Chapter 10
mGlu5 Receptors in Parkinson's Disease and MPTP-Lesioned Monkeys: Behavior and Brain Molecular Correlates

Nicolas Morin and Thérèse Di Paolo

Abstract Glutamate overactivity is well documented in Parkinson's disease (PD) and dyskinesias induced by L-3,4-dihydroxyphenylalanine (L-DOPA), the gold-standard treatment for this disease. The contribution of metabotropic glutamate receptors type 5 (mGlu5 receptors) in PD and L-DOPA-induced dyskinesias (LID) was the topic of investigations in human PD patients and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys.

Behaviorally, it has been shown that the prototypical mGlu5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) as well as the mGlu5 receptor antagonists 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) and mavoglurant (AFQ056) acutely attenuated LID in MPTP monkeys. Moreover, a chronic 1-month administration of MPEP to previously drug-naïve MPTP monkeys (de novo treatment) attenuated the development of LID. Acute and chronic MPEP treatments of MPTP monkeys maintained the antiparkinsonian effect of L-DOPA. Mavoglurant was also shown in some clinical studies to reduce LID in PD patients.

Using the selective mGlu5 receptors ligand [3H]ABP688, mGlu5 receptor-specific binding was measured by autoradiography in brains slices of normal and PD patients in relation to motor complications associated with an L-DOPA treatment. PD patients with motor complications (either LID or wearing-off) had higher [3H]ABP688-specific binding compared to those without motor complications and controls in putamen, external and internal globus pallidus. In monkeys with a MPTP lesion and controls, [3H]ABP688- and [3H]MPEP-specific bindings were elevated in the striatum of dyskinetic L-DOPA-treated MPTP monkeys but not in MPTP monkeys without LID compared to controls.

The brain molecular correlates of the long-term effect of a 1-month administration of MPEP with L-DOPA that attenuated the development of LID were shown to

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extend beyond mGlu5 receptors. In the basal ganglia, it has been showed that the L-DOPA-induced changes of NMDA and AMPA ionotropic glutamate receptors as well as mGlu2/mGlu3 receptors were prevented with the addition of MPEP. Moreover, MPEP normalized the L-DOPA-induced changes of dopamine D2 receptors, their associated signaling (ERK and Akt) and neuropeptides (preproenkephalin, prepro-dynorphin), as well as the serotonin receptors 5-HT$_{2A}$ and 5-HT$_{1B}$.

In conclusion, these results have shown in humans and in a nonhuman primate model of PD reduction of LID with mGlu5 antagonism. In the basal ganglia, LID were associated with changes of various glutamatergic, dopaminergic, and sero-toninergic markers that were normalized with adjunct treatment with an mGlu5 antagonist supporting the mGlu5 receptor as a good target for the treatment of LID.

Keywords Parkinson's disease • L-DOPA-induced dyskinesia • Motor complications • Glutamate receptor • Basal ganglia • Direct pathway • Indirect pathway • Receptor interaction

Abbreviations

5-HT	serotonin
6-OHDA	6-hydroxydopamine
Akt	protein kinase B
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
cAMP	cyclic adenosine monophosphate
DA	dopamine
DHA	docosahexaenoic acid
dipraglurant	ADX-48621
ERK	extracellular signal-regulated kinase
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GSK3β	glycogen synthase kinase-3 β
GP	globus pallidus;
iGlu	ionotropic glutamate
KA	kainate
L-DOPA	levodopa (L-3,4-dihydroxyphenylalanine)
LID	L-DOPA-induced dyskinesias
MAPK	mitogen-activated protein kinase
mavoglurant	AFQ056
mGlu	metabotropic glutamate
MPEP	2-methyl-6-(phenylethynyl)pyridine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTEP	3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine
NAM	negative allosteric modulator

NMDA   *N*-methyl-D-aspartate
PD   Parkinson's disease
PI   polyphosphoinositide
SERT   serotonin transporter
STN   subthalamic nucleus

10.1 Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is likely to increase due to the aging population (Siderowf and Stern 2003). The cardinal motor manifestations of PD, tremor, bradykinesia, and rigidity are secondary to a loss of dopamine in the striatum (Olanow et al. 2009; Toulouse and Sullivan 2008). PD is principally attributed to the death of dopamine (DA) neurons in the substantia nigra, but other neurotransmitters and neuromodulators, such as glutamate, serotonin (5-HT), and adenosine, are also affected (Toulouse and Sullivan 2008). Gene mutations in familial PD are reported, but the cause for the majority of PD cases remains unknown (Olanow et al. 2009). There is currently no cure for PD. Neuroprotection or disease modification defined as an intervention that would protect or rescue vulnerable neurons, thereby slowing, stopping, or reversing disease progression, is not yet available for PD, but laboratory studies are finding promising agents (Olanow et al. 2009).

