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Neural substrates and potential treatments for levodopa-induced dyskinesias in Parkinson's disease

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Abstract: Parkinson's disease (PD) is primarily a motor disorder that involves the gradual loss of motor function. Symptoms are observed initially in the extremities, such as hands and arms, while advanced stages of the disease can affect blinking, swallowing, speaking, and breathing. PD is a neurodegenerative disease, with dopaminergic neuronal loss occurring in the substantia nigra pars compacta, thus disrupting basal ganglia functions. This leads to downstream effects on other neurotransmitter systems such as glutamate, γ -aminobutyric acid, and serotonin. To date, one of the main treatments for PD is levodopa. While it is generally very effective, prolonged treatments lead to levodopa-induced dyskinesia (LID). LID encompasses a family of symptoms ranging from uncontrolled repetitive movements to sustained muscle contractions. In many cases, the symptoms of LID can cause more grief than PD itself. The purpose of this review is to discuss the possible clinical features, cognitive correlates, neural substrates,

as well as potential psychopharmacological and surgical (including nondopaminergic and deep brain stimulation) treatments of LID.

Keywords: deep brain stimulation (DBS); dopamine; levodopa-induced dyskinesia; Parkinson's disease.

Introduction

Levodopa-induced dyskinesia (LID) is a complication that arises in Parkinson's disease (PD). The severity of LID can vary, as in many cases they can be more problematic than the original PD symptoms. While it is generally believed that LID is linked to extended dopamine (DA) therapy (i.e. levodopa), there are multiple factors that contribute to the incidence of the condition. There are also multiple pharmacological treatments that have been shown to be effective in patients and animal models of LID. Our aim is to illustrate the variety of theories underlying LID and cover a range of treatments, further highlighting the range of neurotransmitters, cortical and subcortical areas that play a role in LID. We will begin with the clinical features of LID and various risk factors that increase the patient's chance of experiencing LID. We will then discuss the neural substrates that have been shown to have abnormal functioning in PD patients or have an effect on LID symptoms. We will then review a number of pharmaceutical and surgical treatments that were shown to ameliorate LID symptoms.

Clinical features and findings in primate models of PD

While most PD patients undergo levodopa treatment, the reported incidence rate of LID is approximately 30%–80% (Fabbrini et al., 2007). The large variance is due to the many factors that contribute to the risk of developing LID, which include gender (Zappia et al., 2005), age of onset of PD (Kumar et al., 2005), duration of levodopa treatment,

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the size of the dosage (Zappia et al., 2005), and genetics (Kaplan et al., 2014; Rieck et al., 2015). Additionally, methodological variations in measuring LID (e.g. self-report detection vs. detection by a thorough neurological examination) and a lack of a standardized test may explain the differences among the different reports of LID.

LIDs are heterogeneous, usually presenting as range if involuntary movements. The most common are described by chorea (accidental, rapid, irregular, and aimless motions that seem to flow from one part in the body to another) and dystonia (sustained muscle contractions). Uncommon forms of LID include akathasia (excessive motor restlessness), blepharospasm (involuntary contraction of the eyelid muscles), a high stepped overshooting gait, rapid alternating motions of legs, and mixed pattern of abnormal movements (Fahn, 2000), respiratory, and ocular dyskinesia (Fabbrini et al., 2007). Further, LID tends to develop first on the side most affected by PD and will more often appear in the legs before the arms (Sacks et al., 1970; Ballard et al., 1985). This could be relevant to early dopaminergic damage in dorsolateral striatum, the region related to leg movement control (Fahn, 2000).

