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Glutamate receptors as therapeutic targets for Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms including tremor and bradykinesia. The primary pathophysiology underlying PD is the degeneration of dopaminergic neurons of the substantia nigra pars compacta. Loss of these neurons causes pathological changes in neurotransmission in the basal ganglia motor circuit. The ability of ionotropic and metabotropic glutamate receptors to modulate neurotransmission throughout the basal ganglia suggests that these receptors may be targets for reversing the effects of altered neurotransmission in PD. Studies in animal models suggest that modulating the activity of these receptors may alleviate the primary motor symptoms of PD as well as side effects induced by dopamine replacement therapy. Moreover, glutamate receptor ligands may slow disease progression by delaying progressive dopamine neuron degeneration. Antagonists of NMDA receptors have shown promise in reversing motor symptoms, levodopa-induced dyskinesias, and neurodegeneration in preclinical PD models. The effects of drugs targeting AMPA receptors are more complex; while antagonists of these receptors exhibit utility in the treatment of levodopa-induced dyskinesias, AMPA receptor potentiators show promise for neuroprotection. Pharmacological modulation of metabotropic glutamate receptors (mGluRs) may hold even more promise for PD treatment due to the ability of mGluRs to fine-tune neurotransmission. Antagonists of mGluR5, as well as activators of group II mGluRs and mGluR4, have shown promise in several animal models of PD. These drugs reverse motor deficits in addition to providing protection against neurodegeneration. Glutamate receptors therefore represent exciting targets for the development of novel pharmacological therapies for PD.

Keywords

Parkinson's disease; basal ganglia; NMDA receptor; AMPA receptor; metabotropic glutamate receptor; neurodegeneration; levodopa-induced dyskinesia

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder affecting up to three percent of people aged sixty-five and over worldwide [1–3]. PD is characterized by motor

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symptoms including bradykinesia, tremor, rigidity, postural instability, and gait disturbances, as well as nonmotor symptoms such as sleep disturbance and cognitive impairment [4]. The primary pathology giving rise to motor impairments is the degeneration of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc), which provide dopaminergic input to the striatum and other basal ganglia nuclei under normal conditions. The loss of dopaminergic innervation of the striatum causes major physiological disruptions in the basal ganglia-thalamocortical motor circuit, which plays a critical role in controlling motor activity [5]. Dopamine replacement therapies, including the dopamine precursor levodopa (L-3,4-dihydroxyphenylalanine, L-DOPA) and dopamine receptor agonists are the primary pharmacological agents used for symptomatic treatment of PD [6]. While these treatments provide relief of motor symptoms for several years in most patients, motor complications and psychiatric side effects develop in a subset of individuals, and end-of-dose “wearing off” of the drug effects limits their long-term efficacy [6,7]. Adjunct therapies such as monoamine oxidase (MAO) inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and anticholinergic drugs modestly improve the efficacy and tolerability of levodopa therapy, but highly effective and tolerable pharmacological treatments for the late-stage motor symptoms of PD have not yet been identified [6]. Moreover, no currently employed pharmacological agents slow the progressive neurodegeneration that ultimately worsens PD symptoms. The lack of disease-modifying therapeutics for PD is largely due to the current deficit of knowledge of the cellular events underlying SNc degeneration. The limitations of current pharmacological treatments for PD highlight the need for nondopaminergic therapeutic strategies for both symptom treatment and disease modification. Fortunately, advances in our understanding of the anatomy and function of the basal ganglia circuitry have opened the door for identification of novel therapeutic strategies for treating PD and slowing its progression (for review, see DeLong and Whichmann, 2007) [5]. Because glutamate receptors mediate and modulate synaptic transmission throughout the basal ganglia motor circuit, and pharmacological manipulation of these receptors can alter both normal and aberrant neurotransmission such as that observed in the parkinsonian brain, glutamate receptors have been suggested as promising therapeutic targets for treating PD.

The basal ganglia and Parkinson’s disease

Despite extensive investigation, the cellular mechanisms underlying the degeneration of midbrain dopaminergic neurons in PD are not well understood. Insight from genetic and toxin-based animal models suggests that oxidative stress, mitochondrial dysfunction, aberrant processing of proteins by the ubiquitin-proteasome system, inflammation, and activation of apoptotic pathways all play roles in dopaminergic cell death [8–11]. However, there is also evidence that the process of dopaminergic cell death may not be entirely cell autonomous, and that increased glutamatergic transmission may contribute an excitotoxic component to the barrage of cellular insults that lead to degeneration in the SNc [11].

A simplified model of the basal ganglia motor circuitry provides a scaffold for understanding how indirectly compensating for SNc degeneration by modulating synaptic transmission at other synapses within the basal ganglia may provide opportunities for nondopaminergic therapeutic strategies (Fig. 1) [12]. The striatum is the primary input nucleus of the basal ganglia. It receives excitatory input from several areas of the cerebral cortex, including the primary motor cortex and other motor areas. The major output nuclei of the basal ganglia, the substantia nigra pars reticulata (SNr) and the internal globus pallidus (GPi, entopeduncular nucleus (EPN) in rodents), receive information from the striatum via two major pathways. The direct pathway consists of inhibitory projections from the striatum to the output nuclei (Fig. 1A). Conversely, the polysynaptic indirect pathway terminates in excitatory projections to the output nuclei from the subthalamic nucleus (STN) (Fig. 1B). D_2 dopamine receptor-expressing GABAergic neurons in the striatum send

inhibitory projections to the external globus pallidus (GPe), and the GPe sends inhibitory projections to the STN. Increasing the activity of the indirect pathway therefore results in disinhibition of the STN and increased excitatory drive to the output nuclei. Dopamine from the SNc acts on D_1 dopamine receptors in the striatum to increase the activity of the direct pathway (Fig. 1A), whereas D_2 dopamine receptor activation in the striatal neurons of the indirect pathway reduces their activity (Fig. 1B). It is thought that the delicate balance between inhibition of the output nuclei by the direct pathway and excitation by the indirect pathway is critical for normal control of motor activity, and that modulation of striatal activity by dopamine plays a crucial role in maintaining this balance.

In the parkinsonian brain, the absence of dopaminergic modulation of striatal activity leads to an overall increase in excitatory drive in the GPi and SNr, which in turn reduces thalamocortical neurotransmission and impairs the activity of additional brainstem nuclei involved in the control of motor activity (Fig. 1C). When dopaminergic modulation of striatal activity is lost, increased inhibitory tone at the striatopallidal synapse in the indirect pathway causes disinhibition of the STN. In support of this model, electrophysiological recordings from both human PD patients and parkinsonian animals have demonstrated increased activity and burst firing of STN neurons [13–17]. This hyperactivity is heavily implicated in the etiology of PD motor symptoms, and has been hypothesized to cause excitotoxicity in the remaining dopaminergic neurons of the SNc. The putative excitotoxic insult may contribute to the progressive loss of these neurons and concurrent worsening of motor symptoms. In agreement with this model, lesions of the STN reduce 6-hydroxydopamine-induced degeneration of SNc neurons in rats [18]. According to this model of the parkinsonian basal ganglia, counteracting the pathological hyperactivity of the STN, either directly or by reducing the overall activity of the indirect pathway, may alleviate the motor symptoms of PD and have the potential to slow disease progression.

