The Fluctuating Parkinsonian Patient – Clinical and Pathophysiological Aspects

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ABSTRACT: Although levodopa-related motor response complications remain challenging from a pathophysiological and therapeutic standpoint, major advances have been made in the last decade, supporting the development of several promising drugs. Eventually, these drugs may help us to prevent, alleviate, or even "deprime" these frequent and disabling complications. Knowledge of the basic mechanisms and hypotheses underlying this fascinating conversion in the parkinsonian brain allows neurologists to understand the rationale behind emerging treatment strategies.

RÉSUMÉ: Le patient parkinsonien fluctuant – Aspects cliniques et physiopathologiques. Les complications motrices associées à la dopathérapie chez le Parkinsonien constituent toujours un défi au plan théorique et thérapeutique mais des progrès majeurs ont été réalisés durant la dernière décennie, favorisant le développement de plusieurs médications prometteuses. Il n'est peut-être pas loin le jour où ces nouveaux agents pourront prévenir, soulager ou même renverser pour de bon ("déprogrammer") ces complications fréquentes et handicapantes. Une connaissance des mécanismes fondamentaux à l'origine de cette fascinante conversion dans le cerveau parkinsonien et des hypothèses explorées permet aux neurologues de mieux comprendre la logique entourant les stratégies correctrices en émergence.

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It is estimated that approximately 10% of levodopa-treated patients with Parkinson's disease (PD) develop motor response complications each year so that daily oscillations in motor performance eventually mar the clinical response of the majority of patients, most often with co-existing various dyskinesias. Unfortunately, these complications may become as disabling as the disease itself. In this section, the clinical manifestations and possible mechanisms of this unique pharmacological and biochemical brain conversion are discussed. Recent supplements on levodopa-induced dyskinesias published in Movement Disorders (1999) and Annals of Neurology (2000) constitute excellent references for those who wish state of the art in current research.

The spectrum of response fluctuations

With respect to the timing of oral levodopa dosing, response fluctuations can be divided in predictable and unpredictable types (Table 1).

Predictable motor oscillations usually become manifest first. This may take the form of nocturnal or early morning akinesia, with recurring parkinsonism following the prolonged drug-free interval of the night. Eventually, patients notice re-emergence of tremor and disability during the day within two to three hours (or even less) after each levodopa dose (so-called "wearing-off"). Recent data extracted from the DATATOP Extension Study revealed that one half of levodopa-treated patients had developed "wearing-off" after 18 months on therapy.[1] Such return in disability is usually gradual over minutes but may become more abrupt. Approximately 15% of levodopa-treated patients may also experience chaotic and random oscillations in motor performance with sudden, unpleasant interruption of ongoing activities for a variable period of time, catching them by surprise and rendering them wary of leaving home (so-called "on-off" phenomenon). These fluctuations have no apparent relation to the timing of oral levodopa dosing. Response oscillations may not only cause profound akinesia and painful dystonia, but they may also produce extraordinary nonmotor symptoms that are often not well-recognized (Table 2). For instance, "off" patients may sweat profusely, become tachycardic, depressed, anxious, even panicky.[2-4]

Another complication familiar to patients is the apparent complete response failure to a given dose, particularly in the afternoon ("no-on"). Interestingly, "hemiparkinsonian" rats with severe 6-hydroxydopamine (OHDA)-induced nigrostriatal lesions occasionally display this phenomenon following repeated

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Table 1: Levodopa-related motor response fluctuations in Parkinson's disease

Predictable
end-of-dose deterioration ("wearing-off ")
diphasic/beginning-of-dose/end-of-dose (exaggeration of) akinesia
nocturnal/early morning akinesia
Unpredictable
random "on-off", "yoyoing"
"no-on"

Table 2: Motor and nonmotor symptoms in parkinsonian "off" state

Motor	**Autonomic**
recurring parkinsonism	tachycardia
dystonia	sweating
	drooling
Sensory	dysphagia
paresthesias, sensory loss	urinary frequency/urgency
pain	anismus
akathisia	pallor
restless legs syndrome	dyspnea
	dilated pupils
Cognitive/psychiatric	blood pressure changes
moaning/screaming	belching
cognitive changes	abdominal bloating
anxiety/panic	nausea
depression	limb edema
	facial flushing

intraperitoneal levodopa injections, while partially lesioned animals do not.[5] Pharmacokinetic, as well as pharmacodynamic, factors may play a role. Another unusual motor complication consists of a brief paradoxical beginning-of-dose deterioration in parkinsonian symptoms occurring shortly after absorption of a dose of dopaminergic medication.[6] A transient decrease in endogenous dopamine turnover due to preferential autoreceptor activation at the onset of action may be implicated. This must be distinguished from other adverse effects such as hypotension or somnolence.

