Levodopa-Induced Dyskinesia: Facts and Fancy. What Does the MPTP Monkey Model Tell Us?

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ABSTRACT: Levodopa-induced dyskinesia, one of the most frequent long-term side effects of antiparkinsonian therapy, is often attributed to denervation supersensitivity of dopamine receptors and perhaps more specifically the D-1 receptor. The available evidence based not only on clinico-pathological studies in patients but also on results of experiments performed on methyl-phenyl-tetrahydropyridine (MPTP)-treated monkeys suggests that the mechanisms may be more complex than heretofore believed. Thus it appears that no single receptor is the sole culprit, that some form of denervation supersensitivity is probably involved but not in the form of increased density of dopamine receptors. Moreover, other neurotransmitter systems must be considered such as GABA, excitatory amino acids and peptides. The MPTP monkey model remains very useful for predicting the potential of new drugs for inducing dyskinesia. Such trials however must be performed in drug-naïve animals.

RESUME: Dyskinesies induites par la levodopa: faits et mythes que nous enseigne le modele du singe traité par le MPTP? Les dyskinesies induites par la levodopa, un des effets secondaires a long terme les plus frequents de la therapie antiparkinsonienne, sont souvent attribuees a une hypersensibilite de denervation des recepteurs dopaminergiques et peut-être plus specifiquement du recepteur D-1. Les donnees disponibles, bases non seulement sur des etudes clinico-pathologiques chez des patients, mais aussi sur les resultats d’expériences effectuees chez les singes traités par le MPTP, suggèrent que les mécanismes peuvent être plus complexes que nous le croyons antérieurement. Ainsi, il ne semble pas que le responsable soit un seul recepteur. Une certaine forme d’hypersensibilite de denervation est probablement impliquée, mais par sous la forme d’une augmentation de la densite des recepteurs dopaminergiques. De plus, d’autres systemes de neurotransmetteurs doivent être considérés, tels le systeme GABA, les acides aminés excitateurs et les peptides. Le modele des singes traites au MPTP demeure tres utile pour predire le potentiel de nouveaux medicaments a induire des dyskinesies. Cependant, de tels essais doivent être effectues chez des animaux nait.

What Does Clinical Experience Teach Us?

Since the first descriptions of this common side effect many important observations have been made which may give us leads as to the pathophysiology of dyskinesia. Dyskinesia may be of different types: dystonic, choreic, myoclonic, ballistic and may occur at the peak of the effect of levodopa or towards the beginning and/or end of the effect. For the purpose of the present discussion, we will limit ourselves to the most frequent form of dyskinesia which is choreic or choreoathetoid in nature and occurs at the peak of the motor effect, often being inseparable from the therapeutic action. It occurs in 30 to 80% of patients treated with levodopa. In our own sample of 117 patients the prevalence was found to be 42%.

Dyskinesias are a result of substantial loss of the dopaminergic nigrostriatal pathway. In fact they appear sooner in patients with severe denervation such as those in whom the syndrome was induced by MPTP. Moreover they almost always appear on the side where the parkinsonian signs first appeared, that is the most denervated side. These facts would therefore suggest that the denervation process plays an important role in their development.

In severely affected patients dyskinesias generally appear after months of treatment, although in some instances they are seen after a few days. However they are never seen after a single dose of levodopa. Their incidence is lower in groups of patients who are treated with lower doses of levodopa and in patients treated instead with dopamine agonists. This would suggest the treatment itself plays a priming role. Once dyskinesias have appeared, they seem to become progressively more severe, despite a constant dose and they can be attenuated by reducing the dose of levodopa at the cost of increased disability.

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It is our impression that the intensity is dose-dependent although this is disputed by certain authors. 8

One of the most interesting pharmacological clues that we have is the fact the patients treated from the beginning with the dopamine D-2 agonist bromocriptine instead of levodopa develop remarkably less dyskinesia and fluctuations after a few years. 4

This is also true for patients treated with a combination of levodopa and bromocriptine. 7 This would suggest that the therapeutic benefit of replacement therapy is somehow linked to the D-2 receptor while dyskinesia would be linked to the other type: the D-1 receptor.

In summary, these observations when put together would suggest that under conditions of denervation, the striatum (or another structure) reacts in an abnormal fashion to repetitive stimulation of the D-1 receptor and that this leads to dyskinesia. If true, treatment with selective D-2 agonists should provide relief without dyskinesia. Moreover since the processes of denervation and the repetitive interaction of the drug with the receptors both seem to play a role, if we could learn to control and understand these processes, we might be able to avoid these side-effects.

The development of the MPTP monkey model 9,14 has provided us with an invaluable tool to test these hypotheses and study the effect of new selective agents in a paradigm that allows definite conclusions: single drug therapy under controlled conditions in drug-naïve animals followed by histochemical, electrophysiological and eventually biochemical analysis of the brain. 11,15,18 We will thus review some of the statements often heard concerning dyskinesia and what answers can be provided by pharmacological studies in the MPTP model.