Restoring lost DA with its precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), introduced 50 years ago still remains a very effective and commonly used treatment for PD (Mercuri and Bernardi 2005). However, up to 80% of PD patients will develop motor complications after 10 years of treatment with L-DOPA (Olanow and Koller 1998). These motor complications include motor fluctuations and abnormal involuntary movements, such as L-DOPA-induced dyskinesias (LID), and contribute to limit the quality of life in PD patients and can be very difficult to manage (Fabbrini et al. 2007). Motor fluctuations such as "wearing-off" are also common. Wearing-off is defined as a reduced duration of benefit from an individual L-DOPA dose and a recurrence of parkinsonian symptoms before the next normal dose of L-DOPA (Fahn et al. 2004). Hence, most PD patients initiated with DA agonist monotherapy will eventually require L-DOPA as disease progresses, and after 10 years their motor complications appear similar as they would have if started initially on L-DOPA therapy (Katzenschlager et al. 2008; Parkinson Study Group 2009). This suggests that disease progression plays the major role in the onset of dyskinesia rather than the type of dopaminergic drug treatment used. Involuntary movements such as LID are paralleled by aberrant forms of plasticity characterized by changes in various neurotransmitter systems and their intracellular signaling pathways (Jenner 2008).

Aside from some benefit of amantadine, that has anti-glutamatergic properties, no drug is yet available for LID (Meissner et al. 2011). Glutamate neurotransmission is increased in the basal ganglia in PD and LID (Klockgether and Turski 1993;

Chase and Oh 2000; Calon et al. 2003a). The pathophysiology and the mechanisms involved in the development of LID are still not fully understood. However, altered dopaminergic and nondopaminergic neurotransmission in the basal ganglia is observed in LID (Blandini and Armentero 2012). Treating LID with adjunct drugs targeting nondopaminergic neurotransmitter systems is proposed such as glutamate to indirectly modulate basal ganglia DA neurotransmission (Brotchie 1998; Morin et al. 2014a). Much emphasis has therefore been placed on finding alternative non-dopaminergic drugs that could circumvent some or all these problems. The design of novel agents to prevent dyskinesias requires elucidation of the adaptive changes produced in the parkinsonian brain by repeated administration of L-DOPA. The use of adjunct drugs to modulate basal ganglia DA neurotransmission is an important strategy to treat LID (Brotchie 1998, 2003; Henry et al. 2001; Calon and Di Paolo 2002; Blanchet et al. 1999; Grondin et al. 1999).

LID are typically observed at the peak of the effect of L-DOPA in PD patients. There is also diphasic dyskinesia at the beginning and at the end of the L-DOPA dosing cycle appearing with the rise and fall of DA levels in the brain (Luquin et al. 1992) and off-dystonia (Marsden et al. 1982). LID occur in 30–80% of PD patients treated with L-DOPA (Barbeau 1980; Nutt 1990). Two conditions are necessary for their appearance: (1) the loss of DA in the nigrostriatal pathway and (2) treatment with L-DOPA or DA agonists. The development of dyskinesias in man usually requires daily treatment for 3–5 years in idiopathic PD (Klawans et al. 1977), and for parkinsonism induced in man by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), it occurs after only weeks or months of treatment (Ballard et al. 1985). The same applies to MPTP monkeys where only weeks of L-DOPA therapy are enough before dyskinesias appear (Falardeau et al. 1988; Bedard et al. 1986). MPTP primates respond to DA therapies in a similar manner than idiopathic PD patients (Jenner 2003a, b) and are currently the best model for studying LID.

Glutamate is involved in many physiological functions through its interactions with ionotropic glutamate (iGlu), ligand-gated channel, and metabotropic G-protein-coupled glutamate (mGlu) receptors. iGlu receptor drugs suppressing glutamate excitatory transmission often create undesirable side effects (Johnson et al. 2009), whereas acting on mGlu receptors could lead to a subtler and/or circuit-selective modulation of excitatory transmission (Conn et al. 2005). Pharmacologic characterization of mGlu5 receptors and its selective negative allosteric modulators (NAMs) shows therapeutic potential in animal models of PD (Grégoire et al. 2011; Johnston et al. 2010; Morin et al. 2010) and recently efficacy in human PD (Berg et al. 2011; Stocchi et al. 2013). mGlu5 receptors have been shown to play a crucial role in regulating L-DOPA-induced motor behavior, but the mechanisms involved remain unclear (Gasparini et al. 2013).

This review will cover relevant studies investigating mGlu5 receptor subtypes in the pathophysiology of PD and LID. Brain biochemical correlates of motor complications in PD patients and MPTP-lesioned monkeys will be reviewed (Morin et al. 2014a).