Abnormal involuntary movements

The majority of PD patients eventually experience levodopa-induced dyskinesias (LID). These can cause disability and injuries, restrict treatment choices, and increase medical cost. Young patients and those requiring higher daily doses of levodopa are particularly vulnerable.[7] In the DATATOP Extension Study, one quarter of patients followed prospectively showed dyskinesias within 18 months on levodopa therapy.[1] The mean (±SD) daily dose of levodopa at the emergence of dyskinesia was significantly greater (387±169 mg) than the dose administered to nondyskinetics at the same follow-up visit (338±140 mg). This raises the possibility that the dosage by itself is important, or may be interpreted as an indication that the severity of the disease or changes in the presynaptic handling of dopamine in the dyskinetic group required a greater dose (see discussion below). The intensity of dyskinesias varies substantially from negligible (with unawareness) or mild (cosmetic) to totally disabling. They can be classified according to phenomenology or, more often, in relation to a levodopa response cycle.

"Peak-dose" dyskinesias are first observed and are linked to peak levodopa plasma levels. They may be short-lived or occur during the entire period of the motor benefit ("interdose" or "square-wave" dyskinesias). The intensity is variable and surprisingly bearable or tolerated in many cases. They most commonly affect the limbs and trunk, to take the form of choreic or choreoathetoid movements, whereas dystonic movements are less common and involve the craniocervical region (grimacing, torticollis). The side of the body initially affected by the disease is more commonly dyskinetic at first and this asymmetry persists throughout the course of treatment. Dyskinetic movements are activated by motor and mental tasks.

"Diphasic" dyskinesias, originally described as "D-I-D" for "dystonia-improvement-dystonia",[8] are occasionally seen at the onset and offset of clinical benefit from each individual dose, with the onset-of-dose portion often more prominent. They are linked to critical (transitional) rising and falling levodopa plasma levels. They are asymmetric but the movement disorder is often dystonic (or choreoballic in others) and predominates in the legs. Diphasic dyskinesias, albeit less common, may be violent and painful and less well-tolerated by patients.

"Off-period" dystonia is seen in 20-30% of PD patients using levodopa for more than five years. This commonly occurs in early morning, long after the last dose, at times of subthreshold levodopa plasma levels. It disappears upon levodopa withdrawal for more than 24 hours. It typically involves the distal lower extremity and may cause a painful cramp of the calf, ankle plantar flexion or inversion, curling of the toes, or dorsiflexion of the great toe ("striatal toe"). The upper limb and neck are occasionally involved. Like other dyskinesias, it is more common on the initially, or more severely, affected side but bilateral cramps may occur. "Off-period" dystonia may also occur on a more regular basis during the day whenever the patient is turning off. Untreated, it may last for hours until the patient is totally off. It responds to pharmacological attempts to reduce the amount of daily "off" time.

Infrequently, myoclonic jerks, restlessness, akathisia, and unusual focal dyskinesias (oro-buccal movements reminiscent of tardive dyskinesias, trunkal dyskinesias resembling the Pisa syndrome, respiratory dyskinesias, ocular dyskinesias) may be observed.

One should not get the impression of an absolute frontier or dichotomy between different motor response complications and dyskinesias. In fact, there is a continuum between dystonic movements occurring on a rigid background in the off state and choreic movements occurring on a hypotonic background at the

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peak drug response.[9] The dyskinesias spread to different body parts according to a consistent pattern in a given patient, often starting in the most parkinsonian foot and then spreading in an ascending wave to change in character from dystonia to chorea. Detailed analysis of the motor response fluctuations and dyskinesias, ideally with the help of home diaries and UPDRS-IV ratings, helps in understanding the pathophysiology and managing these complicated patients. An oral levodopa test conducted in the morning 12 hours off medication may be desirable in selected and difficult cases to help sort things out and offer the best treatment strategy.

