. The importance of this finding has been somehow reinforced with the LFP recording given consistency to the notions that the pattern but not the frequency of discharge was the most relevant feature in the pathophysiology of LID. Current interpretation of the benefit of surgical interventions in the GPi (lesion and DBS) are more aligned with a disruption of a DAergic induced abnormal synchronization of neuronal activity along nuclei of the motor circuit (Hammond

et al., 2007). Recent contributions highlighted the role of cortico-striatal and striato-cortical connections, with the demonstration using functional imaging that dyskinetic PD patients display an immediate hypersensitivity of preSupplementary Motor Area (preSMA) and putamen to L-dopa, that would herald the failure of neural networks to suppress involuntary dyskinetic movements (Herz et al., 2014, 2015). Such result resonates with experimental findings in AIM 6-OHDA rat model showing (i) that pronounced LFP oscillations in the primary motor cortex following L-dopa treatment are interrupted by the application of a DA antagonist onto the cortical surface leading to the dyskinetic symptoms disappearance (Halje et al., 2012), (ii) that spine enlargement and the resultant hyperexcitability of intratelencephalic-type pyramidal neurons in the primary motor cortex (M1) (Ueno et al., 2014) and (iii) that synaptic downscaling of cortico-striatal synapses across sleep episodes (Galati et al., 2015) might contribute to the abnormal cortical neuronal plasticity in LID. The finding that abnormal cortical oscillations are a key pathophysiological mechanism calls for a revision of the prevailing hypothesis that links LID to an altered sensitivity to DA only in the striatum. Indeed, it has been proposed that the cortical exposure to L-dopa would drive the aberrant behaviour of the basal ganglia (Halje et al., 2012).

4.3.2. Ex Vivo electrophysiology

The first paper addressing the electrophysiological plastic changes in neurons recorded from rats displaying dyskinetic movements dates back to 2003 (Picconi et al., 2003). This paper demonstrated for the first time that dyskinetic motor abnormalities are coupled to an absence of bidirectional synaptic plasticity in the striatal projecting neurons (Picconi et al., 2003), opening the way to future studies on the possible synaptic mechanisms underlying LID (Fig. 2).

The experimental model is the well characterized unilaterally 6-OHDA-lesioned rat (Schwartz and Huston, 1996a). Six weeks after the DA denervation, animals lose cortico-striatal plasticity, both long-term potentiation (LTP) and long-term depression (LTD) (Calabresi et al., 1992; Centonze et al., 1999b; Picconi et al., 2003) (Fig. 2B). Notably, the degree of DA denervation influences these two forms of plasticity in different ways, nearly full DA loss blocks the induction of both LTP and LTD, while partial DA depletion allows LTP induction but selectively alters its maintenance, leaving LTD induction and maintenance unaffected (Paille et al., 2010) (Fig. 2B).

Chronic L-dopa treatment (Cenci et al., 1998; Picconi et al., 2003) at a therapeutic dosage allows restoration of LTP in all the

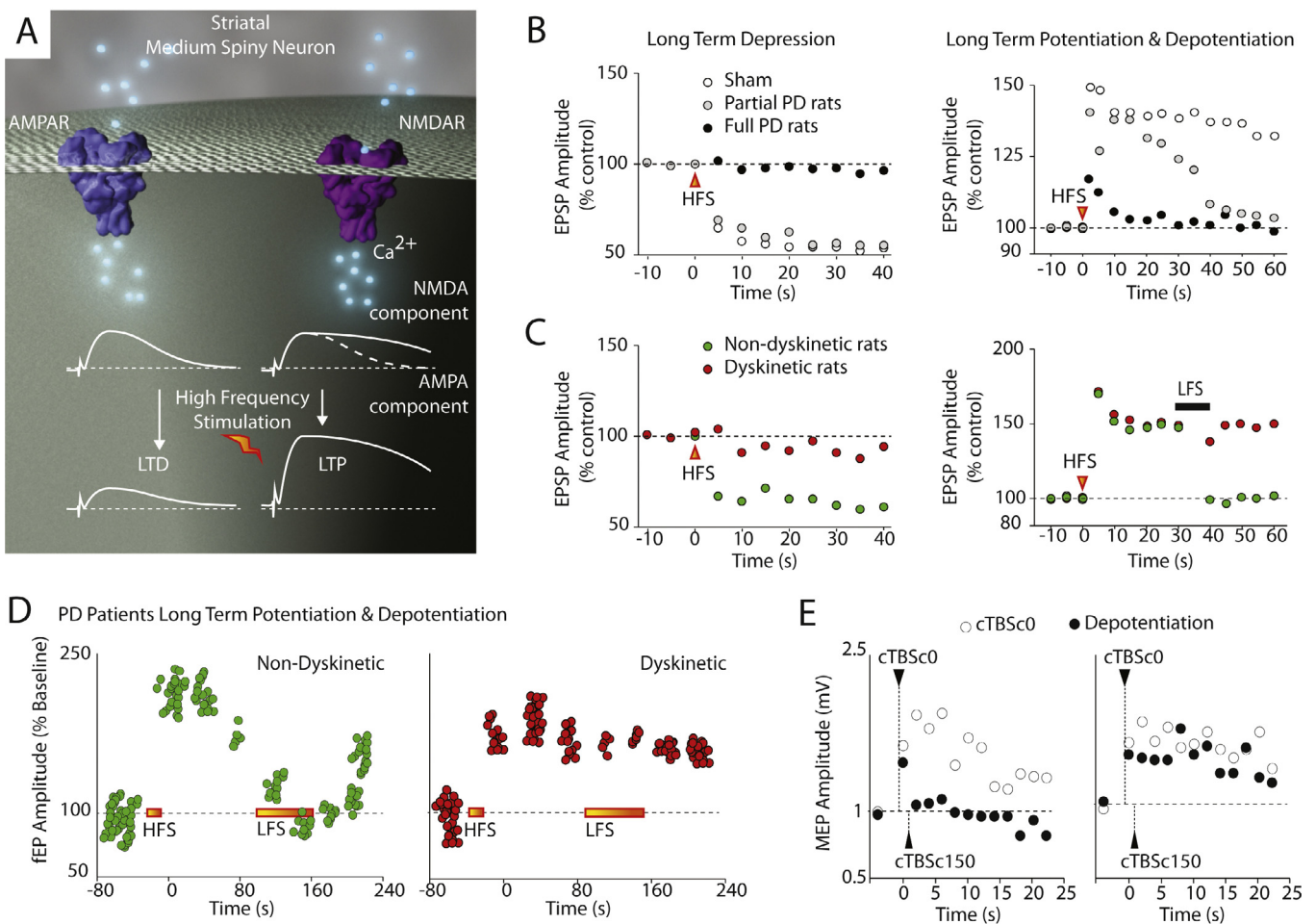


Fig. 2. Bidirectional synaptic plasticity in Parkinson's disease (PD) and L-dopa induced dyskinesia (LID) in striatal medium spiny neurons (MSNs). (A) Long-term depression (LTD) and long-term potentiation (LTP) in MSNs mediated by a high frequency stimulation (HFS). (B) Fully dopamine (DA)-denervated rats (black circles) lose both form of synaptic plasticity. Partially denervated rats present a normal LTD (grey circles, left graph) but only a short-term potentiation (grey circles, right graph). (C) Chronic L-dopa treatment restores bidirectional synaptic plasticity (LTD, LTP and depotentiation) in Non-Dyskinetic animals (green circles) while the Dyskinetic rats (red circles) lose the capability to depotentiate the previously induced LTP by a low frequency stimulation (LFS) protocol. (D) LFS induces the depotentiation of previous HFS-mediated LTP in individual patients, in ON medication without dyskinesias at time of test (green circles, left graph). LFS is not capable of depotentiating previous HFS-mediated LTP in dyskinetic patient during ON phase (red circles, right graph). (E) In healthy subjects, continuous theta burst stimulation (cTBSc0) protocol induces motor evoked potential (MEP) (left graph). cTBSc150 applied 1 min after cTBSc0 is able to depotentiate the potentiation to baseline levels (left graph). In dyskinetic PD patients the same protocol does not modify the potentiation induced by cTBSc0 (right graph).

parkinsonian rats (Fig. 2C) and distinguishes two different drug-induced behavioural responses. Animals that do not develop dyskinesia, e.g. the “therapy responsive” rats, display the anti-parkinsonian effects of the drug and the physiological bidirectional synaptic plasticity (LTD, LTP and depotentiation). Conversely, dyskinetic rats show severe LID and normal LTP while they do not express either LTD or depotentiation induced by the low frequency stimulation (LFS) protocol (Fig. 2C). Notably, the intrinsic properties of striatal medium spiny neurons (MSNs) recorded from dyskinetic and non-dyskinetic rats did not show differences (Picconi et al., 2003). Such loss of bidirectional plasticity at corticostriatal synapses may cause a pathological storage of non-essential motor information that would normally be erased, leading to the development and/or expression of abnormal motor patterns. Interestingly, this loss of bidirectional synaptic plasticity has also been found in PD patients in ON and OFF phases of L-dopa therapy. The loss of depotentiation of previously induced HFS-mediated LTP has been demonstrated in patients in ON medication during dyskinesia both in the substantia nigra (Prescott et al., 2014) (Fig. 2D) and in the cerebral motor cortex (Huang et al., 2011d) (Fig. 2E).

The biochemical studies indicated that the loss of depotentiation observed in dyskinetic animals is attributable to specific changes occurring along the D₁R signalling pathway leading to abnormally high levels of Thr34-phosphorylated dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) and consequent inhibition of protein phosphatase 1 activity (Picconi et al., 2003; Santini et al., 2010a, 2007). This seminal work provided the first demonstration that combining electrophysiological, behavioural and molecular analysis is possible to study the biological features of LID in rodent experimental models.

A further step forward was the electrophysiological characterization of depotentiation loss in chronically treated 6-OHDA-lesioned rats with two different regimen of L-dopa (Picconi et al., 2004); a direct correlation between the daily dosage of L-dopa and the induction of dyskinetic movements was demonstrated. Moreover, this study established a critical pathophysiological link between the lack of synaptic depotentiation and LID expression. The phenotypic nature or anatomical identity of the striatofugal neurons was however unknown in these studies.

Starting from the observation that striatal cyclic guanosine monophosphate (cGMP) signalling is decreased in dyskinetic rats (Giorgi et al., 2008), Picconi and colleagues explored the possibility that LTD, which strictly relies on the nitric oxide-dependent activation of protein kinase C (PKC), is also altered in dyskinetic rats. Chronic L-dopa-treated rats developing LID do not show this form of synaptic plasticity (Picconi et al., 2011). Phosphodiesterase (PDE) inhibitors increase cGMP levels leading to the activation of PKG that represents a critical factor for LTD induction following high frequency stimulation (Calabresi et al., 1999, 2007; Centonze et al., 1999a). Nitric oxide produced by NOs-positive striatal interneurons activates cGMP/PKG pathway that can be in turn modulated by PDE inhibitors, such as Zaprinast[®] and UK-343664 (Calabresi et al., 2007; West and Tseng, 2011). Accordingly, a low dose of PDE inhibitors applied *in vitro* rescues *ex vivo* the activity-dependent LTD in striatal slices obtained by dyskinetic rats. Moreover, intra striatal injection of these drugs in behaving dyskinetic rats rescues LTD, as measured in *ex vivo* slices, and reduces LID (Picconi et al., 2011).

Uziel's group investigated the contribution of a basal hyperglutamatergic tone in the development of LID and the effect on DA-dependent bidirectional synaptic plasticity (Errico et al., 2011).

Mutant Ddo^{-/-} mice lacking the D-Aspartate Oxidase (Ddo) enzyme, display abnormally high levels of the excitatory free amino acids D-aspartate and NMDA (Errico et al., 2008), and show an aberrant striatal synaptic plasticity. In the MSNs recorded from

Ddo^{-/-} mice, similar to what observed in dyskinetic animals, LFS protocol failed to depotentiate the high frequency stimulation-induced LTP (Errico et al., 2011). When subjected to 6-OHDA lesions, Ddo^{-/-} mice display increased sensitivity to L-dopa and earlier onset of LID (Errico et al., 2011), further supporting the concept that increased glutamatergic release is a critical risk factor to develop LID.

An interesting study from Anthony Grace's group (Belujon et al., 2010) provided evidence in support of a more complex pattern of plastic changes occurring in the striatal output neurons, by studying corticostriatal synaptic plasticity alterations in denervated rats chronically treated with L-dopa. In particular, the authors studied corticostriatal LTD using *in vivo* extracellular recordings from striatonigral pathway and striatopallidal pathway neurons in anesthetized rats (Belujon et al., 2010). The authors confirm by the use of an *in vivo* experimental approach that LID might be due to an induction of aberrant plasticity, with their data suggesting that this alteration occurs in striatal indirect pathway neurons (i.e. projecting to GPe) combined with an inability to de-depress established plastic responses in direct pathway neurons (i.e. projecting to GPi/SNr).

Nash and co-workers further advanced our understanding of the pathological plasticity affecting the striatofugal pathways in LID (Thiele et al., 2014). They applied spike-timing dependent plasticity protocols to cortico-striatal synapses in slices from 6-OHDA-lesioned mouse models of parkinsonism and LID, generated in BAC transgenic mice with eGFP targeting the direct or indirect output pathways, with and without L-dopa present. While naive mice showed bidirectional synaptic plasticity, i.e. LTP and LTD, in both striatal output pathways, both pathways exhibited unidirectional plasticity, irrespective of stimulation paradigm, in both parkinsonism and dyskinesia (Thiele et al., 2014). In parkinsonian animals, the indirect pathway only exhibited LTP whereas the direct pathway only showed LTD. A symptomatic dose of L-dopa restored bidirectional plasticity on both pathways to levels comparable to naive animals. In the presence of L-dopa in dyskinetic animals, the indirect pathway exhibited only LTD whereas in the direct pathway, only LTP could be induced. Therefore, switching from bidirectional to unidirectional plasticity drives global changes in striatal pathway excitability, and underlies parkinsonism and dyskinesia, with opposite changes in nature of plasticity (Thiele et al., 2014).

4.4. Morphological changes related to LID

4.4.1. Morphological re-sculpting of neurons and circuits in LID

As presented in this review, decades of research have revealed numerous pharmacological, neurochemical and neurophysiological abnormalities in the brain of dyskinetic patients and animal models of PD. An abundance of data clearly implicates enhanced glutamate signalling and persistent LTP in the absence of bidirectional plasticity as central to the behavioural sensitization phenomenon of LID. The basal ganglia, and in particular the striatum are involved with procedural learning of goal-directed and routine/habit' motor behaviours. Striatal motor learning is not only mediated by glutamatergic mechanisms but is uniquely sculpted by feedback from ascending nigral DA neurons that act to reinforce or inhibit action selection (e.g. Shen et al., 2008). An accumulation of evidence suggests that LID represent a form of pathological experience-dependent learning secondary to aberrant synaptic plasticity (Fieblinger et al., 2014a; Graybiel, 1995; Picconi et al., 2003, 2005; Pisani et al., 2005). While experience-dependent alterations in behaviour are known to involve structural modifications of synaptic connectivity, only recently has the nature of structural and synaptic remodelling of MSNs in response to LID begun to be investigated. Emphasis has been put upon afferent

inputs, as the striatofugal pathways appear not to be phenotypically modulated in dyskinetic versus non-dyskinetic animals (Nadjar et al., 2006).

A series of studies are providing novel insights into the morphological adaptations of striatal MSNs and re-wiring of basal ganglia circuits in the dyskinetic brain. It has been known for many years that there are profound effects of DA depletion on the architecture of the primary efferent neurons of the striatum, the MSNs, including retraction of dendrites and loss of dendritic spines (e.g. Day et al., 2006; McNeill et al., 1988; Soderstrom et al., 2010). Anatomically, cortico-striatal glutamate afferents preferentially synapse onto the spines that stud MSNs, and thus with spine retraction in the parkinsonian striatum there is a loss of axospinous glutamatergic synapses (Day et al., 2006; Ingham et al., 1989, 1998; Zhang et al., 2013b). There remains controversy on whether striatal DA depletion results in spine loss specifically in MSNs of the indirect pathway or occurs in MSNs of both striatofugal pathways (i.e. indirect and direct) (Day et al., 2006; Suarez et al., 2014; Villalba et al., 2009). However consensus is beginning to suggest a specific dynamic of spine re-modelling that occurs with dyskinesia-inducing L-dopa treatment. Studies using transgenic mice with green fluorescent protein or tdTomato under the control of D₁R or D₂R regulatory elements have allowed selective visualization of the dynamic changes in the D₁R direct versus D₂R indirect pathway MSNs in dyskinetic parkinsonian subjects. Using such mice, Suarez and colleagues (2014) and Fieblinger and colleagues (2014a), both show that there is a decrease in spine density per μm of dendritic length in indirect pathway MSNs (iMSNs) with severe striatal DA depletion but that high dose L-dopa results in restoration of spine density in these neurons that is not different from that seen in the control striatum. In contrast and similar to what was reported previously (Day et al., 2006), Fieblinger et al. (2014a) found that DA depletion did not affect spine density per μm of dendritic length (although there was a loss of total number of spines due to retraction of dendritic length) on direct pathway MSNs (dMSNs) but interestingly they observed that dyskinetic high dose L-dopa resulted in significant reduction in spine density and further decline in total number of spines on the dMSNs. While Suarez and colleagues (2014) found that spine density in their mice decreased in both iMSNs and dMSNs with striatal DA depletion, similar to Fieblinger et al. (2014a), they too found that in the dyskinetic striatum, spine density in iMSNs was restored to control levels and significantly reduced in dMSNs. A similar spine remodelling paradigm has been observed in the 6-OHDA rat model of PD. Specifically, Nishijima et al. (2014) reported decreased spine density of iMSNs and no change in dMSNs in the DA depleted rat striatum, with LID development being uniquely associated with loss of spine density on dMSNs and apparent restoration of spine density in iMSNs.

With the re-establishment of dendritic spines it would be anticipated that there should be re-establishment of cortico-striatal input onto MSNs in the dyskinetic striatum. Using stereological immunoelectron microscopic and light microscopic 3-D neuron reconstruction in Golgi impregnated neurons, Zhang and colleagues (2013b) examined whether the two major glutamatergic striatal afferent pathways (i.e. the cortico-striatal and thalamo-striatal afferents) formed new or altered contacts onto dendrites or spines of striatal MSNs in parkinsonian rats treated with L-dopa that either developed dyskinesia or remained dyskinesia free. Using immunohistochemistry markers specific to cortico-striatal (VGlut1) or thalamo-striatal (VGlut2) terminals, this study provided the first structural evidence that cortico-striatal, but not thalamo-striatal remodelling was linked directly to dyskinesia per se (Zhang et al., 2013b). While this study did not examine which population of MSN was involved with cortico-striatal remodelling, they found that the initial loss of cortico-striatal axospinous synaptic input following a

nigrostriatal DA lesion was followed by a restoration of these corticostriatal synapses to control levels exclusively in dyskinetic rats. Based on the dendritic spine studies discussed above, it could be predicted that this restoration occurred on iMSNs. Indeed, in a thorough and elegant series of electrophysiological studies, Fieblinger and colleagues (2014a) concluded that of the many cell-specific plasticity responses that they observed, the only adaptation exclusively associated with LID was the restoration of iMSNs axospinous synapses. Despite what might appear as “physiological remodelling”, ultrastructural evidence has provided important insight that the synaptic restoration found in the striatum of dyskinetic subjects involved the re-establishment of atypical synaptic input patterns onto structurally modified MSNs. Specifically, Zhang et al. (2013b) found that the restoration in spine density involved a significant increase in the number of large mushroom spines and the occurrence of atypical multisynaptic cortico-striatal input onto individual spines. Thus, in the dyskinetic striatum, an increase in spine head size appears to expand the active zone area through multiple inputs rather than through expansion of a single active zone. The larger active zone with new calcium-permeable glutamate receptors inserted into the post-synaptic membrane of mushroom spine with multisynaptic input could be theorized to be a structural correlate of the enhanced LTP associated with LID (Belujon et al., 2010; Picconi et al., 2003). While this body of evidence clearly implicates aberrant remodelling of iMSNs axospinous synapses in the phenomenon of LID, the additional pruning of dendritic spines and axospinous synapses of the dMSNs should not be discarded. The studies by Fieblinger et al. (2014a) indicate that the loss of spines on dMSN occurs with both low and high dose L-dopa, dissociating it from the induction of LID per se but these authors provided a detailed discussion of a more complex, perhaps timing dependent relationship of synaptic remodelling in this particular pathway.

While the striatum is undoubtedly of great importance in the manifestation of LID, the elucidation of a dramatic re-wiring, or ‘mis-wiring’ of cortico-striatal input highlights a new horizon of exploration that is needed for fully elucidating the neurobiology of LID. Specifically, clinical and preclinical data suggest that particular regions of the overlying cortex play an under-appreciated role for cortico-basal ganglia network remodelling in the dyskinetic brain (Finlay et al., 2014; Halje et al., 2012; Ostock et al., 2011; Ueno et al., 2014) and that there may be alterations in patterns of connectivity in the dyskinetic brain (Cerasa et al., 2015; Finlay et al., 2014). Briefly, human imaging studies using fMRI and PET have demonstrated that anatomical abnormalities in a variety of cortical regions are linked specifically to dyskinetic versus non-dyskinetic status in PD patients (for review see, Cerasa et al., 2015; Finlay et al., 2014). Further, in parkinsonian rats, infusion of either a 5-HT_{1A} agonist (Ostock et al., 2011) or a DA antagonist (Halje et al., 2012) into the M1 motor cortex were found to attenuate LID. The primary motor cortex (M1) normally projects to the dorsolateral striatum (e.g. Ramanathan et al., 2002; Wall et al., 2013) and is involved in motor learning (Hosp and Luft, 2013). Thus, two questions arise from these clinical and preclinical observations: (i) do physiologically relevant cortical regions (e.g., M1 cortex) re-establish the abnormal synaptic input (Zhang et al., 2013b) that leads to the pathological behavioural consequence of LID; or (ii) is afferent input to the striatum from atypical cortical regions (e.g. those that show significant increase in grey matter volume in LID patients; Cerasa et al., 2011, 2013) the source of the aberrant circuit re-wiring seen in the dyskinetic striatum? Understanding the anatomical source of re-established cortico-striatal input and molecular signals that initiate the maladaptive structural plasticity could lead to a novel therapeutic approach aimed at restoring physiological remodelling and lasting anti-dyskinetic therapy. While clinical evidence suggestive of neuro-anatomical remodelling in dyskinetic PD patients is critical,

current neuroimaging techniques lack resolution and exploratory studies in patients are unethical for elucidating answers to such questions. As such, relevant animal models continue to be valuable and necessary.

As research continues in preclinical models, knowing the right questions to ask will be paramount. One particularly cogent variable that has been suggested to be important, and which has largely remained unexamined in LID research is the timing of when the brain is examined in relationship to experimental manipulations (Fieblinger et al., 2014a; Nadjar et al., 2009). As reviewed by Nadjar and colleagues (2009), there is a void in our understanding of whether L-dopa priming is a feature inherent to the treatment or the disease/individual. The common view of priming for LID (for details see Section 4.5) is that repeated exposure of the DA depleted striatum to non-physiological DA during L-dopa treatment modifies and sensitizes the brain such that over time the chance of eliciting dyskinetic behaviour increases. Nadjar et al. (2009) posit the interesting proposition that “priming does not exist per se but is the direct and intrinsic consequence of the loss of DA innervation of the striatum, meaning that the first injection of DAergic drugs only exacerbates those mechanisms (sensitization) but do not induce them. In support of this concept, a significant portion of 6-OHDA lesioned rats and MPTP-lesioned marmosets and macaque monkeys develop LID during the first-ever administration of L-dopa (for review, see Nadjar et al., 2009). In humans, the occurrence of LID has also been noted after just a few days of treatment in the case of MPTP-intoxicated individuals (Ballard et al., 1985; Langston and Ballard, 1984) or while being challenged with L-dopa as part of PD diagnosis (see Nadjar et al., 2009). Inarguably two key parameters for the induction of first drug exposure LID, regardless of the species, are the extent of DA depletion and time between intoxication and DA agonist drug administration. It is notable however that severe striatal DA depletion and non-physiological DA replacement alone are insufficient to induce LID, both in humans and rodents (e.g. Cotzias et al., 1969; Konradi et al., 2004; Zhang et al., 2013b). The question remains, why do some individuals (rodent, non-human primate or human) not develop LID, or show remarkable resistance? Genomic and proteomic studies (e.g. Konradi et al., 2004; reviewed in Heiman et al., 2014; Nadjar et al., 2009) are revealing that there are robust and specific alterations of particular genes or proteins within the striatum of dyskinetic subjects, suggesting that expression of one or more specific molecular triggers may induce/permit the plastic changes underlying long-term adaptations of striatal circuits that result in LID. It is reasonable to suggest that structural adaptations in the brain underlie the long-lasting behavioural consequences known to occur once LID are established in humans and experimental animals, and that these structural adaptations render palliative pharmacological approaches ineffective or suboptimal by administering drugs into a significantly altered target environment. However, it is unclear whether the cortico-striatal synapse plasticity and dynamic alterations of dendritic spines are a secondary event linked to the expression of dyskinesia, rather than a series of events that occur over time during a primary induction phase. It is further unclear the extent of brain structures involved in LID specific mis-wiring, whether they are responsible for the long-lasting behavioural consequences of LID, and if so, whether “depriming” is a possible therapeutic option.

4.4.2. Striatal remodelling and graft-induced dyskinesia

Given what is now known about the degree of functional and structural remodelling that occur in the parkinsonian dyskinetic brain (see Section 4.4.1), it is not surprising that clinical trials of embryonic DA neuron transplantation in PD patients resulted in an overall suboptimal therapeutic benefit and induction of additional

aberrant behaviour. The idea of replacing DA neurons lost to PD by engrafting new ones has strong biological rationale and based on early preclinical studies appeared to offer great hope as an additional therapeutic option. While the overall lack of clinical efficacy was disappointing, the induction of graft-induced dyskinesia (GID) was an unacceptable side effect that resulted in a moratorium against clinical grafting trials. GID are another form of therapy-mediated dyskinesia linked specifically to the engraftment of embryonic DA neurons into the parkinsonian striatum rather than pharmacological drug administration. There have been many clinical and preclinical studies and reviews aimed at elucidating and discussing the underlying cause of GID. The tendency has been to promote single factors in the aetiology of this movement disorder. However, similar to LID, it is likely that a constellation of adaptations of neurons and circuits are linked to the expression of GID. While there is general consensus that LID and GID likely have distinct underlying pathology based on differential behavioural expression patterns and pharmacological responses (for review, see Breger and Lane, 2013; Garcia et al., 2011; Steece-Collier et al., 2012) a significant body of evidence suggests that similar to LID, DA, 5-HT and glutamate systems may all have some role in GID. It is not the intention of this review to consider the pros and cons of the various proposed mechanisms, but instead as an extension of the previous section we present here thoughts on whether the mis-wired striatum into which DA neurons are grafted might: (1) contribute to the emergence of GID, and (2) benefit from these grafts.

From a very simplistic view, grafted neurons likely act as biological mini-pumps capable of providing tonic DA release in a way that could provide more effective symptomatic benefit than seen with pharmacological drug replacement. If this is the means by which grafted neurons are providing therapeutic benefit, it is reasonable that the graft should contain exclusively or primarily ventral mesencephalic DA neurons, and not for example, neighbouring mesencephalic 5-HT neurons that are also capable of synthesizing and releasing DA but in a non-regulated fashion (see Section 5.2, e.g. Shin et al., 2014, 2012b). A provocative and likely impact associated with grafting these biological mini-pumps is that DA neuron grafts may also be able to reverse the pathology linked to disease-mediated DA depletion and/or pharmacological DA replacement. Indeed, in both clinical (Freed et al., 2001; Hagell et al., 2002; Olanow et al., 2003) and preclinical (Lane et al., 2006a,b; Lee et al., 2000a; Maries et al., 2006) grafting studies, a functional ventral mesencephalic graft can significantly reduce the severity of LID over time. Such findings could be taken to suggest that the reversal of LID behaviour is the consequence of homeostatic re-organization of the structural adaptations in the brain that underlie LID; however, this remains to be determined. In contrast to ventral mesencephalic grafts reducing the severity of LID and other motor deficits, in some patients and in particular preclinical models, maturation of the graft results in an emergence of new graft-associated dyskinetic behaviours (i.e. GID). Given the direct link between synaptic changes and LID, it is reasonable to suggest that GID are also mediated by aberrant synaptic organization.

While critical assessment of numerous factors including the level of DA depletion, pre-transplant LID expression, and the ratio of 5-HT:DA neurons in the graft have all been associated with the occurrence of GID, a void remains in understanding precisely how and why these variable impact graft success. Clinically the degree of DA depletion outside the graft has been found to significantly correlate with GID (Piccini et al., 2005). Striatal DA depletion and LID lead to significant loss of dendritic spines on MSNs, the dynamics of which are discussed above (Section 4.4.1). Presumably related to the loss of these normal spinous contact sites on MSNs, it has long been known that grafted DA neurons form new synapses

with dendrites (and the soma) more frequently than with spines (Freund et al., 1985; Leranthe et al., 1998; Mahalik et al., 1985; Triarhou et al., 1990).

How significant is such an anatomical anomaly and is it possible that a DA neuron making a new synaptic contact onto the “wrong” part of the MSN (dendrite rather than spine) could have such a dramatic impact on MSN activity and hence on behavioural output? While the perfect preclinical model of GID is lacking, the presence of a VM graft placed into the DA-depleted striatum of rats can induce the emergence of new graft-associated dyskinetic behaviours that have many qualities similar to GID in PD patients (Lane et al., 2009, 2006a,b; Maries et al., 2006; Steece-Collier et al., 2009). Using the 6-OHDA lesioned rat and intrastriatal grafting of embryonic VM neurons, Soderstrom and colleagues (2008) used immuno-electron microscopy to examine whether abnormalities in synaptic profiles correlated with graft-derived aberrant behaviours. Similar to previous studies, they found that as the grafts matured the proportion of TH-positive contacts onto the dendrites significantly increased, however this study provided the first direct evidence that a decrease in the number of spine contacts was significantly correlated with an increase in the graft-derived aberrant behaviours (Soderstrom et al., 2008). Perhaps more significantly, ultrastructural evidence in this model indicated that in rats exhibiting these graft-associated dyskinetic behaviours not only were the grafted synapses making contact with the wrong part of the MSN but the type (i.e. symmetry) of synapses was also atypical. So-called “symmetric” synapses are classically associated with inhibitory neurotransmission, and “asymmetric” with excitatory neurotransmission (see Klemann and Roubos, 2011). In the normal striatum, DAergic terminals predominantly make symmetric and rarely asymmetric synapses (Freund et al., 1985). Soderstrom et al. (2008) found that as grafts matured over time the incidence of asymmetric (presumably excitatory) TH-positive synapses was seen to increase from 4% up to 38%. An increase in the number of asymmetric synapses formed by grafted DA neurons has also been reported in the grafted parkinsonian monkey striatum (Leranthe et al., 1998). Thus, rather than normal symmetric DAergic input that predominately occurs on the necks of dendritic spines modulating the degree of excitatory corticostriatal input that reaches the dendritic shaft from the same spines, there are asymmetric DAergic inputs directly onto the dendritic shaft in the grafted striatum of animals exhibiting these novel post-graft dyskinesia (Soderstrom et al., 2008). Non-TH (presumably host-derived) asymmetric synapses were noted to contact the soma and proximal dendrites of the grafted cells. These connections also were correlated with an increased incidence of the GID-like behaviours in this model (Soderstrom et al., 2008). Similar to the cortico-striatal re-wiring associated with LID it is possible that these may be new cortico-striatal endings that would be expected to stimulate grafted cells, potentially giving rise to the irregular spontaneous discharge and fast firing rate of grafted DAergic neurons (Fisher et al., 1991; Trulsson and Hosseini, 1987) and the generation of graft-associated dyskinetic behaviours.

