Review Article

Metabotropic Glutamate Receptors for Parkinson’s Disease Therapy

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Excessive glutamatergic signalling within the basal ganglia is implicated in the progression of Parkinson’s disease (PD) and in the emergence of dyskinesia associated with long-term treatment with L-DOPA. There is considerable research focus on the discovery and development of compounds that modulate glutamatergic signalling via glutamate receptors, as treatments for PD and L-DOPA-induced dyskinesia (LID). Although initial preclinical studies with ionotropic glutamate receptor antagonists showed antiparkinsonian and antidyskinetic activity, their clinical use was limited due to psychiatric adverse effects, with the exception of amantadine, a weak N-methyl-d-aspartate (NMDA) antagonist, currently used to reduce dyskinesia in PD patients. Metabotropic receptor (mGlu receptor) modulators were considered to have a more favourable side-effect profile, and several agents have been studied in preclinical models of PD. The most promising results have been seen clinically with selective antagonists of mGlu5 receptor and preclinically with selective positive allosteric modulators of mGlu4 receptor. The growing understanding of glutamate receptor crosstalk also raises the possibility of more precise modulation of glutamatergic transmission, which may lead to the development of more effective agents for PD.

1. Introduction

Parkinson’s disease (PD) is a chronic progressive neurodegenerative disorder of the central nervous system (CNS), characterised by a gradual loss of dopaminergic neurotransmission. Cardinal symptoms of PD include tremor, bradykinesia, and rigidity. Levodopa (L-DOPA) is considered the standard of care for providing symptomatic relief in PD [1]. However, long-term L-DOPA treatment leads to the appearance of motor complications in the majority of responding patients and severely affects their quality of life [2]. After 9 years of L-DOPA treatment, ~90% of PD patients experience dyskinesia [3]. The dyskinesia that develops is often a combination of choreic and dystonic abnormal involuntary movements, collectively termed L-DOPA-induced dyskinesia (PD-LID).

Once PD-LID is established, increasing the L-DOPA dose typically worsens dyskinesia and this may prevent the use of L-DOPA at optimal doses required to control motor fluctuations. There are currently no licensed therapies for the treatment of PD-LID, although a number of clinical strategies are employed including adding dopamine agonists, monoamine oxidase inhibitors, adenosine (2A) receptor antagonists, catechol-O-methyl transferase inhibitors, and anticholinergic drugs as part of a L-DOPA-sparing strategy [4–7] and the use of amantadine [8]; see Tambasco et al. 2012 for a recent review [9].

The precise mechanisms of PD-LID are not completely understood, but excessive glutamatergic transmission within the basal-ganglia is thought to play a key role in the pathophysiology of PD and PD-LID [10, 11]. Therefore, therapeutic agents that regulate glutamate transmission are valid targets for drug development to alleviate motor symptoms associated with PD and PD-LID (Table 1). In this paper we will review attempts to develop therapeutic agents capable of normalising defective glutamatergic transmission via modulation of glutamate receptors.
**Table 1:** Glutamatergic agents cited within the text with their pharmacological profile, main target/s, and mode of action.

| Target                                      | Agent                  | Pharmacological action     |
|---------------------------------------------|------------------------|----------------------------|
| AMPA receptor                               | GYKI-52466             | Noncompetitive antagonist   |
|                                             | GYKI-53405             | Noncompetitive antagonist   |
|                                             | NBQX                   | Competitive antagonist      |
|                                             | Perampanel             | Noncompetitive antagonist   |
| AMPA/kainate receptor                       | Tezampanel (LY293558)  | Competitive antagonist      |
|                                             | Talampanel (LY300164)  | Noncompetitive antagonist   |
| AMPA/NMDA receptor                          | CPP                    | Competitive antagonist      |
|                                             | Amantadine             | Noncompetitive antagonist   |
|                                             | APV                    | Competitive antagonist      |
|                                             | CGP-43487              | Competitive antagonist      |
| NMDA receptor                               | Ifenprodil             | Noncompetitive antagonist   |
|                                             | PAMQX                  | Competitive antagonist      |
|                                             | Remacemide             | Noncompetitive antagonist   |
|                                             | Traxoprodil            | Noncompetitive antagonist   |
| mGlu1 receptor                              | EMQMCM                 | Noncompetitive antagonist   |
| mGlu2 receptor                              | LY379268               | Competitive agonist         |
| mGlu4 receptor                              | PHCCC                  | PAM                        |
| mGlu4/mGlu5 receptor                        | SIB-1893               | PAM/noncompetitive antagonist|
| mGlu5 receptor                              | Dipraglurant (ADX48621)| Noncompetitive antagonist   |
|                                             | Mavoglurant (AFQ056)   | Noncompetitive antagonist   |
|                                             | MPEP                   | Noncompetitive antagonist   |
|                                             | MRZ-8676               | Noncompetitive antagonist   |
|                                             | MTEP                   | Noncompetitive antagonist   |
| mGlu7 receptor                              | AMN082                 | PAM                        |
| mGlu8 receptor                              | DCPG                   | Competitive agonist         |

### 2. Basal Ganglia Circuitry in Parkinson’s Disease

A balance between inhibition and excitation of the major output nuclei of the basal ganglia is important for normal motor control. This is achieved via direct and indirect inhibitory projections (GABAergic) from the striatum (caudate nucleus/putamen) to the globus pallidus internal (GPI)/substantia nigra pars reticulate (SNr) and excitatory projections (glutamatergic) from the subthalamic nucleus (STN) to the substantia nigra pars compacta (SNc) and GPI/SNr. Appropriate dopaminergic input from the SNc to the striatum plays a key role in maintaining this balance [12]. In patients with PD, degeneration of dopamine nigral neurons within the SNc results in loss of dopaminergic modulation and increases the overall excitatory drive in the basal ganglia, disrupting voluntary motor control and causing the characteristic symptoms of PD [13]. The progressive depletion of the endogenous dopaminergic signalling combined with the compensatory exogenous supply of dopamine (DA) precursor L-DOPA induces profound changes in the neurotransmitter network of the basal ganglia [14]. An imbalance in the DA receptors, particularly between D1 and D2 receptor subtypes mainly expressed in the direct and indirect striatal output pathways, respectively, has been identified in dyskinetic nonhuman primates [15, 16]. In rodents, genetic ablation of the D1 receptor subtype but not the D2 subtype abolished the L-DOPA-induced dyskinesia. These results suggest a key role for the D1 receptor in the development of PD-LID [16]. However, a role for D2 receptors in the onset and expression of L-DOPA induced dyskinesias is also documented [17]. Additional changes in other dopamine receptor subtypes such as D3 and D5 have also been identified [18].

