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Normal and Physio-Pathological Striatal Dopamine Homeostasis

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1. Introduction

The neurotransmitter Dopamine (DA) exerts a dual function in the striatum (STR), the latter comprising the caudate and putamen nuclei, the main structures in the central nervous system from which it is released. During the last 50 years, numerous studies have highlighted the role of DA in sensory/motor loops. Along with a phasic function exerted in synaptic or close apposition structures, a modulatory role for extracellular DA has also been demonstrated based on the slow and tonic extracellular diffusion of the amine. This duality is probably supported by a metabolic polymorphism, particularly of the release mechanism. The present chapter focuses on works carried out *in vivo* over the last two decades on the control of DA homeostasis in the STR during normal and pathological conditions. It is now generally accepted that the level of extracellular DA is not simply the consequence of dribbling from the synapse after phasic (firing-dependent) overflow but is maintained through tonic, largely non-synaptic, regulatory processes.

The duality of DA release *in vivo* will first be described. An example of an experimental situation allowing this situation to be characterized will be given, followed by a brief overview of the relevant literature from the last three decades.

The tonic regulatory process remains incompletely understood and still requires thorough analysis. In recent years, *in vivo* and *in vitro* studies have led to the development of theoretical models based on the concept of the reversion of the well-known uptake mechanism involving the DA transporter protein (DAT). In particular conditions, DAT could be involved in the control of the extracellular DA concentration through its ability to perform what is called reverse DA transport (DA-RT). Psychotropes from the amphetamine family are known to induce the release of DA through this mechanism, but the physiological involvement of DA-RT has rarely been addressed.

A large number of regulatory processes have been described concerning tonic DA release. Only two aspects of these regulatory processes will be considered here. Specific experiments devoted to showing the role of DA synthesis and extracellular calcium ions will be described and discussed.

The two first paragraphs will be devoted to the duality of normal DA neurotransmission. It is however crucial to understand how the two different mechanisms of release (tonic and phasic) could maintain their equilibrium in pathological situations. Numerous animal models of neurodegeneration have been created. To date, only situations mimicking the early phases of parkinsonian neurodegeneration have been used to explore this equilibrium. Original results will also be presented here. These will provide new information on the regulatory modulation of the tonic and phasic release occurring during the initial pre-symptomatic compensatory phases of Parkinson's disease.

2. The dual DA release process

The extracellular DA concentration in the caudate nucleus could be relevant to something other than the electrical activity of dopaminergic cells. Increased DA release was even observed in the STR under experimental conditions that decreased cell firing in the substantia nigra (SNc, Romo et al., 1986). Since the first proposal by Raiteri et al. (1977) that DA could be released by a calcium-independent and carrier-mediated process, numerous authors have claimed that the firing-dependent release of DA does not explain all the reported alterations in the extracellular DA concentration and that an additional release mechanism must exist (Liang and Rutledge, 1982; Parker and Cubeddu, 1986; Vizi and Labos, 1991). In 1991, A. Grace gathered relevant data and proposed the presence of two modes of release of the amine in the STR (Fig 1), one 'phasic', taking place within the millisecond range, and controlled by the firing running on DA axons, and a 'tonic' mode, taking place over minutes or hours and mainly dependent on various direct influences on the DA terminals including that of Glutamate (GLU). Using differential pulse amperometry (DPA) simultaneously associated with local superfusion and HPLC detection we observed this dual release of DA in response to axonal stimulation and the application of GLU agonists (Fig. 2; Olivier et al., 1995).

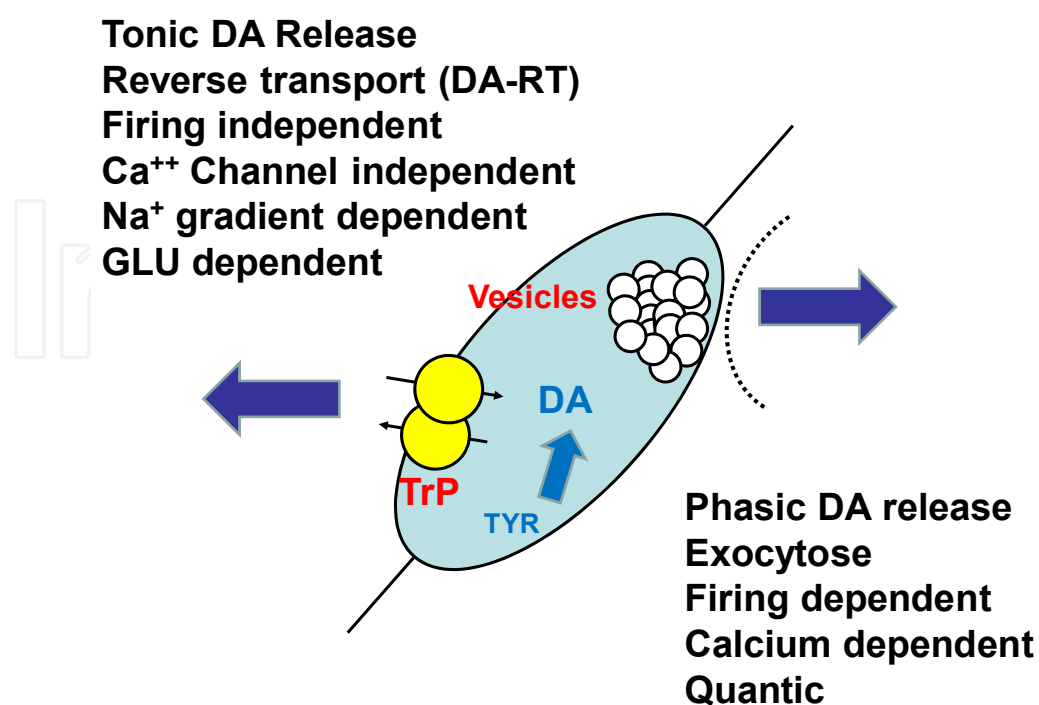


Fig. 1. The dual release of DA through vesicles exocytose or DA transport (TrP).

2.1 Spontaneous and evoked DA release

Dual release can be demonstrated by the simultaneous use of two probes. DPA uses a carbon fiber electrode to detect the DA released following stimulation of the DA axons in the Medial Forebrain Bundle (MFB) in the lateral hypothalamus. Every 4 minutes, a 20-second stimulation-train pulse produces a large increase in the amperometric signal in the STR that is strictly restricted to the stimulation period (Fig. 2, Olivier et al., 1995). The amplitude of the peaks that occur is roughly constant over time. As discussed elsewhere by Gonon (1988) and Suaud-Chagny et al. (1992), the increase in the oxidation current under these conditions is likely to be mainly due to the DA released, despite the fact that some of this increase could be due to dihydroxyphenyl acetic acid (DOPAC), the first DA metabolite. Stimulation of the MFB alters the differential oxidation current but is ineffective in terms of the amount of regional extracellular basal DA measured through a cannula close to the probe used for DPA. The DA collected through the superfusion system originates from a region considerably larger than the carbon fiber. The carbon fiber is only sensitive to events occurring in the range of μm from its surface whereas the superfusing probe collects diffusing molecules from within several hundreds of microns. Differences also arise from the duration of the measurements. Stimulation of the MFB only lasts for a short period of the collection time (here 0.08%). Given this short period of time, any increase in the release of the amine remains undetectable in the superfusing fluid. The superfusing methods are particularly useful for detecting 'regional' fluctuations whereas voltammetry reports local events.

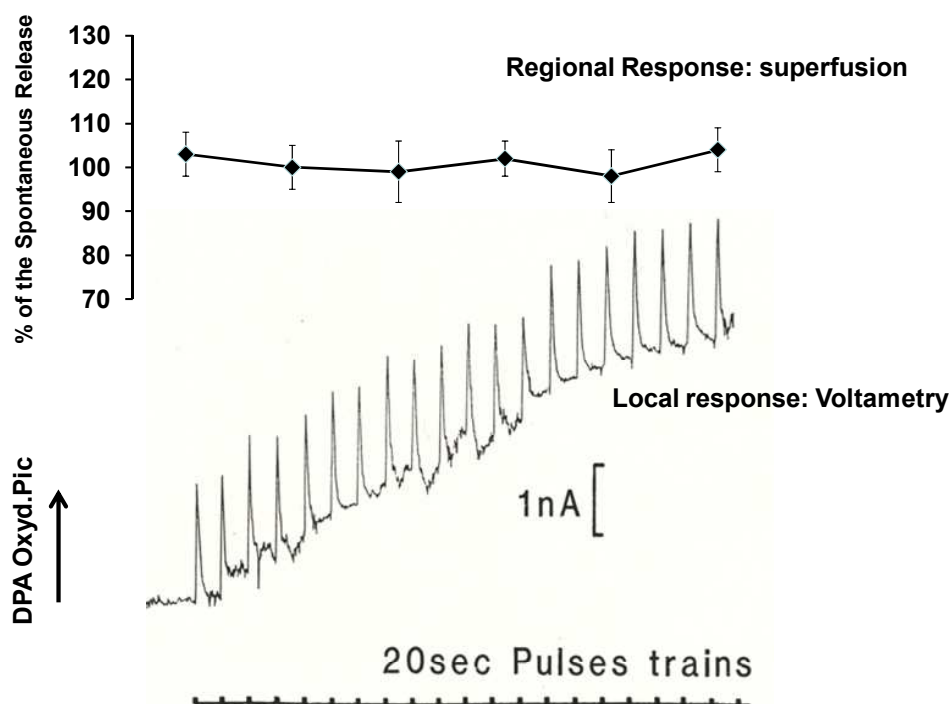


Fig. 2. The effect of MFB stimulation on tonic (up) and phasic down DA release

Superfusion in the presence of cadmium ions:

To block the voltage-dependent calcium channel, 100 μM cadmium was added to the artificial LCR supplying the cannula. This treatment blocks the stimulation-evoked release of DA detected using DPA (Fig. 3). The same effect can be obtained using 1 mM cobalt (not shown) in place of cadmium and remains unchanged in the presence of 0.5 μM GBR12909, a DAT inhibitor. Surprisingly, in the presence of cadmium or cobalt the amount of DA detected in the superfusing fluid greatly increased during the first 40 minutes of application (Fig. 3). Over this period of time, the DA collected fell below control values. When 0.5 μM GBR12909 was simultaneously added with cadmium, no further increase in the amount of DA was detected in the superfusing fluid.

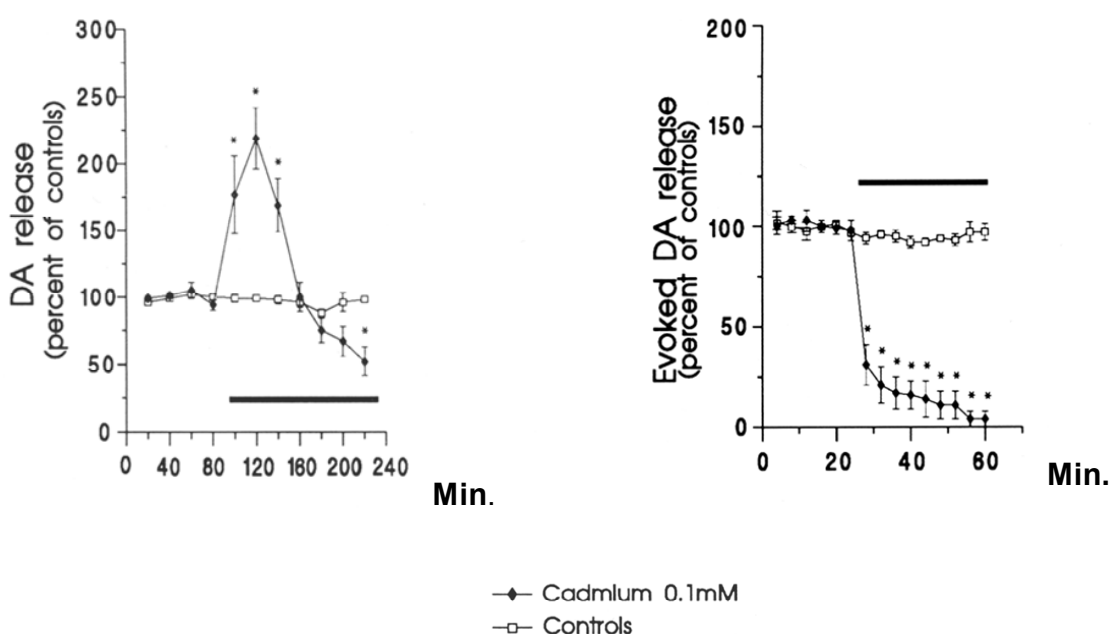


Fig. 3. Blockade of calcium channels via local application of cadmium

Local superfusion with GLU agonists:

Addition of the GLU agonists NMDA (1 mM) and kainate (0.1 mM) to the superfusing fluid increased the amount of DA collected through the push-pull cannula and reduced the amperometric signal evoked by MFB stimulations (Fig. 4). The reduction in the amperometric signal was not counteracted by the presence of 0.5 μM GBR12909. In contrast the increase in the spontaneous release measured through the cannula in response to NMDA or Kainate application completely disappeared.