It is widely known that dyskinesias appear after dopaminergic therapy and that a time lag is present between the start of treatment and the appearance of LID. While dyskinesias are more often associated with levodopa, there are reports that have found that other DA agonists can cause dyskinesia (Rascol et al., 2000). Rascol et al. (2000) found that after 5 years of treatment, the occurrence of dyskinesia regardless of levodopa supplementation was 20% in a group of PD patients on ropinirole and 45% in a group of PD patients on levodopa. Similar results have been reported using pramipexole (Holloway et al., 2004). Interestingly, a recent study found that the rates of dyskinesia were similar in PD patients treated with levodopa in comparison to patients treated with DA agonists or inhibitors for monoamine oxidase B (MAOB), a DA degrading enzyme (Gray et al., 2014). As we discuss below, it is possible that the differential effects of levodopa vs. DA agonists can be related to the affinity of the different DA medications to D1 receptors.

There are several factors that influence the risk of developing LID. Not surprisingly, the administration of levodopa at a high dosage in somewhat advanced PD patients is associated with higher rate of LID (Parkinson Study Group, 1996). Kumar et al. (2005) found that early-onset PD is accompanied by a higher occurrence of LID. They reported that after 5 years from the onset of PD, patients first diagnosed between 40 and 59 years of age have a 50% chance of developing LID, compared to the 16% chance in patients diagnosed with PD after the age of 70. The reason underlying this tendency is not completely

obvious, although it may be due to age-related variations in levodopa dynamics in PD (Sossi et al., 2006).

Gender has also demonstrated to be a risk factor, with females three times more likely to develop LID than males are (Zappia et al., 2005). The authors suggest that this could be due to the female hormone estrogen, which may affect the individual's sensitivity to levodopa. The existence and extent of nigral denervation (disease severity) are also important risk factors as nigral deterioration plays a role in the production of LID in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD in monkeys (Di Monte et al., 2000). The monkeys in Di Monte et al. (2000) developed dyskinesias within weeks of starting levodopa, suggesting intensity of the nigral lesion as a significant risk factor. Additionally, when administering a standard dose of levodopa, LID happens almost exclusively in patients with idiopathic PD. Normal people and those with other neurological diseases do not suffer LID after levodopa therapy (Chase et al., 1973).

In addition, studies found that the levodopa dosage is associated with the severity of LID: larger doses of levodopa are accompanied also by extended dyskinesias (Nutt et al., 1992). However, dosage is not the only contributing factor of LID onset. Potts et al. (2014) found that LIDs do not appear in the early stages of DA treatment in MPTP monkeys but appear to be related to the severity of the MPTP PD symptoms. Additionally, in human populations, studies have revealed an increase in the frequency of LID over the course of the disease (Duvoisin, 1974; Parkinson Study Group, 1996). Further, a recent study found that LID onset was not significantly different between a levodopa-treated Italian cohort and an untreated Ghanaian cohort (Cilia et al., 2014). Additionally, the onset of LID appeared to be linked to disease duration. Sharma et al., (2006) have also demonstrated an association with weight loss and LID, where PD patients who develop LID are also more likely to have lost weight since the onset of PD. As not all patients on dopaminergic treatment show signs of LID (Fabbrini et al., 2009), there are likely other factors involved, such as genetics. Specific kinds of genetic polymorphism of the DA receptor D2 gene have been accompanied by decreasing risk of developing peak-dose dyskinesias (Oliveri et al., 1999). In a recent study by Kaplan et al. (2014), a single nucleotide polymorphism on the DA transporter gene was also found to be associated with the risk of onset of LID. The adenosine A2A (ADORA2A) gene is located at chromosome 22q11.23 and encodes ADORA2A receptors. These receptors are predominantly distributed in striatum and suppress the D2 receptors activity. Rieck et al. (2015) reported a positive correlation between LID and the ADORA2A gene polymorphism rs2298383 and rs3761422.

This may be due to adenosine effect on release of DA in striatum.