The cellular mechanisms by which the dopaminergic neurons are lost are not fully understood, although excessive glutamatergic transmission has been implicated [19, 20]. Glutamate is the main excitatory neurotransmitter in the CNS and normal brain function requires balanced glutamatergic neurotransmission. As a result of striatal dopaminergic denervation, the glutamatergic projections from the STN to the basal ganglia output nuclei become overactive with reduced regulation of glutamate receptors [19]. The resultant excessive excitation by glutamate through the basal ganglia circuitry can be toxic to any remaining dopaminergic neurons, leading to further loss of dopaminergic transmission and progression of PD symptoms [21]. Normalisation of motor function is initially seen with L-DOPA treatment. However, as the severity of PD increases, the substantial
3. Glutamate Receptors in Parkinson’s Disease

Glutamate receptors modulate glutamatergic neurotransmission in the brain and play a role in memory, learning and motor control; glutamatergic dysfunction is implicated in a range of neurological disorders [25–27]. Two classes of glutamate receptor have been described: ionotropic glutamate receptors (iGlu receptors) [28], and metabotropic glutamate receptors (mGlu receptors) [26].

3.1. Ionotropic Glutamate Receptors. iGlu receptors are ligand-gated ion channels composed of four large subunits that form a central pore within the cell membrane. The iGlu receptors include the NMDA (N-methyl-d-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate ([2S,3S,4S]-3-[carboxymethyl]-4-prop-1-en-2-yl-pyrrolidine-2-carboxylic acid) receptors, all of which share a similar structure but differ in their amino acid sequences, subunit combination, and agonist sensitivity/selectivity. Within the CNS, iGlu receptors are responsible for fast excitatory transmission [28]. Their important role in mediating glutamatergic neurotransmission identifies the iGlu receptors as potential therapeutic targets for symptomatic management in PD and PD-LID.

3.1.1. AMPA Receptors. Within the mammalian CNS, the majority of fast excitatory synaptic transmission is mediated by AMPA receptors [29]. AMPA receptor function is critical for synaptic plasticity. The potential for therapeutic AMPA modulation for PD is yet to be conclusively proven. Preclinical studies of AMPA receptor antagonists 6-nitro-sulfamoylbenzo-quinoxaline-dione (NBQX) and GYKI-52466 failed to show antiparkinsonian activity when they were administered alone [30–34]. NBQX has shown some antiparkinsonian activity in another study where it reversed reserpine-induced muscle rigidity, but not akinesia in monoamine-depleted rats, and motor deficits in MPTP-lesioned Rhesus monkeys [35]. In another study, NBQX was combined with the competitive NMDA receptor antagonist 3-carboxy-piperazin-propyl phosphonic acid (CPP) and reversed the shortened duration of L-DOPA-induced motor responses [36]. Interestingly, NBQX [31, 32, 34] and CPP [30, 31] both potentiate the antiparkinsonian effects of coadministered dopaminergic agents. L-DOPA-sparing effects have also been shown in preclinical models with GYKI-52466 and GYKI-53405 [37, 38].

Increased AMPA receptor activity has been implicated in the development of LID [11, 39]. The competitive AMPA/kainate receptor antagonist LY293558 (tezampanel) reversed and prevented LID in parkinsonian rats [40] and the non-competitive AMPA/kainate antagonist LY300164 (talampac) decreased LID in MPTP-treated monkeys by up to 40% [41]. Another non-competitive AMPA receptor antagonist, perampanel, showed promising results in preclinical studies, reducing L-DOPA-induced motor defects 6-OHDA-primed rats [42] and dyskinesia in MPTP-treated monkeys [43]. Unfortunately, these results have not successfully translated to the clinical setting, and initial phase II and III trials of perampanel were terminated because of lack of efficacy [44–46].

3.1.2. NMDA Receptors. NMDA receptors mediate glutamatergic excitation in the striatum and STN; NMDA-mediated signalling in the brain is thought to be involved in both neural plasticity and neurotoxicity [24]. Dysfunctions in NMDA receptor trafficking in striatal neurons result in the altered synaptic plasticity seen in animal models of PD and dyskinesia [47]. Several antagonists of NMDA receptors have shown therapeutic potential in animal models of PD: neuroprotective activity, by limiting the extent of nigrostriatal damage [48], or behavioural effects through the improvement of motor symptoms of PD [49, 50] and preventing or reducing LID [51–55]. Administration of competitive NMDA receptor antagonists such as CPP, CGP-43487, and APV, which target the glutamate binding site, or PAMQX, which binds to the glycine site in NMDA heterodimers, has also been shown to potentiate dopaminergic therapies in preclinical PD models [34, 56, 57]. There is also evidence of synergism between AMPA and NMDA antagonists in animal models of PD and LID [31, 58]. Further evidence of crosstalk between receptors involved in PD pathophysiology comes from studies showing interactions with 5-HT (2A) receptors [59, 60] and adenosine (2A) receptors in animal models [61], raising the possibility of adenosine (2A) or 5-HT (2A) receptor modulation as a novel therapeutic strategy for PD. NR2B-selective, non-competitive NMDA receptor antagonists, tnaxoprodil and ifenprodil, have shown therapeutic potential in animal models of PD-LID [50, 52, 62, 63].

Despite positive results in preclinical studies, clinical development of NMDA antagonists has been hampered by the side effects of these compounds, including psychosis, impaired learning, and disruption of motor function [64], which pose substantial problems with chronic use. This observed absence of a therapeutic window is likely due to the wide expression of NMDA receptors throughout the CNS and their key involvement in many physiological processes.

The greatest success with NMDA antagonists in PD and PD-LID has been seen with amantadine, a weak non-competitive NMDA receptor antagonist. Amantadine is
approved for the treatment of PD and is widely used to treat PD-LID (off-label indication), due to its inclusion in international guidelines [65, 66]. Antidyskinetic activity with amantadine has been reported in both 6-OHDA rodent and MPTP primate models of LID [60, 67, 68]. Clinical benefits with amantadine in PD-LID have been seen in an increasing number of clinical trials [69–74] and the benefits appear to be long lasting [75, 76]. An extended-release formulation of amantadine, amantadine ER (ADS–5102), is currently in clinical trials for PD-LID. Other non-competitive NMDA receptor antagonists that have been investigated in the clinical setting include remacemide, which has failed to show benefit in the symptomatic management of PD and LIDs [77–80]. The non-competitive NMDA receptor antagonist, traxoprodil has shown clinical efficacy in two small studies [81, 82].

3.1.3. Kainate Receptors. The existence of kainate receptors has been known for some time, yet little is understood about their contribution to the pathology of PD or the potential of kainate receptors as therapeutic targets in PD and PD-LID. This is primarily due to a lack of selective pharmacological agents to help elucidate the complex molecular mechanisms underlying these conditions.

3.2. Metabotropic Glutamate Receptors. The limitations of targeting iGlu receptors in PD combined with the high expression of mGlur receptors in the basal ganglia and their diverse modulatory roles has raised the interest in mGlur receptors as alternative targets for modulating glutamate hyperactivity in PD [12, 27]. mGlur receptors belong to the G-protein-coupled receptor family and are membrane-bound and activated by extracellular ligands. Unlike the fast excitatory glutamatergic transmission mediated by iGlu receptors, mGlur receptors have a more modulatory role, responsible for fine tuning glutamatergic transmission [26]. Eight mGlur receptor subtypes have been cloned and classified into three groups according to sequence similarity, signal transduction mechanism, and pharmacological properties [26]. Group I (mGlur1 and 5) receptors are coupled to activation of phospholipase C and mediate postsynaptic excitatory effects. They are mainly located postsynaptically and regulate glutamate transmission through negative and positive regulation of potassium and calcium ion channels. Group II (mGlur2 and 3) and Group III (mGlur4, 6, 7, and 8) receptors are negatively coupled to activation of phospholipase C and mediate postsynaptic excitatory effects. They are mainly located postsynaptically and regulate glutamate transmission through negative and positive regulation of potassium and calcium ion channels. Of these 8 subtypes, mGlur5 and mGlur4 receptors are of particular interest as therapeutic targets in PD given their expression and distribution in the basal ganglia.