2.2 From quantal release to reverse transport, the duality of DA release

These experimental observations constitute the most simple and direct evidence of the presence of a double mechanism of release of DA from the DA terminals in the STR. A large set of complementary data will now be briefly reviewed.

Can DA homeostasis be regulated by the firing-evoked synaptic release of DA?

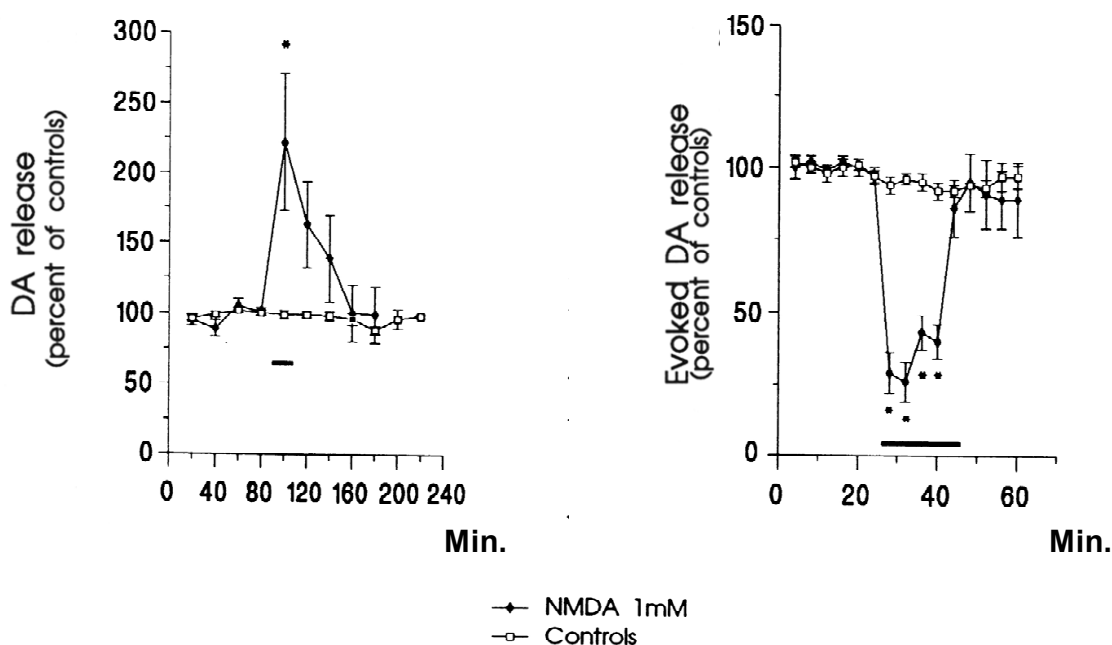


Fig. 4. The dual effect of GLU receptor blockade

The first evidence that regional extracellular DA and synaptic DA are not governed by the same mechanism is derived from the fact that although they should vary in parallel, that is clearly not the case. Many observations based on voltammetry have confirmed the ability of DA axons transiting through the MFB to carry an electrical potential, since an increase in extracellular DA can occur in response to electrical stimulations of the MFB (see above, Ewing and Wightman, 1984; Ewing et al., 1983; Gonon and Buda, 1985; Kuhr et al., 1986; Stamford et al., 1986). The voltammetric approach can only be used in a very restricted region of the space due to the size of the probes used. When using methods suitable for larger regions (microdialysis, push-pull cannula systems), it became clear that to alter DA levels in the STR, stimulation of the DA afferents required axonal recruitment and stimulation frequencies outside the physiological range (Grace, 1991; Olivier et al., 1995). Indeed, more than 60–70% of DA varicosities were found to be asynaptic, and DA synapses represent only about 1.8–7% of all striatal synapses (Decarries and Mechawar, 2000). Even if DA cell firing can elicit DA release in the STR for a brief period of time, the synaptic DA released may not be the only contributor to extracellular DA levels and would not be expected to be responsible for homeostatic DA control in the STR (Grace, 1991; Levi and Raiteri, 1993; Olivier, 1995). DA concentration is probably only partially monitored by nigral DA firing cells and DA homeostasis is unlikely to be controlled by spill-over of the amine from synaptic events.

Using DAT to re-visit DA release: DA-RT

It has been known for many years that exocytosis is not the only outward process of the neurotransmitter exchange between neurons and the extracellular space (Stein, 1967). Regarding monoamines, several models in the peripheral nervous system have been proposed that are generally based on exchange diffusion (Bogdanski and Brodie, 1969; Paton 1973a, 1973b). Concerning the release of DA in the central nervous system, DAT was thought to be partly involved in DA release by some authors (Marchi et al., 1985; Olivier et al., 1995; Raiteri et al., 1979) and the mechanism of this carrier-mediated release came from

observations on psychostimulants and amphetamine-like substances (Butcher et al., 1988; Fisher and Cho, 1979; Leviel, 2001; Levi and Raiteri, 1993; Nash and Brodtkin, 1991). In this process, transmitter molecules are transported outside the cell, most likely via an exchange-diffusion process. This mode of transfer has been extensively studied and various mathematical models have been proposed over the course of the last four decades (Chubb et al., 1972; Stein, 1990, for a review; Thoenen et al., 1969; Wheeler et al., 1993; Ziance and Rutledge, 1972).

During the 1980s, several studies were devoted to the regulatory mechanism of DA release in the STR and the substantia nigra pars reticulata (SNr). Particular attention was given to the control of striatal release, which is known to be regulated by GLU. It appeared that, in addition to a spike-mediated DA efflux, GLU-induced amine overflow could occur independently of any sodium or calcium transfer. This would mean that some of the extracellular DA, the NMDA-mediated DA that is released, is not dependent on the firing of DA neurons (Carter et al., 1988; Cheramy et al., 1986; Giorgiueff et al., 1977; Jhamandas and Marien, 1987). The NMDA-mediated release of DA even remained unchanged when the nigrostriatal pathway was blocked with lesions or tetrodotoxin (Keefe et al., 1992, 1993). Recently, using voltammetry associated with electrochemical detection, the same type of observation was again reported (Borland and Michael, 2004). Such observations had already led Anthony Grace to propose, at the beginning of the 1990s, that DA could be released in the STR following two different types of mechanism (Grace, 1991): first, the firing-dependent exocytosis of quantal amounts of amine previously stored in specific pools, and, simultaneously, NMDA-mediated release.

More recently, Falkenburger et al. (2001) confirmed the existence of DA-RT in slices from rat SNc. This explained at least part of the dendritic release of DA. The presence of the somato-dendritic release of DA from the nigrostriatal cells has been known for many years (Cheramy et al., 1981) but the mechanism of this release was, and remains, an open question. As in the experiment conducted by Olivier and co-workers, the demonstration was based on the use of DAT inhibitors (GBR 12909, GBR 12935) that were able to block the GLU-induced release of DA. In a more recent study (Opazo et al., 2010), the voltammetric current corresponding to outward moving DA was increased by adding 1-Aminocyclopentane-trans 1,3 dicarboxylic acid (*trans* ACPD), an activator of the GLU group I mGLUR, to rat nigral slices. This confirmed the role of GLU in this type of DA release. It was also demonstrated that protein kinase C (PKC) activation produced a robust increase in external DA levels that was reversibly inhibited by GBR 12935, a well-known DAT inhibitor. These observations confirmed the identities of the two DA releasing processes. These observations were also made *in vitro* in an engineered neuroblastoma cell line (SH-SY5Y cells) stably expressing DAT (Opazo et al., 2010).

The two release processes act simultaneously in both the SNc and the dSTR. As mentioned above, and given the various morphologies of DA neurons (Arluison et al., 1978; Gauthier et al., 1999; Gerfen et al., 1987; Prensa et al., 2000), the possibility that some types of DA neurons could be specialized in one or the other of the release modes cannot be excluded. For instance, it is noteworthy that mesencephalic DA neurons from the ventral tegmental area poorly express DAT (Blanchard et al., 1994; Ciliax et al., 1999; Mengual and Pickel, 2004; Nirenberg et al., 1996; Sesack et al., 1998). The dual release function of DA neurons may not be equally distributed throughout the whole population of DA cells. The term

'volume transmission', developed in the 1980s (Agnati et al., 1986) and recently used to characterize DA neurotransmission, does not refer to a mode of release but rather to a mode of extracellular transmission. The terms 'phasic release' and 'tonic release' most frequently refer to the pattern of discharge of the DA axons (regular or bursting). The most appropriate terms that have emerged to date to qualify the present types of neurotransmitter release are 'quantal' for the firing-dependent process and 'reverse transport' (DA-RT) or 'lateral release' for the carrier-mediated mechanism. We also use the term 'lateral release' to refer to the non-synaptic localization of this mechanism, due to the extra-synaptic position of the DA transporter. In this case, 'axial release' could refer to synaptic transmission.

3. Regulatory mechanisms

It has already been shown that the extracellular level of calcium (Ca^{++}) ions has an important influence on neurotransmitter release (Katz and Miledi, 1970; Augustine et al., 1987; Smith and Augustine, 1988; Mulkey and Zucker, 1991) and on enzyme activities (Kapatos and Zigmond, 1982; El Mestikawy et al., 1983; Haycock, 1993). Since transient increases in Ca^{++} within nerve terminals are spatially restricted (Lipscombe et al., 1988; Meldolesi et al., 1988; Miller, 1991) it may be hypothesized that Ca^{++} independently affects multiple processes within the different ultrastructural compartments of the nerve terminal. The metabolism and release of DA in the STR constitute an appropriate experimental model with which to investigate the potentially distinct effects of Ca^{++} . In the dopaminergic neurons DA synthesis depends on the activity of tyrosine hydroxylase (TH), the rate-limiting enzyme in its synthetic pathway (Levitt et al., 1965). This enzyme is activated by phosphorylation under the control of various protein kinases, including two Ca^{++} -dependent ones, the Ca^{++} -phospholipid-dependent protein kinases (PKC) and the Ca^{++} -calmodulin-dependent protein kinase (PKII) (El Mestikawy et al., 1983; Albert et al., 1984; Zigmond et al., 1989; Haycock, 1993).

Below we will present further data about the dual control exerted by Ca^{++} ions on DA synthesis and on DA-releasing processes. The apparent challenge between synthesis and release in the effects of Ca^{++} is coming from the fact that DA-RT acts on cytoplasmic DA, unlike exocytosis, which affects a previously vesicularised stored pool of DA. It can thus be hypothesized that DA-RT should be more sensitive to those treatments affecting synthesis.

3.1 Synthesis, calcium ions and DA release – Experimental report

We describe here the only method known to evaluate DA synthesis and release simultaneously *in vivo* in anesthetized rats. The method is based on the measurement of the specific activity (DA_{sa}) of the DA released during continuous superfusion of the tissue with the tritiated DA precursor, [^3H]tyrosine. It was previously observed that the neosynthesized amine is released preferentially to an oldly stored pool. Taking advantage of this metabolic specificity, it can be postulated that: 1) increased DA_{sa} during higher levels of release reflects enhanced synthesis and 2) decreased DA_{sa} associated with increased levels of release reveals the involvement of stored amine (vesicular) and suggests reduced or insufficient synthesis. The DOPAC efflux is also considered to be a robust index of DA synthesis (Zetterström et al., 1988; Leviel et al., 1989). In other words, any treatment reducing synthesis should reduce cytoplasmic DA_{sa} and the DOPAC efflux. In contrast, any treatment activating synthesis should elevate DA_{sa} and the DOPAC efflux.