While this model of the basal ganglia has proven useful for making predictions about the therapeutic potential of novel targets for treating PD symptoms, recent studies have shown that the interconnections between basal ganglia nuclei are more complicated. For example, information flows through the indirect pathway via routes other than the major route described above (see Smith et al., 1998, Parent et al., 2001, and Yelnik 2002 for review) [19–21]. In addition, the STN sends major excitatory projections to the output nuclei of the basal ganglia and also projects to the striatum and the GPe, creating a reciprocal circuit between the GPe and STN [19–21]. While the SNc primarily sends dopaminergic projections to the striatum, it also innervates the other key nuclei of the basal ganglia to varying extents [22], and the loss of these projections in PD must also be considered. While much attention has been focused on the effects of removing dopaminergic modulation from the striatum, the loss of dopamine in other basal ganglia structures, particularly the STN, may contribute to PD symptoms as well [23]. In the context of this more complex view of basal ganglia organization and pathophysiology, it has been hypothesized that in addition to imbalance between activity of the direct and indirect pathways, complex changes in neuronal firing patterns and oscillatory activity may contribute to the pathogenesis of PD symptoms, particularly tremor (see Heimer et al., 2006, and Leblois et al., 2006) [24–26]. It is therefore possible that predictions about novel therapeutic targets based on the more simplified model may not be entirely valid, and unexpected results in preclinical studies may in some cases be attributed to these limitations. Nonetheless, the classical model of changes in basal ganglia function in PD has played a critical role in the identification of many types of receptors as novel targets for symptom treatment and disease modification, and has led to many successful preclinical studies implicating glutamate receptors as promising targets for PD treatment.

Fast excitatory neurotransmission in the central nervous system (CNS) is primarily mediated by ionotropic glutamate receptors, a class of multimeric ligand-gated cation channels that have been categorized into three groups based on their ligand sensitivity (see Dingledine et al., 1999 for comprehensive review) [27]. The multimeric amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are composed of different combinations of four subunits, GluR1–4. N-methyl-D-aspartate (NMDA) receptors are composed of combinations of subunits NR1, NR2A-D, and NR3; these receptors require glycine as a coagonist. Finally, the kainate receptors are encoded by at least two gene families and are composed of multimers of the GluR5-7 and KA1-2 subunits. Electrophysiological studies indicate that NMDA receptors, which are expressed widely throughout the basal ganglia, directly mediate excitation of neurons in the striatum, GP, STN, SNr, and SNc [28–31]. NMDA receptors are known to mediate excitotoxicity caused by high levels of glutamate [32], so activation of these receptors in the SNc may contribute an excitotoxic component to SNc degeneration. Unfortunately, the precise role that NMDA receptor-mediated excitotoxicity may play in the progression of PD has not been established in humans, and the potential contribution of other types of glutamate receptors to the development and progression of PD symptoms remains unclear. However, because glutamate receptors are differentially distributed throughout the basal ganglia [29,30,33], and it is known that pharmacological manipulation of these receptors can alter transmission through both the direct and indirect pathways, glutamate receptors represent promising targets for modifying aberrant neurotransmission in the parkinsonian brain and slowing excitotoxicity-mediated disease progression.

Animal models of Parkinson's disease

Animal models of PD provide important tools for evaluating the ability of novel drugs to reverse motor symptoms and slow the progressive neurodegeneration associated with the disease. While there are genetic models that are based upon specific gene mutations observed in familial cases of PD, these models often fail to recapitulate aspects of the human disease such as dopamine neuron degeneration and severe motor deficits, and have proven more useful for studying the pathogenesis of familial PD on a cellular level rather than for evaluating novel therapeutic strategies [34,35]. Due to the drawbacks of these models, they are not currently useful for assessing the therapeutic potential of novel drugs targeting glutamate receptors.

Evaluation of novel targets for symptomatic treatment of PD often relies on pharmacological and toxin-based models of PD in mice, rats, and nonhuman primates, which are generally reliable for producing parkinsonian motor symptoms [36]. Pharmacological models are commonly used for studying the thereapeutic potential of compounds targeting glutamate receptors because they are convenient and relatively inexpensive. Pharmacological agents used to induce PD symptoms include neuroleptics such as the mixed D_1/D_2 dopamine receptor antagonist haloperidol, which induces aspects of parkinsonism such as muscle rigidity, akinesia, and catalepsy [37]. Reversal of these effects can be measured using techniques such as electromyography, monitoring of locomotor activity, and measurement of catalepsy [37]. Another pharmacological tool widely used to assess novel antiparkinsonian agents is reserpine, which depletes catecholamines by inhibiting their uptake into presynaptic vesicles by the vesicular monoamine transporter (VMAT) [38]. Reserpine produces profound akinesia in rodents, and reversal of this akinesia, which is usually assessed by measuring locomotor activity, is thought by some to be predictive of antiparkinsonian efficacy [36,37]. Because there is a lack of standardization of the use of these models by different investigators, it is possible that similar pharmacological models will yield different results due to different methodologies. It is therefore important that careful attention be paid to methods when interpreting and comparing results from these models. In addition, it is important to bear in mind that pharmacological agents that induce

parkinsonism in rodents are reversible and do not recapitulate the morphological aspects of the disease, and therefore may not accurately mimic all aspects of the disease caused by SNc degeneration.

Toxin-based models of PD are useful for studying therapeutic strategies for both motor symptom treatment and neuroprotection (for review, see Terzioglu and Galter, 2008; Betarbet et al., 2002, and Schober, 2004) [35,36,39], and have been used extensively for studying the disease-modifying potential of novel compounds that act on glutamate receptors. The dopaminergic neuron-selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is used in mice and primates to study the cellular mechanisms underlying dopaminergic cell death. MPTP can be administered systemically, but must be converted in the brain to the active metabolite 1-methyl-4-phenyl-2,3,-dihydropyridinium ion (MPP^+) by MAO-B. MPP^+ is selectively transported into dopaminergic nerve terminals by the dopamine transporter [40], and causes neurodegeneration by disrupting mitochondrial function [41]. In primates, MPTP administration closely recapitulates the behavioral features of PD, and is considered the most predictive model for antiparkinsonian efficacy of novel drugs in humans [37]. Protection against MPTP-induced nigrostriatal lesion in mice is also a widely used assay for possible disease-modifying therapeutics for PD [36]. Another commonly used neurotoxin is 6-hydroxydopamine, which causes selective degeneration of midbrain dopamine neurons when directly infused into the striatum, nigrostriatal tract, or SNc of rats [42,43]. Unilateral 6-hydroxydopamine lesion causes lateralized motor behaviors in rats such as circling behavior and forelimb-use asymmetry, and novel therapeutics can be evaluated for their ability to reverse these effects [44]. Partial bilateral 6-hydroxydopamine lesions cause akinetic deficits in reaction time tasks, and the reversal of these deficits may represent possible antiparkinsonian effects in earlier stages of PD [45]. Protection against 6-hydroxydopamine-induced nigrostriatal damage is also a method for evaluating possible disease-modifying agents. While there is no animal model of PD that perfectly recapitulates the human disease, these models provide useful tools for assessing the therapeutic potential of new targets and compounds.