Basic facts

The basic mechanisms underlying fluctuations and dyskinesias in PD remain mysterious but clinical (postmortem brain studies, *in vivo* neuroimaging studies, pharmacological data) as well as preclinical data acquired in animal models of dopamine depletion furthered our understanding of the induction process. This section will focus on dyskinesias, but the mechanisms underlying other motor response complications probably overlap.

Presynaptic parkinsonism with loss of nigrostriatal neurons is a prerequisite in the genesis of LID which are nearly always worse on the most parkinsonian (denervated) hemibody. The severely dopamine depleted brain is particularly vulnerable to the development of response complications as the experience of the "frozen addicts" intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and treated with levodopa suggests. However, differences in nigrostriatal damage appear insufficient to explain levodopa-related motor response complications. First, excessive synaptic dopamine levels, resulting from large oral doses of levodopa in normal monkeys[10] or crack cocaine intoxication in humans (so-called "crack dancing"),[11] may produce dyskinesias. Secondly, the positron emission tomography (PET) [^{18}F]fluorodopa uptake rate (Ki), correlating well with the number of dopamine cells in the substantia nigra and with striatal dopamine levels, overlaps between "wearing-off" fluctuators and stable responders.[12] Recently, the presynaptic handling of dopamine, in the context of exogenous levodopa chronic intake, has been suggested to change over time in patients developing "wearing-off" fluctuations who showed indirect evidence for increasing dopamine turnover over time.[13] In that study, dopamine turnover was determined prospectively by PET over three years and variations in synaptic dopamine levels estimated by [^{11}C]raclopride (dopamine D_2/D_3 receptor ligand). No definite explanation was provided for the difference in dopamine turnover observed between fluctuators and stable responders, but the younger age of the former group was thought to play a role and the authors challenged the idea that "wearing-off" is directly levodopa-related. This change in turnover may well contribute to the nonphysiological stimulation of dopamine receptors.

Nonetheless, pharmacological sensitization and early alterations in drug response occur following priming with levodopa and short-acting dopamine agonists in animal models of severe dopamine depletion and PD patients. For instance, levodopa produces an early and dramatic sensitization in 6-OHDA rats showing a pronounced increase in the magnitude of response within days and an apparent "wearing-off" effect (gradual shortening in the response duration) over three weeks, clearly related to the severity of the dopaminergic lesion.[5] Unlike PD patients, these animals have a stable nigrostriatal lesion and their developing drug response alterations under treatment cannot be attributed to a progressive loss in presynaptic buffering capacity, albeit a progressive change in dopamine turnover could still operate. However, an apparent "wearing-off" phenomenon has also been observed in MPTP-lesioned monkeys during the first few weeks of treatment with a direct-acting postsynaptic selective D_1 agonist,[14] suggesting that downstream changes in the striatopallidal circuitry are crucial. In PD, drug sensitization in the form of a short duration response of increasing magnitude with levodopa (evident following a three-day washout) and progressively more severe dyskinesias over time, may take place as early as one year following levodopa initiation.[15] This suggests that the "biochemical conversion" precluding the development of motor response complications may begin early. Still, this latency of onset provides a window of opportunity to test counteracting preventive strategies.

Intact striatum and striatal efferent pathways are also required for LID to manifest. In most cases of postsynaptic parkinsonism, lasting dyskinesias following exposure to levodopa will usually not develop due to extension of the neuronal loss to the striatopallidal complex, as seen in multiple system atrophy. This suggests that plastic postsynaptic changes are key elements.