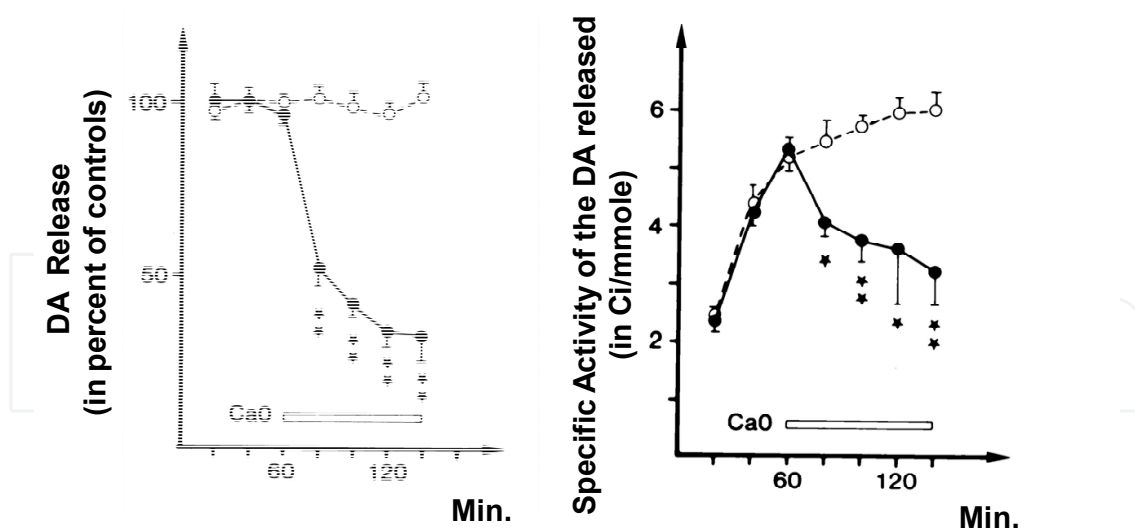


Fig. 5. Superfusion with CSF from which Ca^{++} was omitted

Superfusion with calcium-free medium and α -methyl para-tyrosine (α -mpt)

We already know that local superfusion with the calcium channel blockers cadmium and cobalt enhances regional DA release and blocks firing-induced exocytosis. Removing Ca^{++} ions from the superfusing medium (Ca0) led to a sharp decrease in DA release, stabilizing at around 30% of the basal value after about 80 min. This effect was accompanied by a lowering of the specific activity of DA_{sa} and of $[^3\text{H}]\text{DOPAC}$ (Fig. 5). The addition of α -mpt, a TH inhibitor, did not modify the effect of Ca0 treatment: the DA collected in each 20-minute fraction also stabilized at around 30% of the spontaneous values (Fig. 6). These two effects were thus not additive, and the lowering of the DA_{sa} produced by superfusion with Ca0 was of the same amplitude as that observed in the α -mpt treatment. This observation strongly suggests that the main effect of Ca0 could be the inhibition of DA synthesis (Olivier et al., 1999).

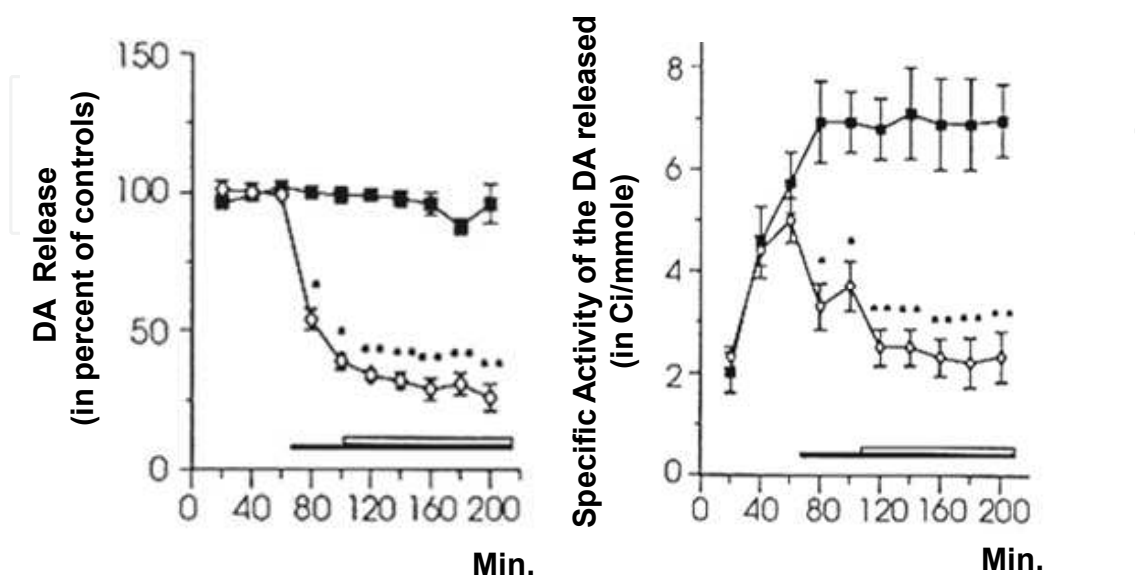


Fig. 6. The inhibition of DA synthesis during superfusion in the absence of Ca^{++}

Superfusion with calcium ionophore (A23187): The forced entry of calcium

Adding the Ca^{++} ionophore A23187 (1 $\mu\text{mol/l}$) to the superfusing fluid for 20 min had no effect on the spontaneous release of DA or DAsa (Fig. 7). However, an increase in DOPAC (25%) was associated with a 50% increase in the $[\text{3H}]\text{DOPAC}$ concentration.

It is possible to evaluate the effect of the calcium ionophore A23187 on DA synthesis 'in vivo'. A high dose of amphetamine can be superfused to produce the maximum overflow of the intraterminal DA. Thus 1 hour after administering 20 min of 1 mmol/l amphetamine, the total intraterminal DA had increased, particularly the DA_{sa} (Olivier et al., 1999). This demonstrates a large increase in synthesis during this period of time.

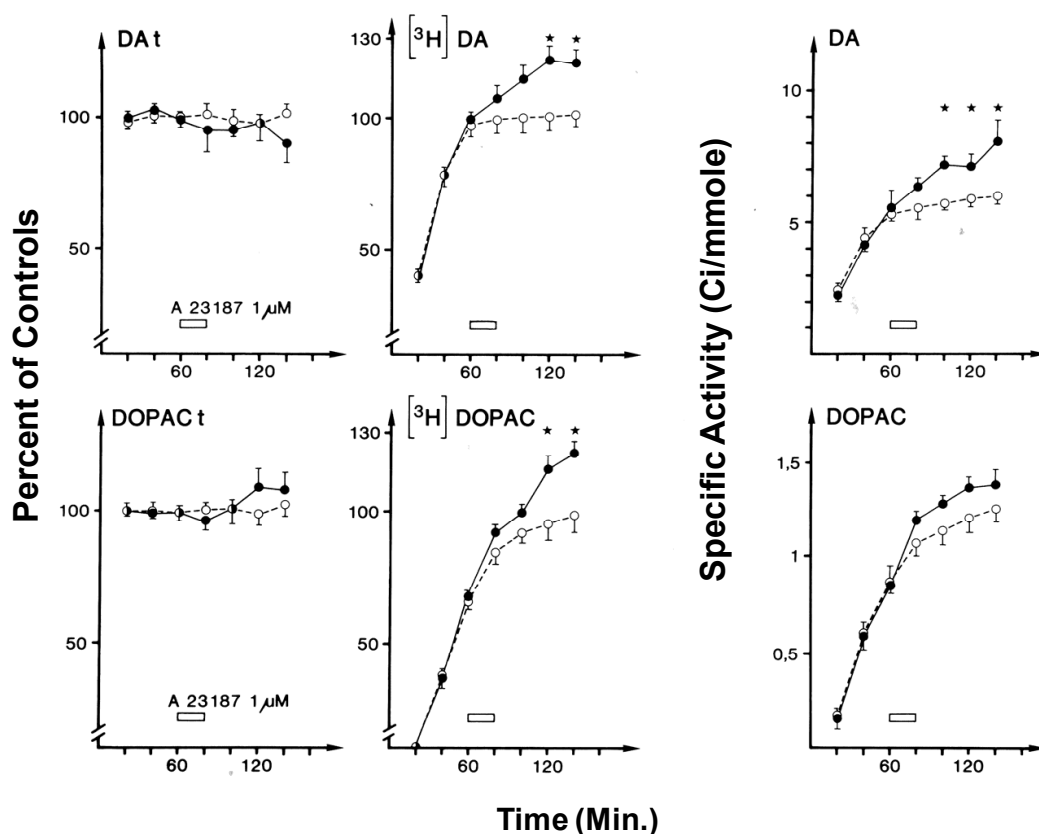


Fig. 7. Superfusion with the Ca ionophore A23187 increases DA synthesis and DOPAC efflux

3.2 The effect of extracellular calcium ions on DA-RT

The above observations confirm that Ca^{++} ions are involved in different steps of DA metabolism, including not only the processes of release (Augustine et al., 1987) but also synthesis (Kapatos and Zigmond, 1982; El Mestikawy et al., 1983; Haycock et al., 1984). We have not directly measured the enzymatic activity of TH, but alterations in synthesis were revealed by the dynamic variations in DA_{sa} and the $[\text{3H}]\text{DOPAC}$ efflux. Indeed the DA_{sa} can be used as an index of DA synthesis (Herdon et al., 1985) since the newly synthesized DA has a higher specific activity than the stored amine (Leviel et al., 1989). $[\text{3H}]\text{DOPAC}$ might also be considered as a good index of amine synthesis according to many authors (Herdon

et al., 1985; Soares-Da-Silva, 1987; Zetterström et al., 1988; Leviel et al., 1989; Soares-Da-Silva and Garrett, 1990a, 1990b), who have proposed that extracellular DOPAC originates from an unreleased and recently synthesized pool of dopamine.

Ca⁺⁺ ions in the regulation of DA synthesis:

Removal of Ca⁺⁺ from the superfusing fluid induced a large decrease in DA_{sa} and in [³H]DOPAC efflux, suggesting reduced DA synthesis. Furthermore the addition of a TH inhibitor, namely α -mpt, to a Ca⁺⁺-free superfusing fluid did not further decrease the DA_{sa} or the [³H]DOPAC, suggesting that the activity of TH is already maximally inhibited by Ca⁺⁺ removal. TH activity could be inhibited by a rise in DA feedback inhibition resulting from the lowering of Ca⁺⁺-dependent exocytosis (Leslie et al., 1985; Zucker and Lando, 1986; Westerink et al., 1988). However, the intracellular accumulation of DA should result in increased DOPAC efflux, which was not observed. Conversely, the reduced DA_{sa} revealed that even to maintain a low rate of DA release, stored amine (with a low specific activity) has to be involved, showing that in the absence of extracellular calcium ions, DA synthesis is unable to sustain the lower DA release (30% of the control value).

Superfusion without Ca⁺⁺ in the CSF appears to be able to reduce synthesis. Forced Ca⁺⁺ entry could have the opposite effect. Indeed a low dose of the Ca⁺⁺ ionophore A23187 (1 μ mol/l) slightly increased [³H]DA and [³H]DOPAC efflux, suggesting an increase in DA synthesis (Fig. 7). Such activation of synthesis was confirmed by the potentiation of the amphetamine-induced [³H]DA release that followed pretreatment with A23187 1 μ mol/l (Olivier et al., 1999).

This set of simple data is consistent with the concept that moderate Ca⁺⁺ entry is positively coupled with DA synthesis and that its absence from the extracellular medium is negatively coupled with DA synthesis (Kapatos and Zigmond, 1982; El Mestikawy et al., 1983; Haycock et al., 1984).

Ca⁺⁺ ions in the regulation of DA-RT:

Surprisingly, *in vivo* blockade of the Ca⁺⁺ ion channel with Cd⁺⁺ ions activates DA-RT from the DA terminals, an effect that was inhibited by further application of GBR 12909, a DAT inhibitor. The mechanism by which Cd⁺⁺ affects DA-RT is not clear. For a long time, reversal of the Na⁺ gradient was proposed to reverse DA transport (Roth et al., 1976; Amejddki-Chab et al., 1992; Levi and Raiteri, 1993; Okada et al., 1990). It was also proposed by Olivier et al. (1999) that Cd⁺⁺ indirectly alters DA-RT via Na⁺/K⁺ ATPase activity, a hypothesis also proposed for the action of AMPH (Khoshbouei et al., 2003; Pal et al., 1993).

