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Pathophysiology of Drug-Induced Dyskinesias

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1. Introduction

Parkinson's disease (PD) is a common neurological movement disorder that is characterized by bradykinesia, muscle rigidity and tremor due to progressive loss of dopaminergic nigrostriatal neurons. Currently, pharmacological treatment with levodopa (LD), the precursor of dopamine (DA), or other DA replacement therapies, such as synthetic DA agonists, are used to ameliorate parkinsonian symptoms. Although these treatments are effective at alleviating parkinsonism during the early stages of the disease, most advanced PD patients develop disabling, motor complications known as drug-induced dyskinesias. In this chapter, we define drug-induced dyskinesias as abnormal, excessive involuntary movements that occur with oral, pharmacological anti-parkinsonian medications for PD. One classic example is LD-induced dyskinesias. These disabling movements limit the effectiveness of pharmacological treatments.

The aim of this chapter is to introduce the phenomenology of drug-induced dyskinesias and evaluate the current theories for drug-induced dyskinesias, covering recent studies that identify the underlying pathophysiological changes on the biochemical/molecular (receptors, enzymes, and neurotransmitter systems), cellular (basal ganglia connections), electrophysiological (basal ganglia neuronal activity) and behavioral level that have been proposed to influence the development of drug-induced dyskinesias. We will also describe various treatment strategies currently utilized for drug-induced dyskinesias including adjunct pharmacological therapies and functional neurosurgery, most of which are currently limited in effectively diminishing drug-induced dyskinesias or unattainable for many patients. Because of the disabling nature of drug-induced dyskinesias, understanding the factors that contribute to the onset of drug-induced dyskinesias in PD will allow for the development of improved and novel treatment strategies that prevent or mitigate drug-induced dyskinesias without diminution of anti-parkinsonian effects.

2. Behavioral characteristics of drug-induced dyskinesias

2.1 Drug-induced dyskinesias in Parkinson's disease

Peak-dose dyskinesias are the most common form of dyskinesias and occur in 75% to 80% of the patients experiencing dyskinesias (Zesiewicz et al., 2007). The major risk factor has been considered to be severity of the disease. Peak-dose dyskinesias are due to a high dose of LD and represent an overdosed state. The plasma levels of LD are high and there is presumably excess striatal DA. Chorea is the most common form of involuntary movement in these cases. However, in later stages, dystonia can also occur. Chorea is more prominent in the head, trunk and upper limbs (Thanvi et al., 2007). Reducing the individual dose of anti-parkinsonian medication ameliorates the dyskinesias but can cause deterioration of parkinsonism. Hence these patients typically need more frequent dosing of anti-parkinsonian medication. Sustained-release LD formulations may prolong the duration of dyskinesia.

Diphasic dyskinesias develop when plasma levels are rising or falling but not with peak levels. These dyskinesias predominantly occur in the lower limbs and tend to be dystonic or choreiform. Treatment of diphasic dyskinesias is more difficult than peak-dose dyskinesias. Higher doses of LD can induce peak-dose dyskinesias and other adverse effects, while lower doses cause worsening of parkinsonism. The use of DA agonists with a longer duration of action and LD as supplementary drug is the most effective approach.

Off-period dystonia occurs when the plasma levels of DA are low, particularly in the early morning. It can be precipitated by anxiety or attempts to walk. It is characterized by painful spasms of the foot on the more affected side. It is treated by preventing the "offs". This can be achieved by use of DA agonists or sustained release LD formulations (Zesiewicz et al., 2007).

2.2 Preclinical animal models of drug-induced dyskinesias

2.2.1 Rodent models

Unilateral injection of the neurotoxin 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB) induces selective loss of nigrostriatal neurons (Ungerstedt & Arbuthnott, 1970) in the rat. This causes extensive loss of nigrostriatal neurons unilaterally (>95% loss), and significant loss of DA. This leads to a hemiparkinsonian rat model of PD that exhibits motor deficits in the forelimb contralateral to lesion. Administration of pharmacological DA replacement therapies such as LD or DA agonists induces abnormal involuntary, dyskinetic movements and contralateral rotational behavior. These abnormal involuntary movements are separated into orolingual dyskinesias (rapid protrusion of the tongue and chewing movements), truncal and neck dystonic posturing in the direction contralateral to lesion and hyperkinetic/dystonic posturing of the forelimb contralateral to lesion (Cenci et al., 1998; Steece-Collier et al., 2003; Lieu et al., 2010). Similar to the hemiparkinsonian rat, 6-OHDA can be injected into the MFB or striatum to create hemiparkinsonian dyskinetic mice (Lundblad et al., 2004; Pavon et al., 2006). In mice, knockout of the PitX3 gene prevents the development of nigrostriatal neurons. LD exposure induces dyskinesias in these animals in the form of hyperkinetic movements of the forelimbs and hindlimbs (Ding et al., 2011).

2.2.2 Primate models

Primates have played an important role in understanding the pathophysiological basis of drug-induced dyskinesias and in preclinical experimental therapeutics targeted at

diminishing or preventing drug-induced dyskinesias. Investigators have utilized various species to model drug-induced dyskinesias that include squirrel monkeys, common marmosets, macaques and vervet nonhuman primates (Boyce et al., 1990; Pearce et al., 1995; Heimer et al., 2006; Liang et al., 2008). Exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) leads to selective loss of dopaminergic nigrostriatal neurons, and is used in primates to induce parkinsonism. LD and other pharmacological DA replacement therapy induces hyperkinetic, abnormal involuntary movements (choreoathetosis, violent jerks, flailing of the limbs), dystonic, abnormal posturing in the extremities and trunk, and orolingual dyskinesias (purposeless protrusion of the tongue). This animal model displays dyskinesias more clinically similar to drug-induced dyskinesias in PD when compared to the parkinsonian rodent.

The extent of nigrostriatal damage necessary to induce dyskinesias in animal models has demonstrated varying results. In rats and mice, development of dyskinesias is typically after extensive loss of nigrostriatal neurons via MFB lesion, typically upward to 95% loss of dopaminergic neurons when compared to the unlesioned side. Single striatal injection of 6-OHDA as described previously (Sauer & Oertel, 1994) induces a partial lesion with approximately 50% degeneration. These rats do not develop dyskinesias with LD exposure. However, higher doses of 6-OHDA and multiple striatal injection sites can lead to extensive degeneration where such animals develop dyskinesias similar to the MFB-lesioned rat (Winkler et al., 2002). In the primate, some have demonstrated that normal monkeys without MPTP exposure or monkeys with minor nigrostriatal degeneration develop dyskinesias, whereas other investigators argue the necessity that extensive nigrostriatal damage bilaterally is essential for the development of dyskinesias (Kurlan et al., 1991; Pearce et al., 2001; Togasaki et al., 2001; Heimer et al., 2006; Liang et al., 2008). We have recently shown that macaque rhesus monkeys that are clinically hemiparkinsonian by intracarotid MPTP do not develop dyskinesias with chronic LD treatment (Lieu et al., 2011), indicating that bilateral parkinsonian rhesus monkey is a more suitable model for drug-induced dyskinesias in this species. We hypothesize that one mechanism by which hemiparkinsonian rhesus monkeys do not develop dyskinesias is by interhemispheric inhibition. This may be through the small percentage of nigrostriatal neurons from the contralateral hemisphere innervating the denervated striatum. In the hemiparkinsonian rat, our group has shown that there is a loss of interhemispheric nigrostriatal neurons in the hemiparkinsonian dyskinetic rat. However, interhemispheric nigrostriatal neurons are retained in normal and partial-lesioned non-dyskinetic rats (Lieu et al., 2009). This suggests that loss of interhemispheric nigrostriatal neurons may play a role in the development of drug-induced dyskinesias.