10.2   Nonhuman Primate Models of L-DOPA-Induced Dyskinesias

Similar etiology and functions of a particular human disease are two important characteristics to model a disease. The neurotoxin MPTP closely mimics both behavioral changes and cellular loss as seen in PD (Albanese et al. 1993). The administration of MPTP in primates promotes the development of rigidity, bradykinesia, and tremor, which are the primary motor features of PD. MPTP induces neuronal death of dopaminergic cells through a cascade of intracellular reactions by targeting specifically cells expressing the DA transporter (Smeyne and Jackson-Lewis 2005). MPTP-treated primates remain after nearly 30 years the gold standard for the study of PD and LID, as well as to evaluate the efficacy of novel compounds (Morin et al. 2014a). Acute and de novo experimental approaches are used to test new antiparkinsonian and antidyskinetic pharmacological agents. In acute approaches, animals are rendered parkinsonian with the administration of MPTP and then chronically treated with L-DOPA for several weeks, until they express well-established, constant, and stable LID. Then, the acute effects of compounds are tested with the co-administration of L-DOPA, and the motor behavior of the animals is evaluated (Grégoire et al. 2009, 2011; Bezard et al. 2004). This approach allows rapid testing of new compounds and its tolerability, and animals may be used for several studies (Morin et al. 2014a). These animals can also be used in a chronic treatment paradigm to measure possible development of tolerance to the investigated drug. In the de novo approach, two or more groups of never treated animals are rendered parkinsonian and then treated with L-DOPA alone or in combination with the new agent. This approach allows verifying if the compounds tested can reduce or prevent the development of LID and evaluating if the duration of the L-DOPA effect decreases over time, a motor complication also called "wearing-off" (Morin et al. 2012; Samadi et al. 2006; Rylander et al. 2010; Grégoire et al. 2008; Hadj Tahar et al. 2004). Moreover, measurements of biochemical changes in the brains are made possible if the animals are euthanized at the end of the protocol (Morin et al. 2012; Samadi et al. 2008a; Ouattara et al. 2010).

As observed in PD patients, the macaque monkey model will display its own pattern of parkinsonian symptoms (Rajput et al. 2009). Indeed, LID involves one or more parts of the body, and each of them should therefore be quantified separately (Hadj Tahar et al. 2000). Several scales are currently available to measure and quantify dyskinesia and were recently reviewed (Fox et al. 2012). Objective measures of bradykinesia with specific motor tasks are also important to separate the antidyskinetic from antiparkinsonian activity of compounds tested (Jourdain et al. 2013). Finally, monkeys will tend to exhibit a worsening of motor symptoms before and after an acute L-DOPA challenge (Kuoppamäki et al. 2002), as seen in some PD patients (Evans et al. 2012). Thus monkey model can replicate PD conditions and underlines their usefulness in the study of new treatments (Morin et al. 2014a).

Individual titration of L-DOPA is often needed to elicit the same amount of LID among the animals (Grégoire et al. 2011; Johnston et al. 2010) even if these animals

are equally denervated (Guigoni et al. 2005). However, positive correlations between L-DOPA dose and the duration and the severity of LID were observed (Kuoppamäki et al. 2007). Moreover, in dyskinetic macaques, the administration of L-DOPA after drug holiday lasting few weeks will trigger the same LID as measured before. The same observation was made in PD patients in whom L-DOPA was stopped (Goetz et al. 1982; Mayeux et al. 1985). This supports the feasibility of acute studies with the same animals therefore keeping the number needed and consequently reducing the costs.

The reappearance of LID after a withdrawal indicates that permanent or at least long-term changes are occurring in the brain basal ganglia and these changes may be studied in postmortem brain tissues. Wearing-off, described as shortening in the duration of response to L-DOPA with gradual reappearance of parkinsonian symptoms, is another important motor side effect of chronic L-DOPA administration (Fahn et al. 2004). Parkinsonian patients usually experience such end-of-dose deterioration after several months or years of treatment (Pahwa and Lyons 2009). Wearing-off can be also replicated in de novo MPTP monkeys with a shortening of the antiparkinsonian effect of L-DOPA as reported after 2 weeks of treatment (Morin et al. 2013a). Thus, the MPTP-lesioned monkey model is probably one of the best models for studying LID and PD in humans, and this model has brought significant advances for the treatment of LID. For example, docosahexaenoic acid (DHA) and cabergoline were shown to reduce the severity or delay the development of LID in MPTP-lesioned monkey in chronic and de novo treatments (Samadi et al. 2006; Belanger et al. 2003).

10.3   Glutamate Neurotransmission in PD and L-DOPA-Induced Dyskinesias

Glutamate is the brain most abundant excitatory neurotransmitter mediating as much as 70% of synaptic transmission in the central nervous system, and its overactivity is well documented in PD and LID (Klockgether and Turski 1993; Morin and Di Paolo 2014; Samadi et al. 2007). Amantadine, a noncompetitive antagonist at N-methyl-D-aspartate (NMDA) receptors, is currently the only drug used in the clinic shown to reduce the severity of LID in some PD patients without worsening parkinsonian symptoms (Meissner et al. 2011; Verhagen Metman et al. 1998a; Sawada et al. 2010). Amantadine also improves akinesia, rigidity, and tremor (Olanow et al. 2009). However, the antidyskinetic effect of amantadine may be transient and is often lost within the first year of treatment (Stocchi et al. 2008). In addition, many PD patients cannot tolerate high doses of amantadine because of cognitive impairment, which significantly limits its use (Stocchi et al. 2008).