After applying a Ca⁺⁺ ionophore, A23187, DA synthesis increased. With the classical model used for DA-RT of an exchange diffusion process, it is clear that the cytosolic DA constitutes the direct substrate for internal DAT-sites, regardless of its affinity. Thus, from these experiments, and despite the fact that DA-RT can be considered as being firing-independent, many observations during the last decade have confirmed indirect calcium action on DA-RT (Fog et al., 2006; Gnegy et al., 2004; Kantor et al., 2001; Page et al., 2004).

Numerous reports highlight the role of Ca⁺⁺ in the amphetamine-dependent DA-RT. The Ca⁺⁺ chelator BAPTA-AM reduced amphetamine-induced DA efflux as measured by amperometry. A particularly interesting observation was that superfusion of rat striatal slices with 50 μ M BAPTA-AM suppressed the amphetamine-induced release of endogenous

DA. However, the same treatment had no effect on basal DA in the absence of AMPH. These studies demonstrated that AMPH-induced and DAT-mediated currents producing substrate efflux require internal Ca^{++} release from intracellular stores and that amphetamine can stimulate dopamine efflux by regulating cytoplasmic Ca^{++} levels (Gnegy et al., 2004). It has also been shown that Ca^{++} /calmodulin-dependent protein kinase-II (CaMKII) plays a key role in the amphetamine-mediated efflux of DA in heterologous cells and dopaminergic neurons. CaMKII binds to the distal C terminus of DAT and co-localizes with DAT in dopaminergic neurons. The distal serines of the N terminus of DAT were phosphorylated by CaMKII *in vitro* and the mutation of these serines eliminated the stimulatory effects of CaMKIIa. A mutation of the DAT C terminus, impairing CaMKIIa binding, also impaired AMPH-induced DA efflux. Thus, it was suggested that the binding of CaMKIIa to the DAT C terminus facilitates phosphorylation of the DAT N terminus, which is responsible for the AMPH-induced dopamine efflux (Fog et al., 2006).

A non-amphetaminic effect of CaMKII was also reported. Pseudo-phosphorylation of the hDAT N-terminal serines (S/D mutation), which appear to be phosphorylated by CaMKII, is largely able to evoke the reverse transport of DA even in unclamped cells, i.e. at resting membrane potential. This showed that activation of this enzymatic system (DAT) constitutes a mechanism of release by itself, even in the absence of amphetamine or any exogenous trigger. CaMKII is the most abundant kinase in the brain and could play a role in the regulation of various neurotransmitters (Colbran et al., 2003; Griffith, 2004). It is well known that local increases in Ca^{++} concentration and the CaMKII complex interact with the transduction of several neuronal signals, whether from DA neurotransmitters or not. Numerous proteins, such as the NR2B subunit of the NMDA receptor, could be involved in tonic release processes. It was recently proposed that tonic hyperactivity of the GLU afferents to the dopaminergic striatal terminals could maintain tonic-activated DA overflow in the rat STR following a 6-OHDA lesion of the SNc (Dzahini et al., 2010), and mechanisms such as those presently known to be evoked could be responsible for the effects observed. The same type of tonic hyperactivity could also be present in the mesencephalic region of the SNc. Sustained hypertonic GLU neurotransmission is often observed and reported in experimental and natural situations of neuro-degeneration, and could maintain secondary amine overflow without immediate consequences, but cause insidious degeneration.

The main finding of recent reports about the regulatory processes of the DAT protein is the complete dissociation between inward (uptake) and outward (release) efflux. Until recently DAT was considered to be an exchange diffusion system with a stoichiometric equilibrium linking the two functions. It is now clear that this concept should be revisited and that the inward regulatory processes differ from the release mechanism.

In summary, three steps in DA metabolism occur to determine the extracellular DA concentration: synthesis, exocytosis and reverse transport (fig.8). Directly or indirectly, Ca^{++} ions modulate each of these. Thus carrier-mediated release (DA-RT) appears to be indirectly and negatively coupled with calcium entry, whereas synthesis and exocytosis are directly and positively coupled with Ca^{++} entry.

3.3 Intraterminal DA metabolism: From synthesis to release

The observations presented here and the numerous reports about DA synthesis, storage and release have enabled the proposal of a general model of the striatal DA terminal in

physiological conditions (Leviel et al., 1989). As mentioned above, components of this model may be attributed to different DA neurons. In the model presented in Fig. 8, a central pool of cytosolic DA constitutes the central point of the functional organization. Three input and four output routes are then described. The major way of supplying this central pool is via DA synthesis. A secondary supply mechanism could involve the intraterminal egress of DA from the vesicular storage pool. The third input comprises DA uptake transport.

The first and major output of cytoplasmic DA involves the formation of DOPAC by the MAO enzyme. The second use of cytoplasmic DA involves terminal overflow through DA-RT. A small proportion of the synthesized DA is vesicularized in a neosynthesized pool constituting the preferentially releasable compartment of the amine, and is released by exocytosis. Some of this vesicularized amine supplies a storage compartment (old stored DA).

This model takes into account the different mechanisms of DA release and DA metabolism that can be independently regulated. For example, reduced exocytotic release (by the blockade of calcium channels) can be accompanied by increased DA-RT, leading to an increase in extracellular amine. Thus even if the depolarization of DA axons is clearly responsible for exocytotic DA release, the preterminal influences could lead to secondary release that is differentially regulated, producing the paradoxical observations that are often reported (Leviel et al., 1989).

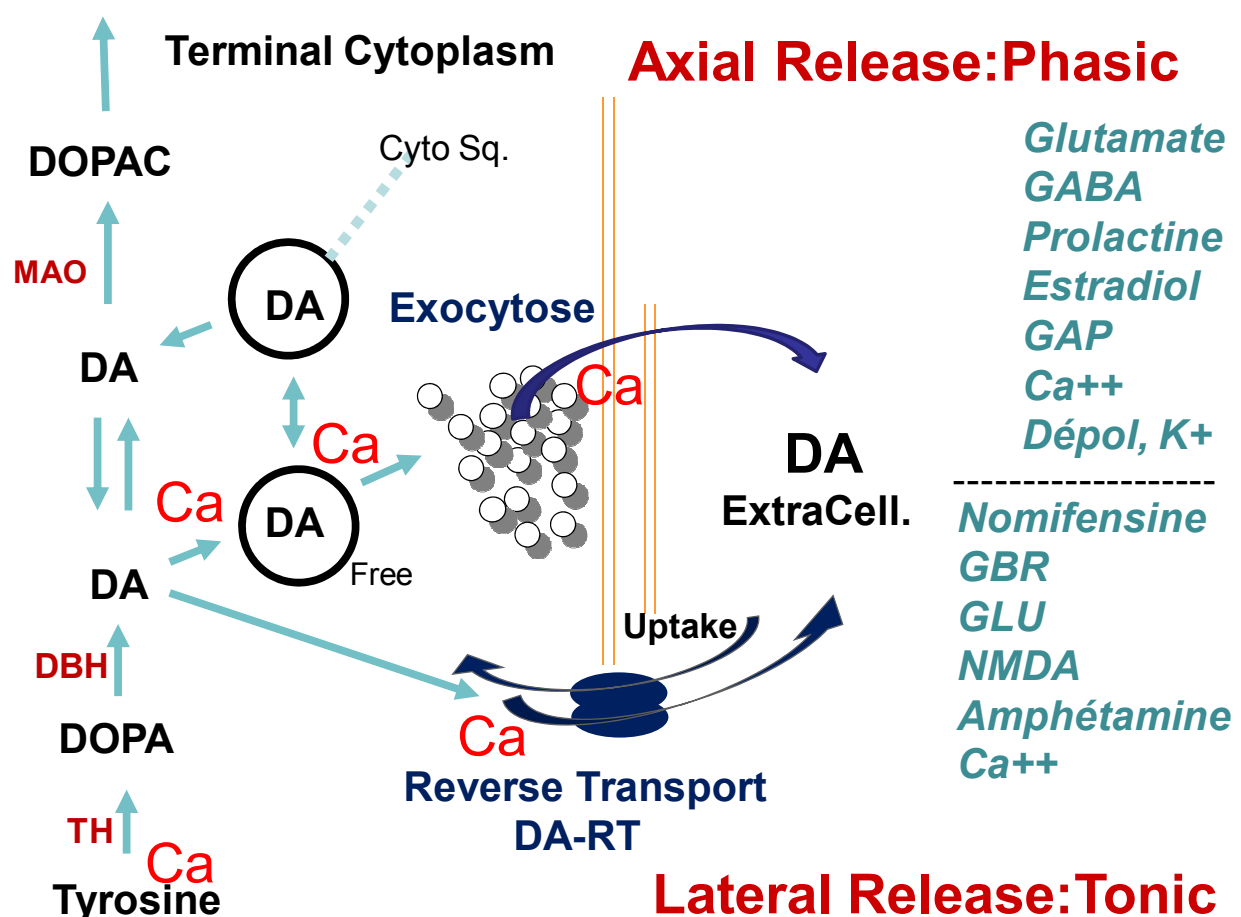


Fig. 8. The four-compartment model of intraterminal DA metabolism including dual release

4. Evolving DA release with DA cell degeneration

4.1 Progressive DA denervation of the STR enhances DA transport in synaptosomal preparations

Why address the consequences of DA cell degeneration? So far we have described the equilibrium between two mechanisms that release DA, but only one of these is likely to be able to maintain DA homeostasis in the extracellular space. For a long time it was thought that the progressive degeneration of the DA cells of the SN, such as observed in Parkinson's disease (PD), is accompanied by the preservation of the DA concentration in the STR, a region that is innervated by DA axons. Basic observations have ascertained that DA metabolism is activated in spared dopaminergic terminals of the partially denervated STR. Both increased DA synthesis and reduced storage capacity were recurrently reported (see Zigmond et al., 1990 for a review). This was considered to be the possible cause of the unmodified (or even sometimes increased) extracellular DA level in this region (Stackowiak et al., 1987; Altar and Marien, 1989; Espino et al., 1995; Dentresangle et al., 2001; Dzahini et al., 2010). Nevertheless, no changes in either the firing pattern or the efficacy of release were observed in nigral DA cells following a moderate partial lesion (Hollerman and Grace, 1990; Dentresangle et al., 2001). On the contrary, spared DA neurons were described as hypoactive and pre-apoptotic (Pasinetti et al., 1989). This adaptation is unlikely to be the result of the electrical hyperactivity of the surviving nigral DA cells.

Extracellular DA is taken up into dopaminergic terminals. In partially lesioned rats, the long-term reduction of this DA uptake may allow more diffusion in tissues (Snyder et al., 1990; van Horn et al., 1992; Gerhardt et al., 1996). This hypothesis is reinforced by the fact that the depolarization of cells bearing the DA transporter reduces their ability to take up extracellular amine (Roth et al., 1976; Zahniser et al., 1998). GLU neurotransmission could be involved in this process. Indeed GLU is responsible for tonic membrane depolarization in CP (Wilson et al., 1995) and GLU neurotransmission is known to be hyperactive following a partial lesion (Lindfors and Ungerstedt, 1990; Samuel et al., 1990; Iwasaki et al., 1992; Wullner et al., 1994).

Reduced DA uptake due to a reduced number of DA terminals is however unable to account for the maintained dopaminergic function as the extracellular DA concentration should also be correlated with a reduction in the number of release sites. No changes in the number of uptake sites *per neuron* were reported and the binding of the transporter ligands was even considered to be a good index of the terminal depopulation (Maloteaux et al., 1988; van Horne et al., 1992). Thus normal or increased levels of extracellular DA, associated with a reduced number of dopaminergic terminals, imply an increased release/uptake ratio *per terminal*. GLU neurotransmission in the STR may mediate this increase. GLU was reported to increase DA synthesis (Desce et al., 1992; Fillenz, 1993; Castro et al., 1996), to activate DA release (Giorgiueff et al., 1977; Cheramy et al., 1986; Leviel et al., 1990; Keefe et al., 1992) and to reduce DA uptake (Lin and Chai, 1998). The mechanism by which basal DA release is altered is however poorly understood. In the absence of any change in DA cell activity, alterations should involve DA-RT. This concept of activation of the DA metabolism through local GLU-dependent activation of DA-RT from the striatal DA terminal in response to the DA cell depopulation is widely debated. The following paragraph addresses this problem by analyzing the results of experiments based on progressive or very partial lesions of the nigrostriatal DA pathway in the rat.

