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Molecular Basis of Levodopa-Induced Dyskinesias

Frédéric Calon, BSc, BPharm, MSc,* Richard Grondin, PhD,*† Marc Morissette, PhD,* Martin Goulet, PhD,* Pierre J. Blanchet, MD, PhD,† Thérèse Di Paolo, PhD,* and Paul J. Bédard, MD, PhD†

A series of experiments were performed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of parkinsonism for the purpose of understanding the mechanism of dopaminergic dyskinesias. Dyskinesias can be induced in this model by de novo treatment with levodopa, or selective D1 or D2 agonists, provided the drugs are short acting and administered in the pulsatile mode. Biochemical analysis of the brains revealed several alterations in dopamine receptor-binding and messenger RNA message following denervation and dopaminergic treatment, but none that clearly correlated with the presence of dyskinesias. On the other hand, γ -aminobutyric acid (GABA)_A binding was increased in the internal segment of the globus pallidus of dyskinetic MPTP monkeys. This was observed consistently and could be associated with an exaggerated response to GABAergic inhibitory inputs in this strategic structure. Increased preproenkephalin message was also found to correlate with dyskinesias and may be linked to changes in GABA receptors. Treatments that caused dyskinesias induced, in the striatum, chronic Fos proteins of the Δ FosB family which, when coupled with Jun-D, form AP-1 complexes that can affect several genes, including enkephalin and *N*-methyl-D-aspartate receptor. We suggest that levodopa-induced dyskinesias represent a form of pathological learning, which results from deficient gating of glutamatergic inputs to the striatum by dopamine.

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Levodopa-induced dyskinesias (LID) are, with motor fluctuations, common side effects of levodopa therapy in Parkinson's disease (PD), and are generally seen in the same patients.^{1,2} Although dyskinesias (with a special pattern) are observed in some cases at the onset and end of the levodopa response, they are seen typically at the peak of the effect of each dose of levodopa. They can be viewed quantitatively as an excess of movement or qualitatively as a problem in selecting the appropriate motor program or pattern. They occur in 30–80% of parkinsonian patients treated with levodopa.³

An extensive nigral denervation, which is the basic biochemical alteration in PD, appears to be a necessary condition for the appearance of LID.² Indeed, levodopa given at dosages comparable with those administered in PD generally does not induce dyskinesias in normal animals or in human patients not suffering from PD.^{2,4,5} Occasional patients treated with levodopa for years and then later shown not to have nigral degeneration did not develop dyskinesias.⁶ Moreover, LID almost always appear first on the most denervated side and are usually more prominent in the more severely affected patients.⁴ However, dyskinesias have been reported in normal

monkeys following chronic levodopa treatment with very high doses (80 mg/kg).⁷ Interestingly, these were associated with several of the typical biochemical alterations that we believe underlie this phenomenon and which will be described later.

Furthermore, intact functioning of the other nuclei of the basal ganglia is most generally required.² Indeed, inhibition of neuronal activity by surgical lesion or deep brain stimulation in the internal segment of the globus pallidus (GPI) and the subthalamic nucleus markedly reduces LID in PD patients.^{8–15} Moreover, patients suffering from striatonigral degeneration usually do not respond well to levodopa and consequently are less prone to the development of LID.

Role of Dopaminergic Therapy

The appearance of dyskinesias usually requires daily treatment over several months. The same applies to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of parkinsonism, where treatment with doses of between 50 mg and 100 mg of levodopa must usually be administered daily or twice daily for weeks before dyskinesias appear.^{16,17} Once they have appeared,

From the *Centre de Recherches en Endocrinologie Moléculaire, Le Centre Hospitalier Universitaire de Québec, and Faculty of Pharmacy, Laval University, Québec, Canada; and †Unité de Recherche en Neuroscience, Le Centre Hospitalier Universitaire de Québec; and Department of Medicine, Faculty of Medicine, Laval University, Québec, Canada.

Address correspondence to Dr Bédard, Unité de Recherche en Neuroscience, Le Centre Hospitalier Universitaire de Québec, Pavillon CHUL, 2705 Boulevard Laurier, Québec, Québec G1V 4G2, Canada.

however, even if treatment is stopped entirely for several weeks, the first dose will still trigger the same dyskinesias, indicating that treatment with levodopa has modified the response of the brain to dopamine (DA) and that this modification is long lasting.

