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The Pharmacology of L-DOPA-Induced Dyskinesia in Parkinson's Disease

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Abstract	172
I. Introduction.....	173
II. Review Terms of Reference and Presentation	173
III. The Classic Model of the Functional Organization of the Basal Ganglia	174
IV. The Dopaminergic System.....	176
A. Striatal Dopamine Denervation	176
B. Pulsatile Dopaminergic Therapy	177
C. Dopamine Receptors.....	180
V. The Glutamatergic System	182
A. NMDA Receptors.....	183
1. Postmortem Studies.....	183
2. Pharmacological Studies.....	184
B. AMPA Receptors	186
1. Postmortem Studies.....	186
2. Pharmacological Studies.....	186
C. Metabotropic Glutamate Receptors.....	187
1. Metabotropic Glutamate Receptors Type 2/3.	187
2. Metabotropic Glutamate Receptors Type 5.	188
D. Glutamate Release	188
E. Altered Synaptic Plasticity.....	189
VI. The Opioid System	190
A. Preproenkephalin and Preprodynorphin.....	190
B. Opioid Receptors	191
VII. The Serotonergic System	193
A. 5-HT _{1A/1B} Receptors	193
B. 5-HT _{2A} Receptors.....	195
C. Serotonin Transporter	195
VIII. The GABAergic System	196
IX. The Adenosine System	197
X. Cannabinoid Neurotransmission.....	198
A. Cannabinoid Receptors	198
B. Endogenous Cannabinoids.....	199
XI. Adrenergic Neurotransmission.....	199
XII. Histaminergic Neurotransmission	201

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XIII. Cholinergic Neurotransmission	202
XIV. Tachykinin Neurotransmission	203
XV. Transcription Factors and Intracellular Signaling	204
A. Transcription Factors	204
B. DARPP-32, ERK1/2, and Histone Deacetylation	205
C. Other Abnormal Intracellular Cascades	207
XVI. Emerging Concepts in Dyskinesia	209
A. Angiogenesis and Blood-Brain Barrier	209
B. Inflammation	209
C. Fatty Acids	209
D. Exocytosis	210
E. Thyrotropin Releasing Hormone	210
XVII. Concluding Remarks	210
References	211

Abstract—L-3,4-Dihydroxyphenylalanine (L-DOPA) remains the most effective symptomatic treatment of Parkinson's disease (PD). However, long-term administration of L-DOPA is marred by the emergence of abnormal involuntary movements, i.e., L-DOPA-induced dyskinesia (LID). Years of intensive research have yielded significant progress in the quest to elucidate the mechanisms leading to the development and expression of dyskinesia and maintenance of the dyskinetic state, but the search for a complete understanding is still ongoing. Herein, we summarize the current knowledge of the pharmacology of LID in PD. Specifically, we review evidence gathered from postmortem and pharmacological studies, both

preclinical and clinical, and discuss the involvement of dopaminergic and nondopaminergic systems, including glutamatergic, opioid, serotonergic, γ -aminobutyric acid (GABA)-ergic, adenosine, cannabinoid, adrenergic, histaminergic, and cholinergic systems. Moreover, we discuss changes occurring in transcription factors, intracellular signaling, and gene expression in the dyskinetic phenotype. Inasmuch as a multitude of neurotransmitters and receptors play a role in the etiology of dyskinesia, we propose that to optimally alleviate this motor complication, it may be necessary to develop combined treatment approaches that will target simultaneously more than one neurotransmitter system. This could be achieved via

ABBREVIATIONS: 2-AG, 2-arachidonyl glycerol; ACP-103, pimavanserin; 5-HT, serotonin; 5-HT_{1A}, serotonergic type 1A receptor; 5-HT_{1B}, serotonergic type 1B receptor; 5-HT_{2A}, serotonergic type 2A receptor; 6-OHDA, 6-hydroxydopamine; A₁, adenosine 1 receptors; A_{2A}, adenosine 2A receptors; A_{2B}, adenosine 2B receptors; A₃, adenosine 3 receptors; AADC, aromatic L-amino acid decarboxylase; ACh, acetylcholine; AIMS, abnormal involuntary movements; Akt, protein kinase B; AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propionic acid; BrdU, 5-bromo-2'-deoxyuridine; CalDAG-GEF1/2, calcium and diacylglycerol guanine nucleotide exchange factor types 1 and 2; CALM-PD, comparison of the agonist pramipexole versus levodopa on motor complications of Parkinson's disease; cAMP, cyclic adenosine monophosphate; CB₁, cannabinoid type 1 receptor; Cdk5, cyclin-dependent kinase 5; cGMP, cyclic guanosine monophosphate; COMT, catechol-O-methyltransferase; CREB, cAMP response element-binding protein; CSF, cerebrospinal fluid; D₁, dopamine D₁ receptor; D₂, dopamine D₂ receptor; D₃, dopamine D₃ receptor; D₄, dopamine D₄ receptor; D₅, dopamine D₅ receptor; DARPP-32, DARPP-32, dopamine- and cAMP-regulated phosphoprotein of 32 kDa; DAT, dopamine transporter; DHA, docosahexaenoic acid; EGR1, early growth response protein 1; EMA, European Medicines Agency; ERK, extracellular signal-related protein kinase; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; FAAH, fatty acid amide hydrolase; FDA, US Food and Drug Administration; FIRST-STEP, favorability of immediate-release carbidopa/levodopa versus stalevo short-term comparison in early Parkinson's; FosB, FBJ murine osteosarcoma viral oncogene homolog B; GABA, γ -aminobutyric acid; GAD, glutamic acid decarboxylase; GAD₆₅, glutamic acid decarboxylase isoform 65; GAD₆₇, glutamic acid decarboxylase isoform 67; GDNF, glial cell-line derived neurotrophic factor; GluR1, subunit GluR1 of AMPA receptors; GluR2, subunit GluR2 of AMPA receptors; GluR3, subunit GluR3 of AMPA receptors; GP, globus pallidus; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; GPR18, G protein-coupled receptor 18; GPR55, G protein-coupled receptor 55; GPR119, G protein-coupled receptor 119; GRK6, G protein-coupled receptor kinase 6; GSK3, glycogen synthase kinase 3; GTP, guanosine triphosphate; GTPase, guanosine triphosphatase; GTP γ S, [³⁵S]guanosine 5'-O-[γ -thio] triphosphate; H₂, histamine receptor type 2; H₃, histamine receptor type 3; HDAC, histone deacetylase; IC₅₀, half-maximal inhibitory concentration; K_i, inhibition constant; L-, levo; L-DOPA, L-3,4-dihydroxyphenylalanine; LI-AIMS, L-DOPA-induced abnormal involuntary movements; Leu, leucine; LID, L-DOPA-induced dyskinesia; LTD, long-term depression; LTP, long-term potentiation; M100,907, volinanserin; MDMA, 3,4-methylenedioxymethamphetamine; Met, methionine; mGlu2, metabotropic glutamate receptors type 2; mGlu3, metabotropic receptors type 3; mGlu5, metabotropic glutamate receptors type 5; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger ribonucleic acid; MSK-1, mitogen- and stress-activated kinase 1; mTOR, mammalian target of rapamycin; NGF1-A, nerve growth factor-induced protein 1A; NHP, nonhuman primate; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; NR1, subunit NR1 of NMDA receptors; NR2A, subunit NR2A of NMDA receptors; NR2B, subunit NR2B of NMDA receptors; pAkt, phosphorylated Akt; PD, Parkinson's disease; PDE5, phosphodiesterase type 5; PET, positron emission tomography; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; POMC, proopiomelanocortin; PPD, prodynorphin; PPE-A, preproenkephalin-A; PPE-B, preproenkephalin-B; PPT, preprotachykinin; Ras-GRF1, Ras-guanine nucleotide-releasing factor 1; RBD, rapid-eye-movement sleep behavior disorder; Rhes, Ras homolog enriched in striatum; SERT, serotonin transporter; SN, substantia nigra; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; STRIDE-PD, stalevo reduction in dyskinesia evaluation in Parkinson's disease; SV_{2A}, synaptic vesicle glycoprotein 2A; TRH, thyrotropin releasing hormone; TRPV₁, transient receptor potential vanilloid type 1; VEGF, vascular endothelial growth factor.

three ways as follows: 1) by developing compounds that will interact simultaneously to a multitude of receptors with the required agonist/antagonist effect at each target, 2) by targeting intracellular signaling

cascades where the signals mediated by multiple receptors converge, and/or 3) to regulate gene expression in a manner that has effects on signaling by multiple pathways

I. Introduction

In their ground-breaking study, Ehringer and Hornykiewicz (1960) discovered that dopamine levels were reduced in the striatum of patients suffering from Parkinson's disease (PD). This led to the introduction of dopamine replacement therapy, in the early 1960s, with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) (Cotzias et al., 1967, 1969a,b; Barbeau, 1969a,b; Cotzias, 1969). At first, L-DOPA was administered without a peripherally acting aromatic L-amino acid decarboxylase (AADC) inhibitor, such as carbidopa or benserazide, and the doses of L-DOPA required to achieve therapeutic efficacy were higher than those used today. AADC inhibitors were added to L-DOPA during the second half of the 1960s and first half of the 1970s (Barbeau et al., 1971; Marsden et al., 1973a,b). AADC inhibitors allowed for the reduction of L-DOPA doses, a faster onset of an antiparkinsonian benefit, and a decrease in side effects of dopamine on the cardiovascular and gastrointestinal systems (Cotzias et al., 1969b; Anonymous, 1974). However, shortly after the introduction of L-DOPA as a therapy for PD, motor complications such as dyskinesia and wearing-off were observed following repeated administration of the dopamine precursor (Barbeau, 1971; Parkes et al., 1971; Weiss et al., 1971; Marsden et al., 1973a,b). In a recent community-based study, the mean time to onset of dyskinesia was 6.6 years (Evans et al., 2011). However, other groups have reported that up to 56% of PD patients experience dyskinesia as early as 2.9 years after introduction of L-DOPA (Blanchet et al., 1996a), and this percentage climbs to 95% after 15 years of therapy (Hely et al., 2005). Patients with earlier-onset PD tend to be more prone to develop L-DOPA-induced dyskinesia (LID) than patients with later onset (Kumar et al., 2005). Dyskinesia has a negative impact on quality of life (Dodel et al., 1998; Damiano et al., 2000; Pechevis et al., 2005), sometimes being more disabling than PD itself (Fahn, 2000). Although some patients often prefer experiencing dyskinesia than being in the off-state and unable to move (Hung et al., 2010), new, more effective therapies are still required for severe disabling dyskinesia to afford patients an improved quality of benefit while in the on-state.

The clinical phenomenology of dyskinesia is complex, and a wide range of presentations have been described, including neck, truncal, facial, and limb chorea and dystonia (Nutt, 1990; Luquin et al., 1992b). The pattern of dyskinesia varies with respect to the time of onset in relation to L-DOPA intake. Peak-dose

dyskinesia occurs when plasma levels of L-DOPA are high and tends to be predominantly chorea with some dystonia (Muentner and Tyce, 1971; Lees et al., 1977). Diphasic dyskinesia, or "onset and end-of-dose dyskinesia," occurs when plasma levels of L-DOPA are either rising or falling ("low-dose dyskinesia"), but not when they are stable, and tend to be predominantly dystonic (Muentner et al., 1977; Lhermitte et al., 1978).

Therefore, LID appears to be a complex set of phenomena, in terms of both clinical presentation and pharmacokinetics. This complexity perhaps explains why, despite extensive preclinical and clinical research focused on increasing the pharmacotherapeutic arsenal, few agents have successfully been shown to reduce dyskinesia or to successfully translate from preclinical to clinical settings. One reason has been that the majority of research to date have focused on peak dose (high L-DOPA dose) dyskinesia, and many PD subjects may experience a mixture of peak and diphasic dyskinesia. Another reason might be that, as will be seen in this review article, there is evidence for abnormalities in several neurotransmitter systems in dyskinesia and that the traditional approaches, which usually focus on a single target, may not be appropriate. The following sections will summarize the current knowledge on the pharmacology of LID. It is important to bear in mind that although all of the mechanisms described herein probably contribute, to a certain extent, to the etiology of LID, no single factor has been identified as a requisite culprit in the pathophysiology of dyskinesia.

II. Review Terms of Reference and Presentation

The data from animal models reviewed in the present article include only those from the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned nonhuman primate (NHP) and the 6-hydroxydopamine (6-OHDA)-lesioned rat and mouse. Both chorea and dystonia are considered in the NHP, whereas abnormal involuntary movements (AIMs), the rodent correlate of dyskinesia (Lee et al., 2000; Cenci and Lundblad, 2007), are considered when discussing dyskinesia in the rodent.

Mechanisms underlying sensitized rotational behavior occurring upon repeated administration of L-DOPA or dopamine agonists in the hemi-parkinsonian rodent are not included in the present article, because interpretation of this behavior is controversial (Lane et al., 2006; Marin et al., 2006b), or at least difficult, being regarded both a marker of antiparkinsonian efficacy (Duvoisin et al., 1982; Traub et al., 1985;

Prikhojan et al., 2000) and priming/sensitization of a hyperkinetic response, part of which could be related to dyskinesia (Carey, 1991; Konitsiotis and Tsironis, 2006). Moreover, compounds such as yohimbine, clozapine, and naloxone, all of which effectively alleviate AIMs, do not reduce rotational behavior, whereas volinanserin (M100,907) effectively reduces rotations without alleviating AIMs (Taylor et al., 2006), highlighting differences between the pharmacology of the two phenomena (Lundblad et al., 2002).

Additionally, with a few exceptions that are specifically noted, studies performed in animal models of PD that describe molecular changes without behavioral correlates are excluded from this article, because it is impossible to correlate the postmortem findings with dyskinesia. For the same reasons, studies performed in idiopathic PD patients with motor complications, but where such complications are limited to wearing-off and do not include dyskinesia, are not reviewed. In addition, several postmortem studies performed using the brains of dyskinetic PD patients are reviewed, although critical information may be missing in each of these studies, such as the time of last administration of L-DOPA and/or dopamine agonist prior to death. Indeed, because the patients may not have died at time of peak dyskinesia expression, it is unclear whether the molecular changes reported are representative of the on-state or the off-state of chronic L-DOPA treatment.

Throughout this article, the term “priming” refers to the behavioral and molecular sensitization phenomena occurring after the first dose of L-DOPA. Priming is not necessarily associated with the expression of dyskinesia but by definition leads to changes in response to subsequent L-DOPA challenges that result in the emergence of overt dyskinesia and its subsequent development into a more severe phenotype, as well as the maintenance of the brain in the dyskinetic state, even when off treatment (Jenner, 2002; Nadjjar et al., 2009). Once priming has occurred, lower doses of L-DOPA or dopamine agonists are sufficient to elicit dyskinesia, and their therapeutic window is narrowed (Mouradian et al., 1989; Verhagen Metman et al., 1997).

Only peer-reviewed articles are included in the current review. Data presented as abstracts in scientific meetings have therefore been excluded.

Throughout the article, unless specified otherwise, the term L-DOPA refers to the combination of L-DOPA and an AADC inhibitor. Lastly, several pharmacological molecules are discussed in this review. It is important to bear in mind that, although they exhibit selectivity for a certain target, some of them are not very selective and their biologic effect, although usually attributed to a specific pharmacological target, might in fact come from an interaction with off-target receptors.

III. The Classic Model of the Functional Organization of the Basal Ganglia

To understand the mechanisms potentially underlying the pharmacological actions reviewed below, it is first helpful to review the anatomic circuitry underlying LID and consider neurotransmitter and receptor distribution among the components of that circuit. According to the classic cortico-basal ganglia-thalamo-cortical model of the organization of the basal ganglia (Figs. 1 and 2), the cerebral cortex sends excitatory glutamatergic inputs to the striatum. These inputs are modulated by nigrostriatal dopaminergic projections that exert an excitatory effect, via dopamine D₁ receptors, on the substance P/dynorphin-containing striatofugal neurons of the direct pathway and an inhibitory effect, via dopamine D₂ receptors, on the enkephalin-containing striatofugal neurons of the indirect pathway. Striatofugal neurons of the direct pathway send inhibitory γ -aminobutyric acid (GABA)-ergic projections to the output structures of the basal ganglia, the globus pallidus (GP) pars interna (GPi), and substantia nigra (SN) pars reticulata (SNr), which also emit GABAergic fibers, toward the ventral tier (ventrolateral and ventroanterior nuclei) of the thalamus. In the indirect pathway, striatofugal GABAergic axons contact the globus pallidus pars externa (GPe), which sends GABAergic fibers toward the subthalamic nucleus (STN). The STN then emits glutamatergic axons toward the output structures of the basal ganglia. Glutamatergic thalamocortical fibers complete the loop. Reciprocal GABAergic fibers connect the GPe with the GPi/SNr. The direct and indirect pathways exert opposing effects on movements and an imbalance in their activity is believed to lead to hypokinetic (i.e., parkinsonism) or hyperkinetic (i.e., dyskinesia) movement disorders. Although not traditionally part of the classic model of the basal ganglia, cortico-STN projections, sometimes referred to as the “hyperdirect pathway,” have been recognized (DeLong, 1990; Parent, 1990; Parent and Hazrati, 1995a,b; Parent et al., 2000; Nambu et al., 2002; DeLong and Wichmann, 2007; Koprach et al., 2009).

According to the model of the organization of the basal ganglia described above, in the dyskinetic state, administration of L-DOPA leads to excessive activity of striatal projection neurons of the direct pathway. This model is based very simply upon a consideration of average frequency of firing, over time courses of minutes and hours, of projections between the component nuclei (Eusebio and Brown, 2007; Hammond et al., 2007). Thus, D₁-mediated transmission along the direct pathway becomes overactive, which leads to excessive activity along the direct pathway; D₂-mediated activity along the indirect pathway also becomes overactive, but this results in a reduction in activity along the indirect pathway. Overactivity of the

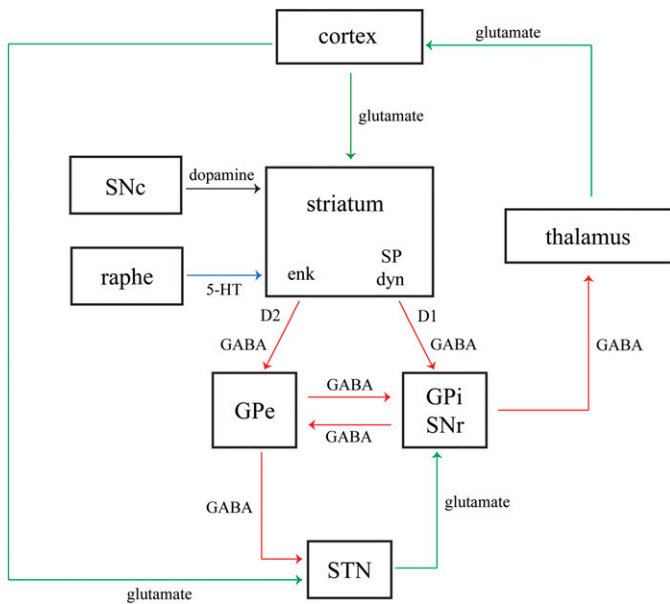


Fig. 1. See text for description of the model of the organization of the basal ganglia and for a description of the changes occurring in the dyskinetic state and references. Green lines indicate glutamatergic excitatory transmission, whereas red lines indicate GABAergic inhibitory transmission. Figure 1 is modified from Huot et al. (2011a).

direct pathway and underactivity of the indirect pathway ultimately result in cortical overexcitation and dyskinesia (DeLong, 1990; Parent, 1990; Parent and Hazrati, 1995a,b; Parent et al., 2000; DeLong and Wichmann, 2007; Koprach et al., 2009). In accordance with a cortical overexcitation in the dyskinetic state, metabolic neuroimaging studies have demonstrated overactivity of the supplementary motor area and motor cortex when dyskinetic PD patients were compared with nondyskinetic PD patients and normal subjects (Rascol et al., 1994b, 1998; Brooks et al., 2000).

However, this classic explanation of dyskinesia pathophysiology is too simplistic, and we consider it more a metaphor to allow hypothesis building than a model that captures the true processing nature of the circuit, and indeed, it revolves around dopamine, a subset of dopamine receptors, glutamate, GABA, and does not fit with several pieces of experimental data. For example, in the dyskinetic MPTP-lesioned NHP and in dyskinetic PD patients, there is no evidence of hypoactivity of the GPe (Vila et al., 1997), which argues against gross hypoactivity of the indirect pathway in the dyskinetic state. Moreover, according to the classic model of the basal ganglia, lesions or deep brain stimulation of the GPi should suppress thalamo-cortical inhibition, thereby resulting in an exacerbation of dyskinesia severity, whereas the opposite is seen in the NHP (Iravani et al., 2005) and in clinic (Parkin et al., 2002). These caveats aside, it is remarkable how useful such a simple metaphor has proved. In agreement with the opposite reduction in activity of the

output structures in the dyskinetic state, the administration of the dopamine agonist apomorphine to the MPTP-lesioned NHP inhibits firing of the GPi (Filion, 1979) and similar findings have been reported in PD patients (Hutchinson et al., 1997). Moreover, as will be described in detail below, the distribution of neurotransmitter receptors and their function within different components of the circuits has led to the identification of novel targets for LID and many of these have generated hypotheses that have been tested in pharmacological studies that have led to clinical trials across several classes of drug.

These successes notwithstanding, to reconcile these conflicting data with the classic average frequency model of the basal ganglia, it has been proposed that both the frequency and pattern of firing play a critical role in dyskinesia genesis and relief of parkinsonism, dyskinesia genesis being more related to the pattern of firing and the improvement of parkinsonism being more related to the frequency of firing (Boraud et al., 2001). However, although an advance, this may not be completely sufficient to explain the pathophysiology, because frequency of firing also appears to be an important etiological contributor to dyskinesia, as a frequency firing of 4–10 Hz in the STN is associated with dyskinesia in PD patients (Alonso-Frech et al., 2006). Similar results were obtained in the 6-OHDA-lesioned rat, where in vivo recording of neurons of the SNr disclosed an increase in 4–10 Hz local-field potential during dyskinesia expression (Meissner et al., 2006). In addition to frequency of firing, abnormal synchronization of the output structures of the basal ganglia may play a role in dyskinesia pathophysiology, and interruption of this abnormal synchronization is thought to mediate the antidyskinetic efficacy of internal pallidotomy or deep-brain stimulation of the GPi (Brown and Eusebio, 2008; Obeso and Lanciego, 2011).

Additional criticisms relating to the classic model of the organization of the basal ganglia come from several anatomic studies that have discovered an important collateralization in the inner basal ganglia circuitry, thus arguing against the simple functional dichotomization highlighted above (Parent et al., 2000; Levesque and Parent, 2005b; Nadjjar et al., 2006). Also against the classic view of the basal ganglia model is the fact that D₁ and D₂ receptors are not completely segregated but appear to be coexpressed on 15–20% of striatal projection neurons (Surmeier et al., 1996; Aizman et al., 2000; Deng et al., 2006b). In addition, the model does not take into account the interneurons present in core structures of the basal ganglia such as the striatum and the STN (Cicchetti et al., 2000; Levesque and Parent, 2005a; Huot and Parent, 2007) nor the involvement of many functionally important striatal afferents that employ several nondopaminergic transmitters such as serotonin (Lavoie and Parent, 1990,

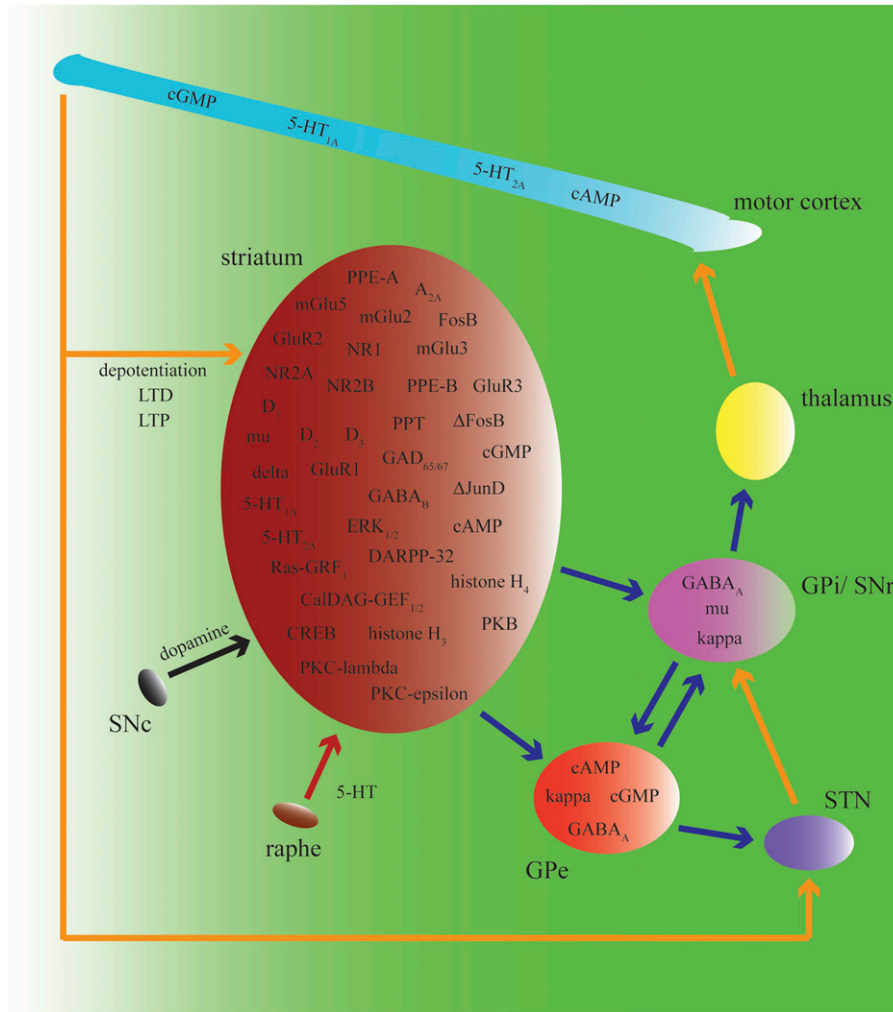


Fig. 2. Summary of the anatomic localization of the changes in neurotransmitter receptor protein and messenger ribonucleic acid (mRNA) levels, as well as abnormal synaptic plasticity along the cortico-basal ganglia-thalamo-cortical loop in dyskinesia. As can be seen, the majority of changes occur within the striatum, highlighting the critical role of the structure in the pathophysiology of dyskinesia. References are provided throughout the text. Only receptors/mechanisms for which there is experimental evidence are included. For instance, as the site(s) of action of α -adrenoceptor antagonists remains speculative, α -adrenoceptors are not included. The orange lines represent glutamatergic excitatory transmission, whereas the blue lines represent inhibitory GABAergic transmission. Modified from Huot P and Fox SH (2011) Nondopaminergic treatments for Parkinson's disease. Neurodegen Dis Manag, with permission from Future Medicine Ltd.

