

Synaptic dysfunction in Parkinson's disease

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Abstract

In neuronal circuits, memory storage depends on activity-dependent modifications in synaptic efficacy, such as LTD (long-term depression) and LTP (long-term potentiation), the two main forms of synaptic plasticity in the brain. In the nucleus striatum, LTD and LTP represent key cellular substrates for adaptive motor control and procedural memory. It has been suggested that their impairment could account for the onset and progression of motor symptoms of PD (Parkinson's disease), a neurodegenerative disorder characterized by the massive degeneration of dopaminergic neurons projecting to the striatum. In fact, a peculiar aspect of striatal plasticity is the modulation exerted by DA (dopamine) on LTP and LTD. Our understanding of these maladaptive forms of plasticity has mostly come from the electrophysiological, molecular and behavioural analyses of experimental animal models of PD. In PD, a host of cellular and synaptic changes occur in the striatum in response to the massive loss of DA innervation. Chronic L-dopa therapy restores physiological synaptic plasticity and behaviour in treated PD animals, but most of them, similarly to patients, exhibit a reduction in the efficacy of the drug and disabling AIMs (abnormal involuntary movements) defined, as a whole, as L-dopa-induced dyskinesia. In those animals experiencing AIMs, synaptic plasticity is altered and is paralleled by modifications in the postsynaptic compartment. In particular, dysfunctions in trafficking and subunit composition of NMDARs [NMDA (*N*-methyl-D-aspartate) receptors] on striatal efferent neurons result from chronic non-physiological dopaminergic stimulation and contribute to the pathogenesis of dyskinesias. According to these pathophysiological concepts, therapeutic strategies targeting signalling proteins coupled to NMDARs within striatal spiny neurons could represent new pharmaceutical interventions for PD and L-dopa-induced dyskinesia.

Introduction

One of the most intriguing properties of the brain is the capability to undergo synaptic plasticity processes. In fact, the number, morphology, position, molecular phenotype and strength of synapses continue to modify as a function of neurons' requirements. These events take place in the nervous system during its development, but also after a variety of insults, and, interestingly, they represent the basis for learning and memory [1].

In the last two decades, there has been a growing interest in the comprehension of these phenomena in the striatum, in physiological as well as pathological conditions. The efforts put into this research field are attributable to the crucial function of the striatum within the BG (basal ganglia) circuit. In fact, the striatum plays a fundamental role in the regulation of voluntary movements, behavioural control, cognitive function and reward mechanisms [2]. Among the BG nuclei,

the striatum is the major input station of glutamatergic innervation arising from the cortex and the thalamus. In addition, it is a primary target of DA (dopamine) innervation arising from the SNc (substantia nigra pars compacta). The integrative action exerted within striatal projecting neurons on this converging information determines the final output of the striatum on to the other BG structures. Intuitively, prominent neurological disorders, principally characterized by motor symptoms, such as PD (Parkinson's disease) or Huntington's disease, develop as a consequence of striatal dysfunction [2], which can propagate throughout the BG circuit.

Recently, there has been a general consensus in valuating abnormalities in synaptic plasticity events as a potential cellular mechanism of impaired striatal function underlying certain movement disorders. This review provides an overview of plastic changes occurring at striatal synapses in PD.

Synaptic plasticity in the striatum

The neuronal population in the striatum consists of 95 % of MSNs (medium spiny neurons), projecting cells characterized by numerous spines on their dendritic trees, which represent the locus of synaptic plasticity events. MSNs undergo the two principal forms of synaptic plasticity in the brain: LTP (long-term potentiation) [3–5] and LTD (long-term depression) [6,7]. Both forms of plasticity are induced by repetitive activation of the cortical excitatory afferents impinging on

Key words: dopamine, dyskinesia, *N*-methyl-D-aspartate receptor (NMDA receptor), Parkinson's disease, striatum, synaptic plasticity.

Abbreviations used: AIM, abnormal involuntary movement; AMPA, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid; BG, basal ganglia; CaMKII, Ca^{2+} /calmodulin-dependent protein kinase II; DA, dopamine; DARPP-32, dopamine- and cAMP-regulated phosphoprotein of 32 kDa; HFS, high-frequency stimulation; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; MAGUK, membrane-associated guanylate kinase; MSN, medium spiny neuron; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PKA, protein kinase A; PP, protein phosphatase; PSD, postsynaptic density; SAP, synapse-associated protein; SNc, substantia nigra pars compacta.

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MSNs, *in vitro* as well as *in vivo*. The most common protocol utilized to obtain persistent changes in the efficacy of synaptic transmission is the HFS (high-frequency stimulation) of the corticostriatal fibres.