Neural substrates of LID

Despite considerable improvement, the pathogenesis of LID is not completely understood. In the basal ganglia, it was found that abnormal function of either the striatum or subthalamic nucleus (STN) is associated with dyskinesia in unilateral 6-hydroxydopamine (6-OHDA) lesioned male Sprague-Dawley rats (Soghomonian, 2006). Other studies suggest that prefrontal cortex (Cerasa et al., 2012) or cerebellum (Kishore and Popa, 2014) dysfunction can lead to dyskinesia in PD patients. Rat experiments show evidence that altered activation of the premotor cortical area is the neural mechanism underlying LID (Halje et al., 2012; Richter et al., 2013). Using functional magnetic resonance imaging (fMRI) and an inhibition task, a reduction in activity of right inferior frontal cortex was observed when LID patients successfully inhibited their response (Cerasa et al., 2015a,b). Additionally, increased activity of medial frontal cortex caused by levodopa dissipated after an incorrect response in PD+LID patients (PD patients with LID), but not in PD-LID patients (PD patients without LID) (Cerasa et al., 2015a,b). Cerasa et al. (2015a,b) also stress the pivotal regulatory role of inferior frontal cortex on LID in PD patients. A resting state fMRI study revealed that the connectivity of the right inferior frontal cortex is positively related with the right putamen and negatively with the left motor cortex in the LID group, while the continuous repetitive trans magnetic stimulation of inferior frontal cortex diminish LID. Using fMRI, Herz et al. (2015) assessed brain connectivity of PD patients after supplementation with one dose of levodopa. A positive correlation existed throughout movement suppression between later risk of developing LID and post-levodopa rise in brain connectivity between primary motor cortex and putamen (Herz et al., 2015). Additionally, altered levodopa connectivity between putamen and both presupplementary motor area and primary motor cortex act as a significant predictor for the severity of LID (Herz et al., 2015). Connectivity between the putamen and other cortical areas, however, did not predict LID severity (Herz et al., 2015).

Several studies implicate alterations to different neurotransmitters for the occurrence of LID, including DA (D1, D2, and D3 receptors), serotonin (5HT), γ -aminobutyric acid (GABA), and glutamate (Bibbiani et al., 2005; Rylander et al., 2010; Politis et al., 2014). It was suggested that sustained physiological stimulation caused by irregular administration of levodopa leads to downstream changes to striatal output in such a manner that

triggers dyskinesias (Bibbiani et al., 2005). In addition, disruption to DA D2 receptors in the indirect pathway can cause disinhibition of the primary motor cortex (via pallidothalamocortical motor pathway), leading to LID (Rascol et al., 1998). Studies also found that overstimulation of D1 receptors can cause dyskinesia (Aubert et al., 2005; Berthet and Bezard, 2009; Berthet et al., 2009; Moustafa et al., 2013), as well as alterations in both D1 and D2 receptors (Iravani et al., 2012). Specifically, Ye et al. (2014) suggested that the oversuppression of D2 receptors plays a pivotal role in the induction of LID. This was supported by the reduction in LID symptoms in a 6-OHDA model of PD in Sprague-Dawley rats when D2 receptor expression was increased. Additionally, Cote and Kuzhikandathil (2015) reported an association between LID and an abnormally increased expression of DA D3 receptors in the dorsal striatum.

Marín et al. (2015) investigated the expression of preproenkephalin (which is a marker of D2 receptors in the indirect basal ganglia pathway) and preprodynorphin mRNA (which is not only a marker of D1 receptors in the direct basal ganglia pathway, but also a compensatory plastic change observed in LID). Marín et al. (2015) reported that the administration of 6-OHDA to rats elevated preproenkephalin with preserved preprodynorphin mRNA expressions in the striatum. The initial induction of right-sided lesion reproduced a higher level of expression of preprodynorphin and preproenkephalin mRNA in the subsequent left lesion side with more profound LID, suggesting that there is an increase in activity of D1 receptors in the direct basal ganglia pathway. Further, a positive correlation existed between LID and both preprodynorphin mRNA expression and orolingual dyskinesias in the bilateral model.