Key targets for the symptomatic treatment of PD

Insights from the successes of non-pharmacological treatments for PD have allowed the identification of nondopaminergic pharmacological targets for alleviating the motor symptoms of PD. Surgical interventions that counteract inappropriate STN activity have proven highly efficacious in both primate models and humans with PD (reviewed in Walter and Vitek, 2004, and Wichmann and DeLong, 2006) [46,47]. Either surgical lesion or deep brain stimulation (DBS) of the STN or GPi significantly improves motor symptoms such as tremor, bradykinesia, and rigidity, although the precise mechanism by which DBS has this effect remains unclear [48]. Unfortunately, surgical interventions for PD are not widely available due to the difficulty and cost of the procedure, and the fact that many PD patients are not candidates for such an invasive surgery. The finding that lesions of the STN or GPi improve parkinsonian symptoms suggests that pharmacological agents that reduce STN activity may provide substantial relief of motor symptoms. In addition, DBS of the GPi or STN robustly increases “on” time in patients taking levodopa, suggesting that pharmacological reversal of STN or GPi hyperactivity could dramatically improve long-term levodopa efficacy [46]. Reducing the activity of the indirect pathway by inhibiting corticostriatal or striatopallidal transmission may also be useful therapeutic strategies for modifying aberrant basal ganglia output.

NMDA receptors

Because NMDA receptors mediate glutamatergic excitation of neurons in the striatum and STN [29], antagonists of NMDA receptors would be predicted to reduce activity through the

indirect pathway, possibly by acting at both striatal and extrastriatal sites. Consistent with this prediction, several antagonists of NMDA receptors have been shown to have antiparkinsonian effects in various animal models of PD including haloperidol-treated rats and MPTP-treated monkeys (for more comprehensive reviews of early studies involving ligands of ionotropic glutamate receptors, see Marino et al., 2003, Greenamyre and O'Brien, 1991, Ossowska, 1994, and Schmidt and Kretschmer, 1997) [30,49–51]. Interestingly, an assortment of competitive antagonists (e.g., SDZ 220–581), noncompetitive antagonists (e.g., MK-801, dextrorphan, MRZ 2/579, CP-101,606,), and glycine site antagonists (e.g., MRZ 2/570, L-701,324, 7-chlorokynurenate, (R)-HA-966) reverse catalepsy and muscle rigidity induced by dopamine receptor blockade in rats [52–63]. Numerous studies demonstrate that NMDA receptor antagonists such as MK-801 and MRZ 2/579 also reverse akinesia and other motor disturbances in monoamine-depleted rodents [53,64–74], although antagonists targeting the glycine binding site on NMDA receptors are not consistently efficacious in this model [53]. Importantly, NMDA receptor antagonists such as CP-101,606 and MK-801 also have behavioral effects predictive of antiparkinsonian activity in 6-hydroxydopamine-lesioned rats and MPTP-lesioned monkeys, indicating that NMDA receptor blockade is efficacious in chronic models of PD [63,75–82]. Antiparkinsonian effects of NMDA receptor antagonists are observed after direct site infusions into several rodent basal ganglia nuclei, including the striatum, STN, EPN, and SNr, suggesting that blockade of NMDA receptor activity in the striatum, indirect pathway, and output nuclei of the basal ganglia all contribute to the antiparkinsonian effects of these drugs [54,74]. Another possible mechanism by which NMDA receptor antagonists could mediate antiparkinsonian effects is by reducing acetylcholine release from striatal cholinergic interneurons [83]. Interestingly, some NMDA receptor antagonists have been shown to potentiate the antiparkinsonian effects of levodopa and suppress the expression of motor fluctuations and dyskinesias associated with chronic levodopa administration (levodopa-induced dyskinesias, LIDs) in both rat and primate models, suggesting that these drugs may be most efficacious in combination with levodopa therapy [67,69,72,73,78,84–90].

The widespread expression and diverse physiological roles of NMDA receptors raise concern that global inhibition of these receptors could cause severe adverse effects such as psychosis, impaired learning, and disruption of motor function [91]. Although these potential side effects have cast doubt on the possibility that NMDA receptors represent promising therapeutic targets, recent evidence that pharmacologically targeting specific combinations of NMDA receptor subunits has renewed interest in this target. The NR2B subunit is highly expressed in the striatum and other basal ganglia nuclei, suggesting that drugs selective for NR2B-containing receptors may have more specific effects on NMDA receptor function in brain regions relevant to PD pathophysiology [92–95]. Recently, NMDA receptor blockers that are selective for NR2B subunit-containing receptors have been developed and evaluated for antiparkinsonian effects. For example, traxoprodil (CP-101,606) reverses haloperidol-induced catalepsy in rats and decreases parkinsonian motor symptoms in MPTP-lesioned monkeys [63]. Ifenprodil, another NR2B-selective NMDA receptor antagonist, also reduces motor symptoms in MPTP-treated primates [80,81]. In addition, these drugs improve the efficacy of levodopa and reduce the appearance of LIDs in animal models, suggesting that a combination treatment approach may show clinical utility [63,84].

The only antiglutamatergic pharmacotherapy currently used to treat PD in humans is amantadine, which has been shown to noncompetitively block NMDA receptors at therapeutically relevant brain concentrations [6,96–98]. While the clinical utility of amantadine monotherapy remains questionable, double-blind, placebo-controlled studies have shown that amantadine reduces dyskinesias and motor fluctuations in patients receiving levodopa [96,99]. These findings suggest that further development of NMDA receptor

antagonists may provide useful adjunct therapies for increasing the efficacy and tolerability of levodopa. In addition, amantadine therapy is associated with delayed onset of dementia in humans with PD, suggesting yet another potential benefit of NMDA receptor blockade in the management of PD [100]. However, preclinical studies have revealed a wide array of off-target pharmacological actions of amantadine, including blockade of σ-1 receptors and nicotinic receptors [101]. These findings call into question whether the beneficial effects of amantadine are mediated by its antiglutamatergic activity. In a recent study employing a preclinical model of LIDs, the NMDA receptor antagonists MK-801 and HA-966 failed to exhibit antidyskinetic activity, whereas the σ-1 receptor antagonist BMY-14802 suppressed LIDs, suggesting that the antidyskinetic activity of amantadine may be mediated by inhibition of σ-1 receptors [102]. Another weak NMDA receptor antagonist, remacemide, has also been evaluated PD patients both as a monotherapy and as an adjunct therapy to reduce motor fluctuations and LIDs in conjunction with levodopa treatment [103–106]. Despite the fact that remacemide has antiparkinsonian effects in rodent and primate models of PD [86], clinical studies have failed to find any benefit of remacemide in humans, casting doubt on the promise of weak NMDA receptor antagonists for symptomatic management of PD. More promisingly, a recent clinical trial found that the NR2B-selective antagonist traxoprodil reduces LIDs in levodopa-treated PD patients [107], suggesting that selectively blocking NR2B-containing NMDA receptors may be a useful antidyskinetic strategy. Conversely, the NR2B-selective antagonist ifenprodil did not provide any benefit when coadministered with levodopa in a pilot study in humans [108]. Further clinical studies using more selective drugs targeting NMDA receptors will therefore be necessary to provide sound proof-of-concept that targeting glutamate receptors will yield efficacious antiparkinsonian agents.