3. Differential diagnosis of dyskinesias

Drug-induced dyskinesias need to be differentiated from other hyperkinetic disorders in patients. They are as follows:

3.1 Tremor

In contrast to drug-induced dyskinesias which are involuntary, continual, abrupt, brief and irregular, tremors are oscillatory, rhythmic and regular and tend to affect the more distal parts of the upper extremities. Peak-dose dyskinesias, by definition, will appear only after

administration of anti-PD medications (typically 60-90 min) while tremor in PD will frequently mitigate upon administration of anti-PD medication. Rarely, diphasic dyskinesias may have to be distinguished from lower extremity tremor. Diphasic dyskinesias and tremor are both seen when anti-PD medication levels are low. However, on administration of anti-PD medications, diphasic dyskinesias tend to disappear sooner and abruptly as compared to parkinsonian tremor, which will mitigate slowly.

3.2 Huntington's disease

Chorea is a frequent manifestation of Huntington's disease. However, Huntington's chorea is easily distinguished by the family history, absence of temporal relation to dosing of anti-PD medications and by presence of several other typical findings in Huntington's disease that separates this entity from PD. This issue is more complicated in juvenile Huntington's disease. In this case, typically the patient is parkinsonian (Roos, 2010), does not exhibit chorea and is often treated with anti-PD medications. In this scenario, if the patient develops choreiform movements, they need to be distinguished from drug-induced dyskinesias as opposed to natural occurrence due to progression of Huntington's disease. Following points may be used to make this distinction:

- a. Drug-induced dyskinesias have a temporal course to timing of anti-PD medications while chorea occurring in Huntington's disease is random and has no temporal course.
- b. Juvenile Huntington's disease is a more severe form and invariably the patient will have more symptoms in other neurological domains beyond simple parkinsonism (dementia, ataxia, etc.)

A third scenario is when an adult Huntington's disease patient is treated with anti-dopaminergic medications (e.g. Haloperidol). This drug can produce tardive dyskinesias which need to be distinguished from drug-induced dyskinesias.

3.3 Tics and stereotypies

Tics are abrupt, brief, repetitive and stereotyped movements which vary in intensity and are repeated at irregular intervals (Jankovic, 2009). Patients usually have a generalized urge preceding the actual movement or local discomfort in the region of the body where the tic appears. Tics can be voluntarily suppressed but these result in mounting inner tension leading to a rebound of tics. Tics can also persist during sleep. Stereotypies are involuntary, patterned, repetitive, continuous, coordinated, ritualistic movements or utterances. Unlike tics, stereotypies are not preceded by an urge and usually occur during periods of stress, excitement or when engrossed. They can be ceased by distraction or initiation of a new activity.

Tics and stereotypies can be differentiated from dystonia by the absence of worsening on attempted movements. Tics and stereotypies can be differentiated from drug-induced dyskinesias which are choreiform. Also, drug-induced dyskinesias cannot be voluntarily suppressed.

3.4 Tardive dyskinesias

These are involuntary movements that are seen as a complication of long-term DA receptor antagonist therapy and present with rapid, repetitive, stereotypic movements involving oral, buccal and lingual areas. In cases where the patient is currently on DA receptor antagonists and exhibits signs of parkinsonism and oro-bucco-lingual involuntary

movements, it is easy to make the distinction between tardive dyskinesias and drug-induced dyskinesias. However, in very rare cases where the patient has been previously treated with one or more DA receptor antagonists for a short period but such information is not available at the time of clinical presentation, it becomes essential to differentiate between drug-induced dyskinesias and tardive dyskinesias. In such cases, the predominant oro-bucco-lingual involvement, lack of limb and trunk involvement and the absence of improvement on withdrawal of drugs help to differentiate tardive dyskinesias from drug-induced dyskinesias.

3.5 Myoclonus

Myoclonus is a sequence of repeated, often nonrhythmic, brief shock-like jerks due to sudden involuntary contraction or relaxation of one or more muscles. Myoclonus can be differentiated from dystonia by the lack of distinctive postures. Rhythmic myoclonus can be distinguished from chorea occurring in drug-induced dyskinesias by the predictable timing of movements. Asynchronous multifocal myoclonus is more difficult to distinguish but can be done so due to the simpler, shock-like movements of myoclonus compared to the more complex, randomly distributed movements in chorea.

4. Physiology of drug-induced dyskinesias

4.1 Functional models of the basal ganglia

Our current understanding of the functional connectivity for PD is based on the classic rate model of the “direct” and “indirect” pathways of the basal ganglia motor loop (Albin et al., 1989; Alexander et al., 1990; DeLong, 1990). In this model, the dopaminergic nigrostriatal pathway modulates the activity of two separate pathways in the striatum (STR) (DA D1-receptor mediated “direct” and DA D2-receptor mediated “indirect” pathways). With subsequent loss of DA due to nigrostriatal degeneration (neurons originating from substantia nigra pars compacta (SNC) and terminating in the STR) (Fig. 1A), the activity of the motor loops is altered, leading to parkinsonism. In the parkinsonian “direct” pathway, γ -Aminobutyric acid (GABA)-ergic striatal input to the globus pallidus interna/substantia nigra reticulata (GPI/SNR) is reduced, leading to a disinhibition and overactivity of the GABAergic GPI and SNR. In the parkinsonian “indirect” pathway, there is an increase in GABAergic striatal neuron activity to the globus pallidus externa (GPE) leading to inhibition of the GABAergic GPE. This leads to disinhibition of the glutamatergic subthalamic nucleus (STN) and overactivity of this nucleus. This pathway also causes increased activity of the GPI and SNR. Taken together, in the parkinsonian state, both the “direct” and “indirect” pathways lead to an excessive inhibition of the motor thalamus (THAL) and subsequently the motor cortex (CTX).

Based on this model, DA replacement therapy should result in balanced activity of the “direct” and “indirect” pathways (Fig. 1B). However, our group as well as other investigators has demonstrated that with oral pharmacological DA replacement treatment, various basal ganglia nuclei activity do not become “balanced” as the classic rate model would suggest (Heimer et al., 2002; Heimer et al., 2006; Gilmour et al., 2011).

The classic model described above would also predict that drug-induced dyskinesias would be accompanied by increased thalamocortical activity, reduced inhibitory output from GPI/SNR to the THAL, and therefore reduced STN glutamatergic output in the “indirect”

pathway and increased striatal output in the “direct” pathway (Fig. 1C). While some studies have supported this hypothesis, others have argued against it utilizing lesioning and electrophysiological studies of various basal ganglia nuclei (Bergman et al., 1990; Hamada & DeLong, 1992; Papa et al., 1999; Baron et al., 2000). Therefore, this model does not adequately explain the pathophysiology of drug-induced dyskinesias.