4.2 Experimental observations

To address this issue, partial and progressive destruction of the dopaminergic terminals of the STR was achieved and various biochemical parameters were monitored. The injections were not directly located in the striatal tissue but in the lateral ventricle. Recurrent 6-OHDA injections were administered week after week, locally in the rat STR. In these lesioned rats, metabolic alterations of DA were followed along with the kinetic parameters of the uptake process in synaptosomal preparations. These parameters (apparent K_m and V_{max}) are correlated with the number of uptake sites determined in binding experiments with a ligand of the DAT carrier protein, GBR12935. The possible role of GLU neurotransmission in these alterations was also investigated.

Neither behavioral disturbance nor loss of weight was observed during treatment. Following successive injections, however, progressive biochemical alterations developed in both the median and lateral part of the STR, ipsilaterally to the injected ventricle.

Control values for tissue DA were 54.9 ± 9.3 ng/mg prot and 45.7 ± 6.9 ng/mg prot for the median and lateral STR respectively. For tissue DOPAC, the control values were 27.19 ± 3.6 ng/mg prot and 26.4 ± 4.11 ng/mg prot in the median and lateral STR respectively. The first changes observed were in tissue DA, which began to decrease after the first two injections, reaching only 23.3 and 29.6% (median and lateral STR respectively) of the values of the sham-injected animals after the 8th injection (Fig. 9). The decrease in tissue DOPAC was

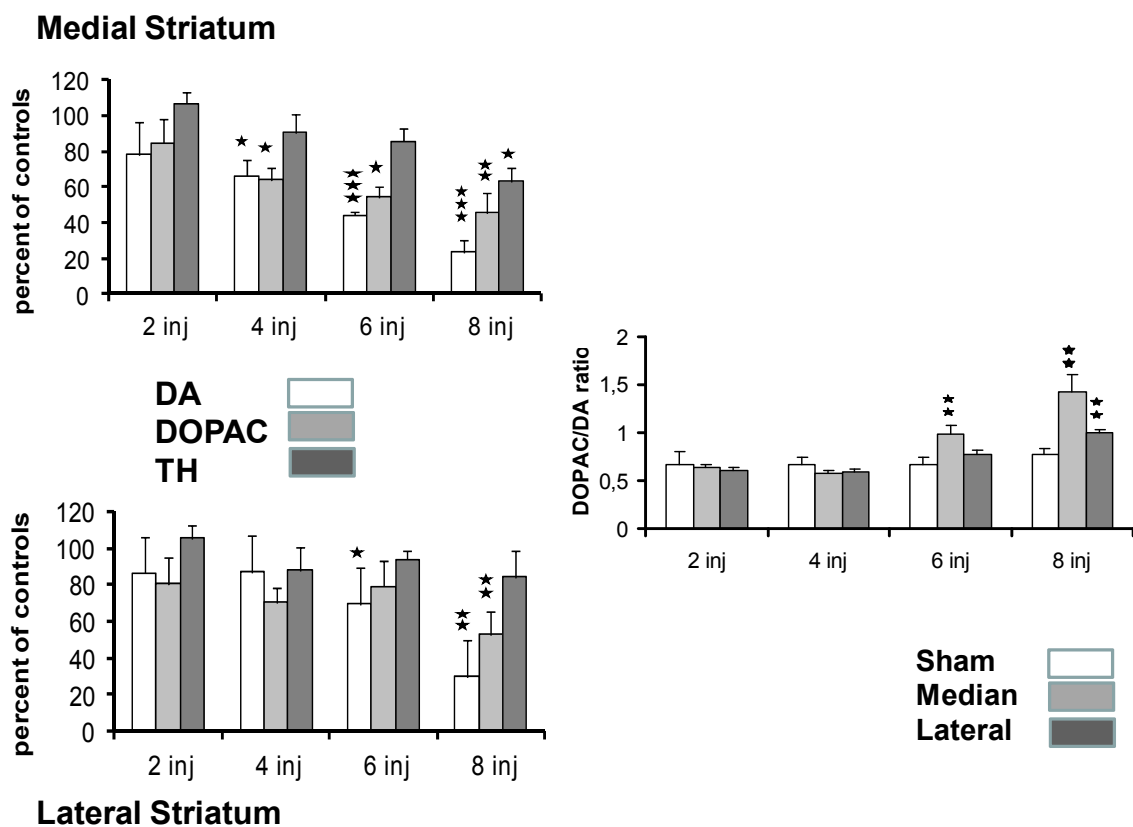


Fig. 9. Tissue DA, DOPAC and TH (left). Mean TH activity indexed by DOPAC/DA ratio (Right).

slower, reaching 45.5 and 52.7% (median and lateral STR respectively) of the controls after the 8th injection. The tissue DOPAC/DA ratio (0.494 in the control rats) increased significantly only after the 6th injection, reaching a value of 1.4 in the median part of the STR after the 8th injection (Fig. 9). The tissue content of TH (Fig. 9) decreased very slowly and the differences compared with control rats (8.94 ± 0.60 UTH in the median STR; 9.24 ± 0.81 UTH in the lateral STR) were only significant after the 8th injection (63 and 84.4% of controls in the median and lateral STR respectively). These alterations were first detected in the medial part of the STR (in the more lesioned part) and 2 weeks later, more laterally. Thus an immediate alteration of tissue DOPAC and DA was observed, followed by a delayed increase in the DOPAC/DA ratio and a late reduction in the amount of TH.

Binding of [^3H]GBR12935 was measured in synaptosomes prepared from rats that had been injected for 8 weeks. The B_{max} in the sham-operated group was 3.82 pmole/mg prot. In the lesioned group, B_{max} fell to 2.31 pmole/mg prot (60.4%) but returned to 3.42 pmole/mg prot in lesioned animals treated daily with MK801 (89.5% of sham-operated group). The ability of synaptosomes to load [^3H]DA was not greatly affected in lesioned animals. The slopes of the [^3H]DA accumulation curves were: 0.101 pmole/mg prot/min for the sham-operated animals, 0.089 pmole/mg prot/min for the lesioned group (88.6% of the sham-operated group, n.s.) and 0.098 pmole/mg prot/min for the lesioned animals treated with MK801 (97.1% of the sham-operated group, n.s.) (Fig. 10). However, the ratio between [^3H]DA accumulation and [^3H]GBR12935 binding (in pmol/pmol of [^3H]GBR12935/min, data not shown) was 0.026 (100%) for the sham-operated animals, 0.038 for the lesioned group (146.5%; $P < 0.05$) and 0.028 for the lesioned animals treated with MK801 (108.5% of the sham-operated group, n.s.).

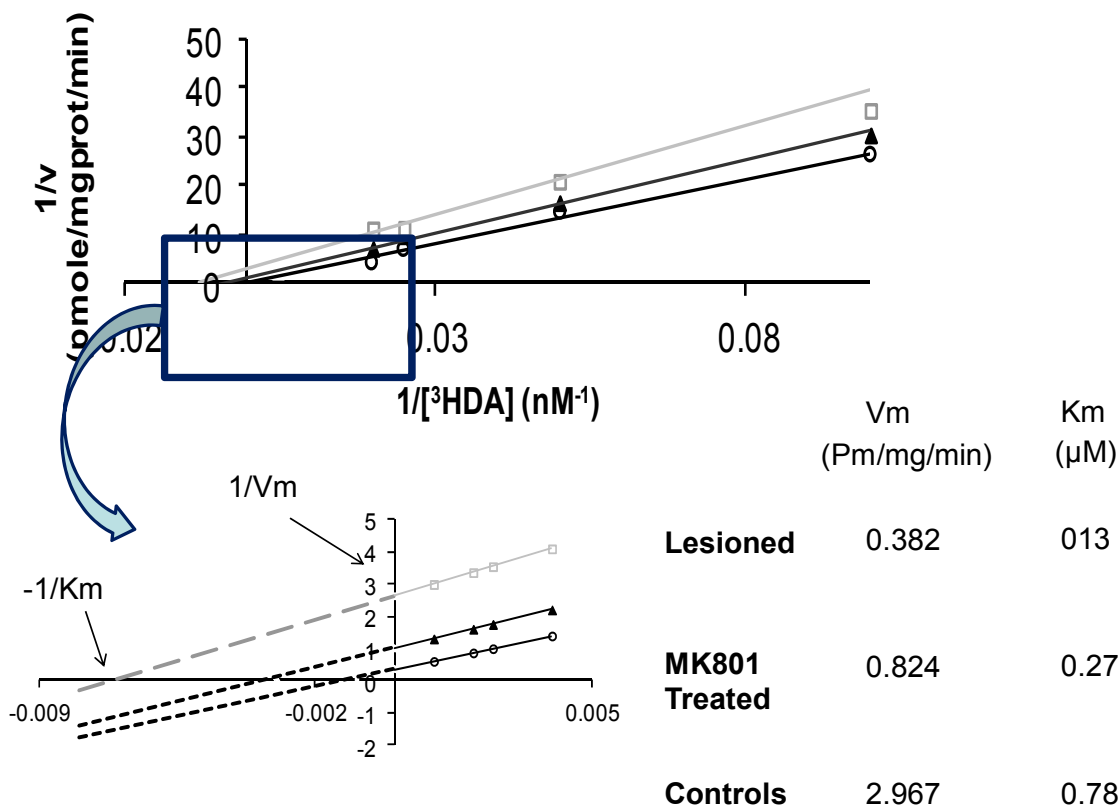


Fig. 10. Lineweaver-Burk plot of [^3H]DA capture in striatal synaptosomes

The apparent K_m and V_{max} of the [3 H]DA transport reaction were calculated by linear regression (Fig. 10). The slopes of the curves obtained for lesioned-only animals and lesioned plus MK801-treated animals were both significantly different from that of sham-operated animals ($P < 0.05$). The values of V_{max} were 2.967, 0.382 and 0.824 pmole/mg prot/min respectively for sham-operated, lesioned and lesioned + MK801-injected rats. The K_m values were 0.78, 0.13 and 0.27 μ M respectively.

4.3 Nigrostriatal lesion reduces DA uptake but increases DA transport

The reduction in the levels of tissue DA and DOPAC appeared soon after the first injection. The DOPAC/DA ratio, reflecting TH protein activity (Lavielle et al., 1978; Bannon & Roth, 1983; Zetterström et al., 1988; Nissbrandt et al., 1989; Soares da Silva & Garret, 1990), and the amount of TH protein in the tissue remained unchanged during the first 6 weeks. This reduction in intraterminal DA stores that is not associated with changes in DA synthesis is consistent with the observations that we report below of increased basal DA release during the very early phases of denervation (Dentresangle et al., 2001; Dzahini et al., 2010).

After six and eight injections, both the tissue DA and DOPAC continued to decrease and tissue levels of TH protein began to decline. In contrast, the DOPAC/DA ratio increased, confirming a delay in increased DA synthesis. This could be the result of decreased intraterminal DA. TH activity is under the control of cytoplasmic amine levels through an end-product regulatory process (Ames et al., 1978; Mann and Gordon, 1979; Zigmond et al., 1989; Fillenz, 1993). Therefore increased TH activity, which is often reported after partial lesion of the DA pathway (Zigmond et al., 1990) could be, at least in part, a consequence of reduced intraterminal DA pools. The simultaneous reduction in the amount of tissue TH protein may occur in one of two ways: (1) a reduction in the number of DA terminals, or (2) increased protein turnover associated with the increased catalytic activity (Vrana and Roskoski, 1983; Lavergne et al., 1994).

This set of results is consistent with the hypothesis that the preservation of extracellular DA after partial destruction of the nigro-striatal DA pathway is due to activation of basal DA release. However, as already mentioned, this is unlikely to be the result of electrical activation of DA neurons in the SNc. Thus, alterations in DA transport at the level of the DA terminals in the STR are more likely.

The amplitude of the denervation produced by eight injections of the toxin was evaluated initially. The amount of TH protein and the binding of transport sites are considered to be valid indices of DA pathway denervation (van Horne et al., 1992; Maloteau, 1998). In the present experiment, tissue TH protein levels were reduced to 63% of the levels found in controls, and the B_{max} of [3 H]GBR12935 was reduced to 60.4% of the value found in sham-operated animals. Thus, about 40% of DA terminals may have degenerated after eight injections of the toxin.