1991), acetylcholine (ACh) (Heckers et al., 1992; Mesulam et al., 1992), or histamine (Steinbusch et al., 1986; Panula et al., 1989). However, as will be seen below, the classic model can be used to predict drug effects and identify potential therapeutic benefit if its net influence on overall output of a pathway in the model is known. For instance, although cholinergic interneurons are not represented, the effect of cholinergic drugs on the direct and indirect pathways can be modeled and the therapeutic benefits of such predicted (Pisani et al., 2007). Moreover, the classic model focuses exclusively on the sensorimotor territory of the basal ganglia, whereas metabolic changes in the associative and limbic subdivisions of the basal ganglia were demonstrated at peak dyskinesia in the MPTP-lesioned macaque (Guigoni et al., 2005b). Therefore, although several references will be made to the model of the basal ganglia organization throughout this

article, and we believe it remains an important and likely the most useful model for the generation of hypotheses, these limitations must be kept in mind.

IV. The Dopaminergic System

A. Striatal Dopamine Denervation

Striatal dopamine depletion appears to be an important factor in the pathophysiology of LID (Boyce et al., 1990; Pearce et al., 1995). Dyskinesia is more prevalent in advanced PD when there is more dopamine terminal loss (Hauser et al., 2006). A 50% reduction in dopamine transporter (DAT) binding appears sufficient to permit the development of dyskinesia after treatment with antiparkinsonian doses of L-DOPA in the MPTP-lesioned NHP, but LID in mildly denervated animals tend to be less severe and sporadic (Di Monte et al., 2000). In the

MPTP-lesioned marmoset, intraventricular administration of glial cell-line derived neurotrophic factor (GDNF) led to the reversal of established dyskinesia; although the antidyskinetic mechanism of GDNF has yet to be established, an increase in nigral dopaminergic cells occurred in that study, suggesting that a reversal of nigrostriatal denervation was involved (Iravani et al., 2001). In agreement with the importance of striatal dopamine depletion in the etiology of dyskinesia, a postmortem study found lower dopamine levels in the putamen of dyskinetic when compared with nondyskinetic L-DOPA-treated PD patients (Rajput et al., 2004).

On the other hand, some severely parkinsonian macaques (Guigoni et al., 2005a) and 6-OHDA-lesioned rats (Cenci et al., 1998; Lee et al., 2000) never develop LID, suggesting that, although the extent of lesion is an important determinant in the emergence of dyskinesia, other factors are also involved. One of these factors might be the magnitude of L-DOPA doses administered. Hence, normal, non-MPTP-lesioned NHPs develop dyskinesia following treatment with high, nontherapeutically relevant, doses of L-DOPA (Pearce et al., 2001; Togasaki et al., 2001, 2005). Total daily dose of L-DOPA was also identified, in clinical settings, as a risk factor to the development of LID in PD patients (Sharma et al., 2008).

These data suggest that, although dopamine denervation may not be required for LID, it may be a permissive factor that, when present, leads to the emergence of LID more rapidly, with lower L-DOPA doses and with a more severe phenotype.

B. Pulsatile Dopaminergic Therapy

The short half-life of L-DOPA, approximately 1.5–2 hours, leading to alternating peaks and troughs of high and low plasma levels (Cedarbaum, 1987; Gancher et al., 1987), is believed to play an important role in the development of dyskinesia and underlies the concept of continuous dopaminergic stimulation to avoid dyskinesia (Olanow et al., 2000; Stocchi and Olanow, 2004). In the normal state, dopamine release is both tonic and phasic, implying that basal levels of dopamine never fall below a certain threshold (Grace, 1995; Goto et al., 2007). In the parkinsonian state, especially in late stages of the disease where the “buffering capacity” of the DAT has disappeared (Sohn et al., 1994), tonic dopamine release eventually disappears and dopamine release becomes exclusively phasic, i.e., pulsatile, following each dose of L-DOPA.

Changes in dopamine vesicular release and reuptake with disease progression might contribute to exacerbate the fluctuation of dopamine levels (de la Fuente-Fernandez et al., 2004a). Hence, DAT binding levels in the putamen of dyskinetic PD patients are lower when compared with nondyskinetic PD patients (Troiano et al., 2009). Although DAT downregulation might lead

to enhanced synaptic levels of dopamine and thus a greater antiparkinsonian benefit, it will also exacerbate peak dopamine levels associated with each L-DOPA administration (de la Fuente-Fernandez et al., 2004b) and might thus be a key determinant in the etiology of LID. However, although LID severity correlates with peak L-DOPA plasma concentration, there is a ceiling above which LID severity does not increase despite higher L-DOPA dose, while duration of antiparkinsonian benefit further increases (Metman et al., 1997).

To elucidate the contribution of pulsatile dopamine receptor stimulation in the etiology of dyskinesia, several preclinical and clinical studies compared the time to onset of dyskinesia upon administration of L-DOPA or dopamine agonists or upon administration of dopamine agonists with variable half-lives. As presented in Table 1, with the exceptions of apomorphine and lisuride, dopamine agonists have longer half-lives than L-DOPA, and their administration therefore results in more continuous stimulation of dopamine receptors. As will be seen in the next paragraphs, there is now evidence, although some controversy persists, that starting therapy with a dopamine agonist delays the onset of dyskinesia compared with L-DOPA, but the data cannot be attributed simply to their longer duration of action, because dopamine agonists all exhibit greater potency for the members of the dopamine D₂ receptors family over members of the D₁ receptors family (Table 1). As will be seen in the next subsection, it is believed that stimulation of D₁ receptors is critical in the priming process, leading to the expression of dyskinesia.

In accordance with a role for pulsatile dopaminergic therapy in the induction of dyskinesia, the short-acting dopamine agonist apomorphine induced more AIMs than the longer-acting dopamine agonists pramipexole and pergolide in the 6-OHDA-lesioned rat (Papathanou et al., 2011). Perhaps quite surprisingly though, in the MPTP-lesioned marmoset, de novo administration of apomorphine or pergolide led to dyskinesia of the same severity (Maratos et al., 2003). De novo continuous administration of the dopamine receptor agonists apomorphine and rotigotine induced less dyskinesia than de novo once or twice daily administration of these drugs in the MPTP-lesioned NHP (Bibbiani et al., 2005a; Stockwell et al., 2009). Moreover, in the MPTP-lesioned NHP, continuous administration of rotigotine alleviated dyskinesia induced by chronic pulsatile therapy with rotigotine or L-DOPA (Stockwell et al., 2010). De novo administration of ropinirole (Maratos et al., 2001; Jackson et al., 2007) or pramipexole (Tayarani-Binazir et al., 2010) also led to less dyskinesia than de novo therapy with L-DOPA in the MPTP-lesioned marmoset.

Similar results were achieved in PD patients treated initially with ropinirole, which successfully delayed the

TABLE 1

Half-life and pharmacological profile of the dopamine agonists tested in clinical trials cited in this article

Affinities are provided as the pKi [except for L-DOPA, where affinities are provided as the pIC₅₀ (half-maximal inhibitory concentration)] and are from Sokoloff et al., 1990, Sunahara et al., 1991, Van Tol et al., 1991, Newman-Tancredi et al., 1997, Millan et al., 2002, Newman-Tancredi et al., 2002, Scheller et al., 2009, and Alachkar et al., 2010, whereas half-lives are from Taylor and Lavery, 1969, Cedarbaum, 1987, Gancher et al., 1987, Uitti and Ahlskog, 1996, Wright et al., 1997, Fariello, 1998, Kaye and Nicholls, 2000, Stocchi et al., 2001, and Cawello et al., 2009. Values for dopamine and L-DOPA are provided for comparison purposes. Because the drugs A-77,636 and ABT-431 (adrogolide) are not used in clinic, they are not included.

	Half-Life	D ₁	D ₂	D ₃	D ₄	D ₅
	<i>hours</i>					
Apomorphine (Apokyn)	0.75	6.43	D _{2S} (7.46), D _{2L} (7.08)	7.59	8.36	7.83
Bromocriptine (Parlodel)	3–8	6.16	D _{2S} (8.30), D _{2L} (7.83)	8.17	6.43	6.27
Cabergoline (Dostinex)	65–110	6.67	D _{2S} (9.21), D _{2L} (9.02)	9.10	7.25	7.65
Dopamine	1.25–4.8	5.63	D ₂ : 6.32	7.60	7.55	6.64
L-DOPA (Sinemet)	1.5–2	5.59	D ₂ : 6.04		<5	
Lisuride (Dopergin)	1–7	7.19	D _{2S} (9.47), D _{2L} (9.18)	9.55	8.34	8.45
Pergolide (Permax)	3–4	6.47	D _{2S} (7.50), D _{2L} (7.59)	8.26	7.23	7.48
Pramipexole (Mirapex)	10–16	< 5	D _{2S} (6.02), D _{2L} (5.77)	7.98	6.89	<5
Ropinirole (Requip)	5–6	< 5	D _{2S} (6.17), D _{2L} (6.03)	7.43	6.07	<5
Rotigotine (Neupro)	4–7	7.08	7.77	9.14	D _{4.2} (8.41), D _{4.4} (7.82), D _{4.7} (8.22)	8.20

onset of dyskinesia compared with initial therapy with L-DOPA (Rascol et al., 2000, 2006a). However, the dyskinesia-sparing effect of ropinirole was lost when L-DOPA was added (Rascol et al., 2006a) but, after 10 years, the patients initially randomized in the ropinirole arm exhibited significantly less severe dyskinesia than patients initially randomized in the L-DOPA group (Hauser et al., 2007). Similarly, in the Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) study, significantly fewer subjects treated initially with pramipexole exhibited dyskinesia than subjects treated initially with L-DOPA after a 2-year follow up (Parkinson Study Group, 2000). After a 6-year open-label follow up, the majority of patients initially randomized to pramipexole were taking L-DOPA, but significantly fewer patients initially receiving pramipexole were experiencing dyskinesia than those who started directly on L-DOPA therapy (Parkinson Study Group, 2009). Similar to ropinirole and pramipexole, initial treatment with bromocriptine also delayed the emergence of dyskinesia when compared with initial treatment with L-DOPA (Montastruc et al., 1994).

However, as mentioned above, comparing dopamine agonists and L-DOPA introduces the bias of differential receptor stimulation and does not allow for comparison based solely on duration of action and, as a corollary, pulsatility of dopamine receptor stimulation. However, in contrast to the studies cited above, chronic administration of the selective and long-acting D₁ agonist A-77,636 led to a gradual reduction in dyskinesia severity, in the primed MPTP-lesioned common marmoset (Pearce et al., 1999). Although that last study was not a de novo study, it highlights the importance of pulsatile dopamine receptor stimulation in the pathophysiology of LID.

Another way to circumvent the problem might be to increase duration of L-DOPA action by inhibiting its breakdown with a catechol-O-methyltransferase (COMT) inhibitor (Rascol et al., 2005; Schrag, 2005).

Hence, it was suggested that de novo administration of L-DOPA in combination with the COMT inhibitor entacapone would reduce the development of LID. Although such an approach was effective in attenuating the development of the shortening of motor failure (Marin et al., 2005) and AIMs (Marin et al., 2006a) in the 6-OHDA-lesioned rat as well as dyskinesia in one study performed in the MPTP-lesioned marmoset (Smith et al., 2005), it led to quicker development of LID in another study performed in the MPTP-lesioned marmoset (Smith et al., 2003). The discrepancy between these two NHP studies could be explained, at least partly, by different administration regimens, as more frequent, lower doses of L-DOPA with entacapone reduced the priming.

The results achieved by de novo administration of L-DOPA with entacapone versus L-DOPA as monotherapy in clinical studies are also contradictory. Thus, the combination was ineffective in the context of a 134-week study (STalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease, STRIDE-PD), where it shortened the time to dyskinesia onset (Stocchi et al., 2010), i.e., apparently accelerated the priming process. In contrast, no difference in time to LID onset could be demonstrated in a shorter study (Favorability of Immediate-Release carbidopa/levodopa versus STalevo; Short-Term comparison in Early Parkinson's, FIRST-STEP, 39 weeks) (Hauser et al., 2009). A careful examination of the studies might explain why adding entacapone to L-DOPA in early PD did not delay the onset of dyskinesia. First, one must note that the studies were not real de novo studies, as many patients were on dopaminergic drugs, mostly dopamine agonists. In the case of the STRIDE-PD study, the majority of patients developing dyskinesia were on higher L-DOPA-equivalent doses than those remaining dyskinesia free. In the case of the FIRST-STEP study, perhaps a 39-week duration was too short to demonstrate an effect. Moreover, it would have been interesting to compare the administration of more

frequent, smaller doses of L-DOPA/entacapone to the three and four times a day regimens that were used in both studies, as perhaps these administration paradigms did not allow sufficient continuous stimulation of dopamine receptors, although adherence to such more frequent regimens might have been complicated.

Pulsatile L-DOPA delivery is also likely involved in the maintenance of the dyskinetic state once priming has occurred. Thus, in the MPTP-lesioned NHP, a reduction in severity of established dyskinesia was achieved following continuous administration of rotigotine (Stockwell et al., 2010) or by administration of the long-acting dopamine agonist cabergoline (Hadj Tahar et al., 2000b). In clinical settings, continuous daytime delivery of intraduodenal L-DOPA, over a 6-month period to PD patients with severe motor complications led to a reduction in previously established dyskinesia compared with intermittent administration (Stocchi et al., 2005). Similar results were achieved with continuous intravenous infusion of the dopamine agonist lisuride over a 3-month period (Baronti et al., 1992). The minimal amount of time required for continuous dopaminergic stimulation to alleviate established LID is unknown, but 48 hours of uninterrupted i.v. L-DOPA administration seems too short (Juncos et al., 1987c), whereas 7–12 days is enough to modulate the dyskinesia threshold dose (Mouradian et al., 1990).

Similar results were obtained in a study in which ropinirole prolonged release was added to L-DOPA in patients not optimally treated 3 years after disease onset; in that study, the addition of ropinirole prolonged release, in contrast to increasing the dose of L-DOPA, led to a reduced appearance of dyskinesia (Watts et al., 2010). In contrast, in studies in which controlled-release forms of L-DOPA were administered, leading to constant L-DOPA plasma levels over 4–6 hours, there was no reduction in dyskinesia severity after chronic administration compared with standard release L-DOPA (Juncos et al., 1987a, b), and the apparent reduction in dyskinesia achieved with ropinirole might in fact be due to preferential stimulation of D_2/D_3 receptors rather than its longer duration of action. The results of these two studies with controlled-release forms of L-DOPA pave the way to an important, as yet unanswered question: what does the term “pulsatility” mean and what duration of action should any antiparkinsonian compound have to lead to “non-pulsatile” stimulation of dopamine receptors? Although widely referred to in the dyskinesia literature, the concept of pulsatility remains poorly defined, but from a physiologic point of view, one might suggest that any mode of dopamine replacement therapy that is not continuous is necessarily pulsatile, regardless of the half-life of the molecule. Accordingly, and despite the results of the studies cited above, it would be misleading to pretend that administration of L-DOPA

controlled release leads to continuous dopaminergic administration, its duration of action being only slightly longer than that of L-DOPA standard release (Yeh et al., 1989; LeWitt, 1992; Hammerstad et al., 1994).

Although very few studies have specifically addressed this issue, the moment of initiation of dopaminergic therapy might also have an impact on the development, but not severity, of dyskinesia. Thus, in the 6-OHDA-lesioned rat, when L-DOPA was initiated 4 weeks after lesion, significantly fewer animals developed AIMs compared with when L-DOPA was initiated 12 weeks after lesion, but AIMs severity in dyskinetic animals did not differ between groups when assessed 22 days after the initial dose of L-DOPA (Marin et al., 2009a). This issue was never assessed in controlled clinical studies, and it is therefore difficult to predict whether the same phenomenon would occur in idiopathic PD patients, but long-term follow up of patients from the ELLDOPA study (Fahn et al., 2004) might eventually provide an answer to this question, as with disease progression all PD patients eventually require L-DOPA (Nutt et al., 2000). However, starting dopaminergic therapy early in the disease process might not be a promising approach to delay dyskinesia onset, as cumulative L-DOPA dose and L-DOPA equivalent dose have been established as clinical variables associated with dyskinesia development (Hauser et al., 2006). However, although cumulative L-DOPA dose is an important contributory factor in the etiology of LID, the frequency of L-DOPA administration, hence pulsatility of dopamine replacement therapy, might be more important. Thus, in a study performed in the 6-OHDA-lesioned rat, rats treated with higher L-DOPA dose developed AIMs quicker than rats treated chronically with lower doses and that had received more cumulated L-DOPA when AIMs first appeared (Tsironis et al., 2008).

Thus, despite some of the limitations mentioned above in the interpretation of the available data, it appears that longer-acting agents or continuous delivery of L-DOPA are associated with either a delay in LID onset or a reduction in established LID severity. Unfortunately, the antiparkinsonian benefit conferred by dopamine agonists is not as potent as the one obtained with L-DOPA and dopamine agonists cannot be administered as monotherapy in advanced PD, and as such, initiating dopaminergic therapy with a dopamine agonist may only delay dyskinesia onset. On the other hand, the limitations of continuous delivery of L-DOPA at the moment are obvious, because no pill exists that would provide round-the-clock delivery of the drug. Intravenous administration of the drug can hardly be envisioned outside of hospital-based settings, and intraduodenal infusion is an invasive approach that would not be justifiable in early PD where good control of the symptoms is easily achieved with two of

three times daily administration of dopaminergic agents. As such, research must continue to develop an oral formulation that will allow constant plasma L-DOPA levels throughout the day.

C. Dopamine Receptors

Dopamine exerts its effects by interacting with five subtypes of receptors, D₁₋₅ (Missale et al., 1998; Beaulieu and Gainetdinov, 2011). D₁ and D₅ receptors stimulate adenylyl cyclase activity and constitute the D₁-like family of dopamine receptors (Civelli et al., 1993). In contrast, D₂, D₃, and D₄ receptors reduce the activity of adenylyl cyclase and form the D₂-like receptor family (Gingrich and Caron, 1993). The D₂ receptor has two variants, D_{2S} and D_{2L}, whereas the D₄ receptor has three variants, D_{4.2}, D_{4.4}, and D_{4.7} (Seeman and Van Tol, 1994). D₁ and D₂ receptors are the most abundant of dopamine receptors within the striatum (Sokoloff and Schwartz, 1995) and are the most extensively studied in PD and LID.

Dopamine receptor supersensitivity was initially proposed as a mechanism underlying LID. Several autoradiographic receptor binding studies investigated D₁ and D₂ receptor levels in the parkinsonian and dyskinesic states. However, they provided little information to support a potential involvement of these receptors in dyskinesia. Thus, D₂ receptor binding levels were increased in the striatum of L-DOPA-naive 6-OHDA-lesioned rats (Creese et al., 1977), MPTP-lesioned NHPs (Graham et al., 1993), and PD patients (Lee et al., 1978). This increase in D₂ receptors was not maintained after chronic L-DOPA therapy in the MPTP-lesioned NHP (Graham et al., 1993) and PD patients (Lee et al., 1978). Unlike the D₂ receptor, D₁ receptor binding levels did not change in PD (Lee et al., 1978; Shinotoh et al., 1993) or in the MPTP-lesioned NHP (Aubert et al., 2005), regardless of L-DOPA treatment. In contrast, in the 6-OHDA-lesioned rat, D₁ receptor mRNA was reduced in the L-DOPA-naive parkinsonian state, but the reduction was reversed following treatment with the D₁ agonist SKF-38,393 (Gerfen et al., 1990). Similar findings were encountered in positron emission tomography (PET) studies. Thus, D₁ binding levels were unchanged when PD patients, with and without dyskinesia, were compared with healthy controls 4 hours after last dose of L-DOPA, whereas D₂ binding levels were reduced in both dyskinesic and nondyskinesic PD patients compared with normal subjects, again 4 hours after last dose of L-DOPA (Turjanski et al., 1997).

More insight can be gathered from studies looking at the subcellular distribution of D₁ and D₂ receptors, which indicate specific abnormalities in subcellular distribution of D₁ but not D₂ receptors in dyskinesia. Thus, in the MPTP-lesioned NHP killed 1 hour after the last dose of L-DOPA, in nondyskinesic animals, D₁ receptors were recruited at the synaptic membrane of

striatal neurons, whereas they were recruited at both the synaptic membrane and the cytoplasmic compartment in dyskinesic animals (Guigoni et al., 2007). Hypoactivity of the 20S proteasomal subunit of striatal medium spiny neurons could be an important determinant in this altered distribution of D₁ receptors in dyskinesia (Berthet et al., 2012). Indeed, hypoactivity of the 20S proteasomal subunit would impair degradation of D₁ receptors, which might account for their recruitment at both the synaptic membrane and the cytoplasmic compartment (Berthet et al., 2012).

However, in the 6-OHDA-lesioned rat killed 45 minutes after the last dose of L-DOPA, treatment with L-DOPA induced an internalization of D₁ receptors (Muriel et al., 2002). These findings in the rat were similar to those encountered in idiopathic PD, where chronic L-DOPA treatment was associated with a preferential cytoplasmic localization of D₁ receptors compared with healthy control individuals (Muriel et al., 1999). Therefore, if it seems clear that subcellular distribution of D₁ receptors is altered in the dyskinesic state, the type of alteration seems to be variable across species and it is not clear whether this abnormal distribution is a mechanism responsible for the development, expression, or maintenance of LID. To elucidate this question, it would be important to repeat those experiments and to include a group of animals that would be killed at different times during the priming phase and a group of dyskinesic animals that would be killed while in the off-state. Similarly, the information provided by human studies with respect to the expression of the dyskinesic phenotype remains limited. Indeed, the majority of PD patients included in these studies did not die at peak dyskinesia expression and as such, the postmortem changes described are not those encountered when dyskinesia is being acutely expressed but rather reflect the off-state of PD patients treated chronically with L-DOPA. Nevertheless, an internalization of D₁ receptors in the dyskinesic state might represent an endogenous compensatory mechanism aimed at alleviating dyskinesia.

There is also evidence for overactive D₁-mediated signaling in dyskinesia. Thus, in brain slices from MPTP-lesioned macaques killed at peak expression of dyskinesia, D₁ agonist-induced [³⁵S]guanosine 5'-O-[γ-thio]triphosphate (GTPγS) binding correlated linearly with dyskinesia severity (Aubert et al., 2005).

In agreement with abnormal cellular distribution of D₁ receptors and overactive D₁-mediated transmission in dyskinesia, internalization of D₁ receptors is accompanied by a reduction of dyskinesia severity. Thus, lentiviral-induced striatal overexpression of G protein-coupled receptor kinase 6 (GRK6) led to an internalization of D₁ receptors in the dyskinesic 6-OHDA-lesioned rat and the MPTP-lesioned macaque (Ahmed et al., 2010); this was associated with a reduction of established L-DOPA-induced-AIMs

(LI-AIMs) and LID in rat and macaque, respectively (Ahmed et al., 2010).

D₁ receptors also appear to play a role in the priming process leading to the expression of dyskinesia. Thus, de novo treatment with the D₁ agonist SKF-81,297 led to the development of AIMs in the 6-OHDA-lesioned rat (Dupre et al., 2007; Jaunaraajs et al., 2009), and de novo administration of the D₁ agonist SKF-82,958 led to the development of dyskinesia in the MPTP-lesioned macaque (Blanchet et al., 1996b; Goulet et al., 1996). To our knowledge, only one de novo study with a selective D₁ agonist was performed in PD patients; in that study, no dyskinesia was reported after treatment with the D₁ partial agonist CY-208,243 (Emre et al., 1992).

D₂ receptors also appear to be involved in dyskinesia, although they are traditionally regarded as being less involved than D₁ receptors, perhaps because of the de novo studies with dopamine agonists and of the postmortem data discussed above. However, although D₁ receptors are traditionally considered as the pillars of dyskinesia, D₂ receptors play an important role. Thus, once priming has occurred, both D₁ and D₂ agonists can induce AIMs in the 6-OHDA-lesioned rat (Dupre et al., 2007) and dyskinesia in the MPTP-lesioned NHP (Pearce et al., 1995; Fasano et al., 2010) and in idiopathic PD patients (Olanow et al., 1994; Blanchet et al., 1998a; Rascol et al., 1999, 2001b; Schapira et al., 2011). Moreover, viral vector-induced overexpression of RGS2-9, a guanosine triphosphatase (GTPase) protein that inhibits D₂ receptor downstream signaling, alleviated established LID in the MPTP-lesioned macaque and LI-AIMs in the 6-OHDA-lesioned rat (Gold et al., 2007). Additionally, in MPTP-lesioned NHPs with established LID, selective stimulation of D₁ receptors with A-77636 (Pearce et al., 1999) and A-86929 (Grondin et al., 1997; Pearce et al., 1999) induced less severe dyskinesia than L-DOPA, suggesting that simultaneous stimulation of both and D₁ and D₂ receptors leads to more severe dyskinesia expression than selective stimulation of either D₁ or D₂ receptors. A study performed in the MPTP-lesioned NHP with established LID, where several D₁-selective and D₂-selective agonists were administered, has also suggested that selective stimulation of D₂ receptors elicits more severe dyskinesia than selective stimulation of D₁ receptors (Blanchet et al., 1993).