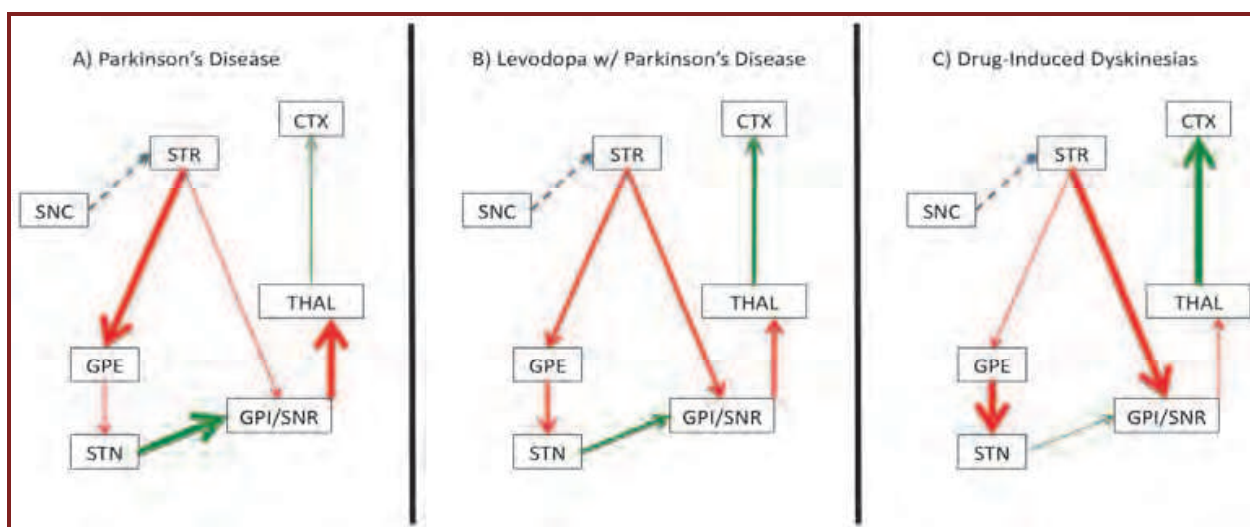


Fig. 1. Classic rate model of the basal ganglia. Red – GABA (Inhibitory); Green – Glutamate (Excitatory); Blue – Degenerated Dopaminergic Nigrostriatal Pathway. Size of arrows indicate extent of activity. In the normal state, the “direct” and “indirect” pathways would appear the same as Fig. 1B, except that SNC is intact.

4.2 Continuous versus pulsatile dopaminergic stimulation

DA is constitutively available in the brain, specifically via the nigrostriatal pathway in the normal state. With loss of DA in PD, the brain no longer has constitutive availability of DA, thus DA receptors are no longer tonically stimulated. It has been proposed that chronic intermittent, pulsatile treatment with pharmacological DA replacement therapies such as LD or DA agonists leads to supersensitivity of dopaminergic receptors (Chase et al., 1989). After oral administration of pharmacological anti-PD medications, plasma levels of these therapies will fluctuate throughout the day based on pharmacokinetics and half-life of the drug in PD patients, thus providing intermittent activation of DA receptors. Presence of intact nigrostriatal neurons allows the brain to store, release and re-uptake DA on demand. Since LD is a prodrug and has to be converted to DA, remaining intact nigrostriatal neurons are able to buffer, store, release on demand, and reuptake DA in early stages of PD. However, as the disease progresses to more advanced stages, there is extensive loss of nigrostriatal neurons and these mechanisms fail, leading to a more pulsatile activation of dopaminergic receptors. Drugs with longer half-lives, combinational pharmacological therapies and cell transplantation studies have provided evidence that continuous dopaminergic stimulation can both provide better symptomatic relief and mitigate/prevent drug-induced dyskinesias. Although there are groups working on biomarkers for drug-induced dyskinesias like positron emission tomography, there is no conclusive evidence that it can predict occurrence of dyskinesias (Feigin et al., 2001; Eidelberg, 2009).

5. Biochemical and molecular mechanisms of drug-induced dyskinesias

5.1 DA receptors

DA receptors are metabotropic G-protein-coupled receptors widely expressed throughout the basal ganglia but mainly in the striatum. The two main family subtypes of DA receptors are D1-like and D2-like receptors. The pathophysiological mechanisms of drug-induced dyskinesias have been attributed to striatal DA receptor supersensitivity. Earlier studies have shown that the presence of mRNA encoding for D1 receptors decreases and D2 receptors increases in response to dopaminergic denervation in earlier rodent studies (Gerfen et al., 1990), which is further confirmed in PD patients and MPTP-treated monkeys (Lee et al., 1978; Alexander et al., 1993; Morissette et al., 1996). More recently, Aubert et al. found differential changes of D1 and D2 receptor expression in dyskinetic monkeys, showing an increase in D2 mRNA and D2 ligand-binding compared to controls. D1 mRNA is also downregulated in MPTP monkeys but comparable to normal in LD treated parkinsonian monkeys. Further, they demonstrate that increased D1 receptor signaling is linearly related to dyskinesias (Aubert et al., 2005). It had been also been reported that there is an increase in both membrane and cytoplasmic striatal D1 receptor expression in MPTP-treated dyskinetic monkeys compared to normal monkeys, with only moderate changes in D2 receptor expression (Guigoni et al., 2007).

Therefore, previous studies demonstrate that plastic changes of DA receptors occur in response to DA denervation and pharmacological dopaminergic treatments. The notion of DA receptor supersensitivity is a combination of alterations to striatal DA receptor expression and subsequent G-protein second messenger signaling (see below). Although our understanding of DA receptor plasticity and supersensitivity has been studied mainly in the striatum for the underlying molecular changes associated with dyskinesias, future studies that examine alterations to the extrastriatal DA and receptor expression in the GPE, GPI, STN and SNR are warranted (Rommelfanger & Wichmann, 2010).

5.2 Second messenger signals

Neuronal second messenger signaling cascades are important for synaptic plasticity, modulation of downstream proteins and control of gene transcription factors (immediate early gene expression) which are modulated by DA receptors (Fig. 2). It has been reported that there is a significant increase of phosphorylation of ERK (P-ERK) in the DA denervated striatum in dyskinetic animals, and that blockade of ERK phosphorylation with the MEK1/2 inhibitor SL-327 or Ras inhibitor lovastatin significantly decreases dyskinesias (Pavon et al., 2006; Schuster et al., 2008; Ding et al., 2011). It has further been shown that phosphorylation of ERK increases in MSN after acute LD exposure but chronic LD exposure translates into a decrease in MSN ERK phosphorylation and reciprocal increases in cholinergic striatal interneurons. Similarly, another related second messenger signal, the DA- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) has also been implicated in the onset of drug-induced dyskinesias (Santini et al., 2010). More specifically, increased phosphorylation on the Thr34 (P-Thr34) site of the protein seems to be associated with onset of drug-induced dyskinesias (Guan et al., 2007). We have shown that striatal DARPP-32 expression is selectively decreased in dyskinetic hemiparkinsonian rats compared to normal rats (Lieu et al., 2008). In the normal rat, we found relative uniformity of DARPP-32 immunohistochemical staining throughout the striatum bilaterally. However, in the LD-treated dyskinetic rat, we found decreased staining in dorsolateral areas of the striatum in

the unlesioned hemisphere and an overall decrease in the density of staining in various regions of the lesioned hemisphere. Studies in dyskinetic rats and monkeys evaluating the transcription factors Δ FosB and Δ JunD within the striatum have also been implicated in the onset and maintenance of dyskinesias (Pavon et al., 2006; Berton et al., 2009; Cao et al., 2010). As mentioned previously, these maladaptive changes of second messenger signals are likely to be the direct result of DA receptor supersensitivity.