Once "primed", LID persist and do not remit spontaneously, except in cases of multiple system atrophy with ongoing striatal degeneration, or when levodopa is considerably reduced or stopped. However, LID will be triggered back with even the first dose of levodopa following temporary drug withdrawal, suggesting that powerful lasting synaptic modifications, akin to a memory phenomenon maintain the brain in a primed state. Even though dopamine agonists are far less likely to induce dyskinesia when given to drug-naive parkinsonian subjects, they may produce or increase dyskinesia at certain doses once LID are primed. Thus, distinct mechanisms are responsible for the generation of dyskinesia after the dopamine-depleted brain has switched its way to respond to dopamine receptor stimulation from one mode (antiparkinsonian efficacy) to another (dyskinesia production).

The first piece of evidence that dyskinesias are not inevitable following replacement therapy in PD came from a bedside experiment in which bromocriptine was administered chronically to drug-naive patients. An agonist of the D_2 receptor family with partial D_1 antagonistic properties, bromocriptine produced few dyskinesias in such conditions,[16-18] an observation that held true in MPTP monkeys given large doses of bromocriptine chronically producing a similar antiparkinsonian effect compared with the gold standard levodopa.[19] However, when administered to levodopa-primed nonhuman primate and human parkinsonian subjects, it may produce dyskinesias. Thus, bromocriptine (and other dopamine agonists) given in monotherapy prior to levodopa somehow displays properties capable of preventing the priming events of dyskinesia. Since dopamine replacement therapy (with exogenous levodopa intake) stimulates all dopamine receptor subtypes (D_1+/D_2+) compared with bromocriptine (D_1-/D_2+), a simple subtraction exercise suggested that common D_2 receptor occupancy was

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responsible for antiparkinsonian efficacy while the D_1 receptor was held accountable for dyskinesias. Thus, the table was set for the synthesis of highly selective D_2 receptor agonists that would solve the problem. Biology proved once again to be no simple arithmetic as a large body of evidence generated in the Bédard Laboratory (Quebec City, Canada) using MPTP monkeys suggested. Several dopamine agonists of different receptor subtype selectivity and biological half-life were administered to groups of animals in drug-primed or *de novo* conditions. In dyskinetic animals, acute challenge with several D_2/D_3 agonists (including bromocriptine) consistently reproduced LID, whereas D_1 agonists were less prone to produce choreic dyskinesias for a similar antiparkinsonian effect.[20] These observations suggest that: 1) levodopa priming sensitizes D_2 receptor responses to a greater extent than D_1 receptor responses, perhaps making D_2 receptor-mediated mechanisms more important in the hierarchy of events leading to LID; 2) pharmacological activation of D_1 receptors is not mandatory for the production of dyskinesias. One might also speculate that levodopa priming produces a mismatch in D_1:D_2 cooperation in favor of D_2 receptor-mediated mechanisms, that may be accentuated by the cytoplasmic translocation of D_1 receptors in striatal neurons previously observed in the human PD brain and rat brain following treatment with levodopa or a short-acting D_1 agonist, respectively.[21] Other pharmacological experiments in primed MPTP monkeys using selective D_1 and D_2 antagonists, or a combination of selective agonists, have suggested that both D_1 and D_2 receptor-mediated mechanisms contribute to the production of dyskinesia.[22]

The role of pulsatile dopamine receptor stimulation

The case that intermittent rather than continuous dopamine receptor stimulation creates a new functional state in the basal ganglia altering motor control has gained widespread support in the last 10 years. In 6-OHDA-lesioned rats, intermittent levodopa treatment affected rotational behavior and induced far more neurochemical abnormalities in the striatum than continuous levodopa[23-24] or dopamine D_2 agonist treatments.[25] In drug-naive MPTP-lesioned monkeys, chronic administration of D_1 or D_2 agonists providing sustained receptor occupancy, through continuous delivery with an implanted subcutaneous minipump or a very long biological half-life, produced little or transient dyskinesias compared with the repeated administration of short-acting drugs, which were all found to be highly dyskinesigenic in monkeys with severe striatal dopamine denervation (i.e. >90%).[26-27] Interestingly, sustained D_1 receptor occupancy led to early and profound tachyphylaxis with complete loss of response, while sustained D_2 receptor occupancy produced only partial tachyphylaxis with some loss in motor benefit. Thus, pulsatile dopamine receptor stimulation appears to be more important than the targeted dopamine receptor subtype in the genesis of LID. Sustained dopamine receptor occupancy may not only prevent the priming of dyskinesia in *de novo* conditions but also partially "deprime" existing fluctuations in advanced patients. Elegant demonstration of this came from the Chase Laboratory (National Institute of Neurological Disorders and Stroke, Bethesda, USA) where the continuous intravenous delivery of levodopa for up to 12 days prolonged the duration of action of levodopa by 30% and ameliorated response fluctuations in PD patients, which only gradually returned to baseline once oral levodopa treatment was resumed, suggesting that changes in neural function responsible for priming are reversible to some extent.[28] Thus, dyskinesias appear preventable and reversible when dopamine receptors are stimulated correctly.