The direction of the plasticity (weakening or strengthening), at least *in vitro*, is critically dependent upon the level of membrane depolarization and the ionotropic glutamate receptor subtypes involved. The increase, as well as the decrease, in synaptic efficacy are expressed as changes in evoked excitatory postsynaptic potentials or currents (EPSPs and EPSCs respectively) principally mediated by NMDA (*N*-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) glutamate receptors. Striatal LTP, under our experimental conditions, is usually induced after delivery of HFS in Mg^{2+} -free external medium [3]. This experimental procedure allows the activation of NMDARs (NMDA receptors) which is mandatory for corticostriatal LTP induction. In fact, NMDAR activation requires the coincidence of presynaptic glutamate release and strong postsynaptic membrane depolarization to relieve the Mg^{2+} block of the channel.

In contrast, LTD is induced by the same stimulation protocol in the presence of Mg^{2+} ions, since NMDARs are not involved in this form of synaptic plasticity. A further type of synaptic plasticity occurring in MSNs is the depotentiation, induced by an LFS (low-frequency stimulation) protocol after the induction of LTP. Depotentiation represents a homeostatic mechanism which allows the reversal of previously induced strengthening of synaptic efficacy in order to remove redundant synaptic information and, consequently, increase storage capability [8,9]. In terms of signalling pathway, this form of synaptic plasticity is strictly dependent on the activation of PPs (protein phosphatases) [10] recruited after activation of DA receptors. The activated signalling cascades converge on the modulation of the protein DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa) which, in turn, regulates phosphorylation levels of several target proteins, such as NMDARs [11].

Role of DA in synaptic transmission and plasticity

DA acting on D_1 - and/or D_2 -like receptors plays a critical role in driving all the above-mentioned forms of synaptic plasticity. The specific involvement of DA in these phenomena has been thoroughly established by the study of synaptic plasticity in striatal neurons recorded *in vitro* from PD-affected rats. In fact, PD is primarily a movement disorder characterized by a severe neurodegeneration of dopaminergic neurons of the SNc, projecting to the striatum.

The most common PD animal model is obtained by the hemilateral injection of 6-OHDA (6-hydroxydopamine) toxin into the nigrostriatal terminals, causing nearly complete degeneration of dopaminergic neurons and consequently a deep deficit of DA in the striatum.

Dopaminergic deafferentation leads to severe alterations in striatal basal synaptic transmission and plasticity. Several

reports suggest that DA deficit causes an overactivity of the glutamatergic transmission expressed in part as an increase in excitatory spontaneous activity of MSNs [12–14]. This effect reflects reduced activation of presynaptic D_2 receptors, which in physiological conditions, control glutamate release [15].

The increased glutamate level in the synaptic cleft [16], out of dopaminergic control, is consequently responsible for the overactivity of NMDARs and AMPARs (AMPA receptors) on MSNs. At the postsynaptic level, decreased activation of D_2 receptors leads to a disinhibition of voltage-gated ion channels and increased influx of Ca^{2+} [17]. This overload in Ca^{2+} seems to be a key factor in the degeneration of the spines observed in PD-affected animals, as in PD patients [17–21]. Dendritic spines are known to be the locus of synaptic plasticity in physiological conditions [22]. Therefore the profound alterations of spines observed in PD are obviously associated with impairment of synaptic plasticity. Indeed, delivery of HFS in corticostriatal slices, collected from PD-affected rats, fails to induce either LTP [5] or LTD [13]. The absence of these two phenomena might be the cellular basis underlying the abnormalities in striatal output within the BG and consequently the prime mover in the appearance of PD symptoms [4,23].

These experimental observations have shed light on the pivotal role that DA exerts in modulating glutamatergic transmission and synaptic plasticity within the striatum. Specifically, DA acting on D_1 receptors is determinant in the induction of LTP, whereas activation of both D_1 and D_2 receptors is required for LTD [9,24,25]. Bath-applied DA in denervated striatum as well as co-application of D_1 and D_2 receptor agonists restore LTD [6,24]; in contrast, D_1 receptor agonists or DA fail to restore LTP [26].

NMDAR alterations in 6-OHDA-denervated striata

The inability of bath-applied DA in rescuing LTP in DA-depleted striata is most likely to be dependent on the modifications occurring in PSD (postsynaptic density), a region highly enriched in NMDARs.