The interesting paradox of DA grafts in PD is that on one hand they can apparently de-prime the LID brain while inducing a new set of aberrant circuitry resulting in the emergence of GID. The ability to significantly reduce LID for prolonged periods of time suggests that these cells are not simply acting as mini-pumps that elevate striatal DA tone. Indeed, while pharmacological L-dopa can restore DA to the parkinsonian striatum and continue to shape synaptic strength, the manner in which it is shaped is divorced from the normal outcome of action selection because it is not driven phasic DA release/signalling (Fieblinger et al., 2014a). Phasic stimulation or suppression of striatal DA, (i) acts to adjust the relative strength of competing inputs critical for normal experience-dependent motor learning and action selection, and

(ii) is dependent on specific anatomical input to nigral DA neurons (Redgrave et al., 2008). Thus, simply flooding the striatum with DA in the absence of phasic changes to provide saliency to particular situations would be predicted to result in aberrant synaptic plasticity and aberrant motor output. Based on an abundance of preclinical and clinical data, it is clear that DA grafts can restore some degree of physiologically relevant signalling within the basal ganglia that reverses LID behaviours and thus arguably provides a better mechanism of DA replacement than pharmacological approaches. The challenge remains to determine how to prevent GID and tap into the beneficial mechanisms by which new DA neurons can re-store physiological signalling to improve motor dysfunction.

4.4.3. Non-neuronal factor involvement in dyskinesia

Over the past decade, an accumulation of preclinical and clinical evidence has suggested that important non-neuronal morphological variables that appear to participate in the pathophysiology of LID are angiogenesis and alterations in blood flow. Using the 6-OHDA-lesioned rat, Westin and colleagues (2006) first demonstrated that in rats that developed LID there was proliferation of vascular endothelial cells and a significant increase in total blood vessel length in the basal ganglia output nuclei. They also found downregulation of an endothelial barrier antigen on vessel walls and visible extravasation of serum albumin. These data indicated that in the brains of rats that developed LID there was an induction of angiogenesis as well as a compromise of the blood–brain barrier. Importantly, these changes were found to be not only specific to dyskinetic rats but also specific to nuclei of the basal ganglia (Westin et al., 2006). An additional series of preclinical studies have investigated mechanisms of LID-associated vascular changes finding differential involvement of D₁R and D₂R (Lindgren et al., 2009) and the involvement and potential therapeutic efficacy of angiotensin type 1 receptor blockade (Munoz et al., 2014). Congruent findings in both parkinsonian rats and PD patients further demonstrated that there is an upregulation of vascular endothelial growth factor associated with the microvascular changes involved with LID pathophysiology (Ohlin et al., 2011). Alterations in cerebral vasculature and blood flow are uniquely regulated by synaptic activity to ensure that blood delivery matches neuronal energy needs (Ko et al., 2015), and alterations in blood brain barrier occurs in several neurodegenerative disorders. However, as reviewed by Ko and colleagues (2015), a series of complex functional imaging studies involving PET (human studies) or microPET (rodent studies) imaging of [¹⁸F]FDG as a marker of synaptic activity and [¹⁵]H₂O for blood flow have revealed that there is an uncoupling of cerebral metabolic rate and rCBF that is uniquely and differentially effected in LID compared to non-LID parkinsonian subjects. While the impact of L-dopa in subjects expressing LID is CBF- cerebral metabolic rate uncoupling and compromise of blood brain barrier integrity, the exact mechanism by which these events occur and how these changes are linked to LID expression remains equivocal. As reviewed by Ko and colleagues (2015), L-dopa converted to DA binds to vascular receptors likely resulting in vasodilatation and increase in local blood flow. These authors speculate that the newly formed vessels may be supersensitive to DA and the resultant increase in rCBF after L-dopa administration might lead to “an increase in perfusion pressure, and a treatment state-dependent breach of blood brain barrier in brain regions characterized specifically by increased local dopa decarboxylase expression and comparatively large numbers of vascular DA receptors” (Ko et al., 2015). Understanding the molecular triggers for vascular changes seen in dyskinetic subjects and why some individuals show a more pronounced dissociation of CBF- cerebral metabolic rate, angiogenesis and expression of LID will undoubtedly foster the development of new treatment strategies directed at ameliorating LID in PD.

Puzzlingly enough, the role of astrocytes in such complex pathological changes has almost remained untouched. The current concept of basal ganglia organization and function excludes the most numerous cells in the brain (Tsacopoulos and Magistretti, 1996). For decades, astrocytes have been regarded as passive partners of neurons in the central nervous system, but this view has been challenged and they are now integrated in the concept of “tripartite synapse”. Indeed astrocytes have a multitude of processes that are intertwined within the neuropil ensheathing synaptic contacts, they possess receptors and reuptake sites for neurotransmitters, so they sense and integrate synaptic activity. Charron and co-workers therefore characterized anatomically the PD-related modifications in astrocytic morphology, the changes in astrocytic network connections and the consequences on the spatial relationship between astrocytic processes and asymmetric synapses in normal and PD-like conditions in experimental and human PD (Charron et al., 2014), unravelling a dramatic regulation of striatal astrocytosis supporting the hypothesis of a key role in (dys)regulating corticostriatal transmission. Such PD-related astrocytosis is not diminished by L-dopa treatment in non-dyskinetic or in dyskinetic experimental and human PD (Bortolanza et al., 2014; Charron et al., 2014), shedding light upon a possible role played by astrocytes in LID pathophysiology, notably upon the L-dopa-induced rise in inducible nitric oxide-synthase immunopositive astrocytes (Bortolanza et al., 2014). Consistent with this finding, a number of pharmacological studies show that nitric oxide-synthase inhibition decreases AIMs in L-dopa-treated 6-OHDA lesioned rats (Bortolanza et al., 2014; Padovan-Neto et al., 2015; Takuma et al., 2012) and dyskinesia in aphakia mice (Solis et al., 2015), while such intervention induces akinesia or catalepsy in normal rodents (Del Bel et al., 2004). That nitrinergic neurons participate to this action is envisioned as the main nitric oxide-synthase inhibitor is the 7-nitroindazole, a neuron-specific inhibitor of that enzyme. However, 7-nitroindazole treatment decreases the number of nitric oxide-synthase immunopositive astrocytes and the AIMs in the 6-OHDA-lesioned rat (Bortolanza et al., 2014) suggesting that the drug specificity is not so great and that astrocytes might well be a major site for such development of nitrinergic transmission in the newly formed tripartite synapse.

4.5. Priming leads to LID

The phenomenon of “priming” has often been called into question to explain the onset of dyskinesia in PD patients on DA replacement therapy. Priming can be defined as the presence of neurochemical and functional aberrant modifications in the DA-denervated basal ganglia that eventually lead to the emergence of dyskinesia in response to the repeated administration of L-dopa or DA agonists (Jenner, 2008).

The features of priming have been extensively investigated in experimental models of PD, such as the MPTP-treated primate and the 6-OHDA-lesioned rat (Blanchet et al., 2004; Jenner, 2003; Morelli et al., 1989; Simola et al., 2007), although it is in the 6-OHDA-lesioned rat that the great majority of information on the behavioural and neurochemical correlates of priming has been obtained. In this model, priming is usually produced by means of a two-step administration of DAergic agonists, which includes an induction phase and an expression phase, the latter being the step where the effects of priming are evident (Morelli et al., 1989). The manifestation of priming is behavioural, and consists in the emergence of a vigorous, sensitized, contralateral rotational behaviour stimulated by a dose of a D₁R agonist that is otherwise ineffective in unprimed rats (Morelli et al., 1989, 1993). Drug-stimulated contralateral rotations in the 6-OHDA-lesioned rat are indicative not only of anti-parkinsonian effects but also of pro-dyskinetic potential (Lane et al., 2006a,b) (but see

Lundblad et al., 2002); therefore, the sensitized rotational behaviour featuring priming was considered as an index of an abnormal drug-induced motor response (Morelli et al., 1993). In addition, several studies have shown that priming is associated with a series of neurochemical maladaptive modifications in the DA-denervated striatum that are similar to those observed in animal models of experimental dyskinesia elicited by the chronic administration of DA replacement therapy. These include changes in the production of cyclic adenosine monophosphate (cAMP), phosphorylation of DARPP-32, and expression of mRNAs encoding for the immediate early genes dynorphin, and glutamate acid decarboxylase 67 kDa (GAD67), which all critically regulate the activity of the striatal output neurons (Barone et al., 1994; Carta et al., 2003; Consolo et al., 1999; Crocker et al., 1998; Pinna et al., 1997; van de Witte et al., 1998). Interestingly, priming is best manifested when D₁R, but not D₂R, are selectively stimulated in the expression phase; moreover, priming is a time-dependent phenomenon, which is only fully expressed after a critical time from its induction has elapsed (Morelli et al., 1989). On the basis of the evidence indicating that D₁Rs play a major role in the emergence of dyskinesia (Aubert et al., 2005; Guigoni et al., 2007), and considering that maladaptive changes produced by DA replacement therapy in the DA-denervated basal ganglia may require some time to develop and thus influence movement performance, the features of priming suggest that this phenomenon could mimic the initial events associated with drug-induced dyskinetic movements.

Further support to this view comes from the finding that both these phenomena are attenuated by the blockade of glutamate receptors, either ionotropic or metabotropic (Hadj Tahar et al., 2004; Morelli and Di Chiara, 1990; Morin et al., 2013, 2014; van de Witte et al., 2002). In this regard, it is also noteworthy that cortical glutamatergic neurons form synapses onto striatal MSNs of the striatonigral and striatopallidal pathways, and that these synapses demonstrate functional long term changes, with the occurrence of LTP and LTD (Calabresi et al., 2007; Kreitzer and Malenka, 2008). Abnormalities in synaptic plasticity in the DA-denervated striatum have been suggested to play a critical role in the genesis of dyskinesia, by favouring a pathologic form of motor learning following the stimulation of DA receptors by DA replacement therapy (Picconi et al., 2003; Pisani et al., 2005). Recent studies have shown that priming in the 6-OHDA-lesioned rat may be relevant to the aberrant modifications in motor learning thought to occur in PD. Thus, it has been demonstrated that the performance of rotations during priming induction is necessary for the manifestation of the sensitized motor response on priming expression, as this effect was completely abolished when primed rats were prevented from rotating in response to the initial DAergic challenge (Frau et al., 2013; Simola et al., 2009). This finding could indicate that the performance of drug-induced movements upon a first pharmacological stimulation of DA receptors may generate an aberrant motor memory trace in the DA-denervated striatum, and that this trace may eventually favour the emergence of an abnormal motor response following a later DAergic pharmacological challenge (Simola et al., 2009). Of further relevance to this hypothesis, primed 6-OHDA-lesioned rats that could rotate during priming induction, but not rats that were prevented from doing so, displayed a selective increase in the mRNA encoding for the immediate early gene *zif-268* in dynorphin-positive neurons of the striatonigral pathway when challenged with a pro-dyskinetic D₁R agonist on priming expression (Frau et al., 2013). Remarkably, it has been demonstrated that the expression of *zif-268* is not only induced by drugs with a high dyskinetic potential (Carta et al., 2010a,b), but is also enhanced in certain forms of learning, or following LTP (Bozon et al., 2002; Lanahan and Worley, 1998; O'Donovan et al., 1999; Tischmeyer and Grimm, 1999), further

supporting the relevance of the results obtained in primed 6-OHDA-lesioned rats to aberrant motor learning.

As mentioned in Section 4.4.1, the DAergic denervation itself is the major effector of the maladaptive neurochemical and functional changes that underlie dyskinesia and priming may not be an absolute requirement for their manifestation (Nadjar et al., 2009). This view is supported in the first place by earlier data obtained in 6-OHDA-lesioned rats showing that the neurochemical effects of priming take place only in the DA-denervated striatum, but not in the intact striatum (Consolo et al., 1999; Morelli et al., 1990). Furthermore, it has been observed in the same model that sensitized rotations induced by a D₁R agonist may occur even without prior DAergic stimulation, if this effect is evaluated after a sufficient length of time (e.g. 60 days) from the DAergic denervation (Morelli et al., 1989), thus allowing maladaptive striatal changes to take place. Experiments in MPTP-treated primates have demonstrated that the first administration of L-dopa elicits proteomic changes in the striatum that are superimposable to those observed after chronic exposure to the drug (Scholz et al., 2008). In line with this, studies in rats (Andersson et al., 1999; Cenci et al., 1998; Putterman et al., 2007; Winkler et al., 2002), mice with 6-OHDA lesions (Darmopil et al., 2009; Ding et al., 2011; Won et al., 2014) and aphakia mice with developmental loss of selective nigrostriatal projection (Ding et al., 2007; Li and Zhou, 2013) have shown that dyskinetic movements can be observed even after the first exposure to either L-dopa or a D₁R agonist, without the need for a previous priming and further increase with repeated exposure. Whether priming is a phenomenon that exists by itself, being associated with maladaptive neurochemical and functional changes, or it merely consists of the speeding up of aberrant changes that are primarily arising from the DAergic denervation has still to be ascertained. Nevertheless, the possibility may exist that priming associated with DA replacement therapy would affect the propensity of the pharmacologic treatment to elicit dyskinetic movements. Thus, drugs with a marked D₁R component (e.g. L-dopa and apomorphine) have been shown to be the most effective in inducing priming in experimental models, and are also those with the higher dyskinetic potential in the clinical setting, e.g. the stopped ABT-431 D₁R agonist (Rascol et al., 2001b). Conversely, drugs that chiefly stimulate D₂R, e.g. PPX and ropinirole, are less effective in inducing priming, and also have a lower dyskinetic potential, as indicated by clinical evidence showing that the treatment with these agents induces milder dyskinesia than those elicited by L-dopa (Bagetta et al., 2012).

4.6. Presynaptic component of LID pathophysiology

4.6.1. Handling of L-dopa in the striatum

Whereas alterations in signalling cascade of striatal MSNs are ultimately responsible for the appearance of the abnormal motor response to L-dopa, as they affect gene expression, an increasing body of evidence shows that these alterations are secondary to changes in the presynaptic compartment (relative to the striatal neurons), which are induced by the progressive loss of the DAergic terminals. Indeed, progression of DA neuron degeneration represents the first and most important risk factor for development of dyskinesia. Accordingly, L-dopa does not usually induce dyskinesia during the first few years of administration in patients, when sufficient spared DA terminals are present; similarly, partial DA lesioned animals are resistant to development of LID, while complete DA lesioned animals can present dyskinesia already at the first L-dopa administration. Ulusoy and colleagues have confirmed in an elegant study that the state of the nigrostriatal DAergic compartment determines the susceptibility of rats to the induction of LID; in fact, rats in which the DA levels were reduced by about 70% using a short-hairpin RNA-mediated knockdown of

the TH enzyme (shTH), without affecting the integrity of presynaptic terminals, were refractory to LID development (Ulusoy et al., 2010). Interestingly, L-dopa failed to induce dyskinesia in shTH-treated rats even when they were previously rendered dyskinetic by sub-chronic apomorphine treatment; this suggests that the preserved presynaptic DAergic terminals provide a buffering system for the exogenously administered L-dopa, and mediate regulated release and reuptake of DA resulting in physiological DA receptor stimulation at striatal neurons (Carta and Bezard, 2011; Ulusoy et al., 2010). That said, a report by Pons and colleagues (2013) investigated the common phenomenon of LID in patients with TH deficiency, a population of individuals with a structurally intact nigrostriatal DA system. TH deficiency is an autosomal recessive disorder that results in a deficiency in the production of DA, noradrenaline, and epinephrine, which is also treated with L-dopa (Pons et al., 2013). In contrast to the incidence of LID in PD being 30–90%, the incidence in TH-deficient patients is 100% with emergence occurring within the first few days to months of onset of treatment (Pons et al., 2013). The occurrence of LID in these patients suggests that while DA depletion is a critical factor involved in the development of LID, loss of presynaptic terminals is not. In a commentary on the report by Pons, Bezard and colleagues (2013b) discuss that data from these dyskinetic TH-deficient patients suggests a scenario where LID may be primarily related to postsynaptic mechanisms including DA receptor super sensitivity and downstream abnormalities in intracellular signalling cascades within MSNs. The critical question posed by Bezard et al. (2013b) is whether dyskinesia in PD and TH-deficiency patients are induced by a similar or by a different mechanism, reasoning that it is possible that LID may develop in different ways, not only by disturbed presynaptic DA release and synaptic kinetics but also by abnormal receptor stimulation.

In PD, there is a well-established relationship of LID to loss of striatal DA terminals. The ability to properly handle exogenous L-dopa is dramatically diminished as the DA neuron degeneration progresses, and fewer and fewer spared DA terminals can mediate L-dopa conversion and feedback control release of DA. Recent experimental evidence indicate that when most of DAergic neurons have degenerated, 5-HT neurons come to play a major role in conversion of L-dopa to DA, and in the appearance of AIMs (Carta and Bezard, 2011; Carta et al., 2007; Munoz et al., 2008) (Fig. 3). In fact, it is known since early studies that 5-HT neurons are able to take up exogenously administered L-dopa, convert it to DA (Tison et al., 1991), and store it into synaptic vesicles (Arai et al., 1994, 1995); this is due to the presence of the same machinery expressed by DAergic neurons, i.e. the AADC enzyme and VMAT transporter. 5-HT neurons are expected to contribute to DA release also in early stages of disease; such contribution may initially be beneficial due to the presence of the spared DA terminals that can buffer 5-HT neuron-derived DA and avoid excessive DA receptor stimulation (Carta and Bezard, 2011; Carta et al., 2010a,b). In support of this view, it has been shown that a 30% reduction of striatal L-dopa-derived DA release is induced upon removal of 5-HT nerve fibres in intact animals (Nevalainen et al., 2013a).

By contrast, in a situation of advanced DA denervation, the 5-HT neurons become the main site of L-dopa conversion to DA (Fig. 3). In fact, removal of 5-HT innervation by 5,7-dyhydroxytryptamine administration reduced L-dopa-derived extracellular DA levels by about 80% in the striatum of complete DA-lesioned rats (Tanaka et al., 1999). However, the loss of spared DAergic terminals, which could buffer 5-HT neuron-derived DA release, triggers the appearance of dyskinesia due to the absence of a feedback control mechanism for DA release on 5-HT neurons (Fig. 3). In fact, DAergic terminals express the D₂R and the DAT, which can regulate the firing rate of these neurons and the reuptake of the neurotransmitter from the synaptic cleft, respectively. The absence of a

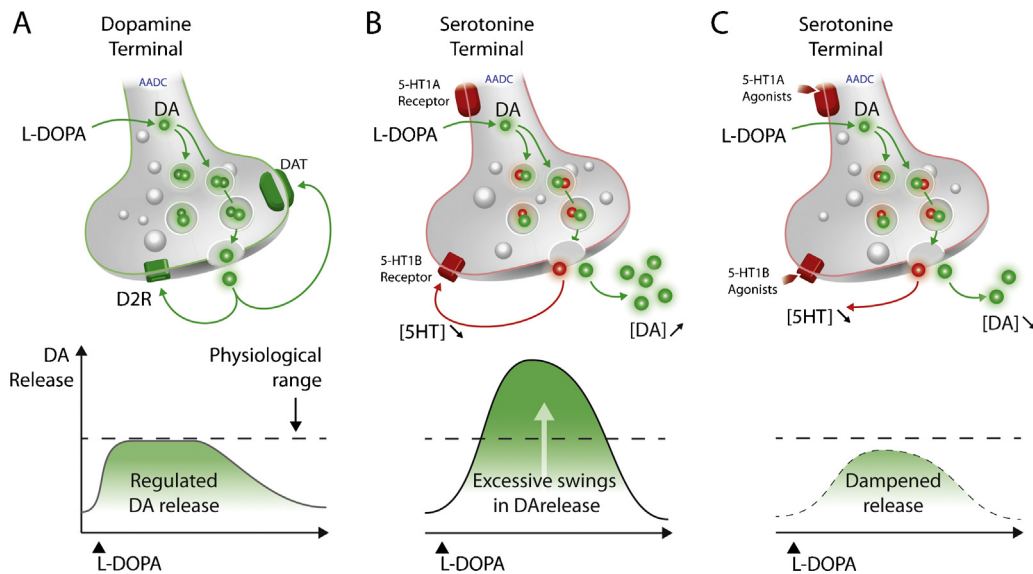


Fig. 3. Handling of L-dopa in L-dopa induced dyskinesia (LID) pathophysiology. (A) Normal L-dopa handling. Dopaminergic terminals convert L-dopa into dopamine (DA) which is released in the synaptic cleft in a controlled way due to the expression of a fine regulatory mechanism composed of the dopaminergic D2 receptor (D2R) and the dopamine active transporter (DAT) proteins. Indeed, D2R and DAT can regulate the firing rate of dopaminergic neurons and DA reuptake, respectively, leading to a regulated DA release. (B) Aberrant L-dopa handling. In a situation of advanced DA denervation, the serotonergic (5-HT) neurons become the main site of L-dopa conversion to DA. However, the loss of the last spared dopaminergic terminals, which could buffer 5-HT neuron-derived DA release, triggers the appearance of LID due to the absence of the D2R/DAT feedback control mechanism for DA release on 5-HT neurons. The absence of this mechanism makes 5-HT neuron-derived DA release uncontrolled, contributing to swings in synaptic DA levels, and promoting pulsatile stimulation of striatal postsynaptic DA receptors. (C) The silencing of serotonergic neurons through 5-HT_{1A/1B} auto-receptor agonists decreases excessive swings in DA release and related LID.

mechanism of fine regulation of synaptic DA levels in 5-HT neurons makes 5-HT neuron-derived DA release uncontrolled, contributing to swings in synaptic DA levels, and promoting pulsatile stimulation of striatal postsynaptic DA receptors (Carta and Bezard, 2011; Mosharov et al., 2015) (Fig. 3). In agreement with this view, removal of striatal 5-HT terminals by a selective toxin is able to completely suppress LID in 6-OHDA-lesioned rats (Carta et al., 2007; Eskow et al., 2009).

Silencing of 5-HT neurons firing can also be achieved by pharmacological targeting of 5-HT auto-receptors. According to a major role of 5-HT neurons in mediating DA release and induction of LID, activation of 5-HT_{1A} receptors (which are mostly located on cell bodies) and/or 5-HT_{1B} receptors (located on axon terminals) was shown to produce a dose dependent reduction of LID. In particular, combination of 5-HT_{1A} and 5-HT_{1B} receptor agonists (8-OH-DPAT and CP-94253, respectively) was found to induce a synergistic effect, with suppression of LID at ineffective doses of the individual drugs (Carta et al., 2007; Munoz et al., 2008, 2009). Reduction of L-dopa-derived DA release was confirmed to account for the anti-dyskinetic effect in following microdialysis (Lindgren et al., 2010) and PET-imaging rodent studies (Nahimi et al., 2012). However, significant reduction of L-dopa-induced DA release was also seen with selective targeting of 5-HT_{1A} receptors (Inderberg et al., 2015b; Kannari et al., 2001).

Dampening of 5-HT release by 5-HT₁ receptor agonists did not only reduce LID, but it has also been shown to prevent induction of postsynaptic alterations at striatal neurons, such as increased expression of Δ FosB and altered NMDA receptor subunits distribution (Munoz et al., 2008).

It should be noted that 5-HT₁ receptors are not only expressed presynaptically, as auto-receptors, but are also present postsynaptically in non-5-HT neurons; activation of these receptors has been shown to reduce striatal glutamate and GABA release and produce anti-dyskinetic effect (Bishop et al., 2009; Dupre et al., 2008; Zhang et al., 2008). However, it is worth pointing out that combination of 8-OH-DPAT and CP-94253, or administration of the

5-HT_{1A/1B} agonist eltoprazine at doses able to suppress LID, were shown to be ineffective against dyskinesia induced by apomorphine, suggesting that, at least at moderate doses of 5-HT₁ receptor agonists, the anti-dyskinetic effect is due to activation of 5-HT auto-receptors (Bezard et al., 2013c; Munoz et al., 2009).

Experimental 5-HT₁ receptor agonists (8-OH-DPAT and CP-94253) induced striking anti-dyskinetic effect not only in parkinsonian rats, but also in MPTP-treated dyskinetic macaques, without affecting disability score (Munoz et al., 2008), suggesting a possible clinical application of this approach to treat dyskinesia. Similar effect on LID was seen with the mixed 5-HT_{1A/1B} receptor agonist eltoprazine (Bezard et al., 2013c). Albeit partial reduction of the therapeutic efficacy of L-dopa was seen in those animals following eltoprazine administration, this drug is currently under clinical evaluation for treatment of LID.

Interestingly, the first single-dose, double-blind study in 22 dyskinetic patients has found a significant reduction of LID without exacerbation of motor disability (Svenningsson et al., 2015). However, it should be noted that the reduction of LID in the latter study was not superior to what observed with amantadine in previous clinical studies as pointed in a commentary of the above study (Bezard and Carta, 2015). Therefore, a number of issues remain to be addressed in future studies: first, whether escalation of the eltoprazine doses and/or modification of the time of administration relative to L-dopa could improve the anti-dyskinetic efficacy; second, whether eltoprazine would remain efficacious after weeks of daily treatment; indeed, it is possible that long-term administration may lead to autoreceptor desensitization, and therefore to reduced therapeutic efficacy. Although no tolerance was observed after 6 weeks of daily eltoprazine administration in rodents (Bezard et al., 2013c), the situation may be different in higher species; in fact, the 5-HT autoreceptors are suggested to desensitize upon chronic administration of selective 5-HT reuptake inhibitors (SSRIs), which explains the delayed efficacy of SSRIs in depressed patients, where alleviation of symptoms can be seen only after 2–4 weeks of daily treatment

(Hjorth et al., 2000; Pineyro and Blier, 1999). Therefore, it will be extremely important to verify whether similar effects are induced by chronic eltoprazine. This is a critical issue in determining the clinical feasibility of this approach for dyskinesia.

Clinical feasibility of pharmacological silencing of 5-HT neurons to treat dyskinesia in patients raised concerns not only for possible induction of autoreceptor tolerance, but also because it may reduce the therapeutic efficacy of L-dopa, as seen in preclinical studies (Bezard et al., 2013a,c). In fact, in advanced stages of disease, 5-HT neurons may not only be responsible for dyskinesia, but also for the residual therapeutic effect of L-dopa, as they represent the main site of conversion to DA; thus, in a situation of advanced DAergic degeneration, reduction of LID may be unavoidably accompanied by parallel reduction of the therapeutic effect. However, it should be noted that Iderberg and co-workers have recently demonstrated that selective targeting of 5-HT₁ receptors can yield significant reduction of dyskinesia without reducing the therapeutic effect of L-dopa in parkinsonian rats (Iderberg et al., 2015c). Last but not least, the effect of chronic silencing of 5-HT neurons on mood should be carefully evaluated, particularly as advanced PD patients often present mood disturbances.

An interesting alternative to selective 5-HT₁ receptor agonists may be represented by drugs acting on the 5-HT transporter. Indeed, selective 5-HT transporter inhibitors, such as fluoxetine and citalopram, have been shown to reduce dyskinesia with similar efficacy as 5-HT₁ receptor agonists, without affecting the therapeutic efficacy of L-dopa in rats (Bishop et al., 2012; Conti et al., 2014). Thus, as suggested by two recent works, compounds that indirectly facilitate 5-HT autoreceptor activation may be more effective therapeutics compared to 5-HT₁ receptor agonists as they might reduce LID while better preserving therapeutic action of L-dopa (Lindenbach et al., 2015; Tronci et al., 2015). Moreover, while SSRIs appear to exert their action by activation of 5-HT₁ auto-receptors, as seen with selective 5-HT₁ receptor agonists, they may provide the advantage to dampen dyskinesia without reducing synaptic 5-HT levels. This would be mostly important as SSRIs are widely used to treat symptoms of depression in parkinsonian patients. Moreover, inhibition of neurotransmitter reuptake by 5-HT transporter blockade may also reduce swings in extracellular DA levels. It remains to be established why no anti-dyskinetic effect has been reported in patients under SSRIs treatment, despite their extensive use also in dyskinetic subjects; thus, it is possible that the anti-dyskinetic mechanism is triggered at doses of drugs that are higher than those used to treat depression, as recently suggested by Fidalgo and co-workers, who found full suppression of LID by administration of a high dose of citalopram to MPTP-treated macaques (Fidalgo et al., 2015). Such view should however be balanced by an intriguing clinical finding (Mazzucchi et al., 2014) reporting that SSRI exposure in patients with PD protected them from LID, but showed that SSRI exposure not only delayed LID onset but also appeared to reduce the LID severity. Clinical investigations are warranted to clarify this issue.

Whereas clinical feasibility of 5-HT neuron targeting remains to be fully proved, an imaging study has provided important evidence that the 5-HT system may play similar role in patients as in animal models. In this study, in agreement with a previous post-mortem investigation (Rylander et al., 2010b), PD patients with LID were shown to have relative preservation of 5-HT terminals compared to patients with stable response to L-dopa, which correlated with the severity of LID. In patients with LID the same L-dopa dose induced significantly higher striatal synaptic DA levels than in non-dyskinetic patients, in agreement with an earlier PET study (de la Fuente-Fernandez et al., 2004). Most importantly, the 5-HT_{1A} receptor agonist buspirone, orally administered 15 min before L-dopa, significantly reduced the L-dopa-evoked rise in striatal synaptic DA levels and attenuated LID (Politis et al., 2014).

Although previous studies have already reported a partial reduction of LID by buspirone administration (Bonifati et al., 1994), this study provides the first direct evidence that such reduction is linked to diminished synaptic striatal DA release.