Dopamine receptors

The appearance of LID in dopamine-depleted conditions has long been thought to be related to a state of denervation supersensitivity in the striatum. Indeed, postmortem studies have revealed increased D_2 receptor density in the putamen, and neuroimaging techniques (PET or SPECT) demonstrated a 10-30% increase in drug-naive PD subjects *in vivo* using different radioligands. Similarly in MPTP-lesioned monkeys, autoradiographic studies have revealed an increase in striatal D_2 receptor density by up to 50% correlating with dopamine loss >90%, along with some increase in mRNA levels particularly in caudal regions. Striatal D_1 receptor density was largely spared in human postmortem or *in vivo* PET studies, but MPTP monkeys with extreme dopamine loss have shown increased D_1 density comparable to the D_2 subtype. However, chronic treatment with levodopa largely reverses the elevation in D_2 mRNA levels[29-30] and, interestingly, continuous D_2 agonist treatment providing sustained D_2 receptor occupancy downregulates D_2 binding with a selective reversal in D_2 mRNA levels, an effect which may explain the low dyskinesigenic potential of such treatments.[29] Changes in D_1 density following dopamine replacement therapies have been less consistent with either sparing, reversal of denervation-induced increase, or a trend for an increase in striatal D_1 binding observed.[29] Using PET and selective D_1 and D_2 radioligands, no difference between dyskinetic and nondyskinetic PD patients was observed.[31] Although the striatal plasma membrane staining of D_1 receptors was spared in a study of levodopa-treated PD patients and D_1 agonist-treated rats, D_1 receptors were modified and relocalized in the cytoplasm, a drug effect which may be partly responsible for some of the levodopa-related response complications.[21] Thus, no clear changes in dopamine D_1 and D_2 receptor binding properties correlate with the development of LID. However, the supersensitivity theory cannot be totally dismissed on that basis as the supersensitive pharmacological responses observed with pulsatile dopamine receptor stimulation suggest. Changes in coupling with stimulatory G proteins may still operate in spite of the lack of consistent changes in membrane receptor density.

Other experiments conducted in the unilateral 6-hydroxydopamine-lesioned rat model have implicated the dopamine D_3 receptor. In this model, sensitization following repeated pulsatile levodopa treatment caused enhanced contraversive rotations correlating with increased and ectopic (expression outside associative and limbic territories in the striatum) D_3 receptor number and mRNA levels in the striatum, blocked by a D_1 antagonist and partly reproduced following pulsatile D_1 agonist treatment.[32] These results were not confirmed in the postmortem PD brain.[33-34] Thus, the role of the D_3 receptor in LID remains uncertain.

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GAMMA-AMINO BUTYRIC ACID (GABA) RECEPTORS