Given this 40% reduction in the number of binding sites in the synaptosomal preparation of lesioned rats, the kinetic parameters of the DA uptake process are apparently paradoxical. First, the global DA uptake was only reduced by 11% (insignificant decrease), and when adjusted according to the number of sites (reduced by 40%), it was actually increased (146% of controls). This observation suggests an increase in the efficiency of the transport process, compensating for the reduction in the population of DA terminals. Second, the V_{max} , which

is an index of transport capacity, was only 12% of the value in control rats. This observation shows that a large number of sites, still bound to [^3H]GBR12935, had become unable to carry DA. Third, it can be concluded from the low K_m value that the affinity of DA for the carrier protein had increased. These results strongly suggest that moderate DA denervation of the STR results in a reduction in the number of functional DA transporters able to carry DA, but an increase in their affinity, which is responsible in turn for an increased rate of transport. We will see below that a new way to see the structure of the DAT protein could underline this paradoxical data. Indeed DAT is no longer considered as only an uptake processor but rather as a dual actor of the DA transport regulating extracellular DA homeostasis.

5. Presynaptic GLU – Induced activation of DA release in the STR after partial nigral lesion

The behavioral and biochemical recovery, after partial unilateral lesion, of the dopaminergic nigrostriatal path has been reported in various species from rodents to primates (Hefti et al., 1985; McCallum et al., 2006; Boulet et al., 2008; Perez et al., 2008). This recovery is thought to result from normalization of the extracellular dopamine (DA_{ext}) in the STR that was initially reduced by the lesion (Robinson and Whishaw, 1988; Castaneda et al., 1990; Zigmond et al., 1990; Emmi et al., 1996). However, it remains unclear whether this compensation results from overactive nigral neurons, as is proposed to occur after LevoDOPA treatment (Grace, 2008), from direct preterminal influences in the STR (Dentresangle et al., 2001), or from both. A role for GLU in this phenomenon has been proposed given that the GLU tone increases in various regions of the basal ganglia following SNc lesions, including in the STR (Calabresi et al., 1993; Cepeda et al., 2001; Tang et al., 2001), the SNc (Turski et al., 1991; Bezard et al., 1997) and the subthalamic nucleus (Benazzouz et al., 1993; Amalric et al., 1995; Phillips et al., 2006). This was confirmed by the fact that behavioral and biochemical recovery were inhibited by chronic treatment with GLU receptor (GLU_R) antagonists including MK801 (see the preceding paragraph) and 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (CPP) (Emmi et al., 1996). The nature of the mechanisms evoked by GLU remains unclear however, because compensatory mechanisms occur very early or following very partial lesions, at a stage at which the spontaneous activity of midbrain DA neurons was not found to be altered (Hollerman and Grace, 1990) and when the impulse/release ratio in the terminal region appeared unchanged (Dentresangle et al., 2001). To complicate the situation, it is now well known that GLU can enhance DA release independently from the spontaneous electrical activity of the midbrain DA neurons (Leviel et al., 1990; Keefe et al., 1992; Olivier et al., 1995, 1999).

5.1 Experimental observations

To understand the functional link between DA and GLU during the compensatory process a very partial and laterally located lesion of the SN was produced in rats using 6-OHDA. Three weeks after this lesion, it was possible to compare the metabolic consequences of a large denervation in the lateral part of the STR with those in a medial region spared by the denervation. Cartography of the tonic extracellular DA and DOPAC concentration was performed using *in vivo* voltammetry. In rats with similar lesions medial and lateral microdialysis approaches allowed us to measure the extracellular GLU concentration. The effect of GLU antagonists (amantadine, memantine and riluzol) on neurotransmission and their neuroprotective action on tonic DA enhancement were also tested.

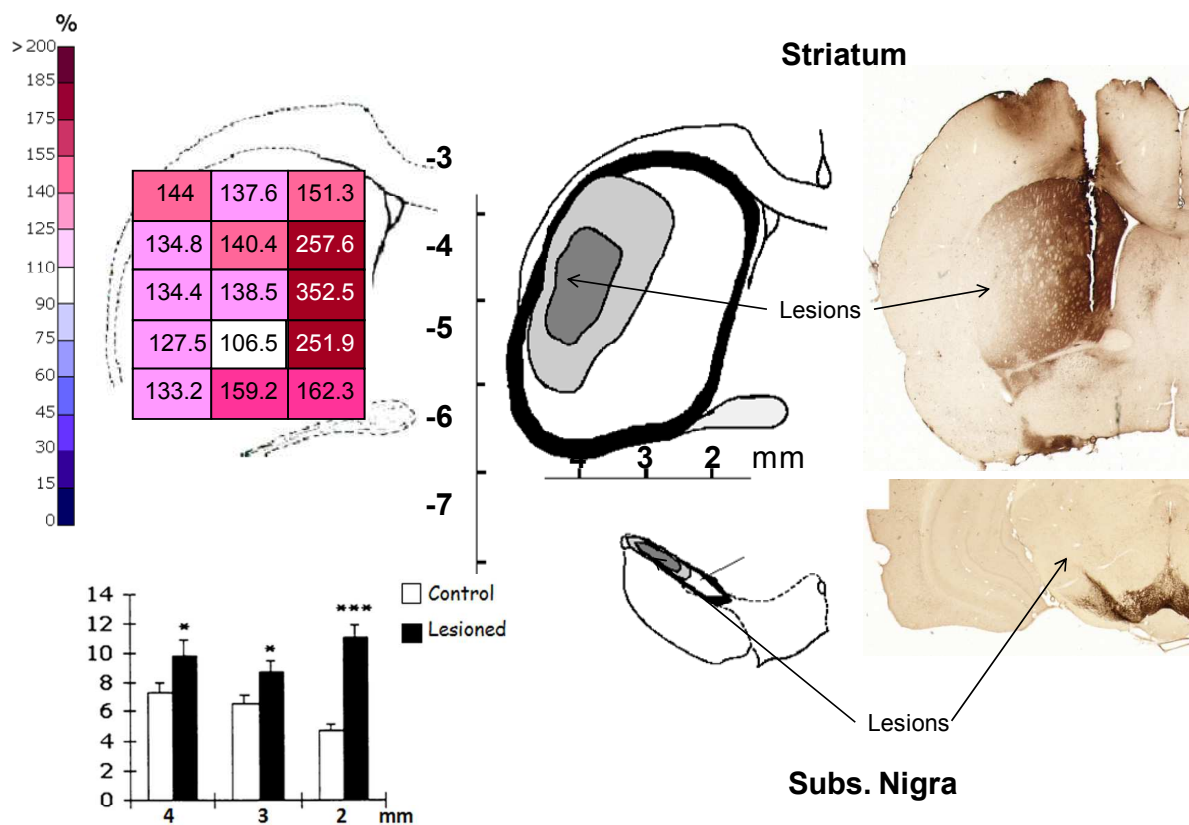


Fig. 11. Lateral lesion of the SN and its consequences for striatal DA denervation and release

Cartography of the STR using voltammetry

The STR was stereotaxically explored in one coronal plane (8.2 mm anterior to the ear axis) to localize biochemical changes *in vivo*. Figure 11 shows the extracellular concentrations of DA expressed in nM and as the ratio (in %) between values obtained in lesioned and control animals in each homologous striatal area for each subregion explored. In the lesioned animals, DA measured in the intact median region (lat. 2) showed a notable increase (352%, $p < 0.001$) in comparison with control values. This effect was less pronounced in the intermediate and lateral striatal areas (lat. 3–4) but was nevertheless present. In the most completely DA-deafferented striatal regions, DA levels did not differ significantly from control values, being only slightly higher. In contrast, the extracellular level of DOPAC decreased enormously (26% of control values; $p < 0.001$) in the lateral part of the STR in comparison with values detected in the homologous striatal region of the control group. In the medial region DOPAC concentrations remained poorly affected (Dzahini et al., 2010).

Effects of partial lesions of the SN and microdialysis results

Voltammetry furnishes excellent stereotaxic localization of biochemical alterations but the use of pargyline to detect DA could produce a bias in the measurements. To better quantify the changes observed with voltammetry, and to extend the measurements to amino acids, the medial spared region was implanted with a microdialysis probe, and superfusates were subjected to HPLC and two analyses, one for catecholamines and the other for amino acids. In sham-operated and untreated rats, the spontaneous extracellular concentrations of DA (7.28 ± 0.36 nM), DOPAC (9.19 ± 1.1 μ M), HVA (6.54 ± 0.59 μ M), GLU (10.0 ± 0.27 μ M), GABA

($0.42 \pm 0.06 \mu\text{M}$) and ASP ($0.47 \pm 0.05 \mu\text{M}$) were in the range of previously reported values. Importantly, DA was in the nano molar range in the extracellular space whereas metabolites and amino acids were in the micro molar range. Three weeks following the lesion in the lateral part of the SN, an increase in DA was detected in the medial STR ($29.2 \pm 0.28 \text{ nM}$). Simultaneously an increase in GLU was observed ($24.4 \pm 0.75 \mu\text{M}$). In contrast, the DA metabolites, DOPAC ($10.8 \pm 0.10 \mu\text{M}$) and HVA_{ext} ($8.86 \pm 0.90 \mu\text{M}$), remained unchanged. Likewise, GABA ($0.63 \pm 0.17 \mu\text{M}$) and ASP ($0.47 \pm 0.05 \mu\text{M}$) were not significantly altered.

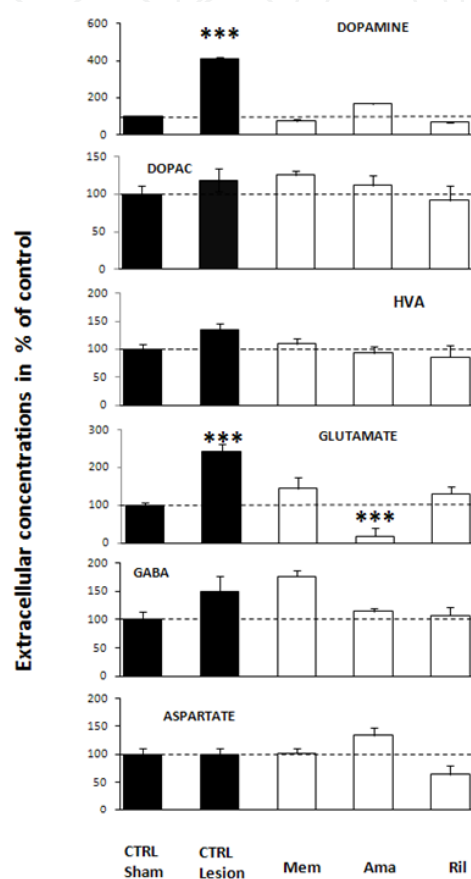


Fig. 12. Tissue DA and amino acid in the striatum 3 weeks following lesioning of the SN using 6-OHDA

Treatment of lesioned rats with GLU antagonists

Treatment with chronic memantine, amantadine or riluzol seemed to counteract the tonic increase in DA induced following the lesion that was observed via voltammetry and confirmed using microdialysis (Fig. 12). Only a moderate increase in DA persisted following chronic amantadine administration ($12.4 \pm 1.26 \text{ nM}$ versus $7.28 \pm 0.36 \text{ nM}$ in controls). The DA concentration remained at basal levels following treatment with memantine and riluzol (Fig. 12). Acute treatments with the same substances were less efficient at counteracting the increase in DA but the same trends were apparent (15.1 nM , 24.1 nM and 24.4 nM respectively for memantine, amantadine and riluzol versus 29.2 nM in the controls, Dzahini et al., 2010). The GLU antagonists did not interact with the DA metabolites DOPAC and HVA. The results are presented in Fig. 12 as percentages of the values obtained in lesioned rats.

The extracellular GLU concentration increased tonically after the lesion ($24.4 \pm 0.75 \mu\text{M}$ versus $10.0 \pm 0.27 \mu\text{M}$ in controls). This effect was counteracted by treatment with either chronic or acute memantine ($47.1 \pm 2.3 \mu\text{M}$ and $27.1 \pm 1.53 \mu\text{M}$ respectively). Chronic riluzol also counteracted the lesion-induced increase in GLU after chronic application ($21.8 \pm 0.68 \mu\text{M}$) and acute riluzol drastically reduced GLU ($0.7 \pm 0.05 \mu\text{M}$). GLU was also reduced after both chronic and acute amantadine treatment ($1.04 \pm 0.4 \mu\text{M}$ and $0.74 \pm 0.26 \mu\text{M}$ respectively). No alterations in GABA or ASP were detected in response to the treatment of lesioned rats with GLU antagonists. The results obtained after chronic treatments are presented in Fig. 12 as the percentage of values obtained in lesioned rats. The results obtained after acute treatments are presented elsewhere (Dzahini et al., 2010).

