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Priming for L-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease?

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Abstract

Involuntary movements, or dyskinesia, represent a debilitating complication of levodopa therapy for Parkinson's disease ultimately experienced by the vast majority of patients. This article does not review the increased understanding of dyskinesia pathophysiology we have seen during the past few years but, instead, specifically focuses upon the very first molecular events thought to be responsible for the establishment of dyskinesia and generally grouped under the term of "priming". Priming is classically defined as the process by which the brain becomes sensitized such that administration of a dopaminergic therapy modifies the response to subsequent dopaminergic treatments. In this way, over time, with repeated treatment, the chance of dopaminergic stimulation eliciting dyskinesia is increased and once dyskinesia has been established, the severity of dyskinesia increases. In this opinion review, however, we aim at strongly opposing the common view of priming. We propose, and hopefully will demonstrate, that priming does not exist *per se* but is the direct and intrinsic consequence of the loss of dopamine innervation of the striatum (and other target structures), meaning that the first injections of dopaminergic drugs only exacerbate those mechanisms (*sensitization*) but do not induce them. Chronicity and pulsatility of subsequent dopaminergic treatment only exacerbates the likelihood of developing dyskinesia.

2. Introduction

Parkinson's disease is a progressive neurodegenerative disorder that is observed in approximately 1% of the population over 55 and consists of a syndrome including bradykinesia, rigidity, postural abnormalities and tremor. The principal pathological characteristic of PD is the progressive death of the pigmented neurons of the substantia nigra pars compacta (SNc) (Hassler, 1938). The discovery, in 1960, that degeneration of the dopamine (DA) supplying neurons of the SNc causes parkinsonism (Ehringer and Hornykiewicz, 1960) opened the way for the development of pharmaceutical therapies for PD that act to enhance synaptic DA transmission using the DA precursor L-3,4-

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dihydroxyphenylalanine (L-dopa) (Birkmayer and Hornykiewicz, 1961; Carlsson et al., 1957).

The initial exuberance surrounding the positive effects of L-dopa in PD soon gave way to the recognition that long-term levodopa therapy is confounded by the development of adverse events related to fluctuations in motor response. These motor fluctuations include on-off fluctuations, sudden, unpredictable changes in mobility, and the wearing-off phenomenon, a decrease in the duration of action of levodopa. However, the most debilitating class of motor fluctuation is involuntary movements known as L-dopa-induced dyskinesia (LID) (Duvoisin, 1974). Dyskinesia can be broadly categorised into chorea (hyperkinetic, purposeless dancelike movements) and dystonia (sustained, abnormal muscle contractions). With increasing duration of treatment, there is an increase in both the frequency and the severity of dyskinesia (Marsden et al., 1982). Ultimately, the majority of L-dopa-treated patients experience dyskinesia, with up to 80% of patients having dyskinesia within 5 years of treatment (Rascol et al., 2000). It should be noted that treatment-related dyskinesia are not solely a problem of L-dopa and that DA receptor agonists are also capable of eliciting dyskinesia and within the context of this review, the commonly-used term, LID, will be used, as it is widely understood, to describe DAergic treatment-related dyskinesia generally.

The past few years have seen an unprecedented increase in understanding the neural mechanisms underlying LID manifestation in PD (Bezard et al., 2001; Brotchie, 2005; Cenci, 2007), associating them with a sequence of events that include pulsatile stimulation of DA receptors, downstream changes in proteins and genes, and abnormalities in non-DAergic transmitter systems, all of which combine to produce alterations in the neuronal firing patterns that signal between the basal ganglia and the cortex.

This article, however, will NOT review those new findings but will, instead, specifically focus upon the very first molecular events thought to be responsible for the establishment of LID and generally grouped under the term of “priming”. Priming is classically defined as the process by which the brain becomes sensitized such that administration of DAergic therapy modifies the response to subsequent DAergic treatments (Brotchie, 2005). In this way, over time, with repeated treatment, the chance of DAergic stimulation eliciting LID is increased and once LID has been established, the severity of dyskinesia increases.

In this review, we aim at strongly opposing the common view of priming. We propose, and hopefully will demonstrate, that priming does not exist *per se* but is the direct and intrinsic consequence of the loss of DA innervation of the striatum (and other target structures).