AMPA receptors

Because increased glutamatergic transmission in the basal ganglia is thought to contribute to the motor symptoms of PD, and AMPA receptors mediate glutamatergic neurotransmission, blockade of AMPA receptors has also been proposed as a potential therapeutic strategy. Unfortunately, preclinical studies have suggested that AMPA receptor antagonists do not have activity predictive of antiparkinsonian action when administered alone. For example, systemic administration of the AMPA receptor antagonists 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX) and GYKI 52466 fails to reverse haloperidol-induced catalepsy in rats [109], and NBQX increases catalepsy induced by the D_1 receptor antagonist SCH 23390 while having no effect on the catalepsy induced by the D_2 receptor antagonist raclopride [61]. NBQX also fails to improve motor symptoms in 6-hydroxydopamine lesioned rats and MPTP-lesioned monkeys when administered alone [87,110,111]. Furthermore, GYKI 52466 does not reverse akinesia in monoamine-depleted rats, and fails to improve the efficacy of levodopa administration in the same model [112]. However, other studies have found antiparkinsonian effects of AMPA receptor antagonists, both alone and in combination with dopaminergic therapies. For example, NBQX has been reported to reverse reserpine-induced muscle rigidity (but not akinesia) in rats and motor deficits in MPTP-lesioned primates [113]. Interestingly, when combined with levodopa, AMPA receptor antagonists such as NBQX improve the ability of levodopa to reverse motor deficits in SNc-lesioned rats and primates [87,110,111], suggesting that AMPA receptor blockade may be useful for improving the efficacy of levodopa treatment. It is possible that differences in the efficacy of AMPA receptor antagonists in various animal models of PD are due to the different methods of inducing parkinsonism (i.e., drug-induced versus toxin-induced). AMPA receptor antagonists have shown more promise in models of PD that mimic SNc degeneration using neurotoxins, and results from these studies may be more predictive of antiparkinsonian potential in humans.

Preclinical evaluation of AMPA receptor antagonists in the treatment of LIDs has yielded more promising results for potential uses of these drugs in PD treatment. An increase in AMPA receptor activity has been implicated in the development of LIDs, suggesting that AMPA receptor antagonists may be therapeutically useful for alleviating LIDs [114,115]. Supporting the idea that AMPA receptor activation contributes to LIDs, the AMPA receptor potentiator CX516 increases the occurrence of LIDs in MPTP-lesioned monkeys that have been treated with levodopa [116]. Interestingly, the noncompetitive AMPA receptor antagonist LY300164 (talampanel) improves motor symptoms and reduces LIDs in MPTP-lesioned monkeys [116]. The anticonvulsant drug topiramate, which has been shown to be an AMPA receptor antagonist, also reduces LIDs in MPTP-lesioned nonhuman primates [117]. In levodopa-treated 6-hydroxydopamine-lesioned rats, the competitive AMPA receptor antagonist LY293558 reduces LIDs [118], further supporting the idea that blocking AMPA receptors may reduce motor complications associated with levodopa therapy. Interestingly, combined blockade of AMPA and NMDA receptors with low (ineffective) doses of antagonists targeting each type of receptor alleviates LIDs in both rats and primates [119], suggesting that weak simultaneous blockade of these types of glutamate receptors could represent a viable option for reducing dyskinesias.

Recent clinical trials have evaluated the effectiveness of drugs targeting AMPA receptors for treating LIDs, although the results of these trials are not yet available. The AMPA receptor antagonist talampanel has been evaluated in human PD patients receiving levodopa therapy both alone and in combination with amantadine to test its ability to alleviate LIDs. A clinical trial was also initiated to evaluate the effectiveness of topiramate in treating LIDs, but this trial was terminated prior to completion. Data obtained from these trials may indicate whether or not AMPA receptor antagonists have a promising future as adjunct therapies for improving levodopa treatment.

Metabotropic glutamate receptors

Another class of glutamate receptors representing a therapeutic target for PD is the metabotropic glutamate receptor family (mGluRs); these G protein-coupled receptors (GPCRs) are differentially expressed throughout the basal ganglia (Fig. 2) [33]. These receptors modulate excitatory and inhibitory synaptic transmission by both pre- and postsynaptic mechanisms [33], making them attractive targets for modifying pathological changes in basal ganglia neurotransmission. There are eight subtypes of mGluRs, which are divided into three groups according to their sequence homology, ligand-binding profile, and G protein-coupling specificity (for review, see Pin and Duvoisin, 1995, Conn and Pin, 1997, and Pin and Acher, 2002) [120–122]. The group I mGluRs include mGluR1 and -5, which couple to Gq to activate phospholipase C, raise intracellular calcium levels, and activate protein kinase C. Group II consists of mGluR2 and -3, which are coupled to Gi/o, and mediate the inhibition of adenylyl cyclase. Group III mGluRs include mGluR4, -6, -7, and -8. These receptors also signal through Gi/o, and are generally located presynaptically where their activation modulates ion channel activity and causes a reduction in neurotransmitter release. A comprehensive review of the known physiological roles of these receptors in the basal ganglia is beyond the scope of this article, but has been performed elsewhere [33]. Here we will discuss the physiological roles of mGluRs that are relevant to therapeutic strategies for PD treatment, and results from studies evaluating subtype-selective mGluR ligands in animal models of PD.

Group I mGluRs are expressed both pre- and postsynaptically throughout the basal ganglia (Fig. 2), where common effects of activation of these receptors are to counteract the effects of dopamine and to directly excite key nuclei that are overactive in the parkinsonian brain [28,33,123,124]. In addition, activation of group I mGluRs potentiates NMDA receptor currents in the striatum and STN [28,31]. Antagonists of these receptors would be predicted

to have antiparkinsonian effects by reducing excitatory drive in overactive parkinsonian basal ganglia nuclei. Consistent with this hypothesis, several negative allosteric modulators of mGluR5 have antiparkinsonian effects in animal models. The mGluR5 negative allosteric modulators 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) reverse parkinsonism in 6-hydroxydopamine lesion and haloperidol rat models of PD following systemic administration [125–131]. Interestingly, treatment of 6-hydroxydopamine-lesioned rats or reserpinized mice with adenosine A_{2A} receptor antagonists effectively alleviates akinesia, and the combined administration of submaximal doses of MPEP and A_{2A} receptor antagonists produces a marked reversal of akinesia, suggesting that combining mGluR5 and A_{2A} receptor blockade may be highly efficacious in the symptomatic treatment of PD [127,132]. Similarly, a combination of doses of MPEP and the NMDA receptor antagonist MK-801 that are not effective alone reverse akinetic deficits in a reaction time task caused by 6-hydroxydopamine lesion, suggesting that simultaneous blockade of mGluR5 and NMDA receptors may be an effective combination therapy for PD [131]. Importantly, this type of combination therapy could increase the utility of NMDA receptor antagonists for treating PD by reducing the dose requirement and the associated side effects of NMDA receptor blockade.