Riluzole, a nonselective inhibitor of glutamate neurotransmission, was shown to reduce the severity of L-DOPA-induced motor complications in 6-hydroxydopamine (6-OHDA)-lesioned rat model of PD (Papa et al. 1995; Marin et al. 1996;

Engber et al. 1994; Marin et al. 2000). Moreover, in the same animal model, the glutamate transporter GLT1 was reported to be increased (Oueslati et al. 2007; Robelet et al. 2004). However, riluzole was not effective in humans to reduce the expression of LID (Braz et al. 2004; Bara-Jimenez et al. 2006). Despite intensive search, no drug other than amantadine has demonstrated in the clinic an antidykinesic effect that is not associated with a worsening of parkinsonism (Olanow et al. 2009) underlying the complexity of brain changes associated with dyskinesias. mGlu receptors are topics of more recent interest in PD (Samadi et al. 2007).

Inhibiting glutamate neurotransmission in PD can also be neuroprotective since glutamate overactivity is excitotoxic (Planells-Cases et al. 2006; Gardoni and Di Luca 2006). Motor complications are in part L-DOPA dose related; protecting DA neurons could delay motor complications by using less L-DOPA. Moreover, nonmotor features of PD such as depression and anxiety are common (Olanow et al. 2009) and could benefit from mGlu receptor drugs such as mGlu5 receptor antagonists that show anxiolytic and antidepressant activity (Palucha and Pilc 2007; Witkin et al. 2007).

10.4   Ionotropic Glutamate Receptors and L-DOPA-Induced Dyskinesias

iGlu receptors are classified into NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptors (Finlay and Duty 2014; Michaelis 1998; Dingledine et al. 1999), and they mediate fast excitatory neurotransmission, whereas mGlu receptors mediate slower modulatory neurotransmission (Samadi et al. 2007). The blockade of NMDA and AMPA receptors with specific antagonists was shown to reduce the development of L-DOPA-induced motor complications in 6-OHDA-lesioned rat model (Marin et al. 2000). Moreover, in both parkinsonian patients with LID (Calon et al. 2003a) and dyskinetic MPTP monkeys (Calon et al. 2002; Huot et al. 2013), important increases in striatal NMDA and AMPA receptor-binding levels were observed. The NMDA antagonist, CI-1041, is reported to prevent the development of LID in parkinsonian monkeys (Hadj Tahar et al. 2004) and associated brain molecular changes (Morissette et al. 2006). Interestingly, in these monkeys, CI-1041 also prevented the increase of striatal mGlu5 receptor levels (Ouattara et al. 2011). Clinical trials also show the antidyskinetic profile of dextrorphan, dextromethorphan, and amantadine, known to block NMDA receptors (Meissner et al. 2011; Sawada et al. 2010; Blanchet et al. 1996, 1997; Verhagen Metman et al. 1998b, 1999; Snow et al. 2000; Rajput et al. 1998; Ruzicka et al. 2000; Luginger et al. 2000).

Kynurenic acid antagonizes glycine B site of AMPA, NMDA, and KA receptors (Schwarcz and Pellicciari 2002; Hilmas et al. 2001; Stone 1993, 2000; Moroni 1999) and inhibits glutamate release (Carpenedo et al. 2001; Nemeth et al. 2006). RO 61-8048 an inhibitor of kynurenine hydroxylase activity increases kynurenic

acid levels (Stone 2001). In MPTP monkeys, an acute treatment with RO 61-8048 reduced the severity of LID (Samadi et al. 2005); chronically in de novo treated MPTP monkeys, it reduced their development (Grégoire et al. 2008).

Recent studies have explored the role and the implication of NMDA and AMPA receptor subunits in rodent and nonhuman primate models of PD in LID including the glycine site, NMDA GluN2D subunits, AMPA receptor subunit composition, and NMDA/AMPA receptor ratio (Finlay and Duty 2014; Bagetta et al. 2012; Kobylecki et al. 2010; Zhang et al. 2014; Errico et al. 2011; Heresco-Levy et al. 2013). Nevertheless, significant adverse effects such as cognitive impairment in many patients can occur which limit the use of an iGlu receptor antagonist (Stocchi et al. 2008b; Stayte and Vissel 2014). Recent efforts were devoted to pharmacologically manipulate glutamate transmission with selective mGlu receptor ligands.