Moreover, selective stimulation of D₂ receptors with (+)-PHNO led to the development of dyskinesia in the MPTP-lesioned NHP and, once the priming had occurred, administration of (+)-PHNO in the presence of the D₁ antagonist SCH-23,390 was sufficient to elicit dyskinesia (Luquin et al., 1992a). Additionally, following induction of dyskinesia with (+)-PHNO, stimulation of D₁ receptors with CY-208,243 induced dyskinesia as severe as these induced by (+)-PHNO in the MPTP-lesioned macaque (Gomez-Mancilla and Bedard, 1992a).

These data are of critical importance in the understanding of dyskinesia, as de novo administration of either D₁-selective or D₂-selective dopamine agonists seems sufficient to lead to the development of dyskinesia and, once the priming has occurred, administration of either D₁-selective or D₂-selective dopamine agonists is also sufficient to elicit dyskinesia. Therefore, it may well be that dopamine agonists used de novo in clinical trials generated less dyskinesia than L-DOPA because of their longer half-life rather than their selectivity for D₂ receptors. Accordingly, de novo pulsatile administration of the D₂ agonist U-91356A led to the development of more severe dyskinesia than continuous administration of U-91356A in the MPTP-lesioned NHP (Blanchet et al., 1995). As such, we propose that duration of dopamine receptor stimulation, reflected by the half-life of the drug, is at least as important as selectivity of receptor stimulation and development of novel pharmacotherapeutics should therefore take these observations into consideration.

D₃ receptors also appear to play a role in the induction and expression of LID, although they have been far less studied than D₁ and D₂ receptors. Thus, administration of the selective D₃ agonist PD-128,907 to primed MPTP-lesioned macaques induced dyskinesia, which was comparable to apomorphine in terms of severity (Blanchet et al., 1997). Additionally, chronic de novo treatment with the highly selective D₃ receptor antagonist S-33,084 attenuated the development of dyskinesia without affecting L-DOPA antiparkinsonian benefit in the MPTP-lesioned marmoset (Visanji et al., 2009a); however, in the same study, S-33,084 did not reduce established LID, and, in another study, S-33,084 was ineffective against ropinirole-elicited dyskinesia in primed marmosets (Silverdale et al., 2004). In another study, performed in the MPTP-lesioned macaque, antagonizing D₃ receptors with nafadotride led to a reduction of previously established LID, although this was associated with a reduction in L-DOPA antiparkinsonian action (Bezard et al., 2003), whereas treatment with the D₃ partial agonist BP897 reduced dyskinesia severity without adversely affecting parkinsonism (Bezard et al., 2003). In contrast, in the MPTP-lesioned squirrel monkey, BP897 only exerted a mild antidyskinetic effect and impaired L-DOPA antiparkinsonian action (Hsu et al., 2004). Part of the discrepancy between these studies may result from the pharmacology of the agents used, because there has been some discussion as to the selectivity of nafadotride (Bezard et al., 2003) and BP897 (Pilla et al., 1999), whereas part may result from the models used. More evidence for a role of D₃ receptors in dyskinesia and sensitized behavior comes from a study performed in the 6-OHDA-lesioned rat, where intrastriatal administration of oligonucleotide antisense to D₃ receptor mRNA reduced rotational behavior (van Kampen and Stoessel, 2003).

The fate of D₃ receptors in LID has also been investigated in postmortem studies. Thus, in the common marmoset killed 3 hours after last L-DOPA administration, D₃ receptor binding levels were unchanged following MPTP administration and chronic L-DOPA therapy (Hurley et al., 1996a). D₃ receptor binding levels also remained stable in the striatum of PD patients treated with L-DOPA (Hurley et al., 1996b). In contrast, chronic L-DOPA treatment led to an increase in D₃ receptor levels in the striatum of the 6-OHDA-lesioned rat and in the putamen and GPi of the MPTP-lesioned macaque (although time of death with respect to drug administration was not mentioned in the article, this group historically has typically killed animals at time of peak dyskinesia expression) (Bezard et al., 2003). Given that the marmoset appears to model changes in D₃ receptors seen in PD patients and that the pharmacological characterization of S-33,084 is better established, D₃ antagonists likely have potential to prevent development of LID, whereas their effect in reducing established LID may be minimal. However, if antagonizing D₃ receptors might be an effective way to prevent the priming leading to the expression of LID, it is unknown whether selectively stimulating D₃ receptors would itself be sufficient for dyskinesia to develop. Further studies are needed to answer that question, which in turn will refine our understanding of the role of D₃ receptors in LID.

Although the mechanisms underlying the involvement of D₃ receptors in dyskinesia have been far less studied than those of D₁ and D₂ receptors, it seems that a cross-talk with D₁ receptors is involved, at least according to studies performed in the 6-OHDA-lesioned rat which used rotations as the behavioral end point (Bordet et al., 1997, 2000). A cross-talk between D₁ and D₃ receptors was suggested in these two studies, because stimulation of D₁ receptors led to increases in striatal D₃ mRNA and binding levels (Bordet et al., 1997, 2000). Accordingly, in a study that used AIMs as the behavioral end point, antagonizing D₃ receptors with ST-198 restored normal levels of membrane-bound D₁ receptors in the dyskinetic 6-OHDA-lesioned rat killed 60 minutes after last treatment administration (Berthet et al., 2009). In this way, D₃ signaling might be permissive for D₁ stimulation to lead to overactivity of the direct pathway, as discussed above, a critical component of the pathophysiology of LID, and as such may be a more attractive target for an antidyskinetic therapy than D₁ antagonists, which would also likely reduce antiparkinsonian benefit.

Very few studies have assessed the effect of antagonizing D₄ receptors on LID. Early evidence of a potential antidyskinetic efficacy comes from a study performed in the MPTP-lesioned NHP, in which the clozapine analog JL-18 effectively alleviated LID (Hadj Tahar et al., 2000a). However, JL-18 is not selective for D₄ receptors but also exhibits high affinity for

serotonergic type 2 (5-HT₂), muscarinic, and D₂ receptors (Liegeois et al., 1995), and the contribution of these off-target sites could not be excluded in that study. Moreover, JL-18 impaired L-DOPA antiparkinsonian action at high dose, an effect that might well have been mediated by an interaction with D₂ receptors. More recently, the potent and selective D₄ antagonist L-745,870 significantly reduced LID severity, while increasing duration of on-time without disabling dyskinesia, in the MPTP-lesioned macaque (Huot et al., 2012a). That last study determined pharmacokinetic parameters and brain levels of L-745,870 associated with an antidyskinetic effect and established that L-745,870 alleviated LID at brain levels at which it blocked > 90% of D₄ receptors while remaining selective for the primary target.

To our knowledge, no postmortem study measuring D₄ receptor levels in animal models of PD experiencing LID or in dyskinetic PD patients has been performed, and the site(s) and mechanism(s) underlying the antidyskinetic effects of D₄ receptor blockade have yet to be determined. Whether D₄ receptors are also involved in the priming process leading to LID expression is also unknown.

Table 2 summarizes some of the key concepts put forth in the dopamine receptors subsection.

V. The Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter within the brain (McEntee and Crook, 1993). Glutamate exerts its effects via ionotropic and metabotropic receptors and plays an important role in synaptic plasticity (Raiteri, 2006) (vide infra). As shown in Figs. 1 and 2 and discussed above, glutamate is a key player in the physiology of the basal ganglia and has been, for that reason, extensively studied in PD and LID.

Several postmortem and pharmacological studies have investigated the involvement of the glutamatergic system in dyskinesia. Overactive glutamatergic transmission is believed to be an important contributor to both the development and expression of LID. In particular, the classic model suggests overactivity of glutamatergic corticostriatal projections as being critical to overactivity of the direct pathway. That said, there are other areas where increased glutamatergic transmission is involved, e.g., subthalamic efferents, and receptor distribution across the circuit or pharmacodynamic differences may underlie the ability of some anti-glutamate agents to reduce LID whereas others do not. As will be seen in this section, although it is clear that *N*-methyl-D-aspartate (NMDA) and metabotropic glutamate (mGlu) receptors type 5 (mGlu5) play a significant role in dyskinesia, the involvement of α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors remains uncertain. The

key points put forth in this section are summarized in Table 3.

A. NMDA Receptors

1. Postmortem Studies. NMDA receptors consist of tetramers comprising at least one NR1 and one NR2 (NR2A-D) subunit, usually two of each (Dingledine et al., 1999), although they may also contain one NR3 subunit (Sasaki et al., 2002). Glutamate binds to the NR2 subunits, whereas the positive allosteric modulator glycine binds to the NR1 subunit (Paoletti and Neyton, 2007). Although all of these glutamate subunits, especially NR1, can be divided into multiple variants due to splicing (Stephenson, 2006), attention has been paid mostly to the NR2A and NR2B subunits in LID. NR2A and NR2B subunits lead to different receptor-mediated current kinetics, NR2B-mediated current decaying slower than that mediated by NR2A (Lu et al., 2001).

Changes in NMDA receptor levels have been documented in the dyskinetic state. Thus, in the L-DOPA-treated dyskinetic MPTP-lesioned squirrel monkey killed after a 3-day drug washout, NMDA binding levels were decreased in the striatum compared with MPTP-lesioned, nondyskinetic animals (He et al., 2000). Changes in NMDA subunit levels have also been reported in the dyskinetic state. Thus, in the striatum of L-DOPA-naive MPTP-lesioned macaques, NR1 and NR2B subunit levels were reduced, whereas NR2A subunit levels were unchanged compared with normal macaques (Hallett et al., 2005). However, in macaques with established LID killed 60 minutes following last drug administration, NR1 and NR2B subunit levels were normalized, and NR2A subunit levels were upregulated compared with nonparkinsonian macaques (Hallett et al., 2005). In the dyskinetic MPTP-lesioned common marmoset killed 8 days following last L-DOPA administration, NR2B subunit levels were increased in the striatum but unchanged in the GP, whereas NR1 subunit levels were unaltered compared with nonparkinsonian animals (Hurley et al., 2005). In the MPTP-lesioned macaque rendered dyskinetic with the D₁ agonist SKF-82,958 and killed in the off-state, striatal levels of NR1/NR2A but not NR1/NR2B heteromers were increased compared with nonparkinsonian animals

(Calon et al., 2002b). A study examining absolute levels of NR1/NR2A and NR1/NR2B heteromers in the striatum of dyskinetic PD patients found no differences compared with healthy controls or PD patients without motor complications (Calon et al., 2003b).

In addition to numerical regulation of NMDA receptors and their subunits, there is also evidence of altered phosphorylation and cellular distribution in the dyskinetic state. In the striatum of the 6-OHDA-lesioned rat treated chronically with L-DOPA (dyskinetic status unknown but the animals displayed evidence of sensitization) and killed 1 hour after last L-DOPA injection, the number of phosphorylated NR1 subunits was decreased compared with control animals but increased compared with 6-OHDA-lesioned rats not exposed to L-DOPA (Napolitano et al., 2006). In the striatum of the dyskinetic 6-OHDA-lesioned rat (time of sacrifice with respect to last L-DOPA dose not mentioned), there was a redistribution of NR2B subunits from synaptic to extrasynaptic sites in the plasma membrane and the number of postsynaptic NR2A subunits was increased (Gardoni et al., 2006). In the striatum of the 6-OHDA-lesioned rat killed 12 hours after last L-DOPA administration, NR1/NR2B heteromers were redistributed toward subcellular compartments, and, after chronic L-DOPA therapy, their membrane levels were normalized but they were abnormally phosphorylated (Oh et al., 1998; Dunah et al., 2000). Stimulating D₁ receptors was demonstrated to play a key role in the redistribution and phosphorylation of NR1/2A/2B subunits (Dunah and Standaert, 2001). Although the cellular pathways ultimately leading to abnormal phosphorylation of glutamate subunits remain largely unknown, Src and Lyn kinases are unlikely to mediate it, because their mRNA and protein levels were reduced in the striatum of the 6-OHDA-lesioned rat treated chronically with L-DOPA killed at peak dyskinesia compared with unlesioned and L-DOPA-naive 6-OHDA-lesioned rats (Napolitano et al., 2006).

A major issue that complicates the interpretation of data are that the majority of the postmortem studies cited above were performed with animals killed in the off-state or in studies in which the behavioral correlate was not described, and it is therefore impossible to attribute many of the changes enumerated to

TABLE 2
The dopaminergic system in dyskinesia

-
- Striatal dopamine depletion is not a prerequisite for development of dyskinesia, if high doses of L-DOPA are administered.
 - Pulsatile dopamine replacement therapy appears as a key etiological factor in the development of LID.
 - Initial therapy with longer-lasting dopaminergic agents can delay the onset of dyskinesia.
 - Continuous delivery of dopamine agonists or L-DOPA can reduce the severity of established dyskinesia.
 - Dopamine receptor supersensitivity.
 - Overactive D₁-mediated neurotransmission.
 - Recruitment of D₁ receptors at the synaptic membrane.
 - Lentiviral-induced internalization of D₁ receptors alleviates LI-AIMs in the 6-OHDA-lesioned rat and LID in the MPTP-lesioned NHP.
 - Each of D₁, D₂, and D₃ receptors are involved in the development and expression of dyskinesia.
 - Cross-talk between D₁ and D₃ receptors.
-

TABLE 3
The glutamatergic system

Only data from postmortem studies where animals were killed in the on-state at peak dyskinesia expression are included.

- NMDA receptors
 - NR2A subunits are upregulated in the striatum of the dyskinetic MPTP-lesioned macaque.
 - Selective NR2B blockade alleviates established dyskinesia.
 - Reducing NR2A levels at the membrane prevents the priming process but does not suppress established dyskinesia.
 - NR1 blockade exacerbates established dyskinesia but might prevent the priming process.
 - Amantadine is efficacious at reducing dyskinesia.
- AMPA receptors
 - AMPA receptor levels are unaltered in the striatum of the dyskinetic MPTP-lesioned NHP.
 - GluR2/3 subunit levels are increased at the synaptic membrane in the striatum of the dyskinetic MPTP-lesioned NHP.
 - GluR1 subunit phosphorylation is increased in the dyskinetic MPTP-lesioned NHP and 6-OHDA-lesioned rat.
 - The antidyskinetic efficacy of selective AMPA antagonists is uncertain.
 - The effect of selective AMPA antagonists on the priming process leading to dyskinesia expression is unknown.
- Kainate receptors
 - The antidyskinetic efficacy of selective kainate antagonists is uncertain.
- mGlu receptors
 - There are no documented changes in mGlu2/3 levels at peak dyskinesia expression.
 - mGlu2/3 agonists do not alleviate dyskinesia.
 - There are no documented changes in mGlu5 levels at peak dyskinesia expression.
 - mGlu5 antagonists both prevent development and suppress expression of established dyskinesia.
 - mGlu1 antagonists do not reduce dyskinesia.
- Glutamate release
 - There is a potential antidyskinetic effect of decreasing glutamate release with glutamate release inhibitors.
- Synaptic plasticity
 - Corticostriatal depotentiation is altered in slices from dyskinetic 6-OHDA-lesioned rats.
 - Corticostriatal LTD is altered in the dyskinetic 6-OHDA-lesioned rat.
 - LTP-like plasticity is deficient in the motor cortex of dyskinetic PD patients.
 - Preventing dendritic spine pruning prevents development of LI-AIMs in the 6-OHDA-lesioned rat.

something else than the off-state or chronic L-DOPA therapy. However, it seems clear that NR2A subunits are involved in the acute expression of LID. Although it remains unknown whether the increase in NR2A subunit levels occurs along the direct or the indirect pathway, an increase along the direct pathway might explain the overactivity of the direct pathway in LID. While NR2B subunits might be involved in the expression of the off-state, the studies cited above do not support their involvement in acute expression of LID, although this conception will be challenged in the next subsection.

Unfortunately, the above discussion, based on post-mortem studies, pays no heed to whether abnormal NMDA receptor functioning is a component of the mechanisms responsible for the development, expression, or maintenance of LID; indeed the designs of the studies discussed do not allow for such. However, as will be seen in the next subsection, at least with respect to development and expression, there are clear indications that NMDA-mediated signaling is a significant contributor to LID process.

2. Pharmacological Studies. In 2006, the American Academy of Neurology recommended the use of amantadine (Level C evidence) for the treatment of dyskinesia (Pahwa et al., 2006). More recently, the Movement Disorders Society stated, in an evidence-based medicine review, that amantadine was efficacious to alleviate LID (Fox et al., 2011). However, it is interesting that currently no agent, including amantadine, has been given an indication for treatment of LID, or dyskinesia generally, by either the United States Food and Drug Administration (FDA) or the

European Medicines Agency (EMA). The action of amantadine is to reduce peak dose, established LID without compromising antiparkinsonian benefits in the mouse (Lundblad et al., 2005), rat (Dekundy et al., 2007) NHP (Blanchet et al., 1998b), and human (Verhagen Metman et al., 1998d, 1999; Del Dotto et al., 2001), and nonselective antagonism of NMDA receptors is regarded as the mechanism whereby amantadine, dextrorphan, and dextromethorphan exert their antidyskinetic effects (Blanchet et al., 1996c; Verhagen Metman et al., 1998a,b,c,d; Luginer et al., 2000). However, amantadine is not universally effective (Callaghan et al., 1974; Sawada et al., 2010), can be poorly tolerated by some patients, and may elicit psychiatric complications (Postma and Van Tilburg, 1975; Verhagen Metman et al., 1998d). In addition, there have been suggestions of tachyphylaxis of the antidyskinetic efficacy of amantadine (Metman et al., 1999; Thomas et al., 2004). Moreover, remacemide, another nonselective NMDA antagonist, failed to alleviate dyskinesia in a clinical trial (Parkinson Study Group, 2001). There thus remains a pressing unmet clinical need and requirement for the development of novel antidyskinetic NMDA antagonist molecules. This might seem quite surprising, because several negative allosteric and orthosteric modulators of NMDA receptors and their subunits have been tested and have shown efficacy in preclinical settings. Data gathered from these preclinical studies suggest that NMDA receptors are involved in both acute expression and development of dyskinesia.

With respect to acute expression of dyskinesia, blockade of the NMDA ion channel by administration

of magnesium sulfate alleviated established LID in the MPTP-lesioned NHP (Chassain et al., 2003). Antagonizing the glycine-binding site by increasing kynurenic acid levels with Ro-61-8048 also alleviated established LID, although modestly, in the MPTP-lesioned macaque, without affecting L-DOPA antiparkinsonian action (Samadi et al., 2005). Accordingly, the glycine prodrug milacemide had no effect on established LID in a small clinical trial (Giuffra et al., 1993). A study performed in the MPTP-lesioned NHP suggested that nonselective blockade of NMDA receptors might have different effects on chorea and dystonia, chorea being improved with high dose of LY-235,959, whereas dystonia was exacerbated (Papa and Chase, 1996). However, this preferential antichorea effect was not encountered in another study in which the nonselective NMDA antagonist, MK-801, was administered to the MPTP-lesioned NHP, although a reduction in LID severity was achieved along with a reduction in L-DOPA antiparkinsonian action (Gomez-Mancilla and Bedard, 1993). It should also be pointed out that the preferential antichorea effect of nonselective NMDA antagonists was not encountered in the clinical trials that studied amantadine, dextromethorphan, or dextropropranolol, and as such, the data suggesting preferential antichorea effect of nonselective antagonists are too weak to make any recommendations.

The data from the pharmacological studies cited in the previous paragraphs almost uniformly indicate an antidyskinetic effect of nonselective NMDA antagonists. However, based on the results obtained in clinic with amantadine and remacemide, their efficacy is clearly limited and the loss of L-DOPA antiparkinsonian efficacy upon administration of MK-801 remains a concern, because it suggests that such molecules might have a very narrow therapeutic window.

Studies have also examined the effect of antagonists at subunits of NMDA receptors and these are very informative in terms of determining which NMDA subunits are critical to be blocked to acutely alleviate or prevent the development of LID, which will ultimately lead to the development of more selective and better tolerated antidyskinetic agents. Thus, negative allosteric modulation of NMDA receptors with the NR2B antagonist Co-101,244/PD-174,494 alleviated LID in the MPTP-lesioned macaque (Blanchet et al., 1999). The results obtained with dual NR1/NR2B antagonists are more difficult to interpret, as traxoprodil exerted a mild antidyskinetic effect in a phase II clinical trial (Nutt et al., 2008), whereas it exacerbated dyskinesia severity in the MPTP-lesioned NHP (Nash et al., 2004). Likewise, dual blockade of the NR1A/2A subunits with MDL-100,453 exacerbated LID in the MPTP-lesioned NHP (Blanchet et al., 1999). In the 6-OHDA-lesioned rat, selective reduction of the number of NR2A subunits at the synaptic membrane by intrastriatal delivery of the peptide

TAT2A did not lead to a suppression of well-established AIMs (Gardoni et al., 2011).

With respect to interference with the priming process, *de novo* treatment with the dual NR1A/2B antagonist CI-1041 prevented the development of LID in the MPTP-lesioned NHP (Hadj Tahar et al., 2004; Morissette et al., 2006b). Antagonizing the glycine-binding site by increasing kynurenic acid levels with Ro-61-8048 also reduced development of LID in the MPTP-lesioned macaque (Gregoire et al., 2008). In the 6-OHDA-lesioned rat, chronic treatment with the NR2B antagonist Ro-631,908 in combination with L-DOPA did not prevent the emergence of AIMs (Rylander et al., 2009), whereas reducing the number of NR2A subunits at the synaptic membrane by systemic injection of the peptide TAT2A reduced the development of LI-AIMs (Gardoni et al., 2011).

By taking a step back and examining the data from the studies performed with selective antagonists of specific NMDA subunits, a certain number of conclusions can be drawn with respect to the role played by each subunit in LID. Thus, it appears that, unlike what might be expected based on the findings of the postmortem studies cited in the previous subsections, selective blockade of NR2B subunits is effective at reducing established LID but is of little value in altering the priming process. In contrast, reducing the number of NR2A subunits at the synaptic membrane—similar effects would likely be achieved upon selective NR2A blockade—appears to be effective in preventing the priming process but does not effectively suppress established LID, which is also in contrast to what might be expected based on the findings of the postmortem studies cited above. Antagonizing NR1 subunits appears to play a deleterious effect on established LID, as the antidyskinetic effect of selective NR2B antagonists is no longer present with dual NR1/NR2B antagonists. However, NR1 subunits might play a role in the priming process, as dual blockade of NR1/NR2B subunits effectively prevents the development of dyskinesia, whereas selective NR2B blockade has no effect. We therefore propose that development of future NMDA antagonists should focus on blocking NR2B subunits for reduction of established LID while avoiding antagonizing both NR1 and NR2A subunits. In contrast, development of future NMDA antagonists to counteract the priming process should be centered on blocking NR1 and NR2A subunits while avoiding NR2B subunits. It is at present unknown if dual blockade of NR1/NR2A subunits would be more effective than selective blockade of either to prevent the priming.

The data from the pharmacological studies, without contradicting them, raise serious questions on how to interpret findings from the postmortem studies. Hence, at peak dyskinesia expression, NR2B subunit levels were normal in the NHP, whereas NR2A subunits

were upregulated. On the basis of pharmacological studies, it seems that antagonizing NR2B subunits provides the most consistent antidyskinetic benefit, whereas NR2A blockade seems of little value in the context of established LID. Perhaps a reappraisal of our interpretation of the postmortem studies is needed, because a crude alteration of receptor levels is not necessarily predictive of the antidyskinetic efficacy of modulating this receptor.

B. AMPA Receptors

AMPA receptors consist of double dimers, each containing one GluR2 subunit and either one GluR1, GluR2, GluR3, or GluR4 subunit (Greger et al., 2007), although the GluR2 subunit is sometimes absent, in which case AMPA receptors are permeable to calcium ions (Dingledine et al., 1999). GluR2 homomers are permeable to chloride anions (Burnashev et al., 1996). The ionic conductance of AMPA receptors varies according to their subunit composition and the editing of the GluR2 subunit (Dingledine et al., 1999).

1. Postmortem Studies. The fate of AMPA receptors in the dyskinetic state is unclear, because one study demonstrated that AMPA receptor levels were not altered in MPTP-lesioned macaques killed 20 minutes after apomorphine administration compared with controls (Silverdale et al., 2002), whereas another study examined MPTP-lesioned macaques killed in the off-state and revealed decreases in AMPA binding levels in the anterior striatum but increases in the posterior striatum in both L-DOPA-naive and L-DOPA treated dyskinetic states (Ouattara et al., 2010b). In dyskinetic PD patients, AMPA receptor binding levels were decreased in the caudate but not in the putamen compared with healthy controls (Calon et al., 2003b). As for NMDA receptors, the discrepancy between the studies might relate to the fact that data were collected in both the on- and off-states, as well as the fact that apomorphine instead of L-DOPA was used in the sole study that did not disclose numerical alterations of AMPA receptors in dyskinesia.

Similar to NMDA receptors, there seem to be changes in the subcellular distribution of AMPA receptor subunits in the dyskinetic state. Thus, in the striatum of the dyskinetic MPTP-lesioned NHP killed at peak dyskinesia expression, GluR2/3 subunit levels were increased at the synaptic membrane, whereas GluR1 subunit levels were unchanged compared with both nonparkinsonian and parkinsonian untreated animals (Santini et al., 2010; Silverdale et al., 2010). However, GluR1 phosphorylation at Ser845 was markedly increased in the striatum of the L-DOPA-naive and the dyskinetic MPTP-lesioned macaque (Santini et al., 2010). These data suggest that GluR2/3-mediated neurotransmission is enhanced when dyskinesia is being maximally expressed.

In the striatum of the L-DOPA-naive 6-OHDA-lesioned rat, GluR1 subunit levels were decreased at the synaptic membrane, and the number of phosphorylated GluR1 subunits at Ser831 was decreased; chronic treatment with L-DOPA significantly increased the number of GluR1 subunits and the number of phosphorylated GluR1 subunits at Ser831 at the plasma membrane, whether the animals were killed 3 or 24 hours following last L-DOPA administration (Ba et al., 2006). These discrepancies in GluR1 absolute numbers between the rat and NHP LID models are important to point out, as they suggest that selectively antagonizing GluR1 subunits might alleviate LID in the rat but not necessarily in the NHP. However, 3 hours post-L-DOPA administration, rats are often wearing off, if not completely off and, as such, findings of abnormal GluR1 may be more reminiscent of the wearing-off state than the dyskinetic state. Taken together, these postmortem studies suggest a lack of involvement of GluR1 subunit in LID.