3. Current concept(s) of priming

The classical definition is that priming is induced by acute dopamimetic treatment in a denervated brain. An easily quantitative model of priming, also called behavioural sensitization, has been developed, based on repeated exposure to drugs acting as direct or indirect stimulants of central DA transmission. This model utilizes rats unilaterally denervated of ascending DA nigrostriatal neurons by an intracerebral injection of the neurotoxin 6-hydroxydopamine (6-OHDA). When such lesioned animals are treated with DA receptor agonists, animals rotate contralaterally, away from the side of the lesion. This robust behavioural paradigm still serves, some 30 years since its introduction, as the standard for determining the effect of DA depletion in the striatum (Anden et al., 1970). In this model, administration of a so-called “priming” dose of a DA receptor agonist sensitizes the animal to the effect of a subsequent challenge with DA agonists. This model suggests that a first-ever administration of DA agonist is required for priming, and that dyskinesia

and priming are members of the same continuum, dyskinesia developing with chronicity of the treatment.

Based on this model of behavioural sensitization, phenomena were divided as follows:

- i. *First-ever administration*, followed by a second administration, both resulting in *priming*, i.e., behavioural sensitization (Di Chiara et al., 1992).
- ii. *Maintenance of priming*: Chronic DAergic treatment induces dyskinesias that never stop and their severity increases with chronicity of the treatment (Nutt, 2007). Once, established and even in the absence of treatment, the brain maintains its primed state such that, a single acute L-dopa or DA agonist administration given many months, and even years, after cessation of initial therapy (“drug holiday”) will elicit LID at almost the same severity. A major challenge, to date little addressed, is to understand the process by which this memory for dyskinesia is maintained.
- iii. *Depriming* is a conceptual idea suggesting that it would be possible to disrupt the processes responsible for maintaining the brain in its primed state, as it is possible to erase mnemonic traces by forgetting processes (such depriming therapies could be of value in resetting the clock with respect to the problem of dyskinesia).

However, there is no consensus around these definitions. Even though specialists manipulate the same concepts, they do not use a common vocabulary and on the contrary different concepts are grouped under the term of priming. While some groups focus on receptor sensitivity as the main feature of priming (Bezard et al., 2001; Muriel et al., 1999), others define priming as a behavioural manifestation (Di Chiara et al., 1992). Moreover, some consider a single administration of a dopaminergic agent efficient enough for priming whereas others consider that priming occurs after at least two injections or more (Di Chiara et al., 1992; Gerfen, 2000). Eventually, the great number of paradigms used to study priming shows how confused is the priming concept.

4. Behavioural evidences supporting key role of DA depletion

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

Sensitization to dopaminergic drugs, i.e., L-dopa, DA agonists or DA-releasing agents, was first defined as a behavioural phenomenon in the 6-OHDA-treated rat rodent model of PD. Indeed, repeated exposure to drugs acting as direct or indirect stimulants of central DA transmission results in sensitization to their behavioural stimulant properties, i.e., turning (rotation) of the animal towards the side opposite to the lesioned one (contralateral turning) (Ungerstedt, 1971). This provides a simple model of behavioural sensitization particularly suitable for studies of its neural and molecular mechanisms, as investigations in patients are almost impossible. Indeed, PD diagnosis includes a positive response to L-dopa (Albanese, 2003), therefore preventing accurate assessment of this phenomenon.

Di Chiara's group has popularized the behavioural sensitization paradigm and has extensively dissected out the respective contribution of DA receptor subtypes (Di Chiara *et al.*, 1992; Morelli *et al.*, 1993a; Morelli *et al.*, 1990; Morelli and Di Chiara, 1987, 1990; Morelli *et al.*, 1991; Morelli *et al.*, 1987, 1992a; Morelli *et al.*, 1989; Morelli *et al.*, 1992b; Morelli *et al.*, 1993b) as well as non-DA receptors (see below). In this model, they and others demonstrated that the first-ever administration of a DA agonist sensitizes the animal to the effect of a subsequent challenge with DA agonist (Di Chiara et al., 1992; Morelli and Di Chiara, 1987; Morelli et al., 1991; Morelli et al., 1989). However, a low dose of D1-like receptor agonist (SKF 38393) administered to drug-naïve rats 60 days after 6-OHDA lesion induced contralateral turning behaviour without previous pre-treatment with a DA agonist

(Morelli et al., 1989). This latter experiment suggested that pre-treatment with DA agonist is not an absolute requirement for the induction of the D1-dependent supersensitivity and contralateral turning behaviour but would in fact act as a facilitatory factor.