3.2.1. Group I mGlur Receptors. Group I receptors mGlur1 and 5 share a high degree of sequence homology but their expression patterns within the brain differ considerably (Figure 2), suggesting that they may have distinct functional roles in brain physiology and pathophysiology.
The role of mGlu1 receptor in PD and PD-LID was examined using the selective antagonist, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methane sulphonate (EMQMCM), in 6-OHDA primed rats [83]. Treatment with EMQMCM induced some improvement of dyskinesia, altered downstream molecular signalling pathways, and attenuated L-DOPA-induced gene expression. However, these effects were achieved at a dose which blocked the antiakinetic (antiparkinsonian) action of L-DOPA. Together, these data do not support the use of mGlu1 receptor antagonists as a treatment for PD-LID.

The high expression of mGlu5 receptor in the caudate nuclei, putamen and basal ganglia [85, 86], and its postsynaptic localisation, make the mGlu5 receptor an attractive target to modulate the excessive glutamatergic neurotransmission induced by the loss of dopaminergic innervation. The first attempts to inhibit the mGlu5 receptor were made with competitive and nonselective antagonists. These early tool compounds had poor in vivo properties and brain penetration resulting in an inability to identify a role for the mGlu5 receptor. The identification and use of more specific tool compounds such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) enabled the hypothesis to be tested in various animal models of PD. The first confirmation of the potential to modulate excessive glutamatergic neurotransmission via inhibition of mGlu5 receptor came from the work of Spooren et al. [87]. They showed that MPEP could attenuate unilateral rotating behaviour in the rat 6-hydroxydopamine (6-OHDA) lesion model. Shortly after, Breyse et al. [88] provided further supportive data, by showing how chronic (but not acute) treatment with MPEP could improve akinesia in the 6-OHDA rat model. However, in this study no effects on haloperidol-induced catalepsy were observed following MPEP treatment [88]. In rats with nigrostriatal lesions, MPEP virtually abolished abnormal involuntary movements [89]. Using 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]pyridine (MTEP), which has superior specificity and bioavailability to MPEP, a reduction of haloperidol-induced catalepsy and muscle rigidity in rats was seen [90].

More recently, mGlu5 receptor expression was shown to be enhanced within the posterior putamen and globus pallidus of parkinsonian monkeys experiencing dyskinesia following chronic L-DOPA treatment [91] and in human postmortem brains of parkinsonian patients with dyskinesia and wearing off [92]. In addition, animal models of PD-LID show upregulation of mGlu5 receptor genes, reflecting long-term changes associated with the development of dyskinesia [93]. There is also evidence of crosstalk between mGlu5 receptors and NMDA receptors in the striatum and subthalamic nucleus [94, 95], and it is possible that therapeutic modulation of mGlu5 receptors may have beneficial effects on NMDA receptor signalling in PD. Additionally, mGlu5 receptors and adenosine A(2A) receptors are coexpressed in D2 striatal neurons and interact to regulate the downstream effects of mGlu5 receptor activity [96–99].

The first evidence for the therapeutic potential of mGlu5 antagonists in PD-LID was presented by Hill et al. [100] using the noncompetitive antagonist, SIB-1893, to ease LIDs in MPTP-lesioned monkeys. Interestingly, SIB-1893 was identified initially as a relatively weak mGlu5 receptor antagonist (IC{sub 50} = 2.3 µM) [101], whereas further characterisation revealed SIB-1893 to also be a positive allosteric modulator (PAM) of the mGlu4 receptor [102].

The use of MTEP confirmed that antagonism of mGlu5 receptor attenuates LID in 6-OHDA lesioned rats [103, 104] and MPTP-lesioned monkeys [105]. In MPTP-lesioned monkeys, MPEP showed antiparkinsonian effects and reduced the development of LID [106]. Similar results were seen with both MPEP and MTEP in MPTP-lesioned monkeys treated with L-DOPA [105]. Other selective mGlu5 receptor antagonists that have shown preclinical antidykinetic effects include 6,6-dimethyl-2-phenylethynyl-7,8-dihydro-6H-quinolin-5-one (MRZ-8676) [100], dipraglurant (ADX48621; Addex Press Release), and mavoglurant (AFQ056), which reduced dyskinesia in L-DOPA-treated MPTP-lesioned monkeys [100]. In addition, mavoglurant did not adversely affect the response to L-DOPA in MPTP-lesioned monkeys, but did potentiate the effects of low doses of L-DOPA [107].

In contrast to other therapeutic approaches in PD, the wealth of preclinical data supporting the potential of mGlu5 receptor antagonists in treating PD and LID has been confirmed clinically by two drug candidates, mavoglurant [108, 109] and dipraglurant [110]. Both have shown significant antidykinetic activity in patients with moderate-to-severe PD-LID. Follow-up trials with both mavoglurant and dipraglurant are ongoing.

3.2.2. Group III mGlu Receptors. Among the Group III mGlu receptors, mGlu4, 7, and 8 are expressed at multiple synapses throughout the basal ganglia and mainly localised presynaptically [12, 85]. Their activation inhibits neurotransmitter release, a mechanism implicated in the pathophysiology of PD [111–113]. Preclinical studies with selective Group III mGlu receptor competitive agonists reversed akinesia and
haloperidol-induced catalepsy in rodent models of PD [114–116].

Similarly, PAMs targeting mGlu4 receptor have shown some antiparkinsonian activity in animal models of PD. For example, N-phenyl-7-(hydroxyimino) cyclopropa[b] chromen-1a-carboxamide (PHCCC) reversed risperidone-induced akinesia in rats [117] and reduced striatal dopamine neuron degeneration in MPTP-treated mice [118]. However, PHCCC has low potency and poor aqueous solubility and demonstrates antagonism at mGlu1 receptors at a similar potency to that at mGlu4 receptors [117]. Therefore, agents exhibiting greater potency and selectivity for mGlu4 receptors have been sought to clarify the therapeutic potential of targeting this receptor subtype in PD. One such agent, VU0155041, has shown antiparkinsonian activity in haloperidol-induced catalepsy and 6-OHDA lesioned rats [119, 120]. VU0155041 also demonstrated synergy when coadministered with the adenosine (2A) receptor agonist prelaminant, as well as L-DOPA, suggesting a potential L-DOPA-sparing mechanism [120]. Similarly, 5-methyl-N-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl) thiazol-2-amine (ADX88178), a PAM with high bioavailability and specificity for mGlu4 receptor, has antiparkinsonian activity including potentiation of L-DOPA effects, without increasing LID [121].