Thus, although the fate of AMPA receptors in dyskinesia has been much less studied than the fate of NMDA receptors, a few important conclusions can be drawn. First, as mentioned above, they do not support an involvement of GluR1 subunits in established LID. Second, abnormal GluR2/3 transmission appears to be present in established dyskinesia. However, several holes remain in our comprehension of the role of AMPA receptors in dyskinesia. For instance, although AMPA binding levels are increased in the acutely dyskinetic apomorphine-treated NHP, it remains unknown whether these changes occur along the direct or the indirect pathway. An increase in AMPA-mediated glutamatergic transmission along the direct pathway might account for its overactivity in dyskinesia. Moreover, by putting data from all NHP studies together, the increase in AMPA receptors might well be predominantly made of GluR2 subunits and perhaps GluR2 homomers that would have implications on chloride conductance of the AMPA channels. This opens the way to speculate that antidyskinetic therapies based on modulation of ionic channels might represent a new approach against LID and several such molecules are used in clinic; as such it would not be complicated to move forward to clinical trials rapidly. In agreement with this possibility, the potassium $K_v7.2-7.5$ channel openers retigabine and flupirtine, two clinically available molecules (Porter et al., 2007; Stoessel et al., 2010), alleviated the severity of established LI-AIMs in the 6-OHDA-lesioned rat (Sander et al., 2012).

2. Pharmacological Studies. In agreement with the findings of the postmortem studies cited above, pharmacological studies have suggested an antidyskinetic effect of dampening AMPA-mediated transmission, although some doubts persist on the antidyskinetic potential of selective AMPA antagonists, because the

molecules studied were not selective for AMPA receptors. Indeed, in the MPTP-lesioned NHP, the GluR2/NMDA antagonist IEM-1460 (Kobylecki et al., 2010) and the AMPA/kainate antagonists LY-300,164 (Konitsiotis et al., 2000) and topiramate (Silverdale et al., 2005) reduced the severity of established LID. Interestingly, administration of subthreshold doses, ineffective as monotherapy, of the AMPA/kainate antagonist GYK-47,261 (Abraham et al., 2000) in combination with low doses of either of the nonselective NDMA antagonists MK-801 or amantadine led to a significant reduction in LID in the MPTP-lesioned NHP (Bibbiani et al., 2005b).

At the clinical level though, the only AMPA antagonist evaluated and reported, perampanel, did not alleviate dyskinesia in a phase II trial (Eggert et al., 2010). Those results shed serious doubt on the antidyskinetic efficacy of AMPA antagonists, because perampanel is highly selective for AMPA receptors (Rogawski, 2011), indeed more selective than any of the drugs cited in the previous paragraph. Two phase I/II trials were performed with the AMPA antagonist talampanel (Clinical trials NCT00036296 and NCT00108667), but the results have not been reported.

To our knowledge, only one study examined the effect of AMPA antagonists, in that case dual GluR2/NMDA blockade, on the development of LID. In that study, concomitant administration of IEM-1460 and L-DOPA during the priming phase reduced the induction of AIMs, without impairing L-DOPA antiparkinsonian action, in the 6-OHDA-lesioned rat (Kobylecki et al., 2010).

These pharmacological data need be reinterpreted in light of the postmortem studies discussed in the previous section. However, before doing so, it is important to state that a molecule acting on a specific target might affect downstream signaling processes sufficiently to alleviate dyskinesia, irrespective of the absolute number of binding sites or the phosphorylation status of these binding sites, usually a receptor. As such, changes in binding levels might be an indicator, although might not necessarily be predictive of the action of a pharmacological agent. Thus, at peak dyskinesia expression, no changes were encountered in AMPA binding levels in the MPTP-lesioned NHP, and as such, the lack of antidyskinetic effect of perampanel is perhaps not surprising. This highlights the importance of killing the animals in the on-state at peak dose dyskinesia when postmortem studies are examining a receptor potentially involved in LID; indeed, the postmortem study performed in the NHP in which animals were killed in the off-state was not predictive of the lack of efficacy of perampanel, because changes in AMPA binding levels were detected in the off-state, but these likely have little to do with the expression of the dyskinetic phenotype. However, at peak dyskinesia, synaptic levels of the GluR2/3

subunits were increased in the striatum of the MPTP-lesioned NHP. The failure of perampanel to alleviate LID might be due to the fact that it is an AMPA antagonist that does not discriminate between subunits, and it may well be that a selective blockade of the GluR2/3 subunits is required to alleviate LID while antagonizing AMPA receptors. The antidyskinetic efficacy of such selective compounds has not been tested at present, but we propose that future AMPA antagonists being developed as antidyskinetic agents should focus on dual blockade of these two subunits. The effects of selective AMPA receptor blockade on the development of LID in the context of de novo studies remain largely unexplored.

C. Metabotropic Glutamate Receptors

mGlu receptors are seven transmembrane domain G protein-coupled receptors (Conn and Pin, 1997; Kunishima et al., 2000). Eight types of mGlu receptors have been identified, mGlu1–8 (Foord et al., 2005). mGlu receptors have been further divided in three groups, based in part on similar signal transduction mechanisms. Thus, mGlu1 and mGlu5 receptors form Group I, mGlu2 and mGlu3 form Group II, while mGlu4, mGlu6, mGlu7, and mGlu8 receptors form Group III (Swanson et al., 2005; Gladding et al., 2009).

As will be seen in this section, few postmortem studies have been performed that investigated the fate of mGlu receptors in dyskinesia. Hence, only receptor binding studies have investigated the numerical regulation of mGlu in dyskinesia and several important questions remain, such as the phosphorylation state or the membrane/subcellular distribution of these receptors in dyskinesia. Moreover, the postmortem studies were mostly performed when animals or patients were in the off-state and thus provide only limited information about the role played by these receptors in the expression of dyskinesia. More insight can be garnered from pharmacological studies that modulated mGlu-mediated transmission in LID.

1. Metabotropic Glutamate Receptors Type 2/3. In dyskinetic L-DOPA-treated MPTP-lesioned macaques killed 24 hours after treatment, mGlu2/3 binding levels were increased in the putamen and GPe but unchanged in the caudate, STN, GPi, and SNr compared with MPTP-lesioned, L-DOPA-naive NHPs; no alterations in mGlu2/3 levels have been reported in L-DOPA-naive MPTP-lesioned NHPs (Samadi et al., 2008a). In PD patients, with and without dyskinesia, mGlu2/3 receptor levels were reduced in the caudate and GPi, but not in the putamen and GPe, compared with controls (Samadi et al., 2009). These discrepancies between mGlu2/3 levels encountered in dyskinetic idiopathic PD patients and dyskinetic MPTP-lesioned NHPs are quite surprising, because both studies were done by the same group with the same radioligand and both involved subjects in the off-state. Regardless of

these discrepancies, these studies did not establish an involvement of mGlu2/3 receptors in LID. In agreement with a lack of altered mGlu2/3-mediated transmission in LID, mGlu2/3-mediated transmission at the corticostriatal synapse in striatal slices from 6-OHDA-lesioned rats treated chronically with L-DOPA was not different to that from normal, nonparkinsonian rats (Picconi et al., 2002).

The lack of involvement of mGlu2/3 receptors in LID was further suggested by a pharmacological study conducted in the 6-OHDA-lesioned rat where the mGlu2 agonist LY-379,268 had no effect in preventing the development or acutely suppressing the expression of LI-AIMs (Rylander et al., 2009). The antidyskinetic efficacy of mGlu2/3 receptor agonists has not been tested in the MPTP-lesioned NHP or in clinical settings, but it is unlikely that this avenue will be pursued further.

2. Metabotropic Glutamate Receptors Type 5. mGlu5 receptors are abundant within the striatum, where they are located postsynaptically on striatal projection neurons (Testa et al., 1995). mGlu5 and NMDA receptors appear to be intimately connected, with a reciprocal positive-feedback interaction (Alagarsamy et al., 1999a,b), and as such, antagonizing mGlu5 receptors is another way to reduce overactive glutamatergic transmission in LID.

In the L-DOPA-naive MPTP-lesioned NHP, mGlu5 binding levels were increased in the striatum and increased further following L-DOPA treatment, the last dose being administered 24 hours prior to sacrifice (Samadi et al., 2008b; Ouattara et al., 2011). mGlu5 mRNA levels were also increased in the striatum of dyskinetic MPTP-lesioned macaques compared with L-DOPA-naive MPTP-lesioned macaques or nonparkinsonian macaques when they were killed 4 hours after last L-DOPA dose (Ouattara et al., 2010a). In PD patients, mGlu5 binding levels were elevated in the putamen and both segments of the GP when dyskinetic subjects were compared with nondyskinetic patients (Ouattara et al., 2009). Results of these postmortem studies argue for overactive mGlu5-mediated transmission in the dyskinetic state.

Pharmacological studies have confirmed mGlu5 receptors in both development and acute expression of LID. Hence, in studies performed in the 6-OHDA-lesioned rat where the mGlu5 antagonist MTEP was administered de novo with L-DOPA, MTEP administration led to significantly less severe AIMs than vehicle treatment (Mela et al., 2007; Rylander et al., 2009). In another study, acute challenges of MTEP effectively suppressed established AIMs, without altering the antiparkinsonian action of L-DOPA (Dekundy et al., 2006). More recently, the mGlu5 negative allosteric modulator MRZ-8676 was shown to significantly reduce established LI-AIMs in the rat, the effects of which showed no tolerance over a 6-day

treatment period (Dekundy et al., 2011). In the MPTP-lesioned NHP, the mGlu5 antagonists AFQ056 (Gregoire et al., 2011), ADX-48,621 (Hill et al., 2010), fenobam (Rylander et al., 2010a), MPEP (Morin et al., 2010), and MTEP (Johnston et al., 2010b) reduced the severity of previously established LID. With MTEP, however, an antidyskinetic effect was obtained only at high dose and was accompanied by a reduction of L-DOPA antiparkinsonian efficacy (Johnston et al., 2010b), suggesting that although negative allosteric modulation of mGlu5 receptors alleviates LID, the compounds might have a narrow therapeutic window and the antidyskinetic benefit might come at the expense of a reduction in L-DOPA antiparkinsonian action. At the clinical level, AFQ056 is the only mGlu5 antagonist that has been reported on to date to successfully alleviate established LID (Berg et al., 2011). A phase IIa trial with ADX-48,621 is currently recruiting participants (Clinical trial NCT01336088).

Although it remains to be established if the increase in striatal mGlu5 receptor levels described above in the dyskinetic state occurs predominantly on striatofugal neurons of the direct pathway, an increase in striatal mGlu5 levels along the direct pathway would explain its overactivity in the dyskinetic state and provide an anatomic rationale for antagonizing mGlu5 receptors in LID. A second mechanism underlying the antidyskinetic efficacy of mGlu5 antagonists might be a reduction in GABA release within the SNr (Mela et al., 2007), which would ultimately lead to a greater inhibition of the thalamus and a reduction of cortical excitation.

As seen above, along with mGlu5 receptors, mGlu1 receptors form the Group I family of mGlu receptors (Bonsi et al., 2005). In contrast to mGlu5 receptors, antagonizing mGlu1 receptors did not prevent the development (Rylander et al., 2009) nor alleviate the expression of established (Dekundy et al., 2006) AIMs in the 6-OHDA-lesioned rat. The antidyskinetic potential of mGlu1 antagonists has not been assessed in the MPTP-lesioned NHP or in PD patients and, based on the negative results obtained in rat studies, mGlu1 receptors do not appear to represent a promising antidyskinetic target.

D. Glutamate Release

In agreement with overactive glutamatergic transmission in LID and the antidyskinetic effect of various glutamate receptor antagonists, studies have demonstrated increased levels of glutamate in the striatum and increased levels of the GLT1 glutamate transporter in the basal ganglia of the dyskinetic 6-OHDA-lesioned rat (Jonkers et al., 2002; Robelet et al., 2004; Dupre et al., 2011). Accordingly, decreasing glutamate release was proposed to be an effective way to alleviate dyskinesia. Thus, the glutamate release inhibitor riluzole alleviated established AIMs in the 6-OHDA-

lesioned mouse (Lundblad et al., 2005) and rat (Dekundy et al., 2007) and decreased duration of on-time with severe dyskinesia in a small pilot study (Merims et al., 1999) but was ineffective in another (Bara-Jimenez et al., 2006). Similarly, another glutamate release inhibitor, naftazone, alleviated established dyskinesia in a *N*-of-1 trial (Rascol et al., 2011). Neither riluzole nor naftazone impaired L-DOPA antiparkinsonian benefit. Although promising, these results remain largely preliminary and additional better controlled studies are needed to confirm the value of reducing glutamate release in LID.

E. Altered Synaptic Plasticity

In accordance with changes in glutamatergic transmission, there is evidence for altered synaptic plasticity at the corticostriatal synapse in dyskinesia. Thus, in striatal slices prepared from dyskinetic 6-OHDA-lesioned rats, long-term potentiation (LTP) appeared normal, but subsequent depotentiation was impaired (Picconi et al., 2003, 2008). In contrast, depotentiation was not impaired in striatal slices from 6-OHDA-lesioned rats treated chronically with low dose L-DOPA that did not develop AIMs (Picconi et al., 2008). There is also evidence of altered corticostriatal long-term depression (LTD) in the dyskinetic 6-OHDA-lesioned rat (Picconi et al., 2011). However, these data, except those from Picconi et al., (2008) in which the animals were killed while in the on-state, were obtained *ex vivo* in striatal slices without L-DOPA or dopamine added to bath and thus probably represent a correlate of a primed patient off L-DOPA treatment. However, even in the study in which animals were killed in the on-state, the time required to prepare the slices and the subsequent perfusion with artificial cerebrospinal fluid (CSF) might lead to a condition akin to the off-state. The mechanisms defined might thus represent a component of the process responsible for priming and maintaining the striatum in the primed state, as they are consistent with corticostriatal overactivity. However, the situation is not analogous to that when L-DOPA is present and LID observable. Although technically challenging, further studies are required to assess plasticity *in vivo* in the on-state to assess a role for abnormal plasticity in the expression of LID.

Indirect evidence of altered LTD was also provided by pharmacological studies that targeted the nitric oxide synthase (NOS). Nitric oxide (NO) is involved in corticostriatal LTD (Calabresi et al., 1999), and stimulation of D₁ receptors increases NO efflux in the striatum (Sammur et al., 2006). NOS inhibitors were demonstrated to reduce established LID in the MPTP-lesioned marmoset (Jenner, 2008) and the 6-OHDA-lesioned rat (Padovan-Neto et al., 2011). Although no formal assessment of neuronal plasticity was performed in those studies, restoring normal corticostriatal LTD might be a mechanism whereby NOS

inhibitors alleviated LID and LI-AIMs, though further studies are needed to confirm that hypothesis.

Very few clinical studies have evaluated synaptic plasticity in LID in PD patients, possibly because the tools to do so are, at present, limited, and invasive approaches would undoubtedly raise ethical questions. However, repetitive transcranial magnetic stimulation (Barker et al., 1985) is a technique that is being increasingly used and that has the ability to provide insights on synaptic plasticity, though it is limited to the processes occurring in the cortex, thus being insensitive to subcortical changes (Fitzgerald et al., 2006). A study using repetitive transcranial magnetic stimulation has demonstrated deficient LTP-like plasticity in the motor cortex of dyskinetic PD patients (Morgante et al., 2006). In that study, subjects were tested 1 hour after L-DOPA intake and were in the on-state. The results of that study are difficult to reconcile with the general idea of overactivity of the cortex in LID expanded above, and further studies are needed to see how reduced LTP in the motor cortex might contribute to LID.

The results of the aforementioned studies are very informative in showing altered plasticity in LID, but they do not establish abnormal synaptic plasticity as an etiological factor or a consequence of LID. There is, however, evidence that altered synaptic plasticity might be a critical condition underlying the development of dyskinesia. Thus, it appears that synaptic pruning is a necessary condition for AIMs to develop. Indeed, antagonizing the calcium channels Ca_v1.2–1.3 with isradipine as early as the day after administration of 6-OHDA prevented the pruning of dendritic spines on striatal medium spiny neurons as well as the emergence of AIMs upon chronic L-DOPA treatment (Schuster et al., 2009). In contrast, initiating isradipine treatment at a later stage, where significant pruning of dendritic spines had occurred, was insufficient to prevent AIMs development upon chronic dopaminergic therapy (Schuster et al., 2009). Starting isradipine concomitantly with L-DOPA was also ineffective at preventing the development of AIMs (Rylander et al., 2009). At the moment, the results linking synaptic pruning and LID are limited to the 6-OHDA-lesioned rat model of PD, but should these results to be replicated in a higher model such as the MPTP-lesioned NHP, they might have some important therapeutic implications, as nondopaminergic medications such as dihydropyridine calcium channel blockers might have to be started as soon as diagnosis is made to preserve as many dendritic spines as possible and delay or prevent the development of dyskinesia. As such medications are widely used for other indications, they would be readily amenable to clinical trials. However, as dihydropyridine calcium channel blockers are effective antihypertensive agents (Cutler, 1998), their efficacy might be limited in advanced PD, where

orthostatic hypotension is frequent (Senard et al., 2001).

VI. The Opioid System

A. *Preproenkephalin and Preprodynorphin*

The high molecular weight opioid precursor preproenkephalin-A (PPE-A) is expressed by striatopallidal neurons of the indirect pathway, whereas preproenkephalin-B (PPE-B; sometimes termed preprodynorphin, PPD) is expressed on striatonigral neurons of the direct pathway (see below). PPE-A can be processed to generate leucine (Leu)-enkephalin and methionine (Met)-enkephalin (Noda et al., 1982), whereas PPE-B contains the determinants for α - and β -neoendorphin, dynorphin-A, and leumorphin (dynorphin-B and related peptides of shorter length) (Horikawa et al., 1983). Proopiomelanocortin (POMC) is another opioid precursor and codes for β -endorphin (Chretien et al., 1979).

Endogenous opioid peptides exert their biologic effects through binding to opioid receptors. Leu- and Met-enkephalin are considered the endogenous ligands of δ -opioid receptors (Quock et al., 1999), whereas the dynorphins, the neoendorphins, and leumorphin bind primarily to κ -opioid receptors (Chavkin et al., 1982), and β -endorphin exhibits high affinity for μ -opioid receptors (Wang et al., 1993). The endomorphins (endomorphin-1 and -2) are endogenous opioid peptides that exhibit high affinity for the μ -opioid receptors (Fichna et al., 2007), but their opioid precursor has not been identified yet, and their role in parkinsonism and dyskinesia, if any, has yet to be determined. It is noteworthy that all endogenous opioids exhibit a preferential affinity for one type of receptor, but also bind to the others (Corbett et al., 2006). Nociceptin (orphanin FQ) is a neuropeptide that binds to the nociceptin receptor (also referred to as the orphanin FQ receptor or κ -type 3 opioid receptor) (Mollereau et al., 1996). The nociceptin receptor has a high degree of homology to each of μ -, δ -, and κ -opioid receptors, but endogenous opioids, with the exception of nociceptin, exhibit little or no affinity for it (Henderson and McKnight, 1997). Other opioid receptors have been identified, such as the opioid growth factor receptor (initially termed zeta-opioid receptor) (Zagon et al., 2000), whereas whether ε and λ receptors belong to the opioid receptors remains unsettled (<http://www.iuphar-db.org/DATABASE/FamilyIntroductionForward?familyId=50>); their role in parkinsonism and LID, if any, has yet to be determined.

In PD and dyskinesia, several postmortem studies have assessed levels of PPE-A and PPE-B mRNA. Given their respective patterns of expression, PPE-A mRNA is used as a marker of activity of the indirect pathway, whereas PPE-B mRNA is used to study the direct pathway (Bezard et al., 2001; Ravenscroft et al.,

2004). In contrast, POMC has been relatively unexplored (Halabe Bucay, 2008). Indeed, the fate of β -endorphin in PD and dyskinesia is unclear, as one study found higher plasma levels of β -endorphin in PD patients treated with L-DOPA or not (Franceschi et al., 1986), whereas another study found unchanged plasma levels and reduced CSF levels of β -endorphin (Nappi et al., 1985). Neither of these two studies established correlations with dyskinesia. Many pharmacological studies have studied modulation of opioid receptors; they will be summarized in the next subsection. The major points discussed in this section are summarized in Table 4.

Data regarding PPE-A expression following chronic L-DOPA administration and development of AIMs in rodents or LID in NHPs or PD patients can initially appear contradictory, although it is now clear that they need to be interpreted in light of information on the time of death with respect to last dose of L-DOPA. In the rat, 6-OHDA lesion increased levels of PPE-A mRNA and subsequent treatment with L-DOPA—last dose given 24 hours before death—reversed this increase (Zeng et al., 1995). In contrast, in another study in which rats were killed 2 days after last dose, chronic treatment with L-DOPA resulted in a further increase in PPE-A mRNA (Westin et al., 2001).

In the common marmoset, MPTP administration led to increased striatal levels of PPE-A mRNA (Tel et al., 2002). Following chronic treatment with L-DOPA and the development of dyskinesia, PPE-A mRNA levels were reduced (but time of administration with respect to killing was not defined) (Tel et al., 2002). Similar changes in PPE-A mRNA levels were encountered in one study in the macaque following MPTP lesioning, being increased, and subsequent treatment with L-DOPA, decreased (although again, the time of administration with respect to killing was not defined) (Herrero et al., 1995). In contrast, another study performed in the macaque in which the animals were killed in the off-state, found increased striatal PPE-A mRNA levels in L-DOPA-treated dyskinetic MPTP-lesioned macaques compared with L-DOPA-naive, parkinsonian macaques and nonparkinsonian animals (Tamim et al., 2010). In contrast, in the MPTP-lesioned squirrel monkey, killed 3–4 hours or 3 days after L-DOPA administration, PPE-A mRNA levels were increased in the striatum compared with unlesioned animals, and levels remained high after L-DOPA treatment and emergence of dyskinesia (Quik et al., 2002). The situation in PD patients thus appears similar to that in the squirrel monkey study, because PPE-A mRNA was increased in the putamen of dyskinetic L-DOPA-treated subjects (Calon et al., 2002a), presumably because there was significant delay in both studies between last treatment and analysis of expression. Interpreting data from these studies with respect to dyskinesia is thus difficult, but

TABLE 4
The opioid system in dyskinesia

- Changes in PPE-A mRNA levels in the striatum of the 6-OHDA-lesioned rat and MPTP-lesioned NHP killed in the off-state are inconsistent.
- Striatal PPE-B mRNA levels are increased after chronic L-DOPA therapy in the 6-OHDA-lesioned rat and the MPTP-lesioned NHP, whether killed in the on- or off-state.
- μ -Receptor levels are reduced in the striatum and GPi of dyskinetic NHPs killed in the on-state.
- μ -Mediated signaling is overactive in the striatum and GPi of MPTP-lesioned NHPs killed in the on-state.
- The selective μ antagonists cyprodine and ADL5510 in the MPTP-lesioned NHP reduce dyskinesia.
- δ -Receptor levels are unchanged in the striatum of dyskinetic NHPs killed in the on-state.
- δ -Mediated signaling is overactive in the striatum of MPTP-lesioned NHPs killed in the on-state.
- The selective δ antagonist naltrindole reduces dyskinesia in the MPTP-lesioned NHP.
- κ -Receptor levels are reduced in the GPe and GPi of dyskinetic NHPs killed in the on-state.
- κ -Mediated signaling is overactive in the caudate nucleus and motor cortex of MPTP-lesioned NHPs killed in the on-state.
- The selective κ agonist U50-488 reduces dyskinesia in the MPTP-lesioned NHP.
- Morphine and meperidine alleviate dyskinesia in the MPTP-lesioned NHP.
- Naloxone and naltrexone did not demonstrate convincing antidyskinetic efficacy in small clinical studies.

on balance, we would suggest that in the unprimed parkinsonian state off treatment, PPE-A expression is increased compared with the normal state and that priming alters this. Thus, in the primed situation on treatment with dyskinesia, PPE-A expression, elevated by parkinsonism, is reduced, and in the primed state but off treatment, PPE-A expression is elevated above that in the untreated parkinsonian state.

Similar issues, with respect to timing of assessment of expression of PPE-B and L-DOPA administration also make it difficult to draw strong conclusions as to how changes in PPE-B expression might be associated with priming and dyskinesia. In the 6-OHDA-lesioned rat, PPE-B mRNA levels were decreased in the striatum in the untreated state, whereas chronic treatment with L-DOPA—last dose administered 2 days before death—led to an increase in PPE-B mRNA levels compared with the levels encountered in the nonparkinsonian and L-DOPA-naive parkinsonian states (Westin et al., 2001). In another study, also performed in the rat, 6-OHDA lesion did not result in a decrease in striatal PPE-B mRNA levels (Bishop et al., 2009). However, when rats were killed 2 hours after L-DOPA administration, i.e., in the on-state and during AIMs expression, PPE-B mRNA levels were significantly elevated compared with L-DOPA-naive animals or nonparkinsonian animals (Bishop et al., 2009).

In the common marmoset, MPTP administration reduced striatal levels of PPE-B mRNA (Tel et al., 2002). Following chronic treatment with L-DOPA and the development of dyskinesia, the decrease in PPE-B mRNA levels was reversed (but time of L-DOPA administration with respect to killing was not defined) (Tel et al., 2002). A study in which the animals were killed in the off-state found increased PPE-B levels in the striatum of L-DOPA-treated dyskinetic MPTP-lesioned macaques compared with L-DOPA-naive parkinsonian macaques and nonparkinsonian animals (Tamim et al., 2010). In another study performed in the MPTP-lesioned macaque and in human PD patients, striatal PPE-B mRNA levels were increased in dyskinetic macaques—killed in the on-state after apomorphine injection— and primed dyskinetic PD

patients who likely died while in the off-state (Henry et al., 2003).