Positron emission tomography was used by Smith et al. (2015) to compare 5HT and DA systems in the globus pallidus in PD patients with LID (PD+LID), PD patients without LID (PD-LID), and healthy controls. Preserved binding of 5HT receptors was observed among PD+LID, while PD-LID patients exhibited a decrease in binding of 5HT receptors in globus pallidus, compared to healthy individuals. Further, selective 5HT reuptake inhibitors have been suggested to delay LID onset and reduce the severity of the symptoms (Mazzucchi et al., 2015). Cheshire et al. (2015), however, oppose the role of 5HT pathway in the pathogenesis of LID. Comparing brain samples from PD patients and healthy controls, they found preserved 5HT in putamen, 5HT neurons in dorsal raphe nucleus and serotonergic transporters in corpus striatum, and reduced 5HT in caudate among PD patients, similar to healthy controls. Importantly, no correlation existed between 5HT markers and LID or its severity. Using the specific

radiological receptor binding autophagy radioligand [³H] GR125743, Morin et al. (2015) found a positive correlation between serotonin receptor binding and the severity of LID in both PD patients and a MPTP monkey model of PD.

The hyperactivity of glutamatergic systems [using *N*-methyl-*D*-aspartate (NMDA) receptors] in the basal ganglia may also have a role in the occurrence of LID (Chase et al., 2003). Additional support for this theory arises from animal studies where the NMDA antagonist dextrophan combined with levodopa was found to reduce dyskinesias in MPTP-treated monkeys (Blanchet et al., 1996) and from clinical observations of the efficiency of amantadine, a weak NMDA antagonist, in treating LID (Rodnitzky and Narayanan, 2014). Interestingly, in rat models, the effects of NMDA antagonists are dependent on whether dyskinesia is due to impairment in the indirect or direct striatal pathway (Flores et al., 2014). An increase in striatal post-synaptic glutamate-5 receptors (mGlu5) has been noted in PD patients and animal models of PD (Morin and Di Paolo, 2014). Mellone et al. (2015) reported an abnormal ratio of GluN2A/GluN2B subunit of NMDA receptors in the striatum of postmortem brain specimens from 16 PD patients, 6-OHDA model of PD in male Sprague-Dawley rats, and MPTP monkey model of PD suffering from LID. There was a significant sole elevation of synaptic localization of GluN2A subunit among PD patients. LID in the two animal models benefited from the manipulation of scaffolding protein post-synaptic density protein 95 of GluN2A subunits (Mellone et al., 2015). Thus, the manipulation of NMDA receptor subunits aiming to deteriorate synaptic GluN2A could be one of the future therapeutic modalities for LID. Further, dipraglurant and mavoglurant, two new glutamate antagonists that target mGlu5 receptors, are currently undergoing pre-clinical testing trials for the treatment of LID (Rascol et al., 2014). Both have been shown to reduce dyskinesia severity in MPTP macaque monkeys while also demonstrating anti-Parkinsonian properties (Bezard et al., 2014). In addition to glutamate, postmortem studies found an increased concentration of GABA(A) receptors in the internal globus pallidus in dyskinetic patients compared to nondyskinetic patients (Calon et al., 2003). Other studies implicate striatal GABA and other interneurons in the occurrence of LID (Levy and Hallett, 2002; Gittis et al., 2011).

Medications and deep brain stimulation to treat LID

Pharmacological treatment of LID can take multiple directions: they may mimic the actions of levodopa with

the hopes of reducing LID through different activation routes. They may also target other neurotransmitters that play a role on the striatal pathways such as glutamate and GABA. Novel treatments have taken a different path, instead focusing underlying genes [i.e. phosphodiesterase 10A (PDE10A)] or cellular support compounds [i.e. docosahexaenoic acid (DHA)]. Please refer to Table 1 for a list of drugs and their actions and effects on levodopa treatment. In severe cases where the patient is unresponsive to medications, surgical interventions may be used. These may involve pallidotomy, subthalamotomy, or deep brain stimulation (DBS).