Recently, Smith and co-workers have suggested, in a PET imaging study, a possible pro-dyskinetic role also for the pallidal 5-HT innervation (Smith et al., 2015). In fact, in this study, PD patients without LID showed a significant reduction of pallidal 5-HT transporter binding compared with healthy controls, while this was within the normal range in dyskinetic patients. Levels of pallidal 5-HT transporter binding correlated positively with severity of LIDs. Moreover, ¹¹C-raclopride PET detected a significant rise in pallidal synaptic DA levels of patients with LID after a L-dopa challenge but not in patients with a stable response. Thus, the increased pallidal 5-HT function may result in further dysregulation of thalamocortical signals and therefore contribute to the expression of dyskinesias (Smith et al., 2015).

Overall, an extensive body of evidence points to DA released as false transmitter from 5-HT neurons as the single most important presynaptic trigger of LID (Carta and Bezard, 2011; Carta and Tronci, 2014; Cenci, 2014).

4.6.2. Handling of L-dopa outside the striatum

Experimental evidence in animal models suggests that false transmitter release of DA from 5-HT neurons is not restricted to the striatum. In fact, L-dopa induces an ectopic release of DA in a pattern that follows the widespread innervation of the entire forebrain by 5-HT raphe neurons (Azmitia and Segal, 1978), as it was demonstrated using a multisite microdialysis approach with four probes implanted simultaneously in the ipsilateral 6-OHDA-lesioned side (Navailles et al., 2013). The increase in DA release induced by an acute administration of L-dopa also occurs in the prefrontal cortex, hippocampus and SNr (Navailles et al., 2010a,b, 2011a). This extrastriatal DA release is also sensitive to 5-HT lesion, 5-HT pharmacological manipulation and high-frequency stimulation of the STN, a surgical approach in PD able to inhibit 5-HT neuronal firing (Navailles et al., 2010a,b; Temel et al., 2007). All these brain regions display various levels of 5-HT terminal density and express DA receptors (Seeman, 1980) on which the newly synthesized DA can exert its numerous effects and promote DA transmission. The magnitude of the increase in extracellular DA concentration induced by a therapeutic dose range of L-dopa (3–12 mg/kg) is far higher in extrastriatal brain regions than in the striatum compared to the physiological situation, due to the denser serotonergic innervation (Navailles et al., 2010b). DA released from 5-HT neurons in extrastriatal territories may contribute to both therapeutic efficacy of L-dopa and side effects.

4.7. Impact of L-dopa on 5-HT transmission and relationship to LID

L-dopa, by entering 5-HT neurons, mediates numerous changes in 5-HT neuron homeostasis (Navailles et al., 2011a; Navailles and De Deurwaerdere, 2012). The production of massive amounts of DA has tremendous impact on 5-HT function at the level of the metabolism, the activity and the morphology of 5-HT neurons (Navailles and De Deurwaerdere, 2012). Some changes in 5-HT indexes have been associated with the emergence of LID and should be taken into consideration to better control 5-HT transmission and L-dopa's side effects (Fox et al., 2009; Navailles and De Deurwaerdere, 2012; Scholtissen et al., 2006).

Most studies have shown that L-dopa reduces striatal 5-HT tissue concentrations in chronic L-dopa-treated rats (Carta et al., 2007; Gil et al., 2010, 2011; Lindgren et al., 2010; Navailles et al., 2011a) although a trend towards an increase was also reported (Carta et al., 2006). These differences may account for the time of

sacrifice after the last L-dopa administration, i.e. 1 h, 3 h, 24 h or more. When considering peak-dose dyskinesia, it is consistently observed that L-dopa administered within 1–3 h before sacrifice decreases 5-HT tissue levels, while increasing DA tissue levels in the striatum (Carta et al., 2007; Gil et al., 2011; Navailles et al., 2011a). According to these opposite 5-HT/DA changes (Gil et al., 2010), the severity of LID is both correlated with striatal DA (positively) and 5-HT tissue levels (negatively and more stringently than DA levels) (Gil et al., 2011). Moreover, an acute treatment with the serotonin precursor 5-hydroxytryptophan, which increases 5-HT and decreases DA tissue levels induced by L-dopa, is able to reduce the appearance of LID in the AIM rat model (Tronci et al., 2013) as well as in the dyskinetic macaque model (Ko et al., 2014a). Some studies have found a positive correlation between LID and 5-HT tissue levels in the striatum (Eskow et al., 2009) and prefrontal cortex (Carta et al., 2006) or no correlation between LID and 5-HT tissue levels in the striatum (Carta et al., 2006). In these studies, biochemical measurements were performed within a timeframe that does not allow for a direct correlation with LID, i.e. either 72 h (Carta et al., 2006) or 1 week (Eskow et al., 2009) after the last L-dopa administration. Regardless of this timeframe, tissue 5-HT levels in the striatum and cortex, but not the SNr, are systematically found to be higher in dyskinetic versus non-dyskinetic rats (Carta et al., 2007; Gil et al., 2011; Lindgren et al., 2010).

When considering 5-HT extracellular levels and LID, two parameters emerge as critical indicators, i.e. the reactivity of 5-HT terminals to L-dopa challenge (indexed by 5-HT release) and basal 5-HT extracellular levels after chronic L-dopa treatment. Firstly, the reactivity of 5-HT terminals is modified in a region-dependent manner that echoes the region-dependent ability of L-dopa to increase DA release after a chronic L-dopa treatment (see above; (Navailles et al., 2011a). Indeed, the lack of sensitivity of striatal 5-HT terminals to L-dopa, i.e. no change of 5-HT release after acute or chronic treatment (Lindgren et al., 2010; Navailles et al., 2010b, 2011a; Navailles et al., 2013), is associated with a relatively preserved effect on DA release. On the other hand, the highest sensitivity of 5-HT terminals to L-dopa observed in the SNr, i.e. potentiation of L-dopa-induced decrease in 5-HT levels after chronic treatment (Navailles et al., 2011a), leads to the most profound loss of efficacy of L-dopa to increase DA release (Navailles et al., 2011a). Secondly, as for 5-HT tissue levels, basal 5-HT extracellular levels are higher in the striatum, but not SNr, of awake dyskinetic compared to non-dyskinetic animals (Lindgren et al., 2010). The authors suggested that the denser 5-HT innervation in the striatum of dyskinetic animals could account for the higher basal 5-HT levels.

Among the different 5-HT indexes explored in relation to LID, the strongest correlations were found between 5-HT tissue levels or 5-HT terminal density and AIMs scores, in line with the idea that the status of the presynaptic DA releasing compartment, namely the integrity of 5-HT neurons, is a critical determinant of both induction and maintenance of LID. The region-dependent effects of L-dopa on 5-HT and DA releases may reflect the regional heterogeneity of 5-HT terminals characterized by the variable expression of numerous regulatory proteins (Navailles et al., 2011b). Beyond this intrinsic 5-HT neuronal heterogeneity, chronic L-dopa treatment by itself is known to modify the morphology of these 5-HT neurons and the synaptic plasticity in various brain regions (Berthet et al., 2009; Picconi et al., 2005, 2010; Prescott et al., 2009; Rylander et al., 2010b; Zeng et al., 2010).

4.8. Impact of L-dopa on amino acids: relationship to LID

There are many relationships between LID and amino acids. Anatomically, DA and 5-HT receptive cells are GABAergic neurons,

interneurons and glutamatergic neurons. In the basal ganglia, it is postulated that the multiple changes occurring in this network and the increased DA function induced by L-dopa concur to decrease the activity of output GABAergic neurons of the SNr and the GPi (Albin et al., 1989; DeLong, 1990; Nambu, 2008). Clinically, both STN-DBS and GPi-DBS efficiently reduce LID in humans (Bejjani et al., 2000; Krack et al., 1997, 1999, 2003). In animal models, the data are mitigated regarding the efficacy of STN-DBS on LID reporting an exacerbation (Oueslati et al., 2007), a reduction (Simonin et al., 2009) or no alteration (Gubellini et al., 2006).

These differences could account for the fact that the changes of glutamate release induced by L-dopa depend on the dose, the species and the brain region examined. The acute administration of L-dopa at 25 mg/kg increases glutamate release measured by intracerebral microdialysis in the striatum of naïve and 6-OHDA rats (Jonkers et al., 2002). After chronic L-dopa treatment, basal extracellular glutamate levels are consistently increased in the striatum and/or SNr, and associated with an increase in the glial glutamate transporter (Dupre et al., 2011; Robelet et al., 2004). Specifically in dyskinetic animals, basal extracellular levels of glutamate are similar to those reported in non-dyskinetic rats. However, differences in glutamatergic reactivity are observed on glutamate release induced by various doses of L-dopa (4, 12 or 100 mg/kg) or a depolarizing stimulus (Dupre et al., 2011; Nevalainen et al., 2013b; Robelet et al., 2004). It has been reported in peak-dose LID that glutamate release in the GP and SN was not altered by 15 mg/kg L-dopa in mice while it was enhanced in the SNr, but not the GP or dorsolateral striatum of rats after 6 mg/kg (Bido et al., 2011; Mela et al., 2012). Nevertheless, riluzole, a glutamate release inhibitor alleviates established AIMs in the 6-OHDA-lesioned mouse (Lundblad et al., 2005) and rat (Dekundy et al., 2007). In clinical trials, the effects of riluzole or another glutamate release inhibitor naftazone are mitigated (Bara-jimenez et al., 2006; Merims et al., 1999; Rascol et al., 2012). Overall, these studies bring evidence for a hyperactivity of glutamatergic neurons in response to chronic L-dopa that may operate in a region-dependent manner.

Accordingly, L-dopa is expected to change GABA release in the basal ganglia (Bezard et al., 2001d; Cenci, 2007b). In dyskinetic mice, L-dopa enhances GABA release in the SNr and GP (Bido et al., 2011). Although this effect is reduced by the non-selective NMDA receptor antagonist amantadine, L-dopa does not enhance glutamate extracellular levels in both regions (Bido et al., 2011). In dyskinetic rats, peak-dose LID are also associated with an increase in GABA release in the SNr (but not in the striatum) that is prevented by amantadine in line with a concomitant surge in nigral glutamate levels (Mela et al., 2007, 2012). These data suggest that the STN may facilitate the activity of the striatonigral GABAergic pathway at terminal level. Indeed, STN-DBS induced forelimb dyskinesia associated with glutamate release in the SNr of hemiparkinsonian rats (Boulet et al., 2006). Interestingly, STN-DBS at a lower intensity that did not induce forelimb dyskinesia, also increased nigral GABA release but without altering glutamate release (Boulet et al., 2006). An enhanced reactivity of GABAergic terminals in the SNr of dyskinetic animals, as also proposed from *in vitro* studies (Rangel-Barajas et al., 2008) is compatible with a consequent inhibition of the nigrothalamic GABAergic tone (Albin et al., 1989; Chevalier and Deniau, 1990). Accordingly, L-dopa decreases GABA release in the thalamus of 6-OHDA rats or MPTP-treated monkeys that displayed severe dyskinesia after 6 months treatment with L-dopa (Marti et al., 2007; Porrás et al., 2014). However, it remains to be determined whether the decrease in thalamic GABA release induced by L-dopa is magnified in case of peak-dose LID.

In conclusion, the impact of neurotransmitters on peak-dose LID is a complex mechanism regarding the neurochemical

environment created by L-dopa (Navailles and De Deurwaerdere, 2012). It requires a synaptic increase in DA release, even modest, from 5-HT terminals. High magnitude of variations in synaptic DA levels could favour the development of LID. Such swings and/or aberrant release of DA from L-dopa may occur in many brain regions other than the striatum. This is an important point because LID is associated with changes of cellular activity in sensorimotor, associative and limbic territories (Bastide et al., 2014b; Guigoni et al., 2005c). L-dopa also alters 5-HT extracellular levels directly and in a region-dependent manner as well as amino acids transmission. Notably, LID is associated with a higher GABA release in the SNr and a lower GABA release in the thalamus. Regarding the presynaptic release of other neurotransmitters, some preclinical studies indirectly suggest that peak-dose LID could also be associated with putative modifications of release in acetylcholine (Di Chiara et al., 1994; Zhang et al., 2013a), noradrenaline (Delaville et al., 2011), opioidergic peptides or endogenous cannabinoid reactivity (Huot et al., 2013). Such predictions are expected to be validated soon since the behavioural evaluation of LID in animals has been considerably improved in the past years (see above) and the *in vivo* assessment of neurochemical environment has benefited from the coupling of intracerebral microdialysis with powerful neurochemical method analysis (Cenci and Ohlin, 2009; Navailles et al., 2013).

4.9. Postsynaptic changes in striatal medium spiny neurons

4.9.1. LID is associated with an increased IEG expression

The IEGs are a class of genes rapidly transcribed in response to an external stimulus (McClung et al., 2004; Okuno, 2011). Although there are a lot of genes potentially involved in LID, the IEG encoding the transcription factor FosB has received particular attention. Indeed, FosB and, especially, its alternatively spliced isoform called Δ FosB are highly expressed in the dorsolateral striatum of dyskinetic monkeys and rodents (Andersson et al., 1999; Bastide et al., 2014b; Berton et al., 2009; Cenci and Konradi, 2010; Cenci et al., 1999; Feyder et al., 2011, 2014; Fisone and Bezard, 2011; McClung et al., 2004). In rodents, increased Δ FosB expression is restricted to dMSNs (Andersson et al., 1999; Darmopil et al., 2009; Fasano et al., 2010; Feyder et al., 2014) where activation of extracellular signal-regulated protein kinase (ERK) is also occurring (Darmopil et al., 2009; Santini et al., 2009a). Indeed, activation of ERK and of its nuclear downstream effector, mitogen- and stress-activated kinase 1 (MSK1), have been involved in the increase in Δ FosB expression associated to LID (Fasano et al., 2010; Fasano and Brambilla, 2011; Feyder et al., 2014). As striatal Δ FosB immunoreactivity is correlated with the severity of LID in rodents (Andersson et al., 1999; Bastide et al., 2014b; Feyder et al., 2014; Pavon et al., 2006), enhanced expression of Δ FosB appears to be causally related to the development of dyskinesia. Thus, striatal infusion of a *fosB* anti-sense oligonucleotide attenuates the development of AIMs over chronic course of L-dopa treatment in the rat (Andersson et al., 1999). In order to regulate the transcription of its targets genes, Δ FosB must form heterodimers with a member of the Jun transcription factor family, most commonly JunD. In the striatum of dyskinetic rats, Δ FosB and JunD were found to be the main contributors to DNA-protein complexes containing CREB responsive elements (CRE) or activator protein 1 (AP-1) enhancers (Andersson et al., 2001). The importance of Δ FosB/JunD heterodimers to the development of LID was demonstrated by Berton et al. (2009). In this study, the authors showed that overexpression of a truncated variant of JunD (Δ JunD), which acts as a dominant negative inhibitor of Δ FosB, dramatically reduced the severity of LID (Berton et al., 2009). Using a selective inactivation procedure, a recent study further demonstrated both in rat and macaque that the electrical activity

of striatal FosB/ Δ FosB neurons mediates LID and also blunts the anti-parkinsonian effect of L-dopa (Engeln et al., 2014a). Conversely, in the rat, viral vector-induced overexpression of Δ FosB exacerbates LID (Cao et al., 2010). In line with these observations, it has been recently shown in mice that overexpression of Δ FosB induced specifically in the striatonigral dMSNs, exacerbates LID. In contrast, functional inactivation of Δ FosB in the same neuronal population reduces dyskinesia (Feyder et al., 2014).

Zif268 (or NGFI-A/Krox24/Egr1), another IEG coding for a transcription factor, has been involved in LID pathophysiology. L-dopa administration increases zif268 in the striatum (Bastide et al., 2014b) with an enhanced expression of zif268 mRNA in both striatopallidal and striatonigral MSNs (Feyder et al., 2011). Interestingly, repeated administration of L-dopa to 6-OHDA-lesioned rats normalizes the levels of zif268 mRNA in neurons of the indirect pathway, but not in those of the direct pathway (Carta et al., 2005). The lack of normalization of zif268 expression in the dMSNs may be due to the persistent activation of ERK observed in these cells in association with dyskinesia (Gerfen et al., 2008; Lebel et al., 2010; Pavon et al., 2006; Santini et al., 2007; Westin et al., 2007).

Zif268 promotes the expression of the activity-regulated cytoskeletal-associated protein ARC (or arg3.1) (Li et al., 2005a), an IEG involved in synaptic plasticity (Bramham et al., 2008). Interestingly, LID is also accompanied by increased ARC expression in the striatum (Bastide et al., 2014b; Sgambato-Faure et al., 2005). In the hippocampus, zif268-induced expression of ARC is involved in the induction of the late phase of LTP (Li et al., 2005a). Therefore, it is possible that the persistent overexpression of zif268 and ARC is involved in the suppression of depotentiation at corticostriatal synapses, observed in association with LID (cf. above) (Picconi et al., 2003).

4.9.2. Gene expression signature associated to LID

To date, very few studies have characterized the pattern of gene expression associated with LID. Basically, four main studies have explored this issue in rodents by using a microarray transcriptomic approach; two of them in the rat model of PD (El Atifi-Borel et al., 2009; Konradi et al., 2004) and two more recent ones in 6-OHDA-lesioned mice (Charbonnier-Beaupel et al., 2015; Heiman et al., 2014). Konradi and collaborators examined the pattern of striatal messenger RNA expression of over 8000 genes in a rat model of PD and LID (Konradi et al., 2004). The authors approached this issue by comparing 6-OHDA-lesioned rats chronically treated with saline or L-dopa, and subdivided the L-dopa-treated animals into dyskinetic and non-dyskinetic cases. The striatum of dyskinetic rats showed a profile of increased transcriptional activity of GABAergic neurons, accompanied by changes in a gene network involved in calcium-dependent signalling, with a particular upregulation of genes involved in calcium homeostasis. A dysregulation of genes involved in structural and synaptic plasticity was also observed. Finally, the pattern of gene expression in dyskinetic rats pointed to an imbalance between high metabolic demand and a reduced capacity for energy production in the striatum.

Using a similar rat model, El Atifi-Borel and collaborators compared the effects of acute versus long-term L-dopa treatment on the profiles of striatal gene expression in the DA-depleted striatum, examining nearly 5000 genes (El Atifi-Borel et al., 2009). Acute and chronic treatments regulated a common set of 16 genes mainly implicated in signal transduction, transcription, translation, homeostasis processes and synaptic transmission. The transcriptomic response was enhanced by long-term L-dopa treatment. The main differences between the two treatments include genes involved in protein synthesis, metabolism, cell proliferation, neurite outgrowth and synaptogenesis. Long-term L-dopa administration was thus proposed to be associated with

structural cellular alterations in the striatum. However, in this study, the gene changes were not directly correlated to dyskinetic behaviour.

A recent elegant study used a combination of a hemiparkinsonian mouse model of PD and a refined mRNA translational profiling approach called translating ribosome affinity purification (TRAP) to identify cell-type-specific gene-expression changes in dMSNs and iMSNs as induced by DA depletion and pharmacological DA replacement (Heiman et al., 2014). DA depletion followed by chronic low- or high-dose L-dopa treatment was associated with massive changes in mRNA translation in dMSNs, compared with relatively modest changes in iMSNs. Many of the gene-expression changes observed in dMSNs correlated with the severity of AIMs, strongly suggesting that dMSNs are involved in the genesis of LID. The large gene profiling obtained in this study suggests that CREB, AP-1, and ERK signalling are major drivers of the transcriptional response to chronic high-dose L-dopa administration in dMSNs. Interestingly, several homeostatic changes induced by the treatment were observed in dMSNs, such as the up-regulation of MAPK-signalling phosphatases to counteract the abnormal high activity of the MAPK cascade in LID. However, these homeostatic mechanisms failed to dampen the up-regulation of an AP-1-regulated gene network (including transcription factors of the *Jun* and *Fos* family). The profound molecular adaptations of dMSNs and the limited response of iMSNs during dyskinesia treatment with L-dopa support the use of DAergic agents with preferential D2-like receptor activity as a first-line therapy to prevent dyskinesia in PD.

The molecular signature induced by L-dopa in the DA-depleted striatum was further uncovered by a recent important study performed in 6-OHDA-lesioned mice (Charbonnier-Beaupel et al., 2015). The study focused, in particular, on ERK-dependent gene expression changes induced by the first administration of L-dopa and associated with the early development of AIMs in hemiparkinsonian mice. A time-course analysis (0–6 h after treatment with L-dopa) identified an acute signature of 709 genes, among which genes involved in protein phosphatase activity were over-represented, suggesting that a negative feedback on ERK activation is recruited by L-dopa itself. L-dopa-dependent deregulation of 28 genes was blocked by pretreatment with an inhibitor of ERK activation, SL327, and 26 genes were found differentially expressed between highly and weakly dyskinetic animals following treatment with L-dopa. The intersection list revealed five genes: *FosB*, *Th*, *Nptx2*, *Nedd4l*, and *Crm4l*. *Nptx2* encodes neuronal pentraxin II (or neuronal activity-regulated pentraxin, Narp), involved in the clustering of glutamate receptors. The increase in *Nptx2* expression after L-dopa and its blockade by SL327 was confirmed by quantitative RT-PCR. Using an escalating L-dopa dose protocol, LID severity was decreased in Narp knockout mice or after overexpression of a dominant negative form of Narp in the striatum. In conclusion, the authors identified a molecular signature induced by L-dopa in the DA-denervated striatum, dependent on ERK and associated with LID (Charbonnier-Beaupel et al., 2015). Of particular interest was the result that Narp may be considered as a new therapeutic target in the early phases of LID development. These findings further corroborate the suggestion that changes in the composition of glutamate receptors at corticostriatal and/or thalamostriatal synapses are important element of the maladaptive plasticity that leads to LID.

A recent study examined the involvement of chromatin modifications in the aberrant gene expression associated to LID. Using a mouse model it was shown that L-dopa, via D₁R-mediated activation of DARPP-32 and ERK/MSK1, increased the levels of histone H3 phosphorylation at Ser28 (H3S28p), specifically in dMSNs (Sodersten et al., 2014). Notably, this phosphorylation occurred at genomic regions modified by trimethylation of the

adjacent Lys27 (K27me3), a mark linked to the repressive control exerted on gene expression by Polycomb group (PcG) proteins (Simon and Kingston, 2013). Previous work showed that phosphorylation of Ser28 in the context of Lys27 trimethylation leads to displacement of PcG proteins and increased gene transcription (Gehani et al., 2010). In line with this observation, genome wide analysis by ChIP-sequencing, in combination with expression analysis by RNA-sequencing, revealed that L-dopa-induced H3K27me3S28p correlates with increased expression of a subgroup of genes normally repressed by PcG proteins. These genes include transcription factors implicated in synaptic plasticity, such as *Atf3* (Green et al., 2008) and *Npas4* (Ramamoorthi et al., 2011), which controls of the expression of *Arc*, *Egr1* and *c-Fos* (Ramamoorthi et al., 2011). Importantly, it was also found that different subsets of PcG target genes are specifically induced by acute or chronic L-dopa, further suggesting that the development and manifestation of dyskinesia are mediated by the action of distinct molecular components (Sodersten et al., 2014).

In another interesting study, Ruiz-DeDiego et al. showed the involvement of the calcium-binding protein, downstream regulatory element antagonistic modulator (DREAM), in the control of the expression of FosB and dynorphin-B in response to chronic administration of L-dopa (2015). Importantly, these authors also show that AIMs severity is decreased in dominant active DREAM transgenic mice and, conversely, increased in DREAM knockout mice (Ruiz-DeDiego et al., 2015). DREAM acts by binding to downstream regulatory element sites on DNA and repressing gene transcription. Notably, increased calcium, or activation of cAMP signalling counteracts the repressive action of DREAM (Carrion et al., 1999; Ledo et al., 2000). Taken together, these observations indicate that the abnormal activation of cAMP and Ca²⁺ signalling produced by L-dopa may lead to dyskinesia through increased expression of genes normally repressed by DREAM.

4.9.3. Dopamine receptor signalling

The two major families of DA receptors, generally referred to as D₁-type and D₂-type, are classically defined by their opposite regulation of cAMP synthesis. D₁R and D₅R, which belong to the type-1 group, are coupled to G_{αs}/G_{αolf} proteins, which promote adenylyl cyclase activity and cAMP synthesis (Fig. 4A). Conversely, D₂R, D₃R and D₄R, which constitute the type-2 group, are coupled to G_{αi/o} proteins, which inhibit adenylyl cyclase and thereby reduce intracellular levels of cAMP (Herve et al., 1993; Stoof and Keibian, 1981; Zhuang et al., 2000) (Fig. 4B).

Considerable attention has been devoted to the participation of D₁R-mediated changes produced by the L-dopa-derived DA in the development and manifestation of dyskinesia on the ground that (i) both experimental models and PD patients exhibit a strong behavioural sensitization at the level of D₁R (Rascol et al., 2001b), that (ii) such sensitization is supported by a huge increase in D₁ receptor-mediated canonical and non-canonical signalling (see the sections below), that (iii) blunting the electrical activity of mainly D₁R-expressing MSNs improves dyskinesia severity in experimental models (Engeln et al., 2014a) and that (iv) eliminating direct pathway D₁R-expressing MSNs dramatically reduces AIMs in the 6-OHDA mouse model of LID (Revy et al., 2014).

4.9.3.1. D₁ receptor canonical pathway. Studies in experimental models of PD indicate that the number and affinity of D₁R is unchanged following DA depletion (Aubert et al., 2005; Breese et al., 1987; Joyce, 1991; Marshall et al., 1989; Savasta et al., 1988). Similar results were obtained in post-mortem samples from parkinsonian patients (Hurley et al., 2001; Pimoule et al., 1985; Shinotoh et al., 1993). However, the loss of DAergic input to the striatum and the development of dyskinetic behaviour in response to chronic administration of L-dopa are accompanied by increased

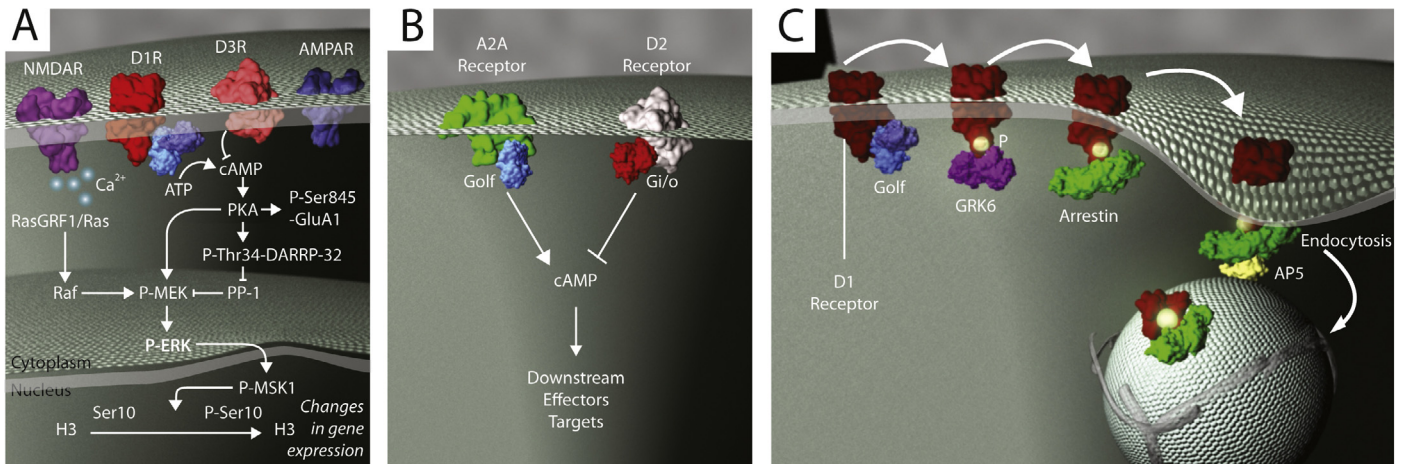


Fig. 4. Dopaminergic receptors signalling pathways. (A) D1 receptor (D1R) signalling. Dopamine-stimulated D1R activates the adenylyl cyclase (AC) which increases the synthesis of cyclic adenosine monophosphate (cAMP) activating the protein kinase A (PKA) in contrast to the D3 receptor (which cross-talks with D1R). PKA then phosphorylates GluA1 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor and the dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32). Phosphorylation at the T34 specific threonyl residue converts DARPP-32 into a selective inhibitor of protein phosphatase-1 (PP-1). This, in turn, suppresses the dephosphorylation of numerous downstream targets of PKA. Activated-D1R, cross talking to N-methyl-D-aspartate (NMDA) receptor, leads also to activation of extracellular signal-regulated protein kinases (ERK) controlling transcriptional and translational mechanisms. PKA/DARPP-32 and ERK/mitogen- and stress-activated kinase 1 (MSK1) signalling lead to phosphorylation of histone H3 in the nucleus, inducing changes in gene expression. (B) D2 receptor (D2R) signalling. Adenosine promotes cAMP synthesis through A2A receptors that activates PKA signalling which directly phosphorylates several substrates. In contrast, dopamine-stimulated D2R inhibits cAMP production and PKA signalling. (C) Mechanism of D1R homologous desensitization: Dopamine-stimulated D1R activates G proteins (G α olf). G protein-coupled receptor kinases (GRK) then phosphorylate D1R and reduce G proteins coupling, inducing an increased affinity for arrestins. Arrestin binding on D1R prevents the association of new G proteins, definitely blocking further D1R activation. Arrestins are able to bind clathrins and trigger D1R endocytosis into endosomes. Then, D1R is either driven into lysosomes to be degraded or phosphatases assure D1R recycling to the plasma membrane.

recruitment of D₁R at the plasma membrane of MSNs, which may be caused by impaired receptor internalization and trafficking (Berthet et al., 2009; Guigoni et al., 2007).

In addition to this phenomenon, other changes have been proposed to contribute to the increase in D₁R transmission associated with LID. Studies performed in 6-OHDA-lesioned rats and in post-mortem samples from parkinsonian patients showed that loss of striatal DA is accompanied by increased levels of G α olf (Alcacer et al., 2012; Corvol et al., 2004; Herve et al., 1993; Rangel-Barajas et al., 2011). In 6-OHDA-lesioned rats, G α olf overexpression subsides during chronic L-dopa administration and does not correlate with the severity of LID (Corvol et al., 2004; Rangel-Barajas et al., 2011). In contrast, elevated G α olf has been associated with LID in a mouse model of PD (Alcacer et al., 2012) as well as in PD patients who had received a prolonged L-dopa treatment (Corvol et al., 2004). However, in the same mouse model of PD and LID, reduced expression of G α olf did not affect dyskinetic behaviour (Alcacer et al., 2012) (cf. below).