Substantially, the lesion produced a large increase in DA and GLU in the medial STR that was not accompanied by noticeable alterations in the two DA metabolites or the other two amino acids that were measured. The three treatments with GLU antagonists seemed to affect DA metabolism in the same way, counteracting the lesion-induced increase in DA. These treatments had differential effects on GLU.

Twenty-one days after the lesion, the denervated part of the STR (lateral) exhibited biochemical responses previously described after high levels of DA cell depopulation: a drastic reduction in DOPAC and an unmodified or slightly increased DA (Zigmond et al., 1984; Altar et al., 1987). In contrast, a large increase in DA (two- to three-fold) and a modest alteration in DOPAC was observed using voltammetry and confirmed using microdialysis in the spared part of the STR (medial). In this case, the levels of DA probably resulted from permanent (tonic) enhancement of the spontaneous release of DA. It has been shown that partial lesions leave the stimulation/release ratio unmodified (Dentresangle et al., 2001). A much larger lesion of the DA cell population seems to be required to alter the spontaneous pattern of discharge of nigral DA cells (Hollerman and Grace, 1990; Harden and Grace, 1995) or stimulation-induced DA release (Stachowiak et al., 1987). These observations strongly suggest that after lateral SN lesion, a global process activates tonic DA release by an indirect mechanism acting presynaptically in the STR.

It has been claimed that recovery of the DA in the STR after partial lesions of the SN could be related to alterations in GLU neurotransmission (Calabresi et al., 2000; Emmi et al., 1996; Kashani et al., 2007). However, the mechanism and the location of this alteration remain unknown. We found that 3 weeks after the lesion, GLU was clearly enhanced in the medial STR. When GLU neurotransmission was pharmacologically interrupted by specific GLU blockers (riluzol, memantine and amantadine), a reduction in extracellular GLU activation was observed, with a simultaneous reduction in the tonic DA increase induced by the nigral lesion.

Amantadine and memantine were proposed to have some neuroprotective effects after discovering the importance of NMDA receptor-mediated excitotoxicity as a factor underlying neurodegeneration in Parkinson's disease (Greenamyre and O'Brien, 1991). Indeed antagonists of NMDA receptors have been shown to inhibit neurodegeneration of the DA system induced by MPP⁺ and methamphetamine (Sonsalla et al., 1989; Turski et al., 1991). In our case, the effect of the two GLU antagonists was to counteract the increase in GLU and DA induced by the nigral lesion. Several studies have suggested that NMDA-induced DA release could be the main regulatory mechanism of extracellular DA (Bannon et al., 2001; Leviel, 2001; Mortensen and Amara, 2003), and our observations are consistent

with the hypothesis of a NMDA-induced mechanism causing stable dopaminergic hypertony. The effects of riluzol strengthen this hypothesis. First proposed to inhibit GLU release (Mantz, 1992), its action has also been attributed to persistent blockade of the sodium current (Del Negro, 2005). In our hands, riluzol reduced the release of GLU in sham-operated animals and counteracted the lesion-induced GLU and DA as well (Dzahini et al., 2010).

6. Conclusions: DA/GLU, a deleterious partnership?

To summarize the present results and referenced data, the most original outcome is that DA release in the STR is not simply a readout of activity in DA neurons that provide a diffuse DA tone in the extracellular space. Rather, DA can be released by at least two different mechanisms with different kinetics, locations and regulatory processes. Based on the data reported here, a working hypothesis can be proposed: that a weak reduction in the DA cell population in the SNc leads to metabolic alterations in the STR that result in further death of DA terminals in this region. The development of this process could follow three major steps (Fig. 13): 1) the activation of diencephalic structures, thalamic or sub-thalamic nuclei that

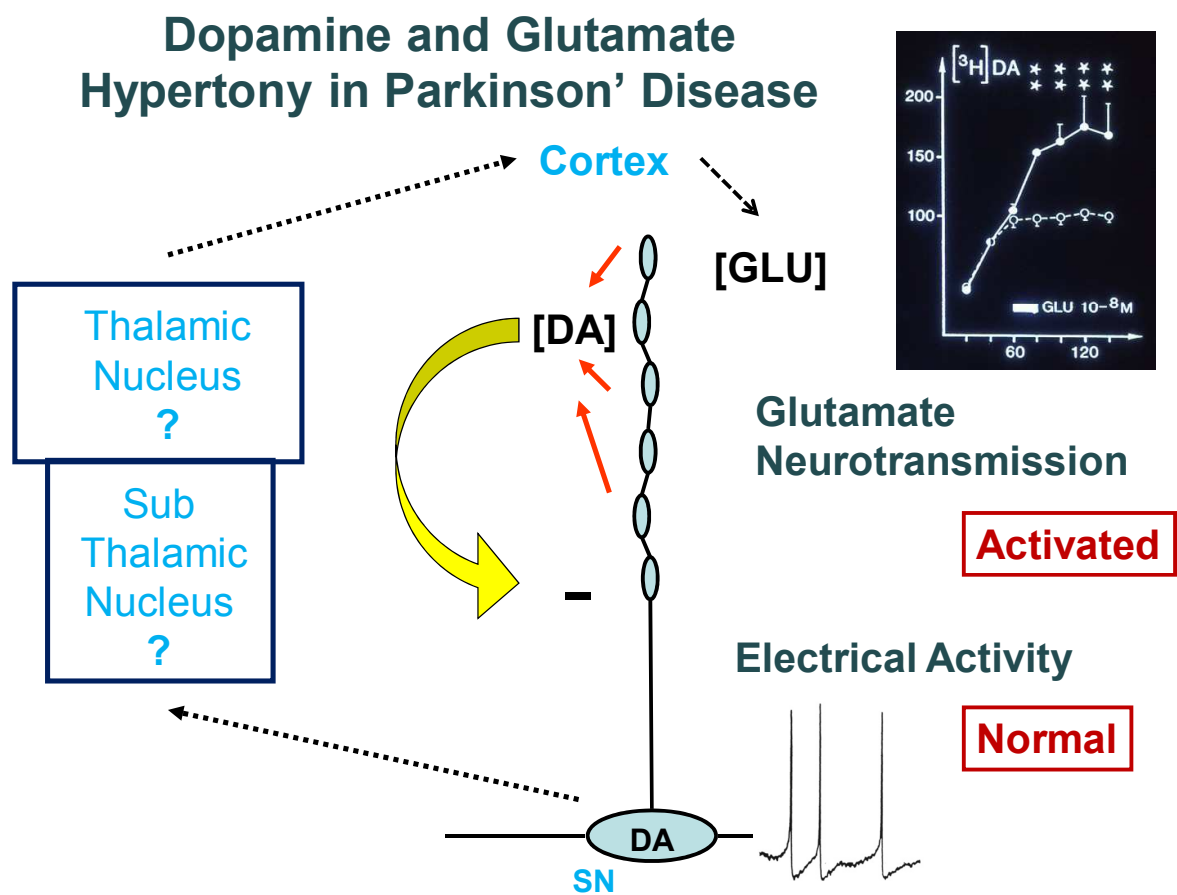


Fig. 13. A working hypothesis of the mechanism involved in the presymptomatic phase of PD

project toward cortical regions; 2) in turn, a tonic increase in some of the corticostriatal pathways that we know to be responsible for different controls of the striatal GABA neurons

and DA terminals; 3) indirect activation through GLU afferents to DA terminals of tonic DA release, which initially constitutes autotherapy allowing the behavioral compensation observed in Parkinson's disease. However the toxic effect of DA on the DA terminal (production of H_2O_2 when present in excess) could constitute a secondary pathological agent, maintaining the degenerative process. Each of the three steps mentioned here require further elucidation and demonstration, but a large set of data in each case is consistent with this hypothesis.

DA homeostasis constitutes one of the functions of the DAT via DAT-RT. This is under the control of many regulatory processes including tonic GLU neurotransmission. Experiments regarding the consequences of partial lesions seem to indicate a role for this GLU-dependent regulation in the tonic DA overflow and in maintaining a permanent excess of extracellular DA. It remains to be determined how local GLU can induce the presynaptic and tonic activation of DA release. This could be achieved directly through GLU receptors located on DA terminals or indirectly through heterologous neurotransmission systems such as GABA or ACH.

7. Technical procedures

7.1 Animals

Male Wistar rats (Iffa-Credo France) weighing 250 g were used in the studies reported here. They were maintained and sacrificed in accordance with the European Communities Council Directive (86/609/EEC). The animals were anesthetized with 1.5% isoflurane in pure oxygen in air or were injected with chloral hydrate (400 mg/kg) and spontaneously inspired (Leviel et al., 1989; Olivier et al., 1995). When necessary they were placed in a stereotaxic device. For the short interventions (less than 1 hour), a mixture of ketamine/rompun was used (150/10 mg/Kg). Rectal temperature was maintained at 38 °C. Cardiac and respiratory rhythms were continuously monitored.

7.2 Lesions of the lateral SN

The lateral part of the SN was unilaterally injected with a solution of 6-OHDA (3 µg free base in 1 µl isotonic saline containing 0.2% ascorbic acid, pH 4). The stereotaxic coordinates were, in mm: Ant.: 3.5, Lat.: 2.5 and Ht.: 3.4. The horizontal plane passed through the interaural axis and incisor bar. Unlesioned rats were only submitted to nigral injection of the vehicle (Dentresangle et al., 2001; Dzahini et al., 2010).

7.3 Surgery and procedures for recurrent ventricular injections

Animals were anesthetized with ketamine (150 mg/Kg; Panpharma), maintained in a stereotaxic device and implanted with a cannula (0.71 mm o.d. with a removable mandrel) in the anterior part of the left lateral ventricle. The head of the cannula was sealed with acrylic cement, embedding screws set in the cranial bone. The stereotaxic coordinates were the following (in mm): AP: 0.48; LM: 1; H: 6 from the bregma (following Paxinos and Watson, 1986). Rats were allowed to recover for 2 weeks. In order to inject 6-OHDA (30 min after administering 25 mg/kg imipramine i.p. to protect noradrenergic neurons), the mandrel of the cannula was removed and replaced by an injector connected, through a thin

catheter, to a microsyringe. Weekly injections of 10 μl of a solution (0.1% ascorbic acid in 0.9% NaCl) with or without 35 μg of 6-OHDA were given to awake and freely moving animals. Four groups of 12 animals received 2, 4, 6 or 8 weekly injections of the toxin (n=6) or the toxin vehicle only (n=6). A fifth group (n=6) of rats received 8 weekly injections of the toxin and a daily injection of 2 mg/kg MK801 (i.p.).

7.4 Medial Forebrain Bundle (MFB) stimulation

A bipolar electrode was implanted in the medial forebrain bundle (MFB) containing the DA ascending fibers (coordinates: A:5; L:1.3; Ht:2). Every 4 minutes, the MFB was stimulated for 20 seconds by 20 bursts (one per second) of 25 positive square pulses, each lasting 0.5 ms, with a 2 ms interpulse interval (40 Hz theoretical frequency). Each burst was triggered 300 ms after the measurement of DPA (Dentresangle et al., 2001; Dzahini et al., 2010).

7.5 Voltammetric investigations

Difference Normal Pulse Voltammetry (DNPV) and Differential Pulse Amperometry (DPA) were performed using treated carbon fiber electrodes produced as described previously (Olivier et al., 1995; Dentresangle et al., 2001). Their active part was the surface of one pyrolytic carbon fiber (SOFICAR, France), 250 μm long and 8 μm in diameter. A stainless steel tweezer fixed on the interaural bar was used as an auxiliary electrode and the Ag/AgCl reference electrode was a silver wire coated with AgCl. This was maintained in contact with the skull by means of a sponge moistened with Phosphate Buffer Saline (PBS) solution (PBS, pH 7.4). The three electrodes were connected to a pulse voltammetric system (Biopulse, SOLEA Tacussel, France). Carbon-fiber electrodes were electrochemically treated as previously described (Gonon et al., 1984). To calibrate the electrodes, voltammograms were recorded *in vitro* in a standard solution of DOPAC or DA and ascorbic acid in PBS. The values of the oxidation potentials and the amplitude of the peaks were stabilized after 4–5 successive scans (10 to 15 min). Their values were 60 mV for ascorbic acid, 60 mV for DOPAC and 90 mV for DA. It had previously been verified that the amplitude of the oxidation peak for these substances is linearly correlated with their concentrations. The oxidation potentials for DA and DOPAC were however too close to be properly differentiated *in vivo* and DA was three orders of magnitude lower than DOPAC. Thus, for adequate detection of DA, DOPAC formation was inhibited by pretreatment with pargyline (75 mg/kg, i.p.), an inhibitor of monoamine oxidase.