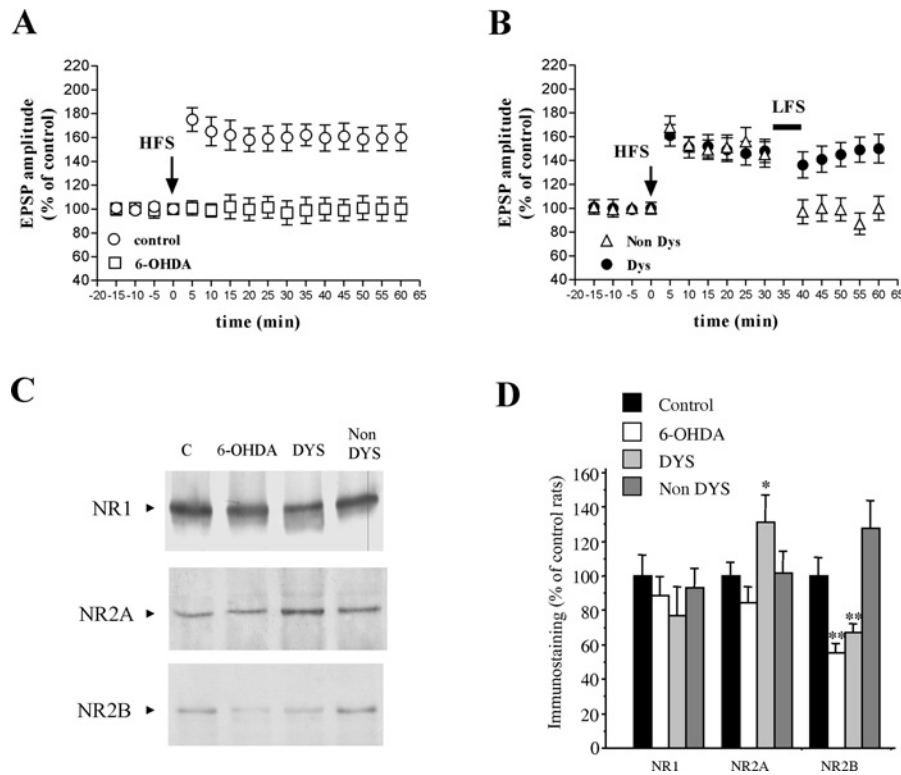
In fact, activation, correct assembly and localization of the NMDAR complex within the synapse is determinant in the induction of LTP [27]. NMDARs are thought to consist of four subunits: two obligatory NR1 and two NR2 subunits (two of NR2A–NR2D). The latter determine not only the gating properties, but also different signalling pathways downstream of NMDAR, thus conferring different roles in neuronal function.

In the postsynaptic compartment, NMDAR is coupled to interacting elements, i.e. members of MAGUK (membrane-associated guanylate kinase) proteins such as PSD-95, SAP (synapse-associated protein) 102 and SAP97 [28,29].

The receptor linkage to PSD-95 controls the interaction between the receptor, the intracellular proteins and the signalling enzymes. In DA-denervated striatum, NMDA-NR1 subunit and PSD-95 protein levels are selectively reduced in the PSD [27,29]. Moreover, binding of NR2B

Figure 1 | Role of NMDAR subunits in striatal spiny neuron synaptic plasticity in an experimental model of dyskinesia

(A) HFS (arrow) of corticostriatal glutamatergic fibres induces LTP in MSNs recorded from control (○, physiological conditions), but not in PD-affected (□) rats. (B) Effect of HFS and LFS respectively on L-dopa-treated non-dyskinetic (Non Dys; △) and dyskinetic (Dys; ●) rats. (C) Western blot analysis of the NR1, NR2A and NR2B subunits in control, PD, non-dyskinetic (Non DYS) and dyskinetic (DYS) rats. (D) Quantification of Western blotting for NR2A, * $P < 0.05$, dyskinesia compared with control; NR2B, ** $P < 0.01$, dyskinesia compared with control and 6-OHDA compared with control; $n = 8$ for each group). EPSP, excitatory postsynaptic potential. Modified from [26] and [29] with permission.



to SAP102 and SAP97 (which regulate the delivery of the NMDAR subunit to the membrane) is significantly reduced in DA-denervated rats; accordingly, NR2B protein levels are reduced in PSD [29]. It is well established that functional characteristics, subcellular distribution and anchoring to plasma membranes of NMDARs are regulated by their phosphorylation state, in physiological and pathological conditions. CaMKII (Ca²⁺/calmodulin-dependent protein kinase II) and tyrosine-dependent phosphorylation of NMDARs increase after nigrostriatal denervation, leading to receptor sensitization [30,31]. We found that CaMKII overactivity is a result of increased levels of α CaMKII autophosphorylation [27]. Since CaMKII is crucial for synaptic plasticity events [32,33], its hyperphosphorylated state in the 6-OHDA striatum could account for the lack of LTP. In this view, treatments that restore normal levels of CaMKII activity and its autophosphorylation in the PSD rescue LTP in DA-denervated striatum and improve motor performances in PD-affected animals [27].