The foregoing observations would therefore suggest that denervation and nonphysiological dopaminergic stimulation combine to elicit persistent changes in the basal ganglia, which are consistent with an excessive or poorly regulated response to dopaminergic agents. This suggests a learning phenomenon in the biological sense, akin to kindling or long-term potentiation.

Several studies have shown that bromocriptine, an agonist of the D2 receptor family with some reported D1 antagonistic properties, was much less likely to elicit or induce dyskinesias when administered de novo to parkinsonian patients or to MPTP monkeys that had never received levodopa.^{16–18} This led to the hypothesis that stimulation of the D1 DA receptor was somehow responsible for dyskinesias, and that a selective D2 agonist would solve the problem. However, things proved to be less simple, as we soon observed in MPTP monkeys that other D2-like DA receptor agonists were just as likely as levodopa to induce dyskinesias in drug-naïve MPTP monkeys.¹⁹

Moreover, we have recently shown that once dyskinesias have been induced by levodopa, they can be blocked or antagonized by both D1 or D2 antagonists. There is, however, a parallel return of parkinsonian symptoms, with the notable exception of when treating with clozapine in small doses. The pharmacology of clozapine is complex and it is difficult to relate its action simply to the D1 receptor.²⁰ In fact, we have found that dyskinesias can be induced by either D1- or D2-selective DA agonists, provided they are relatively short acting (clinical effect lasting less than 5 hours). The same agonists delivered by minipump in a continuous manner did not induce dyskinesias, emphasizing the role of pulsatile dopaminergic stimulation in their development.²¹

Biochemical and Molecular Mechanism of Dyskinesias *DA Receptors*

Denvervation supersensitivity of DA receptors has been generally recognized as the most plausible mechanism of dyskinesias. Indeed, striatal D2 DA receptor-binding sites are increased in postmortem tissue of untreated parkinsonian patients^{22–25} and in MPTP monkeys.^{16,26–29} Results from binding studies of D1 receptors in the striatum are less consistent, but nigrostriatal lesion generally induces no effect on this DA receptor subtype in PD patients^{30–33} and MPTP monkeys.^{21,27–29,34}

However, LID are almost never seen with the first levodopa dose when the supersensitivity is expected to be present. Furthermore, the DA denervation-induced increase of striatal D2 receptor protein is generally

reversed after chronic levodopa treatment in human PD^{22–25,32,35–37} and MPTP monkeys.^{16,17,27,29,38} Expression of the messenger (mRNA) coding for the D2 receptor protein is also reported to be increased in the posterior striatum of MPTP monkeys and reversed towards control level after chronic levodopa therapy.³⁹ Positron emission tomography studies also show the same pattern of striatal DA D2 receptor up-regulation in untreated PD, which returns to normal or below normal after exposure to levodopa.^{40–42}

In MPTP monkeys, dopaminergic treatments that led to dyskinesias were followed by changes in striatal D1, D2 and D3 receptor-binding, and D1 and D2 mRNA, which demonstrate important crosstalk between the D1/direct and the D2/indirect output systems.^{21,34,39,43–45} In general, the change in D2 mRNA was in the same direction as that of the ligand binding, while the modulation of the D1 mRNA was most often at variance with the binding results, suggesting that the regulation of the D1 receptor by pharmacological agents is not primarily through synthesis. These effects, however, were not well correlated with the development of dyskinesias as such.^{21,34,39,43,44} Overall, binding and *in situ* hybridization studies in the brain of PD patients and MPTP monkeys, from our group and from others, have generally failed to demonstrate any correlation between D1 and D2 DA receptor supersensitivity and the occurrence of dyskinesias.