Fact or Fancy? Dyskinesia is Due to Denervation Supersensitivity of Dopamine Receptors

Several studies have shown that dopamine D-2 receptors are increased in density in the striatum of parkinsonian patients not currently undergoing treatment. 21-23 Some of these studies 21-23 have shown that treatment with levodopa reverses this increase so that if denervation supersensitivity is defined as an increased density of receptors it would be maximal before treatment and tend to be reduced by treatment, which is not compatible with the appearance and progressive increase in dyskinesia during treatment.

Increases in D-1 receptor binding in Parkinson’s disease have also been observed. 24-26 Interestingly, according to Rinne et al., 25 this was especially true in patients treated with levodopa and displaying dyskinesia.

In the MPTP monkey model, nigrostriatal damage is required for induction of dyskinesia. 14,27 We have also observed increases in both D-2 (with [3H] spiperone) 18,19 and D-1 receptors (with [3H] SCH-23390) 28 following treatment with MPTP. However in both cases, the upregulation was reversed by treatment with L-Dopa or dopamine agonists in animals who had developed prominent dyskinesia.

This would seem to minimize the role of denervation supersensitivity. However, in more recent work (unpublished) using both antagonist and agonist ligands for the D-2 and D-1 receptors, we have seen that in the striatum of MPTP monkeys D-2 binding to both the antagonist and agonist is increased maximally in the more posterior regions, but that chronic treatment with dopamine agonists reverses both. In the case of D-1 receptors, denervation is followed by increased binding to the antagonist in the posterior regions but decreased binding to the agonist, indicating a shift to the low affinity state. Chronic treatment with dopamine agonists reverses this situation so that there is a shift to the high affinity state of the D-1 receptor.

Moreover the study of receptors in extrastriatal regions has disclosed some very interesting observations. For instance in the substantia nigra and internal globus pallidus, denervation is followed by no change or increased total binding to [3H] SCH-23390 but a shift to decreased binding to the agonist [3H] SKF-38393. Thus although we do not yet have the total picture of changes in dopamine receptors, we must pay attention not only to the density but to the affinity of dopamine receptors for the agonist. We must also pay more attention to extra striatal output structures which are rich in dopamine (D-1) receptors such as the globus pallidus and substantia nigra pars reticularis. Interestingly Robertson and Robertson 29 believe that a large part of the action of L-Dopa is exerted on D-1 receptors in these output structures. Moreover Parent & Smith 30 have identified a direct nigropallidal (internal division) dopaminergic pathway which seems more resistant to MPTP. 31

The concept of denervation supersensitivity could also be broadened to include synapses placed downstream from the dopaminergic receptors. For instance changes in activity of striatal output cells can affect GABAergic transmission in the globus pallidus. Robertson et al. 32 have reported that MPTP-induced parkinsonism is accompanied by decreased [3H] flunitrazepam binding in the external division of the globus pallidus.

Fact or Fancy? Dyskinesia is the Result of Stimulation of D-1 Receptors

As mentioned above, the fact that bromocriptine is less likely to induce dyskinesia would seem to support this conclusion. If true, selective D-1 agonists should induce prominent dyskinesia with little therapeutic benefit while D-2 agonists should do the opposite. It would thus appear logical to develop selective and potent D-2 agonists. In a recent study Boyce et al. 33 report that the powerful D-2 agonist (+)-PHNO administered to monkeys who had already developed dyskinesia on L-Dopa does not reproduce the same dyskinesia. We have recently performed similar experiments and found that in our hands all D-2 agonists tried on animals who had developed dyskinesia on L-Dopa reproduced the same movements. These included Quiniprole 0.1-0.5 mg/kg, (+)-PHNO (2-10 µg/kg), bromocriptine 5 mg/kg, Terguride and RU-24213.

On the other hand the D-1 agonist SKF-38393, 5-15 mg/kg as reported earlier 18,19,34,35 had no motor effect and did not reproduce the L-Dopa induced dyskinesia. Another D-1 agonist CY-208243 36 was also tried but at a dose of 0.1 mg/kg produced a locomotor activation without dyskinesia while at 0.5 mg/kg (a dose which may not be selective) it also produced dyskinetic movements.

The effect of the D-2 agonists was blocked selectively by the D-2 antagonist sulpiride while that of CY-208243 was antagonized selectively by SCH-23390, 0.05 mg/kg.

Thus, these results do not support an exclusive link between dyskinesia and the D-1 receptor on one hand and the motor response and the D-2 receptor on the other hand. Our results would rather suggest that the D-2 receptor is more important for both aspects of the motor response.
These results were obtained in animals who had already developed dyskinesia with L-Dopa. As mentioned above, L-Dopa seems to exert a priming effect on dyskinesia. Once primed, the animals will respond to most dopamine agonists by dyskinetic movements even after two months without treatment (unpublished results). Interestingly this also includes bromocriptine, a drug which appears less likely to induce priming by itself in humans or monkeys. It is therefore possible that the process of “priming” is different from the capacity to elicit dyskinesia once the animal has been primed with levodopa.