While the physiological basis for the antiparkinsonian effects of mGluR5 antagonism remains unclear, several possible sites of action exist. Intrastriatal infusion of group I mGluR agonists causes activation of the indirect pathway and a concurrent reduction in motor activity, suggesting that antagonism of mGluR5 may produce antiparkinsonian effects by reducing activity at the striatopallidal synapse [133,134]. Consistent with this hypothesis, intrastriatal infusion of the mGluR1 antagonists LY367385 and 7-(hydroxyimino)cyclopropa[b]chromen-1*a*-carboxylate (CPCCOEt) or systemic administration of MPEP reduces haloperidol-induced increases in striatal proenkaphalin mRNA in rats, a marker for increased striatopallidal activity [135]. Application of the group I mGluR agonist 3,5-dihydroxyphenylglycine (DHPG) to rat brain slices directly excites STN and SNr neurons after haloperidol treatment, suggesting that antagonists of group I mGluRs may also exert antiparkinsonian effects by reducing the hyperactivity of STN and/or SNr neurons [28,123,124]. Interestingly, infusion of MPEP into the STN of rats with unilateral 6-hydroxydopamine lesions significantly attenuates motor asymmetries, whereas infusion of MPEP into the SNr or EPN has no effect, suggesting that blockade of mGluR5 in the STN may be at least partially responsible for the antiparkinsonian effects of mGluR5 antagonists [136]. In rats with partial bilateral 6-hydroxydopamine lesions, a model representing the early stages of PD, increased metabolic activity in the STN and SNr is reduced by chronic MPEP administration, suggesting that blockade of mGluR5 may reverse the increased activity of these nuclei, possibly contributing to the alleviation of motor symptoms achieved with chronic administration of mGluR5 antagonists [125,137,138]. Finally, mGluR5 antagonists may also have antiparkinsonian effects by reducing the activity of striatal cholinergic interneurons (for review, see Pisani et al., 2003) [139].

Recently, an upregulation of mGluR5 in the posterior putamen and pallidum of MPTP-treated monkeys has been associated with development of LIDs, suggesting that mGluR5 antagonism may prevent and/or alleviate LIDs [140]. Consistent with this hypothesis, systemic administration of MTEP reduces LIDs in 6-hydroxydopamine-lesioned rats chronically treated with levodopa [141–144]. These findings suggest the exciting possibility that mGluR5 antagonism may be a useful adjunct to levodopa therapy for alleviation of LIDs in addition to a viable option for symptomatic treatment of PD. Excitingly, the mGluR5 antagonist AFQ056 has entered a human trial for the treatment of LIDs. Addex Pharmaceuticals has also recently announced the completion of a Phase I trial and the initiation of a Phase IIa proof-of-concept study for another mGluR5 antagonist, ADX48621. This compound is also being evaluated for its ability to treat LIDs in PD patients. The results

of these studies are eagerly anticipated, as they may provide the first proof-of-concept studies in humans suggesting that targeting mGluRs as an adjunct therapy to levodopa treatment is a viable therapeutic option for improving the management of PD symptoms.

In contrast to mGluR5, less effort has been focused on evaluating the potential antiparkinsonian effects of mGluR1 antagonism. One study evaluating the effects of systemic administration of the mGluR1 antagonist (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) found that mGluR1 antagonism only weakly reversed haloperidol-induced catalepsy and failed to alleviate LIDs in rats [141]. These findings suggest that mGluR1 may not be a promising target for treating the motor symptoms of PD, or for decreasing side effects associated with levodopa therapy.

Evidence from electrophysiological studies demonstrates that activation of presynaptic group II mGluRs at the STN-SNr synapse reduces excitatory synaptic transmission, suggesting that agonists or positive allosteric modulators of these receptors may be beneficial for treating PD [145,146]. Consistent with this hypothesis, intranigral or intracerebroventricular administration of the group II mGluR agonist (2S,2’R,3’R)-2-(2’,3’-dicarboxycyclopropyl)glycine (DCG-IV) reverses reserpine-induced akinesia in rats [147]. Another group II mGluR agonist, LY354740, reverses haloperidol-induced catalepsy and muscle rigidity after systemic administration in rats, providing evidence that systemic group II mGluR activation may be beneficial in PD [145,148]. Similarly, intracerebroventricular administration of the group II agonist LY379268 was shown to reverse reserpine-induced akinesia in rats [149]. However, in the same study, systemic LY379268 failed to reverse motor deficits caused by chronic reserpine treatment and unilateral 6-hydroxydopamine lesion, raising concerns that this therapy may not be useful in a chronic state of dopamine depletion [149]. Importantly, the ability of LY354740 to depress STN-SNr transmission is reduced in reserpinized rats, suggesting that group II mGluR activation in the SNr may have less effect in the parkinsonian brain, possibly limiting the therapeutic potential of these targets for alleviating motor symptoms of PD.

While the effect of intranigral administration of DCG-IV suggests that reducing STN-SNr transmission may underlie group II mGluR agonist-mediated reversal of motor deficits, other potential therapeutic mechanisms of action exist. For example, activation of group II mGluRs expressed presynaptically at corticostriatal synapses may reduce the activity of the indirect pathway, potentially reversing motor deficits [150]. Interestingly, the potency of LY379268 and DCG-IV in reducing corticostriatal transmission is increased in 6-hydroxydopamine-lesioned rats, and this effect is abolished by chronic L-DOPA administration, suggesting that antiparkinsonian efficacy related to striatal effects may be increased in the parkinsonian brain [151]. Another alternative mechanism by which group II mGluR agonists may have antiparkinsonian effects is by activation of mGluR2 receptors expressed on cholinergic interneurons in the striatum, which reduces acetylcholine release [139,152].