10.5 Metabotropic Glutamate Receptors and L-DOPA-Induced Dyskinesias

The mGlu receptors constitute a family of G-protein-coupled receptors comprising eight subtypes that are classified into three groups based on the signal transduction pathway, homology of the amino acid sequence, and receptor pharmacology (Pisani et al. 2003; Conn and Pin 1997). Group I (mGlu1, 5) couples to Gq and stimulates polyphosphoinositide (PI) hydrolysis, while groups II (mGlu2, 3) and III (mGluR4, mGluR6, mGluR7, mGluR8) couple to Gi/Go and inhibit increase in cyclic adenosine monophosphate (cAMP) (Conn and Pin 1997). All mGlu receptor subtypes are mainly located in the brain basal ganglia, except mGlu6 receptor found primarily in the retina (Niswender and Conn 2010) (Fig. 10.1). Presynaptically localized group II and group III mGlu receptors are thought to represent the classical inhibitory autoreceptor mechanism suppressing excess glutamate release from presynaptic terminals (Schoepp 2001). The majority of group I mGlu receptor, including mGlu5, is located postsynaptically on the perisynaptic annulus of dendritic spines, which lead to enhanced neuronal excitation (Lujan et al. 1997).

While the term "antagonist" is widely used when applied to ligands that inhibit the function of specific mGlu receptors, the more appropriate term is "negative allosteric modulator" (NAM), since they inhibit the function of the receptor at a site distal to the actual orthosteric ligand-binding domain of the receptor and only in the presence of glutamate (Olive 2009). Group I NAM may also function as inverse agonists; in cell-based assays they can inhibit the basal (constitutive) activity of group I mGlu receptors in absence of any orthosteric agonist or even when the glutamate-binding domain is removed or mutated (Olive 2009). Moreover, mGlu receptors have a higher affinity for glutamate than iGlu receptors (Conn et al. 2005; Marino et al. 2002). On the basis of these considerations, combined with the rich distribution and diverse physiological roles of mGlu receptors within the basal ganglia, recent attention has been placed on these receptors as alternative targets to
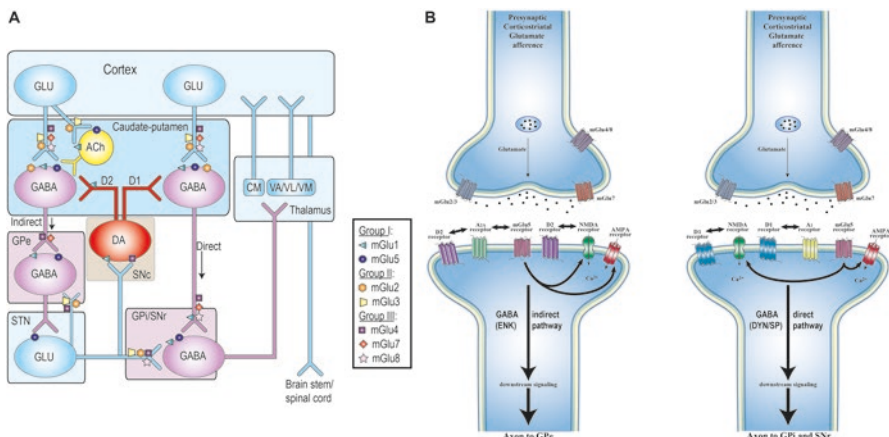
Fig. 10.1 (**a**) Schematic representation of the localization of metabotropic glutamate receptor subtypes (groups I, II, and II) in the basal ganglia motor circuit. mGlu6 receptor subtype (group III) is absent from the figure since it is present only in the retina (Conn et al. 2005; Rascol et al. 2014; Amalric 2015). In the classical and simplified pathophysiological model (not mentioning the collateral projections from the direct to indirect pathway) of the basal ganglia in PD, reduced dopamine input by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) has a dual effect on the striatal efferents that project to the GPe (indirect pathway) and the GPi (direct pathway). Increased or facilitated neuronal activity of the indirect pathway, via decrease of the D2 receptor inhibition, increased activity of striatal GABA neurons projecting to the GPe. Over-inhibition of GABA neurons in the GPe disinhibits the STN, which, in turn, overdrives inhibitory output neurons in the GPi and SNr projecting to the thalamus, overall resulting in a decrease in thalamocortical input. (**b**) Postsynaptic receptors on striatal GABA efferences susceptible to be antagonized to counteract excessive corticostriatal glutamate transmission (absence of glutamate release regulation by D2 autoreceptors on corticostriatal neurons) seen in PD state in order to normalize activities of the direct and indirect pathway. Among these, mGlu5 seems to be a relevant target since this receptor acts primarily as modulator of synaptic activity. The *double arrow* indicates that these receptors can form complexes (heteroreceptor) providing a high degree of complexity and plasticity at different levels of basal ganglia circuitry (Fuxe et al. 2015)

modulate glutamate hyperactivity in PD and LID (Conn et al. 2005). Studies in animal models and PD patients indicate that antagonists of group I mGlu receptor, especially mGlu5 receptor, could be considered as a suitable therapeutic approach in PD and LID.