PPE-B is often regarded as a molecular change associated with dyskinesia. Although there is a clear correlation with the primed state, this conception has to be re-examined in light of the aforementioned studies. Thus, it appears that indeed PPE-B mRNA levels are elevated whether the animals are killed or patients die in the on- or off-state, i.e., during dyskinesia expression or not. As such, striatal PPE-B should be regarded as a molecular marker of chronic L-DOPA therapy, but should not be seen as a specific marker of dyskinesia, because the expression of the dyskinetic phenotype does not seem required for striatal PPE-B mRNA upregulation.

In contrast to their precursors, endogenous opioids have seldom been studied in the brain of animal models of PD or of PD patients. Thus, a postmortem study assessed endogenous morphine-like immunoreactivity in experimental parkinsonism and idiopathic PD, but dyskinesia was not the primary aim of the study (Charron et al., 2011). However, a PET study using the nonselective opioid antagonist [^{11}C]diprenorphine as the radiotracer found reduced binding levels in the putamen and thalamus of dyskinetic PD patients compared with control individuals and non-dyskinetic PD patients as well as reduced binding levels in the caudate of PD patients compared with control individuals (Piccini et al., 1997). In that last study, patients were scanned in the off-state. However, reduced [^{11}C]diprenorphine binding in dyskinetic PD patients suggests increased levels of endogenous opioids in the striatum and thalamus of dyskinetic subjects, although it is impossible to be more specific as to which endogenous opioid(s) might be elevated. It nevertheless tallies well with the observations made in pharmacological studies in which opioid receptor antagonists alleviated LID (see next subsection).

B. Opioid Receptors

Alterations in the opioid system at the receptor level are also encountered in the parkinsonian and dyskinetic phenotypes. Thus, compared with normal

animals, μ -opioid receptor levels were significantly reduced in the ventrolateral putamen and GPi of MPTP-lesioned NHPs treated chronically with L-DOPA—last dose administered 1 hour before being killed—regardless of their dyskinetic status (Aubert et al., 2007), whereas they were unaffected by MPTP administration alone. μ -Opioid receptors were decreased in the GPe of untreated MPTP-lesioned NHPs and this decrease was partly reversed by L-DOPA administration, regardless of the occurrence of dyskinesia (Aubert et al., 2007). In the 6-OHDA-lesioned rat, μ receptors were increased in the premotor and motor cortex of dyskinetic animals when compared with L-DOPA-treated nondyskinetic animals—last dose administered 3 days before death—whereas their levels in the basal ganglia were reduced in the parkinsonian state but unaltered by L-DOPA, whether AIMs were present or not (Johansson et al., 2001). In PD patients treated chronically with L-DOPA, μ -receptor binding levels were reduced in both the caudate and putamen compared with nonparkinsonian individuals (Fernandez et al., 1994). Thus, there appears to be variability in μ -receptor levels depending on the area of the brain studied and the time of death, and it is difficult to correlate μ -receptor levels with the dyskinetic phenotype.

However, a postmortem study that used [35 S]GTP γ S as a marker of G protein-coupled receptor signaling found hyperactive μ -mediated opioid signal transduction in the striatum and GPi of dyskinetic MPTP-lesioned NHPs killed 3 hours after last administration of L-DOPA (Chen et al., 2005). This functional study points out that absolute levels of μ -opioid receptors are not necessarily a good marker of their activity in the dyskinetic state and suggests that other factors, such as phosphorylation status or membrane versus subcellular distribution, must also be altered in the dyskinetic state. Pharmacological studies have provided supportive evidence of increased μ -mediated opioid transmission in the dyskinetic state. Thus, the μ -receptor antagonists cyprodine and ADL5510 both alleviated LID in the MPTP-lesioned NHP without affecting L-DOPA antiparkinsonian efficacy (Henry et al., 2001; Koprach et al., 2011).

As with μ receptors, δ -receptor numbers are not found to be altered in any consistent way across brain regions in LID. However, enhanced signaling at δ receptors appears to be a mechanism by which they could contribute to the expression of LID. Thus, in the MPTP-lesioned NHP killed in the on-state, in no brain region assessed were δ -opioid receptor levels significantly different to those in control animals, regardless of L-DOPA administration (Aubert et al., 2007; Hallett and Brotchie, 2007). However, δ -receptor levels were increased in both the motor and premotor cortex of dyskinetic 6-OHDA-lesioned rats killed in the off-state compared with nondyskinetic animals (Johansson

et al., 2001). Those findings in both the NHP and the rat are in contrast to those in PD patients treated chronically with L-DOPA where δ -receptor binding levels were decreased in the putamen compared with nonparkinsonian individuals (Fernandez et al., 1994). However, in the MPTP-lesioned NHP, there is evidence of increased δ -mediated signaling in the dyskinetic state. Thus, using [35 S]GTP γ S, a postmortem study in which the animals were killed 3 hours after L-DOPA administration found enhanced δ -mediated opioid signaling in the striatum of dyskinetic MPTP-lesioned NHPs (Chen et al., 2005). In agreement with hyperactive δ -mediated transmission in dyskinesia, the δ -receptor antagonist naltrindole reduced LID in the MPTP-lesioned NHP without affecting L-DOPA antiparkinsonian efficacy (Henry et al., 2001).

κ Receptors were unaltered in the untreated MPTP-lesioned NHP, but their levels were reduced in both the GPe and GPi in animals treated chronically with L-DOPA and killed 1 hour after last dose (Aubert et al., 2007). In contrast, in the dyskinetic 6-OHDA-lesioned rat killed 3 days after last administration of L-DOPA, κ -receptor levels were decreased in the striatum and SN of dyskinetic animals, but unaltered in the GP, compared with nondyskinetic 6-OHDA-lesioned rats (Johansson et al., 2001). As for μ and δ receptors, in the NHP, [35 S]GTP γ S binding suggested hyperactive κ -mediated signaling in the caudate nucleus and motor cortex of dyskinetic MPTP-lesioned NHPs killed 3 hours after L-DOPA administration (Chen et al., 2005). Paradoxically, despite overactive κ -mediated signaling in LID, antagonizing κ receptors with norbinaltorphimine did not reduce LID in the MPTP-lesioned NHP (Henry et al., 2001), whereas stimulation of κ receptors with U50-488 reduced established AIMs in the 6-OHDA-lesioned rat and dyskinesia in the MPTP-lesioned squirrel monkey, although at the expense of impairing L-DOPA antiparkinsonian action (Cox et al., 2007).

Perhaps highlighting the importance of κ -mediated neurotransmission over μ and δ transmissions in the acute expression of LID, nonsubtype selective stimulation of opioid receptors with morphine alleviated established LID as well as dyskinesia elicited by selective stimulation of either D₁ or D₂ receptors in the MPTP-lesioned NHP (Samadi et al., 2004), whereas meperidine alleviated LID in the MPTP-lesioned NHP (Gomez-Mancilla and Bedard, 1993). Neither morphine nor meperidine adversely affected the antiparkinsonian action of L-DOPA.

The antidyskinetic efficacy of nonsubtype selective opioid receptor antagonists has also been evaluated in preclinical and clinical studies. Thus, the nonselective opioid receptor antagonist naloxone alleviated established LI-AIMs in the 6-OHDA-lesioned rat (Lundblad et al., 2002), although it was ineffective in the MPTP-lesioned macaque (Gomez-Mancilla and Bedard, 1993),

whereas naltrexone, another nonselective opioid antagonist, alleviated LID in the MPTP-lesioned marmoset (Henry et al., 2001). In clinical settings, naltrexone (Rascol et al., 1994a; Manson et al., 2001) did not produce antidyskinetic effects consistent between studies, whereas naloxone was ineffective in a controlled study (Fox et al., 2004). The lack of clear efficacy of nonsubtype selective opioid receptor antagonists in the clinic may reflect the fact that the antidyskinetic benefit conferred by blocking μ and δ receptors was offset by blockade of κ receptors.

If the failure of nonsubtype selective opioid antagonists to alleviate LID in clinical trials is indeed due to their blockade of κ receptors and if the antidyskinetic efficacy of the nonsubtype selective opioid agonists is primarily mediated via an agonist effect at κ receptors, then selective stimulation of κ receptors might be a promising, yet largely unexplored, antidyskinetic target.

To our knowledge, only one study examined blockade of the nociceptin/orphanin FQ receptor to alleviate LID. In that study, J-113397 worsened LID in the MPTP-lesioned NHP (Visanji et al., 2008).

Thus, selective modulation of the opioid system appears a promising way to alleviate LID by antagonizing μ and δ receptors or perhaps by stimulating κ receptors, yet several questions remain. For instance, although postmortem studies have suggested overactive opioid transmission within the basal ganglia in the dyskinetic state, these studies do not tally well with other postmortem studies that have demonstrated reduced receptor levels, thereby suggesting that changes beyond numerical regulation of opioid receptors such as abnormal phosphorylation or neuronal distribution are also likely to contribute to the dyskinetic phenotype. Moreover, why would stimulation of κ receptors alleviate LID when there is evidence of enhanced striatal κ -mediated signaling in dyskinesia? It is possible, but unproven, that increased κ -mediated transmission in LID is in fact an endogenous compensatory mechanism that is ineffective under normal circumstances, but which becomes effective when enhanced with κ agonists. Additionally, the precise effects of modulating the different opioid receptors within the basal ganglia on GABAergic, glutamatergic, and dopaminergic transmissions remain unknown.

VII. The Serotonergic System

The serotonergic system has been far less studied than the dopaminergic and glutamatergic systems in LID, although it is believed to play a key role in the pathophysiology of LID. However, serotonin (5-HT) itself does not appear to play a determinant role in the etiology of LID, and the serotonergic system appears more as a vector whereby abnormal dopaminergic and

glutamatergic transmissions occur in the striatum. As such, modulation of the 5-HT system in LID appears to be a way to modulate the two neurotransmitters at the heart of the dyskinetic phenotype, dopamine and glutamate. Moreover, if there is pharmacological and postmortem evidence indicating an involvement of the 5-HT system in the pathophysiology of LID, the mechanisms underlying this involvement are largely unknown. Indeed, very little is known regarding the membrane versus intracellular localization or the phosphorylation state of the different 5-HT receptors or the 5-HT transporter (SERT) in dyskinesia. Likewise, the intracellular signaling after binding to 5-HT receptors or transporter in the dyskinetic state also remains unexplored, and forthcoming studies investigating these mechanisms are needed. An exhaustive review article about the serotonergic system in PD and dyskinesia was recently published (Huot et al., 2011a).

A. 5-HT_{1A/1B} Receptors

Both serotonergic type 1A and type 1B (5-HT_{1A} and 5-HT_{1B}) receptors are coupled to a G_{i/o} protein (Nichols and Nichols, 2008). They have been extensively studied in PD and dyskinesia, and anatomic sites of action and pharmacological mechanisms underlying their antidyskinetic effect have been identified. Thus, serotonergic raphestriatal fibers are equipped with the enzyme AADC (Arai et al., 1996) and can therefore synthesize dopamine from L-DOPA (Gershanik et al., 1978; Tison et al., 1991; Arai et al., 1994, 1995; Tanaka et al., 1999; Maeda et al., 2005). 5-HT terminals also participate in the reuptake of synaptic dopamine (Berger, 1978; Berger and Glowinski, 1978). Following degeneration of the nigrostriatal system, raphestriatal serotonergic terminals were demonstrated to release dopamine, which acts as a “false neurotransmitter,” i.e., in an environment devoid of the autoregulatory mechanisms required for physiologic dopaminergic transmission, and this phenomenon was demonstrated to be a key determinant in the development and expression of LID (Carta et al., 2007, 2008a, b; Nevalainen et al., 2011). Accordingly, in the 6-OHDA-lesioned rat, administration of L-DOPA to animals with dual lesions of the medial forebrain bundle and rostral raphe nucleus did not lead to the development of AIMs (Eskow et al., 2009). Further experimental evidence as to the involvement of the 5-HT system in LID came from experiments performed in the 6-OHDA-lesioned rat in which intrastriatal grafts of serotonergic neurons exacerbated established AIMs in primed animals (Carlsson et al., 2007). In agreement with an abnormal release of dopamine in the striatum in motor complications, neuroimaging studies performed in PD patients have provided evidence in favor of nonphysiologic dopaminergic transmission and altered pharmacokinetics of L-DOPA (de la Fuente-Fernandez et al., 2001). Stimulation of 5-HT_{1A} receptors alone or in

combination with 5-HT_{1B} receptors reduces raphes-triatal dopamine release (Eskow et al., 2009; Lindgren et al., 2010) and is believed to be a key mechanism whereby 5-HT_{1A} agonists alleviate dyskinesia.

However, the antidyskinetic actions of 5-HT_{1A} agonists are not solely mediated by their effect on raphes-triatal dopamine release. Thus, in the 6-OHDA-lesioned rat, the antidyskinetic effect of 5-HT_{1A} receptor stimulation was paralleled by a reduction of striatal glutamate levels (Dupre et al., 2011), thereby linking 5-HT_{1A}-mediated and glutamatergic transmissions. Direct stimulation of cortical 5-HT_{1A} receptors also alleviated LI-AIMs in the 6-OHDA-lesioned rat (Ostock et al., 2011), so reduction of corticostriatal glutamate release likely represents a second mechanism by which 5-HT_{1A} agonists alleviate dyskinesia. At the postmortem level, a study performed in the MPTP-lesioned macaque found altered 5-HT_{1A} receptor levels in the cortex and striatum of dyskinetic macaques treated chronically with L-DOPA killed at peak dyskinesia expression, also suggesting altered corticostriatal 5-HT_{1A}-mediated neurotransmission in the dyskinetic state (Huot et al., 2012c).

Experimental evidence points toward an additional mechanism or site of action for the antidyskinetic effect of 5-HT_{1A} agonists. Thus, stimulation of 5-HT_{1A} receptors alleviated AIMs induced by the D₁ agonist SKF-81,297 independently of striatal glutamate levels (Dupre et al., 2011). As dopamine agonists directly stimulate dopamine receptors, a reduction in raphes-triatal L-DOPA-derived dopamine release is unlikely to play a key role in 5-HT_{1A}-mediated reduction of SKF-81,297-induced AIMs. Those data suggest different pathophysiological mechanisms underlying L-DOPA-induced and dopamine agonist-induced dyskinesia (Huot and Brotchie, 2011) or an additional site of action of 5-HT_{1A} agonists within the basal ganglia circuit, for instance the thalamocortical synapse (Huot et al., 2011b). The STN might well be another site of action of 5-HT_{1A} agonists, as suggested by a study conducted in the 6-OHDA-lesioned rat in which injection of the nonselective 5-HT_{1A} agonist sarizotan in the STN alleviated LI-AIMs (Marin et al., 2009b). However, an intra-STN site of action is hard to reconcile with the classic model of the basal ganglia, as it would ultimately disinhibit glutamatergic thalamocortical transmission, thereby exacerbating LID, yet a reduction was observed experimentally.

However, despite the strong antidyskinetic mechanisms highlighted above, the antidyskinetic efficacy of 5-HT_{1A} agonists has been rather disappointing in clinical settings, and there is also evidence that they may impair L-DOPA antiparkinsonian action. Indeed, a reduction of L-DOPA antiparkinsonian action was encountered in the NHP with *R*(+)-8-OH-DPAT (Iravani et al., 2006) and sarizotan (Gregoire et al., 2009) and in clinical trials with tandospirone (Kannari et al.,

2002) and sarizotan (Goetz et al., 2007). Moreover, two phase III studies performed with sarizotan failed to show any antidyskinetic efficacy when compared with placebo (Muller et al., 2006; Rascol et al., 2006b; Goetz et al., 2008); one of several reasons for this may be that doses were selected low to avoid loss of antiparkinsonian benefit and in so-doing reduced antidyskinetic efficacy to a level that could not be clearly demonstrated. Similarly, the antidyskinetic efficacy of the 5-HT_{1A} agonist and D₂ antagonist bupirone has been conflicting in clinical studies, and the antiparkinsonian efficacy of L-DOPA has been impaired in several patients (Hammerstad et al., 1986; Kleedorfer et al., 1991).

It has been suggested recently that to effectively alleviate dyskinesia without exacerbating parkinsonism with 5-HT_{1A} agonists, it might be necessary to stimulate specific subpopulations of 5-HT_{1A} receptors. Indeed, stimulating postsynaptic corticostriatal 5-HT_{1A} receptors along the direct pathway would alleviate LID without impairing L-DOPA antiparkinsonian efficacy, whereas stimulating presynaptic 5-HT_{1A} receptors at the thalamocortical synapse would result in reduced cortical excitation, which might impair L-DOPA antiparkinsonian action (Huot et al., 2011b). 5-HT_{1A} agonists displaying such anatomic selectivity are currently under development (Newman-Tancredi, 2011), although none is available clinically. Another approach to alleviate LID using 5-HT_{1A} agonists and possibly minimizing the effect on L-DOPA antiparkinsonian action might be to combine subthreshold doses of 5-HT_{1A} and 5-HT_{1B} agonists, which was demonstrated to be more effective than stimulation of each receptor alone to reduce LID in the MPTP-lesioned macaque (Munoz et al., 2008).

There is also evidence that stimulation of 5-HT_{1A/1B} receptors interferes with the priming process, leading to the expression of LID. Thus, *de novo* administration of combined 5-HT_{1A/1B} agonists with L-DOPA reduced the development of AIMs in the 6-OHDA-lesioned rat (Munoz et al., 2008). The mechanisms underlying this reduction in priming are not fully elucidated but are likely to be related, although not necessarily exclusive, to an interference with the dopamine- and glutamate-mediated priming processes mentioned in the previous sections.

Although mechanistic studies assessing 5-HT_{1B} receptors in LID are fewer than those for 5-HT_{1A} receptors, the adaptor protein p11, a component involved in the expression of 5-HT_{1B} receptors at cell surface (Svenningsson and Greengard, 2007), was demonstrated to play an important role in the antidyskinetic action of stimulating 5-HT_{1B} receptors in the 6-OHDA-lesioned mouse with established AIMs (Zhang et al., 2008b). To conclude this section, it is important to point out that, despite sharing 93% amino acid homology, primate and rodent 5-HT_{1B} receptors exhibit different pharmacological profiles (Adham

et al., 1992). Such different pharmacological profiles may make the transition difficult from rodent to NHP or human.

B. 5-HT_{2A} Receptors

Serotonergic type 2A (5-HT_{2A}) receptors are Gαq protein-coupled receptors (Nichols and Nichols, 2008). 5-HT_{2A} receptors have been extensively studied in PD and LID, and postmortem and pharmacological studies have provided indirect evidence of altered 5-HT_{2A}-mediated neurotransmission in the dyskinetic state. Thus, in the MPTP-lesioned macaque killed 1 hour after L-DOPA administration, 5-HT_{2A} receptor levels were increased in the motor cortex and striatum of dyskinetic animals (Huot et al., 2012b). Moreover, antagonizing 5-HT_{2A} receptors with the atypical antipsychotics clozapine and quetiapine led to a reduction of established AIMs severity in the 6-OHDA-lesioned rat (Lundblad et al., 2002) and LID in the MPTP-lesioned primate (Oh et al., 2002; Visanji et al., 2006). It should be noted though that both clozapine and quetiapine bind to several other serotonergic and nonserotonergic receptors (Huot et al., 2011a) and that, although their antidyskinetic efficacy is usually attributed to antagonizing 5-HT_{2A} receptors, a contribution of these other targets cannot be excluded, therefore limiting the interpretation of these pharmacological studies. More selective compounds such as the R-enantiomer of 3,4-methylenedioxymethamphetamine (MDMA) (Huot et al., 2011c) and pimavanserin (ACP-103) (Vanover et al., 2008) also alleviated LID in the MPTP-lesioned NHP. In clinical settings, clozapine (Durif et al., 2004) as well as the more selective 5-HT_{2A} antagonists ritanserin (Maertens de Noordhout and Delwaide, 1986; Meco et al., 1988) and pimavanserin (Roberts, 2006) all alleviated dyskinesia.

Unlike 5-HT_{1A} receptors, the mechanisms underlying the antidyskinetic action of 5-HT_{2A} antagonists remain largely unexplored, but it has been suggested that modulation of nigrostriatal dopamine release and corticostriatal glutamate release might both play a role (Huot et al., 2011b, 2012b). With respect to nigrostriatal dopaminergic transmission, 5-HT_{2A} receptor activation increases nigrostriatal dopamine release (Lucas and Spampinato, 2000), and, as a corollary, blocking 5-HT_{2A} receptors should decrease nigrostriatal dopamine release. In vivo microdialysis studies in which a selective 5-HT_{2A} antagonist, for instance volinanserin, would be injected systemically in the SNc and in the striatum are needed to validate this hypothesis. The obvious problem of this hypothetical mechanism though is that reducing nigrostriatal dopamine transmission might lead to a reduction of L-DOPA antiparkinsonian action and, as such, 5-HT_{2A} antagonists might theoretically impair L-DOPA antiparkinsonian action. In clinical settings, both clozapine (Wolters et al., 1990) and quetiapine (Reddy et al.,

2002), as well as the more selective 5-HT_{2A} antagonist ritanserin, (Maertens de Noordhout and Delwaide, 1986; Meco et al., 1988) were reported to impair L-DOPA antiparkinsonian action and, as for 5-HT_{1A} agonists, 5-HT_{2A} antagonists might have a very narrow antidyskinetic window that might eventually limit their usefulness as antidyskinetic molecules. Studies with more selective 5-HT_{2A} antagonists are needed to investigate that possibility and, as for 5-HT_{1A} agonists, perhaps the ideal 5-HT_{2A} antagonist will have to block selectively certain subpopulations of 5-HT_{2A} receptors, such as those located on corticostriatal terminals (Huot et al., 2011b) to alleviate LID without impairing L-DOPA antiparkinsonian action. With respect to corticostriatal glutamate release, there is evidence that 5-HT_{2A}-mediated neurotransmission increases presynaptic glutamate release (Aghajanian and Marek, 1997) and postsynaptic NMDA-mediated depolarization (Neuman and Rahman, 1996). Accordingly, intrastriatal administration of the selective 5-HT_{2A} antagonist volinanserin to L-DOPA-naive MPTP-lesioned mice resulted in a reduction of striatal glutamate levels (Ansah et al., 2011). However, such a 5-HT_{2A}-mediated reduction in striatal glutamate levels has yet to be demonstrated in the L-DOPA-treated dyskinetic state.

C. Serotonin Transporter

The SERT could play a role in the expression of LID, although the data presented here may also be interpreted differently, as they suggest that manipulation of presynaptic and/or synaptic levels of 5-HT and/or dopamine (via SERT modulation or other mechanisms) plays a role in the expression of LID. Hence, chronic administration of the selective SERT inhibitor citalopram (Celexa) alleviated LI-AIMs in the 6-OHDA-lesioned rat (Kuan et al., 2008), whereas acute challenges of fluoxetine (Prozac) could not suppress established AIMs (Dekundy et al., 2007). At the clinical level, daily administration of fluoxetine over a fortnight alleviated apomorphine-induced dyskinesia compared with baseline (Durif et al., 1995). It remains unknown why only subchronic/chronic SERT modulation may exert an antidyskinetic effect, but this may have to do with depletion of presynaptic vesicles. Indeed, in the 6-OHDA-lesioned rat, there is a correlation between striatal SERT levels and AIMs severity (Rylander et al., 2010b) and in the MPTP-lesioned macaque, development of LID is associated with increased striatal SERT levels (Rylander et al., 2010b). In addition to participating in L-DOPA-derived dopamine release in the dyskinetic state, raphestriatal terminals, via a SERT-mediated mechanism, also participate in dopamine reuptake in the presynaptic terminal (Berger, 1978; Berger and Glowinski, 1978). It is therefore conceivable that acute inhibition of SERT did not alleviate AIMs, as it would increase synaptic levels of dopamine. However,

without SERT inhibition, dopamine would normally be taken up by the presynaptic terminals and stored in synaptic vesicles and eventually be released. With chronic SERT inhibition, this vesicle repackaging process cannot happen, because dopamine is degraded in the synaptic cleft and it is possible that that chronic SERT inhibition leads in fact to a relative depletion of presynaptic dopamine vesicles within raphestriatal terminals, thereby accounting for the antidyskinetic efficacy of chronic treatment with a SERT inhibitor. However, it should be emphasized that this explanation remains hypothetical and electron microscopic studies are needed to verify this hypothesis. Another explanation might involve a reduction in dopamine release mediated by presynaptic 5-HT_{1A} receptors (Yamato et al., 2001). These explanations might also account for the concerns of impairing L-DOPA antiparkinsonian action upon administration of selective SERT inhibitors (van de Vijver et al., 2002), although that issue remains controversial (Gony et al., 2003). To conclude on SERT inhibitors and dyskinesia, it should be emphasized that many trials have been performed with SERT inhibitors in PD and that only rarely have these reported an improvement in dyskinesia, although dyskinesia reduction was not necessarily an endpoint of these studies.

VIII. The GABAergic System

GABA is the major inhibitory neurotransmitter in the mammalian brain (Watanabe et al., 2002). GABA is synthesized from glutamate (Roberts and Frankel, 1950) via the enzyme glutamic acid decarboxylase (GAD) (Roberts and Frankel, 1951) and exerts its effects via two types of receptors, GABA_A and GABA_B. GABA_A receptors are present within the brain and are essentially ligand-gated ion channels permeable to the chloride anion (Mehta and Ticku, 1999), whereas GABA_B receptors are G protein-coupled receptors that are widely expressed in the brain (Bettler et al., 2004).

As discussed above, GABA transmission is central to the basal ganglia physiology. As such, modulating GABAergic transmission represents an attractive way to alleviate LID. For instance, enhancing GABAergic transmission from the GPi/SNr to the thalamus would result in inhibition of the thalamocortical pathway, which would decrease cortical excitation and alleviate LID. However, the ubiquity of GABA within the brain might lead to adverse effects or even mitigate possible antidyskinetic benefit while modulating this system.

Several postmortem studies that examined the GABAergic system in the dyskinetic state were performed. Unfortunately, in none of them were the animals killed in the on-state in which dyskinesia was maximal. As such, they are more informative about the fate of the GABA synthesizing enzyme or GABAergic receptors in the off-state following chronic L-DOPA

treatment and provide no information related to the acute expression of dyskinesia.