Another signalling component contributing to the abnormal D₁R-mediated transmission involved in LID is the adenylyl cyclase type 5 (AC5), which is highly expressed in striatal MSNs (Glatt and Snyder, 1993; Mons and Cooper, 1994) and is stimulated in response to D₁R-mediated activation of G α olf (Herve et al., 1993; Zhuang et al., 2000). Evidence obtained using 6-OHDA-lesioned rats shows that DAergic depletion increases the levels of this enzyme in the striatum (Rangel-Barajas et al., 2011). A similar increase is also observed in the SNr, which is innervated by the D₁R-expressing striatal dMSNs (cf. above) (Rangel-Barajas et al., 2011). Interestingly, these effects are maintained during repeated administration of L-dopa, but only in animals displaying severe dyskinesia (Rangel-Barajas et al., 2011). Recently, direct evidence of the involvement of AC5 in LID was obtained in genetically modified mice. In particular it was shown that AC5 knock-out mice exhibits attenuated LID. In addition, genetic inactivation of AC5 prevented the ability of L-dopa to activate cAMP as well as ERK signalling (Park et al., 2014).

Taken together the results of the studies described above indicate that a persistent sensitization of canonical signalling downstream of D₁R is implicated in LID (Fig. 4A). This sensitization is sustained by several features, such as an increased recruitment of D₁R at the cell surface, an increased D₁R-mediated GTP γ S activity, an up-regulation of both G α olf and AC5 in the striatal dMSNs (Aubert et al., 2005; Berthet et al., 2009; Guigoni et al., 2007; Park et al., 2014; Rangel-Barajas et al., 2011). Altogether, these modifications are likely to influence DAergic transmission in the striatum and may underlie the enhancement in the ability of L-dopa to increase the levels of cAMP and to activate cAMP-dependent protein kinase (PKA).

The importance of augmented PKA activity in dyskinesia is indicated by the observation that, in 6-OHDA-lesioned rats, intrastriatal injections of the PKA inhibitor Rp-cAMPS reduces LID (Lebel et al., 2010). Striatal MSNs express high levels of DARPP-32, which is phosphorylated by PKA on a specific threonyl residue (T34). Phosphorylation at T34 converts DARPP-32 into a selective inhibitor of protein phosphatase-1 (PP-1). This, in turn, suppresses the dephosphorylation of numerous downstream targets of PKA, thereby amplifying behavioural responses produced by activation of cAMP signalling (Borgkvist and Fisone, 2007; Fienberg et al., 1998; Greengard, 2001). Several lines of evidence indicate that PKA-mediated phosphorylation of DARPP-32 is implicated in dyskinesia. Experiments performed in rodents and non-human primates show that LID correlates with increased levels of DARPP-32 phosphorylated at T34 (Lebel et al., 2010; Picconi et al., 2003; Santini et al., 2007, 2010a, 2012). Moreover, this effect is exerted specifically in the striatal dMSNs, which express D₁R (Santini et al., 2012). Knock-out of DARPP-32 or mutation of the phosphorylation site for PKA, both attenuate LID (Santini et al., 2007, 2012). A similar reduction of dyskinetic behaviour is also observed in mice in which DARPP-32 is selectively inactivated in the striatal dMSNs (Bateup et al., 2010). Interestingly, in MPTP-lesioned non-human primates, increased phosphorylation of DARPP-32 persists from first ever administration up to three months of L-dopa chronic

administration, suggesting that DARPP-32 is implicated not only in the development but also in the maintenance and manifestation of LID (Santini et al., 2010a).

The abnormal activation of PKA/DARPP-32 signalling observed in experimental models of LID may have profound repercussions on synaptic plasticity. As shown by Picconi et al., LID is associated with blockade of depotentiation at cortico-striatal synapses. Notably, depotentiation is prevented by inhibition of PP-1 (Picconi et al., 2003). Therefore, it is possible that the increase in DARPP-32 phosphorylation associated to LID contributes to the loss of depotentiation by reducing PP-1 activity. Another possible mechanism by which increased PKA/DARPP-32 signalling prevents depotentiation involves changes in the state of phosphorylation of the GluA1 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Increased PKA-dependent phosphorylation of GluA1 at Ser845 correlates with dyskinetic behaviour (Santini et al., 2007, 2010a). This effect is strictly dependent on concomitant phosphorylation of DARPP-32, since it is abolished in DARPP-32 knock-out mice (Santini et al., 2007). Phosphorylation of GluA1 at Ser845 promotes glutamatergic transmission (Banke et al., 2000; Mangiavacchi and Wolf, 2004) and may participate in the block of depotentiation observed in dyskinetic rats (Picconi et al., 2003).

In conclusion, sensitized D₁R signalling along the canonical cAMP pathway is required for the development and manifestation of LID (Fig. 4A). The identification of downstream targets of PKA ultimately responsible for the emergence of dyskinetic behaviour represents a promising avenue with regard to the development of efficacious anti-dyskinetic therapies. Several questions remain to be addressed. For instance, it has been shown that the reduction of L-dopa-induced phosphorylation of DARPP-32 and GluA1, achieved through downregulation of G α olf, does not affect dyskinesia, possibly because a partial downregulation of this signalling pathway has no effect on the induction of ERK signalling (Alcacer et al., 2012). These findings suggest that supersensitive D₁R in the DA-denervated striatum recruit non-canonical signalling components via alternative routes. Accordingly, a recent study has demonstrated that the D₁R-dependent induction of ERK1/2 signalling in the DA-denervated striatum can be inhibited by antagonizing phospholipase C (PLC), protein kinase C (PKC), or calcium mobilization from internal stores (Fieblinger et al., 2014b). These signalling components are normally associated with the activation of Gq- and not G α s/ α olf-coupled receptors.

Notwithstanding these recent findings it has also been established that a pronounced inactivation of the PKA/DARPP-32 cascade attenuates dyskinesia (Bateup et al., 2010; Lebel et al., 2010; Santini et al., 2007, 2012). Thus, further studies are needed to clarify the relationship between hyperactive cAMP-dependent signalling and the recruitment of non-canonical calcium-dependent signalling components in the dyskinetic striatum. In this regard it is particularly important to consider the cross-talk between cAMP signalling and transduction pathways implicated in activity-dependent synaptic plasticity, such as those controlled by the Ras-dependent activation of extracellular signal-regulated protein kinases (Ras-ERK) and the mammalian target of rapamycin complex 1 (mTORC1).

4.9.3.2. D₁ receptor non-canonical pathways. Newer evidence indicates that D₁R do crosstalk to glutamate signalling (mainly NMDA receptors) and thus can engage additional non-canonical pathways in LID (Fig. 4A). The best-characterized pathways implicated in LID are the Ras-ERK and the mTORC1 cascades, which also exert important function in a number of neuronal processes, including learning and memory (Costa-Mattioli et al., 2009; Fasano and Brambilla, 2011). In the now classical paper by Gerfen et al., ERK dependent signalling was shown to be aberrantly

hyperactivated in the DA depleted striatum, following D₁R activation. Accordingly, this early report also demonstrated that phospho-ERK (pERK) positive signal, a measure of ERK phosphorylation and activation, in the DA depleted brain, was almost entirely restricted to enkephalin negative cells, i.e. dMSNs (Gerfen et al., 2002). Hence, these initial observations led to the hypothesis that the denervation-induced supersensitivity of D₁R leads to the activation of non-canonical signalling responses involving ERK_{1/2} in dMSNs. It should be noted, however, that psychostimulants such as cocaine, which greatly increase extracellular DA levels, can also induce ERK1/2 activation in dMSNs, as originally shown by Caboche and collaborators (Valjent et al., 2000), by favouring the activity of the direct striatal pathway, which promotes action selection (Albin et al., 1989; DeLong, 1990). This cellular response may mediate the motor activation elicited by both psychostimulants in the normal brain and DAergic agonists (including L-dopa) in the DA-depleted brain. However, an excessive striatal activation of ERK1/2 is specifically linked with a dyskinetic motor output, as indicated by the finding that diminishing the striatal levels of pERK_{1/2} selectively diminishes the AIM scores without interfering with the anti-parkinsonian action of L-dopa (Fasano et al., 2010).

The first reports clearly implicating an abnormal ERK activation in LID came in 2006 (Pavon et al., 2006) and 2007 (Westin et al., 2007). Thus, Pavon and co-workers reported that pERK levels were significantly increased in the denervated striatum already by a single administration of L-dopa, and further enhanced with a chronic treatment over 25 days (Pavon et al., 2006). Importantly, pERK enhancement in the chronic L-dopa condition was also associated with a significant upregulation of FosB/ Δ FosB immunoreactivity. A positive linear correlation between striatal levels of phosphorylated ERK and the L-dopa-induced AIM scores was then provided by Westin et al. (2007). The latter study showed that both acute and chronic L-dopa administration rapidly induced the phosphorylation of ERK and MSK-1 in the DA-denervated striatum. Strong cellular immunoreactivity for pERK was detected in both the medial and the lateral striatum in a time interval ranging between 20 and 120 min after a single dose of L-dopa, a time window which parallels the time course of the AIMS. Interestingly, at 24 h, the cellular immunostaining for pERK was back to the basal levels (Westin et al., 2007). This study also reported that bromocriptine, an anti-parkinsonian drug with low dyskinesio-genic potential, did not induce any significant increase in either pERK or pMSK-1 immunoreactivity, further strengthening the link between a large activation of ERK and the development of involuntary movements. Further to these results, the study reported that the striatal activation of ERK signalling by L-dopa was dependent on the D₁ class of DA receptors. Indeed, the D₁R antagonist, SCH23390, completely suppressed pERK and pMSK-1 induction, as well as FosB/ Δ FosB upregulation, in animals treated with L-dopa (Westin et al., 2007). On the contrary, co-treatment with raclopride, a D₂R antagonist, had no effect on the L-dopa-induced response. The direct link between LID, D₁R and ERK activity was later substantiated by the Moratalla group, by showing that genetic ablation of D₁R but not D₂R suppresses AIMS in the mouse and concomitantly prevents ERK phosphorylation, phospho-acetylation of Histone H3 (pACh3) (a direct substrate of MSK-1) and FosB/ Δ FosB accumulation (Darmopil et al., 2009). Finally, upregulation of pERK and pACh3 levels specifically in the dMSNs was later corroborated using the aforementioned BAC transgenic EGFP expressing mice (Santini et al., 2009a).

These observations did ascribe a pivotal role of ERK signalling in LID. However, they did not demonstrate that a reduction of the activity of this signal transduction pathway could ameliorate the dyskinetic symptoms. Fisone's group provided the initial evidence (Santini et al., 2007). In this paper it was shown that pERK increase

well correlated with AIMs severity of 6-OHDA-lesioned mice, as well as the enhancement of phosphorylation of GluA1 (pSer845) and most importantly DARPP-32 (pThr34) (Greengard et al., 1999). Previous work had proposed that in MSNs, active DARPP-32 (pThr34) could stimulate ERK activity by suppressing the activity of the striatal-enriched protein tyrosine phosphatase (STEP), a direct substrate of PP-1 (Valjent et al., 2005). Hence, in the DARPP-32 knock-out animals, not only AIMs are significantly attenuated but also pERK and pGluA1 are reduced. Finally, systemic administration of SL327, a specific inhibitor of the MEK1/2 kinases upstream of ERK1/2, robustly attenuated LID in mice, providing not only a conclusive demonstration that aberrant ERK activity is part of the pathophysiology of LID but also opening interesting therapeutic possibilities for treating dyskinesia by targeting this signalling pathway (Fasano et al., 2010; Santini et al., 2007). Indeed, an initial attempt to translate these findings in a potential therapy was based on the use of lovastatin, which besides its wide use to treat hyperlipidemia in humans, has also been shown to prevent the membrane localization of Ras proteins, the upstream activators of ERK signalling, effectively reducing the activity of this cascade in vivo in the brain (Li et al., 2005b). In the rat model of LID, treatment with lovastatin effectively prevented LID formation and reduced both pERK induction and FosB/ Δ FosB levels (Schuster et al., 2008). Unfortunately, while the treatment with another statin, simvastatin, did reduce LID and attenuate ERK signalling in the non-human primate model of PD and LID, a pilot trial with a small group of patients failed to reveal any therapeutic effect (Tison et al., 2013), at a dose of 40 mg per day, i.e. the maximal dose with absence of side-effects that failed in reducing ERK1/2 activation in the periphery while it did achieve reduction in dyskinesia in MPTP-lesioned macaques (see Fig. 3; Tison et al., 2013). Failure was thus a problem of bioavailability rather than due to the target itself.

Despite this initial negative result, interesting alternative approaches are available to reduce ERK activity in dyskinesia in order to attenuate LID. For instance, indirect manipulation of ERK activity can be achieved either by modulating both group I mGluRs (mGluR1 and 5) using specific antagonists or negative allosteric modulators or nociceptin/orphanin FQ receptors using specific agonists (Marti et al., 2012; Rylander et al., 2009). In both cases, pharmacological treatments in experimental rodent models did not only reduce AIMs but also attenuated pERK.

One of the potential problems in LID research is the fact that targeting certain signalling intermediates or receptors aberrantly altered in the initial phases of L-dopa exposure (priming) may be effective in reducing dyskinesia symptoms but this therapeutic effect may be lost at later stages, a condition more relevant to most PD patients, due to tolerance or additional compensatory cellular mechanisms. Some evidence tends to suggest that ERK activity in dMSNs may decline during chronic L-dopa treatment. In the macaque model, levels of phosphorylation of both ERK_{1/2} and of the ribosomal protein S6 (pS235/236), an indirect cytoplasmic target of ERK, were found maximal upon initial L-dopa treatment but then declined significantly after 3 months treatment, although did not return to basal level (Santini et al., 2010a). Note however that ribosomal protein S6 phosphorylation was recently found to actually require the cAMP/PKA/DARR-32/PP-1 cascade and not the mTORC1, PKC and ERK signalling (Biever et al., 2015). The decline in activity after chronic treatment was not observed for either DARPP-32 (Thr34) or GluA1 (Ser845) suggesting that, while ERK signalling may be more implicated in priming, cAMP signalling may be still relevant for the expression of dyskinesia. However, this simplistic idea has been complemented by other experimental observations. First, a study performed using both 6-OHDA-lesioned mice and the Pitx3/aphakia mouse model of PD, showed that L-dopa-induced striatal ERK activation does not subside

during long-term treatment, but rather shifts from being predominantly localized to MSNs to occurring in cholinergic interneurons (Ding et al., 2011). Ablating those cholinergic interneurons leads to improvement of AIMs (Won et al., 2014). The ERK activation shift has been confirmed in the macaque model of PD and LID (Beard, unpublished). Second, lentiviral vectors (LV)-mediated inactivation of striatal Ras-ERK signalling (predominantly in MSNs) was found to significantly improve LID in already dyskinetic monkeys, which had been treated with L-dopa for several months prior to the LV delivery (Fasano et al., 2010). Third, in heterozygous mice for G α olf, L-dopa-induced cAMP-dependent signalling was attenuated while ERK activity and AIMs remained high, suggesting that the role of ERK is preponderant over that of canonical G α olf-mediated signalling in inducing dyskinesia (Alcacer et al., 2012).

Till recently, the investigation of the role of ERK in brain functions in general and in LID in particular has been largely limited to the core components of this signalling pathway, i.e. MEK_{1/2} and ERK_{1/2} protein kinases. However, upstream mechanisms connecting both DA D₁R and glutamate receptors have been proved to be relevant in the onset of dyskinesia. Ras-GRF1, is a neuronal specific and striatal enriched guanine-nucleotide exchange factor for Ras proteins, previously implicated in cognitive processing as well as in synaptic plasticity and acting as a signalling integrator between D₁R and glutamatergic ionotropic receptors (Brambilla et al., 1997; Fasano and Brambilla, 2011; Fasano et al., 2009). In 2010, Brambilla's group showed that the genetic ablation of Ras-GRF1 in the mouse significantly ameliorates AIMs by reducing both pERK and FosB/ Δ FosB levels (Fasano et al., 2010). Importantly, suboptimal doses of SL327, the MEK inhibitor, potentiate the anti-dyskinetic effect observed in the Ras-GRF1 knock-out mice, suggesting that a combination therapy targeting both upstream and downstream components of the Ras-ERK pathway may be more effective for treating LID symptoms. The relevance of these observations was also supported by a gene therapy approach in the non-human primate model, in which fully dyskinetic monkeys were injected with LV expressing a cocktail of Ras-GRF1 and ERK dominant negative constructs. This treatment significantly reverted LID symptoms without attenuating the anti-parkinsonian action of L-dopa, strongly supporting the idea that Ras-ERK inhibition in already affected individuals may provide a valid therapeutic approach for LID. The fact that Ras-GRF1 inhibition does not completely suppress dyskinesia symptoms may imply that other exchange factors for Ras-proteins could also be implicated in this process. Ras-GRF2, a close homolog of Ras-GRF1 could likely be one of these candidates. However, compelling behavioral, histochemical and neurochemical evidence exclude its involvement in LID process (Bido et al., 2015). Two additional valid candidates may be CalDAG-GEF1 and CalDAG-GEFII, two striatal enriched Ras-ERK regulators, whose levels were shown altered upon DA depletion and L-dopa treatment (Crittenden et al., 2009). In addition, direct coupling of D₁R to ERK signalling is believed to play a crucial role in LID. In this respect, evidence has elucidated a novel mechanism in which the D₁R-mediated ERK_{1/2} activation in the striatum is dependent on the formation of a signalling complex containing the protein tyrosine phosphatase Shp-2 that persists in dyskinetic animals (Fiorentini et al., 2011, 2013). Thus, Shp-2 may become in the near future an additional interesting target associated to the striatal ERK signalling. Moreover, as mentioned above, signalling components traditionally associated with Gq-coupled receptors appear to be involved in the induction of ERK_{1/2} activation downstream of the D₁R in PD models (Fieblinger et al., 2014b). These signalling components could be explored for the treatment of LID in the future.

Very recently, Brambilla and colleagues have elucidated some striatal synaptic mechanisms connecting Ras-GRF1 and ERK to LID. A combination of both ERK pharmacological blockade and Ras-GRF1 deficient mice revealed a complex scenario, involving this

signalling cascade in striatal plasticity (Cerovic et al., 2015). First of all, in mouse naïve striatal slices, inhibition of ERK using U0126, a MEK inhibitor, resulted in a complete inhibition of both cortico-striatal LTP induction and of its reversal, depotentiation. On the contrary, ERK activity seems to be not implicated in cortico-striatal LTD and LTP maintenance since U0126 does not block these two processes. Interestingly, in striatal slices from Ras-GRF1 KO mice, only dMSNs do not show LTP while long-term plasticity is unaffected in iMSNs. This evidence strongly argues for relevant differences in the engagement of different components of the Ras-ERK pathway within the two major populations of striatal cells. In addition, early evidence suggested that Ras-GRF1 controls ERK activity predominantly in dMSNs (Fasano et al., 2010). As additional confirmation, more recent evidence indicate that ERK signaling in cholinergic interneurons is not altered in either untreated or acutely exposed mice to L-DOPA, but only increases upon repeated L-DOPA administration, in a Ras-GRF1 independent manner. This finding may explain the presence of residual dyskinetic symptoms in Ras-GRF1 deficient mice, possibly due to the intact ERK activity in cholinergic interneurons (Bido et al., 2015).

The relevance of this observation is in line with the previous report showing an involvement of Ras-GRF1 in LID and suggesting a central role of the sole direct striatal pathway in the process (Fasano et al., 2010). Furthermore, analysis in DA depleted slices, using the 6-OHDA mouse model revealed that repeated L-dopa treatments not only render animals highly dyskinetic but also profoundly alter the synaptic responses to Ras-GRF1 and ERK modulation. Indeed, both ERK inhibition and Ras-GRF1 depletion facilitates depotentiation, thus indicating that restoration of this synaptic process correlates with an attenuated dyskinetic profile, as found in both SL327 treated and Ras-GRF1 deficient mice (Fasano et al., 2010; Santini et al., 2007). However, the most striking finding, with potentially relevant clinical implications, relates to the LTP responses in slices obtained from dyskinetic animals and treated with the MEK inhibitor. Differently from the naïve condition, U0126 did not block synaptic potentiation in all cells but only in approximately 50% of cases, in a pathway independent manner. This observation firstly indicates that profound synaptic rearrangements occur in the dyskinetic striatum, and secondly, that ERK signalling is only required in a portion of the MSNs, with an apparent stochastic pattern, suggesting that normal cortico-striatal LTP and L-dopa mediated LTP are rather distinct processes (Thiele et al., 2014). Further work will be necessary to unravel the underlying molecular mechanisms, however it is intriguing to speculate that this derangement of synaptic responses in the dyskinetic condition may be linked to different cellular states, possibly connected to pulsatile L-dopa administration, rapid changes in DA availability and wearing off.

It is well recognized that the Ras-ERK cascade is a crucial transducer transmitting signals from the cytoplasm to the nucleus. One of the main downstream effectors implicated in ERK-dependent transcriptional regulation is MSK1. Recent evidence indicates that MSK1 could be involved in LID. Thus, MSK1 knock out mice develop less severe dyskinesia in response to chronic administration of L-dopa (Feyder et al., 2014). In this study, inactivation of MSK1 affects specifically the axial dyskinesia, suggesting that specific components of LID can be controlled by targeting specific signalling pathways downstream of ERK signalling (Feyder et al., 2014). Interestingly, genetic inactivation of MSK1 is accompanied by concomitant reduction of histone H3 phosphorylated at Ser10 and Δ FosB, further supporting the idea of their involvement in LID (Feyder et al., 2014). However, in another study MSK1 appears not to be necessary for the development of LID (Alcacer et al., 2014). Using the same transgenic mouse line, the authors show that the lack of MSK1 in 6-OHDA-lesioned mice blocks or attenuates some previously described L-dopa effects,

including α olf up-regulation and increases of histone H3 phosphorylation and Δ FosB accumulation. The decrease of these biochemical changes was however not sufficient to significantly alter the development of LID. Interestingly, the absence of MSK1 had no effect on L-dopa-induced ERK activation, suggesting an involvement of additional ERK-dependent signalling mechanisms that are independent of MSK1 (Alcacer et al., 2014).

Aside from its role in transcriptional regulation, ERK activity is involved in the modulation of protein translation. This occurs mainly through the control of the mTOR cascade. mTOR is the essential component of mTORC1, which can be activated by ERK and, in turn, phosphorylates S6K1 and the initiation factor 4E-binding protein (Santini et al., 2010b). Through these effectors, mTORC1 promotes initiation of mRNA translation and protein synthesis. mTORC1 is inhibited by rapamycin and rapamycin derivatives (or “rapalogs”). Similarly to ERK, mTORC1 hyperactivation occurs specifically in dMSNs of DA-depleted animals challenged with L-dopa and the degree of phosphorylation of several markers downstream to mTORC1 correlates well with the severity of AIMS (Santini et al., 2009b). The involvement of mTORC1 in dyskinesia was first demonstrated by showing that, in the 6-OHDA mouse model, this condition is strongly attenuated by systemic administration of rapamycin (Santini et al., 2009b). These results were confirmed in the 6-OHDA rat model, using the rapalog, temsirolimus (CCI-779) (Decressac and Bjorklund, 2013). These findings support the idea that excessive de novo protein translation may be responsible for LID pathophysiology (see also, Kultima et al., 2006; Scholz et al., 2008). Remarkably, an upstream component of the mTOR pathway, Rhes, has proven to be involved in the development of LID, further expanding the list of potential therapeutic targets (Subramaniam et al., 2012).

In recent years, the idea of combination therapy has risen as an interesting concept in optimizing novel therapeutic approaches, with clinical trials targeting both Ras-ERK and mTOR cascades already ongoing in oncology (Chappell et al., 2011). The data available on non-canonical intracellular signalling pathways certainly suggest that a similar path could also be taken to treat dyskinesia.

4.9.4. Other dopamine receptors

4.9.4.1. D_2 receptor. While critical involvement of the D_1 R has clearly been demonstrated, the role of the D_2 R has received much less attention, although imbalance in the activity of the two major striatal output pathways supported through over-activation of D_1 R and over-inhibition of D_2 R on the direct and indirect pathway, respectively, is a classic concept (Bezard et al., 2001a; Calon et al., 2000; Olanow and Tatton, 1999; Tintner and Jankovic, 2002). Years of behavioural pharmacology, however, undoubtedly show that D_2 R agonists induce behavioural sensitization (Morelli and Di Chiara, 1987; Morelli et al., 1989) and dyskinesia in primed animals (Bezard et al., 2001a; Jenner, 2008). D_2 R distribution and expression is however not further affected by chronic L-dopa treatment in DA-depleted animals (Aubert et al., 2005; Guigoni et al., 2007), while DA depletion already provokes the classic upregulation. One should admit, however, that D_2 R has probably received less attention because the experimental tools are less developed and/or reliable for the D_2 R than for the D_1 R (antibodies, transmission assays, etc.). The role of the D_2 R is therefore only indirectly emphasized, through, for instance, the adenosine A_{2A} receptors localized on D_2 R-expressing MSNs (see below the detailed discussion of this class of receptors) (Fig. 4B). Other indirect evidence comes from the regulation of D_2 R signalling by regulatory GPCR signalling proteins (RGS). RGS9-2 is a GTPase accelerating protein of $G\alpha$ subunits that inhibits D_2 R-activated G proteins (Rahman et al., 2003) and is expressed almost exclusively in the striatum (Rahman et al., 1999). Regulation of RGS9-2

expression in various animal models of LID (Gold et al., 2007) and in L-dopa-exposed PD patients (Tekumalla et al., 2001) suggests that the striatum attempts to compensate for increased D₂R-mediated signalling by increasing RGS9-2 levels, i.e. that would result in a better “stop” signal of D₂R-mediated transduction. This mechanism obviously fails as MPTP-lesioned monkeys and L-dopa-treated PD patients do develop LID. Gold et al. hypothesized that such compensatory mechanisms might be boosted by further increasing RGS9-2 levels using viral transfer. In keeping with this hypothesis, although RGS9-2 knockout mice do show worse AIMs than wild-type mice (Gold et al., 2007), both dyskinetic 6-OHDA-lesioned rats and dyskinetic MPTP-treated monkeys transfected with RGS9-2 did show reduced severity of LID (Gold et al., 2007). This positive effect is counterbalanced by the observation that the anti-parkinsonian action of D₂R agonists is abolished, an observation that clearly highlights the complex role of the D₂R in LID pathophysiology.

While the D₁R may interact with glutamate receptors through protein-protein interaction (Cahill et al., 2014; Lee et al., 2002; Scott et al., 2006) or through the MAGUK proteins (Fiorentini et al., 2003; Yao et al., 2008; Zhang et al., 2007), much less is known about interaction between D₂R and the various components of the glutamate receptor machinery. Recently, however, an interaction between the excitatory synapse-enriched Calcium/calmodulin-dependent protein kinase II (CaMKII) and the D₂R has been described and shown to be enhanced in dyskinetic 6-OHDA-lesioned rats. Disruption of such interaction using either a specific interaction-dead peptide (Zhang et al., 2014d) or pharmacological inhibition of CAMKII (Yang et al., 2013) reduces AIMs in the same experimental model.

Altogether, while the D₂R sensitization certainly plays a role in LID pathophysiology, strategies aiming at modulating its signalling cascade activity or disrupting its partnership seem ultimately to result into emergence of an anti-L-dopa effect upon parkinsonian symptoms, i.e. reduction of LID severity is achieved at cost of resurgence of parkinsonian symptoms.

4.9.4.2. D₃ receptor. Even less studied, but certainly far more interesting from a therapeutic viewpoint, is the DA D₃R. Interestingly, expression level of the D₃R in the dorsal motor-related striatum correlates with experimental analogues of dyskinesia in mouse (Gross et al., 2003), rat (Bordet et al., 1997) and macaque monkey (Bezard et al., 2003). Furthermore, over-expression of the D₃R in the rat dorsal striatum induces dyskinetic behaviours (Cote et al., 2014). To date, this is the only DA receptor, whose expression levels linearly correlate with LID severity (Azkona et al., 2014; Bezard et al., 2003; Bordet et al., 1997). Interestingly, D₁R and D₃R are co-expressed by the dMSNs (Ridray et al., 1998) and have been shown to directly interact (Fiorentini et al., 2008) through an intramembrane D₁R-D₃R cross-talk (Marcellino et al., 2008) (Fig. 4A). Such cellular co-localization and cross-talk clearly emphasize the putative key role played by the duet in LID pathophysiology.

Attempts have thus been made for dampening the D₃R activity or the cross-talk between the two receptors. Administration of a D₃R-selective partial agonist, BP897, strongly attenuated LID in the MPTP-treated macaque model of dyskinesia, while leaving unaffected the therapeutic effect of L-dopa (Bezard et al., 2003). On the contrary, attenuation of dyskinesia by D₃R antagonists, nafadotride and ST-198, was accompanied by the reappearance of PD-like symptoms (Bezard et al., 2003). These results suggested that the D₃R participates in both dyskinesia and the therapeutic action of L-dopa in the macaque model in which receptor levels and activities were known. Of note, an anti-dyskinetic action of the D₃R antagonists WV10 and PG01037 has been confirmed in the AIM 6-OHDA-lesioned rat model although, in these reports, they

did not interfere negatively with anti-parkinsonian action of L-dopa (Kumar et al., 2009a,b).

In another species, the squirrel monkey, the same partial agonist, BP897, significantly reduced LID, but at the expense of L-dopa's anti-parkinsonian action (Hsu et al., 2004). Thus, in squirrel monkeys, in contrast to macaques, BP897 exerted both anti-dyskinetic and proparkinsonian effects. The discrepant effect of the partial D₃R agonist in these two nonhuman primate species may relate to a differential distribution and/or regulation of D₃R (Bezard et al., 2003; Hsu et al., 2004). The fact that even normal squirrel monkeys present LID (Togasaki et al., 2001), i.e. in absence of nigrostriatal lesion, suggest that pathophysiology supporting similar symptoms is actually rather different between the two species vis-à-vis DA receptor expression and sensitivity. An alternate hypothesis has been proposed, positing that the partial agonist BP897 might actually mediate its anti-dyskinetic action at sites other than D₃R (Visanji et al., 2006b). Visanji et al. used the L-dopa-induced hyperkinesia in reserpine-treated rats, the vertical component of which (rearing) is attenuated by agents with anti-dyskinetic actions in MPTP-lesioned primates and PD patients (Johnston et al., 2005). While BP897 reduced L-dopa-induced rearing, the D₃R antagonist S33084 had no effect on this behaviour either alone or in combination to BP897 (Visanji et al., 2006b). The selective D₂R L741,626 mimicked the influence of BP897 on L-dopa-induced rearing while the D₃R antagonist S33084 reproduced the BP897 attenuation of L-dopa-induced horizontal activity (Visanji et al., 2006b). Authors concluded that, in this acute rat model, BP897 may reduce LID but that receptors other than D₃R might be involved in this action. These two sets of data emphasize the need for conducting pharmacological studies in experimental models in which the target expression, here the DA receptors, is known. While data in the macaque models are coherent with the expression levels of DA receptors, the reserpine rat and squirrel monkey data raise more questions than they solve because of the lack of knowledge of the models.