While LID appears to be the product of overstimulated DA receptors caused by levodopa, it may be exacerbated by the irregular stimulation from levodopa (Bibbiani et al., 2005). Studies found that using continual infusion of levodopa showed success in treating patients with severe PD and revealed no increase in dyskinesia as compared to oral levodopa therapy (Nilsson et al., 2001; Nyholm et al., 2005). Similar results were found with subcutaneous, intramuscular, or intravenous infusion of levodopa (Djaldetti and Melamed, 1996), although the exact reasons and mechanisms of the differential effects of methods of administration on LID are not known. Alternative DA agonists can minimize dyskinesias as found in an animal study using bromocriptine (Bédard et al., 1986), ropinirole (van Boven et al., 2014), and apomorphine (Colosimo et al., 1994; Manson et al., 2002; Deleu et al., 2004). Additionally, drugs may reduce LID by targeting enzymes that break down levodopa. Using a rat model of PD, Marín et al. (2006) investigated the coadministration of entacapone, a chol-*o*-methyltransferase enzyme inhibitor (Agundez et al., 2013), with levodopa reducing more severe dyskinesia in rats when compared to levodopa alone. This action is believed to be caused by the extension of levodopa half-life by entacapone (Marín et al., 2006). This extension of levodopa may smooth out DA fluctuations, creating a similar effect as continuous levodopa infusion.

Alternative treatments for LID also target non-DA systems. Eltoprazine, a mixed 5HT 1A and B receptor agonist, has also been found to improve LID symptoms while maintaining motor coordination when administered with levodopa (Paolone et al., 2015). Rosiglitazone, an antidiabetic drug, stimulates gamma subtype peroxisome proliferator-activated receptors in a unilateral 6-OHDA rat model of PD, which resulted in reduction of LID (Martinez et al., 2015). This effect may be mediated through a levodopa-induced decrease in phosphorylation of extracellular signal-regulated kinase, dynorphin and zif-268, an immediate early gene induced by D1 receptor oversensitivity, in the striatum of the lesioned side (Martinez et al., 2015).

Table 1: Pharmacological treatments for levodopa induced dyskinesia.

Drug	Class	Antidyskinetic effect	Effect on levodopa treatment	Human studies	Animal studies	Comments
Bromocriptine	DA receptor agonist	Acts on the D2 receptor	No effect on levodopa efficacy		Ogawa et al., 1996; de Leeuw van Weenen et al., 2010	
Entacapone	COMT inhibitor	No direct anti-dyskinetic effect	Compliments levodopa/ carbidopa treatment as it inhibits COMT, increasing levodopa efficacy	Kuoppamaki et al., 2015		
Ropinirole	DA receptor agonist	Acts on the D2 receptor, reducing the required dose of levodopa	No effect on levodopa efficacy	Adler et al., 1997; van Boven et al., 2014		
Apomorphine	DA receptor agonist	Acts on D2, D3, and D4 receptors	Can replace or compliment levodopa treatment to enhance outcomes by stimulating D2, D3 and D4 receptors	Colosimo et al., 1994; Manson et al., 2002		
Dipraglurant	mGlu receptor antagonist	Inhibits mGlu receptor type 5	No effect on levodopa efficacy	Rascol et al., 2014		
Mavoglurant	mGlu receptor antagonist	Inhibits mGlu receptor type 5	No effect on levodopa efficacy		Bezard et al., 2014	
Eltoprazine	5HT 1A and B receptor agonist	Inhibits GABA neurons in the direct pathway	No effect on levodopa efficacy	Svenningsson et al., 2015	Paolone et al., 2015	Results have been much stronger in rats and nonhuman primates than in PD patients
Rosiglitazone	Peroxisome proliferator-activated receptors agonist	Increases gene activation in D1 receptors in the striatum	No effect on levodopa efficacy		Martinez et al., 2015	
PPI-1011	EP precursor	Increases DHA storage, improving neuronal function	No effect on levodopa efficacy		Grégoire et al., 2015	

This suggests that antidiabetic drugs such as rosiglitazone may ameliorate LID symptoms in PD patients. While eltoprazine and rosiglitazone target alternative transmitters, they do have an indirect effect on the DA system.