L-Dopa therapy and dyskinetic side effects

Therapeutic strategies in PD consist principally in administration of drugs restoring dopaminergic transmission either

by direct stimulation of DA receptors (D₁ and/or D₂ receptor agonists) [34,35] or by increasing endogenous levels of DA using its precursor L-dopa. Nevertheless, even if L-dopa remains the mainstay for PD therapy, its long-term use is often complicated by fluctuations in the drug efficacy ('on-off' state) and by significantly disabling AIMs (abnormal involuntary movements) called, as a whole, L-dopa-induced dyskinesia. Dyskinetic side effects can become even more incapacitating than the PD state, thus negating beneficial effects deriving from L-dopa therapy.

Chronic L-dopa treatment of PD-affected rats aims to rescue physiological levels of DA in the striatum, improves motor performances (akinesia and asymmetry in forelimb use), reduces overactivity of CaMKII and allows recovery of synaptic plasticity in MSNs [27]. However, PD-affected rats treated chronically with L-dopa experience severe side effects in approx. 50% of cases, resembling the situation that occurs in treated patients [9,36].

From an electrophysiological point of view, L-dopa is able to restore the physiological synaptic plasticity only in those animals which show beneficial effects of the therapy and do not develop dyskinesia. In fact, in slices recorded from non-dyskinetic animals, the mechanism of LTP is rescued

by L-dopa and the LFS protocol is able to induce the depotentiation. Conversely, the depotentiation is completely lost in MSNs recorded from dyskinetic animals [9].

It has been proposed that the impossibility to restore the level of synaptic transmission preceding LTP in dyskinetic animals may represent an aberrant form of plasticity that underlies the appearance of dyskinetic movements [9]. As stated previously, depotentiation at corticostriatal synapses involves PP activity. D₁ and D₂ receptor signalling pathways converge in opposite manners on a common target, DARPP-32 [11]. In particular, DA acting on D₁ receptors increases PKA (protein kinase A) activity, leading to phosphorylation of DARPP-32 at Thr³⁴. In this phosphorylated state, DARPP-32 exerts a potent inhibition of PP1 [11]. Since dyskinetic animals express significantly higher levels of Thr³⁴-phosphorylated DARPP-32 than non-dyskinetic rats and control animals, it is likely that the lack of depotentiation and consequently emergence of dyskinesias are closely related to alterations of the D₁/PKA/DARPP-32 signalling pathway [9].

Involvement of NMDARs in L-dopa-induced dyskinesia

Despite considerable advances, the specific cellular mechanisms leading to the occurrence of dyskinesia have yet to be elucidated. Several potential mechanisms have been proposed and, among them, enhanced activation of the striatal glutamate receptors, particularly the NMDAR subtype, appears to be a major factor in the expression of dyskinetic movements [37].

Strikingly, our previous data indicate that abnormalities in the subcellular distribution of NMDAR subunit NR2B may represent a major causal factor in the complex modifications taking place at corticostriatal glutamatergic synapses during dyskinesia. Of relevance, the PSD of dyskinetic animals exhibits increased levels of NR2A and lower levels of NR2B, which are increased in extrasynaptic sites. These events are paralleled with profound alterations in the binding of NMDAR subunits with their cargo proteins, in particular SAP97 and SAP102 [29].

Impairment of the physiological trafficking of NMDAR subunits from the reticulum toward the PSD may underlie the enhancement of NMDAR signalling in dyskinesia. In conclusion, our data suggest that redistribution of NMDAR subunits represents the principal event in striatal neurons in PD and L-dopa-induced dyskinesia [29,38].

To make this concept more convincing, we have treated non-dyskinetic animals intrastrially with a cell-permeable peptide (TAT2B), able to alter the NR2B synaptic localization by perturbing its binding with MAGUK proteins, mimicking the condition observed in the dyskinetic state. As expected, the TAT2B peptide induced AIMs in non-dyskinetic animals [29].

As a matter of fact, from a clinical point of view, the goal would be to treat dyskinesia, rebalancing the altered ratio in NMDA subunits by administration of TAT2A in dyskinetic animals, aimed to perturb NR2A delivery to the NMDAR complex. Our hypothesis, under present investigation, is that

preventing NMDA subunit ratio imbalance in the PSD, by concomitant administration of TAT2A peptide and L-dopa, may prevent dyskinetic abnormalities. Further studies are required to provide additional experimental support for this hypothesis.

These concepts may expand our understanding of the intricate scenario of dyskinesia at the level of the corticostriatal pathway and support the research into novel strategies to treat dyskinesia.

Funding

This work was supported by the European Community Contract number 222918 (REPLACES) Framework Programme 7-Thematic Priority Health (to P.C.), Ministero della Salute Progetto Strategico 2007 (to P.C. and B.P.), Progetti Finalizzati Ministero della Salute 2006-2008 (to P.C. and B.P.), Progetti Finalizzati Multicentrici Programma Neuroscienze Compagnia di San Paolo (to P.C.) and Fondazione Cassa di Risparmio di Perugia (to P.C.).

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Received 6 August 2009
doi:10.1042/BST0380493