This does not mean that the chapter of DA receptor supersensitivity is now closed. Indeed, one must keep in mind that DA receptor supersensitivity is not necessarily related to a change in the DA receptor number or synthesis.^{46,47} Changes downstream from membrane-bound DA receptors at the level of the intracellular cell signaling mechanism may account for an altered response in striatal output neurons after long-term dyskinesiogenic levodopa administration. For instance, increased levels of the alpha-subunits of Gs, G(olf) and Gi in the striatum of 6-hydroxydopamine (6-OHDA)-treated rats suggest that alteration in the coupling of DA receptor to G-proteins may be involved in the maintenance of DA receptor supersensitivity, and warrants further examination in animal models of LID.^{48,49}

The D3 receptor has been implicated in the development of dyskinesias based on elegant studies performed in the 6-OHDA rat model, which showed that sensitization to levodopa is accompanied by induction of D3 receptors in motor regions of the striatum, and that this induction is blocked by coadministration of a D1 antagonist.⁵⁰ In primates, DA depletion by MPTP administration significantly decreased levels of D3 receptor-binding to *R*-(+)-7-hydroxy-[³H]-N,N-di-n-propyl-2-aminotetralin and this effect was reversed or compensated for by a chronic treatment with a D1-like, but not a D2-like, receptor agonist.⁴⁵ Associative and limbic regions of the

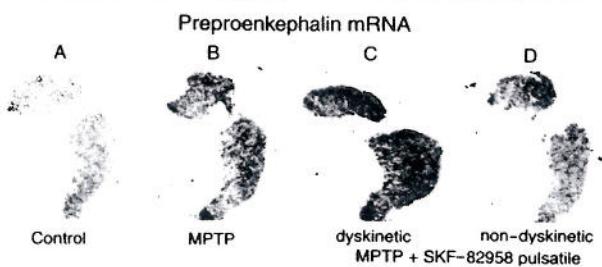
monkey striatum express high levels of DA D3 receptors. The D3 receptor may thus represent an important target for adjunct or direct therapy designed to improve cognitive deficits observed in patients with PD, schizophrenia and other illnesses with frontal lobe cognitive disturbances, but its role in dyskinesias remains uncertain.

Regulation of Neuropeptides in the Two Striatal Output Pathways: Effect of Pulsatile Versus Continuous Mode of Administration

Enkephalin, dynorphin and substance P are opioid peptides that play an important co-transmitter role in the striatopallidal (enkephalin) and striatonigral (dynorphin and substance P) pathways.⁵¹⁻⁵⁴ Studies performed in rats and primates demonstrate quite clearly that selective agonists of D1 and D2 DA receptors are capable of regulating neuropeptides (enkephalin, dynorphin and substance P) in the basal ganglia.^{51,55-58} In primates, the changes in peptide mRNA in response to selective DA agonists were less system specific (direct versus indirect) than in rats and were often apparently crossed. For instance, we observed increased expression of preproenkephalin (PPE) in the striatum after denervation by MPTP, which was not reversed by levodopa or D2-like pulsatile treatment, but was markedly increased by pulsatile treatment with a D1 agonist; interestingly, only in the animals which actually developed dyskinesias (Fig 1).^{55,59} On the other hand, chronic treatment with either the D2-like DA agonist cabergoline or the D1-like DA agonist SKF-82958 was able to restore the decrease in preprotachykinin (PPT) that followed denervation.^{55,59} Thus, it appears that there was a better correlation between changes in PPE and dyskinesias than in the case of PPT. Interestingly, unlesioned monkeys treated chronically with very high doses of levodopa for a toxicological study actually developed dyskinesias and also showed increased PPE message in the striatum.⁷ Furthermore, Piccini and colleagues, using positron emission tomography, have demonstrated a down-regulation of striatal and thalamic ¹¹C-diprenorphine binding to opioid receptor in patients with LID in comparison with other patients devoid of this adverse effect.⁶⁰ This interesting observation is consistent with the aforementioned peptidergic overactivity in LID. The importance of increased striatal neuropeptide transmission in the pathogenesis of LID has been raised by Henry and Brotchie, and they therefore suggested that opioid antagonists may prove to have a beneficial effect in PD.⁶¹

γ-Aminobutyric Acid_A Receptors

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter widely distributed throughout the brain and in the basal ganglia.^{62,63} In particular, GABA is a key neurotransmitter in the two main output pathways of the basal ganglia projecting to the thalamus and originating