mGlu5 receptor levels were shown to be increased in the putamen of dyskinetic compared to non-dyskinetic MPTP monkeys (Samadi et al. 2008) and parkinsonian patients with motor complications (LID or wearing-off) compared to those without motor complications (Ouattara et al. 2011). Moreover, the prototypal mGlu5 receptor antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP), and a more selective analog 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) (Carroll 2008) improved motor performance (Breysse et al. 2002) and showed antidyskinetic activity in 6-OHDA rat model (Levandis et al. 2008; Mela et al. 2007). However, the other group I mGlu receptor drugs were not effective (Dekundy et al. 2006; Rylander et al. 2009). In acute treatment in already dyskinetic MPTP-lesioned

monkeys, the mGlu5 receptor antagonists MPEP, MTEP, fenobam, and AFQ056 (mavoglurant) were found effective to reduce the severity of LID (Morin et al. 2010; Rylander et al. 2010; Gregoire et al. 2011; Johnston et al. 2010). In a de novo treatment, MPEP reduced the development of L-DOPA-induced motor complications (~70%) in a chronic administration of 1 month (Morin et al. 2013a). Similarly, chronic administration of fenobam to drug-naïve monkeys attenuated the development of dyskinesia without compromising the antiparkinsonian effect of L-DOPA (Rylander et al. 2010). Moreover, the mGlu5 receptor antagonists, mavoglurant and ADX-48621 (dipraglurant), were shown to reduce LID in parkinsonian patients and were well tolerated without worsening motor symptoms (Addex Therapeutics 2012; Stocchi et al. 2013; Berg et al. 2011). For more information the reader is referred to a recent review on the use of mGlu5 antagonists for treatment of L-DOPA-induced dyskinesias including a comparison the clinical trials with mavoglurant and dipraglurant. (Rascol et al. 2014).

Group II mGlu receptor agonists have also proven effective in animal models of PD (Pisani et al. 2003). Moreover, an important decrease in mGlu2/mGlu3 receptor density in dyskinetic compared to non-dyskinetic MPTP-lesioned monkeys was observed (Morin et al. 2013b). Furthermore, changes in mGlu2/mGlu3 receptors were only observed in relation to wearing-off in postmortem brains of parkinsonian patients (Samadi et al. 2009).

More recently, agonists of group III receptors were also shown effective in rodent models of PD (Niswender and Conn 2010). In 6-OHDA-lesioned rat model, the administration of mGlu4 receptor agonist Lu AF21934 combined with L-DOPA treatment reduced the effective dose of L-DOPA and reduced the development of LID (Bennouar et al. 2013). mGlu4 receptor agonists can reduce γ-aminobutyric acid (GABA)ergic neurotransmission at striato-pallidal synapse that is overactive in PD (Macinnes and Duty 2008; Matsui and Kita 2003).

mGlu8 receptor is expressed at lower levels than mGlu4 and mGlu7 receptors but widely distributed in the brain; mGlu7 receptor has low affinity for glutamate only becoming active when glutamate levels are high thus serving as a brake for glutamate overstimulation (Niswender and Conn 2010). AMN082, an mGlu7 receptor agonist, was shown to reverse motor dysfunction associated with reduced DA activity in rodent models (Greco et al. 2010). However, the contribution of mGlu7 and mGlu8 receptors in LID is not yet reported.

10.6 The Effect of a Chronic Treatment with MPEP on L-DOPA-Induced Dyskinesias and Brain Biochemical Borrelates

The mechanisms underlying the development of LID are still unknown, but evidence suggests that LID is the result of maladaptive plasticity at striatal synapses (Cenci and Lundblad 2006; Jenner 2008; Calabresi et al. 2010; Iravani et al. 2012). Altered dopaminergic and nondopaminergic neurotransmission in the basal ganglia

is observed in LID (Blandini and Armentero 2012). Glutamate neurotransmission plays a crucial role in the modulation of corticostriatal inputs and striatal output to downstream nuclei of the basal ganglia circuit (Blandini and Armentero 2012). Increased glutamate transmission involves presynaptic changes, such as increased striatal concentration of extracellular glutamate (Dupre et al. 2011) or changes in mGlu2/mGlu3 receptors (Samadi et al. 2008; Gregoire et al. 2009). Postsynaptic changes in AMPA, NMDA, and mGlu5 receptors also seem to play a major role in the development of LID (Duty 2012). mGlu5 receptors are highly expressed in the striatum and other basal ganglia nuclei including subthalamic nucleus (STN), substantia nigra, and globus pallidus (GP) (Ferraguti and Shigemoto 2006). Numerous interactions between mGlu5 receptor and NMDA, D_1 DA, D_2 DA, and A_{2A} adenosine receptors suggest that these receptors may function together as closely associated signaling partners in the appearance of LID (Samadi et al. 2007). mGlu5 receptor activation of NMDA receptors (Pisani et al. 2001) as well as NMDA and mGlu5 receptor co-localization is described (Perroy et al. 2008). The blockade of mGlu5 receptors leads to antidyskinetic actions, which is associated with normalization of firing of striatal signals (Duty 2012). Moreover, chronic mGluR5 NAM treatments are reported to protect DA neurons from MPTP toxicity in mice (Battaglia et al. 2004) and monkeys (Masilamoni 2009). Moreover, Norbin, a neuron-specific protein, can physically interact in vivo with mGlu5 receptors, increases the cell surface localization of the receptor, and positively regulates mGlu5 signaling while maintaining the total amount of this receptor unchanged (Wang et al. 2009). Intracellular mGlu5 receptor was reported to activate signaling cascades distinct from cell surface counterparts (Jong et al. 2009). Thus there is still much to be learned on mGuR5 receptors and their regulation.