Furthering our knowledge of the complex role played by D₃R is the demonstration that the D₃R antagonist ST 198, known to improve dyskinesia severity in rodent and non-human primate analogues of PD (although with anti-L-dopa effect at high dose), restores normal levels of membrane-bound D₁R in dyskinetic 6-OHDA-lesioned rats (Berthet et al., 2009). Interestingly, notwithstanding the impact upon D₃R-mediated signalling, antagonizing the D₃R seems to disrupt the crosstalk between D₁R and D₃R offering an additional mechanism, i.e. release of D₁R, for anti-dyskinetic action of D₃R ligands (Berthet and Bezard, 2009; Berthet et al., 2009).

4.9.4.3. D₄ receptor. The DA D₄R has been largely ignored because of its low density of in the striatum of control subjects and PD patients (Seeman et al., 1993). Both the anatomical localization and the changes in expression induced by DA loss and further L-dopa replacement therapy are unknown in experimental models and PD patients, further highlighting, if needed, the importance for pathophysiological characterization before embarking into pharmacological studies. Despite this lack of knowledge, pharmacological strategies aiming at antagonizing its activity were attempted to address the issue of D₄R involvement in LID. The clozapine analogue 8-methyl-6-(4-methyl-1-piperazinyl)-11H-pyrido(2,3-b)(1,4)benzodiazepine (JL-18) possesses affinity for DA D₄R and demonstrated some efficacy against LID in the MPTP-lesioned macaque model of PD and LID (Hadj Tahar et al., 2000). Although JL-18 is a potent D₄R antagonist, it also exhibits high affinity for 5-HT_{2A}, D₂R, and muscarinic receptors with a rather weak D₄R selectivity, rendering dubious the conclusion of a role of D₄R in LID expression. More recently, L-745,870 (3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-1H-pyrrolo[2,3-b]pyridine), a potent and selective D₄R antagonist, exhibiting nearly 100-fold selectivity for

D₄R over its next target, originally developed to treat schizophrenia, was tested against LID in the AIM 6-OHDA-lesioned rat model (Huot et al., 2015) and the dyskinetic MPTP-lesioned macaque model (Huot et al., 2012a). L-745,870 reduced both AIMs (Huot et al., 2015) and LID (Huot et al., 2012a). It also diminished the L-dopa anti-parkinsonian benefit in the rat model (Huot et al., 2015) but not in the macaque model (Huot et al., 2012a), calling for further investigations. Overall, these data suggest that L-745,870 may have a narrow therapeutic window as an anti-dyskinetic agent in advanced PD, rendering difficult its titration, in addition to the dubious status of D₄R expression in dyskinetic PD patients.

4.9.5. Dysregulation of homologous DA receptor desensitization

As stated above, the deregulation of DA-mediated signalling manifests itself as strongly enhanced responsiveness to DAergic stimulation both at the behavioural and signalling levels via all major striatal DA receptor subtypes (Brown et al., 2005; Bychkov et al., 2007; Cai et al., 2000; Corvol et al., 2004; Gerfen, 2000; Gerfen et al., 2002; Piffl et al., 1992a,b; Ravenscroft et al., 2004; Sgambato-Faure et al., 2005; Tong et al., 2004; Ungerstedt, 1971b). Although the mechanism of DAergic supersensitivity is undoubtedly complex, deregulation of the receptor desensitization machinery is likely to play an important role in LID.

Would this be the case, DA receptors should thus be less internalized in dyskinesia. This hypothesis is clearly counterintuitive as the DA receptors belong to the superfamily of GPCR, known to desensitize rapidly in presence of their ligand (Fig. 4C). In the context of LID, extracellular DA levels are increased and should thus lead to DA receptor desensitization, e.g. through internalization. D₁R, but not D₂R, actually appears overrepresented at neuronal membrane (Berthet et al., 2009; Guigoni et al., 2005a, 2007), hence leading to persistent overactivity of its signalling (Aubert et al., 2005; Guigoni et al., 2005a). Active anchoring at membrane takes place as direct further agonism of D₁R (Berthet et al., 2009), disruption of receptor–receptor (Berthet et al., 2009) or receptor–scaffold protein interactions (Porrás et al., 2012a) are successful strategies for re-instating D₁R internalization resulting into improvement of LID in experimental models.

DA receptors transmit signals in response to a wide variety of stimuli via a uniform mechanism involving coupling of liganded receptors to heterotrimeric G proteins followed by GTP-GDP exchange on α -subunit and dissociation of α -subunit from the $\beta\gamma$ -dimer, both of which activate or modulate effectors (Rasmussen et al., 2011) (Fig. 4C). Activation of a GPCR by an agonist initiates G protein-mediated signalling and at the same time triggers a shutdown mechanism termed homologous desensitization, or desensitization of the receptors that are being activated. The classic model of homologous desensitization of GPCR posits that agonist-activated receptor is first phosphorylated by a G protein-coupled receptor kinase (GRK) [reviewed in Gurevich et al. (2012)]. GRKs specifically recognize receptor conformations conducive to G protein binding and, like G proteins, directly bind active receptors (Huang and Tesmer, 2011). Since this interaction of a GRK with an activated receptor activates the kinase (Palczewski et al., 1991), GRKs are selective towards activated GPCRs. The receptor phosphorylation promotes high-affinity binding of uncoupling proteins arrestin. Arrestin shields the cytoplasmic surface of the receptor, precluding further G protein activation (Krupnick et al., 1997; Wilden, 1995). Arrestin binding also promotes receptor internalization by virtue of direct arrestin interaction with clathrin and AP-2, the main components of the coated pit (Goodman et al., 1996; Laporte et al., 1999), leading to the receptor resensitization and recycling or, in some cases, down-regulation (Morrison et al., 1996; Pan et al., 2003; Wu et al., 2008) (Fig. 4C).

GRK phosphorylation reduces receptor coupling to G proteins (Wilden, 1995), but does not eliminate it. The full signal shutoff is

accomplished by the binding of an arrestin to active phosphorylated GPCR (Attramadal et al., 1992; Krupnick et al., 1997; Lohse et al., 1990, 1992; Wilden, 1995). Arrestin requires more than one phosphate attached to a receptor for high affinity binding (Vishnivetskiy et al., 2007). Arrestins have been shown to compete with G proteins for active GPCRs (Krupnick et al., 1997; Wilden, 1995). However, because the receptor needs to be phosphorylated multiple times before arrestin can bind with high affinity, G protein has a time window with a clear advantage over arrestin, when it can be activated and transmit the signal before the shutoff is complete. For example, light-activated rhodopsin, a prototypical class A GPCR, is capable of sequentially activating dozens of G protein molecules (Leskov et al., 2000). The receptor phosphorylation by GRK is the rate-limiting step in the homologous desensitization process (Violin et al., 2008) and GRK concentration in cells strongly influences the rate and extent of receptor desensitization, as well as the duration and intensity of G protein-mediated signalling (Gainetdinov et al., 1999, 2003, 2004; Iaccarino et al., 1998; Kim et al., 2001; Menard et al., 1997; Pan et al., 2003; Willets et al., 1999, 2004). Active GTP-liganded α -subunits of G proteins are in their turn deactivated via hydrolysis of GTP to GDP by intrinsic GTPase activity of the α -subunits. This intrinsic activity is enhanced by GTPase activating proteins (GAPs) that accelerate G protein deactivation and reduce signalling. The major class of GAPs are RGS (Ross and Wilkie, 2000; Siderovski et al., 1996; Siderovski and Willard, 2005). When the receptor is uncoupled from G protein via GRK-arrestin-dependent desensitization, the signalling is sustained by remaining active G proteins. RGS proteins, by facilitating G protein deactivation, promote complete signal shutoff. RGS availability and function is an important determinant of the signal intensity and duration. Therefore, it is conceivable that RGS function is perturbed in LID contributing to the deregulation of the DA receptor signalling. In some systems, RGSs and not GRKs are rate-limiting for the overall signal shutoff (Krispel et al., 2006). The RGS family is large and diverse (Ross and Wilkie, 2000), with many members expressed in striatal neurons (Gold et al., 1997, 2007). The RGS9-2 isoform is highly enriched in the striatum in comparison with other brain structures (Gold et al., 1997, 2007; Granneman et al., 1998; Kovoor et al., 2005; Rahman et al., 1999, 2003). The concentration of multiple RGS proteins is responsive to changes in the DAergic environment (Ding et al., 2006; Geurts et al., 2002, 2003; Ko et al., 2014b). Any deregulation of this complex well-orchestrated mechanism of termination of the GPCR signalling would result in a profound enhancement of signal duration and/or intensity and is likely to bring about multiple behavioural deficits.

Mammals express seven GRK subtypes, with two isoforms, GRK1 and GRK7, being confined to the retinal photoreceptors and one, GRK4, – largely to testes (Gurevich et al., 2012; Mushegian et al., 2012). Four isoforms, GRK2, 3, 5, and 6, are ubiquitously expressed throughout the brain including the striatum (Ahmed et al., 2008a,b; Bychkov et al., 2008, 2010, 2011, 2013). Since the number of non-visual GRKs is limited and much lower than the number of ~700 mammalian GPCRs they serve, it is generally assumed that each isoform phosphorylates numerous GPCRs. However, studies in GRK KO mice brought forward evidence of in vivo receptor specificity of GRKs [see discussion in Gurevich et al. (2012)]. Furthermore, evidence of differential functional consequence of the receptor phosphorylation by different GRKs [the “barcode” concept (Kim et al., 2005; Liggett, 2011; Nobles et al., 2011; Ren et al., 2005; Zidar et al., 2009)] strongly suggests that GRK isoforms are not interchangeable, but each has a defined function. The receptor specificity and functional role of GRKs in vivo remains to be elucidated (for in depth discussion see Gurevich et al., 2012). The human and rodent striatum expresses all four ubiquitous non-visual GRKs (Ahmed et al., 2008a,b, 2010; Bychkov et al., 2008, 2013). In the rat, GRKs 2 and 5 are equally expressed in the direct and indirect

pathway MSNs, but GRK2 is highly enriched in cholinergic interneurons, as compared to the output neurons, whereas GRK5 is expressed at similar level in both (Bychkov et al., 2013). Unfortunately, the expression pattern of GRK6, the highest expressed GRK in the rodent striatum, is yet undefined. Experiments with GRK knock-out mice demonstrated that mice lacking GRK6 were supersensitive to behavioural effects of DAergic drugs, whereas mice lacking the closest relative of GRK6, GRK5, were not (Gainetdinov et al., 1999, 2003, 2004). The data strongly suggest that GRK6 is primarily responsible for desensitization of DA receptors. Furthermore, the data support the notion that loss of GRK6 results in enhanced responsiveness of DA receptors to DAergic stimulation.

When DAergic neurons degenerate in PD or in animal models of PD, striatal dopaminergic neurons put into place a number of adaptive mechanisms aimed at maintaining the failing signalling (Bezard and Gross, 1998). One effective adaptive response would be a reduction in the level of GRKs. Indeed, in hemiparkinsonian rats, the level of GRKs in the lesioned striatum is decreased, as compared to the intact side, most noticeably that of GRK6 and GRK3 (Ahmed et al., 2008a, 2010). Such effect could be considered adaptive, because it counteracts the effect of the DAergic lesion, allowing, due to resulting DA receptor supersensitivity, for the signal transmission even with the grossly reduced concentration of DA. Importantly, this reduction in the GRK concentration was not reversed by chronic L-dopa treatment (Ahmed et al., 2008a, 2010). GRK6, presumably the main isoform regulating DA receptors, was consistently reduced by DA depletion across striatal subdivisions. The decrease of GRK6A, the splice variant most abundant in the rat brain at the mRNA level (Firsov and Elalouf, 1997) (the protein levels were never compared), reached ~40%, whereas GRK6B splice variant was only marginally reduced (Ahmed et al., 2010). The GRK concentration also tended to be lower in post-mortem striatal samples from PD patients without dementia (Bychkov et al., 2008), which might be the result of years of L-dopa treatment and associated with LID, since the samples were mostly from end-stage patients. Interestingly, in MPTP-treated parkinsonian drug-naïve monkeys, GRKs, particularly GRKs 2 and 6, were elevated as compared to control, and chronic L-dopa reduced the expression to normal in both non-dyskinetic and overtly dyskinetic animals (Bezard et al., 2005). It is conceivable that in this case the increase in the GRK concentration was a part of the pathological process aggravating signalling deficiency. The L-dopa treatment reverts the defect by reducing the GRK concentration, but at the same time the GRK availability could have become grossly insufficient during high signalling periods at the peak of L-dopa concentration. Overall, the background of low GRK availability relative to the demand at the time of high DA concentration generated from peak-dose L-dopa is likely to be a contributing factor to signalling abnormalities associated with peak-dose LID.

This idea was tested by studying the effect of *in vivo* knockdown of GRK6 in the lesioned striatum of hemiparkinsonian rats using LV-delivered miRNA (Ahmed et al., 2010). The reduction in the GRK6 achieved by such knockdown was slightly less than 40% for both GRK6A and GRK6B proteins. The GRK6 knockdown strongly enhanced the frequency of L-dopa-induced contralateral rotations and promoted behavioural sensitization to L-dopa, the phenomenon relevant for LID. Furthermore, rats with reduced GRK6 concentration demonstrated increased frequency of AIMs (Ahmed et al., 2010). These data further support the notion that a deficit in GRK availability, specifically that of GRK6, leads to defective desensitization, enhanced signalling, and ultimately, promotes LID-like behaviour. The fact that a relatively modest loss of GRK6 was sufficient to significantly affect behaviour underscores the critical contribution of the GRK-dependent regulation of the DAergic signalling to LID.

If reduced GRK concentration aggravated LID, then increased GRK availability should ameliorate it. The study employing

LV-mediated overexpression of GRK6A in the DA-depleted striatum showed that increased GRK6 concentration resulted in reduced frequency of L-dopa-induced rotations and lower AIMs scores (Ahmed et al., 2010, 2015). The behavioural improvement was accompanied by amelioration of molecular hallmarks of LID: characteristic upregulation of prodynorphin and preproenkephalin (PPE-A) mRNA and the D₃R concentration in the caudate–putamen were all significantly reduced in the GRK6-expressing rats as compared to the GFP-expressing control (Ahmed et al., 2010) as well canonical and non-canonical signalling pathways (Ahmed et al., 2015). Furthermore, lentiviral overexpression of GRK6 in the putamen of MPTP-lesioned monkeys rendered dyskinetic by chronic L-dopa treatment significantly ameliorated peak-dose LID (Ahmed et al., 2010). As in the case of the rodent model of LID, the behavioural improvement was accompanied by a reduction in the level of prodynorphin mRNA, which was elevated in L-dopa-treated animals. Thus, the data in both the rodent and monkey models of LID support the anti-LID potential of GRK6.

GRK6 is likely to alter the DA-dependent behaviour by facilitating desensitization of DA receptors. This notion is supported by the fact that trafficking of the D₁R is markedly improved in the lesioned striatum of rats expressing GRK6, whereas the D₂R was unaffected (Ahmed et al., 2010). These data appear to be inconsistent with the previous finding in GRK6 knock-out mice. Indeed, behavioural supersensitivity to psychostimulants in these animals seems provoked through a modified signalling via the D₂R but not the D₁R (Gainetdinov et al., 2003). As explained at length in previous sections, DA depletion and subsequent LID development in the course of L-dopa treatment precipitates dramatic changes in the function of striatal DA receptors that become supersensitive to DAergic stimulation (Brown et al., 2005; Bychkov et al., 2007; Cai et al., 2000; Corvol et al., 2004; Gerfen, 2000; Gerfen et al., 2002; Pifl et al., 1992a,b; Ravenscroft et al., 2004; Sgambato-Faure et al., 2005; Tong et al., 2004; Ungerstedt, 1971b; see also Gurevich and Gurevich, 2010 and references therein). It is generally believed that both major receptor subtypes contribute to LID, but the D₁R seems to play a particularly important role (Aubert et al., 2005; Berthet et al., 2009; Guigoni et al., 2005a, 2007), and multiple aberrations in D₁R signalling are readily detectable in the brain of dyskinetic animals (Aubert et al., 2005; Berthet et al., 2009; Gerfen, 2000; Gerfen et al., 1990, 1991, 2002, 1995; Guigoni et al., 2007). In the dyskinetic monkey, LV-mediated expression of GRK6 reduced LID caused by either the selective D₁R agonist SKF 38393 or the D₂R agonist ropinirole, indicating that its anti-LID effect was mediated via both receptor subtypes (Ahmed et al., 2010). The suppression by GRK6 of the L-dopa-induced upregulation of prodynorphin and D₃R receptor mRNA in hemiparkinsonian rats and prodynorphin elevation in parkinsonian monkeys also support the notion of GRK6 acting at the D₁R, since both effects are attributed to the enhanced D₁R signalling (Bordet et al., 1997; Gerfen et al., 1990, 1991). Although no GRK6-induced increase in the D₂R internalization was detected, GRK6 reduced the upregulation of preproenkephalin mRNA expressed in D₂R-bearing neurons (Gerfen et al., 1990, 1991; Le Moine and Bloch, 1995; Morissette et al., 1997), which suggests a GRK6 effect at the D₂R. Thus, the data in the rodent and monkey models of LID collectively point to the involvement of both D₁R and D₂R in the anti-LID action of GRK6.

However, studies in living animals cannot prove that the effect is direct. Since the change in the D₁R trafficking in the rat model was observed, this would suggest a direct GRK6-dependent phosphorylation of the D₁R followed by arrestin binding and intracellular trafficking. The lack of a similar effect on the D₂R leaves room for doubt. However, receptor desensitization may not necessarily be accompanied by internalization (Pan et al., 2003) and trafficking measures could be underestimating the degree of

desensitization. Alternatively, D₂R could be less affected by GRK6, since they are known to be resistant to desensitization (Kim et al., 2001; Tiberi et al., 1996). The data in the monkey model bears out this suggestion. When the animals were treated with selective D₁R or D₂R/D₃R agonists instead of L-dopa, transgenic GRK6 not only suppressed LID but also shortened the overall duration of their effects, including the anti-parkinsonian activity. This mode of action is likely reflective of faster and more profound receptor desensitization due to increased GRK6 availability. GRK6 had only a marginal effect on the duration of D₂R-mediated effects, whereas it substantially shortened that of the D₁R agonist, which again supports the notion of the D₁R as the prime target of GRK6. It is important to bear in mind that striatal neurons express other non-DA GPCRs that modulate LID and could be affected by GRK6. It is possible that the effect of GRK6 on the D₂R-dependent signalling is in fact indirectly mediated by other receptors, such as, for example, the adenosine A_{2A} receptor. The inactivation or inhibition of the A_{2A} receptor is known to modestly ameliorate LID and/or provides limited anti-parkinsonian benefits in parkinsonian animals and humans (Fredduzzi et al., 2002; Lundblad et al., 2003; Pinna et al., 2001; Xiao et al., 2006) (see ad hoc sections). GRK6-dependent desensitization of the A_{2A} receptor would mimic its inactivation bringing about anti-LID and signalling benefits associated with reduced A_{2A} signalling. The inhibition of the lesion-induced upregulation of enkephalin by GRK6 may be the result of such suppression of A_{2A} receptor activity, similarly to the action of the A_{2A} antagonist KW-6002 (Lundblad et al., 2003).

The biggest stumbling block in the development of viable anti-LID therapies has been separating therapeutic and dyskinetic effects of L-dopa. Both functions of the drug are mediated by DA receptors, and over the years of therapy the anti-parkinsonian and dyskinetic effects become so intertwined, that reducing LID may mean losing anti-parkinsonian effect as well. Remarkably, GRK6 suppresses LID in dyskinetic monkeys without compromising the anti-parkinsonian effects of L-dopa. In fact, GRK6 prolongs the anti-parkinsonian effect, especially at the lower L-dopa dose. The duration of the anti-parkinsonian effect of the half-dose in GRK6-expressing animals was even slightly longer than that of the full L-dopa dose in controls. Importantly, the additional time afforded by GRK6 was LID-free (Ahmed et al., 2010). Mechanistically, preservation of the anti-parkinsonian activity coupled with reduced LID likely stems, at least, in part, from GRK selectivity towards active GPCRs (Boguth et al., 2010; Huang et al., 2009, 2011a; Huang and Tesmer, 2011). This initial signalling may be sufficient for the anti-parkinsonian effect but receptor desensitization process prevents it from rising high enough to cause LID. This is hardly surprising, because the receptor desensitization machinery is designed to achieve precisely this effect: to limit the duration and intensity of the signal following receptor activation but not to prevent the signalling event. Additionally, GRK6-dependent rebalancing of the striatal circuitry may also play a beneficial role. The fact that GRK6 extended the anti-parkinsonian effect of L-dopa while shortening that of both D₁R and D₂R selective agonists may be due to the action of L-dopa-derived DA at both D₁R and D₂R. If GRK6 mostly desensitized D₁R, it would shift the overall signalling balance in favour of the D₂R-mediated signalling, reducing the D₁R-dependent LID but sustaining the beneficial effect through still active D₂R. Thus, the receptor desensitization mechanism seems like a perfect target when there is a need to rebalance the runaway signalling. Indeed, the data in the monkey model of PD prove that targeting the receptor desensitization machinery for anti-LID therapy may help to reach an elusive goal of controlling LID without sacrificing the anti-parkinsonian benefits of L-dopa.

GRK-mediated receptor phosphorylation leads to arrestin binding that shields the cytoplasmic surface of the receptor, precluding further G protein activation (Krupnick et al., 1997;

Wilden, 1995). Complete GPCR shutoff is thus achieved only after arrestin binding. In addition to G-protein mediated signalling, many GPCRs, including DA receptors, signal through β -arrestin dependent mechanisms (Beaulieu et al., 2007; Lefkowitz and Shenoy, 2005). The two isoforms of β -arrestin, β -arrestin1 (β arr1) and β -arrestin2 (β arr2) are widely co-expressed in the brain (Attramadal et al., 1992; Gainetdinov et al., 2004). It is now apparent that β -arrestins regulate physiology and behaviours that are independent of G protein signalling through their ability to scaffold multiple intracellular signalling molecules such as kinases and phosphatases (Beaulieu et al., 2007; Lefkowitz and Shenoy, 2005; Luttrell et al., 1999; Xiao et al., 2007). Studies from Marc Caron's laboratory have shown that through D₁R and D₂R, β arr2-mediated signalling plays a major role in DA-dependent locomotion (Beaulieu et al., 2005, 2007; Urs et al., 2011), raising the possibility that targeting β arr2 function in the DA system might be ideal since through its scaffolding of kinases it can facilitate locomotion and simultaneously through its desensitization of G protein signalling reduce dyskinesia, without potentially affecting other neurotransmitter systems. In a recent study, Urs and co-workers provided evidence supporting the hypothesis that up-regulating β arr2 expression not only ameliorates LIDs but also enhances the therapeutic effects of L-dopa (Urs et al., 2015). Four different animal models of PD and LIDs were used to support this notion – (i) the bilateral DA-deficient DAT-knock-out (DDD) mouse model (cf. Section 3.4) (Sotnikova et al., 2006), (ii) the unilateral 6-hydroxydopamine (6-OHDA)-lesioned mouse model (cf. Section 3.3.2), (iii) the unilateral 6-OHDA-lesioned rat model (cf. Section 3.3.1) and (iv) the bilateral MPTP-lesioned macaque model of PD (cf. Section 3.6.2) (Urs et al., 2015). Using these various animal models, Urs and co-workers showed that deletion of β arr2 enhances LIDs and reduces forward locomotion but that over-expression of β arr2 in the motor striatum reduces AIMs or LIDs and enhances the therapeutic effects of L-dopa both in rodent and primate models (Urs et al., 2015). Understanding of the pleiotropic actions of arrestins upon signalling, which parallel the canonical and non-canonical signalings through G protein, has led to the development and application of the concept of biased signalling or functional selectivity. Evidence from the literature has shown that individual signalling pathways through the same receptor have the ability to mediate distinct physiological responses. Moreover, targeting these specific signalling pathways affects specific physiological outcomes without affecting others. Thus leveraging functional selectivity to exploit this dichotomous signalling might prove to be ideal for PD therapy. In the future, either generating allosteric G protein biased antagonists at D₁Rs as a supplement to L-DOPA or generating β -arrestin biased agonists at D₁R and/or D₂R might mimic the actions of L-dopa without inducing dyskinesia.

When DA receptors are completely desensitized with arrestins preventing further coupling to G proteins, previously generated active G proteins may still persist and activate downstream targets. However, neither DA depletion nor subsequent L-dopa treatment altered the expression of RGS9-2 in the monkey striatum (Gold et al., 2007). No changes were seen in other RGS proteins (RGS2, 7, 4 or in the level of RGS anchoring protein G β 5) abundant in the striatum of this model (but see the increase in RGS4 in dyskinetic unilateral 6-OHDA-lesioned rat (Ko et al., 2014b)). Nevertheless, viral upregulation of RGS9-2 resulted in reduced LID coupled with preservation of the anti-parkinsonian effect of L-dopa in dyskinetic MPTP-lesioned monkeys and in the reduction in AIMs scores in hemiparkinsonian rats (Gold et al., 2007). Importantly, the magnitude of the RGS9-2-dependent effects was considerably smaller than that observed in the experiments with GRK6. The likely reason is that RGS9-2 selectively binds to and accelerates deactivation of G α i, but not G α s/olf (Rahman et al., 2003; Ross and Wilkie, 2000). Thus, RGS9-2 quenches the signalling via the Gi-coupled D2 receptor but not via Gs/olf-coupled D₁R, whereas

GRK6 apparently acts via both DA receptors. Since the D₁R deregulation is believed to make the leading contribution to molecular mechanisms responsible for LID (Aubert et al., 2005; Berthet et al., 2009; Feyder et al., 2011; Guigoni et al., 2005a, 2007), targeting exclusively the D₂R is less effective than targeting both. Nevertheless, facilitating the RGS9-2-dependent quenching of the Gi-dependent signalling offered substantial anti-LID benefits in the monkey model of LID, proving that RGS-dependent desensitization of the DA receptor signalling is a critical component of the signalling homeostasis in striatal neurons, and its deregulation is likely to be a part of LID pathophysiology.

In the same way, although less documented, is the putative role of RGS4. As indicated above, RGS4 mRNA was recently found increased in the striatum of the rat analogue of LID, even correlating with peak-dose AIMs (Ko et al., 2014b). Interestingly, suppressing the elevation of RGS4 mRNA levels using an antisense oligonucleotide in the striatum during L-dopa priming attenuates the behavioural and molecular markers of AIMs in 6-OHDA-lesioned rats (Ko et al., 2014b). While the LID severity reduction after overexpression of striatal RGS9-2 in MPTP-lesioned monkeys is specifically related to the attenuation of D₂R (Gold et al., 2007), the question of the identity of the GPCR(s) responsible for this RGS4 effect arises. The effect of RGS4 protein modulation on reduced physiological expression of AIMs may be mediated through mGluR5 receptor interactions (Schwendt and McGinty, 2007). In support of this, a study demonstrated that overexpression of RGS4 proteins in the rat dorsal striatum modulated the mGluR5-mediated activation of p-ERK1/2, mimicking the molecular effects of mGluR5 receptor antagonist, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) on dopaminergic agents (Schwendt et al., 2012). Intriguingly, the molecular effects of suppressing the up-regulation of RGS4 mRNA levels during L-dopa priming i.e. reduced striatal up-regulation of preproenkephalin (PPE)-B, but not PPE-A, mRNA, i.e. indicative of a normalization of LID-related markers in the direct pathway D₁R-expressing neurons are similar to those found following combined de novo treatment of MTEP and L-dopa in 6-OHDA-lesioned rats (Mela et al., 2007). A study also demonstrated that endogenous RGS4 protein levels are involved in striatal LTD, where it was shown that RGS4 proteins mediate sophisticated cross-talk interactions between several GPCRs, such as mGluR group I, dopamine D₂R and adenosine A_{2a} receptors (Lerner and Kreitzer, 2012). This same study also showed that high levels of RGS4 proteins blocked LTD in striatopallidal neurons. It is therefore reasonable to suggest that the persistent up-regulation of striatal RGS4 in L-dopa priming in 6-OHDA-lesioned rat may contribute to an abnormal striatal plasticity in the development of L-dopa-induced AIMs, i.e. loss of LTD regulation (Belujon et al., 2010), the specific mechanisms of which are worthy of further investigation, notably because of the absence of normalization of LID-enhanced PPE-A mRNA levels.

To summarize, known molecular mechanisms of action of GRKs and arrestins suggest that these proteins play a key role in neuronal adaptations, including changes in signalling caused by DA depletion and subsequent L-dopa therapy. The role of RGS proteins in the signalling aberrations associated with LID also deserves attention. Unfortunately, mechanistic information regarding the precise role of GRKs, arrestins, or RGSs in the physiological processes associated with these signalling adaptations is currently very limited. GRK6 appears to be the best therapeutic target with proven efficacy in both rodent and monkey models of LID. Furthermore, as a kinase, GRK6 is a “druggable” target. As a group, kinases are second only to GPCRs as drug targets (Cohen, 2002; Melnikova and Golden, 2004). At the moment, there are no drugs selectively aimed at GRK6 or even at the whole GRK4 subfamily, which includes GRKs 4, 5, and 6. Furthermore, for this particular purpose an activator rather than inhibitor would be needed. To the best of our knowledge, no drug that enhances the activity of any GRK has been found (yet). This is

perhaps not surprising, given the mode of the drug discovery effort for kinases that so far targeted mostly the kinase domain in search for kinase inhibitors (Fischer, 2004; Ma et al., 2008; Melnikova and Golden, 2004; von Ahlsen and Bömer, 2005). The approach has now been expanded to incorporate allosteric type regulators that could act as activators as well as inhibitors (Eglen and Reisine, 2011; Simpson et al., 2009). For GRKs, targeting the GRK-receptor interface offers the best opportunity to find isoform-selective modulators enhancing or inhibiting their activity, although this is by no means a trivial task. Alternatively, drugs regulating the expression, and/or stability of GRKs, arrestins, or RGSs could be developed. Pathway biased agonists for DA receptors that preferentially engage GRK-mediated receptor phosphorylation and arrestin binding are becoming available (Shukla et al., 2011; Violin and Lefkowitz, 2007; Zidar et al., 2009) and can be further developed. Since the receptor desensitization system is a natural mechanism designed to adjust GPCR responsiveness to the intensity and duration of receptor stimulation, manipulation of its capacity is able to yield a precisely fine-tuned regulation of the signalling that could be exploited for efficacious anti-LID therapy.