Activation of the mGlu7 receptor using the PAM, N,N’-dibenzhydrylamine-1,2-diamine dihydrochloride (AMN082), has also shown antiparkinsonian and antidyssynaptic activity in rodent models of PD [12, 122]. Currently, there are no agonists or PAMs, with appropriate oral bioavailability and brain permeability available for targeting the mGlu8 receptor. However, intracerebroventricular injection of the mGlu8 receptor agonist, (S)-3,4-dicarboxyphenylglycine (DCPG), reportedly reversed parkinsonian symptoms in a rat model for PD [123].

3.2.3. Group II mGlu Receptors. Activation of Group II mGlu2 and 3 receptors using competitive agonists has been extensively characterised in animal models. Based on their preclinical profile, these group II agonists have been evaluated in the clinic for anxiety [124] and schizophrenia [125]. In contrast, preclinical data supporting a beneficial effect in PD are limited. Both receptors have been located in key areas of the basal ganglia associated with PD pathophysiology such as the SNr, and their activation is known to inhibit synaptic excitation [85, 126, 127]. However, ligand binding autoradiography in postmortem brain tissue, from MPTP-treated monkeys and patients with PD, suggests that there are no clear changes in the expression of mGlu2 and 3 receptors associated with PD-LID [128, 129]. Systemic administration of the competitive mGlu2/3 receptor agonist LY379268 failed to provide any functional benefit in the 6-OHDA lesioned rat model [130]. Johnson et al. suggested that [131] the lack of subtype specificity and limited brain penetrability of LY379268 were responsible for the absence of efficacy seen following systemic administration [122]. PAMs selective for mGlu2 receptor have an improved pharmacokinetic profile and good brain penetration [123]. In vivo, mGlu2 receptor PAMs have shown that they are valuable alternative to the competitive agonists in a rodent model for panic-like behaviour [132].

Future investigations of PAMs targeting mGlu2 receptors using appropriate animal models will be key to evaluating the potential of this mechanism of action in PD.

4. Conclusions

Nigrostriatal denervation in PD leads to increased glutamatergic transmission in the basal ganglia, which leads to further loss of dopaminergic neurons, progression of PD, and the appearance of PD-LID. Pharmacological modulation of glutamatergic transmission is a key focus for research into novel nondopaminergic agents for PD. Antagonists of iGlu receptors have shown antiparkinsonian and antidyskinetic effects in preclinical studies, but the emergence of adverse effects has limited the clinical value of these agents. Amantadine, a weak NMDA antagonist, is the exception, showing significant anti-dyskinetic effects in the clinical setting. Modulators of mGlu receptors hold greater promise in PD due to their location in the basal ganglia and the development of a number of agents with high potency and selectivity for different mGlu receptor subtypes. In particular, preclinical studies with mGlu5 receptor subtype selective antagonists and PAMs of mGlu4 receptor have shown good efficacy in models of both PD and PD-LID, and there is now growing clinical evidence for mGlu5 receptor antagonism as a valid therapeutic target for PD-LID. Research into glutamate receptor signalling in the basal ganglia is now revealing a hugely complex network involving cross-talk between different glutamate receptors, dopamine, and adenosine receptors. As we understand more about the importance of these interactions, we may be able to develop compounds that can fine tune dopaminergic and non-dopaminergic transmission, leading to better treatments for PD and PD-LID.

Conflict of Interests

Fabrizio Gasparini and Baltazar Gomez-Mancilla are employees of Novartis Pharma AG and hold shares with Novartis Pharma AG. Fabrizio Gasparini and Baltazar Gomez-Mancilla have also received reimbursement from Novartis Pharma AG for travel expenses. The work of Thérèse Di Paolo is supported by funding from the Canadian Institutes of Health Research, The Quebec Consortium for Drug Discovery, and the Natural Sciences and Engineering Research Council of Canada. Thérèse Di Paolo has also received compensation from Novartis Pharma AG for investigating new compounds in vivo as part of a collaborative project and reimbursement for travel expenses. Thérèse Di Paolo is also coauthor on patents with Novartis Pharma AG.

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References

[1] N. B. Mercuri and G. Bernardi, “The “magic” of L-dopa: why is it the gold standard Parkinson’s disease therapy?” Trends in Pharmacological Sciences, vol. 26, no. 7, pp. 341–344, 2005.

[2] G. Fabbriini, J. M. Brotchie, F. Grandas, M. Nomoto, and C. G. Goetz, “Levodopa-induced dyskinesias,” Movement Disorders, vol. 22, no. 10, pp. 1379–1389, 2007.

[3] J. E. Ahlskog and M. D. Mueenter, “Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature,” Movement Disorders, vol. 16, no. 3, pp. 448–458, 2001.

[4] S. Cristina, R. Zangaglia, F. Mancini, E. Martignoni, G. Nappi, and C. Pacchetti, “High-dose ropinirole in advanced Parkinson’s disease with severe dyskinesias,” Clinical Neuropharmacology, vol. 26, no. 3, pp. 146–150, 2003.

[5] A. Faccia and J. Sanchez-Ramos, “High-dose pergolide monotherapy in the treatment of severe levodopa-induced dyskinesias,” Movement Disorders, vol. 11, no. 3, pp. 327–329, 1996.

[6] M. Müngersdorf, U. Sommer, M. Sommer, and H. Reichmann, “High-dose therapy with ropinirole in patients with Parkinson’s disease,” Journal of Neural Transmission, vol. 108, no. 11, pp. 1309–1317, 2001.

[7] J. Kulisevsky and M. Poyurovsky, “Adenosine A2A-receptor antagonism and pathophysiology of Parkinson’s disease and drug-induced movement disorders,” European Neurology, vol. 67, no. 1, pp. 4–11, 2012.

[8] J. Brotchie, “Antidyskinetic actions of amantadine in Parkinson’s disease: are benefits maintained in the long term?” Expert Review of Neurotherapeutics, vol. 10, no. 6, pp. 871–873, 2010.

[9] N. Tambasco, S. Simoni, E. Marsili et al., “Clinical aspects in Neurosciences,” Trends in glutamate-mediated dysregulation in experimental parkinsonism,” Trends in Neurosciences, vol. 23, no. 10, pp. S86–S91, 2000.

[10] F. Calon, A. H. Rajput, O. Hornykiewicz, P. J. Bédard, and T. Di Paolo, “Levodopa-induced motor complications are associated with alterations of glutamate receptors in Parkinson’s disease,” Neurobiology of Disease, vol. 14, no. 3, pp. 404–416, 2003.

[11] K. A. Johnson, P. J. Conn, and C. M. Niswender, “Glutamate receptors as therapeutic targets for Parkinson’s disease,” CNS and Neurological Disorders, vol. 8, no. 6, pp. 475–491, 2009.

[12] P. Jenner, “Molecular mechanisms of L-DOPA-induced dyskinesia,” Nature Reviews Neurosciences, vol. 9, no. 9, pp. 665–677, 2008.

