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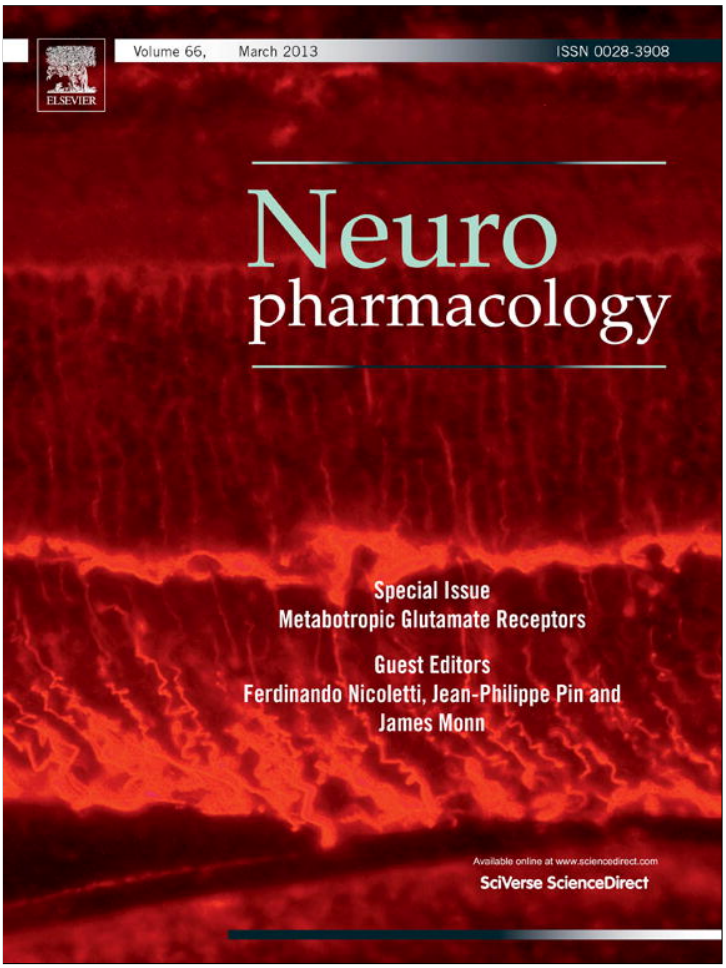

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Invited review

Group III and subtype 4 metabotropic glutamate receptor agonists: Discovery and pathophysiological applications in Parkinson's disease

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ABSTRACT

Restoring the balance between excitatory and inhibitory circuits in the basal ganglia, following the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta, represents a major challenge to treat patients affected by Parkinson's disease (PD). The imbalanced situation in favor of excitation in the disease state may also accelerate excitotoxic processes, thereby representing a potential target for neuroprotective therapies. Reducing the excitatory action of glutamate, the major excitatory neurotransmitter in the basal ganglia, should lead to symptomatic improvement for PD patients and may promote the survival of DA neurons. Recent studies have focused on the modulatory action of metabotropic glutamate (mGlu) receptors on neurodegenerative diseases including PD. Group III mGlu receptors, including subtypes 4, 7 and 8, are largely expressed in the basal ganglia. Recent studies highlight the use of selective mGlu4 receptor positive allosteric modulators (PAMs) for the treatment of PD. Here we review the effects of newly-designed group-III orthosteric agonists on neuroprotection, neurorestoration and reduction of L-DOPA induced dyskinesia in animal models of PD. The combination of orthosteric mGlu4 receptor selective agonists with PAMs may open new avenues for the symptomatic treatment of PD.

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1. Introduction

Parkinson's disease (PD) is a debilitating neurodegenerative movement disorder with a long course and a high prevalence (1 per 1000 individuals in the EU) that increases with demographic ageing. It is widely accepted that the progressive damage to the dopaminergic (DA) neurons of the substantia nigra pars compacta (SNc) leads to the manifestation of the main symptoms of PD, due to a disturbance of the dynamic balance between excitatory and inhibitory neurotransmitters. PD is characterized by motor symptoms including bradykinesia, tremor, rigidity, postural instability, and gait disturbances, as well as non-motor symptoms such as sleep disturbance, depression and cognitive impairment (Chaudhuri et al., 2006). The dopaminergic neurons innervate predominantly the striatum, the primary input station of the basal ganglia, a richly interconnected group of brain nuclei playing a key role in the subtle regulation of voluntary and purposive movements. The loss of nigrostriatal DA neurons results in an excessive activity of glutamatergic neurons at different levels of the basal ganglia (BG) in the corticostriatal pathway (Gubellini et al., 2002, 2004) and the subthalamic nucleus (STN) (Hirsch et al., 2000; Greenamyre, 2001; Chase et al., 2003). This overactive glutamate transmission plays a key role in the expression of PD symptoms (Carlsson and Carlsson, 1990; Blandini et al., 2000) and in the development of DA cell death (Greenamyre and O'Brien, 1991). Several studies suggest that excitatory drive from the STN might contribute to the loss of dopamine neurons in animal models that involve relatively slow, progressive loss of dopamine neurons in rats bearing unilateral injection of 6-hydroxydopamine (6-OHDA) in the striatum or in the