PDE10A is one of the subtypes of PDEs that reproduce degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Thus, it modulates neuronal conductivity through controlling the levels of these second messengers (Menniti et al., 2006). High levels of PDE10A were detected in the substantia nigra, corpus striatum, and globus pallidus (Coskran et al., 2006). Additionally, Seeger et al. (2003) stated a high expression of PDE10A in the striatal medium spiny neurons, which control the excitability of the basal ganglia, of male Sprague-Dawley rats.

In an LID model of unilateral 6-OHAD lesioned young male Sprague-Dawley rats, Giorgi et al. (2008) stated that a significant bilateral declination of both cAMP and cGMP levels in globus pallidus, caudate putamen, and sensorimotor cortex areas was observed. Subcutaneous preadministration of the PDE inhibitor zaprinast reduced the degree of LID. This beneficial effect was mediated by partial preservation of cAMP and cGMP in globus pallidus, caudate putamen, and sensorimotor cortex in both sides through a reduction in cAMP and cGMP degradation (Giorgi et al., 2008). Additionally, stereotaxic injection of PDE inhibitors into the corpus striatum of unilateral 6-OHAD lesioned adult male Wistar rats also reduced LID (Picconi et al., 2011). This beneficial effect may be attributed to restoring of LID-induced altered glutamatergic

striatal synaptic plasticity through regulation of cGMP (Picconi et al., 2011).

Initial lower levels of both cAMP and cGMP were detected during increasing stage of LID in the corpus striatum of a unilateral 6-OHAD model of PD in male Sprague-Dawley rats, followed by their reduction during the decreasing and termination stages of LID (Sancesario et al., 2014). This could be elucidated by an increased degradation of cGMP but not cAMP, as it was evident by a sole increase in the activity of cGMP PDE. Preserved highly expressed PDE10A in the basal ganglia after administration of levodopa in both LID and non-LID groups was manifested. Therefore, the PDE inhibitors had no role in the alleviation of LID symptoms. Yet, antagonizing the reduction in both cAMP and cGMP by preadministration of amantadine abolished the LID (Sancesario et al., 2014).

Positron emission tomography was used to assess PDE10A in the basal ganglia of 24 PD patients receiving levodopa in comparison to 12 healthy individuals (Niccolini et al., 2015). Low levels of PDE10A were detected in the caudate, putamen, and globus pallidus among PD patients. Additionally, there was an inverse relationship between PDE10A level in these brain regions and both disease duration and Unified Parkinson's Disease Rating Scale part-III motor scores (Niccolini et al., 2015). PD-LID patients showed decreased levels of PDE10A, and PD+LID patients also had even lower PDE10A concentrations in the caudate, substantia nigra, and motor thalamic nuclei (Niccolini et al., 2015). The findings of Niccolini et al. (2015) on a human PD population contrast findings from the rat models. This may reflect the complexity of PD in humans compared to the unilateral 6-OHDA rat model of PD.

Recent research has targeted DHA supplements as a viable treatment for PD (Yakunin et al., 2012; Blanchard et al., 2014; Lee et al., 2015). DHA is an omega acid and is one of the main building blocks of the human brain, making up approximately 8% of its dry weight. It is also pivotal in normal cellular functioning (Musket et al., 2006). DHA supplements have been shown to slow cognitive decline in the elderly as well as lower the risk of developing Alzheimer's disease (Cunnane et al., 2013). In animal models of PD, DHA has a neuroprotective effect, decreasing the rate of DA receptor loss (Hacioglu et al., 2012). Further, Grégoire et al. (2015) tested the effect of ethanolamine plasmalogens (EPs) on LID in a MPTP monkey model of PD. EP has many cellular functions, one in particular is its ability to maintain high levels of polyunsaturated fats, such as DHA (Nagan and Zoeller, 2001). Grégoire et al. (2015) treated the monkeys with either DHA or EP. The EP was administered via PPI-1011, a specialized EP precursor that also contains DHA. When given DHA alone, LID

symptoms begun to recede after 10 days; however, when PPI-1011 was administered, symptoms receded after 2 days (Grégoire et al., 2015). These data suggest that while DHA is beneficial for the treatment of LID, it may be much more effective when given with EP. The action responsible for the increase in DHA efficacy may be due to the effect that EP has on polyunsaturated fats, or it may be one of its many other functions (see Nagan and Zoeller, 2001, for a review).