Group III mGluRs are expressed presynaptically at multiple synapses within the basal ganglia (Fig. 2), suggesting that their activation may modulate transmission at these synapses [153,154]. Physiological studies in rat brain slices have shown that the group III mGluR-selective agonist L(+)-2-amino-4-phosphonobutyric acid (L-AP4) reduces synaptic transmission at both the striatopallidal and STN-SNr synapses by presynaptic mechanisms [155–157]. In addition, recent microdialysis studies show that L-AP4 and the group III mGluR agonist L-serine-*O*-phosphate (L-SOP) reduce KCl-evoked GABA release in the rat globus pallidus [158]. These findings suggest that activating one or more of the group III mGluRs may relieve the motor symptoms of PD by either reducing the overall activity of the indirect pathway or by directly reducing STN activity. In agreement with this prediction,

intracerebroventricular administration of L-AP4 or L-SOP has antiparkinsonian effects in both acute and chronic rat models of parkinsonism [156,159]. Impressively, L-AP4 reverses the forelimb use asymmetry caused by unilateral 6-hydroxydopamine lesion to the same extent as L-DOPA, providing compelling evidence that targeting group III mGluRs may be highly efficacious in treating PD symptoms [156]. Consistent with predictions made based on physiological data, intrapallidal infusion of L-SOP has been shown to alleviate reserpine-induced akinesia in rats, supporting the hypothesis that reducing activity at this synapse may have therapeutic efficacy [159]. More recently, intrapallidal infusions of L-AP4 and the group III mGluR agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I [160]) were shown to reverse akinetic disruptions in a reaction time task caused by bilateral 6-hydroxydopamine lesion [161]. Intrapallidal infusion of ACPT-I or the novel group III mGluR agonist 1S-amino-2R-phosphonomethylcyclopropanecarboxylic acid ((1S, 2R)APCPr) also reverses haloperidol-induced catalepsy in rats, providing further support for reducing transmission at the striatopallidal synapse as therapeutic strategy for the symptomatic treatment of PD [156,161–164]

Interestingly, the L-AP4 mediated inhibition of synaptic transmission at the striatopallidal synapse is absent in mice lacking mGluR4, suggesting that mGluR4 activation is primarily responsible for inhibition of striatopallidal transmission, and that selective activation of mGluR4 may have antiparkinsonian effects [156]. Unfortunately, attempts to develop subtype-selective orthosteric agonists of mGluR4 have failed due to the high level of conservation of the glutamate-binding pocket among mGluR subtypes. Recently, the identification of *N*-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC), a positive allosteric modulator that selectively potentiates mGluR4 signaling when compared with other mGluR subtypes, has provided a tool for assessing the therapeutic relevance of selectively enhancing mGluR4 activation [165,166]. PHCCC enhances glutamate-dependent mGluR4 activation by binding to mGluR4 at a site distinct from that of the glutamate-binding site, but has no intrinsic ability to activate the receptor in the absence of glutamate [166]. Excitingly, physiological and behavioral experiments have shown that PHCCC potentiates the L-AP4-mediated inhibition of striatopallidal transmission in rat brain slices [166]. Consistent with this finding, intracerebroventricular infusion of PHCCC reverses reserpine-induced akinesia in rats [166], and systemic PHCCC reverses reserpine-induced catalepsy in mice [167]. Recent work using a newly discovered mGluR4-selective positive allosteric modulator VU0155041 has demonstrated that intracerebroventricular administration of another compound that selectively enhances mGluR4 activity reverses reserpine-induced akinesia and haloperidol-induced catalepsy in rats [168]. Taken together, these results suggest that selectively increasing mGluR4 activation may be a viable approach to ameliorating PD symptoms (for review, see Lavreysen and Dautzenberg, 2008) [169]. In addition, an exciting implication of these data is that enhancing endogenous receptor activation using positive allosteric modulators may be an effective therapeutic strategy when targeting GPCRs.

The potential to reduce the motor symptoms of PD by activating group III mGluRs at STN-SNr synapse is less established. Intranigral infusion of group III mGluR agonists has been shown to reverse reserpine-induced akinesia and haloperidol-induced catalepsy in rats, suggesting a possible antiparkinsonian effect of group III mGluR activation at the STN-SNr synapse [159,162]. However, a more recent study in rats demonstrated that intranigral ACPT-I or L-AP4 worsened akinetic deficits in a reaction time task caused by 6-hydroxydopamine, and intranigral ACPT-I failed to markedly reverse haloperidol-induced catalepsy, suggesting that directly targeting SNr activity may not contribute to the antiparkinsonian effects of intracerebroventricular infusion of nonselective group III mGluR agonists [161]. In the same study, intranigral infusion of the mGluR8-selective agonist (*S*)-3,4-dicarboxyphenylglycine (DCPG) induced mild catalepsy, suggesting that mGluR8

activation may counteract antiparkinsonian effects of activation of other group III mGluRs in the substantia nigra, possibly by reducing inhibitory drive in the SNr. This finding supports the use of subtype-selective activators of mGluR4 for treating PD symptoms.

Glutamate receptors may also be promising targets for treating neurological and psychiatric comorbidities associated with PD, which include depression, anxiety, and cognitive impairment [170]. Excitingly, a recent study found that the mGluR5 antagonist MPEP reversed visuo-spatial discrimination deficits caused by bilateral 6-hydroxydopamine lesion in mice despite the fact that mGluR5 blockade caused cognitive impairment in normal animals [171], suggesting that antagonists of mGluR5 may be useful for treating both motor and cognitive impairments that are caused by dopamine depletion. Antagonists of mGluR5, as well as agonists of group II mGluRs, have anxiolytic-like effects in preclinical models of anxiety and have been validated in proof-of-concept studies in humans (reviewed in Palucha and Pilc, 2007) [172], suggesting that these types of drugs have the potential to treat both motor and psychiatric symptoms of PD. In addition, antagonists of mGluR5 and group II mGluRs, as well as agonists of group III mGluRs, are efficacious in preclinical models of depression [169,172,173], indicating that several subtypes of mGluRs may be targets for the treatment of comorbid depression in PD patients. While these studies indicate that mGluRs may be promising targets for treatment of non-motor PD symptoms, further studies must be performed in parkinsonian animals and humans in order to verify the effects of these drugs on psychiatric symptoms in the context of altered neurophysiological conditions characteristic of PD.

Key targets for disease modification in PD

NMDA receptors are known to mediate excitotoxic cell death caused by glutamate [174], so blockade of NMDA receptors in the SNc would be predicted to slow SNc degeneration caused by excessive STN activity. Consistent with this prediction, intranigral infusion or systemic administration of NMDA receptor antagonists such as MK-801 provides protection against the SNc degeneration induced by intranigral or intrastriatal MPP^+ administration in rats [175,176]. Similarly, NMDA receptor antagonists have been shown to reduce nigrostriatal toxicity caused by systemic MPTP administration in mice and primates [177–179], although some investigators have failed to observe this effect [180,181]. In the 6-hydroxydopamine model of nigrostriatal degeneration in rats, continuous systemic administration of MK-801 reduces cell death in the SNc [137]. Interestingly, chronic administration of the NR2B-selective NMDA receptor antagonist BZAD-01 reduces SNc degeneration and lateralized motor behaviors caused by unilateral 6-hydroxydopamine lesion in rats [182], suggesting that antagonists that specifically target the NR2B subunit may provide neuroprotection as well. Taken together, these results support the hypothesis that NMDA receptor activation contributes to neurodegeneration in PD, and that blockade of NMDA receptors may be a useful disease-modifying strategy for slowing neurodegeneration in PD patients.