[13] J. Brotchie and C. Fitzter-Attas, “Mechanisms compensating for dopamine loss in early Parkinson disease,” Neurology, vol. 72, no. 7, pp. S32–S38, 2009.

[14] I. Aubert, C. Guigoni, K. Håkansson et al., “Increased D5 dopamine receptor signaling in levodopa-induced dyskinesia,” Annals of Neurology, vol. 57, no. 1, pp. 17–26, 2005.

[15] M. M. Iravani, A. C. McCreary, and P. Jenner, “Striatal plasticity in Parkinson’s disease and L-DOPA induced dyskinesia,” Parkinsonism and Related Disorders, vol. 18, no. 1, supplement, pp. S123–S125, 2012.

[16] M. M. Iravani and P. Jenner, “Mechanisms underlying the onset and expression of levodopa-induced dyskinesia and their pharmacological manipulation,” Journal of Neural Transmission, vol. 118, no. 12, pp. 1661–1690, 2011.

[17] A. Berthet and E. Bezard, “Dopamine receptors and L-dopa-induced dyskinesia,” Parkinsonism and Related Disorders, vol. 15, no. 4, supplement, pp. S8–S12, 2010.

[18] F. Blandini, R. H. P. Porter, and J. T. Greenamyre, “Glutamate and Parkinson’s disease,” Molecular Neurobiology, vol. 12, no. 1, pp. 73–94, 1996.

[19] M. A. Cenci, “Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia,” Trends in Neurosciences, vol. 30, no. 5, pp. 236–243, 2007.

[20] E. Esposito, V. Di Matteo, and G. Di Giovanni, “Death in the substantia nigra: a motor tragedy,” Expert Review of Neurotherapeutics, vol. 7, no. 6, pp. 677–697, 2007.

[21] M. A. Cenci, K. E. Ohlin, and D. Rylander, “Plastic effects of L-DOPA treatment in the basal ganglia and their relevance to the development of dyskinesia,” Parkinsonism and Related Disorders, vol. 15, supplement 3, pp. S59–S63, 2009.

[22] A. H. Rajput, M. E. Fenton, S. Birdi, and R. Macaulay, “Is levodopa toxic to human substantia nigra?” Movement Disorders, vol. 12, no. 5, pp. 634–638, 1997.

[23] S. Boyce, N. M. J. Rupniak, M. J. Steventon, and S. D. Iversen, “Nigrostriatal damage is required for induction of dyskiniesias by L-DOPA in squirrel monkeys,” Clinical Neuropharmacology, vol. 13, no. 5, pp. 448–458, 1990.

[24] S. Nakanishi, “Molecular diversity of glutamate receptors and implications for brain function,” Science, vol. 258, no. 5082, pp. 597–603, 1992.

[25] C. M. Niswender and P. J. Conn, “Metabotropic glutamate receptors: physiology, pharmacology, and disease,” Annual Review of Pharmacology and Toxicology, vol. 50, pp. 295–322, 2010.

[26] S. Boyce, N. M. J. Rupniak, M. J. Steventon, and S. D. Iversen, “Nigrostriatal damage is required for induction of dyskiniesias by L-DOPA in squirrel monkeys,” Clinical Neuropharmacology, vol. 13, no. 5, pp. 448–458, 1990.

[27] S. Nakanishi, “Molecular diversity of glutamate receptors and implications for brain function,” Science, vol. 258, no. 5082, pp. 597–603, 1992.

[28] P. A. Loschmann, K. W. Lange, M. Kunow et al., “Synergistic effects of GYKI 52466, a non-competitive AMPA receptor modulator,” Current Neuropharmacology, vol. 10, no. 1, pp. 12–48, 2012.

[29] S. F. Traynelis, L. P. Wollmuth, C. J. McBain et al., “Glutamate receptor ion channels: structure, regulation, and function,” Pharmacological Reviews, vol. 62, no. 3, pp. 405–496, 2010.

[30] B. Zadow and W. J. Schmidt, “The AMPA antagonists NBQX and GYKI 52466 do not counteract neuroleptic-induced catalepsy,” Naunyn-Schmiedeberg’s Archives of Pharmacology, vol. 349, no. 1, pp. 61–65, 1994.

[31] P.-A. Loschmann, K. W. Lange, M. Kunow et al., “Synergism of the AMPA-antagonist NBQX and the NMDA-antagonist CPP with L-Dopa in models of Parkinson’s disease,” Journal of Neural Transmission, vol. 3, no. 3, pp. 203–213, 1991.

[32] P. A. Loschmann, M. Kunow, and H. Wachtel, “Synergism of NBQX with dopamine agonists in the 6-OHDA rat model of Parkinson’s disease,” Journal of Neural Transmission, Supplement, no. 38, pp. 55–64, 1992.

[33] J. Maj, Z. Rogoz, G. Skuza, and K. Kolodziejczyk, “Some central effects of GYKI 52466, a non-competitive AMPA receptor antagonist,” Polish Journal of Pharmacology, vol. 47, no. 6, pp. 501–507, 1995.

[34] H. Wachtel, M. Kunow, and P.-A. Loschmann, “NBQX (6-nitro-sulfamoyl-benzo-quinoxaline-dione) and CPP (3-carboxy-piperazin-propyl phosphonic acid) potentiate dopamine agonist
induced rotations in substantia nigra lesioned rats," *Neuroscience Letters*, vol. 142, no. 2, pp. 179–182, 1992.

[35] T. Klockgether, L. Turski, T. Honore et al., “The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys;” *Annals of Neurology*, vol. 30, no. 5, pp. 717–723, 1991.

[36] C. Marin, A. Jimenez, M. Bonastre, T. N. Chase, and E. Tolosa, “Non-NMDA receptor-mediated mechanisms are involved in levodopa-induced motor response alterations in Parkinsonian rats,” *Synapse*, vol. 36, no. 4, pp. 267–274, 2000.

[37] Z. Juranyi, N. Sziray, B. Marko, G. Levay, and L. G. Harsing Jr., “AMPA receptor blockade potentiates the stimulatory effect of L-DOPA on dopamine release in dopamine-deficient corticostriatal slice preparation,” *Critical Reviews in Neurobiology*, vol. 16, no. 1–2, pp. 129–139, 2004.

[38] K. Megyeri, B. Marko, N. Sziray et al., “Effects of 2,3-benzodiazepine AMPA receptor antagonists on dopamine turnover in the striatum of rats with experimental parkinsonism,” *Brain Research Bulletin*, vol. 71, no. 3, pp. 501–507, 2007.

[39] J. M. Brotchie, “Nondopaminergic mechanisms in levodopa-induced dyskinesia,” *Movement Disorders*, vol. 20, no. 8, pp. 919–931, 2005.

[40] C. Marin, A. Jimenez, M. Bonastre et al., “LY293558, an AMPA glutamate receptor antagonist, prevents and reverses levodopa-induced motor alterations in Parkinsonian rats,” *Synapse*, vol. 42, no. 1, pp. 40–47, 2001.

[41] S. Konitsiotis, P. J. Blanchet, L. Verhagen, E. Lamers, and T. N. Chase, “AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys,” *Neurology*, vol. 54, no. 8, pp. 1589–1595, 2000.