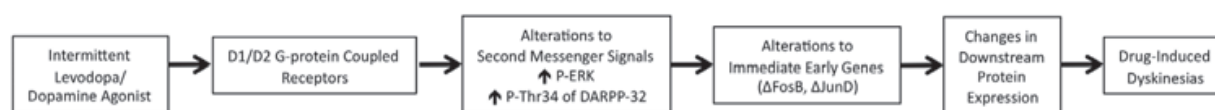


Fig. 2. Signal transduction in drug-induced dyskinesias in Parkinson's disease

5.3 GABA

GABA, being one of the major inhibitory neurotransmitters in the basal ganglia, is present in striatonigral and striatopallidal neurons. These 2 subsets of neurons express 2 isoforms of the GABA synthesizing enzymes, GAD65 and GAD67 (Mercugliano et al., 1992). Systematic administration of LD induces significant increases in GAD gene expression in striatonigral neurons (Soghomonian et al., 1996; Cenci et al., 1998; Carta et al., 2003; Nielsen & Soghomonian, 2004; Katz et al., 2005; Yamamoto & Soghomonian, 2009) and a small increase in GAD gene expression of striatopallidal neurons (Carta et al., 2003; Nielsen & Soghomonian, 2004; Carta et al., 2005). Although GABAergic striatal interneurons are not primarily affected in PD, as a result of progressive DA depletion, expression levels of GABA receptors change in the striatum. Subchronic administration of LD to 6-OHDA-lesioned rats induces marked increases in GABA release in the SNR (Yamamoto et al., 2006), and this increase was blocked by subchronic administration of an mGluR5 agonist (Mela et al., 2007). This suggests that a GlutR5 agonist can efficiently decrease the severity of drug-induced dyskinesias in animal models of PD. Pulsatile dopaminergic stimulation can cause up-regulation of GABA receptors in GPI. GABA receptors were reported to be up-regulated in GPI of primates with drug-induced dyskinesias (Calon et al., 1999) and dyskinetic PD patients (Calon & Di Paolo, 2002). There have been reports on Modafinil preventing the MPTP-induced GABA-A receptor binding in the GPI of MPTP treated marmosets (Zeng et al., 2004). This study showed partial improvement in PD symptoms.

5.4 Glutamate

Glutamate is the main excitatory neurotransmitter in the basal ganglia. During the progression of PD, as a result of DA depletion in basal ganglia and treatment with LD or D1 receptor agonists, the glutamate levels are elevated, and have shown that increased expression of glutamate receptor resulted in dyskinetic behavior (Calon et al., 2002; Ouattara et al., 2010). Calon and colleagues (Calon et al., 2002; Calon et al., 2003) have shown an elevation of NMDA receptor binding in the putamen (53%) during motor fluctuation when compared to patients without motor fluctuation. Later in support of Calon's hypothesis, a number of ionotropic and metabotropic receptor antagonists have been shown to reduce drug-induced dyskinesias. A recent study showed a beneficial motor effect by AFQ056 (a metabotropic glutamate receptor type 5 antagonist) with LD in MPTP monkeys, supporting the therapeutic use of an mGluR5 antagonist to restore normal glutamatergic neurotransmission in PD and decrease dyskinesias (Gregoire et al., 2011).

5.5 Serotonin (5-HT)

Carta et al. (Carta et al., 2007) showed a prodyskinetic effect by the DA released by serotonergic neurons. When they transplanted fetal serotonergic neurons into the DA denervated striatum, the dyskinetic behaviors were induced by a single dose of LD itself in an already primed animal when compared to the pretransplantation score. When fetal dopaminergic neuronal grafts were introduced, this was able to reduce the abnormal involuntary movements significantly. It was previously reported that the partial 5-HT_{1A} agonist buspirone reduced development and expression of drug-induced dyskinesias (Eskow et al., 2007). Recently Politis and colleagues (Politis et al., 2010) showed that dyskinesias were markedly attenuated by systemic administration of a serotonin receptor agonist (5HT_{1A}R agonist) which dampened the transmitter release from serotonergic neurons indicating that the dyskinesias were caused by the serotonergic hyperinnervation. i.e, serotonergic neurons mediate dyskinetic side effects in PD patients with normal transplants. Recently Zeng et al. observed that striatal 5-HT hyperinnervation follows nigrostriatal pathway loss and provide the first evidence in primates that chronic LD treatment and the onset of dyskinesias are associated with a marked hypertrophy of striatal 5-HT axonal varicosities (Zeng et al., 2010).

5.6 Acetylcholine

Acetylcholine has been another neurotransmitter implicated in the modulation of drug-induced dyskinesias. A number of studies have demonstrated that in 6-OHDA lesioned rats and MPTP dyskinetic monkeys, long term exposure to nicotine, which acts on nicotinic acetylcholine receptors, can reduce drug-induced dyskinesias. Interestingly, the nicotinic receptor antagonist mecamylamine can also provide similar effects (Quik et al., 2007; Bordia et al., 2008; Bordia et al., 2010). It has been recently demonstrated that drug-induced dyskinesias can effectively be decreased by selective nicotinic receptor agonists in dyskinetic partially lesioned rats (Huang et al., 2011). The authors suggest that expression of nicotinic receptors on dopaminergic terminals may play a role in modulating dyskinesias. As mentioned previously, studies have also demonstrated an increase in striatal cholinergic interneuron activity in dyskinetic mice (Ding et al., 2011). Thus, although acetylcholine is not as widely expressed as other neurotransmitters (glutamate, GABA, and DA) within the basal ganglia, its role in dyskinesias warrants further research.

5.7 Adenosine

Adenosine A_{2A} receptors are G-protein-coupled receptors that have been implicated in the pathophysiology of drug-induced dyskinesias. Adenosine A_{2A} receptors are mainly present in GABAergic striatopallidal neurons, colocalized with enkephalin and D₂ receptors. Adenosine A_{2A} receptors mRNA levels in the putamen are known to be increased in PD patients with dyskinesias, when compared to normals or PD patients without dyskinesias. Furthermore, specific-binding to adenosine A_{2A} receptors is elevated in dyskinetic PD patients compared to controls in the putamen, and elevated in PD patients when compared to normals in the GPE (Calon et al., 2004). These significant increases in A_{2A} receptor mRNA have been further confirmed in the rat model of drug-induced dyskinesias when compared to sham-treated animals with LD treatment and 6-OHDA lesioned rats without LD (Tomiya et al., 2004). Interestingly, increases in A_{2A} receptor mRNA has been found in normal cynomolgus monkeys displaying dyskinesias with chronic

LD treatment (Zeng et al., 2000). Recently, it had been shown that genetic knock-out of forebrain A2A receptors in mice can attenuate dyskinesias after LD treatment (Xiao et al., 2006).

Adenosine A2A receptor antagonist administration in parkinsonism has been extensively examined, demonstrating that antagonism can increase anti-parkinsonian effects of pharmacological DA replacement therapies without exacerbating dyskinesias in preclinical models and in PD patients (Kanda et al., 1998; Lundblad et al., 2003; Xiao et al., 2006; LeWitt et al., 2008). Taken together, adenosine A2A receptor antagonists and pharmacological DA replacement treatment can be a useful combinational therapy to target dyskinesias.

5.8 Other chemical systems

Other chemical systems besides the traditional neurotransmitters are present throughout the basal ganglia and play an important role in dyskinesias. It has been shown that neuropeptide mRNA levels of striatal preproenkephalin (PPE) and prodynorphin (PPD) are increased in dyskinetic MPTP-lesioned monkeys compared to control MPTP-lesioned monkeys, similar to previous reports in the 6-OHDA lesioned parkinsonian rat (Gerfen et al., 1990; Zeng et al., 2000; Morissette et al., 2006; Guan et al., 2007; Tamim et al., 2010).

Using opioid receptor-stimulated G-protein activation techniques, Chen and colleagues demonstrated that μ -opioid receptor-mediated G-protein activation is increased in the brain, specifically the cortex and basal ganglia in dyskinetic monkeys treated with LD. They also found binding changes in δ - and κ -opioid receptor in these animals (Chen et al., 2005). Furthermore, μ -opioid and δ -opioid stimulated binding in the striatum was positively correlated to dyskinesia severity. In a later study, it was shown that pre-treatment with the κ -opioid agonist U50,488 can reduce drug-induced dyskinesias in the parkinsonian rat and primate (Cox et al., 2007). However, U50,488 had the deleterious effects of reducing the anti-PD effects of LD.