In severe cases, neurosurgery may be a necessary course of treatment. These procedures may include pallidotomy or subthalamotomy or DBS. This procedure involves two electrodes being inserted into the target areas, which deliver pulses of electricity at a set frequency. DBS of the internal globus pallidus (GPi) or STN showed significant success in treating LID. Anderson et al. (2005) reported a reduction of dyskinesias by DBS of both the GPi and STN. This reduction was not because of the diminished requirement for levodopa, as the STN group had a greater reduction in dosage, while the GPi group exhibited a greater reduction in LID. Importantly, the effects of DBS on LID can still be visible after 7 years of treatment (Tsai et al., 2013). Similar findings have also been reported with patients with LID, with symptoms being significantly reduced after bilateral subthalamic DBS (Kim et al., 2015). The actual mechanisms of DBS on LID are unclear; however, there are several hypotheses, the latest of which suggests a disruption effect of the stimulation on the firing of neurons in the target area (Chiken and Nambu, 2016). With the loss of 75% of DA receptors in the striatum, the stimulations from these receptors become inconsistent. To counter this, levodopa is added to the system. This in turn causes these receptors to produce pulsatile stimulation leading to abnormal striatal output, which causes LID (Jenner, 2008). Replacing levodopa with other DA agonists with longer action durations creates a more continuous stimulation that is a closer match to a normal striatum (Jenner, 2008). A similar mechanism may be behind the beneficial effects of DBS. As the striatum feeds both the direct and indirect DA pathways, the abnormal stimulation may be passed downstream to these areas. DBS of the STN or GPi may disrupt the abnormal stimulation and smooth it out with a more continuous one (Chiken and Nambu, 2016).

Jourdain et al. (2015) investigated the effect of unilateral subthalamotomy on glutamate receptors of the basal ganglia of a MPTP model of PD in macaque monkeys. Their findings revealed that unilateral subthalamotomy was capable of antagonizing levodopa-induced elevated binding of NMDA receptors bilaterally in the corpus striatum and contralaterally in the globus pallidus.

Subthalamotomy reduced specific binding of metabotropic glutamate (2/3) receptor bilaterally in the corpus striatum and globus pallidus; both actions decreased LID symptoms in the MPTP model of PD.

Conclusion

LID is a common side effect of DA treatment for PD. LID was found to be caused by abnormalities to both D1 and D2 receptors on the striatum. This may cause abnormal striatal signals, which are then fed down the direct and indirect pathways of the BG and then carried to various areas in the cortex involved in motor planning and inhibition. Non-oral administration of levodopa (including subcutaneous, intramuscular, and intravenous infusion) has a lower chance of causing LID (Djaldetti and Melamed, 1996) than the traditional oral administration does. LIDs have also been shown to be reduced by supplementing DA treatment with drugs that target other neural transmitters such as 5HT agonists, glutamate antagonists or enzymes, or fatty acids. These treatments have been shown to improve LID by increasing the efficacy of levodopa, resulting in lower dosage of levodopa required.

The aforementioned studies show that LID is associated with a complex neurochemical mechanism involving DA, glutamate, 5HT, and GABA. Neural studies also suggest that LID involves abnormalities to many brain areas, including different subregions of the basal ganglia (including the striatum and STN), prefrontal cortex (Cerasa et al., 2012), premotor cortical area (Halje et al., 2012; Richter et al., 2013), and cerebellum (Kishore and Popa, 2014). Future research should focus on exact contribution of different neurotransmitters and brain regions to LID. Due to the number of factors involved in the onset of LID, employing a computer model representing the striato-cortical pathways may allow researchers to isolate the influence the pathway has on the prefrontal cortex, motor area and cerebellum.

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