*Fig 1. Autoradiograms of coronal brain sections showing preproenkephalin messenger RNA (mRNA) expression as determined by *in situ* hybridization in the caudate nucleus and putamen of (A) a control monkey, (B) an untreated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed monkey, (C) an MPTP monkey treated with SKF-82958 (D1-like agonist) in a pulsatile mode exhibiting dyskinesias, and (D) an MPTP monkey treated with SKF-82958 in a pulsatile mode that did not develop dyskinesias.*

from the GPe, and the substantia nigra pars reticulata (SNpr).⁶⁴ In the basal ganglia, the GABA_A receptors are the main site of action of GABA, and these contain allosteric modulatory binding sites of a number of pharmacologically important drugs, including benzodiazepine, barbiturate and ethanol.^{65,66} The GABA_A receptors are pentameric complexes composed of distinct polypeptide subunits forming a chloride ion channel.⁶⁵⁻⁶⁹

GABA neurotransmission is thought to be profoundly altered in PD and all motor disorders involving a basal ganglia dysfunction. Thus, it is logical to assume that some abnormal neurotransmission of GABA plays a key role in the pathophysiology of LID. The implication of GABA in dyskinetic disorders was first proposed for the pathogenesis of tardive dyskinesia (TD).⁷⁰⁻⁷² Several markers of GABAergic activity were shown to be altered in humans with TD and in animals which developed TD-like movements after long-term neuroleptic treatment.⁷²⁻⁷⁴ Moreover, treatment with GABA-mimetic drugs was shown to improve dyskinetic symptoms in human patients.^{70,72,75,76} Furthermore, an up-regulation of GABA_A receptor in the SNpr was associated preferentially with TD-like movements of rats treated with neuroleptics.^{77,78}

In order to establish a parallel with these observations on TD with our own model of LID in MPTP monkeys, we have studied the relationship between GABA_A receptors and the dyskinetic response to various DA-mimetic treatments (Table 1). Semiquantitative autoradiography with ³H-flunitrazepam (³H-FNZ) was performed to measure the benzodiazepine site associated with the GABA_A receptors.^{34,79} MPTP treatment by itself results

Table 1. Summary of Behavioral Assessment and ^3H -Flunitrazepam (^3H -FNZ) Binding Data to the γ -Aminobutyric Acid (GABA_A)/Benzodiazepine Receptor Complex in the Internal Segment of the Globus Pallidus (GPi) of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) Monkeys Treated De Novo with Dopamine Agonists

Experimental group	n	Receptor family	Antiparkinsonian efficacy	Persistent dyskinesia	GPi ^3H -FNZ binding (% of control)
Naive control+saline	6	—	—	—	100 ± 4
MPTP+saline	5	—	—	—	131 ± 8 ^a
MPTP+levodopa	3	D1/D2	Very good	All	155 ± 16 ^a
MPTP+U91356A pulsatile	3	D2	Very good	All	158 ± 4 ^a
MPTP+U91356A continuous	3	D2	Very good (mild tolerance)	None	126 ± 24
MPTP+cabergoline	3	D2	Very good (mild tolerance)	None	103 ± 5 ^{b,c}
MPTP+SKF-82958 pulsatile	3	D1	Very good	2/3	121 ± 7 ^c
MPTP+SKF-82958 continuous	3	D1	None	None	131 ± 16 ^a
Grouped values					
Dyskinetic MPTP monkeys	8	D1 / D2	Very good	All	150 ± 7
Nondyskinetic MPTP monkeys	7	D1 / D2	Very good	None	113 ± 10 ^d

Binding values are expressed as the mean ± SEM (% of controls). Statistical analyses were performed using an analysis of variance followed by post-hoc pairwise comparisons with Fisher's probability of least-significant difference test. The ^3H -FNZ binding value in control animals was 219 ± 18 fmol/mg of tissue.