Another system is the cannabinoid system which is also widely expressed in the basal ganglia, and modulates the activity of other neurotransmitter systems such as glutamate and DA. Cao and colleagues demonstrate the selective antagonism of cannabinoid type 1 receptor can increase the efficacy of LD without affecting the severity of dyskinesias in parkinsonian rhesus monkeys (Cao et al., 2007). Taken together, the biochemical and molecular mechanisms associated with dyskinesias are complex and still warrant further research.

6. Electrophysiological changes in drug-induced dyskinesias

6.1 Globus pallidus externa (GPE) and interna (GPI)

Most of the present electrophysiological studies of drug-induced dyskinesias are linked to an excessive decrease in activity in the GPI. In a study by Fillion et al. (Fillion et al., 1991), the mixed (D1 and D2) DA agonist apomorphine was injected in MPTP monkeys. They showed that all GPI neurons decreased their firing rate following apomorphine. The reverse was true of the predominant neuronal population in the GPE. A similar study by Boraud et al. (Boraud et al., 1998) supports the correlation between dyskinesias and an excessive decrease in the firing frequency of GPI neurons. A similar excessive decrease was reported by Papa and colleagues (Papa et al., 1999) in MPTP-treated monkeys treated with LD. This study showed that during dyskinesias, the firing rates declined profoundly in almost all cells of

GPI, with a decrease as low as 97% in individual cells. From recordings in parkinsonian patients treated with apomorphine, Lozano and colleagues suggested that dopaminergic agents act by decreasing GPI and STN activity, and increasing GPE activity (Lozano et al., 2000). They went on to suggest that drug-induced dyskinesias resulted from a large reduction in GPI firing.

The predominant electrophysiological signature of drug-induced dyskinesias at present is the excessive decrease in GPI activity. However, the idea that the hypoactivity in GPI is the primary mechanism by which drug-induced dyskinesias occurs is challenged by the fact that a pallidotomy, which abolishes activity in GPI, eliminates dyskinesias (Baron et al., 2000; Lozano et al., 2000). As a result, some have suggested that the pathophysiology of dyskinesias is not simply the result of the hypoactivity observed in GPI, but rather the result of a change in the firing pattern output of GPI. This would explain why a pallidotomy eliminates the drug-induced dyskinesias, as the abnormal firing pattern is removed (Obeso et al., 2002).

Other studies have examined the role of oscillatory activity in the basal ganglia with respect to drug-induced dyskinesias. In MPTP monkeys, Heimer and colleagues (Heimer et al., 2006) found increases in oscillatory activity and synchronization in GPI and GPE after induction of parkinsonism, and decreases in both following DA replacement therapy. Although DA replacement therapy had a reversal effect on the changes resulting from MPTP, they noted an imbalance in the oscillatory power and synchronization between GPI and GPE. Further studies on the electrophysiology of drug-induced dyskinesias must take into account the present results and explore the finer aspects of discharge characteristics like the firing patterns, multiple rhythms, oscillations, and synchronization in various regions of the basal ganglia circuitry.

6.2 Subthalamic nucleus (STN) and substantia nigra reticulata (SNR)

Since a change in the firing pattern of neurons from bursting to random pattern has also been implicated in the genesis of dyskinesias, recent work from our laboratory examined the effects of chronic LD treatments on the firing rate and firing pattern of STN and SNR neurons in the stable hemiparkinsonian monkey model of PD without dyskinesias (Gilmour et al., 2011). We also evaluated local field potentials (LFP) of both nuclei before and after LD treatments. We found that LD treatments did not significantly change the mean firing rate of STN neurons or bursting neuronal firing patterns. However, LD treatments induced a significant reduction of the mean firing rates of SNR neurons and a trend toward increased burstiness. The entropy of the spike sequences from STN and SNR was unchanged by LD treatment, but there was a shift of spectral power into higher frequency bands in LFP.

In a recent study that recorded LFP from STN using an externalized deep brain stimulator electrode, a desynchronizing effect of LD was noticed on two separate rhythms of STN (Priori et al., 2004). The oscillatory activity increased at low frequency (2–7 Hz range), while the beta oscillations significantly decreased in the low-beta range. Similar effects were observed with apomorphine. Others have shown that an increase in the theta/alpha band of the oscillatory activity can lead to drug-induced dyskinesias in the presence of excess DA in the SNR of the 6-OHDA-lesioned rat (Meissner et al., 2006). These studies add to the evidence that the imbalance of multiple rhythm systems may lead to drug-induced dyskinesias.

Another recent study examined the activity changes in the SNR of non-parkinsonian monkeys with apomorphine induced orofacial dyskinesias (Nevet et al., 2004). Recordings were performed before (no dyskinesias) and after (with dyskinesias) administration of apomorphine. They found that 96% of the cells recorded exhibited a change in firing rate after the dose of apomorphine, with 70% showing a reduction. As in our study with LD, they did not observe significant changes in firing pattern. As a result, the authors suggest that dyskinesias are more related to a decrease in neuronal firing rate in the SNR, rather than a change in the firing pattern. More work is needed to understand the role of basal ganglia neuronal firing patterns and its relationship to the long-term symptomatic effects of LD treatment.

6.3 Striatal medium-spiny neurons (MSN)

Striatal MSN respond to DA input to the striatum, mediated by D1 (excitatory) and D2 (inhibitory) DA receptors. The “direct” striatal output pathway largely consists of the D1 receptor type, whereas the “indirect” pathway consists of the D2 type. In a recent study, Liang and colleagues (Liang et al., 2008) recorded from MSN of severely parkinsonian monkeys during three periods: 1.) “OFF” states in which the monkeys exhibited parkinsonian disability; 2.) “ON” states in which the monkeys were treated with LD and regained motor control; and 3.) during high doses of LD which induced dyskinesias. During the OFF state, the authors found a significant increase in neuronal firing rate (2.7 – 52Hz), which is in contrast to what has been classically observed in the normal animal (0.5-2Hz). This increase in firing rate was observed in MSN from both the D1 and D2 pathway. In the ON state, an overall increase in activity was observed, although some neurons exhibited an increase in firing rate (63.6%) and some a decrease (33.6%). It is assumed that the increases and decreases corresponded to the excitatory and inhibitory pathways, respectively. In the dyskinetic state, the overall firing rate was similar to that observed in the ON state. However, some neurons showed an increase in firing rate from OFF to ON to ON with dyskinesias, and some neurons showed an increase from OFF to ON and then a decrease during ON with dyskinesias. The authors suggest that this combination of uni- and bidirectional changes with increases in DA leads to an imbalance of MSN activity. Interestingly, this result correlates with the suggestion by others that although enabling movement, this imbalance of striatal activity may result in dyskinesias (Wichmann & DeLong, 1996; Mink, 2003).

7. Graft-induced dyskinesias

Cell grafts have been increasingly researched over the past three decades as a method of endogenously resupplying DA to the depleted basal ganglia in a continuous fashion. The primary type of cells used in the early studies was fetal ventral mesencephalic cells, progenitors to the nigral cells which degenerate in PD. In the 1990s and early 2000s, after animal studies and open-label clinical trials had shown therapeutic benefits of cell transplants, two double-blind placebo-controlled multicenter studies were funded by the National Institutes of Health (NIH).