[42] Y. Hashizume, M. Ohgoh, M. Ueno, T. Hanada, and Y. Nishizawa, “Effect of perampanel, a selective AMPA receptor antagonist, on L-DOPA-induced rotational behavior in L-DOPA primed 6-OHDA hemiparkinsonian rats;” in *Proceedings of the Annual Meeting of the American Academy of Neurology*, P06.102, 2008.

[43] E. Mizuta, M. Ueno, T. Hanada, and S. Kun, “Effects of perampanel, a selective AMPA receptor antagonist, on L-DOPA induced dyskinesia in MPTP-treated cynomolgus monkeys,” in *Proceedings of the Annual Meeting of the American Academy of Neurology*, P06.101, 2008.

[44] K. Eggert, D. Squillacote, P. Barone et al., “Safety and efficacy of perampanel in advanced parkinson’s disease: a randomized, placebo-controlled study,” *Movement Disorders*, vol. 25, no. 7, pp. 896–905, 2010.

[45] A. Lees, S. Fahn, K. M. Eggert et al., “Perampanel, an AMPA antagonist, found to have no benefit in reducing ‘off’ time in Parkinson’s disease,” *Movement Disorders*, vol. 27, no. 2, pp. 284–288, 2012.

[46] O. Rascol, P. Barone, M. Behari et al., “Perampanel in Parkinson disease fluctuations: a double-blind randomized trial with placebo and entacapone,” *Clinical Neuropharmacology*, vol. 35, no. 1, pp. 15–20, 2012.

[47] B. Picconi, G. Piccoli, and P. Calabresi, “Synchrony dysfunction in Parkinson’s disease,” *Advances in Experimental Medicine and Biology*, vol. 970, pp. 553–572, 2012.

[48] P. K. Sonsalla, D. S. Albers, and G. D. Zeevalk, “Role of glutamate in neurodegeneration of dopamine neurons in several animal models of parkinsonism,” *Amino Acids*, vol. 14, no. 1–3, pp. 69–74, 1998.

[49] T. N. Chase and J. D. Oh, “Striatal mechanisms and pathogenesis of Parkinsonian signs and motor complications,” *Annals of Neurology*, vol. 47, no. 4, pp. S122–S130, 2000.

[50] J. E. Nash, S. H. Fox, B. Henry et al., “Antiparkinsonian actions of ifenprodil in the MPTP-lesioned marmoset model of Parkinson’s disease,” *Experimental Neurology*, vol. 165, no. 1, pp. 136–142, 2000.

[51] B. Gomez-Mancilla and P. J. Bedard, “Effect of nondopaminergic drugs on L-DOPA-induced dyskinesias in MPTP-treated monkeys,” *Clinical Neuropharmacology*, vol. 16, no. 5, pp. 418–427, 1993.

[52] P. J. Blanchet, S. Konitsiotis, E. R. Whittemore, Z. L. Zhou, R. M. Woodward, and T. N. Chase, “Differing effects of N-methyl-D-aspartate receptor subtype selective antagonists on dyskinesias in levodopa-treated 1-methyl-4-phenyl-tetrahydropyridine monkeys,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 290, no. 3, pp. 1034–1040, 1999.

[53] A. H. Tahar, L. Grégoire, A. Darré, N. Bélanger, L. Meltzer, and P. J. Bédard, “Effect of a selective glutamate antagonist on L-dopa-induced dyskinesias in drug-naive parkinsonian monkeys,” *Neurobiology of Disease*, vol. 15, no. 2, pp. 171–176, 2004.

[54] S. M. Papa and T. N. Chase, “Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys,” *Annals of Neurology*, vol. 39, no. 5, pp. 574–578, 1996.

[55] M. Morissette, M. Dridi, F. Calon et al., “Prevention of levodopa-induced dyskinesias by a selective NRA1/2B N-methyl-D-aspartate receptor antagonist in Parkinsonian monkeys: implication of preproenkephalin,” *Movement Disorders*, vol. 21, no. 1, pp. 9–17, 2006.

[56] R. Dall’Olio, R. Rimondini, and O. Gandolfi, “The competitive NMDA antagonists CGP 43487 and APV potentiate dopaminergic function,” *Psychopharmacology*, vol. 118, no. 3, pp. 310–315, 1995.

[57] T. Klockgether and L. Turski, “NMDA antagonists potentiate antiparkinsonian actions of L-dopa in monoamine-depleted rats,” *Annals of Neurology*, vol. 28, no. 4, pp. 539–546, 1990.

[58] F. Bibbiani, J. D. Oh, A. Kielaita, M. A. Collins, C. Smith, and T. N. Chase, “Combined blockade of AMPA and NMDA glutamate receptors reduces levodopa-induced motor complications in animal models of PD,” *Experimental Neurology*, vol. 196, no. 2, pp. 422–429, 2005.

[59] G. Riahi, M. Morissette, M. Parent, and T. Di Paolo, “Brain 5-HT2A receptors in MPTP monkeys and levodopa-induced dyskinesias,” *European Journal of Neuroscience*, vol. 33, no. 10, pp. 1823–1831, 2011.

[60] M. A. Paquette, A. A. Martinez, T. Macheta et al., “Anti-dyskinetic mechanisms of amantadine and dextromethorphan in the 6-OHDA rat model of Parkinson’s disease: role of NMDA vs. 5-HT1A receptors,” *European Journal of Neuroscience*, vol. 36, no. 9, pp. 3224–3234, 2012.

[61] M. Morissette, M. Dridi, F. Calon et al., “Prevention of dyskinesia by an NMDA receptor antagonist in MPTP monkeys: effect on adenosine A1 receptors,” *Synapse*, vol. 60, no. 3, pp. 239–250, 2006.

[62] I. J. Mitchell and C. B. Carroll, “Reversal of parkinsonian symptoms in primates by antagonism of excitatory amino acid transmission: potential mechanisms of action,” *Neuroscience and Biobehavioral Reviews*, vol. 21, no. 4, pp. 469–475, 1997.
P. Paoletti and J. Neyton, “NMDA receptor subunits: function and pharmacology,” *Current Opinion in Pharmacology*, vol. 7, no. 1, pp. 39–47, 2007.

M. Horstink, E. Tolosa, U. Bonuccelli et al., “Review of the therapeutic management of Parkinson’s disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson’s disease,” *European Journal of Neurology*, vol. 13, no. 11, pp. 1186–1202, 2006.

R. Pahwa, S. A. Factor, K. E. Lyons et al., “Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology,” *Neurology*, vol. 66, no. 7, pp. 983–995, 2006.

P. J. Blanchet, S. Konitsiotis, and T. N. Chase, “Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys,” *Movement Disorders*, vol. 13, no. 5, pp. 798–802, 1998.

A. Dekundy, M. Lundblad, W. Danyzs, and M. A. Cenci, “Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model,” *Behavioural Brain Research*, vol. 179, no. 1, pp. 76–89, 2007.