We reported that development of LID over a month of treatment was lower by overall ~70% with addition of MPEP to the L-DOPA treatment in de novo MPTP monkeys (Morin et al. 2013a), and this was associated with a normalization of glutamate (Morin et al. 2013b), DA (Morin et al. 2014b), and 5-HT neurotransmission (Morin et al. 2015).

More precisely, in the brain basal ganglia of these monkeys (Morin et al. 2013a), the addition of MPEP to L-DOPA treatment prevented the increase of postsynaptic mGlu5, NMDA NR1/NR2B, and AMPA glutamate receptors, while this treatment prevented the decrease of mGlu2/mGlu3 presynaptic autoreceptors (Morin et al. 2013b). The mGlu5 receptor subtype is highly expressed in striatal medium spiny neurons (Conn et al. 2005; Testa et al. 1994; Paquet and Smith 2003) and plays a key role in modulating the responses mediated by NMDA receptors and L-type calcium channels (Gubellini et al. 2004). In addition, an antagonistic interaction between the D_2 DA receptor and mGlu5 receptors is reported (Fuxe et al. 2008). In rodent models of PD, striatal molecular changes relevant to LID are reported to be reversed by MPEP or MTEP, including delta FosB protein (Jimenez et al. 2009), prodynorphin mRNA (Mela et al. 2007), glutamic acid decarboxylase (GAD65 and GAD67) mRNA (Yamamoto and Soghomonian 2009), and phosphorylated extracellular signal-regulated kinases 1 and 2 (ERK1/ERK2) protein levels (Rylander et al. 2009). Hence, mGlu5 receptor antagonists reverse hyperactive GABAergic transmission in the basal ganglia in rodent models of PD and its downstream

molecular changes associated with LID. Hence, mGlu5 receptor antagonist reversed hyperactive glutamate transmission in the basal ganglia of a primate model of PD thus showing the widespread normalization activity of mGlu5 receptor antagonists in the basal ganglia in PD animal models (Morin et al. 2013a).

Moreover, a chronic treatment with MPEP prevented the decrease of D_2 DA receptors, but it did not affect the D_1 DA receptors (Morin et al. 2014b). MPEP also prevented the increase of striatal preproenkephalin/preprodynorphin mRNA levels and phosphorylated proteins ERK1/ERK2 as well as protein kinase B (Akt) and glycogen synthase kinase-3 (GSK3β) (Morin et al. 2014b). Denervation-induced supersensitivity of D_1 and D_2 receptors was initially recognized as a plausible mechanism of LID (Creese et al. 1977; Lee et al. 1978). Numerous studies measured the density of D_1 and D_2 receptors in the brain of human and animal models, but no general consensus emerged. Postmortem studies have shown that striatal DA receptors particularly the D_2 subtype were increased in PD patients (Lee et al. 1978; Guttman et al. 1986) or unchanged (Quik et al. 1979; Rinne et al. 1981), while both D_1 and D_2 receptor subtypes were increased in MPTP monkeys (Falardeau et al. 1988; Bedard et al. 1986; Gagnon et al. 1990). Administration of L-DOPA was shown to reverse these increases in PD patients (Lee et al. 1978; Guttman et al. 1986) and primates in many studies (Falardeau et al. 1988; Gagnon et al. 1990; Berretta et al. 1997). No general consensus also emerged for DA receptor mRNA (Goulet et al. 1997, 2000; Morissette et al. 1996; Aubert et al. 2005; Herrero et al. 1996). These reports support that LID are more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors and its mRNA. MPEP did not affect D_1 receptor levels and its mRNA but was associated with an increased in D_2 receptors levels, its mRNA, and its associated signaling proteins (Morin et al. 2014b). Furthermore, mGlu receptors also have the potential to regulate the mitogen-activated protein kinase (MAPK) pathway. It has been shown that intracaudate injection of a group I mGlu receptor agonist upregulates ERK1/ERK2 phosphorylation (Choe and Wang 2001). mGlu5 receptor stimulation was also reported to lead to activation of other signaling pathways important for cell survival/proliferation, such as ERK and Akt (Mao et al. 2005).