Changes in mRNA levels of the isoform 67 of the enzyme GAD (GAD₆₇) have been documented in the dyskinetic 6-OHDA-lesioned rat (Cenci et al., 1998). Thus, 3 days after last L-DOPA dose, GAD₆₇ levels were increased in the striatum and GP when dyskinetic rats were compared with nondyskinetic 6-OHDA-lesioned animals and control nonlesioned rats (Cenci et al., 1998). In contrast, in the dyskinetic macaque killed 24 hours after last dose of L-DOPA and in L-DOPA-treated PD patients, GAD₆₇ mRNA levels within the GP were not different from those encountered in nonparkinsonian animals and subjects (Herrero et al., 1996). In the striatum of the MPTP-lesioned macaque killed in the off-state, GAD₆₇ mRNA levels were increased and remained increased following chronic L-DOPA therapy and induction of dyskinesia compared with nonparkinsonian macaques (Levy et al., 1995a); in PD patients chronically treated with L-DOPA, GAD₆₇ mRNA levels were reduced in the striatum compared with healthy control subjects (Levy et al., 1995a). GAD isoform 65 (GAD₆₅) mRNA levels were also increased in the striatum of the MPTP-lesioned macaque treated chronically with L-DOPA killed in the off-state compared with normal controls and L-DOPA-untreated parkinsonian animals (Soghomonian et al., 1996).

Changes in GABA receptor levels have also been found in animals expressing dyskinesia when on but that were killed in the off-state. Thus, in the dyskinetic MPTP-lesioned NHP treated chronically with L-DOPA and killed in the off-state, GABA_A receptor levels were increased in the caudate and GPi (Calon et al., 1995) but decreased in the SNr (Samadi et al., 2008c). Chronic selective stimulation of D₁ or D₂ receptors with SKF-82,958 or cabergoline, respectively, did not change GABA_A binding levels in the striatum of MPTP-lesioned macaques, which remained low compared with controls, although, here again, the animals were killed when off-therapy (Calon et al., 1999). In the NHP, MPTP administration increased GABA_B receptor levels in the GPi, and this increase was maintained but not altered following treatment with the D₁ agonist SKF-82,958 and reduced following treatment with cabergoline (Calon et al., 2000). Changes in GABA receptors have been described in PD patients with motor complications. Thus, GABA_A receptor levels were increased in the GPe and GABA_B receptor levels were increased in the striatum of dyskinetic PD patients (Calon et al., 2003a).

Taken together, these studies are difficult to interpret and do not define a single important role of abnormal GABAergic transmission in LID. As mentioned above, results of these studies do not reflect changes associated with the acute expression of dyskinesia and, as such, further studies with different

terminal time points with respect to L-DOPA administration are needed. Moreover, they are somewhat contradictory with respect to our understanding of the basal ganglia organization. For instance, what might be the resulting effect of an increase in GABA_A receptor levels in the GPi coupled with a decrease in GABA_A receptor levels in the SNr with respect to inhibition of the thalamus? In addition, several questions remain unanswered. For example, is the increase in GABA_A receptor levels within the caudate nucleus on neurons forming the direct or the indirect pathway? Because the two pathways exert opposite effects on movement, this is an important missing piece of information. Additionally, very little is known about the membrane versus subcellular distribution or the phosphorylation status of GABA receptors in LID.

Very few pharmacological studies assessing the antidyskinetic potential of modulating GABAergic transmission in LID have been performed. In the MPTP-lesioned NHP, the positive GABA_A allosteric modulator diazepam alleviated LID without impairing L-DOPA antiparkinsonian action (Gomez-Mancilla and Bedard, 1993), whereas the GABA_B agonist baclofen did not alter LID severity, but reduced L-DOPA antiparkinsonian efficacy (Gomez-Mancilla and Bedard, 1993). Diazepam also exerted a mild antidyskinetic effect in a pilot clinical study (Pourcher et al., 1989). In a case report, zolpidem, a GABA_A-positive allosteric modulator (Smith et al., 2001), significantly alleviated LID (Ruzicka et al., 2000), although antidyskinetic effects of zolpidem were not reported in another clinical study (Daniele et al., 1997). Although the benzodiazepine diazepam effectively reduced dyskinesia in the MPTP-lesioned NHP and in a small clinical study, the use of benzodiazepines to alleviate LID might be complicated by the fact that these drugs are susceptible to tolerance, can cause sedation and dependence (Lader, 2008), and for these reasons, one might be reluctant to initiate them to alleviate LID. Additionally, the benzodiazepine clonazepam is frequently administered to PD patients to alleviate rapid eye movement sleep behavior disorder (RBD) (Boeve et al., 2004), and no improvement in LID has been reported following its administration. Although clonazepam administration in RBD is usually at bedtime, its half-life is between 19 and 60 hours in humans (Riss et al., 2008), and were benzodiazepines effective antidyskinetic agents, one might have expected clonazepam to reduce LID, yet this has not been reported. Accordingly, the anticonvulsant zonisamide, which enhances GABAergic transmission (Yoshida et al., 2005) and interacts weakly with GABA_A receptors (Mimaki et al., 1990), did not alleviate LID in a phase II study (Murata et al., 2007). However, it is noteworthy that zonisamide does not solely interact with the GABAergic system (Leppik, 2004) and its lack of effect on dyskinesia might be attributed to actions at

other sites. Nevertheless, on the basis of the literature summarized herein, stimulating the GABAergic system with the currently available agents does not appear as a promising antidyskinetic therapy.

IX. The Adenosine System

Adenosine is a purinergic neurotransmitter that exerts its effects via four types of receptors, adenosine 1, 2A, 2B, and 3 (A₁, A_{2A}, A_{2B}, and A₃, respectively) (Fredholm et al., 2001; Hasko et al., 2008). In PD and dyskinesia, attention has been drawn to A_{2A} receptors, which will be the primary focus of this section. A_{2A} receptors are primarily coupled to a G_s protein (Olah, 1997). A_{2A} receptors are located on striatal neurons forming the indirect pathway (Morelli et al., 2007; Schiffmann et al., 2007) and can form heterodimers with both D₂ (Canals et al., 2003) and mGlu5 (Ferre et al., 2002) receptors. A_{2A} receptors can modulate NMDA-mediated neurotransmission in striatal slices (Nash and Brotchie, 2000). Thus, A_{2A} receptors can modulate both dopaminergic and glutamatergic transmissions along the indirect pathway, whereas their influence on the activity of the direct pathway is limited.

In normal macaques chronically exposed to high doses of L-DOPA, thereby evoking severe dyskinesia even in the nonparkinsonian state, but killed 5 hours after L-DOPA administration when dyskinesia was not present, A_{2A} receptor mRNA levels were increased in the striatum compared with nondyskinetic animals (Zeng et al., 2000), suggesting an overactivity of the indirect pathway. However, as that study was performed in nonparkinsonian animals, its relevance to dyskinesia in chronic, therapeutically relevant administration of L-DOPA in the parkinsonian state remains to be established, a fortiori because the animals were not dyskinetic at the time of death.

In a study performed in the MPTP-lesioned macaque where dyskinetic animals were killed in the off-state, A_{2A} receptor binding levels were unchanged in the striatum of L-DOPA-treated, dyskinetic MPTP-lesioned macaques compared with L-DOPA-naive parkinsonian macaques or to nonparkinsonian animals (Morissette et al., 2006a). In idiopathic PD, A_{2A} receptor mRNA and receptor binding levels were increased in the putamen of dyskinetic patients compared with nondyskinetic patients (Calon et al., 2004) and were increased in the SNr when PD patients treated chronically with L-DOPA (dyskinetic status unknown) were compared with healthy controls (Hurley et al., 2000). A recent PET study found slightly different results. Indeed, A_{2A} binding levels were increased in the putamen of dyskinetic PD patients in the off-state compared with healthy individuals but not compared with drug-naive PD patients. A_{2A} binding levels were also elevated in the head of the caudate nucleus of dyskinetic PD

patients, but the increase did not reach statistical difference (Mishina et al., 2011).

Pharmacological studies with A_{2A} antagonists have focused on their potential to extend on-time duration, but a few studies have examined their potential antidyskinetic effect. Thus, in the MPTP-lesioned NHP, de novo administration of apomorphine combined with istradefylline attenuated development of apomorphine-induced dyskinesia (Bibbiani et al., 2003). In clinical settings, istradefylline enhanced the antiparkinsonian action of low-dose i.v. L-DOPA while eliciting significantly less dyskinesia than L-DOPA alone (Bara-Jimenez et al., 2003; Bibbiani et al., 2003). However, istradefylline slightly exacerbated dyskinesia severity in placebo-controlled studies (Hauser et al., 2008; LeWitt et al., 2008), but another A_{2A} antagonist, preladenant, significantly increased duration of on-time without troublesome dyskinesia in a phase II study (Hodgson et al., 2010).

Taken together, those studies do not point toward a critical involvement of A_{2A} receptors in the acute expression of LID, although they may be effective in reducing the priming occurring upon chronic administration of dopaminergic agents, perhaps because of a “sparing effect” whereby lower doses of dopaminergic drugs can be administered.

X. Cannabinoid Neurotransmission

A. Cannabinoid Receptors

Cannabinoid type 1 and 2 (CB_1 and CB_2) receptors mediate the actions of endogenous cannabinoids (Pertwee, 2006). CB_1 receptors are found mostly within the nervous system (Matsuda et al., 1990), whereas CB_2 receptors predominate outside of the nervous system (Munro et al., 1993). G protein-coupled receptor 18 (GPR18) (McHugh et al., 2010), G protein-coupled receptor 55 (GPR55) (Hiley and Kaup, 2007), and G protein-coupled receptor 119 (GPR119) (Overton et al., 2006) are also receptors that can be activated by endogenous cannabinoids, but they have been much less studied than CB_1 and CB_2 receptors. With respect to PD and LID, studies have focused on modulation of CB_1 receptors, which are abundant within the basal ganglia (Pacher et al., 2006), where they can modulate release of glutamate and GABA (Howlett et al., 2002). The transient receptor potential vanilloid type 1 (TRPV₁) also displays affinity for endocannabinoids (Ross, 2003) and has mostly been studied in the context of pharmacological experiments (see below).

In the rat, striatal levels of CB_1 receptor mRNA were unchanged following 6-OHDA lesion but increased following chronic L-DOPA therapy when the animals were killed 3 hours after last L-DOPA dose (Zeng et al., 1999). As no behavioral correlate was provided, it is difficult to link the increase in CB_1 receptor mRNA to the dyskinetic phenotype (Zeng et al., 1999). In the

MPTP-lesioned marmoset (time of death with respect to last dose of L-DOPA not mentioned), striatal CB_1 binding levels were not different to those in control animals but were lower than those encountered in MPTP-lesioned, L-DOPA-naive animals (Lastres-Becker et al., 2001). In PD patients treated chronically with L-DOPA, striatal CB_1 binding levels were increased compared with control subjects (Lastres-Becker et al., 2001). In another study, CB_1 mRNA levels were decreased in the striatum and GPe when L-DOPA-treated PD patients were compared with healthy controls (Hurley et al., 2003). Unfortunately, the dyskinetic status of the PD patients was not mentioned in these two studies, and it is difficult to draw strong conclusions related to dyskinesia from either. Moreover, in the case of cannabinoid receptors, their coupling to G proteins seems more important than their absolute levels to initiate a biologic response (Breivogel et al., 1997), and the results of these postmortem studies, which globally suggested but did not demonstrate enhanced CB_1 -mediated transmission in the striatum in dyskinesia, may not accurately reflect changes in cannabinoid transmission in LID. Therefore, studies focusing on the coupling of CB_1 receptors to G proteins or on the intracellular cascades initiated by CB_1 receptors in which animals would be killed in the on-state, are likely to be more informative as to the site of CB_1 involvement in LID.

Despite the inconclusive results of the studies discussed in the previous paragraph, pharmacological studies have suggested an involvement of the cannabinoid system in the expression of LID, although their interpretation is not straightforward. Thus, in the MPTP-lesioned NHP, the CB_1 antagonist rimonabant reduced established dyskinesia without impairing L-DOPA antiparkinsonian action (van der Stelt et al., 2005). However, another CB_1 antagonist, CE, did not alleviate LID in the MPTP-lesioned NHP (Cao et al., 2007). Paradoxically, stimulation of CB_1 receptors with the CB_1 agonist nabilone also alleviated LID in the MPTP-lesioned NHP (Fox et al., 2002a) and in a small clinical pilot study (Sieradzan et al., 2001). However, stimulation of CB_1 receptors with an ethanolic extract of *Cannabis sativa* produced no antidyskinetic effect in a small randomized-controlled trial (Carroll et al., 2004).

The mechanisms whereby CB_1 agonists might alleviate dyskinesia remain hypothetical but include a reduction of corticostriatal glutamatergic transmission (Brown et al., 2003) and a reduction of GABA reuptake in the GPi (Maneuf et al., 1996; Sieradzan et al., 2001; Fox et al., 2002b), although not all endogenous cannabinoids appear to mediate this latter effect (Venderova et al., 2005). However, these proposed antidyskinetic mechanisms for CB_1 agonists are difficult to reconcile with the antidyskinetic efficacy of the CB_1 antagonist rimonabant. The antidyskinetic

mechanism(s) of rimonabant remains unknown, but it was suggested that it could antagonize the effects of the endocannabinoid 2-arachidonyl glycerol (2-AG), the levels of which are elevated in the striatum of the dyskinetic NHP (van der Stelt et al., 2005). However, the mechanism(s) by which elevated striatal levels of 2-AG leads to dyskinesia is itself unclear and further research is needed to resolve the paradox of how both CB₁ agonists and antagonists appear to effectively reduce dyskinesia severity. Another paradox of the studies cited above is the variable antidyskinetic efficacy of different CB₁ agonists and antagonists. Indeed, CB₁ blockade with rimonabant but not with CE alleviates dyskinesia, whereas CB₁ stimulation with nabilone but not with an ethanolic extract of *C. sativa* reduces dyskinesia.

A potential explanation of these two paradoxes may be related to the importance of G protein coupling of CB₁ receptors in their biologic action highlighted above. Thus, it is possible that the different CB₁ modulators tested so far exhibit functional selectivity for different types of G proteins, a phenomenon referred to as “biased agonism” (Huot et al., 2011b; Kenakin, 2011; Newman-Tancredi, 2011). For instance, although they are both CB₁ agonists, nabilone and the ethanolic extract of *C. sativa* might well display affinity for different subpopulations of CB₁ receptors within the basal ganglia, leading to a reduction of LID in one case (nabilone) but not in the other (*C. sativa*). Functional selectivity might also explain the antidyskinetic efficacy of rimonabant and the lack of antidyskinetic efficacy of CE, two CB₁ antagonists, that may well turn out to block certain pathways but not others, with different effects on dyskinesia in the parkinsonian brain. Other pharmacological factors, such as different collateral efficacy or permissive antagonism (Kenakin, 2005) of the CB₁ ligands in the parkinsonian brain, might also account for these differences. Further research is needed to confirm these hypotheses. Another possibility, but valid only for the ethanolic extract of *C. sativa*, is that *C. sativa* comprises two active ingredients, Δ^9 -tetrahydrocannabinol, which acts as a CB₁ agonist, and cannabidiol, which is a CB₁ antagonist (Mechoulam et al., 2007); simultaneous stimulation and blockade of CB₁ receptors with *C. sativa* might thus account for the lack of antidyskinetic effect.

B. Endogenous Cannabinoids

Levels of endocannabinoids in the dyskinetic state have been assessed by only a few studies. As mentioned in the previous subsection, levels of 2-AG are elevated in the striatum of the dyskinetic NHP killed in the on-state, but how such elevated levels of 2-AG would lead to dyskinesia remains unknown (van der Stelt et al., 2005). In the 6-OHDA-lesioned rat (time of death following L-DOPA administration not

defined), levels of the endogenous cannabinoid anandamide in the striatum in L-DOPA-treated rats were not different from those of control animals (Gubellini et al., 2002; Maccarrone et al., 2003).

However, increasing levels of the endocannabinoid anandamide might be a promising way to alleviate LID, although evidence is currently conflicting. Indeed, elevating anandamide levels with the fatty acid amide hydrolase (FAAH) inhibitor URB597 did not reduce LID severity in the MPTP-lesioned marmoset (Johnston et al., 2011), whereas it did so in the MPTP-lesioned macaque (Johnston et al., unpublished). It is believed that activation of TRPV₁ by anandamide is the reason why URB597 might not consistently alleviate dyskinesia. Accordingly, the combination of URB597 and the TRPV₁ antagonist capsazepine effectively alleviated LI-AIMS in the 6-OHDA-lesioned rat (Morgese et al., 2007) and the MPTP-lesioned macaque (Johnston et al., unpublished), although clearly this explanation is only partial because URB597 as monotherapy also effectively alleviated LID in the parkinsonian macaque. The mechanism(s), whereby elevating anandamide levels alleviates LID, is presently unknown, but the mechanisms speculated above for CB₁ agonists might well play a role. The antidyskinetic potential of FAAH inhibitors has not been explored in the clinic yet, but in agreement with a potential antidyskinetic benefit of elevating anandamide, a recent study that measured CSF levels of anandamide found decreased levels in PD patients treated with either L-DOPA or dopamine agonists compared with de novo PD patients or with patients with long-standing PD who underwent a medication washout (Pisani et al., 2010). Unfortunately, the dyskinetic status was not mentioned in the study nor was the time of last drug administration.

XI. Adrenergic Neurotransmission

Adrenaline and noradrenaline exert their effects by activating the adrenergic receptors, also termed adrenoceptors (Foord et al., 2005). Adrenoceptors are G protein-coupled receptors (Vassilatis et al., 2003) and can be divided into α and β receptors. α and β Adrenoceptors can be further divided into nine subtypes. Thus, α adrenoceptors encompass α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , and α_{2C} receptors, while β -adrenoceptors encompass β_1 , β_2 , and β_3 receptors (Kobilka, 2011).

To our knowledge, no postmortem study has investigated the fate of adrenoceptors in dyskinesia, although one study that used rotations as the behavioral marker, investigated α_{2A} and α_{2C} mRNA levels in L-DOPA-treated 6-OHDA-lesioned rats (Alachkar et al., 2012). As such, the current knowledge supporting altered noradrenergic transmission in dyskinesia is based exclusively on pharmacological studies.

α Adrenoceptors appear to play an important role in the expression of the dyskinetic phenotype. Thus, the

nonselective α -adrenergic antagonist yohimbine reduced the severity of established LI-AIMs in the 6-OHDA-lesioned rat, although at the expense of impairing the antiparkinsonian efficacy of L-DOPA (Lundblad et al., 2002; Dekundy et al., 2007). In the MPTP-lesioned NHP, idazoxan, as well as yohimbine and rauwolscine (two nonselective α_1 and α_2 antagonists that also act as 5-HT_{1A} agonists and 5-HT_{2A} antagonists) effectively alleviated LID (Henry et al., 1999); idazoxan also enhanced L-DOPA antiparkinsonian action (Henry et al., 1999). The selective α_2 -receptor antagonist fipamezole also alleviated LID while enhancing L-DOPA antiparkinsonian efficacy in the MPTP-lesioned common marmoset (Savola et al., 2003) and the MPTP-lesioned macaque (Johnston et al., 2010c). At the clinical level, idazoxan effectively alleviated LID (Rascol et al., 2001a) but had no effect on apomorphine-induced dyskinesia (Manson et al., 2000), whereas fipamezole was also effective at relieving LID (Dimitrova et al., 2009; Lewitt et al., 2012).

While α_2 -receptor blockade appears to effectively alleviate LID without impairing L-DOPA antiparkinsonian action, stimulation of α_2 receptors also seems effective to reduce LID, although it may have deleterious effects on L-DOPA antiparkinsonian benefit. Thus, clonidine, an α_2 -receptor agonist, alleviated LI-AIMs in the 6-OHDA-lesioned rat (Dekundy et al., 2007) and LID in the MPTP-lesioned NHP (Gomez-Mancilla and Bedard, 1993) but decreased L-DOPA antiparkinsonian efficacy in both models.

The mechanism(s) underlying the antidyskinetic action of α_2 -receptor antagonists remains hypothetical. Although idazoxan effectively reduced LID, it was ineffective against apomorphine-induced dyskinesia (Fox et al., 2001), suggesting that a direct competition with L-DOPA-derived dopamine and/or noradrenaline plays a role in the antidyskinetic action of α_2 antagonists (Alachkar et al., 2006). This competition would prevent activation of α_{2C} receptors located on medium-sized spiny neurons of the striatonigral pathway and would normalize the activity of the direct pathway, with a resulting reduction of dyskinesia (Johnston et al., 2010c). These actions could be on cell bodies in the striatum, reducing excitability, or on terminals of the direct pathway in the output regions of the basal ganglia, reducing GABA release (Fox et al., 2001; Johnston et al., 2010c). GABA release is reduced indirectly by blockade of α_2 autoreceptors, increasing noradrenaline release and thereby leading to stimulation of α_2 heteroreceptors on GABAergic terminal, which reduces GABA release (Fox et al., 2001; Johnston et al., 2010c). Further studies are needed to confirm these mechanistic hypotheses and to determine if other mechanisms, such an interaction with glutamatergic transmission, are also involved. Reduction of striatal L-DOPA-derived dopamine release by

idazoxan was recently demonstrated in the primed 6-OHDA-lesioned rat (Buck et al., 2010) and may contribute to the antidyskinetic action of α_2 antagonists, although if such an action is functionally important it is surprising that this class of compound has never been associated with a reduction in antiparkinsonian benefit (in the case of yohimbine, loss of antiparkinsonian efficacy could be attributed to an agonist action at 5-HT_{1A} receptors, see above).

Although antagonizing α_2 adrenoceptors appears as an effective way to alleviate dyskinesia, the role of α_1 adrenoceptors is less clear. Thus, in the 6-OHDA-lesioned rat, systemic administration of the α_1 antagonist HEAT effectively reduced AIMs (Buck and Ferger, 2010). In contrast, direct striatal infusion of the α_1 agonist cirazoline did not induce AIMs (Buck and Ferger, 2010). In the MPTP-lesioned macaque, administration of the α_1 antagonist prazosin did not diminish severity of dyskinesia (Visanji et al., 2009b). Further studies are needed to establish whether blockade of α_1 adrenoceptors is indeed an effective antidyskinetic approach and what the mechanisms underlying any such antidyskinetic effects may be.

On the basis of pharmacological studies, β -adrenergic transmission also appears to play a role in the pathophysiology of LID. Indeed, in the 6-OHDA-lesioned rat, the β -adrenergic antagonist (\pm)-propranolol and its enantiomer ($-$)-propranolol reduced the expression and development of AIMs (Dekundy et al., 2007; Lindenbach et al., 2011). However, the effect of propranolol on L-DOPA antiparkinsonian efficacy is unclear (Dekundy et al., 2007; Lindenbach et al., 2011). This difference in the effect of propranolol on L-DOPA antiparkinsonian action in the 6-OHDA-lesioned rat effect might be due to the fact that the authors of the studies have used different measures of antiparkinsonian action. However, propranolol did not attenuate AIMs induced by either SKF-81,297 or quinpirole (Bhide et al., 2010) suggesting that, as for α_2 antagonists, a direct competition with L-DOPA-derived dopamine/noradrenaline might mediate the antidyskinetic action of β -adrenoceptor antagonists. The administration of propranolol to the MPTP-lesioned NHP also alleviated LID, but the antidyskinetic effect was accompanied by a reduction of L-DOPA antiparkinsonian benefit (Gomez-Mancilla and Bedard, 1993). Propranolol also alleviated chorea, but not dystonia, in a small clinical study, without impairing L-DOPA antiparkinsonian efficacy (Carpentier et al., 1996). As mentioned above, direct competition with L-DOPA-derived dopamine/noradrenaline might be a mechanism whereby β -adrenoceptor antagonists alleviate LID, but it remains unknown whether other mechanisms are also involved. Moreover, the exact site where blockade of β -adrenoceptors mediates its antidyskinetic efficacy is also unknown.

Thus, although antagonizing α_2 - and β -adrenoceptors appear as promising antidyskinetic therapies, further studies are needed, especially studies focusing on the mechanisms and the anatomic sites underlying their antidyskinetic efficacy. In addition, the effect of β -adrenoceptor blockade on L-DOPA antiparkinsonian efficacy is a concern that will require exploration in eventual clinical trials. Moreover, the effect of β -adrenoceptor blockade on blood pressure might limit the use of such agents in advanced PD, where autonomic dysfunction and orthostatic hypotension are often present (Goldstein, 2003). As mentioned above, there is recent evidence suggesting that blocking α_1 -adrenoceptors might also alleviate LID (Buck and Ferger, 2010), but, as for β -adrenoceptor blockers, the effect of α_1 -adrenoceptor antagonists on blood pressure might eventually limit their use in advanced PD and therefore their use as antidyskinetic agents. Fortunately, hypotensive effects of α_2 -adrenoceptor blockade in clinical trials with idazoxan and fipamezole have not been reported, and the agents appear safe and well-tolerated in idiopathic PD.

Studies investigating the effect of striatal noradrenergic denervation on development and expression of dyskinesia are difficult to reconcile because each employed different methodologies. Thus, administration of 6-OHDA in the medial forebrain in the absence of desipramine pretreatment, leading to concomitant degeneration of noradrenergic fibers coursing toward the striatum, delayed the priming and attenuated the expression of LI-AIMs compared with desipramine-pretreated rats (Barnum et al., 2012). That study is in agreement with studies cited above that showed a reduction in dyskinesia severity with α - and β -adrenergic antagonists. In contrast, in another study, administration of 6-OHDA without desipramine to rats followed by priming with L-DOPA and then by destruction of the locus coeruleus, exacerbated the severity of LI-AIMs compared with pre-locus coeruleus lesion (Migueluez et al., 2011). Another study found increased AIMs severity with noradrenergic lesion in the 6-OHDA-lesioned rat (Fulceri et al., 2007), whereas another one did not find any difference in LI-AIMs severity (Perez et al., 2009). As mentioned above, there are many differences in these studies in terms of noradrenergic and dopaminergic lesion severity, strain of rat used, and timing of noradrenergic lesion compared with dopaminergic lesion and priming. Notwithstanding these considerations, it seems rather clear that the noradrenergic system modulates the severity of LID. The question is how. In idiopathic PD, the locus coeruleus degenerates early in the disease process, likely earlier than the dopaminergic system (Braak et al., 2003, 2004). Thus, when L-DOPA therapy is commenced, there are already reduced levels of noradrenaline within the striatum, and, as such, the experiment performed by Barnum et al. (2012) in which priming was initiated after noradrenergic lesion was

induced, might be the most clinically relevant one, both in terms of timing and severity of lesion, as in idiopathic PD, striatal noradrenaline levels are usually reduced by approximately 60% (Fahn et al., 1971).