7.6 Superfusion procedures (microdialysis & push-pull cannula)

Animals were submitted to superfusion of the striatum to analyze extracellular DA, DOPA, HVA, GLU, GABA and ASP (Dzahini et al., 2011). They were implanted with a dialysate probe (250 μm in diameter and 4 mm length, cut off 6000 dalton, CMA, Sweden) in the anterior part of the caudate nucleus (Ant.: 8.4 mm; Lat.: 2.5 mm; H.: 6 mm, same stereotaxic references). The cannula was supplied (1 $\mu\text{l}/\text{min}$) with an artificial CSF (in mM, 145 NaCl, 2.7 KCl, 1.0 MgCl_2 , 1.2 CaCl_2 , 0.45 NaH_2PO_4 , 2.3 Na_2HPO_4 , adjusted to pH 7.4).

Push-pull cannulae were used in an experiment devoted to measuring the radioactive form of DA and DOPAC (Leviel et al., 1989, 1990, 1991). The cannulae (1.0 mm outer diameter) were supplied (flow rate: 12.5 $\mu\text{l}/\text{min}$) with an artificial cerebrospinal fluid (CSF) adjusted to pH 7.4 with an $\text{O}_2\text{-CO}_2$ (95:5 v/v) mixture. 3,5- ^3H]TYR (50 Ci/mmol, Dositek, France) was

purified by high performance liquid chromatography (HPLC) on a C₁₈ Microbondapak column (Millipore-Waters, France) using H₃PO₄ (1 mmol/l, pH 3) as a mobile phase. [³H]TYR was added to artificial CSF (80 µCi/ml) 1 hour after implantation and superfusates were collected thereafter as successive 20 minute fractions.

7.7 Biochemical analysis

Dialysates collected for measuring catecholamines were protected with 5 µl perchloric acid (0.05 M) and immediately underwent HPLC analysis. Dialysates collected for amino-acid analysis were maintained at -80 °C and kept frozen until analysis.

The catecholamines DA, DOPAC and HVA were measured in the collected fractions by electrochemical detection with the potential of the working electrode maintained at 0.7 V (Antec-Decade) after HPLC separation (column C₁₈ Brownlee RP18, 5 µm, 2.1 x 220 mm, maintained at 32 °C; Mobile phase: 50 mM KH₂PO₄, 0.1 mM EDTA-Na₂, 0.28 mM sodium octyl sulfate, 6% methanol, adjusted to pH 4.5; flow rate 0.25 ml/min). Catecholamine peaks were identified based on their retention times (Olivier et al., 1995; Dzahini et al., 2010). Extracellular catecholamine concentrations were estimated by evaluating the peak areas of each substance and their respective external standard (analytical software AZUR, Datalys France). The running time for each determination was 25 min. When superfusion was conducted with 3,5-[³H]TYR added to the CSF, the radioactivity corresponding to each HPLC peak was counted using a continuous flow scintillation detector (Packard-Radiomatic, Flo-One B A250) (Leviel et al., 1989, 1990, 1991).

The concentrations of the amino acids GLU, GABA and ASP in the dialysates were determined after HPLC, via laser-induced fluorescence detection (Dzahini et al., 2010). Briefly, 2 µl of sample or standard was derivatized with naphthalene-2,3-dicarboxaldehyde. The resulting mixture was automatically loaded onto a Symmetry Shield-C₁₈ reverse-phase column (100_2.1 mm, 3.5 µm particle size; Waters, Milford, MA), using a refrigerated Triathlon auto injector (Polymer Laboratories, Marseille, France). The mobile phase consisted of 0.04 M NaH₂PO₄, pH6, in a 3-50% acetonitrile gradient. The flow rate was 0.35 ml/min, maintained using two Shimadzu (Kyoto, Japan) LC 10AT pumps. Amino acid peaks were identified based on their retention time. Extracellular amino acid concentrations were estimated by evaluating the peak areas of each amino acid and their respective external standard (analytical software class LC10; Shimadzu). The running time for each determination was 12 min.

7.8 DA and DOPAC tissue concentration

At the end of each experiment, to verify the location of the cannula, the animals were intracardially perfused with a 4% formaldehyde solution, after which the brain was removed, sliced (50 µm) and stained with cresyl violet.

Protein weights were measured using the micro BCA Protein Assay (Pierce, Biorad).

The homogenate (20 µl) was mixed with 20 µl of 0.3 N perchloric acid containing 0.8 mM EDTA, added to an internal standard (3,4-dihydroxybenzylamine) and centrifuged (10,000 g, 10 min). The supernatant of each sample (10 µl) was injected into a C18 reverse-phase microcolumn (Spheri5, RP-18, 220 x 2.1 mm, Browlee labs). The mobile phase consisted of 40 mM KH₂PO₄ (pH 4.5), 0.26 mM octane sulfonic-acid, 15 mg/l EDTA and 11% methanol

(vol/vol), and the flow rate was 0.20 ml/min. The liquid chromatography system (TSP) was coupled to an electrochemical detector (Millipore) with a working electrode set at 0.8 V. The concentrations of DA and its metabolites in CP were calculated for each sample (in ng/mg prot). The results were normalized by expressing the changes in DA and DOPAC levels as percentages of the values obtained in control animals (Dentresangle et al., 2001).

7.9 Preparation of synaptosomes

The method for synaptosomal preparation and measurement of [³H]DA uptake was modified from Masserano et al. (1994). Rat brains were rapidly removed and chopped into 1.6-mm-thick slices, in the sagittal plane corresponding to the *anterior commissura*. The median part of the CP, ipsilateral to the injection site, was pooled for all rats of each group and homogenized in 25 ml cold 0.32 M sucrose (10 up and down strokes, at 850 rpm, in a glass-teflon homogenizer). The homogenate was centrifuged at 800 g for 10 min at 4 °C and the pellet was discarded. The supernatant (S1) was kept on ice until it was resuspended for the [³H]DA uptake or [³H]GBR12935 binding protocols.

[³H]DA uptake: The supernatant (S1, 15 ml) was centrifuged (20,000 × g for 10 min at 4 °C), and the resulting pellet (P2) was resuspended in 20 ml of ice-cold incubation buffer (in mM): NaCl, 125; K₂HPO₄, 1.5; MgSO₄, 1.5; CaCl₂, 1.25; *d*-glucose, 10; HEPES, 25; ascorbic acid, 0.1; pargyline, 1 and EDTA, 0.1, pH 7.4. The buffer was oxygenated with 100% O₂ for 10 min before use. The assays were performed in triplicate with 400 μl of pellet resuspended in 1 ml of incubation buffer. After preincubation of 3 min at 37 °C, the assays were initiated by adding 10 μl of increasing concentrations of [³H]DA (10, 20, 40, 50, 100, 200, 400 nM) for 7 min at 37 °C. Nonspecific values were determined in the presence of Mazindol (1 μM) for 7 min at 4 °C. Assays were terminated by immediate filtration using Whatman GF/B filters soaked in 0.32 M ice-cold sucrose containing 0.05% polyethylenimine. Filters were washed three times with 3 ml of 0.32 M ice-cold sucrose and radioactivity was measured using a Packard TRI-CARB 2100 TR. The apparent *K_m* and *V_{max}* of DA uptake were calculated by linear regression of the reciprocal plot (1/*v* vs. 1/*S*). The protein content in the resuspended pellet P2 was measured using the micro BCA kit (Pierce, Biorad).

7.10 [³H]GBR12935 binding

The [³H]GBR12935 binding protocol was modified from Berger et al. (1985). The supernatant (S1, 10 ml) was centrifuged (20,000 g for 10 min at 4 °C), and the resulting pellet (P2) was resuspended in 13 ml of 50 mM ice-cold Tris-HCl buffer, pH 7.7, containing 120 mM NaCl. Assays were performed in triplicate with 500 μl of pellet suspension and 50 mM Tris-HCl buffer, pH 7.7, containing 120 mM NaCl and 0.01% of Bovine Serum Albumin in a final volume of 2 ml. Incubation was initiated by the addition of 100 μl of [³H]GBR12935 (5 μM) for 45 min at 25 °C. Non-specific binding was determined in the presence of 1 μM Mazindol. Filters were washed three times with 4 ml ice-cold Tris-HCl 50 mM buffer pH 7.7 and radioactivity was counted using a Packard TRI-CARB 2100 TR. The protein content in the resuspended pellet P2 was measured using the micro BCA kit (Pierce, Biorad).

7.11 Determination of TH protein content

TH protein content was measured using a semi quantitative immunoblotting technique as previously described by Garcia et al. (1994). Briefly, after centrifugation of the homogenate

(10,000 g, 30 min), 1.5 µl of supernatant was placed onto a nitrocellulose membrane (Bio-rad 162-147, 0.2 µm). Non-specific binding sites were saturated with 50 mM Tris buffer containing 2% bovine serum albumin. The protein was revealed using, in succession, a mouse monoclonal antibody to TH (10 ng/ml; Boehringer Mannheim), a ¹²⁵I-labeled protein A (S.A: 1.11x 10⁻⁹ Bq/mg, 1850 Bq/ml, Amersham) and 3H-hyperfilms (Amersham). The radioimmunochemical labeling was calibrated using a scale of standard TH protein (extracted from adult rat adrenals and diluted in homogenates of cerebellum). One U of TH (UTH) is defined as the mean TH protein content of 10 µg (wet weight) of adult rat adrenal gland. Optical density measurements were converted into UTH/mg tissue by reference to the standards. Each reading provided the surface area (mm²) of the dot and the TH tissue concentration (UTH/mg tissue). Using the surface area and the TH tissue concentration, the amount of TH (UTH) in the region of interest was calculated and normalized by expressing the amount of TH as a percentage of values in the control rats.

7.12 Immunoprecipitation of TH enzyme

Rats were perfused transcardially with NaCl 9°/∞ and PFA 4%. The brain was then removed and stored in PBS buffer containing 0.1% sodium azide pH 7.4 (PBSA). To evaluate the extent of the lesion in the SN and the extent of CPc denervation, TH immuno precipitation was performed on coronally sectioned slices (40–50 µm thickness). Brains were cut on a cryostat (HM440E, Microm); free-floating slices were collected and stored in PBSA. Sections were incubated in 3% H₂O₂ in PBS to block endogenous peroxidase activity and were then incubated overnight with the primary rabbit anti-TH antibody (Chemicon, Temecula, CA; 1/2500) in 10% normal swine serum, TBS, pH 7.4, containing 2% NGS and 0.2% Triton X-100 for 24 h at 4 °C on a platform shaker. After rinsing in PBS 0.1% plus triton X100, sections were incubated with biotinylated swine anti-rabbit secondary antibody for 30 min at room temperature. This was followed by incubation with Strept-ABC-HRP complex (Dako, Glostrup, Denmark). TH immunoreactive neurons were visualized using 3,3'-diaminobenzidine (DAB) in N²⁺ 0.5% and H₂O₂. To test the specificity of the staining, control sections were processed in an identical manner but with omission of the primary or secondary antibody. All sections were then washed for 10 min in PBS, mounted on slides, dried, dehydrated in increasing grades of ethanol, cleared in toluene, and mounted with DPX and cover slipped. These sections were scanned and analyzed immediately using Imagemaster Labscan V-3.00 (Pharmacia Biotech, Dzahini et al., 2010).

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9. References

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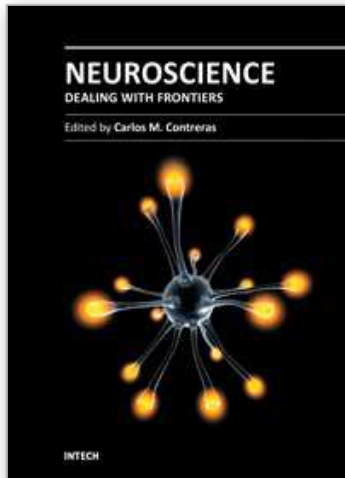
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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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