A major issue with this experimental design is, to our opinion, that the measured endpoint, i.e., the rotational behaviour, encompasses both the antiparkinsonian and the prodyskinetic responses to the various pharmacological agents while in human PD, patients present clearly distinguishable antiparkinsonian AND prodyskinetic responses to a treatment (Cenci et al., 2002). The sensitized behaviour can well be seen as an improved antiparkinsonian response or as representing the hyperkinetic component of the behavioural response to DAergic agents that has to be distinguished from LID and should never be rated as LID (Bezard et al., 2003). In that case, the above-mentioned studies could be seen as investigating the progressive improved behavioural response to antiparkinsonian treatment but not studying the development of LID.

4.2. Abnormal Involuntary movements in the 6-OHDA-lesioned rats

For decades, the Ungerstedt model has constituted the gold standard of the rodent research until a few researchers (too few) began to look at rodents for what they are physically able to perform (for review, see Cenci et al., 2002). Thus, in the late 90s, M.A. Cenci and collaborators developed the abnormal involuntary movement (AIM) rating in the L-dopa-treated 6-OHDA lesioned rat (Cenci et al., 1998) as they observed that rats were not simply displaying a sensitized rotational behaviour but also a series of complex behaviours that were resembling L-dopa-induced dyskinesia (Cenci et al., 2002) affecting the forelimb contralateral to the lesion, the trunk and the orofacial musculature [Andersson, 1999 #283] (Cenci et al., 1998; Lee et al., 2000; Lundblad et al., 2002; Winkler et al., 2002).

A general observation is that a number of animals are displaying AIMs from the very first administration of dopaminergic drug (Andersson et al., 1999; Cenci et al., 1998; Delfino et al., 2004; Johansson et al., 2001). As for the sensitized rotational behaviour, severity of AIMs increases over time and plateaus after a few days. In a recent experiment, Puterman et al. elegantly showed that such AIMs are elicited on the very first day when lesion exceeds a given threshold (see Fig. 3 of Puterman et al., 2007). It is also our own experience that severely lesioned rats display AIMs on the very first day of L-dopa administration even at doses as low as 3mg/kg (carbidopa 15 mg/kg) (Porras, Berthet and Bezard, unpublished observations). These data strongly suggest that the first-ever administration of L-dopa can elicit relatively severe AIMs within a few minutes of administration with a time-course comparable to those later on further displayed by severely dyskinetic animals. It further suggests that a “priming” event is not required for dyskinesia to appear and that the lesion itself is the only prerequisite for such AIMs as normal rats do not display such AIMs either after the first-ever or chronic L-dopa administration.

4.3. Dyskinesia in the MPTP-treated monkey

The serendipitous identification of a neurotoxin causing parkinsonism in humans, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al., 1983), has led to the development of new experimental models; those using non-human primates have proved especially valuable (Bédard et al., 1992; Bezard et al., 1998; Langston et al., 2000). Actually most of the available pharmacology and/or surgical approaches have been finally validated in this model (e.g., Bezard et al., 1998; Drouot et al., 2004; Kordower et al., 2006). A key advantage of this model is that when bilateral parkinsonian syndrome is stabilized, animals stay naive to any DAergic drugs since pharmacological evaluations of the lesion extent are not required. This is now the case as well with the latest development of the rodent models, but such an issue has not plagued the primate field of research. Other issues affect its

reliability that are reviewed elsewhere (Bezard et al., 2001; Jenner, 2003; Langston et al., 2000).

As for the AIM model, however, very few studies have focused on the issue of the “priming” phenomenon in primates, and observations are primarily derived from studies disclosing time courses of LID development or from incidental reports, where information is most of the time hidden in the body text. An experimental design resembling the sensitization rat model, the so-called *de novo* design, has been developed by the team of P. Jenner and used by others later on (Hill et al., 2004; Maratos et al., 2001; Pearce et al., 1998; Pearce et al., 1995; Smith et al., 2005; Smith et al., 2003). Unfortunately, the experimental design has been applied almost exclusively in the marmoset model, the non-human primate species that shows the less severe parkinsonian syndrome and is characterized by a higher hyperkinetic component in its LID-like behaviour. Despite these limitations, it is clear that a significant proportion of the MPTP-lesioned marmosets develops LID after first-ever administration, i.e., on day 1 of the induction protocol (e.g., see Hill et al., 2004; Maratos et al., 2001; Pearce et al., 1998). Similarly, the severely MPTP-lesioned macaque can develop LID at the first-ever administration of a therapeutically-relevant dose of L-dopa (Hill & Bezard, unpublished observations). In a recent experiment where macaques were rendered parkinsonian and left without treatment for several months, 13 out of 20 developed significant LID after the very first administration of 20 mg/kg Modopar (L-dopa: carbidopa; ratio 4:1).