The antidyskinetic effect of MPEP was associated with lower levels of $5\text{-}HT_{2A}$ (Morin et al. 2015) and $5\text{-}HT_{1B}$ (Morin et al. 2015) serotonin receptors, while $5\text{-}HT_{1A}$ receptors and brain serotonin transporter (SERT) remained unaffected (Morin et al. 2015). LID are probably the result of an abnormal adaptation in the striatum due to faulty interaction between glutamate/5-HT and DA inputs in the nigrostriatal pathway. 5-HT neuron terminals in the striatum are suggested to participate in the mechanisms of action of L-DOPA (Navailles and De Deurwaerdere 2012). 5-HT axon terminals can release DA, which is considered as a false neurotransmitter and is probably one of the main presynaptic determinants of LID (Carta et al. 2007). Multiple changes in the basal ganglia glutamate and serotoninergic systems and their specific receptors have been observed (Huot et al. 2013). 5-HT receptor drugs are reported to reduce LID in PD patients (Fox et al. 2009), but changes in 5-HT activity and 5-HT receptors in the brain caused by PD and its pharmacological treatment are not completely understood, and further studies are needed.

Stimulation of $5\text{-}HT_{1B}$ receptors was also shown to reduce dyskinesias induced by D_1 DA receptor agonists (Jaunarajs et al. 2009). This observation suggests that in

order to prevent activation of D_1-expressing neurons, an increase of the inhibitory 5-HT_{1B} heteroreceptors might represent another compensatory phenomenon to prevent activation of the direct pathway neurons, thought to be involved in the expression of LID (Greengard 2001). Moreover, an increase of 5-HT_{1B} autoreceptors might also play a crucial role to regulate or inhibit the release of DA by 5-HT axon terminals. 5-HT axon terminals have been suggested to release DA in a nonphysiological manner following L-DOPA treatment, leading to the development of LID (Carta et al. 2007). Hence, 5-HT neurons can take up L-DOPA and convert it into DA where it is sequestered and stored for subsequent release (Maeda et al. 2005). However, 5-HT neurons lack a DA transporter and D_2 DA autoreceptors, thus leading to excessive nonphysiological DA efflux that promotes LID (Navailles and De Deurwaerdere 2012). Hence, multiple changes in the basal ganglia dopaminergic, glutamate and serotoninergic systems, and their specific receptors have been observed such as modulation in the expression and the activity of subtypes of receptors, G proteins, effectors, transcription factors, and protein kinases (Samadi et al. 2007; Huot et al. 2013).

Moreover, functional interactions between 5-HT_{1B} receptors and GABA should also be considered in the molecular mechanisms of LID. It was reported that L-DOPA administration or stimulation of D_1 receptors in 6-OHDA-lesioned animals increases GABA levels in the substantia nigra pars reticulata (Aceves et al. 1992; Ochi et al. 2004; Yamamoto et al. 2006). GABA concentrations were reported to be high in the striatum of PD patients compared to controls (Kish et al. 1986), and changes in $GABA_A$ and $GABA_B$ receptor levels were also previously observed in the same PD patients, as presented in the present study, with motor complications as compared to those without and controls (Calon et al. 2003b). Hence, 5-HT_{1B} inhibitory receptors located on GABAergic axons of striatal neurons are probably implicated in the alterations of GABA receptors and GABA concentrations measured in these brain areas (Castro et al. 1998). Hence, activation of 5-HT_{1B} receptors could reduce GABA release (Morikawa et al. 2000; Stanford and Lacey 1996). Thus, this upregulation of 5-HT_{1B} receptors in the basal ganglia of dyskinetic monkeys and PD patients with motor complications could be a compensatory mechanism in order to normalize GABA concentrations.

Thus, these reported results suggest that the prevention of the development of motor complications with an mGlu5 receptor antagonist was associated with the normalization of important markers and receptors of glutamate, DA, and 5-HT neurotransmission, supporting the therapeutic use of an mGlu5 receptor antagonist to treat LID.

10.7   Conclusion

Overall, these studies suggest that glutamate receptor stimulation is involved in the pathogenesis of L-DOPA-induced motor complications in PD, and some receptor subtypes, such as mGlu5 receptor subtypes, are potential selective targets for treatment of these adverse effects (Blanchet et al. 1997; Chase and Oh 2000;

Verhagen Metman et al. 2000; Montastruc et al. 1997). mGlu5 receptor antagonists are very promising drugs for the management of various brain disorders, and one of its potential applications is LID therapy. Therefore, it is essential to know the long-term behavioral effects of this class of compounds, and ensuing possible biochemical adaptations of the brain, it is critical to learn as much as possible from MPTP primate models, which closely mimic human PD conditions (Morin et al. 2014a). The mGlu5 antagonist treatment in parkinsonian primates and rats affects not only glutamate receptors but also DA and 5-HT receptors. This may be indirect by restoring glutamate neurotransmission but could also involve the direct interactions of the trio mGlu5-D_2-A_{2A} receptor cross talk (Fiorentini et al. 2013; Fuxe et al. 2007). Moreover, supporting a close mGlu5-A_{2A} receptor interaction, MTEP treatment was reported to decrease mice brain A_{2A} receptor-specific binding and regulate the conditioned effects of cocaine (Brown et al. 2012). The implication of these receptor interactions in mental and neurodegenerative diseases and more specifically in the development and expression of PD symptoms and LID needs further investigation to find novel targets and, ultimately, novel pharmacological treatments.

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