The results were disappointing; some patients received symptomatic benefits, but many patients did not (Freed et al., 2001; Olanow et al., 2003). Additionally, up to half of the patients developed dyskinetic movements that persisted even after multi-day withdrawal of

dopaminergic medications. These symptoms have since been labeled graft-induced dyskinesias (GID) and look similar to diphasic dyskinesias. Several hypotheses have been proposed for the cause of these GID.

One of the first proposed causes of GID was that the grafts were producing "hotspots" of excessive DA in small, localized areas of the striatum. A related factor of dorsal versus ventral striatal placement was suspected. It was suggested that small DA-producing grafts might be reducing the striatal DA supersensitivity only in a small area around each graft, and this imbalanced and patchy reinnervation produced GID. In support of this hypothesis, Ma and colleagues (Ma et al., 2002) saw significantly increased uptake of ^{18}F -dopa in five patients with GID, with the increase localized to small focal areas in the grafted putamen. This hypothesis was also supported by a study by Carlsson and colleagues in a rat model of PD showing differential effects on drug-induced dyskinesias due to rostral versus caudal striatal grafts (Carlsson et al., 2006). However, Piccini and colleagues showed using another ^{18}F -dopa experiment that patients with GID did not show abnormal DA release from graft areas (Piccini et al., 2005), and subsequent post-hoc analysis of larger numbers of grafted patients showed no correlation between striatal reinnervation and GID (Hagell et al., 2002; Olanow et al., 2003).

Another hypothesis was that GID were caused by immune system rejection of the grafts. Early analyses showed that some patients with GID showed low-level inflammation around their grafts (Hagell et al., 2002), and GID worsened in some patients after immunosuppression was stopped (Piccini et al., 2005). However, a recent experiment which induced graft rejection in a rat model did not show an increase in abnormal involuntary movements, suggesting that inflammation and rejection alone may not be the primary cause of GID (Lane et al., 2008).

Because the risk of developing GID has been shown to vary depending on the patient, another hypothesis for the origin of GID is that it stems from the same pathophysiology as drug-induced dyskinesias. All of the original patients in the Freed and Olanow NIH studies who developed GID had previously been exposed to many years of intermittent LD therapy, suggesting possible priming and hypersensitization of the striatum. Pre-transplant drug-induced dyskinesias has been implicated in the development of GID and is increasingly seen as a counterindication for transplant (Lane et al., 2010). Experiments in rodent PD models have similarly shown correlations between pre-transplant drug-induced dyskinesias and post-transplant amphetamine-induced dyskinesias (Lane et al., 2006; Lane et al., 2009; Lane et al., 2009).

Another hypothesis is that GID is the result of aberrant synaptic graft-host connectivity. Studies have previously shown degeneration of dendrites and dendritic spines on the striatal MSN in advanced PD (Stephens et al., 2005). Soderstrom and colleagues recently looked at synaptic connections to dendrites near graft sites, showing that decreases in tyrosine hydroxylase-positive synapses onto striatal dendritic spines and increases in asymmetric excitatory synapses correlate with GID in rat models (Soderstrom et al., 2008). Further studies showed that chronic administration of nimodipine, a calcium channel blocker which had been shown to preserve striatal dendritic spines, reduced GID (Soderstrom et al., 2010). Another approach to avoiding aberrant graft synaptic connectivity has been the use of retinal pigment epithelial (RPE) cells, which produce LD and possibly DA but do not form axons or synaptic connections (Subramanian et al., 2002; Bakay et al., 2004). These RPE cells have been shown to provide symptomatic benefit in both animal

trials and open-label clinical studies. Promising recent research with new inducible pluripotent stem cells and inducible neuron-like cells shows progress toward dopaminergic therapeutic grafts developed from patients' own donor cells (Wernig et al., 2008; Vierbuchen et al., 2010).

A final hypothesis for the cause of GID is the accidental inclusion of serotonergic cells in the dopaminergic graft. Serotonergic neurons are known to be able to convert, store, and release DA under certain conditions (Tanaka et al., 1999). The patients in the Freed NIH study who developed GID had been transplanted with neurons which had been cultured for several days, a technique which is known to increase the proportion of serotonergic neurons compared to dopaminergic neurons. It was recently shown in a rat PD model that serotonergic striatal grafts increased drug-induced dyskinesia activity (Carta et al., 2007; Carlsson et al., 2009). Drug-induced dyskinesias is not identical to GID, as drug-induced dyskinesias is seen during and after the surge in DA which follows LD ingestion (de la Fuente-Fernandez et al., 2004), and some studies show no relationship between GID and serotonergic innervation in the rat model (Lane et al., 2009). However, recent studies in human patients continue to support the serotonergic cogaft hypothesis for GID. Politis and colleagues used ^{11}C -DASB PET to show that two grafted patients with GID showed much higher levels of striatal serotonin receptor expression than other grafted patients without GID (Politis et al., 2010). Furthermore, GID was significantly reduced by systemic administration of buspirone, a 5-hydroxytryptamine agonist which reduces serotonin release.

In summary, the exact cause of GID still remains to be clarified, and several factors may well be involved. Promising hypotheses for reducing GID are garnering increasing experimental support, including selection of patients without severe drug-induced dyskinesias, optimization of novel cell sources and transplant techniques to reduce immune reaction and decrease serotonergic progenitor cells, and pharmacological methods of preserving striatal spines and increasing striatal dopaminergic reinnervation.

8. Adjunct drugs to reduce drug-induced dyskinesias

8.1 Amantadine

Amantadine is a NMDA receptor antagonist and has been found to be efficacious in the treatment of drug-induced dyskinesias without reducing antiparkinsonian benefits. Its antidyskinetic effect gives support to the glutamatergic theory as a pathophysiological mechanism. Double-blind placebo-controlled studies have demonstrated 45% to 60% reductions in dyskinesia. Benefits are typically seen in 3 weeks following initiation of treatment. The benefits of Amantadine have been shown to last for only 8 months to 1 year in some studies (Sawada et al., 2010). A more recent study has shown that the antidyskinetic effects last longer than 1 year and has advocated the continued use of Amantadine for the treatment of dyskinesias (Wolf et al., 2010). Also, discontinuation of Amantadine has been shown to worsen dyskinesias. Amantadine is initiated at a dose of 100 mg/day and can be increased up to 300 mg/day. Potential side effects are confusion, hallucination, edema of feet and livedo reticularis.

8.2 Sarizotan

Sarizotan is a 5-HT_{1A} receptor agonist and is a high affinity antagonist for D₃ and D₄ receptors. The beneficial effects of Sarizotan are probably due to its 5-HT_{1A} agonist

properties. It has been found to reduce dyskinesia in 6-OHDA lesioned rats and in MPTP-lesioned monkeys (Bibbiani et al., 2001). In open label studies, Sarizotan in a dose range of 4 to 20 mg/day showed promising results in decreasing dyskinesias (Olanow et al., 2004). A double-blinded placebo-controlled study demonstrated significant decrease in the duration and severity of dyskinesias on the Unified Parkinson's Disease Rating Scale (UPDRS) with 2 mg/day Sarizotan compared to placebo. UPDRS is a standard rating tool used in clinical research. Other clinical tools to measure dyskinesias (patients' home diary and abnormal involuntary movements scale score) did not show any changes while on this dose. Higher doses were associated with worsening of parkinsonism with no additional anti-dyskinetic benefits (Goetz et al., 2007). Sarizotan is well-tolerated and studies have not shown any adverse effect compared to placebo.