^ap < 0.05 versus control; ^bp < 0.01 versus MPTP + levodopa; ^cp < 0.01 versus U91356A pulsatile; ^dp = 0.01 versus dyskinetic MPTP monkeys.

in a critical loss of dopaminergic activity in the striatum and is believed to cause underactivity of the D1 receptor-regulated striatonigral pathway.^{80,81} This results in an increase in ^3H -FNZ binding in the GPi through a compensatory mechanism, as shown in Table 1. This observation is consistent with previous binding studies in 6-OHDA rats and hemiparkinsonian MPTP monkeys.^{82–84}

Interestingly, dyskinesiogenic treatments are associated with an increased density of ^3H -FNZ binding in the GPi at least as high as in untreated MPTP monkeys, and this elevation is statistically significant versus control animals.^{34,79} In contrast, MPTP monkeys that did not show dyskinetic behavior following DA-mimetic treatment showed a level of ^3H -FNZ binding in the GPi which remained nonsignificantly different from naive controls.^{34,79} Among the 15 monkeys that showed good recovery of their parkinsonian symptoms, 8 monkeys developed dyskinesias, whereas 7 did not. When data from these 15 animals are pooled together, a significant association can be seen between the development of dyskinesias and a higher level of ^3H -FNZ binding in the GPi.

According to the classic model of basal ganglia information processing previously described, LID is associated with an underactivity of GPi neurons projecting to the thalamus. This lack of inhibitory drive in the thalamus generates exaggerated thalamocortical discharges that may promote erroneous motor programs.^{80,81,85,86} The GPi GABA_A /benzodiazepine receptor complex upregulation seen in dyskinetic animals suggests that GPi neurons are supersensitive to GABA_{A} ergic afferents from the

striatum and the external segment of the globus pallidus (GPe). Hence, the stimulation of D1 receptors, which activates the direct pathway from striatum to GPi, and/or of D2 receptors through the indirect pathway (via the GPe) may cause an overinhibition of the GPi, and thus promote the generation of choreic dyskinésias through thalamocortical hyperactivity.^{34,79}

N-Methyl-D-Aspartate Receptors

Glutamate neurotransmission has been shown to be significantly affected in PD at several levels.⁸⁷ For instance, the glutamatergic subthalamopallidal and corticostratial pathways are thought to be overactive following dopaminergic denervation.^{88–90} Several selective glutamate antagonists have been tried in rodent and primate models of PD, as well as in small clinical studies.^{90–92} Despite some conflicting results, it is clear that blockade of glutamate transmission can alleviate parkinsonian symptoms in animal models of PD, although the exact site of action remains elusive.⁸⁸

More interestingly, recent observations show that dysfunction of some glutamatergic systems in the basal ganglia can be related to the development of LID. In MPTP monkeys, systemic administration of LY-235959, a competitive nonselective NMDA antagonist, causes suppression of LID, while leaving the antiparkinsonian response to levodopa unaltered.⁹³ Studies with a noncompetitive allosteric antagonist selective for the NMDA1A–NMDA2B receptor assembly, namely PD 174494, provide similar data.⁹⁴ Improvement of LID with less selective NMDA antagonists was also reported

in human parkinsonian patients.^{95,96} These observations led to the tempting speculation that the antiparkinsonian response and the antidyskinetic process may be mediated by different mechanisms, the former being achieved by DA receptor stimulation and the latter via NMDA receptor blockade.⁹¹

Determination of the site of action of NMDA receptor antagonists underlying their antidyskinetic effects is rather complex, since these drugs given systemically may interact with NMDA receptors located throughout the brain.⁹⁷⁻⁹⁹ However, recent evidence has provided a few hints that striatal NMDA receptors may be involved in these observations and, consequently, in the pathophysiology of LID. Comparison between MPTP monkeys exhibiting dyskinesias from others that did not, following D1 and D2 agonist treatment, shows that ³H-glycine binding was higher in the dyskinetic animals.¹⁰⁰ This is consistent with results showing an increase in binding affinity of NMDA receptors to MK-801 in the striatum of 6-OHDA-lesioned rats experiencing levodopa-induced motor complications.¹⁰¹ In contrast, another study in rats bearing unilateral 6-OHDA lesions brings conflicting results as it shows that ³H-glutamate binding to NMDA receptors is reduced in both hemispheres after levodopa treatment for 21 days.¹⁰² However, in postmortem tissue from parkinsonian patients, an increase in ³H-L-glutamate and ³H-CGP 39653 binding to striatal NMDA receptors has been reported in comparison with normal controls.¹⁰³⁻¹⁰⁵ By contrast, no change in ³H-MK-801, ³H-kainate and ³H-D,L- α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid binding to their respective binding sites has been observed in the same or similar studies.^{103,106} These subjects had been treated with levodopa before death and, consequently, an important number of them may have experienced LID. Although precise information on adverse effects is not described in these reports, it is possible that the increased binding to NMDA receptors is related to the development of LID in these patients.