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Abbreviations

ACPT-I (1*S*,3*R*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid
ADX88178 5-methyl-*N*-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine
AMN082 *N*,*N*′-bis(diphenylmethyl)-1,2-ethanediamine
AMPA 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid
APCPr 1-amino-2-(phosphonomethyl) cyclopropanecarboxylic acid
BG basal ganglia
CRD cystein-rich domain
DA dopamine
DCPG 3,4-dicarboxyphenylglycine
EPN entopeduncular nucleus
GABA γ-aminobutyric acid
GP globus pallidus
GPCR G-protein coupled receptor
HTS high throughput screening
L-AP4 (*S*)-2-amino-4-phosphonobutanoic acid
L-DOPA (*S*)-3,4-dihydroxyphenylalanine
L-SOP l-serine-O-phosphate
LID L-DOPA-induced dyskinesia
LSP1-2111 [((3*S*)-3-amino-3-carboxy)propyl][(4-hydroxy-5-methoxy-3-nitrophenyl)hydroxymethyl]phosphinic acid
LSP1-3081 [(3*S*)-3-(3-amino-3-carboxypropyl(hydroxy) phosphinyl)-hydroxymethyl]-5-nitrothiophene
LSP3-2156 [((3*S*)-3-amino-3-carboxy)propyl][(4-(carboxymethoxy)phenyl) methyl]phosphinic acid
LSP4-2022 [((3*S*)-3-amino-3-carboxy)propyl][(4-(carboxymethoxy)phenyl)hydroxymethyl] phosphinic acid
LuAF21934 (1*S*,2*R*)-*N*-(3,4-dichlorophenyl)cyclohexane-1,2-dicarboxamide
LY2140023 methionine amide of (1*R*,4*S*,5*S*,6*S*)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404039)
mGlu receptor metabotropic glutamate receptor
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NAM negative allosteric modulator
NMDA *N*-methyl-d-aspartic acid
6-OHDA 6-hydroxydopamine
PAM positive allosteric modulator
PCEP 3-amino-3-carboxypropyl-2′-carboxyethyl phosphinic acid
PD Parkinson's disease
PHCCC *N*-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide
PK pharmacokinetic
SAM silent allosteric modulator
SNr substantia nigra pars reticulata
SNc substantia nigra pars compacta
STN subthalamic nucleus
VFT venus flytrap domain
VU0155041 *cis*-2-(3,5-dichlorphenylcarbamoyl) cyclohexanecarboxylic acid
VU0364770 *N*-(3-chlorophenyl)picolinamide
VU0400195 *N*-(3-Chloro-4-((1*R*,2*S*,3*R*,4*S*-bicyclo[2.2.1]hept-5-ene-1,3-dioxo-1H-isoindol-1-yl)phenyl) picolinamide
7TM 7 transmembrane domain

medial forebrain bundle (Piallat et al., 1996; Chen et al., 2000). Furthermore, in the initial presymptomatic phase of PD, it was proposed by Obeso et al. that a reduction in the dopamine-mediated innervation of the STN induces neuronal hyperactivity before significant striatal DA depletion (Obeso et al., 2000b, 2004). Based on this, it is possible that reducing glutamate transmission at that level could also reduce dopamine cell loss.

The discovery of DA deficiency in PD and the therapeutic introduction of levodopa, the precursor of DA, in the mid-1960s revolutionized the treatment of this neurological disease. However, motor fluctuations and dyskinesia (abnormal involuntary movements AIMs) complicate levodopa treatment in most patients (>90%) within 5–10 years of treatment initiation (Fabbrini et al., 2007; Jenner, 2008). Finding alternative pharmacological symptomatic treatments that bypass the DA system and avoid L-DOPA-induced dyskinesia by reducing the overactive glutamate transmission still represents a major challenge.