8.3 Levetiracetam

Levetiracetam is an anti-epileptic drug. It has been found to reduce dyskinesias in MPTP lesioned primates. We were the first to report improvement in drug-induced dyskinesias upon treatment with low doses of Levetiracetam in an open label study (Tousi & Subramanian, 2005). Other open label studies provided mixed efficacy results and poor tolerability due to somnolence. More recently, two double-blinded placebo-controlled studies have evaluated the efficacy and safety of Levetiracetam in the treatment of dyskinesias (Stathis et al., 2010; Wolz et al., 2010). In one study (Wolz et al., 2010), patients received 250 mg/day titrated gradually to a dose of 2000 mg/day over 7 weeks followed by a 4-week maintenance phase. There was a significant difference in UPDRS dyskinesia ratings (duration and severity) between the two groups. There was no significant change in abnormal involuntary movements scale score. In the other study (Stathis et al., 2010), patients received 500 mg/day and 1000 mg/day each for 2 weeks. 'On with dyskinesia' time decreased and 'On without dyskinesia' time increased significantly in the treatment group. Duration of dyskinesias decreased significantly while, severity decreased but the change was not significant. Both studies did not demonstrate worsening of parkinsonian symptoms. The most common side effects are somnolence and dizziness. However, in contrast to the open label studies that reported intolerable side effects leading to high dropout rates, the double-blinded placebo-controlled studies did not report severe adverse effects. The mechanisms of the antidyskinetic effects of Levetiracetam are unknown. It has been hypothesized that it could be due to modulation of the pathological synchronization and desynchronization of neuronal circuits of the basal ganglia and maladaptive DA release and reuptake at the presynaptic level. The recent trials provide promising data that Levetiracetam might be useful for treatment of drug-induced dyskinesias without reducing the efficacy of antiparkinsonian therapy.

8.4 DA agonists

DA agonists are often used as adjuncts to LD in advanced PD. DA agonists exert their pharmacological effect by directly activating the DA receptors bypassing the presynaptic synthesis of DA. These include non-ergot compounds, such as Ropinirole and Pramipexole, and apomorphine. DA agonists when used as the initial form of therapy can help to delay onset of LD-induced complications. In patients who have already developed dyskinesias, addition of a DA agonist may permit a reduction in LD dose without worsening of parkinsonism. The addition of a DA agonist might result in worsening of dyskinesias but this

can be corrected by lowering the dose of LD. If lowering the dose of LD results in increased “off” states, then the agonist dose needs to be increased. However, patients experiencing severe dyskinesias are rarely controlled with this regimen in the long term. Apomorphine being water-soluble can be injected subcutaneously or applied intranasally. The use of continuous subcutaneous apomorphine infusion has been found to abort “off” periods, reduce dyskinesias, and improve PD motor scores, with the added benefit of an LD-sparing effect (Deleu et al., 2004). Apomorphine can cause severe nausea and vomiting due to its fast onset of action. Hence the patient should be pretreated to prevent nausea. Ropinirole and Pramipexole are initiated at a dose of 0.25 mg and 0.125 mg three times a day respectively and titrated to effect (Hinson, 2010). In contrast to the traditional ergot agonists, the non-ergots have a lower risk of complications such as peptic ulcer disease, vasoconstrictive effects, erythromelalgia and valvular heart disease. Other common adverse effects include drowsiness, sleep attacks, confusion, orthostatic hypotension, nausea and leg/ankle edema. Ropinirole has a higher incidence of hypotension and somnolence while Pramipexole is associated with a higher risk of hallucinations (Jankovic & Aguilar, 2008).

9. Surgical management of drug-induced dyskinesias

Drug-induced dyskinesias have a treatment limiting effect on pharmacological approaches in the treatment of PD. In these patients, surgical intervention becomes necessary. Ablative surgeries in the past had a relatively limited role due to the nature of the procedure, irreversibility and the inability to modulate the therapy according to the need of the patient. Since the advent of deep brain stimulation (DBS), surgical options have become more accepted in these patients (Rezai et al., 2008). Both ablative and DBS procedures are effective in the treatment of LD-induced motor complications, such as drug-induced dyskinesias, that cannot be satisfactorily controlled with medical therapies (Guridi et al., 2008). The modalities by which surgical interventions reduce dyskinesias are multifold: 1) Reduction in daily DA intake; 2) Increasing on-time and thus reducing the repetitive LD dosing schedules; 3) Direct anti-dyskinesia effect.

9.1 Ablative procedures

Ablative procedures effective in controlling drug-induced dyskinesias include:

9.1.1 Thalamotomy

The anti-dyskinesia effect of thalamotomy has been variable. Ventral intermedius nucleus (VIM) of thalamus is not a part of the pallidal receiving area and hence does not have an anti-dyskinesia effect (Tasker et al., 1997). A lesion in the pallidal receiving area of thalamus (nucleus ventralis oralis and ventralis posterior VoA and VoP) has been shown to have profound anti-dyskinesia effects (Narabayashi et al., 1984). In a study of thalamotomy in MPTP monkeys, Page et al. found that a lesion of the pallidal outflow receiving areas of the thalamus had a significant anti-dyskinesia effect but similar lesions in cerebellar or nigral outflow receiving areas (VIM) had no anti-dyskinesia effect (Page, 1992; Page et al., 1993).

9.1.2 Pallidotomy

Posteroventral pallidotomy has been shown to have a significant and sustained anti-dyskinesia effect (Lozano et al., 1995; Baron et al., 1996). A randomized, controlled trial by

Vitek et al. (Vitek et al., 2003) comparing unilateral pallidotomy with medical therapy showed improvement in contralateral dyskinesias in all patients with a significant reduction in ipsilateral dyskinesias. Several other studies have confirmed the significant and sustained anti-dyskinesia effect of pallidotomy (de Bie et al., 1999; Merello et al., 1999). The mechanism of action of pallidotomy in reducing drug-induced dyskinesias is more complex. Pallidotomy improves PD symptoms by reducing pallidal neuronal activity, which in turn restores thalamocortical excitability. This should theoretically worsen the drug-induced dyskinesias. The anti-dyskinetic effect of pallidotomy is considered the function of normalizing the pattern of firing of GPI (Guridi et al., 2008). The optimal lesion location within the GPI has been variously argued to be anteromedial (Gross et al., 1999) and posteroventral (Krauss et al., 1997).

9.1.3 Subthalamotomy

Subthalamotomy is performed in a small number of patients due to the risk involved in the procedure. Alvarez et al. (Alvarez et al., 2001) reported no anti-dyskinesia effect of unilateral subthalamotomy in the short-term or long-term (Alvarez et al., 2009) follow-up. Around 15% of patients (14 patients) with unilateral subthalamotomy in this study developed postoperative hemichorea-ballism which required an additional pallidotomy in eight patients (Alvarez et al., 2009). On the other hand, Su et al. (Su et al., 2003) reported a significant reduction (75%) in dyskinesias after unilateral subthalamotomy in their study. They also state that the lesions in patients with anti-dyskinesia effect were larger and probably affected the pallidofugal fibers. With a significant risk of developing postoperative hemichorea-ballism and variable anti-dyskinetic response, subthalamotomy is probably the least useful procedure for treating dyskinesias.

All of these ablative procedures are associated with an increased risk of hemorrhage and bilateral ablative procedures are associated with further risks, including speech, swallowing, and cognitive problems. With the advent of DBS, ablative lesions are now rarely performed.