Although the mechanism whereby the noradrenergic system might contribute to LID has yet to be determined, it is possible to envision a concept similar to “false neurotransmitter” release put forth (see section VII). Indeed, it was demonstrated that, within the striatum of the 6-OHDA-lesioned rat, L-DOPA-derived dopamine can be taken up by the noradrenaline transporter into noradrenergic terminals (Arai et al., 2008). Ultimately, this could result in release of dopamine by coeruleostriatal fibers, that is, by axons not equipped with the autoregulatory mechanisms proper to dopaminergic transmission, thereby exacerbating pulsatile dopamine release. Although this explanation remains hypothetical and requires experimental validation, it nevertheless makes sense from physiologic and compensatory point of views. A direct prodyskinetic action of noradrenaline is also possible, because intrastriatal administration of noradrenaline by reverse in vivo microdialysis elicited AIMs in primed 6-OHDA-lesioned rats (Buck and Ferger, 2009).

XII. Histaminergic Neurotransmission

Histamine exerts its actions via four types of receptors, H_{1-4} (Hill et al., 1997; de Esch et al., 2005), all of which are expressed in the brain (Passani and Blandina, 2011). In PD and dyskinesia, only H_2 and H_3 receptors have been studied. Both H_2 and H_3 receptors are G protein-coupled receptors, but H_2 receptors appear to be coupled to G_s proteins (Hill, 1990), whereas H_3 receptors seem to be coupled to $G_{i/o}$ proteins (Clark and Hill, 1996).

Although no postmortem studies have addressed specifically the status of the histaminergic system in the dyskinetic state, the basal ganglia are enriched with both H_2 and H_3 receptors and there is evidence for altered histaminergic innervation of the basal ganglia in the parkinsonian state. Thus, one study demonstrated increased histaminergic innervation of the SNc and SNr in PD patients, although without providing clinical details concerning L-DOPA treatment and dyskinesia (Anichtchik et al., 2000). Another study found increased histamine levels in the putamen, SNc, GPi, and GPe of PD patients but did not provide information concerning L-DOPA treatment and dyskinesia (Rinne et al., 2002). H_3 receptor mRNA was present in the putamen and both segments of the GP, and one study found increased H_3 mRNA levels in the GPe of PD patients without commenting on dopaminergic therapy or the dyskinetic status of the patients included (Anichtchik et al., 2001). This last study also demonstrated an increase in H_3 protein levels in the SN of PD patients compared with controls, although H_3

mRNA levels were very low in the SN (Anichtchik et al., 2001). In contrast, H₂ receptor levels were not altered in PD, except in the nucleus accumbens, in which they were reduced (Martinez-Mir et al., 1993).

There is pharmacological evidence for an involvement of the histaminergic system in the pathophysiology of LID. Thus, the H₂ antagonist famotidine reduced the severity of peak-dose chorea while increasing quality of on-time in the L-DOPA-treated MPTP-lesioned macaque (Johnston et al., 2010d). In a small clinical study whose endpoint was unrelated to dyskinesia, famotidine alleviated established dyskinesia in two PD patients (Molinari et al., 1995). The H₃ agonists immapip and imetit effectively alleviated L-DOPA-induced chorea but not dystonia in the MPTP-lesioned marmoset; neither immapip nor imetit adversely affected L-DOPA antiparkinsonian benefit (Gomez-Ramirez et al., 2006).

At the moment, the mechanism(s) by which H₂ antagonists exert their antidyskinetic effect remains unknown, but it has been suggested that antagonizing histamine H₂ receptors would modulate SNr activity and striatal ACh release (Johnston et al., 2010d). Moreover, stimulation of H₂ receptors activates striatofugal neurons (Haas et al., 2008); while acting on the direct pathway, stimulation of H₂ receptors would result in overinhibition of the GPi/SNr complex, ultimately leading to cortical overexcitation and LID. Thus, it is possible, although speculative, that H₂ blockade normalizes the activity of the direct pathway, thereby reducing LID. Similarly, the precise antidyskinetic mechanism of H₃ receptor stimulation remains to be demonstrated. However, stimulation of presynaptic H₃ receptors inhibits raphestriatal 5-HT release as well as corticostriatal glutamate release (Haas et al., 2008). In the context of PD and L-DOPA therapy, it is possible, although not yet demonstrated, that stimulating H₃ receptors would inhibit raphestriatal dopamine release and corticostriatal glutamate release, thereby acting in a way similar to 5-HT_{1A} agonists. Normalization of neurotransmission along the direct pathway was also proposed as an antidyskinetic mechanism of H₃ agonists (Gomez-Ramirez et al., 2006), although this mechanism is also unproven.

Interestingly, the preferential antichoreic versus antidystonic efficacy of H₂ antagonists and H₃ agonists suggests that different pathophysiological mechanisms underlie chorea and dystonia. Although such mechanisms remain to be elucidated, they raise the possibility that it may eventually be possible to design therapies aimed at reducing either chorea or dystonia, depending on the need of the patient, thereby potentially minimizing adverse effects of treatment.

XIII. Cholinergic Neurotransmission

The basal ganglia, especially the striatum, receive a dense cholinergic innervation (Mesulam et al., 1992),

and histochemistry with the enzyme acetylcholinesterase was the first technique that identified the striosomes and the matrix compartments of the striatum (Graybiel and Ragsdale, 1978). Moreover, large aspiny cholinergic interneurons of the striatum account for 1–2% of the total neuronal population of the striatum (Cicchetti et al., 2000). As such, ACh is a key neurotransmitter within the basal ganglia (Graybiel, 1990; Parent et al., 1995). ACh exerts its effects by stimulating muscarinic (Caulfield and Birdsall, 1998) and nicotinic (Lukas et al., 1999) receptors.

Pharmacological studies have suggested an involvement of nicotinic neurotransmission in LID. Thus, chronic nicotine administration reduced the expression of LID in the MPTP-lesioned squirrel monkey (Quik et al., 2007) and LI-AIMs in the 6-OHDA-lesioned rat (Bordia et al., 2008). However, in phase II studies—none of which examined the effect of nicotine on LID—transdermal nicotine was poorly tolerated by PD patients (Lemay et al., 2004; Villafane et al., 2007), which undermines the therapeutic potential of the treatment. Paradoxically, chronic administration of the nicotinic antagonist mecamylamine also alleviated LI-AIMs in the 6-OHDA-lesioned rat (Bordia et al., 2010), whereas acute challenges of mecamylamine did not have any effect on LI-AIMs (Dekundy et al., 2007). Following the unexpected discovery that chronic therapy with either nicotinic agonists or antagonists alleviates LID, it was proposed that nicotine alleviated dyskinesia after a desensitization phenomenon that would occur upon chronic administration (Bordia et al., 2010). An interaction with the β_2 subunit of nicotinic receptors seems to be essential to the antidyskinetic action of nicotine (Huang et al., 2011a, 2011b). However, this approach might also be hindered by poor tolerability, as SIB-1508Y, an $\alpha_4\beta_2$ agonist, was poorly tolerated by PD patients in a phase II study (Parkinson Study Group, 2006).

Although PET (Kas et al., 2009), single photon emission tomography (Fujita et al., 2006; Oishi et al., 2007), and postmortem (Court et al., 2000; Schmaljohann et al., 2006) studies have demonstrated reduced nicotinic receptors in the brain and striatum of PD patients, because these studies did not examine nicotinic receptors in the dyskinetic state, they do not suggest an anatomic site at which modulation of nicotinic transmission would alleviate LID. Thus, the mechanism(s) by which and the site(s) at which chronic nicotinic receptor modulation reduces dyskinesia remain unknown. However, nicotinic receptors are expressed on nigrostriatal dopaminergic terminals (Zoli et al., 2002), and in mice striatal slices, stimulation of nicotine receptors led to dopamine release (Zhou et al., 2001). Importantly, in that last study, the β_2 subunit of nicotinic receptors was demonstrated to be critically involved in dopamine release (Zhou et al., 2001), which makes alteration of

nigrostriatal dopamine release the most likely antidyskinetic mechanism of chronic modulation of nicotinic receptors. However, it is difficult to envision how modulation of nigrostriatal dopamine release would effectively alleviate LID in the context of advanced PD or in the 6-OHDA-lesioned rat, where few intact nigrostriatal dopaminergic terminals remain and the majority of L-DOPA-derived dopamine is delivered to the striatum via raphistriatal fibers. Thus, other mechanisms might also be involved. For instance, acute stimulation of nicotinic receptors within the raphe nucleus led to 5-HT release within the nucleus accumbens (Chang et al., 2011). Although it remains speculative, downregulation of nicotinic receptors within the raphe nucleus following chronic treatment with a nicotinic agonist might lead to reduction in raphistriatal dopamine release, thereby reducing LID.

However, no matter how attractive these explanations are, they do not take into account the numerous giant cholinergic striatal interneurons (Cicchetti et al., 2000) that are likely to mediate some of the antidyskinetic effects of nicotinic modulators. It also remains unknown whether chronic stimulation/blockade of nicotinic receptors would also attenuate dyskinesia induced by dopamine agonists, but a successful reduction in dopamine agonist-induced dyskinesia would suggest an additional antidyskinetic mechanism that would not require nigrostriatal or raphistriatal terminals. Moreover, it is difficult to conceive why both stimulation and blockade of nicotinic receptors have to be chronic to produce an antidyskinetic effect. In summary, our understanding of the antidyskinetic effect of nicotinic receptor modulation remains very limited. However, nicotinic transmission itself does not appear to be a core player in the etiology of LID, but, as for many other neuromodulator systems, it may well turn out as an additional way to modulate abnormal dopamine and possibly glutamate striatal neurotransmission.

In contrast to nicotinic neurotransmission, the role of muscarinic transmission is unclear in the etiology of LID. Thus, in an early study, the muscarinic antagonist atropine had no effect on LID in the MPTP-lesioned macaque (Gomez-Mancilla and Bedard, 1993). However, the muscarinic antagonist dicyclomine alleviated LI-AIMs in the *Pitx3^{ak/ak}* mouse, which exhibits striatal dopamine depletion (Ding et al., 2011). To further add to the confusion, there have been case reports in which dyskinesia, mostly oro-buccal, was triggered when antimuscarinic agents were added to dopaminergic therapy (Hauser and Olanow, 1993). The precise mechanism and anatomic localization of such an anti/pro-dyskinetic action remain to be determined.

XIV. Tachykinin Neurotransmission

The tachykinins are a family of neuropeptides encompassing neurokinin A, neurokinin B, and

substance P (Maggio, 1988; Chahl, 2006). As discussed earlier and as illustrated in Fig. 1, substance P is expressed preferentially by the direct pathway. The tachykinins are encoded by preprotachykinin (PPT) (Maggio, 1988; Chahl, 2006). The tachykinins exert their effects by binding to three receptors. Substance P binds to the NK₁ receptor, whereas neurokinin A and B bind to the NK₂ and NK₃ receptors, respectively (Maggi, 1995). NK₁, NK₂, and NK₃ receptors are all present within the brain; however, NK₁ receptors predominate within the striatum, whereas NK₂ receptors are relatively sparse and NK₃ receptors are mostly encountered in the cerebral cortex (Otsuka and Yoshioka, 1993).

The tachykinins, especially substance P, have been extensively studied in PD but with little focus on relationship to dyskinesia. In the 6-OHDA-lesioned rat, striatal PPT mRNA levels were reduced and chronic treatment with L-DOPA, last dose administered 24 hours before death, reversed this decrease (Zeng et al., 1995). In the common marmoset, MPTP administration led to decreased striatal levels of PPT mRNA (Tel et al., 2002). Following chronic treatment with L-DOPA and the development of dyskinesia, PPT mRNA levels returned to baseline (time of administration of L-DOPA with respect to death not defined) (Tel et al., 2002). Similar changes in PPT mRNA levels were encountered in one study in the macaque, following MPTP lesioning and subsequent treatment with L-DOPA (time of administration with respect to death not defined) (Herrero et al., 1995). Interpreting data from these studies with respect to dyskinesia expression is difficult, and without further studies, at present, it is impossible to describe any clear correlation between changes in PPT mRNA levels and the dyskinetic phenotype.

Several studies have measured levels of substance P within the basal ganglia and CSF of PD patients (Mauborgne et al., 1983; Pezzoli et al., 1984; Tenovuo et al., 1984; Grafe et al., 1985; Halliday et al., 1990; Cramer et al., 1991; Fernandez et al., 1992). However, results are variable, depending on the technique used, and for many of these studies, it is not described whether patients were treated with L-DOPA or exhibited dyskinesia. In the L-DOPA-naive, MPTP-lesioned common marmoset, substance P levels were unchanged in the striatum, GP, and SN (Taquet et al., 1988), although another study found decreased substance P immunoreactivity in the sensorimotor striatum in the MPTP-lesioned macaque (Lavoie et al., 1991).

In the 6-OHDA-lesioned rat, acute and chronic administration of L-DOPA significantly increased striatal levels of neurokinin B and substance P mRNA compared with L-DOPA-naive animals when rats were killed in the on-state (Zhang et al., 2008a). However, the behavioral endpoint of that study was rotational

behavior and not AIMs, therefore precluding one to correlate AIMs with increased striatal levels of substance P. In contrast, a study that measured substance P levels in the striatum of 6-OHDA-lesioned rats killed at peak AIMs expression found no increase P levels when compared with control animals and no correlation between substance P levels and AIMs (Hanrieder et al., 2011). In PD patients treated with L-DOPA (dyskinetic phenotype not mentioned), substance P mRNA levels within the striatum were not different to those from control individuals (Levy et al., 1995b).

In contrast to PPT and substance P levels, neurokinin receptors have not been extensively studied in PD and dyskinesia. There is, however, one study published as an abstract that found reduced levels of substance P binding, i.e., reduced NK₁ receptors, in the striatum of dyskinetic PD patients (Whone et al., 2002).

Thus, PPT and substance P have been assessed in numerous studies in PD and related animal models. Although PPT and substance P appear to be decreased in parkinsonism and normalized after L-DOPA therapy, the design of the studies does not allow establishing correlations between PPT and dyskinesia, although the most convincing data, from a study by Hanrieder et al. (2011), in which animals were killed at peak dyskinesia expression, suggest that LID is likely not associated with enhanced substance P levels.

XV. Transcription Factors and Intracellular Signaling

All of the neurotransmitter/neuromodulator systems and exogenous molecules discussed above bind to a receptor, triggering intracellular signaling cascades, modulating transcription factors, and ultimately altering gene expression. Although much remains to be discovered with respect to the molecular basis of dyskinesia, several studies, mostly within the last decade, have identified transcription factors and intracellular cascades playing a direct role in the development or expression of dyskinesia. Moreover, studies performed with molecules that directly interfere with intracellular signaling or expression of transcription factors successfully alleviated established dyskinesia or delayed/prevented the emergence of dyskinesia. The advantages of such approaches are obvious. Indeed, as they represent the converging point of several neurotransmitter systems, they could theoretically be as effective a polypharmacotherapy that would modulate simultaneously all of these neurotransmitters. However, the obvious downside of interfering with intracellular signaling and transcription factors is the possibility of altering gene expression in a way that might be deleterious, for instance that might lead to cancer development or unnecessary systemic effects in the case of systemic delivery.

Although the first point remains a concern, the need to avoid systemic effect will probably warrant in situ delivery of the agents via stereotaxic injections as was done in several of the studies cited in the following subsections. The need to deliver such agents stereotaxically might limit their use as first-line antidyskinetic therapy, but they might eventually become alternatives to deep-brain stimulation surgery once their safety and efficacy have been clearly established in clinical trials.

A. Transcription Factors

The involvement of the transcription factors FBJ murine osteosarcoma viral oncogene homolog B (FosB), Δ FosB, JunB, JunD, Δ JunD, and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) in dyskinesia has been studied. There is convincing evidence that Δ FosB is involved in the pathophysiology of LID, whereas FosB seems to reflect more accurately L-DOPA therapy, whether acute or chronic, than dyskinesia per se. Similarly, changes in JunB and JunD expression appear to be related to L-DOPA therapy but not to dyskinesia, whereas both Δ JunD and CREB appear to mediate an antidyskinetic effect. Table 5 summarizes the key concepts put forth in the current section.

Thus, in the 6-OHDA-lesioned rat, FosB-related protein levels along the direct pathway were increased in dyskinetic animals killed 3 hours after last L-DOPA dose, and striatal infusion of FosB antisense before initiation of L-DOPA prevented AIMs development (Andersson et al., 1999). However, another study demonstrated that striatal FosB levels increased after just a single L-DOPA challenge when development and expression of dyskinesia have not occurred (Cenci et al., 1999), and striatal FosB levels remained high in the off-state 2 days after L-DOPA injection (Cenci et al., 1999; Westin et al., 2001). Thus, the data pointing at FosB as an etiological agent in LID are conflicting here, with data showing that direct striatal infusion of FosB antisense prevents priming associated with chronic L-DOPA therapy, but on the other hand, that FosB levels are elevated in two contexts in which dyskinesia is absent, i.e., before the induction of dyskinesia after a single challenge of L-DOPA and in the off-state. As will be discussed for Δ FosB and c-Fos, it is possible that, under a certain threshold that has yet to be determined, FosB induction is associated with L-DOPA administration, whereas above that hypothetical threshold, it would be involved in the pathophysiology of dyskinesia.

A similar argument can be raised with Δ FosB, although evidence pointing toward a causal involvement is stronger than for FosB. Thus, a study demonstrated elevated Δ FosB levels in the striatum of PD patients treated with L-DOPA, although the dyskinetic correlate was not provided (Calon et al.,

2002b). Similarly, in the 6-OHDA-lesioned rat killed 3 hours after last L-DOPA dose, a single acute challenge of L-DOPA significantly increased Δ FosB levels and chronic treatment further increased these levels (Valastro et al., 2007). In the 6-OHDA-lesioned mouse killed in the on-state, a single acute administration of L-DOPA increased Δ FosB levels, but not to the same extent as chronic L-DOPA treatment. Moreover, dyskinetic, chronically L-DOPA-treated mice exhibited higher Δ FosB levels than nondyskinetic mice chronically treated with L-DOPA (Pavon et al., 2006). Furthermore, and this is perhaps the most convincing evidence in favor of a direct etiological role of Δ FosB in LID, striatal overexpression of Δ FosB induced by viral vector led to the development of a dyskinetic phenotype similar to LI-AIMs, in the absence of L-DOPA administration, in the 6-OHDA-lesioned rat (Cao et al., 2010). In addition, in a study performed in the MPTP-lesioned macaque, a linear relationship was demonstrated between striatal Δ FosB levels and dyskinesia severity (Berton et al., 2009). The results of the studies cited above suggest that Δ FosB is involved in the pathophysiology of LID but also introduce the idea of a critical threshold above which it generates dyskinesia. Indeed, Δ FosB levels tend to increase after a single administration of L-DOPA but are further increased after repeated administration of L-DOPA and when dyskinesia is present. Thus, above a certain threshold, which has yet to be determined, Δ FosB becomes associated with, and may apparently even trigger, dyskinesia.

The expression of the immediate-early gene c-Fos was also demonstrated to be abnormally high in the striatum of the dyskinetic 6-OHDA-lesioned mouse killed 30 minutes after treatment (Santini et al., 2007) and in the striatum (Bishop et al., 2009) and primary motor cortex (Ostock et al., 2011) of the dyskinetic 6-OHDA-lesioned rat killed in the on-state. In the 6-OHDA-lesioned mouse, c-Fos levels were higher in dyskinetic than nondyskinetic animals (Santini et al., 2007), suggesting that, as for FosB and Δ FosB, c-Fos is primarily associated with L-DOPA administration, but might also be associated with LID above a certain threshold.

At the moment, the involvement of Jun-related elements in dyskinesia seems minimal, with the

exception of Δ JunD, which appears to be associated with dyskinesia reduction. Thus, in the 6-OHDA-lesioned rat killed 3 hours after last dose of L-DOPA, striatal JunD levels were increased after a single acute L-DOPA challenge but not following chronic L-DOPA treatment and the emergence of AIMs (Valastro et al., 2007). In the 6-OHDA-lesioned rat, the number of JunB-immunoreactive cells within the striatum was shown to increase following either acute or chronic L-DOPA therapy (Cenci et al., 1999). Taken together, these data do not support an involvement of JunD or JunB in LID. However, in the MPTP-lesioned macaque, striatal overexpression of Δ JunD induced by adeno-associated viral vector alleviated LID in primed animals upon subsequent L-DOPA administration without impairing its antiparkinsonian action (Berton et al., 2009). Although that study did not establish a causative role played by Δ JunD in LID, it certainly established an antidyskinetic effect of intrastriatal delivery of Δ JunD.

As for Δ JunD, CREB appears to mediate an antidyskinetic effect, although its duration seems very limited and as such probably plays a more fundamental role in the priming process rather than in LID expression. Thus, in the 6-OHDA-lesioned rat, intrastriatal injection of CREB antisense to switch off CREB led to more severe AIMs after an acute L-DOPA challenge, but this effect was lost following chronic L-DOPA therapy (Andersson et al., 2001), suggesting that CREB delays, at least partially, the priming.

B. DARPP-32, ERK1/2, and Histone Deacetylation

Dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) is a major downstream target of dopamine transmission in the striatum (Svenningsson et al., 2004). A study found increased DARPP-32 levels in the striatum of MPTP-lesioned macaques killed at peak dose dyskinesia compared with nonparkinsonian macaques (Aubert et al., 2005), whereas another study performed by the same group found increased levels of DARPP-32 abnormally phosphorylated at the Thr34 residue in the dyskinetic MPTP-lesioned macaque killed in the on-state compared with nonparkinsonian animals (Santini et al., 2010). Once phosphorylated at the Thr34 residue, DARPP-32 promotes phosphorylation, thereby enhancing functioning of several cellular

TABLE 5
Transcription factors in dyskinesia

-
- FosB is a marker of L-DOPA treatment, whether acute or chronic, but may be associated with dyskinesia above a certain threshold.
 - Δ FosB appears involved in LID.
 - Striatal Δ FosB levels are higher in dyskinetic 6-OHDA-lesioned mice than in nondyskinetic 6-OHDA-lesioned mice, both groups treated chronically with L-DOPA.
 - Striatal overexpression of Δ FosB led to the expression of AIMs in the 6-OHDA-lesioned rat, in the absence of L-DOPA administration.
 - There is a linear relationship between striatal Δ FosB levels and dyskinesia severity in the MPTP-lesioned macaque.
 - Intrastriatal overexpression of Δ JunD leads to a reduction of established dyskinesia in the MPTP-lesioned macaque.
 - There is no evidence for an involvement of JunB or JunD in dyskinesia.
 - There is possible involvement of CREB in delaying the priming process leading to dyskinesia expression.
-

effectors such as AMPA and NMDA receptors (Greengard, 2001), which play a determinant role in LID, as seen above. Interestingly, in the dyskinetic MPTP-lesioned NHP killed in the on-state, cyclin-dependent kinase 5 (Cdk5) protein levels in the striatum were elevated compared with nonparkinsonian animals (Aubert et al., 2005). Cdk5 phosphorylates DARPP-32 at the Thr75 residue, thereby reducing the ability of DARPP-32 to phosphorylate its substrates (Greengard, 2001). Although speculative, this increase in Cdk5 levels in the dyskinetic MPTP-lesioned NHP perhaps represents an endogenous, albeit largely ineffective, compensatory mechanism aimed at dampening DARPP-32-mediated enhanced phosphorylation in LID. Perhaps emphasizing the importance of the direct pathway over the indirect pathway, conditional ablation of DARPP-32 within striatonigral neurons using Cre-Lox technology significantly attenuated the priming process, leading to the expression of LI-AIMs in the 6-OHDA-lesioned mouse (Bateup et al., 2010).

These studies performed in the mouse and the NHP have identified DARPP-32 as an affected downstream target in LID and introduce the idea that dyskinesia could be perpetuated via a positive regulatory feedback mechanism. Indeed, DARPP-32 phosphorylation is under the control of several neurotransmitter systems and receptors, such as AMPA and NMDA receptors (Greengard, 2001). Signaling via these receptors promotes abnormal phosphorylation of DARPP-32; abnormally phosphorylated DARPP-32 in turn promotes their phosphorylation and increases their activity, thereby perpetuating the abnormal loop. Moreover, if abnormally phosphorylated DARPP-32 is indeed at the core of dyskinesia pathophysiology, as its phosphorylation is regulated by several neurotransmitter systems, many of which do not function within physiologic parameters in dyskinesia, perhaps a pharmacological approach targeting a single receptor is destined to failure, because abnormal transmission mediated by other receptors will still lead to abnormal DARPP-32 phosphorylation. Perhaps this phenomenon is at the source of the tachyphylaxis reported with amantadine evoked above?

In addition to receptors, abnormal DARPP-32-mediated signaling leads to abnormal phosphorylation of intracellular proteins in dyskinesia. Thus, a cascade involving DARPP-32 leading to increased phosphorylation of extracellular signal-regulated protein kinases (ERK) 1 and 2 (ERK1/2) has been described in the dyskinetic 6-OHDA-lesioned mouse killed in the on-state (Santini et al., 2007). In the 6-OHDA-lesioned rat killed in the on-state, stimulation of D₁ but not D₂ receptors was demonstrated to play a critical role in ERK1/2 phosphorylation (Westin et al., 2007). ERK phosphorylation was also increased, although total ERK levels remained unchanged, in the dyskinetic MPTP-lesioned macaque killed in the on-state

compared with nonparkinsonian animals (Santini et al., 2010). In accordance with these observations, concomitant genetic inactivation of DARPP-32 and blockade of the mitogen-activated kinase/ERK kinase with SL327 attenuated the development of LI-AIMs in the 6-OHDA-lesioned mouse (Santini et al., 2007).