4.9.6. Dysregulation of lateral diffusion

As reported above, D₁R is actively anchored at membrane despite high extracellular levels of DA. While impairment of homologous desensitization might certainly account for a significant part of the phenomenon, we should envision as well the possibility that surface diffusion of DA receptors, i.e. away from the signalling area on the neck of the spines, plays an important role as well. The membrane distribution of DA and glutamate receptors at the neuronal surface has indeed been found to be highly dependent on their lateral diffusion properties, which in turn has a huge impact upon their function. Schematically, the measurement of receptor trafficking in neurons greatly benefited from both experimental and conceptual advances made in the field of biophysics and high-resolution imaging (Giepmans et al., 2006). Singer and Nicolson proposed in the 1970s that the plasma membrane is a two-dimensional oriented solution of integral proteins embedded in a viscous ‘phospholipid bilayer’ (Singer and Nicolson, 1972). Proteins move passively within the plasma membrane, through thermal motion of surrounding molecules (i.e. phospholipids), which randomly and continuously change both direction and speed. Experimental evidences have now shown that interactions with obstacles in or beneath the membrane are mostly responsible for the lower value of diffusion where compared to the theoretical one in reconstituted membrane. Of importance in physiology, temperature is a critical factor that influences diffusion within membrane. For instance, a temperature change of 10–15 °C induces approximately a 2-fold change in protein diffusion coefficient within plasma membrane (Axelrod et al., 1976; Tardin et al., 2003). At the experimental level, the surface trafficking of receptors in neurons was demonstrated and monitored by several approaches, ranging from classical electrophysiological recordings to single particle tracking and ensemble imaging approaches (e.g. fluorescent recovery after photobleaching). To date, the lateral diffusion at the neuronal surface has been demonstrated for all explored neurotransmitter receptors or membrane proteins, which include glutamatergic mGlu5, AMPA and NMDA receptors (Ashby et al., 2006; Borgdorff and Choquet, 2002; Groc et al., 2004, 2006; Tardin et al., 2003), glycine receptor (Dahan et al., 2003; Meier et al., 2001), GABA-A receptor (Bouzigués and Dahan, 2007), β₂-adrenergic receptor (Hegener et al., 2004), μ-opioid receptor (Lober et al., 2006). Several reviews have been published on that topic (Bard and Groc, 2011; Choquet and Triller, 2013; Gerrow and Triller, 2010; Ladepeche et al., 2014; Triller and Choquet, 2008).

Regarding the trafficking of surface D₁R, the first study exploring D₁R surface mobility used an ensemble approach in which intracellular and surface D₁R were examined and displayed

that the majority of dendritic D₁R diffused in the plane of the membrane and their mobility was confined by interaction with NMDA receptors (Scott et al., 2006). Using single nanoparticle tracking of solely surface D₁R, Porras et al. and directly demonstrated that D₁ receptor is indeed quite dynamic at the surface of striatal neurons (Porras et al., 2012a). In basal condition, more than 80% of surface D₁R was mobile at the surface of striatal neurons. D₁Rs explore large dendritic area, exchanging from various membrane compartments, including glutamate synapses, at a rather high frequency. Exposure to NMDA reduced the diffusion coefficient for D₁ receptor and caused an increase in the number of D₁R-positive spines (Scott et al., 2006), a situation highly reminiscent of the elevated extracellular levels of glutamate (Robelet et al., 2004) and DA (Lindgren et al., 2010; Meissner et al., 2006) associated with LID. The functional interplay with NMDA receptor can be direct through protein-protein interaction (Cahill et al., 2014; Lee et al., 2002; Scott et al., 2006) or indirect through the PSD-95 protein that interacts and regulates D₁R membrane content (Fiorentini et al., 2003; Yao et al., 2008; Zhang et al., 2007).

The scaffold protein PSD-95 is at the crossroad of glutamate and DA signal modulation (Kim and Sheng, 2004), especially as glutamatergic and DA terminals form the so-called “synaptic triad” at postsynaptic dendritic spines in the striatum (Yao et al., 2004). Lowering PSD-95 levels in neurons increased the overall surface diffusion of D₁R and decreased their surface membrane content (Porras et al., 2012a). Comparable effects were obtained with a TAT-D₁R/PSD95 peptide that prevents the direct interaction between D₁R and PSD-95 (Porras et al., 2012a). This supports the proposition that PSD-95-D₁R interaction governs D₁R surface dynamics in the extrasynaptic compartment. Whether this holds in striatal glutamate synapses remains however unknown. In addition, it cannot be excluded that PSD-95 alters D₁R intracellular trafficking (exocytotic or endocytotic rate) and surface delivery (Fiorentini et al., 2003; Yao et al., 2008; Zhang et al., 2007), which will consequently modulate the dynamics of the surface receptors.

To shed new lights on these issues, studies have been performed, mostly in hippocampal neurons. They schematically demonstrated that D₁Rs laterally diffuse within glutamate synapses, with lower speed (Ladepeche et al., 2013a). The disruption of the interaction between D₁R and PSD95, using variants of PSD95 or D₁R/PSD95 interaction competing peptides, did however not affect D₁R dynamics in glutamatergic synapses (Ladepeche et al., 2013b). Strikingly, preventing the physical interaction between D₁R and the GluN1 subunit of NMDA receptors, using a competing peptide, fully abolished the synaptic stabilization of diffusing D₁R, indicating that D₁R are dynamically retained in glutamate synapse through a mechanism requiring the interaction of the receptor with NMDA receptor (Ladepeche et al., 2013a,b). Such single nanoparticle studies demonstrate that the physical interaction between D₁R and NMDA receptors participate to this cross-talk since the capacity of a glutamate synapse to retain DA receptors, and thus to express DA receptor-mediated signalling, is dependent on their dynamic interaction. Consistently, the direct interaction between D₁R and NMDA receptors has been shown to regulate glutamate synaptic transmission, plasticity, and working memory in rodents (Ladepeche et al., 2013a; Nai et al., 2010). It will be of great interest to investigate the role of the DA and glutamate release on D₁R synaptic anchoring by NMDA receptor, since this molecular dynamic cross-road could serve as a physiological integrator of the DA and glutamate system overall activities. In addition, whether such molecular mechanisms apply to striatal networks, as a whole or in a specific subset of glutamate synapses are key questions that remain to be addressed. Finally, direct other interactors of D₁R are present at the plasma membrane of neurons, including D₂R, D₃R, adenosine A₁ receptor, and N-type

calcium channel (Fiorentini et al., 2008; Gines et al., 2000; Kisilevsky et al., 2008; Marcellino et al., 2008), providing potential other mechanisms for stabilization in different membrane compartments. Dissecting the timing and role of these interacting cascades will likely shed new key lights on the regulation of D₁R surface trafficking and interplay with the glutamatergic signalling in physiology and pathology such as LID.

4.9.7. D₁ receptor stimulation impairs striatal proteasome activity

The above sections presented the complex alterations in DA signalling in D₁R-expressing MSNs supporting the development or expression of LID. Among those, the dysregulation of D₁R expression, lateral diffusion, intraneuronal trafficking, subcellular localization and desensitization that all lead to a pathological anchorage of D₁R at the plasma membrane (Aubert et al., 2005; Berthet et al., 2009, 2012; Guigoni et al., 2007; Porras et al., 2012a).

Parallel to these efforts, experimental evidence has accumulated suggesting that the proteasome plays a significant role in neurotransmitter response and synaptic plasticity in physiological and pathological conditions (Bingol and Schuman, 2006; Citri et al., 2009; DiAntonio and Hicke, 2004; Patrick et al., 2003). Interestingly, a reduced proteasome activity has been observed in PD patients under treatment with L-dopa and DA agonists in peripheral blood lymphocytes (Blandini et al., 2006). Building upon this seminal information, Berthet et al. demonstrated that such decreased proteasomal catalytic activity resulted into the D₁R abnormal trafficking, i.e. its exaggerated cell surface abundance (Berthet et al., 2012). In addition, impairment of the ubiquitin-proteasome system at specific nodes (E3 ligase parkin, poly-ubiquitination, proteasome catalytic activity) in several experimental models of PD led to the same phenomenon, i.e. aberrant behavioural response to DA replacement therapy in PD (Berthet et al., 2012). While those data highlighted the intimate interplay between DA receptor and proteasome activity, the precise mechanisms by which L-dopa affects striatal proteasome activity remained unknown. Such rapid modulation of striatal catalytic activity actually intervenes through D₁R-mediated disassembly of the 26S proteasome in the absence of changes in proteasome subunits expression (Barroso-Chinea et al., 2015), further highlighting the extremely complex impact of L-dopa upon MSNs.

A fascinating resulting hypothesis posits that L-dopa, through impairment of proteasome catalytic activity, would lead to accumulation of undegraded proteins. Scholz et al. hence studied the proteome in DA-depleted striatum of macaque monkeys with and without subsequent acute and chronic L-dopa treatment using two-dimensional difference in-gel electrophoresis and mass spectrometry (Kultima et al., 2006; Scholz et al., 2008). Their data suggested that the DA-depleted striatum is actually so sensitive to de novo L-dopa treatment that the first ever administration alone is able (i) to induce rapid post-translational modification-based proteomic changes that are specific to this first exposure and (ii), possibly, lead to irreversible protein level changes that would not be further modified by chronic L-dopa treatment (Kultima et al., 2006; Scholz et al., 2008). The equivalence between first and chronic L-dopa administration suggests that priming would be the direct consequence of L-dopa-driven impairment in catalytic proteasomal activity (Scholz et al., 2008). An alternate and/or complementary hypothesis involves the D₁R-mediated effect on protein translation discussed above.

4.9.8. Glutamate receptors

In the last decade, several studies indicated that dysfunction of the glutamatergic system plays a key role both in both PD and LID (Calabresi et al., 2010). Alterations in the corticostriatal glutamatergic transmission have been reported not only in animal models of PD and LID (Mellone and Gardoni, 2013; Sgambato-Faure and

Cenci, 2012), but also in PD patients at different disease stages (Ahmed et al., 2011). In particular, the subcellular organization and the functional interactions of glutamate receptors in the striatum appear to be critical both in the pathogenesis of PD and in the onset of LID.

4.9.8.1. NMDA receptors. After chronic treatment with L-dopa, the glutamatergic signalling from the cortex to the striatum undergoes adaptive changes, which lead to an aberrant functioning of NMDA receptors at striatal MSN dendritic spines. NMDA receptor antagonists have been shown to exert a beneficial effect in blocking the development of dyskinesia in experimental models of LID (Hadj Tahar et al., 2004; Nash et al., 2004; Wessell et al., 2004), even though conflicting findings also have been also reported (Nash et al., 2004; Rylander et al., 2009).

Besides NMDA receptor over-activation, alterations in the trafficking and localization of NMDA receptor regulatory subunits at the postsynaptic membrane have been shown in several neurodegenerative disorders (Mellone and Gardoni, 2013; Sanz-Clemente et al., 2013). Consequently, restoring the physiological synaptic NMDA receptor subunit composition could represent an innovative therapeutic strategy to be explored in the close future. A great number of studies have focused on the role of the synaptic distribution and the phosphorylation state of specific NMDA receptor subtypes in animal models of LID. Changes in the localization of NMDA receptor subunits at the striatal synapse have been described in both DA-denervated rats (Picconi et al., 2004) and L-dopa-treated dyskinetic macaques (Hallett et al., 2005), even though the mechanisms regulating NMDA receptor trafficking and function in experimental parkinsonism and LID are far from being elucidated. In physiological conditions, GluN2B-containing NMDA receptors are the major subtype at MSN synapses. However, in L-dopa-treated dyskinetic rats, GluN2B is redistributed to the extrasynaptic membrane, while the synaptic levels of GluN2A are aberrantly increased in the striatum (Gardoni et al., 2006). These events are paralleled by modifications in the association of GluN2B subunit with members of the PSD-MAGUKs family. Moreover, treatment of non-dyskinetic animals with a cell-permeable peptide (CPP) able to reduce the synaptic localization of GluN2B-containing NMDA receptors caused the appearance of dyskinetic behaviours, confirming the importance of a correct balance in NMDA receptor regulatory subunits at synaptic sites (Gardoni et al., 2006). Interestingly, NMDA receptor regulatory subunits might not be the only ones in the spotlight. Indeed D₁R–GluN1 complexes have been uncovered as a major substrate for DA–glutamate interaction in MSNs, which is usurped by psychostimulants (e.g. L-dopa in PD patients) to lead to abnormal signalling and persistent behavioural alterations (Cahill et al., 2014).

The role of PSD-MAGUKs in dyskinesia has also been investigated. More specifically, Nash et al. suggested that the onset of LID is associated with the increase in PSD-95 and SAP97 proteins at the synaptic membrane (Nash et al., 2005). This result was confirmed later in rodent and primate models of LID (Porrás et al., 2012a). Moreover, treatment with a CPP disrupting GluN2A/PSD-MAGUKs interaction demonstrated that a decrease in synaptic GluN2A-containing NMDA receptors induces a significant reduction in the onset of LID in 6-OHDA-lesioned rats (Gardoni et al., 2012).

Early work addressing modifications in the phosphorylation state of NMDA receptor subunits identified increased levels of GluN2B-ptyr1472 in different animal models of LID (Oh et al., 1998; Quintana et al., 2010), and suggested a reduction of AP-2-mediated endocytosis of GluN2B and the consequent increase in its surface content (Sanz-Clemente et al., 2013). For this reason, GluN2B-selective antagonists have been considered a promising

tool for the treatment of LID, but they were proved as difficult to develop due to the induced side-effects.

Overall, the number of studies which are reviewed here strongly substantiate the idea that, in the corticostriatal glutamatergic synapse, molecular disturbances of the NMDA receptor complex initially caused by DA denervation may have a causal role in the development of LID and can represent a target for therapeutic intervention.

4.9.8.2. AMPA receptors. AMPA receptors are highly dynamic in terms of phosphorylation and insertion/endocytosis at the postsynaptic membrane (Shepherd and Huganir, 2007). Therefore, understanding the molecular mechanisms that control the receptor trafficking is essential to determine AMPA receptor involvement in neurological disorders.

Alterations in synaptic AMPA receptor expression, subunit composition and phosphorylation have been observed in animal models of LID and in PD patients. An increase in AMPA receptor binding has been reported in the lateral striatum of dyskinetic animals (Calon et al., 2002; Ouattara et al., 2010b) and in PD patients (Calon et al., 2003). Enhanced AMPA receptor subunit phosphorylation and trafficking to striatal synapses have been also found in experimental models of LID (Ba et al., 2006; Santini et al., 2007; Silverdale et al., 2010). In particular, increased PKA-dependent phosphorylation of GluA1-S845, which is linked to the surface expression of AMPA receptors, has been also described in rodent (Ba et al., 2006; Errico et al., 2011; Santini et al., 2007) and macaque (Santini et al., 2010a) models of LID.

Modifications of AMPA receptor subunit composition have also been reported. A study described an alteration in the ratio between synaptic membrane-associated and vesicular GluA2/3 versus GluA1 subunits in a macaque model of LID (Silverdale et al., 2010). Notably, no changes in the total striatal levels of any AMPA receptor subunit were observed (Hallett et al., 2005; Silverdale et al., 2010), indicating the redistribution of the receptor subunits, in particular of GluA2/3, from the vesicular fraction to the postsynaptic membrane in dyskinesia (Silverdale et al., 2010). Moreover, calcium-permeable AMPA receptors and an increase in GluA1 and GluA2 flip isoforms have been involved in both the induction and subsequent expression of LID (Kobylecki et al., 2010, 2013).

Finally, aberrant function of AMPA receptors also appears to be involved in the induction of LID. Studies performed in preclinical dyskinesia models indicate that selective AMPA antagonists can be effective in reducing LID (Juranyi et al., 2004; Kobylecki et al., 2010; Konitsiotis et al., 2000), thus confirming a role for overactive AMPA receptor transmission in LID.

4.9.8.3. Metabotropic glutamate receptors (mGluRs). Considering their ability to finely modulate the excitatory synapse in the brain without blocking fast excitatory neurotransmission, mGluRs may represent a very interesting target for the treatment of LID (Gasparini et al., 2013; Sgambato-Faure and Cenci, 2012). Among the different mGluRs subtypes, mGluR5 is highly expressed in caudate, putamen and other basal ganglia nuclei, it has a postsynaptic subcellular distribution, and it represents one of the most promising targets to reduce the excessive glutamatergic transmission observed in PD and LID. Different experimental approaches have indicated an increase in mGluR5 expression in putamen and pallidum associated with LID in both non-human primate models of PD and patients (Ouattara et al., 2010a; Samadi et al., 2008). In the last 10 years, specific mGluR5 antagonists or Group II mGluR agonists were tested for their efficacy in improving motor behaviour in animal models of LID. Overall, these studies have shown that mGluR5 antagonists or negative allosteric modulators could reduce LID without affecting the therapeutic

effect of L-dopa. In particular, several mGluR5 negative allosteric modulators, such as MPEP, MTEP, fenobam, AFQ056, dipraglurant and PF470,14 were found to reduce peak-dose LID in animal models while preserving or even potentiating the anti-parkinsonian effect of L-dopa (Bezard et al., 2014; Dekundy et al., 2006; Gregoire et al., 2011; Johnston et al., 2010a; Maranis et al., 2012; Mela et al., 2007; Morin et al., 2010; Rylander et al., 2009; Zhang et al., 2014c). Differently from NMDA receptor antagonists, negative modulators of mGluR5 markedly attenuate D₁R-induced ERK_{1/2} activation in the DA-denervated striatum (Fieblinger et al., 2014b; Rylander et al., 2009). The modulatory role of mGluR5 in the striatal signalling in LID provides further rationale for pursuing anti-dyskinetic therapies that antagonize this receptor (Picconi and Calabresi, 2014).

Group III mGlu receptor agonists have also been studied with regard to their potential anti-parkinsonian and anti-dyskinetic properties (Amalric et al., 2013; Rylander et al., 2009). In particular, it was found that LID was attenuated in the mouse by the orthosteric mGlu4 receptor agonist, LSP1-2111 (Lopez et al., 2011), and in the rat by the PAM, Lu AF21934 (Bennouar et al., 2013). An extensive comparative analysis of the behavioural effects produced by the mGlu4 positive allosteric modulator VU0364770 and the mGlu4 orthosteric agonist LSP1-2111 in 6-OHDA rats showed that neither of the two compounds modified the development of dyskinetic responses elicited by chronic treatment with full doses of L-dopa (Iderberg et al., 2015a). In addition, when given together with L-dopa to rats with already established dyskinesias, neither VU0364770 nor LSP1-2111 modified the AIM scores (Iderberg et al., 2015a). Taken together, these results indicate that pharmacological stimulation of mGlu4 lacks intrinsic anti-dyskinetic activity.

4.9.9. Adenosine receptors

Adenosine A_{2A} receptor antagonists have emerged long ago as a potential treatment for PD. An interesting peculiarity of A_{2A} receptors is their selective localization in the indirect GABA/enkephalinergic striatopallidal pathway (Schiffmann et al., 1991), the stimulation of which leads to the inhibition of motor behaviour (Ferré et al., 1991). Interestingly, an increase in A_{2A} receptors in the striatum of 6-OHDA-lesioned rats and of MPTP-treated primates, as well as in PD patients chronically treated with L-dopa displaying dyskinesia might produce a prevailing tone of A_{2A} receptors, the activation of which interferes with motor activity (Brooks et al., 2010; Calon et al., 2004; Pinna et al., 2002; Ramlackhansingh et al., 2011; Tomiyama et al., 2004). Therefore, attenuation of the enhanced A_{2A} receptor tone could be one of the factors underlying the positive effects produced by A_{2A} receptor antagonists in PD. However the absence of A_{2A} receptors in the direct GABA/dynorphinergic striatonigral pathway, the efferent pathway consistently shown to be involved in dyskinesia, questions the relevance for management of established LID.

The results so far obtained with several A_{2A} receptor antagonists in rodent models of PD suggest indeed that A_{2A} receptor antagonists might have symptomatic therapeutic efficacy in early stages of PD when motor complication are not yet present (Pinna et al., 2007). In particular, studies in 6-OHDA-lesioned rats suggest that A_{2A} receptor antagonists, when administered alone, may ameliorate initiation of movement, gait, and muscle rigidity whilst simultaneously improving the sensorimotor integration deficits and tremor that characterize PD (Pinna et al., 2007; Salamone et al., 2008; Simola et al., 2004). While these drugs potentiate the efficacy of L-dopa co-administered at a low sub-threshold dose, A_{2A} receptor antagonists exhibit contrasted results on LID.

In rodents, A_{2A} receptor antagonists do not induce dyskinesia after chronic treatment and do not exacerbate the dyskinesia in

rats previously sensitized to L-dopa (Jones et al., 2013; Lundblad et al., 2003). They also prevent the development of the sensitization of rotational behaviour in 6-OHDA-lesioned rats (Hodgson et al., 2009; Pinna et al., 2001; Tronci et al., 2007) as well as in hemiparkinsonian A_{2A} knock-out mice (Fredduzzi et al., 2002; Xiao et al., 2006). None of these studies however established clearly a major anti-dyskinetic effect of A_{2A} receptor antagonists upon established AIMs (Lundblad et al., 2003) or LID (Bibbiani et al., 2003). Those mixed results were further confirmed in dyskinetic PD patients. While A_{2A} receptor antagonists have generally demonstrated that their addition to a stable L-dopa regimen reduces OFF time and increase ON periods (Hauser et al., 2008, 2011; LeWitt et al., 2008; Mizuno et al., 2010; Stacy et al., 2008), they do not improve established dyskinesia (Hauser et al., 2008, 2011).

Several conclusions can be drawn from these studies. Firstly, A_{2A} receptor antagonists do not attenuate LID. Secondly, they may delay LID appearance without affecting L-dopa therapeutic efficacy if L-dopa-sparing doses are used. Therefore A_{2A} receptor antagonists may be envisioned as a class of non-dopaminergic drugs that might act positively on PD motor symptoms and potentiate L-dopa therapeutic efficacy without having dyskinetic potential. Recently, a functional heteromer complex formed by A_{2A}, cannabinoid CB1 and DA D₂R (A_{2A}-CB1-D₂ receptor heteromers) has been unravelled. This heteromer, present in normal and DA-depleted striatum, is however lost following acute or chronic treatment with L-dopa in rats (Pinna et al., 2014) and monkeys (Bonaventura et al., 2014). Losing the heteromer complex would affect the proper signalling through the three receptors, rendering inefficient the A_{2A} antagonists.

A₁ receptor has received much less attention and offers contradictory results probably linked to the striatal expression of the receptor where it can antagonistically control activity of striato-nigral dMSNs. On one hand A₁ receptor knock-out mice developed less severe AIMs than wild-type littermates (Xiao et al., 2011) and on the other hand, A₁ receptor stimulation reduces D₁R-mediated GABAergic transmission from striato-nigral terminals and attenuates AIMs in 6-OHDA-lesioned mice (Mango et al., 2014).

4.9.10. Acetylcholine (ACh) receptors

Emerging work indicates that the nicotinic ACh system plays a role in LID. Studies in 6-OHDA-lesioned rats or MPTP-lesioned mice showed that nicotine reduced AIMs up to 60%, including axial, oral and forelimb AIMs (Bordia et al., 2008, 2010; Huang et al., 2011b,c; Quik et al., 2012a). The nicotine-induced decline in L-dopa-induced AIMs persisted with long-term treatment (months) and was observed with varying modes of nicotine treatment including systemic injection, slow-release minipumps or via the drinking water. Notably, there was no worsening of parkinsonism with nicotine administration. In addition, the effect of nicotine on LID has been investigated in MPTP-lesioned squirrel monkeys. These squirrel monkeys were given nicotine in the drinking water, a paradigm that readily lends itself to long-term treatment. Nicotine maximally reduced LID with 60–70% declines in both peak and total LID after several weeks (Quik et al., 2007, 2013c,d). Again, there was no detrimental effect upon parkinsonism. Nicotine led to a similar reduction in LID whether it was given to L-dopa naïve monkeys or animals with established LID; thus, nicotine can be used prophylactically or to reduce existing LID (Quik et al., 2007, 2013d). There was no tolerance to the nicotine-induced decline in LID for the entire study duration (up to 1 year). This is an important point as PD patients generally require life-long treatment with L-dopa (Quik et al., 2007, 2013d). Nicotine's anti-dyskinetic effect remained for several weeks after drug discontinuation, suggesting that long-term molecular changes underlie the improvement.

Studies with varying degrees of nigrostriatal damage showed that nicotine best reduced LID in animal models with a moderate nigrostriatal loss (Bordia et al., 2010; Quik et al., 2013c), suggesting it may not be that effective in late-stage PD.

These studies in animal models have been extended to the clinic; a small phase 1/2 trial in PD patients was recently conducted (NCT00957918). Results await publication in a peer-reviewed journal. Altogether, these findings suggest that nicotine may be useful for the treatment of LID in PD patients.

Nicotine generally exerts its CNS effects by acting at nicotinic ACh receptors (nAChRs), which are ligand-gated ion channel composed of five membrane-spanning subunits. The primary subtypes in mammalian brain are heteromeric $\beta 2^*$ and homomeric $\alpha 7$ receptors, with the asterisk indicating the presence of other nAChR subunits in the receptor complex (Albuquerque et al., 2009; Millar and Gotti, 2009; Quik and Wonnacott, 2011). The most populous subtypes in the basal ganglia are the $\alpha 4\beta 2^*$ and $\alpha 6\beta 2^*$ nAChRs, with $\alpha 7$ nAChRs expressed to a lesser degree (Albuquerque et al., 2009; Millar and Gotti, 2009; Quik and Wonnacott, 2011).

Studies with nAChR knock-out mice indicate that nicotine's anti-dyskinetic effect is mediated via multiple subtypes. $\alpha 6$ nAChR subunit knock-out mice, which lack $\alpha 6\beta 2^*$ nAChRs, had reduced baseline L-dopa-induced AIMs (Quik et al., 2012a). Furthermore, there was no decline in remaining AIMs with nicotine treatment in $\alpha 6$ nAChR knock-out mice compared to wild type mice (Quik et al., 2012a). Thus, nAChRs expressing the $\alpha 6$ subunit are important for both the generation of AIMs and the anti-dyskinetic effect of nicotine. Nicotine also did not reduce LID in $\alpha 4$ nAChR null mutant mice, although baseline AIM scores were unaffected in these mice (Quik et al., 2013b). These data indicate that both $\alpha 6\beta 2^*$ and $\alpha 4\beta 2^*$ nAChRs regulate AIMs although in a somewhat different fashion.

Experiments with $\alpha 7$ nAChR null mutant mice showed that these receptors modulated LID in a manner distinct from that by $\alpha 4\beta 2^*$ and $\alpha 6\beta 2^*$ nAChRs. First, there was an increase in baseline L-dopa-induced AIMs in $\alpha 7$ nAChR knock-out mice, suggesting that $\alpha 7$ nAChRs have an inhibitory impact (Zhang et al., 2013a). Second, nicotine treatment still decreased AIMs in $\alpha 7$ nAChR knock-out. The variable mode of regulation by $\beta 2^*$ and $\alpha 7$ nAChRs may arise because of their differential expression, molecular properties and functional characteristics. For instance, $\alpha 7$ nAChRs are more permeable to calcium, desensitize more rapidly and are linked to alternate intracellular signalling pathways compared to $\beta 2^*$ nAChRs (Changeux, 2010; Giniatullin et al., 2005; Picciotto et al., 2008; Quik et al., 2012b; Wonnacott et al., 2005). In summary, studies with genetically modified mice indicate that $\alpha 4\beta 2^*$, $\alpha 6\beta 2^*$ and $\alpha 7$ nAChRs are all involved in the occurrence of LID, although in distinct manners.

The data with nAChR knock-out mice led to studies testing the effect of nAChR drugs on LID. The general nAChR agonist varenicline reduced dyskinesia in both L-dopa-treated rats and squirrel monkeys, providing proof of principle that the effect of nicotine was nAChR-mediated (Huang et al., 2011c; Zhang et al., 2013a). A role for $\beta 2^*$ nAChRs is suggested from work with A-85380 and a series of Targacept compounds, which all reduced LID in 6-OHDA-lesioned rats (Huang et al., 2011c; Quik et al., 2013a). In addition, the $\beta 2^*$ nAChR agonist TC-8831 reduced LID in parkinsonian macaques and squirrel monkeys, with no worsening of parkinsonism (Johnston et al., 2013; Quik et al., 2013d). Same observation was made with other series with similar pharmacological properties (Zhang et al., 2014a). Determining the precise contribution of the $\alpha 4\beta 2^*$ and $\alpha 6\beta 2^*$ nAChRs to LID has not yet been possible using a pharmacological approach since available drugs act at both receptor subtypes. Studies with $\alpha 7$ nAChR agonists show that these drugs also reduce LID, suggesting that

multiple nAChR subtypes are involved (Di Paolo et al., 2014; Zhang et al., 2014b).

The somewhat paradoxical finding that nAChR agonists and the antagonist mecamylamine both reduce L-dopa-induced AIMs to a similar extent in parkinsonian rats has led to the suggestion that nAChR agonists reduce AIMs via nAChR desensitization (Bordia et al., 2010). This molecular event leads to a functional blockade similar to that observed with antagonists (Buccafusco et al., 2009; Corringer et al., 2006; Picciotto et al., 2008). Long term nicotine treatment also downregulated $\alpha 6\beta 2^*$ nAChRs (Lai et al., 2005). Thus both nAChR-induced desensitization and downregulation may underlie the nicotine-mediated reduction in LID. Dyskinesia are thought to arise because of L-dopa-mediated transient increases in striatal DA release, which leads to disproportionate DAergic stimulation (Carta and Bezard, 2011; Cenci, 2007a; Fisone and Bezard, 2011; Lindgren et al., 2010). Long term nicotine treatment has been shown to reduce striatal nAChR-mediated DA release (Bordia et al., 2013). These combined findings suggest that chronic nicotine treatment desensitizes and/or downregulates nAChRs, with a consequent decline in striatal DA release and subsequent improvement in LID (Bordia et al., 2013).

With respect to the localization of the nAChRs involved in regulating LID, $\alpha 4\beta 2^*$ and $\alpha 6\beta 2^*$ nAChRs on nigrostriatal DA terminals most likely play an important role. Data supporting this idea stems from experiments showing that the nicotine-mediated decline in LID is reduced or absent in animals with severe nigrostriatal damage (Bordia et al., 2013; Huang et al., 2011b; Quik et al., 2013b, 2012a). $\alpha 4\beta 2^*$ nAChRs at other striatal sites, as well as in other brain regions, may also be involved since nicotine is still partially effective in severely lesioned rats (Quik et al., 2013a). The CNS distribution of $\alpha 7$ nAChRs of relevance to the anti-dyskinetic effect of nicotine is currently not known (Quik et al., 2013b). The idea that nAChRs throughout the brain modulate LID expression is not unlikely since the striatal DAergic system is functionally integrated with numerous other neurotransmitter systems.