Recent studies using rodent models of PD suggest that selective potentiators of AMPA receptors may be useful for protection against SNc degeneration [183]. For example, the AMPA receptor potentiators LY404187 and LY503430 protect against SNc degeneration and motor deficits caused by 6-hydroxydopamine lesion in rats and MPTP administration in mice [184–186]. Interestingly, these protective effects occur when the AMPA receptor potentiator is administered after establishment of SNc lesion, suggesting that these compounds act through a neurotrophic effect in animal models of PD-like neurodegeneration. In support of this hypothesis, LY503430 causes a modest increase in expression of brain-derived neurotrophic factor (BDNF) in the substantia nigra [186]. In addition, the AMPA receptor potentiator S18986 protects against age-related loss of neurons

in the substantia nigra in rats [187], suggesting that enhancing AMPA receptor activation may slow the normal loss of these neurons that occurs with age, and perhaps prevent levels of SNc degeneration that cause PD symptoms.

Because increased activity of the STN may cause excitotoxicity in SNc neurons that could contribute to their degeneration, drug therapies that reduce STN activity directly or by reducing the overall activity of the indirect pathway have the potential to act as disease-modifying agents in PD. Indeed, direct infusion of MK-801 into the subthalamic nucleus decreases nigrostriatal lesion formation induced by 6-hydroxydopamine in rats, suggesting that directly blocking excitation of STN neurons slows SNc neurodegeneration [188,189]. Because mGluRs can modulate the activity of the indirect pathway, they may also be targets for reducing additional neurodegeneration caused by progressive SNc degeneration. Interestingly, mice lacking mGluR5 are less sensitive than wild type mice to MPTP-induced nigrostriatal toxicity, suggesting that blockade of mGluR5 may slow neurodegeneration in PD [190]. Consistent with this hypothesis, treatment with the mGluR5 antagonists MPEP or SIB-1893 reduces nigrostriatal damage in response to MPTP in mice [190,191]. In addition, both MPEP and SIB-1893 attenuate methamphetamine-induced nigrostriatal toxicity in mice [192]. Recent studies demonstrate that intranigral or systemic administration of MPEP also reduces the extent of 6-hydroxydopamine-induced nigrostriatal damage in rats, further supporting the use of mGluR5 antagonists to slow the progression of parkinsonian neurodegeneration [137,193,194]. Although the exact mechanisms by which mGluR5 blockade mediates neuroprotection in these models remain unknown, the ability of intranigral MPEP administration to reduce nigrostriatal damage suggests that mGluR5 blockade may mediate neuroprotection in PD models by directly modulating SNc activity. Alternatively, antagonism of mGluR5 in the STN may reduce excitatory STN-SNc transmission, which would be predicted to reduce excitotoxicity caused by excessive STN activity. Further studies will be necessary to fully elucidate the mechanism by which mGluR5 blockade confers neuroprotection in animal models of PD. The other group I mGluR, mGluR1, also mediates direct excitation of SNc neurons, suggesting that blockade of mGluR1 could also reduce excitotoxicity [195]. Consistent with this finding, intranigral administration of the mGluR1-selective antagonist LY367385 protects nigrostriatal projections against 6-hydroxydopamine toxicity in rats [193,194].

Physiological studies have shown that activation of presynaptic group II mGluRs at the STN-SNc synapse reduces excitatory postsynaptic current amplitudes in rat SNc neurons [196,197], suggesting that group II mGluR activation may be neuroprotective. In support of this hypothesis, chronic systemic dosing or subchronic intranigral administration of the group II mGluR agonists LY379268 and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) reduces the extent of 6-hydroxydopamine toxicity in the rat SNc [149,193]. In addition, activation of group II mGluRs by LY379268 or DCG-IV reduces SNc degeneration in mice after intrastriatal MPP^+ or systemic MPTP administration, further supporting a role for group II mGluRs as disease-modifying agents in PD [198–200]. Interestingly, agonists of group II mGluRs also increase the production of the neuroprotective factor BDNF by rat microglia and transforming growth factor-β (TGFβ) by mouse astrocytes, suggesting an alternative mechanism by which activation of these receptors could mediate protection against MPP^+ neurotoxicity [199–203]. Recently, *in vitro* and *in vivo* studies using mice lacking mGluR2 or mGluR3 suggest that the neuroprotective effects of systemically administered LY379268 against MPTP-induced nigrostriatal toxicity are mediated by astrocytic mGluR3 activation, and that coactivation of neuronal mGluR2 may counteract mGluR3-mediated neuroprotection [204]. These findings suggest that selective activation of mGluR3 may yield more robust neuroprotection than a mixed mGluR2/3 agonist, and raise concern that selective activation of mGluR2 may accelerate neurodegeneration.

Several lines of evidence based on cellular and physiological data predict that activation of group III mGluRs in the basal ganglia will have neuroprotective effects in PD. Activation of mGluR4 at the striatopallidal synapse reduces the activity of the indirect pathway, which should reduce overactivity of the STN and in turn reduce SNc excitotoxicity [156,205]. In addition, activation of mGluR4 in rats and both mGluR4 and -8 in mice directly reduces excitatory transmission in the SNc, an effect which is also expected to reduce excitotoxicity caused by STN overactivity [206]. Group III mGluR activation protects against NMDA-induced toxicity in neuron cultures and *in vivo*, and this effect is absent in mice lacking mGluR4, suggesting that mGluR4 is an important mediator of neuroprotection against excitotoxic insult [207–209]. In addition, activation of glial mGluR4 reduces production of RANTES, a chemokine that is involved in neuroinflammation and circulates at higher levels in humans with PD compared with age- and sex-matched controls [210,211]. Consistent with the prediction that group III mGluR activation will have neuroprotective effects in PD, both acute and subchronic intranigral infusion of L-AP4 reduce the extent of 6-hydroxydopamine toxicity in the rat SNc [193,212]. Further, systemic or intrapallidal PHCCC administration reduces the extent of nigrostriatal MPTP toxicity in wild type mice but not in mice lacking mGluR4, further supporting the selective activation of mGluR4 as a therapeutic strategy for neuroprotection in PD [167]. Interestingly, recent studies in rats suggest that intranigral coadministration of MPEP and L-AP4 produces additive protection of the nigrostriatal tract against 6-hydroxydopamine toxicity, providing promising new evidence that simultaneously targeting multiple subtypes of mGluRs may produce more robust neuroprotection than targeting single receptor subtypes [213].

Concluding remarks

For all of the targets mentioned here, selectivity of novel compounds remains a key feature that is just now under development. For example, despite disappointing results with initial NR2B antagonists such as ifenprodil, further exploration of subunit-selective NMDA antagonists should continue to be tested as a possible stand-alone treatment for PD or in combination with levodopa. Additionally, it may be possible to modulate NMDA receptor function indirectly by altering signaling cascades that regulate NMDA receptors, such as those that induce phosphorylation of the channel; these types of strategies may have different outcomes versus direct and chronic inhibition of the channel.