More recently, the involvement of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1), an upstream regulator of ERK1/2 (Kennedy et al., 2005), in dyskinesia was demonstrated in the 6-OHDA-lesioned mouse and the MPTP-lesioned macaque (Fasano et al., 2010). Thus, Ras-GRF1-knockout mice were more resistant to the development of LI-AIMs than Ras-GRF1-wild-type mice (Fasano et al., 2010). Moreover, intrastriatal delivery of a dominant-negative construct of Ras-GRF1, leading to a reduction of Ras-GRF1 expression, attenuated the severity of established LID in the MPTP-lesioned macaque (Fasano et al., 2010). In addition, inhibiting Ras isoprenylation and activity with lovastatin prevented the emergence of LI-AIMs in the 6-OHDA-lesioned rat (Schuster et al., 2008), although in the clinic a similar molecule, simvastatin, did not alleviate established dyskinesia, possibly because too low doses were used (https://www.michaeljfox.org/foundation/grant-detail.php?grant_id=485).

Other upstream regulators of the ERK1/2-mediated cascade, calcium and diacylglycerol guanine nucleotide exchange factor (CalDAG-GEF) 1 and 2, were demonstrated to be affected in LID. Indeed, in the dyskinetic 6-OHDA-lesioned rat killed 24 hours after last L-DOPA administration, striatal CalDAG-GEF1 levels were decreased in the matrix, whereas CalDAG-GEF2 levels were increased in the striosomes (Crittenden et al., 2009). Although this last study suggests abnormal CalDAG-GEF-mediated signaling in LID, because the animals were killed in the off-state, it is possible that CalDAG-GEF levels are altered solely in the off-state of dyskinetic rats, and further studies are needed with animals killed while in the on-state to strengthen the evidence linking CalDAG-GEF and LID. Notwithstanding the limitation of that last study, as CalDAG-GEF is an upstream regulator of ERK1/2, it adds to the evidence identifying ERK1/2 as a central player in the pathophysiology of LID. Hence, as seen above, DARPP-32 signaling, Ras-GRF1 signaling, and CalDAG-GEF signaling all converge downstream toward ERK1/2. Moreover, inhibition of these cascades and subsequent inhibition of ERK1/2 phosphorylation—with the exception of Cal-DAG-GEF—were demonstrated to reduce the priming and/or the acute expression of LID.

ERK then participates in the activation of the mammalian target of rapamycin (mTOR), which plays a key role in protein synthesis regulation and synaptic plasticity (Costa-Mattioli et al., 2009), and activation of mTOR might be an important mechanism involved in the pathogenesis of LID. Thus, in the 6-OHDA-lesioned

mouse, L-DOPA administration and subsequent development of dyskinesia resulted in activation of mTOR and its downstream targets, including S6 kinase, ribosomal protein S6, and 4E-binding protein, in striatonigral neurons (Santini et al., 2009). Importantly, administration of rapamycin and blockade of mTOR receptors prevented the development of LI-AIMs and activation of mTOR and its downstream effectors, without affecting its antiparkinsonian action, in the 6-OHDA-lesioned mouse (Santini et al., 2009). However, rapamycin is a potent immunosuppressant drug (Calne et al., 1989) and its effects on the immune system are likely to limit its usefulness as an antidyskinetic agent. Whether blockade of mTOR would also alleviate established LID remains unknown. Attenuating mTOR activation by switching off the protein Ras homolog enriched in striatum (Rhes) alleviated, but did not abolish, development of LI-AIMs in the 6-OHDA-lesioned mouse (Subramaniam et al., 2011).

Ultimately, this increase in ERK1/2 phosphorylation and downstream effectors such as mTOR has repercussions at the nuclear level. Thus, in the 6-OHDA-lesioned mouse killed in the on-state, increased ERK1/2 phosphorylation resulted in activation of mitogen- and stress-activated kinase 1 (MSK-1) and phosphorylation of histone H₃, two downstream targets of ERK involved in transcriptional regulation (Santini et al., 2007). In contrast, in the MPTP-lesioned NHP killed at peak LID expression, chronic therapy with L-DOPA led to dephosphorylation of histone H₃ (Nicholas et al., 2008), thereby highlighting differences between the rodent and NHP models of PD at the nuclear levels after chronic L-DOPA therapy. In contrast to histone H₃, there is evidence of marked histone H₄ deacetylation in the striatum of both dyskinetic MPTP-lesioned NHPs and dyskinetic 6-OHDA-lesioned mice killed at peak LID expression (Nicholas et al., 2008). Accordingly, in the MPTP-lesioned NHP, inhibiting histone deacetylation with the histone deacetylase (HDAC) inhibitor RGFP109 effectively alleviated LID (Johnston et al., 2010a) and sodium valproate, which acts as a nonselective HDAC inhibitor (Rosenberg, 2007), reduced dyskinesia severity in a small clinical study (Price et al., 1978). Although the genes affected by these changes in chromatin structure remain to be identified, the finding of histone deacetylation in LID adds to the complexity of the phenomenon. Moreover, although the most determining factor in the etiology, if any, of LID has yet to be defined, all of the changes mentioned above appear to converge intracellularly, ultimately resulting in altered gene expression. It is possible, but yet unproven, that those changes in gene expression are ultimately responsible for the abnormal cellular distribution and phosphorylation of dopamine and glutamate receptors discussed above, which might perhaps be seen as a consequence of gene expression

but certainly might also contribute to perpetuate the alteration in gene expression, thereby creating a positive feedback loop that would perpetuate the dyskinetic phenotype. As a corollary, these long-lasting nuclear changes might well be responsible for the fact that, once sensitization has occurred, subsequent exposure to L-DOPA invariably triggers LID. Therefore, perhaps the most effective way to alleviate dyskinesia permanently is to address these nuclear changes. Although the theoretical dangers of such an approach have been highlighted above, certain molecules used in clinical practice such as valproic acid and vorinostat (Hahnen et al., 2008) are HDAC inhibitors, and their antidyskinetic potential could probably be assessed in randomized controlled clinical trials in a near future. The key points mentioned in this subsection are summarized in Fig. 3 and Table 6.

C. Other Abnormal Intracellular Cascades

Although the consequences of abnormally phosphorylated ERK1/2 on chromatin structure were presented in the last section, other abnormal signal transduction pathways in dyskinesia have been identified, but they have not been as thoroughly studied and their overall role in the priming and/or expression of dyskinesia remains to be defined. As such, although they may well play an etiological role in LID, they might also be an epiphenomenon reflecting enhanced intracellular signaling. Moreover, some methodological considerations of the studies, discussed herein, prevent making strong conclusions.

Thus, there is evidence of aberrant protein kinase activity in LID. The Akt (protein kinase B, PKB)/GSK3 (glycogen synthase kinase 3) signaling cascade was demonstrated to be abnormal in LID, because increased levels of pAkt(Ser473)/Akt were discovered in the striatum of L-DOPA-naive and L-DOPA-treated dyskinetic MPTP-lesioned macaques (Morissette et al., 2010). Unfortunately, the animals used in that study were killed in the off-state, which limits the interpretation of data. There is also evidence of abnormal protein kinase C (PKC)-mediated signaling in LID. Thus, in the 6-OHDA-lesioned rat killed in the on-state, chronic L-DOPA treatment led to increases in PKC- ϵ and PKC- λ protein levels in the denervated striatum compared with the unlesioned side (Smith et al., 2007), and de novo administration of the PKC antagonist tamoxifen with L-DOPA prevented these increases in PKC levels (Smith et al., 2007). In the MPTP-lesioned macaque, acute challenges of tamoxifen alleviated the severity of established LID, without impairing L-DOPA antiparkinsonian efficacy (Smith et al., 2007). However, the interpretation of the results of that study is not straightforward. Indeed, tamoxifen is a weak PKC antagonist and it is difficult to conceive how chronically antagonizing PKC in the rat would prevent the L-DOPA-induced

increase in PKC levels, and one must therefore consider that tamoxifen might have alleviated LID via a different, non-PKC-related mechanism, a fortiori because the primary mechanism of action of tamoxifen is to antagonize estrogen receptors (Fabian et al., 1981). However, estrogen receptor blockade might not be the mechanism by which tamoxifen exerted its antidyskinetic action either, because stimulation of estrogen receptors with 17β -, but not 17α -, estradiol alleviated established LID in ovariectomized MPTP-lesioned macaques without affecting L-DOPA anti-parkinsonian efficacy (Gomez-Mancilla and Bedard, 1992b).

Protein kinase A (PKA) also appears to be abnormally regulated in dyskinesia. Thus, in the 6-OHDA-lesioned rat killed 60 minutes after last L-DOPA injection, striatal PKA levels were significantly increased compared with saline-treated 6-OHDA-lesioned rats (Martinez et al., 2011). This increase in striatal PKA levels was reversed by administration of the nonselective cannabinoid agonist WIN-55212-2 (Martinez et al., 2011), and regulation of PKA signaling might therefore be a mechanism underlying the antidyskinetic efficacy of cannabinoid agonists.

Cyclic nucleotide levels also appear affected in dyskinesia. Thus, in the dyskinetic 6-OHDA-lesioned

rat killed in the on-state, levels of cAMP and cyclic guanosine monophosphate (cGMP) were reduced in the cortex, striatum, and GP compared with L-DOPA-naive 6-OHDA-lesioned rats (Giorgi et al., 2008). Subchronic administration of the phosphodiesterase type 5 (PDE5) inhibitor zaprinast partly reversed, although did not normalize, those changes in cyclic nucleotide levels and alleviated established LI-AIMs (Giorgi et al., 2008). Moreover, intrastriatal administration of zaprinast or UK-343,664, another PDE5 inhibitor, alleviated established LI-AIMs and restored normal LTD at the corticostriatal synapse in dyskinetic 6-OHDA-lesioned rats (Picconi et al., 2011). The findings of these studies could have important clinical implications, because compounds such as sildenafil (Boolell et al., 1996) and tadalafil (Daugan et al., 2003a, 2003b) are PDE5 inhibitors currently used for treatment of erectile dysfunction that could be advanced rapidly to clinical trials.

The guanosine triphosphate (GTP)-binding protein $G\alpha_{olf}$ plays an important role in the coupling of D_1 and A_{2A} receptors to adenylyl cyclase in the striatum and is an important regulator of cAMP production (Corvol et al., 2001). In the L-DOPA-naive 6-OHDA-lesioned rat, striatal levels of $G\alpha_{olf}$ were elevated (Corvol et al., 2004) and chronic treatment with L-DOPA or the D_1

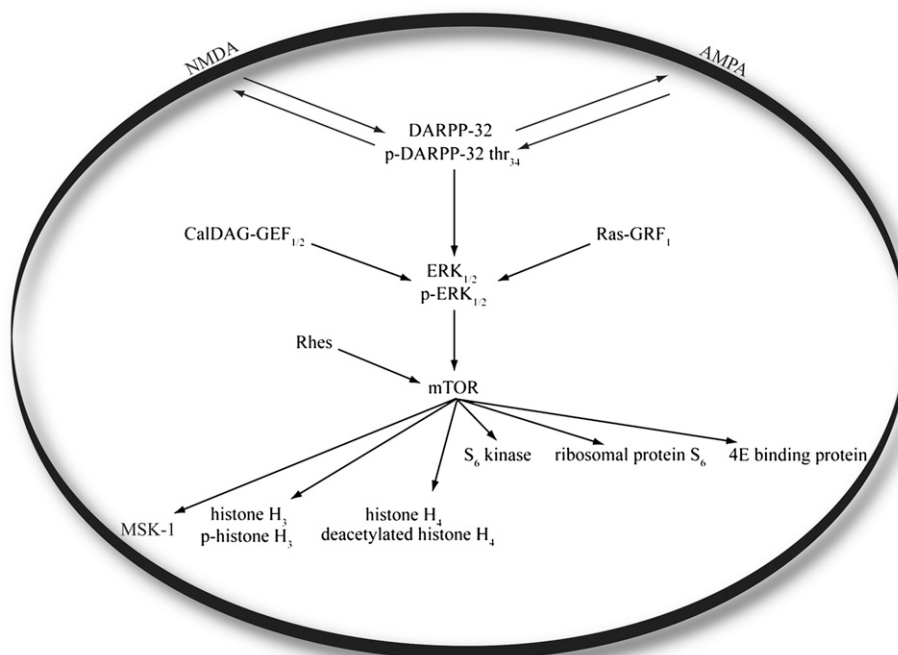


Fig. 3. There is evidence for increased DARPP-32 levels and increased levels of DARPP-32 phosphorylated at the Thr34 residue in dyskinesia. DARPP-32 phosphorylated at the Thr34 residue promotes phosphorylation of several cellular effectors such as AMPA and NMDA receptors. Abnormal DARPP-32-mediated signaling leads to abnormal phosphorylation of intracellular proteins, such as ERK1/2, whereas total ERK levels remain unchanged. The involvement of Ras-GRF1, an upstream regulator of ERK1/2 in dyskinesia, has also been demonstrated. Other upstream regulators of the ERK1/2-mediated cascade, CalDAG-GEF 1 and 2, were demonstrated to be affected in LID: CalDAG-GEF1 levels were decreased in the matrix, whereas CalDAG-GEF2 levels were increased in the striosomes. ERK then participates in the activation of mTOR and its downstream targets, including S6 kinase, ribosomal protein S6, and 4E-binding protein. Ultimately, this increase in ERK1/2 phosphorylation and downstream effectors such as mTOR has repercussions at the nuclear level, such as activation of MSK-1, phosphorylation of histone H₃, and phosphorylation of and histone H₄ deacetylation.

TABLE 6
DARPP-32, ERK1/2, and histone deacetylation in dyskinesia

- DARPP-32 levels are increased in the striatum.
- DARPP-32 abnormally phosphorylated at the Thr34 residue are increased in the striatum.
- ERK1/2 phosphorylation is increased in the striatum.
- Genetic inactivation of DARPP-32 attenuates the development of LI-AIMs in the 6-OHDA-lesioned mouse.
- Blockade of the mitogen-activated kinase/ERK kinase with SL327 attenuates the development of LI-AIMs in the 6-OHDA-lesioned mouse.
- Development of LI-AIMs is reduced in Ras-GRF1-knockout mice.
- Striatal delivery of a dominant-negative construct of Ras-GRF1 attenuates the severity of established LID in the MPTP-lesioned macaque.
- CalDAG-GEF1/2 levels are altered in the striatum of the dyskinetic 6-OHDA-lesioned rat killed in the off-state.
- Histone H₃ is dephosphorylated in the striatum of the dyskinetic MPTP-lesioned NHP.
- Histone H₄ is deacetylated in the striatum of both dyskinetic MPTP-lesioned NHPs and dyskinetic 6-OHDA-lesioned mice killed at peak LID.

agonist SKF-81,297, but not ropinirole (last dose administered 12 hours prior to the sacrifice, implying that the animals were killed in the off-state), normalized striatal levels of $G\alpha_{olf}$ (Corvol et al., 2004). The findings of that study are difficult to reconcile with those mentioned in the previous paragraph, i.e., reductions in cAMP in the striatum of dyskinetic 6-OHDA-lesioned rats. However, as mentioned above, increases in absolute levels of an enzyme, here $G\alpha_{olf}$, may not necessarily reflect its activity, because other factors such as phosphorylation are also important. Moreover, perhaps the increase in $G\alpha_{olf}$ levels represents a compensatory and not an etiological mechanism that aims at restoring normal cAMP levels in dyskinesia. Lastly, reduced cAMP levels in dyskinetic rats were demonstrated in the on-state, whereas increased $G\alpha_{olf}$ were demonstrated in the off-state, perhaps accounting for the discrepancy between studies.

XVI. Emerging Concepts in Dyskinesia

The field of LID is an area of intense and continuous research. Some emerging themes in the pathophysiology of dyskinesia will be briefly reviewed in this section.

A. Angiogenesis and Blood-Brain Barrier

In the dyskinetic 6-OHDA-lesioned rat treated for 2 weeks with L-DOPA and 5-bromo-2'-deoxyuridine (BrdU) and killed 24 hours after last drug administration, there was an increase in BrdU-positive endothelial cells within the denervated striatum, indicating endothelial proliferation in LID (Westin et al., 2006). In a subsequent experiment, stimulation of D₁ receptors and activation of ERK1/2 were demonstrated to be key in the endothelial proliferation process (Lindgren et al., 2009). In agreement with endothelial proliferation, vascular endothelial growth factor (VEGF) levels were found to be increased in the denervated striatum of dyskinetic 6-OHDA-lesioned rats killed 24 hours after last dose of L-DOPA, as well as in PD patients with a history of dyskinesia (Ohlin et al., 2011). VEGF mRNA levels were particularly elevated within the astrocytes and their end-feet processes. These studies

have also suggested increased blood-brain barrier permeability in the dyskinetic state. How angiogenesis and altered blood-brain barrier permeability contribute to dyskinesia remain unknown at the moment. However, these findings tally very well with a PET study that demonstrated increased blood flow and flow/metabolism dissociation in the putamen/GP complex of PD patients in the on-state, whether dyskinetic or not (Hirano et al., 2008).

B. Inflammation

In a study performed in the 6-OHDA-lesioned rat, systemic administration of the endogenous steroid corticosterone and intrastriatal administration of an interleukin-1 receptor antagonist both attenuated the expression of established LI-AIMs (Barnum et al., 2008). In that study, de novo treatment with corticosterone also attenuated the development of LI-AIMs (Barnum et al., 2008). Striatal levels of interleukin-1 β were also found to be elevated in the dopamine-depleted striatum of dyskinetic rats killed 2 hours after last L-DOPA dose (Barnum et al., 2008). The mechanisms by which anti-inflammatory agents alleviate LID are far from being elucidated. However, following corticosterone administration, levels of both PPE-B and PPT mRNA were normalized, suggesting normalization of the activity along the direct pathway.

C. Fatty Acids

Pharmacological studies performed in the MPTP-lesioned macaque have demonstrated that chronic daily administration of the ω -3 fatty acid docosahexaenoic acid (DHA) alleviated established LID while attenuating the priming process when administered de novo with L-DOPA (Samadi et al., 2006; Mahmoudi et al., 2009). Very little is known about fatty acids in PD and animal models of PD in regions known to be associated with motor control. Thus, one postmortem study investigating levels of ω -3 and ω -6 fatty acids in the brain of dyskinetic MPTP-lesioned NHP and dyskinetic PD patients measured ω -3 and ω -6 levels in the temporal cortex (Julien et al., 2006), and, although interesting, the results of that study bring little information with respect to dyskinesia. The mechanism(s) underlying the antidyskinetic action of

DHA remains unknown as does the effect of DHA on dopamine agonist-induced dyskinesia. Moreover, it also remains unknown whether DHA is involved in the pathophysiology of LID or if it simply alleviates LID by modulating dopaminergic and glutamatergic transmissions.

Despite the current lack of understanding of the mechanisms whereby DHA alleviates LID, the potential antidyskinetic efficacy of DHA is promising, because DHA could be advanced rapidly to clinical trials. Indeed, DHA is commercially available and has been associated with beneficial effect on the cardiovascular system (Mozaffarian and Rimm, 2006). However, perhaps somewhat undermining the potential of DHA as an antidyskinetic agent is the fact that, because DHA is readily available over the counter, many dyskinetic PD patients are already taking it and a reduction in dyskinesia severity has not been reported. On the other hand, high doses were required to alleviate LID in the parkinsonian NHP, 100–200 mg/kg p.o., and perhaps the doses taken by PD patients are too low to alleviate LID. Further studies are needed to validate DHA as a clinically relevant antidyskinetic molecule and to determine which doses, if any, are effective and well tolerated.

D. Exocytosis

The synaptic vesicle glycoprotein 2A (SV_{2A}), which is involved in exocytosis (Crowder et al., 1999), might play a role in the pathophysiology of dyskinesia, because it is currently the only known binding site of the anticonvulsant levetiracetam (Lynch et al., 2004). Levetiracetam effectively reduced the severity of dyskinesia elicited by either L-DOPA or the combination of L-DOPA and ropinirole in the MPTP-lesioned marmoset (Hill et al., 2003). In the MPTP-lesioned macaque, levetiracetam effectively alleviated L-DOPA-induced chorea but was ineffective against dystonia (Bezard et al., 2004). Concomitant administration of levetiracetam with amantadine potentiated the antidyskinetic action of amantadine in the L-DOPA-treated MPTP-lesioned marmoset (Hill et al., 2004b). Furthermore, levetiracetam interfered with the priming process when administered de novo in combination with L-DOPA to the MPTP-lesioned marmoset (Hill et al., 2004a). Clinically, however, an antidyskinetic effect of levetiracetam was not demonstrated (Wolz et al., 2010; Stathis et al., 2011; Wong et al., 2011).

The mechanism(s) by which modulation of SV_{2A} activity might alleviate dyskinesia remains to be established. SV_{2A} increases probability of vesicular release by priming vesicles in neurons in the resting state (Custer et al., 2006), and it is possible that modulating SV_{2A} leads to more physiologic release of dopamine and/or glutamate in the striatum. However, at this stage, it is important to emphasize that the antidyskinetic efficacy of modulating SV_{2A} in

preclinical studies does not necessarily indicate perturbed exocytosis or altered SV_{2A} function in dyskinesia, because modulating SV_{2A} may simply, for instance, reduce pulsatility of raphestriatal dopamine release. In vivo microdialysis studies are needed to confirm that possibility, whereas studies measuring SV_{2A} levels and phosphorylation status are needed to see whether its function is perturbed in LID.

However, another argument indicating possible altered exocytosis in LID comes from a study performed in the 6-OHDA-lesioned rat. Thus, chronic therapy with SKF-38,393 and development of AIMs led to an increase, whereas chronic therapy with quinpirole led to a decrease, in striatal mRNA levels of the transcription factor zif-268 when rats were killed 60 minutes after last treatment administration (Carta et al., 2010). Zif-268, also known as EGR1 (early growth response protein 1) or NGF1-A (nerve growth factor-induced protein 1A), is involved in the transcriptional regulation of synaptobrevin II (Petersohn and Thiel, 1996), an important protein in exocytosis (Bock and Scheller, 1999).

E. Thyrotropin Releasing Hormone

A study performed in the 6-OHDA-lesioned rat has found increased levels of thyrotropin releasing hormone (TRH) mRNA and an increase in pro-TRH immunostaining in the dorsal striatum of animals expressing AIMs killed 12 hours after last L-DOPA dosing (Cantuti-Castelvetri et al., 2010). These elevations were present in striatal medium spiny neurons contacting both the GP and the entopeduncular nucleus. How enhanced TRH in striatal projection neurons contribute to LID has yet to be demonstrated, but some hypotheses can be put forth. For instance, TRH increases GABA release in vivo in the hippocampus of anesthetized rats (Deng et al., 2006a). According to the classic model of the organization of the basal ganglia presented above, a TRH-mediated increase in GABA release at the striato-GPi/SNr complex would inhibit the output structures of the basal ganglia, thereby disinhibiting the glutamatergic thalamocortical projections with resulting enhanced cortical excitation. Systemic administration of TRH was also shown to increase striatal dopamine release in anesthetized rats (Kreutz et al., 1990), but the increase in TRH being localized to striatofugal neurons somewhat diminishes the likelihood of that possibility.

XVII. Concluding Remarks

Dyskinesia appears as a complex phenomenon, and several systems are involved in their pathophysiology. Although it is difficult to pinpoint a single factor leading to the development and expression of LID, nonphysiologic, pulsatile dopamine release and synaptic pruning in the previously denervated striatum both

seem to play critical roles. Of the other neurotransmitter systems described, glutamatergic neurotransmission has been most thoroughly studied and there is clear evidence that enhanced glutamatergic transmission is involved in the priming and expression of LID. At the moment, our understanding of dyskinesia, priming and expression, revolves around dopamine and glutamate transmissions and, with a few exceptions, is centered on the striatum. As such, although LID can be clearly modulated by a range of opioid, cannabinoid, and histaminergic drugs, the role played by such neuromodulators in LID pathophysiology is difficult to define. For instance, is enhanced cannabinoid transmission a direct etiological factor in dyskinesia or is it an epiphenomenon secondary to nonphysiologic dopaminergic and glutamatergic transmissions? The 5-HT system is a notable exception and is clearly responsible, in part at least, for the pulsatile delivery of dopamine to the denervated striatum. Ultimately, cellular transcription systems become affected, leading to changes in chromatin structure. The understanding of the intracellular mechanisms underlying the dyskinetic phenotype have progressed over the last few years, and it is now known that cascades involving DARPP-32 and ERK1/2, leading to histone H₄ deacetylation, are abnormal in dyskinesia.

The challenges associated with drug development in a scenario defined by a complexity of the changes affecting many neuromodulator systems perhaps explain why to date amantadine, which for historical reasons was able to somewhat bypass the modern drug development process, is the only widely used antidyskinetic agent. Indeed, as discussed above, it is far from a perfect drug; amantadine effects may wane over time, and if its action is to dampen NMDA-mediated glutamatergic transmission, it does not address the multitude of other abnormal processes occurring in dyskinesia. In view of these diffuse changes described herein, perhaps an approach targeting several neurotransmitter systems simultaneously might be more suited to alleviate dyskinesia and to maintain an antidyskinetic efficacy over a long-term period. Alternatively, the solution may lie in targeting the intracellular/intranuclear changes taking place in dyskinesia; targeting downstream changes might perhaps allow countering more efficiently the changes mediated by abnormal transmission along several neurotransmitter systems at a point where they converge. To date however, such an approach has been limited by difficulty for most drugs to enter the intracellular compartment and the concern of inducing nuclear changes and modifications in gene expression. Additionally, the search for long-lasting formulations of L-DOPA that would provide constant dopamine levels within the brain for extended periods of time must continue, because this could possibly be the best way to prevent the emergence and expression of LID

and, as a corollary, the best and safest antidyskinetic treatment.

These opportunities notwithstanding, the review presented here does illustrate how far the field of pharmacology of dyskinesia has progressed in recent years. The challenge may not be solely one of identifying the appropriate targets but in transitioning therapeutics from phase II to phase III success, a path that amantadine did not have to tread.

Authorship contributions

Wrote or contributed to the writing of the manuscript: Huot, Johnston, Koprach, Fox, Brotchie.

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