The first attempts to pharmacologically oppose glutamate hyperactivity have focused on antagonists at ionotropic glutamate receptors (Blandini and Greenamyre, 1998; Rouse et al., 2000; Greenamyre, 2001; Chase et al., 2003; Smith et al., 2012). To date, these treatments had a limited success due to their considerable non-motor side-effects, ataxia and psychosis in animal studies (Amalric et al., 1995; Starr et al., 1997; Andine et al., 1999) also accompanied with cognitive impairment in humans (Montastruc et al., 1992; Blandini and Greenamyre, 1998). In the last few years, however, the studies on the distribution and roles of metabotropic glutamate (mGlu) receptors in the basal ganglia have opened a promising field of research. Eight mGlu receptors have been cloned from mammalian brain and retina (Pin and Duvoisin, 1995; Conn and Pin, 1997). These mGlu receptors are G-protein coupled receptors and classified into three major groups based on sequence homologies, coupling to second messenger systems and selectivity for various agonists. Group I mGlu receptors, which include mGlu1 and mGlu5 receptors, primarily stimulate phosphoinositide hydrolysis. Group II (mGlu2 and 3 receptors) and group III mGlu receptors (mGlu4, 6, 7 and 8) are negatively coupled to adenylyl cyclase. The mGlu receptors are widely distributed throughout the central nervous system and play important roles in regulating cell excitability and synaptic transmission (Conn and Pin, 1997; Pisani et al., 1997; Awad et al., 2000; Greenamyre, 2001). One of the primary functions of the group II and III mGlu receptors is a role as pre-synaptic autoreceptors involved in reducing glutamate transmission at glutamatergic synapses. They also serve as heteroreceptors involved in reducing GABA release at inhibitory synapses. Finally, postsynaptically localized mGlu receptors (primarily of group I) often play an important role in regulating neuronal excitability and in regulating currents through ionotropic glutamate receptors (Awad et al., 2000; Attucci et al., 2001; Pisani et al., 2001).

Over the recent years, the discovery of selective and potent positive allosteric modulators of mGlu4 receptors, brought important information on the therapeutic potential of this target in PD treatment. On the other hand, orthosteric agonists were not considered as promising drugs due to their difficulty to pass the blood–brain barrier, and to lack receptor subtype selectivity. The goal of this review is to highlight the impact of group III mGlu receptors as a possible target for the symptomatic treatment of PD, neuroprotection of DA neurons during the course of the disease and inhibition of the motor-side effects produced by long term administration of L-DOPA. The review will challenge the

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classical view of modulating allosteric site of group III mGlu receptors (in particular mGlu4 subtype) in the field of drug discovery and provide new arguments in favor of designing selective ligands binding to the orthosteric site to provide symptomatic and neuroprotective treatment.

2. Allosteric versus orthosteric modulation

mGlu receptors are among the most structurally complex G-protein coupled receptors, offering a number of possibilities to develop new and original bioactive and selective compounds regulating their activity (Kniazeff et al., 2011; Rondard et al., 2011). Like any other GPCRs, mGlu receptors have a 7 transmembrane domain (7TM), but they have a large extracellular domain composed of a venus flytrap bilobate domain (VFT) where glutamate binds, and a cystein-rich domain (CRD) that links the VFT to the 7TM. In addition, mGlu receptors are well recognized dimers, covalently stabilized by a disulfide bond (Fig. 1).

The solved structures of various mGlu VFTs are consistent with agonist stabilizing a closed form of the VFT (Kunishima et al., 2000; Tsuchiya et al., 2002; Muto et al., 2007). In addition, it has been well demonstrated that antagonists act by preventing domain closure in the VFT (Bessis et al., 2002). Such detailed information on the structure of mGlu receptors initially revealed a highly conserved glutamate-binding site making quite complex the discovery of subtype selective ligands (Bertrand et al., 2002; Acher and Bertrand, 2005) (Fig. 3A). Indeed, through years of research, most orthosteric ligands targeting mGlu receptors display group-selectivity, but no clear subtype selectivity. In addition, the polarity of these orthosteric agonists was soon considered as an important limitation for their development as therapeutic drugs because it limits their ability to penetrate the brain (Di and Kerns, 2003; Kerns and Di, 2003; Gleeson et al., 2011).

High-throughput strategies were then developed to identify new and original compounds possibly acting selectively at a unique mGlu receptor subtype. Such campaigns identified negative, silent and positive allosteric modulators (NAMs, SAMs and PAMs) of mGlu receptors, most of which display subtype selectivity (Goudet et al., 2004a; Niswender and Conn, 2010; Urwyler, 2011).