As with NMDA receptors, basic science studies have indicated that there is much promise in the modulation of mGluR function in PD. The main limitations for mGluR-based therapeutics at this time are the identification of compounds that are truly selective and systemically active to rigorously test the hypothesis that a certain mGluR subtype may be important in PD. Development of more selective tools and drug leads that are systemically active would also help determine if there are certain subtypes that must be avoided in terms of the induction of unwanted side effects or neurotoxicity. This appears to be particularly important for mGluR2 versus mGluR3 and mGluR4 versus mGluR8. As mentioned above, studies with knockout animals lacking mGluR2 versus mGluR3 suggest that mGluR3 activation in astrocytes may be neuroprotective whereas simultaneous activation of mGluR2 in neurons may counteract this beneficial effect, suggesting that selective mGluR3 activators should be explored for therapeutic value in PD. Additionally, work with group III mGluRs suggests that mGluR4 activation may represent a viable therapeutic avenue for both symptomatic and disease-modifying treatment, whereas coactivation of other L-AP4-responsive receptors, such as mGluR8, may counteract these beneficial effects. For these reasons, development of subtype-selective tools will help unravel the roles and therapeutic potential of different glutamate receptor subtypes. It is postulated that newer approaches targeting allosteric sites on mGluRs will give better specificity or pharmacokinetic profiles as opposed to orthosteric ligands, and eventually may provide avenues to impact only

distinct signaling pathways downstream of the receptor of interest to tailor cellular responses, potentially avoiding side effects.

While the development of selective compounds will certainly help understand which subtypes of receptors mediate specific pro- or antiparkinsonian effects, it remains possible that an ideal treatment for PD will target multiple receptor subtypes. For example, as discussed above, recent studies suggest that intranigral coadministration of an mGluR5 antagonist and a general group III mGluR agonist produces additive protection against 6-hydroxydopamine toxicity, providing promising new evidence that simultaneously targeting multiple subtypes of mGluRs may produce more robust symptom relief or neuroprotection than targeting single receptor subtypes. In addition, it is possible that drugs that have opposing effects on the same types of receptors may be useful for treating different aspects of PD in different patients. For example, AMPA receptor antagonists may alleviate LIDs, whereas enhancing AMPA receptor activation with selective potentiators may have a neuroprotective effect, and these complex and opposing effects must be kept in mind when choosing endpoints for evaluating novel therapeutics in clinical trials. In time, studies using systemically active drugs targeting single or various combinations of glutamate receptors, along with studies in primate models of PD-like neurotoxicity, will be necessary to further determine the individual and combined potential of these receptors in PD patients.

Abbreviations

PD	Parkinson’s Disease
SNc	substantia nigra pars compacta
levodopa, L-DOPA	L-3,4-dihydroxyphenylalanine
MAO	monamine oxidase
COMT	catechol-O-meythyl transferase
SNr	substantia nigra pars reticulata
GPi	internal globus pallidus
EPN	entopeduncular nucleus
STN	subthalamic nucleus
GPe	external globus pallidus
CNS	central nervous system
AMPA	amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
NMDA	N-methyl-D-aspartate
VMAT	vesicular monoamine transporter
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP^+	1-methyl-4-phenyl-2,3,-dihydropyridinium
DBS	deep brain stimulation
LID	levodopa-induced dyskinesia
NBQX	2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione
mGluR	metabotropic glutamate receptor
GPCR	G protein-coupled receptor

MPEP	2-methyl-6-(phenylethynyl)-pyridine
MTEP	3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine
CPCCOEt	7-(hydroxyimino)cyclopropa[b]chromen-1*a*-carboxylate
DHPG	3,5-dihydroxyphenylglycine
EMQMCM	[(3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methane sulfonate]
DCG-IV	(2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine
L-AP4	L(+)-2-amino-4-phosphonobutyric acid
L-SOP	L-serine-O-phosphate
ACPT-I	(1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid
((1S,2R)APCPr)	1S-amino-2R-phosphonomethylcyclopropanecarboxylic acid
PHCCC	(−)-*N*-Phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide
DCPG	(*S*)-3,4-dicarboxyphenylglycine
BDNF	brain-derived neurotrophic factor
SIB-1893	(E)-2-methyl-6-(2-phenylethenyl)-pyridine
2R,4R-APDC	(2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate
TGFβ	transforming growth factor-β

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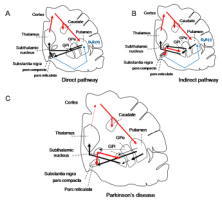

Figure 1. Basal ganglia circuitry in normal and disease states

Shown is a simplified schematic diagram of the direct and indirect pathways of the basal ganglia, regulation of the circuitry by dopaminergic projections from the substantia nigra pars compacta (SNc, shown in gray), and alterations contributing to the motor dysfunctions characteristic of Parkinson's disease. The caudate and putamen collectively comprise the striatum in humans. In this figure, black projections are inhibitory (GABAergic) and red projections are excitatory (glutamatergic). Blue projections are dopaminergic. **A.** Within the direct pathway, GABAergic projections inhibit function of the basal ganglia output nuclei, which consist of the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). These output nuclei send inhibitory projections to the thalamus, which regulates excitatory output to the cortex. Dopaminergic neurons (blue dashed line) arising in the SNc project to D_1-expressing neurons in the putamen area of the striatum that give rise to the direct pathway, and stimulate transmission through the direct pathway. **B.** Within the polysynaptic indirect pathway, striatopallidal projections from the putamen project to the external segment of the globus pallidus (GPe); inhibitory projections from the GPe then project to the GPi and subthalamic nucleus (STN). Dopaminergic neurons arising in the SNc project to D_2-receptor expressing neurons in the striatum that give rise to the indirect pathway and reduce activity of the indirect pathway (blue dashed line). The STN sends excitatory projections to the output nuclei, balancing the inhibitory tone mediated by the direct pathway and balancing the level of inhibition of the thalamus, which modulates excitation of the motor areas of the cortex. **C.** In PD, loss of dopaminergic neurons in the SNc (depicted as a change in color of the SNc from gray to white) results in too little inhibitory transmission via the direct pathway and too much inhibitory tone at the striatopallidal synapse, resulting in increased excitation of the output nuclei via the STN. The overall effect of the loss of dopamine neurons is too little inhibition of the output nuclei via the direct pathway and too much excitation from the indirect pathway. This enhanced excitation of the SNr and GPi is manifested as enhanced GABAergic tone at the level of the thalamus and too little excitation of motor areas of the cortex.

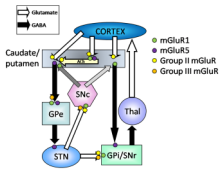

Figure 2. mGluR localization in the basal ganglia

The major nuclei of the basal ganglia are shown and the localization of various mGluR subtypes that are relevant to PD therapeutics is highlighted. Excitatory projections are represented as white arrows and inhibitory projections are represented as black arrows. Overall, the effect of group I mGluR activation (green and purple circles) is to counteract the effects of dopamine, particularly by increasing activity through the indirect pathway. Group II mGluRs (yellow circles) reduce glutamate release at several key synapses including the corticostriatal, STN-SNc, and STN-SNr synapses. Group III mGluRs (orange circles), including mGluRs 4, 7 and 8, are expressed at striatopallidal (predominantly mGluR4; activation of this receptor inhibits GABAergic transmission in the GPe) and the STN-SNr synapses. (GPe, external segment of globus pallidus; STN, subthalamic nucleus; GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta. Adapted from Conn et al., 2005 and Wichmann & DeLong, 1996.)