P. Del Dotto, N. Pavese, G. Gambaccini et al., “Intravenous amantadine improves levodopa-induced dyskinesias: an acute double-blind placebo-controlled study,” *Movement Disorders*, vol. 16, no. 3, pp. 515–520, 2001.

F. P. Da Silva-Júnior, P. Braga-Neto, F. Sueli Monte, and V. Meireles Sales De Bruin, “Amantadine reduces the duration of levodopa-induced dyskinesia: a randomized, double-blind, placebo-controlled study,” *Parkinsonism and Related Disorders*, vol. 11, no. 7, pp. 449–452, 2005.

H. Sawada, T. Oeda, S. Kuno et al., “Amantadine for dyskinesias in Parkinson’s disease: a randomized controlled trial,” *PLoS One*, vol. 5, no. 12, Article ID e15298, 2010.

L. V. Metman, P. Del Dotto, P. Van Den Munchhof, J. Fang, M. M. Mouradian, and T. Chase, “Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson’s disease,” *Neurology*, vol. 50, no. 5, pp. 1323–1326, 1998.

B. Elahi, N. Phielipp, and R. Chen, “N-Methyl-D-Aspartate antagonists in levodopa induced dyskinesia: a meta-analysis,” *The Canadian Journal of Neurological Sciences*, vol. 39, no. 4, pp. 465–472, 2012.

C. G. Goetz, G. T. Stebbins, K. A. Chung et al., “Which dyskinesia scale best detects treatment response? A double-blind placebo controlled multicenter trial using multiple dyskinesia outcomes,” in *Proceedings of the 16th International Congress of Parkinson’s Disease and Movement Disorders*, abstract LBA 11, 2012.

E. Wolf, K. Seppi, R. Katzenschlager et al., “Long-term antidysskinetic efficacy of amantadine in Parkinson’s disease,” *Movement Disorders*, vol. 25, no. 10, pp. 1357–1363, 2010.

F. Ory-Magne, C. Thalamas, M. Galitsky et al., “Long-term effects of amantadine in Parkinsonian (AMANDYSK),” *Movement Disorders*, vol. 27, supplement 14, article 12, 2012.
[91] P. Samadi, L. Grégoire, M. Morissette et al., “mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys,” Neurobiology of Aging, vol. 29, no. 7, pp. 1040–1051, 2008.

[92] B. Ouattara, L. Grégoire, M. Morissette et al., “Metabotropic glutamate receptor type 5 in levodopa-induced motor complications,” Neurobiology of Aging, vol. 32, no. 7, pp. 1286–1295, 2011.

[93] C. Konradi, J. E. Westin, M. Carta et al., “Transcriptome analysis in a rat model of L-DOPA-induced dyskinesia,” Neurobiology of Disease, vol. 17, no. 2, pp. 219–236, 2004.

[94] H. Awad, G. W. Hubert, Y. Smith, A. I. Levey, and P. J. Conn, “Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus,” Journal of Neuroscience, vol. 20, no. 21, pp. 7871–7879, 2000.

[95] A. Pisani, P. Calabresi, D. Centonze, and G. Bernardi, “Enhancement of NMDA responses by group I metabotropic glutamate receptor activation in striatal neurons,” British Journal of Pharmacology, vol. 120, no. 6, pp. 1007–1014, 1997.

[96] M. R. Domenici, R. Pepponi, A. Martire, M. T. Tebano, R. L. Potenza, and P. Popoli, “Permissive role of adenosine A2A receptors on metabotropic glutamate receptor 5 (mGluR5)-mediated effects in the striatum,” Journal of Neurochemistry, vol. 90, no. 5, pp. 1276–1279, 2004.

[97] A. Nishi, F. Liu, S. Matsuyama et al., “Metabotropic mGlus receptors regulate adenosine A2A receptor signaling,” Proceedings of the National Academy of Sciences of the United States of America, vol. 100, no. 3, pp. 1322–1327, 2003.

[98] P. Popoli, A. Pezzola, M. Torvinen et al., “The selective mGlu receptor agonist CHPG inhibits quinpirole-induced turning in 6-hydroxydopamine-lesioned rats and modulates the binding characteristics of dopamine D1 receptors in the rat striatum: interactions with adenosine A2A receptors,” Neuropsychopharmacology, vol. 25, no. 4, pp. 505–513, 2001.

[99] Z. Díaz-Cabiale, M. Vivó, A. Del Arco et al., “Metabotropic glutamate mGlus receptor-mediated modulation of the ventral striopallidal GABA pathway in rats. Interactions with adenosine A2A and dopamine D1 receptors,” Neuroscience Letters, vol. 324, no. 2, pp. 154–158, 2002.

[100] M. P. Hill, S. G. McGuire, A. R. Crossman, and J. M. Brotyhe, “The mGlus Receptor antagonist SIB-1830 reduces L-Dopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson’s disease,” in Proceedings of the Neuroscience Meeting Planner, Society for Neuroscience, San Diego, Calif, USA, 2001.

[101] M. A. Varney, N. D. P. Cosford, C. Jachec et al., “SIB-1757 and SIB-1893: selective, noncompetitive antagonists of metabotropic glutamate receptor type 5,” Journal of Pharmacology and Experimental Therapeutics, vol. 290, no. 1, pp. 170–181, 1999.

[102] J. M. Mathiesen, N. Svendsen, H. Bräuner-Osborne, C. Thomsen, and M. T. Ramirez, “Positive allosteric modulation of the human metabotropic glutamate receptor 4 (hmGluR4) by SIB-1893 and MPEP,” British Journal of Pharmacology, vol. 138, no. 6, pp. 1026–1030, 2003.

[103] A. Dekundy, M. Pietraszek, D. Schaefer, M. A. Cenci, and W. Danysz, “Effects of group I metabotropic glutamate receptors blockade in experimental models of Parkinson’s disease,” Brain Research Bulletin, vol. 69, no. 3, pp. 318–326, 2006.

[104] F. Mela, M. Marti, A. Dekundy, W. Danysz, M. Morari, and M. A. Cenci, “Antagonism of metabotropic glutamate receptor type 5 attenuates L-DOPA-induced dyskinesia and its molecular and neurochemical correlates in a rat model of Parkinson’s disease,” Journal of Neurochemistry, vol. 101, no. 2, pp. 483–497, 2007.

[105] N. Morin, L. Grégoire, B. Gomez-Mancilla, F. Gasparini, and T. Di Paolo, “Effect of the metabotropic glutamate receptor type 5 antagonists MPEP and MTEP in parkinsonian monkeys,” Neuropharmacology, vol. 58, no. 7, pp. 981–986, 2010.

[106] N. Morin, L. Grégoire, M. Morissette et al., “MPEP, an mGlu4 receptor antagonist, reduces the development of L-DOPA-induced motor complications in de novo parkinsonian monkeys: biochemical correlations,” Neuropsychopharmacology, pp. 355–364, 2012.

[107] L. Grégoire, N. Morin, B. Ouattara et al., “The acute antiparkinsonian and antidyskinetic effect of AFQ056, a novel metabotropic glutamate receptor type 5 antagonist, in L-Dopa-treated parkinsonian monkeys,” Parkinsonism and Related Disorders, vol. 17, no. 4, pp. 270–276, 2011.