In the Di Paolo Laboratory (Quebec City, Canada), the autoradiographic study of the density of the $GABA_A$/benzodiazepine receptor complex with [^{3}H]flunitrazepam (FNZ) in MPTPmonkey brains compared dyskinetic and nondyskinetic animals treated with various dopamine replacement agents.[35] MPTP denervation decreased the external pallidum (GPe)/internal pallidum (GPi) [^{3}H]FNZ binding ratio, perhaps reflecting an imbalance in striatal efferent pathways, and this ratio was not normalized by any of the treatments administered. Nonetheless, differences were observed between pulsatile (dyskinesigenic) and continuous (nondyskinesigenic) treatments: pulsatile levodopa or D_2-like agonist treatments tended to restore the reduced [^{3}H]FNZ binding in the GPe but further increased binding in the GPi compared with normal (+55%) and MPTP (+36%) controls. In animals treated continuously with a D_2-like agonist, $GABA_A$ receptors in the GPe and GPi were less affected with values remaining close to untreated MPTP animals. In another autoradiographic study using [^{125}I]CGP 64213 to label $GABA_B$ receptors, MPTP-induced denervation caused increased binding (+29%) in the GPi, unchanged following dyskinesigenic treatment with a short-acting D_1 agonist but partly reversed following treatment with a long-acting D_2 agonist that induced no lasting dyskinesias.[36] Thus, pulsatile dopaminomimetic treatment led to $GABA_A$ receptor upregulation and did not reverse the anomalies in $GABA_B$ receptors brought about by dopamine denervation, creating conditions susceptible to be associated with a supersensitive state in the GPi to GABAergic input, thereby inhibiting pallidothalamic outflow to promote dyskinesia and resurrecting the supersensitivity hypothesis! 2-Deoxyglucose metabolic tracing studies support the idea that basal ganglia outflow from the GPi becomes markedly underactive in dyskinetic MPTP monkeys; they also suggest reduced GABA transmission in the GPe in these animals, causing the GPe to become overactive.[37] Chronic levodopa treatment also increased GABA synthesizing glutamic acid decarboxylase (both GAD65 and GAD67) gene expression in the parkinsonian monkey putamen, perhaps reflecting increased GABAergic transmission.[38] Clearly, levodopa alters GABA signaling in the striatopallidal complex. The resulting disrupted pallidal outflow is, in turn, altered by ventral GPi pallidotomy[39-41] and deep brain stimulation[42-44] to greatly attenuate LID.

OPIOID PEPTIDES

Opioid peptides are used as cotransmitters with GABA by striatal medium spiny neurons. The synthesis of their precursors, preproenkephalin-A(PPE-A, encoding methionine- and leucine-enkephalin) and preproenkephalin-B (PPE-B, encoding leucine-enkephalin, dynorphin A_{1-17} and B_{1-13}, and α-neoendorphin), is clearly regulated by dopaminergic systems and these peptides modulate GABA and glutamate transmission in the basal ganglia. In the 6-hydroxydopamine rat model displaying a drug-induced hyperkinetic behavior, elevated PPE-A and PPE-B expression have been documented following levodopa exposure but not after dopamine agonist treatments,[25] in a manner similar to that found in MPTP monkeys. It was suggested that the changes in preproenkephalin expression induced by exogenous levodopa may have an impact on basal ganglia functions by reducing GABA release in the GPe (PPE-A) and glutamate release in the GPi (PPE-B), thus promoting overactivity of the pallido(GPe)-subthalamic connections and underactivity of the pallido(GPi)-thalamic outflow. In the rat model, the priming of the abnormal behavioral response was temporally correlated with the elevation in PPE-B synthesis in the sensorimotor striatum but not with the rise in PPE-A synthesis.[45] Thus, changes in opioid peptides derived from PPE-B may play a role in the priming events leading to dyskinesia and may be a cause, rather than the result, of the genesis of dyskinesia. Whether changes in PPE-A synthesis play a specific role in the maintenance mechanisms of the primed state remains to be determined. Previous PET findings in PD patients using [^{11}C]diprenorphine (marker of opiate binding) have shown reduced striatal, thalamic, and cingulate binding in dyskinetic compared with nondyskinetic subjects, perhaps due to a compensatory mechanism triggered by enhanced opiate synthesis.[46]

Different opioid antagonists have been tested as adjuncts to levodopa therapy. In MPTP monkeys, the nonselective opioid receptor antagonist naltrexone, the selective μ opioid receptor antagonist cyprodime, and the selective δ opioid receptor antagonist naltrindole significantly reduced peak-dose dyskinesia.[47] Intravenous naloxone has shown antidyskinetic efficacy in small scale clinical studies. More studies are required before opioid receptor antagonists are used as adjunct treatment in PD.[48] Dopaminergic treatments not affecting, or capable of reversing changes in, PPE synthesis may be possible in the future.