Altogether, these data suggest that the key parameters for eliciting LID after the first-ever administration of L-dopa are (i) the extent and pattern of lesion (Guigoni et al., 2005b) and (ii) the lag time between intoxication period and first-ever exposure to L-dopa. Supersensitivity takes time to develop and long-term compensatory mechanisms take place after only a few months of untreated denervated state (e.g., Decamp et al., 1999; Schneider et al., 1999). We acknowledge that additional factors such as the paradigm of lesion induction or the pulsatility of the treatment might be involved (Jenner, 2003; Schneider et al., 2003). However, the regular observation of LID occurring after the first-ever dose of L-dopa strongly supports our hypothesis that the primary factor for LID manifestation is the presence of a marked lesion, large enough and established long enough to allow receptor supersensitivity to develop, without the need for a “priming” event.

4.4. Dyskinesia in human parkinsonism

Although the notion that disease severity, hence extent of lesion, is the main risk factor for LID appearance (Horstink et al., 1990; Olanow et al., 2004), the fact remains that an indisputable evidence supporting our hypothesis cannot be obtained so easily in human PD. The few MPTP-intoxicated humans originally described by J.W. Langston (Langston et al., 1983) are however of special interest in this context. Those atypical patients developed a very severe parkinsonian syndrome that was not distinguishable from end-stage idiopathic parkinsonism. Virtually all of the problems typically encountered with DA precursor and agonist therapy in treating PD have been observed in these patients, including “end-of-dose” deterioration (or “wearing off”), “peak- dose” dyskinesias, “on-off” phenomena, and psychiatric complications (Ballard et al., 1985; Langston and Ballard, 1984). However, these have occurred much earlier than is typically seen when treating the idiopathic disease, i.e., within a few days! From time to time, there are incidental reports of untreated patients who developed LID while being challenged with L-dopa as part of the diagnostic process. Such patients tend to disappear from the developed countries but are more common in developing countries where access to DA agents or to a movement disorders specialist is still limited. Such a rapid evolution of therapeutic side-effects favours the view that at least some of the complications of DA precursor therapy may be related to severity of disease rather than the length of L-dopa therapy (Ballard et al., 1985; Langston and Ballard, 1984). Extending this

view would be that only the extent of lesion, as well as the duration of the untreated period, is the key factor in allowing or not the development of LID, again supporting our hypothesis for the lack of “priming” but rather for the primary cause of LID rooting into the DA denervation.

5. Pathophysiology of DA-depleted and DAergic drug first-ever exposed brain

5.1. DA receptors expression and localization

AIM and LID can occur after the first-ever dose of L-dopa in the rat and primate, respectively, supporting our hypothesis that the primary factor for LID manifestation is the presence of a marked lesion, large enough and established long enough to allow receptor supersensitivity to develop, without the need for a “priming” event. Thus, it seems likely that DA receptors should present an adaptive responsiveness to DA depletion.

Dopaminergic lesion has generally been reported to consistently cause increases in the density of DA D2-like receptors (Alexander et al., 1993; Aubert et al., 2005; Betarbet and Greenamyre, 2004; Decamp et al., 1999; Doudet et al., 2000; Elsworth et al., 1998; Herrero et al., 1996; Morissette et al., 1996; Todd et al., 1996). As expected, only few data have been collected in untreated parkinsonian patients. Even in those so-called “untreated” patients, one can posit that they have been exposed to L-dopa as this is part of the diagnostic process. In humans, positron emission tomography (PET) scanning of striatal D2 DA receptors revealed either normal or raised D2-like receptor level in untreated parkinsonian patients (Brooks et al., 1992; Laulumaa et al., 1993; Sawle et al., 1993).