Native NMDA receptors are heteromeric complexes consisting of NMDAR1 and various NMDAR2 (NMDAR2A–NMDAR2D) subunits.¹⁰⁷ NMDAR1 is essential for the formation of functional NMDA receptor channels, whereas NMDAR2 regulates receptor pharmacological and biochemical properties.^{107,108} In the human brain, mRNA for NMDAR1, NMDAR2B and, to a lesser extent, NMDAR2A subunits was detected in the caudate and putamen.⁹⁷ Using immunohistochemical techniques, it was confirmed that most striatal projection neurons in rats possess both NMDAR2A and NMDAR2B, as well as NMDAR1 subunits.^{109,110}

Several pieces of evidence show that tyrosine phosphorylation of both NMDAR2A and NMDAR2B subunits regulates the activity of NMDA receptors *in vivo*.^{107,111} For instance, a 6-OHDA lesion in the rat induces an increase in tyrosine phosphorylation of the NMDAR2B

subunits and is associated with a slight elevation of striatal tyrosine kinase activity.^{112,113} Chronic levodopa treatment of 6-OHDA rats, which causes fluctuations in the motor response, is also associated with an increase in NRMDA2A and NRMDA2B subunit phosphorylation.¹¹⁴ Furthermore, intrastriatal injection of a tyrosine kinase inhibitor in rats, in order to decrease the ratio of phosphorylated tyrosine, is shown by the same group to decrease the incidence of motor response complications caused by levodopa treatment.^{101,114,115} These results introduce the perspective that modulating the activity of striatal tyrosine kinase may prove to be a suitable strategy to prevent the development of LID.

ΔFosB and Isoforms

Chronic Fos-related antigens (FRAs) are particularly interesting in relation to LID, as they are induced in the brain in a region-specific manner in response to several chronic perturbations, including chemically or electrically induced seizures and psychotropic treatments.^{116,117} Typical neuroleptics (haloperidol and metoclopramide), which readily induce extrapyramidal side effects, given chronically increase ΔFosB (but not c-Fos derivatives or isoforms) in the caudate-putamen (predominantly in enkephalinergic neurons).¹¹⁸ Clozapine, which induces less TDs, does so only in the nucleus accumbens.¹¹⁸ Haloperidol increases FosB in the anterior regions, and pilocarpine, a cholinergic muscarinic agonist, in the posterior regions of the striatum.¹¹⁸ A major challenge is to identify the specific target genes through which changes in ΔFosB lead to altered functioning of the nucleus accumbens and other striatal neurons. However, a large number of isoforms of ΔFosB can be formed from the same gene by alternative splicing. These, in turn, may form a variety of dimers, which can affect several genes. It is therefore important to identify which isoform(s) correlate(s) with the presence or absence of dyskinesias, on the one hand, and to relate the presence of dyskinesias to the degree of expression of the immediate-early gene (IEG), on the other.

ΔFosB and isoforms are induced by denervation in 6-OHDA rats.¹¹⁹ Denervation also induces persistent expression of Jun-D. The two form a dimer, which is responsible for increased AP-1 binding in the striatum. Another isoform of ΔFosB is specifically induced by priming. It is different and it combines with a smaller, more rapidly migrating Jun-D to form a special priming AP-1 complex called pAP-1, which can bind to AP-1 consensus sites or a cyclic AMP response element (CRE) site. Interestingly, there is a CRE site on the PPE gene. Priming can be blocked by the NMDA antagonist MK-801, and this also blocks or reduces the induction of the pAP-1 complex. MK-801 also prevents the increase in the pre-existing denervation-induced AP-1 complex by priming.¹¹⁹

Link Between Δ FosB Isoforms and Dyskinesias

In the striatum of MPTP monkeys, otherwise untreated, we observed by Western blot an increase in Δ FosB, which was present after several months of denervation.¹²⁰ This band was not present in MPTP animals treated chronically with cabergoline, a very long-acting D2 agonist, which therefore provides a continuous stimulation. Interestingly, two out of three of these animals for whom this was the very first exposure to dopaminergic agents displayed typical dyskinesias the first day of treatment, which disappeared in a few days.