GLUTAMATE RECEPTOR-MEDIATED MECHANISMS

Various forms of neuronal plasticity appear to be mediated by glutamate transmission through the N-methyl-D-aspartate (NMDA) receptor. In the past decade, NMDA receptors have also been reported to participate in the development of behavioral sensitization to repeated levodopa administration. In the Chase Laboratory, NMDA receptor blockade with the systemic or intrastriatal administration of the ionic channel blocker MK-801 overcame the desensitization of dopamine D_1 receptor-mediated responses, the sensitization of dopamine D_2 receptor-mediated responses, as well as the shortened duration of motor response to levodopa that occurred as a consequence of chronic levodopa treatment in 6-hydroxydopamine rats.[49] In that model, levodopa treatment altered the expression of specific subunits of NMDA receptors in the striatum elevating NR2B subunit expression by 20%,[50] suggesting that selective blockade of NR2B-containing NMDA receptors or reduction of NR2B subunit expression may reduce dyskinesia. In MPTP-lesioned monkeys, dyskinesias have correlated with an upregulation in striatal glutamate binding but not with specific changes in NMDA NR1 mRNA expression,[51] and adjunct therapy with certain NMDA receptor antagonists attenuated dyskinesias without loss of motor benefit.[52-53] Interestingly, the compounds with the best therapeutic index were subsequently shown to display high selectivity or affinity for the NMDANR2B subunit. In one experiment, the benefit on levodopa-induced chorea was more robust and dystonic movements worsened in a dose-dependent fashion.[52] One agent displaying relative selectivity for the NMDA NR2A subunit was actually pro-dyskinetic and

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produced some synergistic motor effects with levodopa. Antagonism of the α-amino-propionic acid subtype of glutamate receptors also showed antidyskinetic efficacy, albeit of a lesser magnitude, in the same primate model.[54] In PD patients, amantadine, a noncompetitive and nonselective NMDA receptor channel blocker, provides antidyskinetic activity.[55] Although the exact mechanism and site of action of these drugs cannot be entirely determined, the benefit on the shortened levodopa response observed in rats following intrastriatal injection of a tyrosine kinase inhibitor, attenuating in parallel both NMDA NR2A and NR2B subunit phosphorylation, suggests that enhanced tyrosine phosphorylation of striatal NMDA receptor subunits contributes to the apparent NMDA receptor sensitivity and behavioral plasticity (or pathological memory) underlying the altered motor responses that attend chronic levodopa therapy in dopamine-denervated rodents.[56] Thus, it might become possible to prevent the generation of dyskinesia after priming has occurred or even to "deprime" dyskinesia with glutamate antagonist drugs. Finally, NMDA receptor antagonism has shown potential in preventing motor response alterations in combination with levodopa right from the onset of treatment in hemiparkinsonian rats.[57] These results will certainly stimulate the search for bioavailable and well-tolerated glutamate antagonists for clinical use.

Immediate early genes

Evidence that pulsatile dopaminergic treatments inducing dyskinesias in the MPTPprimate model also induce chronic Fos proteins of the ΔFosB family in the striatum has also emerged.[58-59] Coupled with JunD, which is persistently expressed following dopamine denervation, they form dimers called AP-1 complexes that can, in turn, affect several target genes regulating neurotransmitters or modulators including NMDA receptors, dopamine D_1 receptors, enkephalin and dynorphin. cAMP response element binding (CREB) protein phosphorylation may play a role as well. Both CREB phosphorylation and ΔFosB also possibly regulate preproenkephalin expression. This cascade of molecular events is likely to impact on GABAergic and glutamatergic pathways in the basal ganglia that mediate the abnormal response to dopamine replacement therapy.