Recent studies showed that neither D1 mRNA nor D1-like receptor binding is affected by the MPTP-induced DA denervation (Aubert et al., 2005; Graham et al., 1993; Guigoni et al., 2005a). However, MPTP intoxication induces a significant increase in D1 agonist-stimulated 35S-GTP γ S binding without affecting the number of D1-like receptors (Aubert et al., 2005). This finding suggests that striatal DA depletion induces a sensitization of D1-like receptors. Moreover, using electron microscopy techniques, Guigoni et al. analyzed the cellular and subcellular localization of D1 receptor in the medium spiny striatal neurons in MPTP-treated primates and showed that in these animals, D1 receptor distribution was strongly modified by MPTP intoxication. The most striking result was the recruitment of D1 receptors at the plasma membrane of striatal neurons in untreated MPTP-lesioned animals (Guigoni et al., 2007), animals which precisely show such an enhanced sensitivity per D1 receptor (Aubert et al., 2005) [but see Fiorentini, 2006 #337]. It should be acknowledged, however, that not only the lesion, but also the chronic treatment with L-dopa may increase the sensitivity of striatal D1 receptors. In the rat AIM model, striatal D1 receptor mRNA is significantly elevated [Konradi, 2004 #336]. Moreover, Aubert et al. (2005) had showed increased efficiency of D1-agonist induced GTP binding in dyskinetic macaques, and these had been chronically treated with L-DOPA, without inducing a change in the repartition of D1 receptor in the cellular compartments, i.e., there was still the same proportion of D1 receptor at membrane than in the depleted situation [Guigoni, 2007 #285].

Altogether these data strongly suggest that the acknowledged and powerful D1 supersensitivity is related to lesion-induced changes (i) in signalling cascade activity and (ii) in preferential addressing to membrane of the supersensitive receptor.

5.2. Regulation of DA receptors-dependent signalling cascades

In the field of signalling and genic regulation, an extensive work has been performed to describe the effects of the first-ever administration of DAergic drug in comparison to

lesioned animals. Contrary to D2-like receptor, it is generally assumed that D1-like receptor supersensitivity is mostly correlated to an enhanced activity of the intracellular machinery downstream (Berke et al., 1998; Gerfen, 2000; Gerfen et al., 1995; Robertson et al., 1990; Steiner and Gerfen, 1996). Still, most of studies dealing with signalling pathway overactivation in lesioned animals have been performed on animals that were no longer naïve for DAergic drugs. However, few studies compared the lesion-only condition to the lesion+single administration of DAergic agonist condition.

Based on the model of behavioural sensitization, Di Chiara's group suggested that the phosphorylated state of DARPP-32 appeared to be an excellent index of the activity of transduction mechanisms regulated by D1 receptors. As for adenylate cyclase activity, the authors found no effect of lesion on phosphorylated DARPP-32 levels while following DAergic agonist administration, D1 receptor stimulation resulted in an increased phosphorylation of DARPP-32 in the denervated striatum (Barone et al., 1994; Barone et al., 1995). Such data were recently extended in the AIM mouse model (Santini et al., 2007). Contrary to those previous results, Gerfen et al. recently suggested that loss of DAergic innervation was enough to explain supersensitivity of D1 receptors since even after the first-ever agonist administration, differences appeared between unlesioned and lesioned striatum. Indeed, they demonstrated that there was a switch in the regulation of D1 receptor-mediated signal transduction pathways such that ERK1/2 MAPkinase and JNK/SAPkinase signalling pathways were activated in direct striatal projection neurons. The switch to ERK1/2 MAPkinase signalling in direct pathway neurons in the DA-depleted striatum appeared to be responsible for the D1-like receptor-supersensitive response (Gerfen et al., 2002).

Other groups studied overactivation of various signalling pathways after DA denervation. For instance, confirming previous reports, we recently demonstrated that ERK1/2 MAPkinase was already overactivated in drug naïve MPTP-treated monkeys (Bezard et al., 2005). In the same vein, Gerfen's group showed that DA-deficient mice displayed activation of ERK1/2 in the dorsal striatum after D1 receptor agonist treatment (Kim et al., 2006). Again, after D1 receptor agonist administration, ERK1/2 activation is much more important in KO mice than in WT, suggesting that loss of DAergic function induces modifications of striatal neurons that might be responsible for behavioural sensitization (Kim et al., 2006). This result has been independently confirmed with L-dopa in the AIM mouse (Santini et al., 2007) and rat models (Westin et al., 2007). In this latter, the authors further showed that co-administration with a D1-like receptor antagonist blocked ERK1/2 phosphorylation (Westin et al., 2007). Those results are in favour of the concept of "priming" induced by lesion and not by DAergic treatment.

Conversely, a majority of reports investigating ERK1/2 MAPkinase activation after chronic treatments with DAergic agonists (dyskinetic condition) showed a decrease of ERK1/2 activation (Bezard et al., 2005; Kim et al., 2006). This confirms our basic premise that dyskinesia do not result from an enhancement of sensitization but rather are related to plastic changes in basal ganglia induced by the lesion and progressively unravelled/worsened by chronicity and pulsatility of the treatment.