9.2 Deep Brain Stimulation

DBS for PD is routinely performed on patients with medically intractable PD. The targets for DBS in PD have included a number of nodal points in the basal ganglia thalamocortical circuit. These include the VIM of the thalamus, the GPI and the STN (Rezai et al., 2008). VIM DBS predominately improves tremor; GPI and STN have been the primary targets for the treatment of the motor symptoms associated with PD. Though GPI and STN DBS both improve PD symptoms (e.g., tremor, rigidity and bradykinesia), there is a continued debate over which site is more effective in improving motor symptoms, reducing PD medications and controlling medication associated side effects such as drug-induced dyskinesias and motor fluctuations (Krack et al., 1998; Burchiel et al., 1999; Limousin-Dowsey et al., 1999; Allert et al., 2001; Krause et al., 2001; Volkmann, 2004; Anderson et al., 2005). Another area of interest is stimulation of the pedunculopontine nucleus (PPN) for PD.

9.2.1 VIM DBS

VIM DBS provides excellent tremor relief, but does not have anti-dyskinesia effect, as shown in various studies (Benabid et al., 1996; Tasker et al., 1996; Limousin-Dowsey et al., 1999). However, some anti-dyskinesia effect is observed in VIM DBS when the electrode is more

posterior, medial, and deeper, probably modulating the centromedian and parafascicular complex (Caparros-Lefebvre et al., 1993).

9.2.2 GPI DBS

Most major studies have reported that GPI DBS is effective in reducing all the cardinal motor signs of PD as well as improving motor fluctuations, reducing dyskinesias and increasing on time (The Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001). Ghika et al. (Ghika et al., 1998) reported that the mean off time decreased from 40% to 10%, and the mean dyskinesia scores were reduced to one-third. Burchiel et al. reported a significant reduction in dyskinesias (Burchiel et al., 1999), while Kumar et al. reported that the reduction in the total "on" dyskinesias score was 66% (Kumar et al., 2000). Volkmann et al. reported a sustained reduction in dyskinesias at 5 years follow up of 64% (Volkmann et al., 2004). Rodrigues et al. reported a reduction in dyskinesia scores by 76% (Rodrigues et al., 2007) out 4 years. Several such studies have confirmed that pallidal stimulation is associated with a marked reduction in contralateral drug-induced dyskinesias in addition to improvements in "off"-period. The duration of benefit on motor complications following DBS-GPI is sustained. The location of the DBS lead has an effect on the anti-dyskinetic effect of GPI DBS. Bejjani et al. (Bejjani et al., 1997; Bejjani et al., 1998) have demonstrated different clinical effects after stimulation of the dorsal and the posteroventral part of the GP. With stimulation in the more dorsal portions of the pallidum, they reported improvement in akinesia and rigidity, but an exacerbation of dyskinesias. Stimulation in the posteroventral portion of the GP had a pronounced anti-dyskinetic effect, but worsened bradykinesia.

9.2.3 STN DBS

STN DBS has been the established modality of therapy for advanced PD patients since the initial studies by the group of Dr. Benabid in Grenoble. STN DBS has shown a dramatic and sustained anti-dyskinesia effect in various major studies (Limousin et al., 1995; Krack et al., 1997; Limousin et al., 1998; Benabid et al., 2000). The effect of STN DBS on drug-induced dyskinesias is homogeneous and well accepted. Patients undergoing STN DBS have a significant antidyskinetic effect that can be closely correlated with a reduction in LD dose (Guridi et al., 2008). STN DBS improves peak-dose as well as biphasic dyskinesia (Krack et al., 1997). It also results in significant reduction (47%) in LD dose (Krack et al., 1997). The reduction in dose and drug-induced dyskinesias is sustained over a long period. In a survey published by Hamani et al. of multiple studies involving 737 patients in 34 neurosurgery units, STN DBS improved drug-induced dyskinesias by 73% at 6 months and 94% at 12 months in the on-stimulation on-medication state in comparison to the preoperative on-medication scores (Hamani et al., 2005). Long-term studies of bilateral DBS-STN in patients with advanced PD demonstrate the stability of this therapeutic efficacy.

9.2.4 PPN DBS

PPN DBS has been used in a number of PD patients for gait and postural impairment (Tsang et al., 2010). Early studies suggested that PPN DBS could be utilized in patients who respond poorly to anti-PD medications or other neurosurgical treatments (Plaha & Gill, 2005). This was later confirmed in patients receiving both PPN and STN DBS (Stefani et al., 2007). Although the authors suggest that this procedure is appropriate for treating

parkinsonian symptoms, they indicate that PPN DBS is not suitable in targeting drug-induced dyskinesias. In 2010, Ferraye and colleagues found that PPN DBS only provided modest amelioration of parkinsonian symptoms. According to their findings, dyskinesias were not alleviated with PPN stimulation (Ferraye et al., 2010).

9.2.5 DBS Conclusion

It is evident that DBS is an effective therapy for PD patients with motor complications like drug-induced dyskinesias. The primary benefit of DBS is on dyskinesia and “off” time. Stimulation of both the GPI and the STN are effective in treating the motor features of PD and LD related motor complications like drug-induced dyskinesias, but the preferable target remains a controversial topic. It is possible that stimulation of the GPI has a more direct effect in blocking dyskinesias, while reduction in dyskinesias with STN DBS may primarily relate to a reduction in LD dose. A recent study compared the effects of STN DBS and GPI DBS (Follett et al., 2010). Subthalamic and pallidal DBS resulted in improvement in motor function, reduction in dyskinesias and reduction in dose of dopaminergic medications. Effects on motor function and dyskinesias did not differ significantly between the two groups. Patients undergoing subthalamic stimulation required a significantly lower dose of dopaminergic agents than did those undergoing pallidal stimulation. The difference may be an important consideration in patients having side effects, as a reduction in medications may lead to a better quality of life.

10. Key points for the pathophysiology of drug-induced dyskinesias

- The classic rate model of the basal ganglia does not completely explain drug-induced dyskinesias.
- Despite numerous advances in understanding the changes to neurochemical sub-systems in the striatum and downstream nuclei in the basal ganglia in dyskinesias, the prevailing hypothesis of D1 and D2 receptor supersensitivity due to loss of continuous dopaminergic stimulation is still the unifying conceptual idea for drug-induced dyskinesias. However, this idea still does not entirely explain the phenomenology of drug-induced dyskinesias.
- Alternate theories for drug-induced dyskinesias include: basal ganglia neuronal firing pattern abnormalities, interhemispheric inhibition, and alterations to second messenger systems as complementary pathophysiological mechanisms.
- Despite significant advances in the field, treatment for drug-induced dyskinesias in PD is largely unsatisfactory for many patients.
- We have made excellent advances in clinical distinction of drug-induced dyskinesias from other syndromes.
- Many new treatments are currently being examined, and understanding the pathophysiological basis of drug-induced dyskinesias will allow for better development of these novel therapies.

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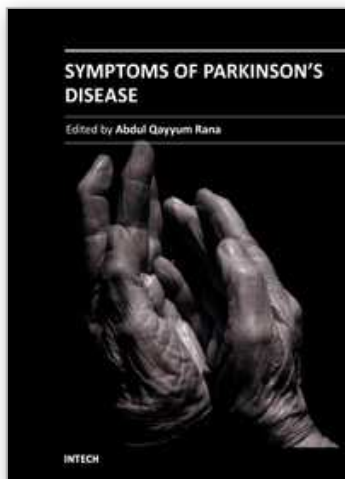
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This book about Parkinson's disease provides a detailed account of various aspects of this complicated neurological condition. Although most of the important motor and non-motor symptoms of Parkinson's disease have been discussed in this book, but in particular a detailed account has been provided about the most disabling symptoms such as dementia, depression, and other psychiatric as well as gastrointestinal symptoms. The mechanisms responsible for the development of these symptoms have also been discussed. Not only the clinicians may benefit from this book but also basic scientists can get enough information from the various chapters which have been written by well known faculty.

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