4.9.11. Peptidergic transmission

4.9.11.1. *Classic opioid transmission.* A role for enhanced peptidergic transmission, either opioidergic or not, has classically been proposed for the generation of LID on the basis of in situ hybridization studies showing that striatal peptidergic precursor expression consistently correlates with LID severity (Aubert et al., 2007; Cenci et al., 1998; Henry et al., 2003; Tel et al., 2002). Parkinsonian and dyskinetic states have been associated with different patterns of expression of precursors of the peptides extensively reviewed in prior contributions (Bezard et al., 2001a; Cenci and Konradi, 2010; Cenci et al., 1998; Jenner, 2008). Parkinsonism is associated with increased expression of the opioid precursor PPE-A mRNA in striatal neurons projecting to the GP in rodents (GPe in primates) and a decreased prodynorphin (PPE-B) mRNA expression in striatal neurons projecting to the SNr in rodents and primates and GPI in primates (Aubert et al., 2007; Cenci et al., 1998; Gerfen et al., 1990; Henry et al., 2003; Morissette et al., 1999; Nisbet et al., 1995; Quik et al., 2002a; Tel et al., 2002; Westin et al., 2001). In the dyskinetic state, expression of PPE-B mRNA is increased whereas PPE-A mRNA is unchanged versus controls, at least when the tissue was taken from animals killed at the peak of dyskinesia severity (Aubert et al., 2007). Interestingly the correlation points out that the striatum and the STN are two key structures, the latter displaying a near ectopic expression of PPE-B mRNA in the dyskinetic state (Aubert et al., 2007), a result in accordance with direct measurement of peptides in the GPI that receives PPE-B-derived peptides from the striatum and the STN (Bourdenx et al., 2014; Nadjar et al., 2006). Only few studies focused on the actual proteome and peptidome of both parkinsonian and dyskinetic

states, three were conducted in the 6-OHDA-lesioned-rodent model (Hanrieder et al., 2011; Nilsson et al., 2009; Valastro et al., 2007) and two in the MPTP-treated macaque model (Bourdenx et al., 2014; Scholz et al., 2008). These studies confirmed the results obtained from previous *in situ* hybridization-based studies. Moreover, the unbiased peptidomic approach led to the identification of previous unreported peptides deriving from the classic precursors, some of them being specific of a given structure and/or DA-tone dependent (Bourdenx et al., 2014; Klintonberg and Andren, 2005). However, the exact biological functions of these new endogenous peptides remain to be determined.

The peptides processed from the different precursors bind with various affinities to the three classes of opioid peptide receptors, which have an overall inhibitory action (Hollt, 1986; Law et al., 2000; Mansour et al., 1994; Sadee et al., 2005). Studies in rodents and macaques have shown an almost similar brain expression of the opioid peptide receptors in normal and pathological conditions (Aubert et al., 2007; Johansson et al., 2001; Mansour et al., 1994). The total binding of opioid receptors decreases in the brains of DA-denervated animals and patients (Aubert et al., 2007; Fernandez et al., 1994; Johansson et al., 2001) and further decreases in dyskinetic animals. In non-human primates, Aubert and colleagues reported a reduction in μ and κ receptor binding in the GPI correlating with dyskinesia severity (Aubert et al., 2007). It suggests that the more severe the LID, the more profound is the decrease in total opioid receptor, κ , and μ binding in the GPI, as shown in rats (Johansson et al., 2001) and in PD patients (Piccini et al., 1997), reflecting an increased release of peptides.

Despite a large research effort, enthusiasm has been dampened because, on the clinical side, the non-subtype-selective opioid receptor antagonist naltrexone and naloxone have failed in clinical trials, showing almost no anti-dyskinetic effects (Fox et al., 2004; Rascol et al., 1994). However, μ opioid receptor antagonists have been shown to efficiently reduce LID in non-human primate models without affecting the anti-parkinsonian action of L-dopa (Henry et al., 2001; Koprach et al., 2011; Potts et al., 2015), thus suggesting that subtype-selective agents would have a better clinical outcome. Taken together with the recent peptidomic-based results showing that regulation of peptidergic processing is highly structure-specific, this suggests that something more complex than a simple subtype-selective agent may be required to fully reverse the effects of the complex changes that occur in basal ganglia neuropeptide transmission in LID (Bourdenx et al., 2014).

If one imagines that μ opioid receptor antagonists might be beneficial against LID based upon the striking negative correlation between μ opioid receptor binding in GPI of AIM 6-OHDA-lesioned rats (Johansson et al., 2001) and dyskinetic MPTP-treated macaques (Aubert et al., 2007) and the increased presence of μ opioid receptor ligands in the same dyskinetic GPI (Bourdenx et al., 2014), a classic pharmacological treatment would undoubtedly act all over the brain and not specifically on the GPI. A preliminary study investigating the impact of intrastriatal versus intrapallidal administration of μ opioid receptor modulators unravelled that only intrapallidal administration is capable of improving LID in dyskinetic MPTP-lesioned macaques (Bezard, unpublished). Modulation of the opioid transmission would certainly become of interest when pharmacology would propose delivery methods enabling to target a given structure instead of the whole brain or if dual compounds are used, such as the mixed κ agonist/ μ antagonist analgesic nalbuphine that was reported to show antidykinetic properties in a primate model of LID (Potts et al., 2015).

Beyond the case of opioid peptides and their receptors, levels in endogenous morphine are regulated by both DA depletion and further L-dopa treatment (Charron et al., 2011). Morphine itself is

indeed endogenously synthesized in the central nervous system (Goumon et al., 2009; Stefano et al., 1996) and endogenous dopamine is thought to be necessary for endogenous morphine formation (Goumon et al., 2009; Stefano et al., 1996). The dramatic upregulation of neuronal endogenous morphine-like compound immunoreactivity and levels in experimental and human PD is only partially normalized by L-DOPA treatment (Charron et al., 2011). The functional consequences of such endogenous morphine upregulation in PD and LID are as yet unknown, but morphine being the natural μ opioid receptor ligand, it is tempting to speculate that endogenous morphine further dysregulate the opioid receptor signalling in LID.

4.9.11.2. N/OFQ-NOP system. Nociceptin/orphanin FQ (henceforth N/OFQ) is a new member of the opioid family discovered in mid 1990s by two separate groups of researchers who named it nociceptin (Meunier et al., 1995) or orphanin FQ (Reinscheid et al., 1995). N/OFQ is a heptadecapeptide with structural homologies with classical opioids, in particular dynorphin A, although the presence of a phenylalanine in its amino terminus instead of the “classical” tyrosine (as in opioid sequence) makes it unable to activate classical opioid receptors (μ , δ and κ) with high affinity (Calo et al., 2000b; Mogil and Pasternak, 2001). Indeed, N/OFQ is the endogenous ligand of the so-called Opioid Receptor Like 1 (ORL1) receptor, renamed N/OFQ peptide (NOP) receptor, which was cloned 1 year before the isolation of N/OFQ (Mollereau et al., 1994) and crystallized (Thompson et al., 2012). The NOP receptor is a classical GPCR which couples to Gi/o, leading to inhibition of cAMP accumulation, closing of voltage gated calcium channels, and opening of inwardly rectifier potassium (K^+) channels. These effects result in generally inhibitory actions over neuronal firing and neurosecretion. In addition, N/OFQ can activate mitogen-activated protein kinases, among which ERK (New and Wong, 2002).

Relevant to PD, the N/OFQ-NOP receptor system is highly expressed in the basal ganglia (Anton et al., 1996; Neal et al., 1999a,b). High levels of N/OFQ+ neurons and fibres were detected with *in situ* hybridization and immunohistochemistry in the GP, entopeduncular nucleus, and in SNr, while in striatum only few, scattered N/OFQ+ neurons were evident. The distribution of the NOP receptor substantially matches that of N/OFQ, with the exception of the subthalamic nucleus where high levels of NOP but only scattered N/OFQ+ neurons were found. Significant levels of N/OFQ immunoreactivity (Witta et al., 2004) and expression (Peluso et al., 1998), as well as N/OFQ binding and NOP receptor expression (Berthele et al., 2003) were also measured in the human basal ganglia. A notable difference between the human and rodent brain, is the high levels of NOP receptor/N/OFQ binding in the caudate/putamen, also observed in non-human primates (Bridge et al., 2003).

The NOP receptor is expressed in midbrain DAergic neurons of the ventral tegmental area and SNc (Norton et al., 2002), and sorted both to the somatodendritic and nerve terminal compartments. NOP receptor activation inhibits the firing of nigral DA neurons (Marti et al., 2004b) and striatal presynaptic DA release (Flau et al., 2002), an effect correlated with motor inhibition (Marti et al., 2004b).

The NOP receptor is a druggable receptor which has unique pharmacological properties with respect to the classical opioid systems, first of all the insensitivity to naloxone (Calo et al., 2000b). This peculiarity has contributed to the definition of NOP as a non-opioid member of the opioid receptor family. Since the initial structure–activity relation studies on N/OFQ analogues (Guerrini et al., 1997; Reinscheid et al., 1996), several NOP selective ligands have been developed by academic and industrial groups (for reviews see (Calo et al., 2000a; Zaveri et al., 2005) with selective

antagonists (Calo et al., 2005), partial agonists (Rizzi et al., 2002), and full agonists (Calo et al., 2011) now available. Evidences linking N/OFQ with PD support a role for the system in parkinsonian symptom pathophysiology (Marti et al., 2004a, 2005) through action at SNr level where extracellular N/OFQ levels rise as a consequence of DA neuron degeneration or functional impairment of DA transmission (Di Benedetto et al., 2009; Gouty et al., 2010; Marti et al., 2005, 2010; Norton et al., 2002).

The question of whether NOP receptor antagonists are dyskinesiogenic was directly addressed in a paper showing that acute systemic administration of J-113397 worsened the severity of AIMs in dyskinetic rats (Marti et al., 2012). This effect was replicated by intracerebroventricular or intranigral injection of UFP-101, consistent with the view that NOP antagonists act where N/OFQ tone is elevated. In fact, injection of UFP-101 in striatum, an area where N/OFQ tone is low or absent, and NOP receptor up-regulated after DA denervation, was without effect (Marti et al., 2012). Although in rats the prodyskinetic effect was mild and limited to the limb subtype of AIMs, these data substantially confirmed previous findings in marmosets (Visanji et al., 2008) warning on the potential motor side-effects of overdosing NOP antagonists as an adjunct to L-dopa therapy.

The finding that NOP receptor blockade worsened AIM expression, suggested that endogenous N/OFQ might physiologically oppose LID. In fact, acute intracerebroventricular injection of N/OFQ or systemic administration of Ro 65-6570 (a NOP receptor agonist) mitigated LID expression in rats, being equally effective against axial, limb and orolingual AIMs (Marti et al., 2012). The anti-dyskinetic effect was observed at doses that per se did not cause hypolocomotion, a typical effect of NOP receptor agonists (Devine et al., 1996; Jenck et al., 1997; Marti et al., 2004a, 2009; Reinscheid et al., 1995), possibly indicating a specific interference with dyskinetic pathways. Opposite to NOP receptor antagonists, N/OFQ attenuated dyskinesia more potently when injected in striatum than SNr.

In vivo microdialysis revealed that N/OFQ prevented LID expression through an action upon striatal GABAergic MSNs projecting to the SNr. In fact, intracerebroventricular administration of N/OFQ markedly attenuated the rise of SNr GABA release associated with LID expression (Mela et al., 2007), a neurochemical response associated with striatal D1 receptor activation (Mela et al., 2012). Consistently, N/OFQ also prevented the reduction of GABA release in ventro-medial thalamus associated with LID, an index of overinhibition of the nigral output (Marti et al., 2012). As previously reviewed, up-regulation of striatal D₁R signalling in LID is associated with an increased activity along the Ras/MEK/ERK kinase pathway (Feyder et al., 2011; Valjent et al., 2005), and a loss of neuron capability to depotentiate striatal synaptic response after LTP induction (Picconi et al., 2003). Consistent with an inhibitory action of N/OFQ upon striatal D₁R signalling (Olianas et al., 2008), application of N/OFQ to striatal slices of naïve animals prevented the increase in ERK phosphorylation induced by a D₁R agonist, and fully restored the depotentiation in slices treated with a D₁R agonist (Marti et al., 2012). The potential of NOP agonists as anti-dyskinetic drugs was further confirmed in MPTP-treated macaques, where the small molecule Ro 65-6570 was able to attenuate LID without compromising the anti-parkinsonian effect of L-dopa (Marti et al., 2012). Although the effect was overall mild (30%) and significant for the dystonic but not the choreiform component, these data provide a solid background for testing more selective and potent NOP agonists for their ability to acutely rescue motor function under LID.

In conclusion, N/OFQ appears to play an important role in PD. In particular, elevation of N/OFQ transmission in SNr following DA neuron loss might exacerbate the physiological, inhibitory role of N/OFQ over movement, justifying the use of NOP receptor

antagonists as symptomatic anti-parkinsonian drugs. Opposite to SNr, DA neuron loss is associated with reduction of N/OFQ expression and up-regulation of NOP receptors in striatum, which might also contribute to dysregulation of D₁R transmission in striato-nigral MSNs. In this case, NOP agonists, by restoring an inhibitory control over D₁R signalling, might work to oppose LID expression. Studies with more selective NOP agonists are needed to confirm these data, and prove that N/OFQ also prevents the development of sensitization to L-dopa, which underlies LID.

4.10. Postsynaptic changes in striatal interneurons

Although MSNs are the majority (about 95%) of the striatal neurons and the major output neurons, they are heavily influenced by interneurons in the striatum. Striatal cholinergic interneurons (ChIs) represent only about 2% of the total striatal neuronal population (Zhou et al., 2002), yet they have richly arborizing axons with large terminal fields within the striatum, suggesting the importance of these neurons in modulating striatal activity (Pisani et al., 2007). The striatum has the highest density of cholinergic markers in the brain (Bolam et al., 1984). ACh tone contributes to DA and glutamate release locally via presynaptic nicotinic receptors on DA and glutamatergic terminals (Kaiser and Wonnacott, 2000; Rice and Cragg, 2004). ChI activity also contributes to plasticity of glutamatergic and GABAergic inputs to this area via both muscarinic and nicotinic receptor activation (Bamford et al., 2010; Pisani et al., 2003, 2007). Striatal synaptic plasticity is dependent upon endogenous ACh acting specifically on M1 receptors, with high levels of ACh facilitating LTP and lower levels facilitating LTD (Bonsi et al., 2008). DA denervation modulates the cholinergic system as well, causing a reduction in M4 mRNA levels (Kayadjanian et al., 1999), along with M4 autoreceptor malfunction, resulting in a loss of negative feedback inhibition and increased ACh release (Ding et al., 2006).

As noted above in Section 4.9.3.2, studies show that striatal ERK activation shifts from being predominantly in dMSNs to ChIs with repeated L-dopa exposure concomitant with behavioural LID development/expression in both unilateral 6-OHDA lesioned and aphakia mouse models of PD (Ding et al., 2011) and in a primate model (Bezard, unpublished). Therefore, this shift of ERK activation from MSN to ChI with chronic L-dopa exposure suggests that priming of LID may occur in MSN initially, but that ChIs “store” and mediate the hypersensitivity to L-dopa. This shift is more dramatic in aphakia mouse model as inhibition of ERK activation in ChIs reduces LID expression (Ding et al., 2011). The selective ablation of striatal ChIs attenuates LID development and expression dramatically (Won et al., 2014).

ChIs have unique membrane properties, exhibiting spontaneous activity with tonic firing patterns (Bennett and Wilson, 1999). ChIs in both dyskinetic aphakia mice and WT mice with 6-OHDA lesions show increase in ERK activation and DA-induced firing rate following repeated L-dopa treatment compared with saline treated non-dyskinetic mice (Ding et al., 2011). Inhibition of ERK activation restores the baseline and DA-induced increases in ChI firing rate in dyskinetic mice to that of non-dyskinetic PD mice (Ding et al., 2011). Together, the electrophysiological data along with biochemical and behavioural results support the hypothesis that expression of LID following repeated L-dopa exposure results from enhanced striatal ChI excitability, and that these changes are mediated by ERK activation (Ding et al., 2011).

The role of antimuscarinic cholinergic drugs in the treatment of LID is controversial, which is in contrast to the role of nicotinic receptors. The best-established treatment for LID is amantadine, which has significant anticholinergic effect as well as anti-NMDA effect. Clinical experience with anticholinergics in PD patients is limited. Parkinsonian symptoms such as tremor and rigidity may

improve after treatment with centrally acting antimuscarinics, such as biperiden (Duvoisin, 1967; Katzenschlager et al., 2003). Although anticholinergic biperiden has been reported to decrease LID in human PD patients (Purcher et al., 1989), others have reported increased dyskinesia with anticholinergic treatment (Birke-Smith, 1974; Hauser and Olanow, 1993; Linazasoro, 1994). In a study of dyskinetic monkeys, the antimuscarinic antagonist atropine changed the nature of dyskinesia from dystonia to chorea (Gomez-Mancilla and Bedard, 1993), suggesting a modulatory role of muscarinic acetylcholine receptor in LID. Thus the controversial results of antimuscarinics on LID in PD likely reflect the complexity of muscarinic systems in the basal ganglia (Lim et al., 2014). Drugs that modulate these receptors are not receptor-subtype specific and can act upon multiple cell types within the striatum in addition to extra striatal sites. As such, the development of more selective muscarinic receptor ligands or other novel approaches to modify striatal cholinergic signalling specifically may provide more effective treatment strategies for LID. Recently, CNS cell subtype-specific gene translation profiling has revealed that the H2 histamine receptors are relatively selectively expressed on ChIs compared to other neuronal populations, including MSNs (Doyle et al., 2008). In mice with LID, the H2 antagonist famotidine reduces ChI firing, which suggests that development of LID induces hypersensitivity to histamine signal via H2 receptors in ChIs. Famotidine also reduces behavioural manifestation of LID in two mouse models (Lim et al., 2015) and a primate model of PD (Johnston et al., 2010b), in agreement with the notion that reducing ChI hyperactivity by H2 receptor blockade can reduce LID. However, a small clinical study has failed to find an effect of famotidine on reducing expression of LID, although this trial used relatively low doses (Mestre et al., 2014). H2 antagonists with better CNS penetration or other novel targets that specifically target ChI may allow more effective modulation of ChI activity to reduce LID. Finally, blocking ChI function prior to the beginning of chronic L-dopa treatment (via cell-selective ablation) (Won et al., 2014) had a much more dramatic effect in reducing subsequent LID than blocking ChI function after LID has already fully developed (via receptor antagonists) (Ding et al., 2011). These experimental studies raise the possibility that preventing the development of ChI hyperactivity early during L-dopa treatment may be more effective than suppressing the expression of LID that has already fully developed using anticholinergics, and that treatments that prevent the development of ChI hyperactive in response to chronic L-dopa may combine well with other drugs that suppress the expression of LID.

4.11. Involvement of additional extrastriatal regions in LID pathophysiology

As the main dopaminergic structure of the brain, the striatum, and generally the other basal ganglia nuclei (i.e. GPe, GPi, SNr, STN), have received most attention to understand the pathophysiology of LID. However, little remains known of the adaptations occurring in other structures, including the dopaminergic ones and the others, following a chronic L-dopa treatment. For instance (as discussed in Section 4.3) (Fig. 5), resonant cortical oscillations are associated with LID suggesting that cortex is a site of LID genesis (Halje et al., 2012). In keeping with that hypothesis, the authors showed a direct link between the cortical oscillations and the D₁R. Local delivery of a D₁R antagonist (SCH23390) at the surface of the primary motor cortex decreased both cortical oscillations and AIM severity in dyskinetic 6-OHDA-lesioned rats compared to cortically infused vehicle animals. Such result clearly suggests a key role of cortical oscillations in the generation of AIMS.

Systematic searches unravelled that extra-basal ganglia structures are involved in LID pathophysiology. 2-Deoxyglucose studies

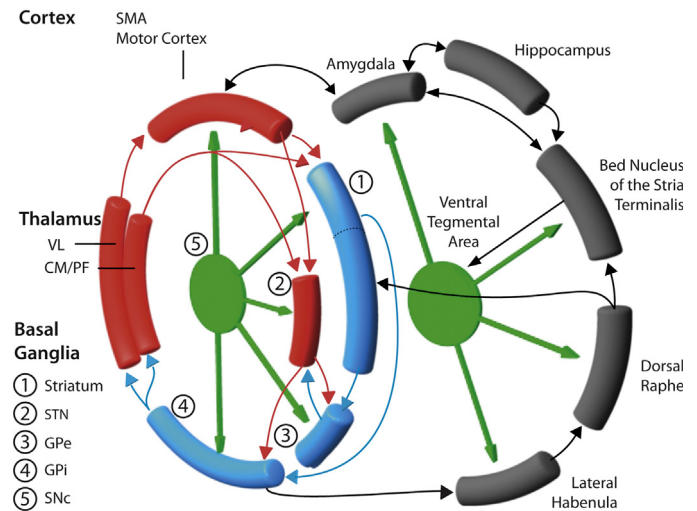


Fig. 5. Anato-functional organization of extended basal ganglia brain regions. Red corresponds to excitatory glutamate pathways in the basal ganglia, blue corresponds to inhibitory GABA (γ -aminobutyric acid)-releasing pathway in the basal ganglia, and green corresponds to the dopamine projections from the substantia nigra pars compacta (SNc) in the basal ganglia or the ventral tegmental area (VTA) outside of the basal ganglia. Black corresponds to the brain regions outside of the basal ganglia connected to these nuclei through the internal part of the Globus Pallidus (GPi) and the cerebral cortex. GPe: external part of the Globus Pallidus. STN: Subthalamic Nucleus. VL: Ventral lateral thalamus. CM/PF: centromedian and parafascicular complex of the thalamus.

showed modifications in 2-deoxyglucose accumulation in structures outside of the basal ganglia both in PD and LID (Fig. 5). Interestingly, Mitchell et al. showed that, besides the classic 2-deoxyglucose uptake pattern in the basal ganglia (Bezard et al., 2001b; Gnanalingham et al., 1995), the lateral habenula (LHb) and the pedunculopontine tegmental nucleus (PTg) stood up among several structures as strongly affected non-basal ganglia nuclei, showing dramatic increases in 2-deoxyglucose accumulation in parkinsonism (Mitchell et al., 1992, 1989). Guigoni and co-workers reported a decrease in 2-deoxyglucose uptake in the bed nucleus of the stria terminalis (BST) only in dyskinetic MPTP-treated macaques (Guigoni et al., 2005c). Beyond that specific result, they showed that changes in metabolic activity of non-motor areas of the basal ganglia and outside was the correlate of dyskinesia manifestation as those structures were the only ones to show a difference between the dyskinetic and non-dyskinetic MPTP-lesioned macaques, suggesting that dyskinesia are linked to a pathological processing of limbic and cognitive information. These metabolic changes might actually reflect the underlying neural mechanisms of not simply motor dyskinesias but also affective, motivational and cognitive disorders associated with long-term exposure to L-dopa. An alternate hypothesis is that dysregulation of affective, motivational and cognitive processes involved in motor planning and execution would be key events in the genesis/expression of LID.

Recently, transcriptional responses induced by LID were investigated by an unbiased whole-brain approach (Bastide et al., 2014b). Nine structures outside the basal ganglia were identified, i.e. the oval (oBST), juxta (jBST), medial (mBST) BST, rostral zona incerta, LHb, hippocampus, pontine nuclei (Pn), cuneiform nucleus (CnF) and PTg, that displayed an overexpression of at least 3 IEG (Δ FosB, ARC, FRA2, Zif268/EGR1) in dyskinetic rats. Interestingly, LID severity significantly correlated with at least one IEG expression profile in the oBST, jBST, LHb, Pn and CnF (Bastide et al., 2014b) (Fig. 5).

In the epithalamus, the LHb receive basal ganglia afferents, especially from the GPi (Hong and Hikosaka, 2008), the main

output structure of the basal ganglia (Fig. 5). The LHB projects mainly to the monoaminergic brain regions like the VTA, the SNC, the serotonergic dorsal and medial raphe and also to the cholinergic laterodorsal tegmentum (Bernard and Veh, 2012; Geisler and Trimble, 2008; Hikosaka et al., 2008). Thus, the LHB acts as an interface connecting the limbic system and the basal ganglia to the monoaminergic centres. As the false transmitter hypothesis involving the serotonergic system in LID pathophysiology addresses the presynaptic component of LID pathophysiology (Carta and Bezard, 2011; Navailles et al., 2010b), the efferent connectivity of the LHB suggests that it may play a role in controlling serotonergic output. Impaired LHB input would thus participate to the aberrant DA release from 5-HT terminals (Carta et al., 2007, 2008a,b; Navailles et al., 2011a; Rylander et al., 2010b). Recently, LHB involvement in LID was investigated (Bastide et al., 2014a). In this study, the authors demonstrated a LID-related pathologic activity of LHB at different functional levels including metabolic, electrophysiological and transcriptional readouts, indicating that increased LHB activity in response to L-dopa treatment is associated with LID expression. Then, selective inactivation of LHB Δ FosB-expressing neurons using the Daun02 methodology both alleviated LID severity and enhanced L-dopa anti-parkinsonian action, suggesting an involvement of LHB both in LID severity and in the anti-parkinsonian effect of L-dopa therapy (Bastide et al., 2014a). Taken altogether these results highlight a key role of LHB in the genesis of dyskinesia, i.e. the involvement of a structure outside of the basal ganglia.

Similarly, and following the initial identification by Guigoni and co-workers (2005c), the BST received experimental attention (Fig. 5). The oBST and jBST are two nuclei belonging to the dorsolateral BST (dlBST) which receive robust monoaminergic inputs featuring 5-HT, noradrenaline and DA (Phelix et al., 1992). The known BST DA inputs originate from VTA, the periaqueductal grey region and the retrorubral field. More importantly, in the oBST, data indicate that exogenous DA can reduce the inhibitory synaptic transmission in a D_2R -like-dose-dependant manner in brain slices of drug-naïve rats (Krawczyk et al., 2011). Moreover, rats self-administering cocaine, i.e. another hyperdopaminergic situation reminiscent in many ways of LID context, display an overexpression of the D_1R (Krawczyk et al., 2013), underlying the hypothesis of a potential role of the BST in LID. Selective inactivation of BST Δ FosB-expressing neurons alleviated LID severity suggesting an involvement of BST in mediating expression of LID (Bezard, Bastide, Georges and Dumont, unpublished). Taken together these results highlight a role of BST in the expression of dyskinesia, further highlighting the role played by structures outside the basal ganglia.

In the brainstem, the Pn primarily projects to the cerebellum (Brodal, 1979, 1980) and, thus, could be considered as a relay structure from the basal ganglia through the STN (Bostan et al., 2010; Wu and Hallett, 2013). As the cerebellum is involved in fine tuning of motor behaviour (Bastian, 2006; Thach et al., 1992; Timmann et al., 2010), it should not be surprising that L-dopa-induced modifications of the transcriptional activity of Pn neurons could influence cerebellum-driven motor functions and impact LID pathophysiology. The CnF, known as a mesencephalic locomotor area, receives DA inputs (Rolland et al., 2009; Takakusaki et al., 2003). Although the origin of its DAergic innervation is still unclear, data indicate that MPTP-treated monkeys undergo a dramatic decrease in CnF DA content (Rolland et al., 2009), providing information about a putative role in parkinsonian symptoms. Moreover, as the CnF projects back to the SNC (Watabe-Uchida et al., 2012), both CnF and SNC/SNr neurons form a direct loop that could play a role in motor-related behaviour, and hence support the involvement of the CnF in LID. Activity modulation of those nuclei and resulting impact upon dyskinesia remain however to be studied.

In the same way, neuronal activity of the locus coeruleus, containing the largest population of central noradrenergic neurons, is altered in dyskinetic 6-OHDA-lesioned rats following *in vivo* single-unit extracellular recordings (Migueluez et al., 2011). Then, studies demonstrated that the prefrontal cortex, the hippocampus and the amygdala displayed a modified monoaminergic neurochemistry both in dyskinetic 6-OHDA-lesioned rats and MPTP-treated macaques following a chronic L-dopa treatment (Engeln et al., 2014b; Navailles et al., 2011a). Taken together, these studies suggest that several structures outside of the basal ganglia nuclei could be involved in LID pathophysiology.

Consequently, the above-mentioned data further support the need to evaluate the functional involvement of regions outside of the basal ganglia to fully uncover the pathophysiology of LID.

5. Development of therapeutics

5.1. Continuous delivery of L-dopa

The fluctuations in DA levels being key in generating LID, a number of attempts have been made for either improving L-dopa delivery (and hence pharmacokinetics), preventing DA catabolism, or producing long-lasting DA agonists. This latter proposal could be achieved either by developing DA agonists with long half-life or by a galenic improvement leading to slow release formulations. The long-standing continuous-versus-intermittent-receptor-stimulation discussion has led to such attempts with however little therapeutic success (Jenner, 2008; Olanow and Obeso, 2000). While the clinical efficacy of DA agonists in delaying dyskinesia onset (Holloway et al., 2004) or in reducing LID severity (Poewe et al., 2007) is unclear (Fox et al., 2011), several approaches to improve the pharmacokinetics and ways of administration of L-dopa are in different stages of clinical development and include novel formulations as well as non-oral routes of drug delivery (LeWitt, 2015; Poewe and Antonini, 2015).

The principle behind constant L-dopa infusion is to bypass gastric emptying and deliver an optimized dose that can be kept stable within the patient's individual therapeutic window. While intravenous administration was shown to achieve parkinsonism improvement without troublesome dyskinesia in otherwise severely dyskinetic patients (Quinn et al., 1982), such route is not an option in real life, for practical and safety (thrombolysis risk) reasons. A gelified version of L-dopa was developed for intrajejunal administration achieving constant plasma L-dopa concentrations over several days of infusion (Nyholm et al., 2005). Such intrajejunal infusion of a gel formulation of L-dopa/carbidopa has first been developed in Europe and almost routinely clinically used for severe fluctuant or dyskinetic patients (Antonini et al., 2007, 2013; Honig et al., 2009). The efficacy of such intrajejunal administration to smooth out motor fluctuations has recently been confirmed in a USA/Europe/New-Zealand randomized, controlled trial (Olanow et al., 2014) opening the way to world-wide use of such pertinent formulation.

Modifying the pharmacokinetic of oral L-dopa is receiving a lot of attention from the industry since the intrajejunal administration route is not without practical limitations. IPX066, an extended-release L-dopa capsule (Hauser et al., 2013; Pahwa et al., 2014; Stocchi et al., 2014), XP21279, an extended-release L-dopa prodrug (LeWitt et al., 2012a, 2014), Accordion Pill CD/LD, a L-dopa gastric retention formulation (LeWitt, 2015), and DM-1992, a pill combining immediate and extended release with gastric retention (LeWitt, 2015; Poewe and Antonini, 2015), have either successfully completed phase III clinical trial (IPX066) or are still in phase II.