In conclusion, while in physiological conditions, DA, by means of D1 receptors, activates PKA, which directly stimulates DARPP-32 phosphorylation, one of the main features of lesion-induced sensitization is the switch from DARPP-32 activation to ERK1/2 MAPkinase in neurons of the direct pathway as it is observed in addiction. Lesion process seems solely responsible for such a mechanism. Switching, however, does not mean that L-dopa ceases to activate the PKA-DARPP-32 pathway. In fact, high levels of P-Thr34-DARPP-32 have been measured in the 6-OHDA striatum in both rats [Picconi, 2003 #78] and mice [Santini, 2007 #333] treated with L-dopa.

5.3. Genic regulation authorized by DA depletion

The first studies examining gene regulation focused on the expression levels of neuropeptides and DA receptors themselves (Gerfen et al., 1990; Gerfen et al., 1991; Young et al., 1986). They showed that following lesions of the nigrostriatal DA system, gene expression in the direct and indirect striatal neurons is affected in opposite directions. In direct pathway neurons, the neuropeptides substance P and dynorphin, as well as the D1 receptor, show decreased mRNA levels (Gerfen et al., 1990; Gerfen et al., 1991; Young et al., 1986), whereas in indirect striatal pathway neurons, the neuropeptide enkephalin and the D2 receptor show increased mRNA levels (Gerfen et al., 1990; Gerfen et al., 1991; Young et al., 1986). These results confirmed that neurons show phenotypic modifications induced by lesion, and that they do not simply respond to the loss of DA with increased expression of DA receptors.

The next set of tools that were used were the so-called immediate early genes (IEGs), such as c-fos, Arc, zif268 and other transcription factors that are responsible for regulating the expression levels of the late response genes (Dragunow et al., 1990; Graybiel et al., 1990; Robertson et al., 1990). Following loss of DA, D1 receptor-bearing projecting striatal neurons in the direct pathway display a supersensitive response to D1-receptor agonist treatment in terms of IEG synthesis (e.g., Arc) (Gerfen, 2003). This supersensitivity develops rapidly following degeneration of the nigrostriatal DA terminals. Moreover, Gerfen's group has prolifically studied IEG regulation associated to priming. For the benefit of the present review, and at odds with most of the other investigation teams, they commonly compare untreated lesioned rats to lesioned rats receiving a first-ever DA agonist treatment.

They demonstrated a dose-dependent increase in IEG (cfos and zif268) induction in D1 receptor-containing neurons in response to a first-ever D1 receptor agonist treatment (Gerfen et al., 1995). In addition, they reported a potentiated increase in IEG levels in the same population of D1 receptor-containing neurons to combined D1 and D2 receptor agonist treatment that is correlated with a decrease in IEG levels in D2 receptor-containing neurons (Gerfen et al., 1995). This synergistic response to combined D1- and D2-receptor stimulation might be mediated by interneuronal interactions involving the activation of D1 and D2 receptors on separate populations of striatal neurons (Gerfen et al., 1995).

To gain a more complete picture of DA-related changes in striatal gene expression, they used differential display PCR applied to the unilateral 6-OHDA rat model (Berke et al., 1998) to compare gene expression between normal and 6-OHDA-lesioned animals that were given either saline or a D1 agonist. Animals were killed 1 or 24 h later, i.e., at peak of behavioural effect and in the drug-exposed OFF situation, respectively (Berke et al., 1998). The first genes to show rapid induction in response to DAergic drugs were transcription factors, confirming previous results (Berke et al., 1998; Cole et al., 1992; Vallone et al., 1997).

SNc lesion has also been associated with an increase of CREB (cAMP-responsive element binding protein) phosphorylation in the denervated side compared to the intact side when stimulated by DAergic drugs (Cole et al., 1994). Δ FosB-related proteins and JunD were the main contributors to both CRE and AP-1 DNA-protein complexes in L-Dopa-acutely treated animals (Andersson et al., 2001), providing another illustration of the lesion-induced changes that enable the system in general and the striatum in particular to respond pathologically to DA stimulation.

The corpus of data is very compelling and supports our claim that the DA depleted brain is hypersensitive to DAergic drug stimulation. One should keep in mind, however, that these

early or late genic regulations are markers of the supersensitive state into which the lesion has put the striatum and brain. Indeed, while these genic regulations take place, DA-depleted animals or patients might already display AIM or LID as we saw earlier. We propose that they assign the ability of the brain to display such drug-induced abnormal movements and further allow their development when not present at the very first injection. In addition, they are certainly involved in the maintenance of the increased responsiveness to DAergic drugs.