[108] D. Berg, J. Godau, C. Trenkwalder et al., “AFQ056 treatment of levodopa-induced dyskinesias: results of 2 randomized controlled trials,” Movement Disorders, vol. 26, no. 7, pp. 1243–1250, 2011.

[109] F. Stocchi, A. Destee, N. Hattori et al., “A 13-week, double-blind, placebo-controlled study of AFQ056, a metabotropic glutamate receptor 5 antagonist in Parkinson’s disease patients with moderate-to-severe L-dopa-induced dyskinesias,” in Proceedings of the 15th International Congress of Parkinson’s Disease and Movement Disorders, vol. 2011, Toronto, Canada, 2011.

[110] F. Tison, F. Durif, J. C. Corvol et al., “Safety, tolerability and anti-dyskinetic efficacy of dipragulant, a novel mGluR5 negative allosteric modulator (NAM), in Parkinson’s disease patients with levodopa-induced dyskinesia (LID),” in Proceedings of the 16th International Congress of Parkinson’s Disease and Movement Disorders, vol. 2012, Dublin, Ireland, June 2012.

[111] M. Amlaie, S. Lopez, C. Goudet et al., “Group III and subtype 4 metabotropic glutamate receptor agonists: discovery and pathophysiologically applications in Parkinson’s disease,” Neuropharmacology, vol. 66, pp. 53–64, 2013.

[112] C. W. Lindsley and C. R. Hopkins, “Metabotropic glutamate receptor 4 (mGlu4)-positive allosteric modulators for the treatment of Parkinson’s disease: historical perspective and review of the patent literature,” Expert Opinion on Therapeutic Patents, vol. 22, no. 5, pp. 461–481, 2012.

[113] T. Matsu and H. Kita, “Activation of group III metabotropic glutamate receptors presynaptically reduces both GABAergic and glutamatergic transmission in the rat globus pallidus,” Neuroscience, vol. 122, no. 3, pp. 727–737, 2003.

[114] S. Lopez, N. Turle-Lorenzo, F. Acher, E. De Leonibus, A. Mele, and M. Amlaie, “Targeting group III metabotropic glutamate receptors produces complex behavioral effects in rodent models of Parkinson’s disease,” Journal of Neuroscience, vol. 27, no. 25, pp. 6701–6711, 2007.

[115] C. Beurrier, S. Lopez, D. Révy et al., “Electrophysiological and behavioral evidence that modulation of metabotropic glutamate receptor 4 with a new agonist reverses experimental parkinsonism,” FASEB Journal, vol. 23, no. 10, pp. 3619–3628, 2009.

[116] O. Valenti, M. J. Marino, M. Wittmann et al., “Group III metabotropic glutamate receptor-mediated modulation of the striato-pallidal synapse,” Journal of Neuroscience, vol. 23, no. 18, pp. 7218–7226, 2003.
G. Battaglia, C. L. Busceti, G. Molinaro et al., “Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine,” The Journal of Neuroscience, vol. 26, no. 27, pp. 7222–7229, 2006.

C. M. Niswender, K. A. Johnson, C. D. Weaver et al., “Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4,” Molecular Pharmacology, vol. 74, no. 5, pp. 1345–1358, 2008.

C. K. Jones, M. Bubser, A. D. Thompson et al., “The metabotropic glutamate receptor 4-positive allosteric modulator VU0364770 produces efficacy alone and in combination with L-DOPA or an adenosine 2A antagonist in preclinical rodent models of Parkinson’s disease,” Journal of Pharmacology and Experimental Therapeutics, vol. 340, no. 2, pp. 404–421, 2012.

E. Le Poul, C. Boléa, F. Girard et al., “A potent and selective metabotropic glutamate receptor 4 positive allosteric modulator improves movement in rodent models of Parkinson’s disease,” Journal of Pharmacology and Experimental Therapeutics, vol. 343, no. 1, pp. 167–177, 2012.

B. Greco, S. Lopez, H. Van Der Putten, P. J. Flor, and M. Amalric, “Metabotropic glutamate 7 receptor subtype modulates motor symptoms in rodent models of Parkinson’s disease,” Journal of Pharmacology and Experimental Therapeutics, vol. 332, no. 3, pp. 1064–1071, 2010.

K. A. Johnson, C. K. Jones, M. N. Tantawye et al., “The metabotropic glutamate receptor 8 agonist (S)-3,4-DCPG reverses motor deficits in prolonged but not acute models of Parkinson’s disease,” Neuropharmacology, vol. 66, pp. 187–195, 2012.

D. D. Schoepp, R. A. Wright, L. R. Levine, B. Gaydos, and W. Z. Potter, “LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress,” Stress, vol. 6, no. 3, pp. 189–197, 2003.

B. J. Kinon, L. Zhang, B. A. Millen et al., “A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia,” Journal of Clinical Psychopharmacology, vol. 31, no. 3, pp. 349–355, 2011.

S. R. Bradley, M. J. Marino, M. Wittmann et al., “Activation of group II metabotropic glutamate receptors inhibits synaptic excitation of the substantia nigra pars reticulata,” Journal of Neurosciences, vol. 20, no. 9, pp. 3085–3094, 2000.

L. Dawson, A. Chadha, M. Megalou, and S. Duty, “The group II metabotropic glutamate receptor agonist, DCG-IV, alleviates akinesia following intranigral or intraventricular administration in the reserpine-treated rat,” British Journal of Pharmacology, vol. 129, no. 3, pp. 541–546, 2000.

P. Samadi, L. Grégoire, M. Morissette et al., “Basal ganglia group II metabotropic glutamate receptors specific binding in non-human primate model of L-Dopa-induced dyskinesias,” Neuropharmacology, vol. 54, no. 2, pp. 258–268, 2008.

P. Samadi, A. Rajput, F. Calon et al., “Metabotropic glutamate receptor II in the brains of parkinsonian patients,” Journal of Neuropathology and Experimental Neurology, vol. 68, no. 4, pp. 374–382, 2009.

T. K. Murray, M. J. Messenger, M. A. Ward et al., “Evaluation of the mGluR2/3 agonist LY379268 in rodent models of Parkinson’s disease,” Pharmacology Biochemistry and Behavior, vol. 73, no. 2, pp. 455–466, 2002.

M. P. Johnson, E. S. Nisenbaum, T. H. Large, R. Emkey, M. Baez, and A. E. Kingston, “Allosteric modulators of metabotropic glutamate receptors: lessons learnt from mGlu1, mGlu2 and mGlu3 potentiators and antagonists,” Biochemical Society Transactions, vol. 32, no. 5, pp. 881–887, 2004.

P. L. Johnson, S. D. Fitz, E. A. Engleman, K. A. Svensson, J. M. Schkeryantz, and A. Shekhar, “Group II metabotropic glutamate receptor type 2 allosteric potentiators prevent sodium lactate-induced panic-like response in panic-vulnerable rats,” Journal of Psychopharmacology, vol. 27, no. 2, pp. 152–161, 2012.