In MPTP monkeys given three injections a day of the short-acting D1 agonist SKF-82958, we observed within one week the development of dyskinesias in two out of the three animals, and there was marked induction in the striatum of Δ FosB only in these two animals. Another group of three animals, which were treated with the same D1 agonist at the same daily dose but in a continuous manner through a minipump, did not develop dyskinesias nor did they show induction of Δ FosB. There is therefore a striking relationship between the induction of persistent dyskinesias and Δ FosB. Other Fos-related proteins are induced transiently but Δ FosB is induced later, and its persistence and presence only in monkeys with dyskinesias suggest a causal link.

IEGs Can Regulate Neuropeptide Gene Expression in The Basal Ganglia

Since proenkephalin and prodynorphin promoters contain both CRE and AP-1 element, it is possible that the expression of these two genes is regulated by increases in both CRE binding protein (CREB) phosphorylation and Δ FosB levels.^{121,122} Interestingly, in our previous experiments, there was a close correlation both in treatment groups and in individual animals between the induction of Δ FosB in the striatum and the increase in PPE expression. There was no such correlation for PPT or preprodynorphin. These neuropeptides, and in particular enkephalin, appear to regulate GABA release in the basal ganglia¹²³ and could therefore be responsible for the changes in GABA receptor binding observed in the GPi.

Conclusion

In conclusion, we believe that FRAs are induced in the striatal neurons by excessive glutamatergic inputs due to absent or abnormal dopaminergic modulation (Fig 2). They form dimers called AP-1 complexes and can affect genes bearing AP-1 sites that regulate neurotransmitters or modulators including NMDA receptors, D1 dopaminergic receptors, enkephalin and dynorphin. CREB and NMDA receptor subunit phosphorylation may also play an important role. These modifications trigger a cascade of other interrelated changes; for instance, in GABAergic and glutamatergic transmission, which are responsible for the abnormal response to

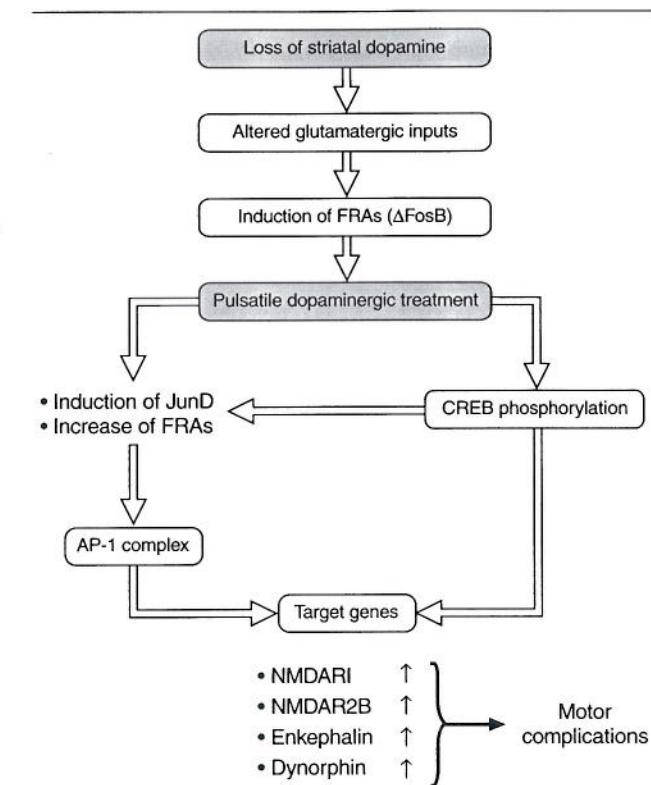


Fig 2. Possible sequence of events in the striatum leading to levodopa-induced dyskinesia. FRAs, Fos-related antigens; CREB, cyclic AMP response element binding protein; NMDA, N-methyl-D-aspartate.

dopaminergic agents that translates into dyskinesias in primates and humans.

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