5.4. Proteomic demonstration of DA depletion-induced priming

Puzzlingly enough, while those earlier studies have focused on gene expression, the actual end-products of genes, i.e., the proteins, have not been studied extensively in these models. The advent of proteomic techniques has simplified the evaluation of expression changes across larger sets of proteins. Proteomic techniques allow complex biology especially as they relate to disease processes, making it possible to unravel the basis of LID manifestation in the DA-depleted brain. To fill this void, the MPTP macaque model was used to study the proteome in DA-depleted striatum with and without subsequent acute and chronic L-dopa treatment using two-dimensional difference in-gel electrophoresis and mass spectrometry (Kultima *et al.*, 2006; Scholz *et al.*, 2008). Interestingly, the experimental design included control monkeys, untreated parkinsonian monkeys, parkinsonian monkeys treated for the first time ever that did not exhibit dyskinesia at the peak of the antiparkinsonian effect, and parkinsonian monkeys chronically-treated with L-dopa for months and displaying overt dyskinesia at the peak of the antiparkinsonian effect (Scholz *et al.*, 2008). The collected data suggest that the DA-depleted striatum is so sensitive to *de novo* L-dopa treatment that the first-ever administration alone was able (i) to induce rapid post-translational modification-based proteomic changes that are specific to this first exposure (as animals were killed 60 min after this first-ever L-dopa administration) and (ii), possibly, to lead to irreversible protein level changes as those were not further modified by chronic (3–4 months) L-dopa treatment (Scholz *et al.*, 2008). The apparent equivalence between the first and chronic L-dopa administrations suggests that priming would be the direct consequence of DA loss, the first L-dopa administrations only exacerbating the sensitization process but not inducing it.

5.5. Electrophysiological features of DAergic drug first-ever exposure

One should therefore ask what would be the electrophysiological characteristics of the first-ever dopamimetic treatment in the DA-depleted brain as such recordings would be concomitant with the expression of abnormal corticostriatal plasticity in *in vitro* experiments or of abnormal behaviours in *in vivo* investigations.

Corticostriatal plasticity is of little help here as, unfortunately, long-term depression (LTD) or long-term potentiation (LTP) (Centonze *et al.*, 1999; Graybiel *et al.*, 1994; Lovinger *et al.*, 2003; Walsh and Dunia, 1993) that are inducible at the excitatory corticostriatal synapse cannot be exhibited by striatal slices obtained from 6-OHDA-denervated rats. In fact, while LTD can be restored after DA-denervation by ensuring DA receptor activation through the application of exogenous DA (Calabresi *et al.*, 1992), LTP requires a chronic L-dopa treatment to be restored (Picconi *et al.*, 2003). These views have, however, been recently challenged and this would possibly require them to be revisited [Shen, 2008 #339]. Altogether these results do not explain why animals could exhibit dyskinesia at the very first injection and therefore suggest that the restoration of the corticostriatal plasticity might be a secondary event but not a primary event in the LID genesis.

Electrophysiological recordings performed in animal models of PD suggest that DAergic neurodegeneration is associated with modifications of single unit activity—pattern, frequency (Bergman *et al.*, 1994; Boraud *et al.*, 2001; Boraud *et al.*, 1998; Lozano *et al.*, 1996; Mallet *et al.*, 2006; Miller and DeLong, 1987; Raz *et al.*, 2000; Yoshida, 1991)—as

well as neuronal population activity—oscillations, synchronization (Bergman et al., 1994; Brown and Williams, 2005; Kuhn et al., 2006; Raz et al., 1996; Raz et al., 2001; Raz et al., 2000). However, despite increased attention, little is known about the effects of the first-ever dopaminergic administration on neuronal electrophysiological activity since either the extent of lesion is tested before electrophysiological recordings using DAergic drugs or those are used for maintaining the animals in ethically acceptable condition. A recent study performed in the unilaterally-lesioned 6-OHDA rat model has, however, addressed this issue of priming by recording the single unit activity and the local field potentials (LFP) in the substantia nigra pars reticulata (SNr), an output structure of the basal ganglia (Meissner et al., 2006). While the classically described L-dopa-induced decreased single unit firing frequency was found only in the chronically L-dopa-treated 6-OHDA lesioned rats, the LFP activity increased significantly in the theta range (4–7 Hz) both in the chronically treated rats and in the 6-OHDA animals that were receiving L-dopa for the very first time. Interestingly, the LFP power was high enough in the chronically treated rats for inducing oscillation in the same frequency range at the single unit level (Meissner et al., 2006). It must be noted that such phenomenon was specific to the 6-OHDA lesioned animals as both acutely and chronically L-dopa-treated normal rats did not display such changes in the theta range of LFP and/or oscillations. These data therefore suggest that the effect is specific of the lesioned animals (Meissner et al., 2006).