We have therefore treated groups of MPTP monkeys who had received no levodopa or dopamine agonists with a single selective agent. Among D-2 agonists, (+)-PHNO (6 μg/kg daily) and quinpirole (0.5 mg/kg daily) induced typical choreoathetoid dyskinesia of the limbs within a week, which is faster than with L-Dopa (3-4 weeks). Bromocriptine (5 mg/kg) induced none even after six weeks. Neither did the D-1 agonist SKF-38393. However the D-1 agonist CY-208243, 0.5 mg/kg induced typical choreothetoid and dystonic movements after two weeks. These results indicate that at the very least the priming effect cannot be attributed solely to the D-1 receptor.

The fact that bromocriptine is capable of producing a locomotor response without dyskinesia must be explained by other peculiarities of this drug, such as its long half life, the fact that is has some D-1 antagonist properties or the fact that it does not discriminate between the high and low affinity state of the D-2 receptor.

**Fact or Fancy? Partial Agonists Would be Less Likely to Induce Dyskinesia**

A partial agonist is usually defined as a drug which, while reproducing the effects of the neurotransmitter, is incapable of producing the maximum effect, and reduce the efficacy of the neurotransmitter or of “full” agonists. In the field of antiparkinsonian agents, the term has often been used to describe agents which seem to have no effect on receptors which are in the low affinity state. Thus, drugs such as -3-PPP or Terguride have little effect on postsynaptic D-2 dopamine receptors under normal conditions but are effective only under conditions of denervation when the receptors are apparently shifted to the high affinity state. Since these agonists interact with a subpopulation of D-2 receptors it was hoped that they might have motor effects without side effects such as dyskinesia.

Unfortunately, in recent experiments involving monkeys which had already developed dyskinesia with L-Dopa we have shown that both Terguride and -3-PPP not only produce locomotor stimulation but elicit the same dyskinesia as L-Dopa. This does not however rule out the possibility that such agents if they were given de novo to parkinsonian patients or MPTP monkeys who have not been exposed to levodopa would not have the “priming” effect and would not elicit dyskinesia.

**Fact or Fancy? The Type of Dyskinesia is Related to the Type of Drug or Receptor**

In a recent report, Boyce et al. have observed that, at the dose given and in their population of MPTP monkeys, the D-2 agonists (+)-PHNO did not reproduce exactly the same dyskinesia as levodopa. More specifically the abnormal movements tended to be more dystonic while levodopa induced movements of a choreic nature. In recent experiments, we have observed in a group of MPTP animals rendered dyskinetic with L-Dopa that animals who had movements mostly of choreic nature had exactly the same movements with several D-2 agonists ((+)

**Fact or Fancy? Testing a New Drug in MPTP Monkeys Will Help Predict Whether it Will Induce Abnormal Movements in Patients**

This statement is partly true. Most studies published to date, including some of our own, involve animals who had received levodopa or other agonists and had already developed dyskinesia. Under such conditions the answer is still useful in the sense that it tells us whether switching a dyskinetic patient over to that agent will solve his problem. However we have not yet encountered an agent which could under such conditions induce a locomotor response without dyskinesia except perhaps the D-1 agonist CY-208243 at a low dose (0.1 mg/kg). It is noteworthy that even bromocriptine which we know elicits few dyskinesias when given de novo to patients or monkeys will reproduce very nicely levodopa-induced dyskinesia under such conditions.

To know whether an agent is capable of inducing the change in the CNS that leads to dyskinesia (priming) one must use MPTP monkeys which have never received even one dose of levodopa or other agonists, as we do not know how much exposure is necessary for the “priming” effect. It is also preferable to wait two months after MPTP-treatment since limb dyskinesia are easier to elicit in this period than immediately after MPTP. A positive response can occur after a few days with potent agonists such as (+)-PHNO but for other drugs it may be necessary to treat the animals daily for a least a month and still a negative response does not entirely rule out that a larger dose or a longer exposure to this particular agent would eventually elicit dyskinesia.

In conclusion, we believe that the MPTP monkey is a useful tool to screen new potential antiparkinsonian agents for their propensity to induce dyskinesia, since up to now the response of the MPTP monkey to such agents has proven remarkably similar to that of humans. Perhaps more importantly however, this model may allow us to understand the mechanism of such side effects since it is possible to study single agents under more rigorous scientific conditions than is possible in patients. Moreover, we now have access to knowledge of the firing pattern of the structures of the basal ganglia during dyskinesias as well as to the changes in various receptors as neurotransmitters and peptides after treatment.

**Acknowledgement**

Supported by MRC of Canada and Parkinson Foundation of Canada.
REFERENCES