Other modulatory influences in the striato-pallidal complex

Besides the strategies to counteract excessive glutamatergic or opioid peptidergic influences in the basal ganglia to attenuate dyskinesia, other nondopaminergic adjunct drugs targeting potentially interesting modulatory receptors are currently tested in animal models.[60] For instance, cannabinoid and α_2 adrenergic receptors are synthesized by striatal output neurons and are expressed on striato-pallidal terminals. Activation of cannabinoid receptors can decrease GABA uptake, whereas activation of α_2 adrenergic receptors reduces GABA release. Since the GPe is thought to become overactive in levodopa-induced dyskinesia, cannabinoid receptor agonists or α_2 adrenergic receptor antagonists might be able to enhance GABAergic inhibition of the GPe to reduce dyskinesia. While the cannabinoid receptor agonist nabilone showed limited antidyskinetic efficacy in PD patients in a recent pilot study,[61] blockade with SR141716A to enhance GABA uptake (possibly at the basal ganglia output stations GPi/SNpr) showed more promising results in MPTP monkeys.[62] The α_2 adrenergic receptor antagonists yohimbine and idazoxan have also shown antidyskinetic efficacy in MPTPmonkeys. Recently, stimulation of serotonin 5-HT_{1A} autoreceptors has been tested as a strategy to modify the release of dopamine. The 5-HT_{1A} agonist and weak D_2 receptor antagonist sarizotan substantially reduced LID in MPTP monkeys, an effect not attributed to D_2 receptor blocking activity since it was largely blocked by a 5-HT_{1A} antagonist.[63] Clinical trials are underway. Enhancing the excitatory influences of serotonin in the basal ganglia through postsynaptic 5-HT_{2C} receptors may also increase pallido-thalamic outflow and relieve dyskinesia. Adenosine A2a receptors are localized on striatal output neurons. Striatal expression of the adenosine A2a receptor gene was found elevated in normal monkeys with LID, providing the basis for the favorable response resulting from the selective adenosine A2a receptor antagonist KW-6002, which demonstrated antiparkinsonian efficacy with little or no dyskinesias in dyskinetic MPTP monkeys.[64] The drug has also been tested in humans.

Physiologicalalterations in the basal ganglia

The biochemical and molecular changes that attend pulsatile levodopa replacement therapy translate in disturbances in neuronal firing pattern and frequency that ultimately affect physiological thalamocortical feedback mechanisms. Detailed electrophysiological studies in MPTP monkeys revealed that dyskinesias are associated with average changes in neuronal firing rates in each pallidal segment (reduction in the GPi, reciprocal increase in the Gpe)[65] to virtual neuronal silencing in the GPi.[66] These results are in accordance with current concepts of basal ganglia disorders[67] and were confirmed in PD patients challenged with apomorphine intraoperatively.[68] Nonetheless, the equation linking GPi underactivity to LID is incomplete and oversimplified[69-70] and hardly explains the antidyskinetic effect of internal pallidal interventions such as pallidotomy and deep brain stimulation. On the other hand, the subthalamic nucleus is certainly a crucial (and perhaps final) basal ganglia station along the dyskinesia railroad. This is suggested by the acute induction of dyskinesias following subthalamic lesions (hemiballism) or micro-electrode placement intraoperatively for deep brain stimulation.[71] Certain electrical parameters can also induce dyskinesias similar to LID in patients under chronic subthalamic nucleus high-frequency stimulation, managed by reducing levodopa dosage.[71] Beyond that station, the dyskinesia railroad appears sufficiently narrow and thin to be broken by selective neurosurgical interventions in the GPi or even the thalamus[72] (ventral intermedius nucleus, possibly with involvement of centre median/parafascicularis complex).

Conclusions

Together with psychiatric and cognitive complications, the fluctuations and dyskinesias seen in treated parkinsonian patients have a great impact on daily living. The pulsatile stimulation of dopamine receptors, attended by loss of nigrostriatal terminals, periodic oral levodopa dosing, and possible alterations in central dopamine turnover, is thought to be responsible for a

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"biochemical conversion" or new functional state sensitizing the basal ganglia to allow inappropriate overactivity of thalamo-frontal projections. Thus, preventing the loss of nigrostriatal terminals in PD would contribute to maintain a more tonic stimulation of dopamine receptors and reduce the risk of developing motor response complications. In the striatum, changes in the phosphorylation state of NMDAreceptor subunits and in opioid levels could have a major impact on the regulation of GABAergic and glutamatergic transmission in the basal ganglia, altering subthalamo-pallidal connections. Recent advances in the understanding of many signaling and modulatory pathways in the basal ganglia provide hope that the alterations underlying levodopa-related complications will soon be attenuated, reversed, or even prevented with novel nondopaminergic strategies.

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