Accordingly, oscillatory activity of cortical neurons is also modified as early as after the first apomorphine administration to 6-OHDA-lesioned rats (Ballion, Bezard & Gonon, unpublished observations). Since such LFP activity is already present in animals receiving for the very first time an L-dopa or apomorphine dose, it suggests that it traces the electrophysiological characteristic of the “developing” LID. How such changes in SNr or in the cortex are induced remains obscure as, puzzlingly enough, the imbalanced electrophysiological spontaneous activity of both populations of striatofugal medium spiny neurons (Mallet et al., 2006) is NOT changed during the very first administration of apomorphine in the 6-OHDA lesioned rat, i.e., striatopallidal neurons remain hyperactive while striatonigral neurons remain almost silent (Ballion, Bezard & Gonon, unpublished observations). Such dissociated behaviours have to be understood to further progress our understanding of the electrophysiological correlates of LID.

6. Conclusion

As stated in the introduction, we oppose the view that priming results from the chronic non-physiological stimulation of DA receptors by considering that (i) priming does not exist *per se* but (ii) is the direct and intrinsic consequence of the loss of DA innervation of the striatum (and other target structures). The DA treatment would only unravel the phenotypical possibilities “permitted” by the lesion, leading the basal ganglia into a totally different state. Therefore, in our view, mechanisms of dyskinesia establishment can be broadly categorized as follows:

- i. *Supersensitivity* takes into account all the mechanisms induced by DAergic lesion in order to compensate for DA loss, such as receptor overexpression/supersensitivity or signalling pathway “overactivability.” The first injections of DAergic agonists only exacerbate those mechanisms (*sensitization*) but do not induce them.
- ii. *Dyskinesias* do not result from an enhancement of priming but rather are related to plastic changes in basal ganglia induced by the DAergic lesion itself (most likely beyond supersensitivity). Chronicity and pulsatility of the treatment only exacerbate the likelihood of developing LID, decrease the dyskinesia threshold

dose of the drug [Mouradian, 1989 #340], and shift the dyskinesia dose-response curve to the left [Carta, 2006 #341].

- iii. *Maintenance* of dyskinesia implies that plastic changes are long-term modifications of the basal ganglia network.
- iv. In this context, *depriming* is a hollow concept that would become a therapeutic possibility, hopefully, only after adequate restoration of striatal DAergic innervation. Instead of “turning back the clock”, a depriming strategy would drive the dyskinetic brain to another allostatic state, different from both the physiological (normal situation) and the pathophysiological ones (DA-depleted brain, parkinsonian situation).

In light of this review, it is obvious that an incredible number of experiments are still needed. This review should also have an impact on the experimental designs that are classically used in the field of LID pathophysiology by prompting researchers to also involve first-ever administered experimental groups. Finally, it suggests that LID appearance is unrelenting whatever strategy you use as it critically depends on the extent and pattern of DA denervation, strongly calling for the development of the still missing therapeutic strategies aiming at managing LID severity.

Abbreviation List

AIM	abnormal involuntary movement
CREB	cAMP-responsive element binding protein
DA	dopamine
DAergic	dopaminergic
DARPP-32	DA- and cAMP-regulated phosphoprotein-32
ERK1/2	Extracellular signal-Regulated Kinase ½
GPI	internal globus pallidus
GRK	G protein-coupled receptor kinases
IEG	immediate early gene
L-dopa	L-3,4-dihydroxyphenylalanine
LFP	local field potential
LID	L-dopa-induced dyskinesia
LTD	long-term depression
LTP	long-term potentiation
MFB	medial forebrain bundle
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
6-OHDA	6-hydroxydopamine
PD	Parkinson's disease
PKA	cAMP-dependent protein kinase A
RGS2	Regulator of G protein Signalling 2
5-HT	serotonin
SNc	substantia nigra pars compacta

SNr	substantia nigra pars reticulata
STN	subthalamic nucleus

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