In the same way, novel enzyme inhibitors enhancing L-dopa efficacy and half-life are also still being developed, including a novel catechol-O-methyltransferase inhibitor with once-daily

pharmacokinetics, and there are studies testing the effects of increasing the dose of amino acid decarboxylase inhibitors given concomitantly with L-dopa. Clearly more original is the proposal that deuterium substitutions in the L-dopa molecule yield DA that appears more resistant to enzymatic breakdown (Malmlof et al., 2010). After initial rodent experiments, such demonstration however awaits further confirmation in primate models before entering clinical testing.

A great step forward has been reached with Prosavin gene therapy, a LV-based gene therapy aimed at restoring local and continuous DA production in patients with advanced PD, that was not aimed to reduce LID in the first place (Palfi et al., 2014). While all Prosavin-treated patients displayed improvement in mean UPDRS part III motor scores off medication at 6 and 12 months compared with baseline, this was not accompanied with occurrence of dyskinesia (Palfi et al., 2014) as with grafting of mesencephalic embryonic neurons. Most common adverse events were however increased on-medication dyskinesia (20 events, 11 patients) and ON-OFF phenomena (12 events, nine patients) (Palfi et al., 2014) suggesting that while continuous production of DA does not lead to dyskinesia, adding further oral L-dopa unrelentingly elicits LID. Larger trial with higher dosages of the Prosavin lentiviral vector-based gene therapy is currently on its way (NCT01856439).

5.2. Serotonin 5-HT_{1A} agonists

Increasing evidence points to the serotonergic system as a key player in the induction and expression of LID (Chase, 2014) in both patients with PD (Bonifati et al., 1994; Politis et al., 2014) and animal models of the disorder (Carta et al., 2007; Dupre et al., 2008; Munoz et al., 2008; Navailles et al., 2010b). Oral administration of the 5-HT_{1A} agonist buspirone was first tested (Kleedorfer et al., 1991). Buspirone reduced L-dopa-evoked striatal synaptic DA release and attenuated LID in a recent small scale investigational study (Politis et al., 2014), somewhat confirming earlier results in other small scale trials (Bonifati et al., 1994; Kleedorfer et al., 1991).

Sarizotan was assessed in 18 PD patients with motor fluctuations and peak-dose LID in a randomized pilot study (Bara-Jimenez et al., 2005). 5 mg of sarizotan decreased AIMs scores by 40% without modifying UPDRS motor scores during an acute intravenous L-dopa infusion. These encouraging results were not confirmed in a large randomized, placebo-controlled, phase IIb dose finding trial. This trial enrolled 398 PD patients with at least moderately disabling LID for at least 25% of the waking day who either received sarizotan 2, 4, 10 mg/d or placebo for 12 weeks (Goetz et al., 2007). Mean improvements in diary-based “ON” time without dyskinesia (primary outcome measure) and AIMs scores at rest and with activity were not different between groups after 12 weeks of treatment. Patients receiving 2 mg/d sarizotan had lower UPDRS IV (Part A: dyskinesias) scores compared to placebo suggesting that sarizotan may have some minor effects that are not perceived by PD patients according to the observations documented in their home-diaries. UPDRS Part A evaluates duration, disability, pain and dystonia of dyskinesias as a composite score. No adverse events were more common in patients treated with sarizotan compared to placebo except for an increase in “OFF” time in patients receiving 10 mg/d sarizotan and a similar trend for 4 mg/d.

Furthermore, experiments using the 5-HT_{1A/1B} receptor agonists eltoprazine and anpirtoline (Bezard et al., 2013a,c) (each of which possess different affinity for these two major 5-HT autoreceptors) have shown them to produce complete suppression of LID in rat and monkey models of PD, albeit in association with a partial loss of the therapeutic efficacy of L-dopa. In recent Phase II trial, Svenningsson et al. provide true translational evidence

supporting the use of eltoprazine against dyskinesia (Svenningsson et al., 2015). Truly translational (i) because they aimed to identify acute doses of eltoprazine that do not affect the therapeutic response to L-dopa (absence of impairment of UPDRS part III scores after vehicle or eltoprazine doses) as in experimental studies, and (ii) because they scored the patients directly, i.e. as in experimental studies, instead of relying upon patient diaries. The findings are truly exciting in that a replication of experimental data has been possible using the same investigational design. Thus, this study provides important validation of pre-clinical data, supporting the use of animal models to identify the mechanism(s) underlying LID, as well as new pharmacological targets. However, it should be pointed out that the reduction of LID in the present study was neither as striking as that in animal models, nor superior to that seen with amantadine in previous clinical studies. Therefore, a number of issues remain to be addressed, including (i) whether escalation of the eltoprazine doses and/or modification of the time of administration relative to L-dopa could improve the anti-dyskinetic efficacy; (ii) whether eltoprazine would remain efficacious after weeks of daily treatment in a classic phase IIb/phase III patient diary-based trial, and (iii) in conjunction with the last point, whether chronic administration would not lead to desensitization of 5-HT_{1A/1B} receptors, or to emergence of the anti-L-dopa effect often reported in animal studies. This is a critical issue in determining the clinical feasibility of this approach for dyskinesia.

5.3. NMDA antagonists

Beyond amantadine, other NMDA antagonists such as dextromethorphan, remacemide, milacemide, CP-101,606 and memantine were assessed for treating LID (Clarke et al., 2001; Giuffra et al., 1993; Merello et al., 1999b; Nutt et al., 2008; Parkinson Study Group, 2001; Shoulson et al., 2001; Verhagen Metman et al., 1998a). It should be noted that none of the drugs exhibited strong anti-dyskinetic effects in the gold standard experimental models of LID (e.g. for memantine, see Tronci et al., 2014).

Dextromethorphan was assessed in 18 PD patients with motor fluctuations and LID in a placebo-controlled cross-over trial (Verhagen Metman et al., 1998a). 12 patients were excluded because of decreased L-dopa efficacy or no benefit at the highest dose. In the remaining 6 patients, dextromethorphan decreased the severity and duration of dyskinesia and severity of motor fluctuations. An on-going trial using AVP-923, a combination of dextromethorphan and quinidine in PD subjects with LID is underway (NCT01767129).

Memantine was tested in 12 PD patients with motor fluctuations and LID in a placebo-controlled cross-over study (Merello et al., 1999b). UPDRS “ON” and “OFF” motor scores were decreased in patients receiving memantine, while dyskinesia ratings were unchanged (Moreau et al., 2013; Varanese et al., 2010).

Remacemide, a non-competitive NMDA channel antagonist, has been evaluated by the Parkinson Study Group in two randomized, placebo-controlled, parallel group study trials. In a pilot study, doses ranging between 150 and 600 mg of remacemide were tested against placebo in 39 PD patients with motor fluctuations and disabling LID (Parkinson Study Group, 2001). There were no differences between the placebo and remacemide group for any of the dyskinesia measures. Adverse events mainly occurred in the group receiving 600 mg remacemide. In a second large scale trial, remacemide was tested against placebo in 279 PD patients with motor fluctuations who experienced more than 25% of the waking day in the “OFF” state (Shoulson et al., 2001). UPDRS motor scores were improved in patients receiving remacemide (only 150 and 300 mg) compared with placebo. No dyskinesia ratings were performed.

CP-101,606 is a selective antagonist of the GluN2B subunit of the NMDA receptor that was assessed in 12 PD patients with motor fluctuations and dyskinesia in a randomized, placebo-controlled cross-over study (Nutt et al., 2008). Patients received either CP-101,606 (low or high dose) or placebo during intravenous L-dopa infusion. Both doses of CP-101,606 similarly reduced dyskinesia scores compared to placebo, while UPDRS motor scores were not different between groups. Many patients receiving CP-101,606 presented dose-dependently abnormal thinking, depersonalization and amnesia limiting the interest of this compound for further development for LID.

Budipine is a NMDA antagonist with widespread action on other neurotransmitter systems. This drug was tested in 7 PD patients with motor fluctuations in an open-labelled trial (Spieker et al., 1999). Motor scores improved and “OFF” time decreased without appearance of dyskinesia in most patients. Larger randomized, controlled clinical studies were stopped or planned trials were not conducted when a prolongation of the QT interval in the ECG was observed with the risk of fatal polymorphic ventricular tachycardia.

Milacemide, a glycine prodrug that positively modulates NMDA transmission, was tested in a placebo-controlled cross-over study in 6 PD patients with motor fluctuations (Giuffra et al., 1993). Milacemide worsened parkinsonian motor signs, mainly rigidity, without any effect on dyskinesia ratings.

Altogether those drugs are relatively disappointing as none achieve similar results than amantadine. It further suggests that amantadine mediates part of its anti-dyskinetic efficacy through other receptors than NMDA receptors.

5.4. mGluR5 negative allosteric modulators

mGluR5 negative allosteric modulators have emerged as a novel and potentially effective class of compounds for the treatment of LID. Few trials have been conducted so far. Two small randomized, double-blind, placebo-controlled, parallel-group phase IIa studies assessed the safety, tolerability and efficacy of marvoglurant (AFQ056) in patients with moderate to severe LID (study 1) or severe LID (study 2) (Berg et al., 2011). Patients received up to 150 mg bid and were evaluated after a 16-day titration phase. Marvoglurant had significant anti-dyskinetic effects versus placebo on the Lang-Fahn Activities of Daily Living Dyskinesia Scale (study 1) and the modified AIMS Scale (study 2). Another small phase IIb trial was inconclusive with conflicting clinician-rated outcome ratings (Kumar et al., 2013). This study was prematurely halted because of enrolment challenges. The largest reported randomized, double-blind, placebo-controlled, parallel-group phase IIb study enrolled 197 patients who were treated for 12 weeks (Stocchi et al., 2013). The highest dose of 200 mg/d reduced significantly modified AIMS Scale scores, while all other doses failed. The data of two additional phase II trials (NCT01491529 and NCT01385592) have yet to be published but were communicated by the company as negative (Rascol et al., 2014).

Dipraglurant, another potent mGluR5 NAM (Duvvey et al., 2013), was tested in a Phase IIa proof-of-concept 4-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial in PD patients with moderate or severe LID. Dipraglurant proved to significantly reduce modified Abnormal Involuntary Movements Scale scores at days 1 and 14, but the difference between active intervention and placebo did not reach significance on day 28. Full disclosure of data in a peer-reviewed publication is pending.

5.5. Antiepileptics

The efficacy of gabapentin on motor severity and activities of daily life was first tested in 19 PD patients with motor fluctuations

and dyskinesia in a randomized placebo-controlled cross-over study (Olson et al., 1997). Total UPDRS scores were lower in patients receiving gabapentin. The effect of gabapentin (up to 2400 mg/d) on motor complications was more specifically investigated in a second randomized, placebo-controlled cross-over trial including 15 PD patients with motor complications and dyskinesia (Van Blercom et al., 2004). Secondary outcome measures included dyskinesia measures. No differences were observed between gabapentin and placebo. Dizziness and accidental falls were more frequent in patients receiving gabapentin.

The anti-dyskinetic properties of levetiracetam were assessed in two small open-label studies (Lyons and Pahwa, 2006; Zesiewicz et al., 2005) after demonstration of moderate efficacy in animal models (Bezard et al., 2004; Hill et al., 2003, 2004a,b). One study reported an increase in “ON” time without or with non-troublesome dyskinesia by 18% in 9 PD patients with peak-dose dyskinesia for at least 25% of waking hours who received up to 3000 mg/d of levetiracetam (Zesiewicz et al., 2005). At the same time, ON time with troublesome dyskinesia decreased by 12%. There was a considerable dropout rate with a withdrawal of 56% of the patients, mostly because of somnolence. The second study was also conducted in 9 PD patients experiencing moderate to severe dyskinesia and receiving up to 3000 mg/d of levetiracetam (Lyons and Pahwa, 2006). This study reported a dropout of 44%, mostly due to worsening of PD symptoms or somnolence. Moreover, of the remaining 5 patients, 4 discontinued levetiracetam after the end of the study because of worsening of PD symptoms and somnolence. A randomized, double-blind, placebo-controlled, parallel-group pilot study in 32 PD patients with moderate to severe LID failed to show a significant reduction in modified AIMS Scale scores, while UPRDS IV item 32/33 sum scores were significantly lower after 11 weeks of treatment compared to baseline in patients receiving levetiracetam (Wolz et al., 2010). Tolerance was better than in the open-label trials. Other small randomized controlled treatment trials reported modest or no effects of levetiracetam on LID (Stathis et al., 2011).

Zonisamide (25–100 mg) was tested in a randomized, placebo-controlled, parallel-treatment study including 347 PD patients with motor fluctuations (Murata et al., 2007) although no proper preclinical study ever showed a positive effect in an experimental of LID. Preclinical evidences however were collected supporting moderate efficacy against essential tremor (Miwa et al., 2011). Zonisamide (50 mg) decreased disabling dyskinesia. However, patients receiving zonisamide complained dose-dependently about more dizziness, apathy and a decrease in body weight (Iwata et al., 2012).

Another antiepileptic drug, topiramate, previously suggested to modestly reduce LID without exacerbating parkinsonism in animal models (Kobylecki et al., 2011; Silverdale et al., 2005), was tested in a single-dose randomized, double-blind, placebo-controlled cross-over trial in dyskinetic PD patients. Interestingly, as in the eltopazine trial mentioned above, dyskinesia severity was assessed by a blinded rater from video recordings as the primary outcome measure. Such setting was comparable to animal studies. Topiramate-treated patients showed however a significant increase in dyskinesia severity compared to baseline (and placebo-treated ones). Five patients withdrew from the study whilst taking topiramate due to adverse effects (only 7 completed the trial). Although methodologically very similar to preclinical studies, the trial unravelled that topiramate might worsen dyskinesia in PD patients and is poorly tolerated.

5.6. Antipsychotics

The efficacy of clozapine, a DA receptor antagonist with antiserotonergic, antimuscarinic, antiadrenergic and antihistaminergic properties, in decreasing LID was evaluated in several small

pilot studies (Bennett et al., 1993, 1994; Durif et al., 1997; Pierelli et al., 1998) and in one larger randomized, placebo controlled trial (Durif et al., 2004). In the latter, patients treated with clozapine gained 2.4 h of ON time without dyskinesia compared to placebo. There was no increase in the duration of OFF periods. Dyskinesia ratings at rest were decreased during the acute L-dopa challenge. However, ratings in the same condition during an activation task were not different. Clozapine had no effect on the anti-parkinsonian action of L-dopa. Adverse events were not more frequent with clozapine except for drowsiness and hypereosinophilia, the latter rapidly resolved after treatment discontinuation.

Olanzapine has shown anti-dyskinetic properties in a small randomized, placebo-controlled cross-over trial (Manson et al., 2000b). However, adverse events were more common with olanzapine, consisting in increased OFF time, increased parkinsonism and increased drowsiness.

Quetiapine, another atypical antipsychotic with few extrapyramidal side effects, was tested in a small randomized, placebo-controlled, cross-over study enrolling 8 PD patients with disabling LID (Katzenschlager et al., 2004). No differences were observed between quetiapine and placebo. The double-blind trial was followed by an open-label period of around 30 days during which patients received up to 50 mg/d of quetiapine. Mild improvement in dyskinesia duration and severity were observed during the open-label period according to patient home diaries.

5.7. Other strategies

Safinamide, a reversible and selective MAO-B inhibitor that also reduces degradation of DA and displays glutamate release inhibitor properties (Caccia et al., 2006), has long been proposed to display anti-dyskinetic properties (Gregoire et al., 2013). A Phase III, multicenter, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of safinamide as add-on to L-dopa in the treatment of PD patients with motor fluctuations (Borghain et al., 2014a,b). Primary endpoint (i.e. overall improvement in LID) was not reached but add-on safinamide in mid-to-late PD with motor fluctuations showed improvement in dyskinesia in patients at least moderately dyskinetic at baseline as well as increase in ON-time without troublesome dyskinesia (Borghain et al., 2014b).

Cannabis was examined in a randomized, placebo-controlled cross-over design in 19 PD patients with LID (Carroll et al., 2004). Cannabis tended to worsen dyskinesia. No serious adverse events were observed.

Nabilone, a cannabinoid, has shown anti-dyskinetic properties in a small randomized, placebo-controlled cross-over study in 7 PD patients who experienced LID during 25–50% of waking hours (Sieradzan et al., 2001). Nabilone decreased dyskinesia by 22% compared to placebo, while the duration of ON time and the percentage of dyskinesia during ON time were not modified. Nabilone had no effect on the anti-parkinsonian action of L-dopa. Two patients were withdrawn from the study because of side effects (vertigo, orthostatic hypotension).

The opioid antagonist naltrexone was assessed in 10 PD patients with end-of-dose wearing OFF and 8 PD patients with dyskinesia in a randomized trial (Rascol et al., 1994). Naltrexone had no effect on motor function or dyskinesia severity and duration. Adverse events (digestive, neuropsychiatric) were more frequent in patients under naltrexone.

The anti-dyskinetic properties of the α 2-adrenergic receptor antagonist idazoxan were evaluated in a single oral dose randomized, placebo-controlled study in 18 PD patients with peak-dose dyskinesia (Rascol et al., 2001a). There was a trend for lower dyskinesia in patients receiving 10 or 20 mg idazoxan. Cardiovascular adverse events were more frequent with idazoxan.

A randomized cross-over trial in 7 PD patients failed to show an effect of idazoxan on LID (Manson et al., 2000a). No differences were observed between idazoxan and placebo in terms of motor function and dyskinesia severity. All patients experienced side effects during idazoxan treatment, which were serious enough in 3 to discontinue study medication.

Fipamezole, another α 2-adrenergic receptor antagonist, was tested in a randomized, double-blind, placebo-controlled, dose-escalating 28-day study involving 179 PD patients from the US and India experiencing LID (LeWitt et al., 2012b). The primary outcome based on LID scale, a modification of the AIMS Scale, was negative for the overall cohort. When only looking at the US subpopulation, patients receiving 90 mg fipamezole t.i.d. showed a significant reduction of LID scores at day 28 compared to placebo. Fipamezole treatment was reported safe and well tolerated.

Propranolol, a beta-adrenergic receptor antagonist, has been regularly suggested to exhibit some anti-dyskinetic potential, without affecting L-DOPA's efficacy. Propranolol, in a dose-dependent manner, reduced LID, without affecting motor performance in the AIM rat model of LID (Bhide et al., 2015) but failed to alter dyskinesia produced by the D1 receptor agonist SKF81297 or the D2 receptor agonist Quinpirole. These findings suggested a pre-synaptic mechanism for Propranolol's anti-dyskinetic effects, possibly through modulating L-DOPA-mediated DA efflux, as unravelled demonstration of propranolol-mediated reduction in L-DOPA-induced DA efflux (Bhide et al., 2015). Therefore, Propranolol's anti-dyskinetic properties appear to be mediated via attenuation of L-DOPA-induced extraphysiological efflux of DA, comparably to 5-HT_{1A/1B} agonists.

A ten day treatment with transdermal high dose 17[beta]-estradiol (0.4 mg/d) was studied in 8 female PD patients with LID in a randomized, placebo-controlled cross-over study (Blanchet et al., 1999). The threshold dose of L-dopa to provide anti-parkinsonian efficacy was reduced. By contrast, the duration of the clinical motor response and dyskinesia ratings were not different between groups. While on estradiol, most patients complained of breast/nipple tenderness and 3 patients reported increased dyskinesia.

6. Concluding remarks

The present review describes the unprecedented accumulation of knowledge on the pathophysiology of LID in particular and of L-dopa-induced disorders in general. One cannot however fail to notice the discrepancy between such knowledge and the yet limited therapeutic armoury. We are indeed basically left with amantadine or DBS to manage the severity of dyskinesia and we have no real option for delaying, or even better prevent the appearance of these troublesome side-effects.

What are the main roadblocks to the clinical translation of antidyskinetic treatments? In general, translational failures are attributed to a poor predictive validity of animal models. In the case of LID, however, animal models share essential pathophysiological features with the human condition and show a large degree of internal consistency. It is therefore important to be aware of two major difficulties inherent to translational research and not simply to LID: on one hand the difference between statistical difference and clinical relevance and, on the other hand, the fundamental difference in the assessment tools used in preclinical and clinical settings.

All anti-dyskinetic strategies that have been shown somewhat efficacious in PD patients were tested in the AIM rat model (L-dopa-treated 6-OHDA-lesioned rat; MA Cenci's lab) and in LID macaque model (L-dopa-treated MPTP-lesioned; E Bezdard's lab) and shown capable of significantly reducing the severity of AIMS in those two models. While this back-validation effort partially supports our claim of predictivity, it also sheds light upon the

importance of magnitude of efficacy. Among the several studies that have reported a significant improvement of AIMs or LID in animal models, the vast majority reports statistically significant results of modest amplitude. One should consider that we work in inbred (rodents) or F2-bred (macaques) animals that are genetically and physiologically homogenous, of same sex and body weight, bearing identical lesions (nigro-striatal for 6-OHDA rat (Cenci et al., 2002; Winkler et al., 2002) and widespread monoaminergic lesions for MPTP macaques (Engeln et al., 2014b; Guigoni et al., 2005b)), scrutinized on- or off-line for the entire duration of pharmacological stimulation (classically from 4 to 10 h post-L-dopa administration). Therefore, small amplitude effects, although significant and scientifically valid, bear the risk of not being replicable in less controlled situations, i.e. in the clinic where patients are genetically heterogeneous, are of either sex, likely experience various degrees and natures of lesions and are seldom clinically followed during the entire exposure to L-dopa. mGluR5 negative allosteric modulators may provide some examples of attrition effects. Some agents that improved AIMs in the rat model, had smaller effects on LID in the macaque models (Bezard et al., 2014; Gregoire et al., 2011; Rylander et al., 2010a; Zhang et al., 2014c). Extensive clinical data are however only available for the mGluR5 antagonist AFQ056 (Berg et al., 2011; Kumar et al., 2013), which has not been cross-validated in rodents and non-human primates. Based on one study performed in a macaque model of LID (Gregoire et al., 2011), one may actually conclude that AFQ056 exerts less potent antidyskinetic effects than other compounds in this category.

Puzzlingly, most clinical trials, small or large scales, are conducted based upon patient diaries reporting the number of hours spent per day without troublesome dyskinesia. We fully understand (and agree) that this must be the final endpoint as it reflects the real life but such setting does not “translate” the basic science settings where individuals would be scrutinized and clinically assessed over time by a trained neurologist. Interestingly, such experimental and pilot settings are applied from time to time and prove to replicate the preclinical findings. Two pivotal examples that use two different settings support the case. Amantadine was first shown efficacious in a small trial in which parkinsonian and dyskinesia scores were obtained during a steady-state intravenous L-dopa infusion, i.e. under direct observation by neurologists in a controlled setting where dyskinesia were deliberately elicited by individually rising the L-dopa plasma levels (Verhagen Metman et al., 1998b). The finding was then confirmed in a more classic trial (Metman et al., 1999). Eltoprazine constitutes the most recent example of such direct translation with first demonstration of efficacy in animal studies (see above) followed by a small clinical trial (Svenningsson et al., 2015) demonstrating anti-dyskinetic potential without impairment of therapeutic anti-parkinsonian response to L-dopa on the basis of direct clinical scoring of patients, i.e. exactly as done in experimental studies.

Investigational clinical trials carefully performed on small number of patients knowingly dyskinetic or made dyskinetic by ad hoc L-dopa intravenous titration have therefore the potential for supporting or invalidating preclinical findings. An example of such invalidation is provided by the failed attempt to reposition simvastatin, thanks to its property of inhibiting striatal Ras-ERK pathway (Tison et al., 2013). A “n-of-1” design randomized, placebo-controlled, 3 cross-over trial was conducted in 10 PD patients with troublesome dyskinesia. Such exploratory trial design is highly suitable for rapid proof-of-concept challenging of a new indication of available drugs for LID management (Rascol et al., 2012). The lack of simvastatin efficacy was found to be due to the lack of target engagement in PD patients due to dose limitation while such target engagement was found in the monkey model (Tison et al., 2013).

In the past few years, the concept of combined therapies has emerged. Since no single drug is capable to abolish LID, even in experimental models, attempts to do so, while reducing their side-effects or their pro-parkinsonian action, support the validity of the concept, i.e. that combination of drugs with different mechanisms of action add their efficacy for a better management of established LID (Bezard et al., 2013c; Bibbiani et al., 2005; Hill et al., 2004b; Ko et al., 2014c; Munoz et al., 2008). Although scientifically valid, and to a certain extent clinically valid provided the drugs are on the market, the industrial development of combined or cocktail therapies is seen as problematic. Besides the intellectual property and marketing issues, the development cost for demonstrating safety appears huge unless we consider existing marketed drugs.

Beyond the issues inherent to pharmacology, the condition itself may prevent development of biological therapies. Experimental studies now rely not simply on pharmacology but also on biological tools such as peptides, antibodies, cellular and gene therapy, etc., for the sake of scientific demonstration, with a clear therapeutic potential. Regulatory agencies (e.g. US Food and Drug Administration and European Medicines Agency) however rightfully consider LID as a side-effect of the PD therapy. Although obvious, this statement is not without consequences, i.e. no “permanent” therapy, e.g. gene therapy, would be approved for treating LID as such approaches are considered only for treating/curing primary conditions, not the side-effects of their treatment.

Altogether, these parameters lead us to propose a simple roadmap for translational therapeutic development for LID in PD. “Efficacy” should be demonstrated in a AIM rodent model (rat or mouse) and then tested in the macaque model of LID, both widely available. Translating experimental findings requires not only jumping from model species to PD patients but also involves using different assessment methods. We strongly suggest, at least in investigational studies, to use very comparable tools for assessing the efficacy, introducing small-scale studies in patients aimed at paving the way to larger scale studies once proof-of-concept is obtained and dose defined. Such small-scale studies should either use the L-dopa intravenous titration or use a “n-of-1” design placebo-controlled, cross-over trial design (provided the test item half-life permits). With these issues in mind, we can confidently envision the development of pharmacological strategies capable of reducing the severity of established dyskinesia in PD patients.

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Glossary

- 5-HT: serotonin
 5-HT: 5-hydroxytryptamine
 6FD: 6-[¹⁸F]fluoro-L-dopa
 6-OHDA: 6-hydroxydopamine
 AADC: L-amino acid decarboxylase
 AADCi: AADC peripheral inhibitors
 AC5: adenylyl cyclase type 5
 ACh: acetylcholine
 AIMS: abnormal involuntary movements
 AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
 AP-1: activator protein 1
 BDNF: brain derived neurotrophic factor
 BST: bed nucleus of the stria terminalis
 CaMKII: Ca²⁺/calmodulin-dependent protein kinase II
 cAMP: cyclic adenosine monophosphate
 CBF: cerebral blood flow
 CDRS: Clinical Dyskinesia Rating Scale
 cGMP: cyclic guanosine monophosphate
 Chls: cholinergic interneurons
 CM/PF: centromedian and parafascicular complex of the thalamus
 CnF: cuneiform nucleus
 CNS: central nervous system
 COMT: catechol-O-methyl transferase
 CPP: cell-permeable peptide
 CRE: CREB responsive elements
 CREB: cAMP response element binding protein
 D₁R: DA D1 receptor
 D₂R: DA D2 receptor
 D₃R: DA D3 receptor
 D₄R: DA D4 receptor
 DA: dopamine
 DAergic: dopaminergic
 DARPP-32: dopamine- and cAMP-regulated phosphoprotein of 32 kDa
 DAT: plasmalemmal DA transporter
 DAWS: DA agonist withdrawal syndrome
 DBS: deep brain stimulation
 DD: DA deficient
 DDD: DA deficient DAT-knock-out mice
 Ddo: D-aspartate oxidase

- DDS*: DA dysregulation syndrome
dMSNs: direct pathway MSNs
DREAM: downstream regulatory element antagonistic modulator
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV
ERK: extracellular signal-regulated protein kinase
FDG: fluorodeoxyglucose
fMRI: functional magnetic resonance imaging
GAD67: glutamate acid decarboxylase 67 kDa
GAPs: GTPase activating proteins
GID: graft-induced dyskinesia
GRK: G protein-coupled receptor kinase
GPCR: G protein-coupled receptor
GPI: internal part of the Globus Pallidus
GPe: external part of the Globus Pallidus
ICD: impulse control disorders
IEG: immediate-early gene
iMSNs: indirect pathway MSNs
jBST: juxta capsular bed nucleus of the stria terminalis
L-dopa: levodopa
L-dopa: L-_{3,4}-dihydroxyphenylalanine
LFP: local field potentials
LHb: lateral habenula
LID: L-dopa-induced dyskinesia
LFS: low frequency stimulation
LTD: long-term depression
LTP: long-term potentiation
LV: lentiviral vector
M1: primary motor cortex
MAO: monoamine oxidase
mBST: medial bed nucleus of the stria terminalis
MFB: medial forebrain bundle
mGluRs: metabotropic glutamate receptors
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSK1: mitogen- and stress-activated kinase 1
MSNs: striatal medium spiny neurons
MTEP: 3-((2-methyl-4-thiazolyl)ethynyl)pyridine
mTORC1: mammalian target of rapamycin complex 1
nAChRs: nicotinic acetylcholine receptors
N/OAQ: Nociceptin/orphanin FQ
Narp: neuronal activity-regulated pentraxin
NE: Norepinephrine
NHPDysR: Non Human Primate Dyskinesia Rating Scale
NMDA: N-methyl-D-aspartate
NOP: N/OAQ peptide receptor
oBST: oval bed nucleus of the stria terminalis
pAcH3: phospho-acetylation of Histone H3
pERK: phosphorylated ERK1/2
PD: Parkinson's disease
PET: positron emission tomography
PKC: protein kinase C
PLC: phospholipase C
PDE: phosphodiesterase
PPE-B: preproenkephalin-B, i.e. prodynorphin
PKA: cAMP-dependent protein kinase
PKG: protein kinase G
Pn: pontine nuclei
preSMA: preSupplementary Motor Area
PP-1: protein phosphatase-1
PPE: preproenkephalin
PPX: pramipexole
PTg: pedunculopontine tegmental nucleus
rCBF: regional cerebral blood flow
RGS: regulatory GPCR signalling proteins
shTH: short-hairpin RNA-mediated knockdown of TH
SNC: substantia nigra pars compacta
SNr: substantia nigra pars reticulata
SSRIs: selective serotonin reuptake inhibitors
STEP: striatal-enriched protein tyrosine phosphatase
STN: Subthalamic Nucleus
TH: tyrosine hydroxylase
TRAP: translating ribosome affinity purification
UPDRS: Unified Parkinson's Disease Rating Scale
VMAT2: vesicular monoamine transporter type 2