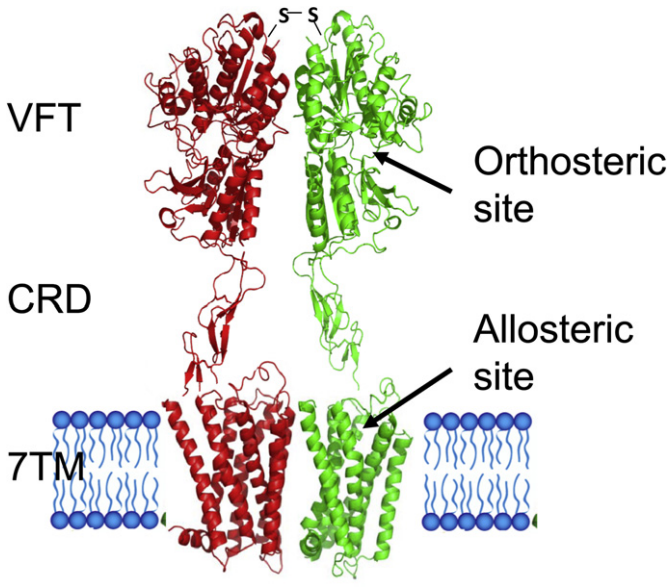

Fig. 1. General structure of a dimeric mGlu receptor. Each subunit is composed of a venus flytrap domain (VFT) linked through a cystein-rich domain (CRD) to a 7 transmembrane helix domain (7TM). The disulfide bond covalently linking the two subunits is shown on top of the VFTs (S–S). The orthosteric site where both agonists and antagonists bind, and the allosteric sites where positive, neutral and negative allosteric compounds bind are indicated.

NAMs act as non-competitive antagonists, and most display inverse agonist activity at their cognate receptors. In contrast, PAMs have no agonist activity when applied alone, but greatly enhance the effect of orthosteric agonists, by increasing either their potency and/or their efficacy. This later property is regarded as a major advantage over the use of agonists for several reasons. First, pure PAMs do no constantly activate the receptor (Goudet et al., 2004a; Niswender et al., 2005; Urwyler, 2011), and are then not prone to induce desensitization either of the receptor itself or of its downstream signaling cascades. Second, the biological effects of PAMs are only observed in the presence of the endogenous agonist, such that the potentiation is effective only where and when the receptor needs to be activated for a biological effect. In addition, these allosteric molecules correspond to optimized compounds that follow the Lipinsky's rules (Lipinski et al., 2001), and that most easily pass the blood–brain barrier, an important property for compounds targeting central receptors (Di and Kerns, 2003; Kerns and Di, 2003; Gleeson et al., 2011).

Detailed studies on the mechanism of action of these allosteric modulators revealed that they interact within the 7TM region of the receptor, and likely in a cavity that corresponds to the retinal binding site in rhodopsin-like class A GPCRs (Litschig et al., 1999; Pagano et al., 2000; Malherbe et al., 2003; Schaffhauser et al., 2003; Chen et al., 2008). Not surprisingly, many NAMs where found to act as inverse agonists, indicating that they stabilize the fully inactive state of the 7TM of mGlu receptors (Pagano et al., 2000; Ango et al., 2001; Carroll et al., 2001; Goudet et al., 2004b). In contrast, PAMs were found to stabilize the 7TM domain in an active conformation, and this was nicely demonstrated in truncated receptors in which the VFT was removed (Goudet et al., 2004b). In such receptors, all PAMs tested so far display an agonist activity (Goudet et al., 2004b; Rondard et al., 2006; Chen et al., 2007, 2008). This indicates that the VFT dimer limits receptor activation by PAMs, but because of the allosteric interaction between the VFT and the 7TM, such an inhibition cannot be total (Parmentier et al., 2002; Rovira et al., 2008). Accordingly, PAMs are expected to have agonist activity, at least partial, and likely at a higher effective dose due to the lower affinity of the 7TM when the VFTs are not occupied by agonists. When this was examined carefully, many PAMs of mGlu receptors displayed agonist activity on the full-length receptors, although often partial and at higher dose (Rondard et al., 2006) (Goudet et al., unpublished data). Such intrinsic agonist effects of PAMs, easily detected with end-point assays such as IP1 accumulation, were more difficult to detect on a fluorescent calcium assay, likely due to the slow binding rate of these hydrophobic molecules. Such observation is consistent with the search for pure PAMs of the sweet and umami taste receptors. Indeed, compounds acting in the 7TM of these receptors had agonist activity, and only those binding together with the agonist in the VFT cleft are pure PAMs (Zhang et al., 2008, 2010; Servant et al., 2011).

With now more than ten years of research in the field of mGlu receptor PAMs, some limitations have been identified in the development of these ligands. Firstly, and as mentioned above, many of these compounds are not strict PAMs, but also display agonist activity (they are then referred as ago-PAMs), and in some cases, this agonist activity can be critical for the *in vivo* effect as recently reported for the mGlu5 receptor PAMs (Noetzel et al., 2012). In addition, due to the high basal glutamate concentration in the brain, PAMs, by increasing glutamate potency, will certainly lead to the activation of the receptor simply by allowing the low basal glutamate concentration to become effective. Accordingly, the main advantage of PAMs – i.e. that they only enhance the effect of

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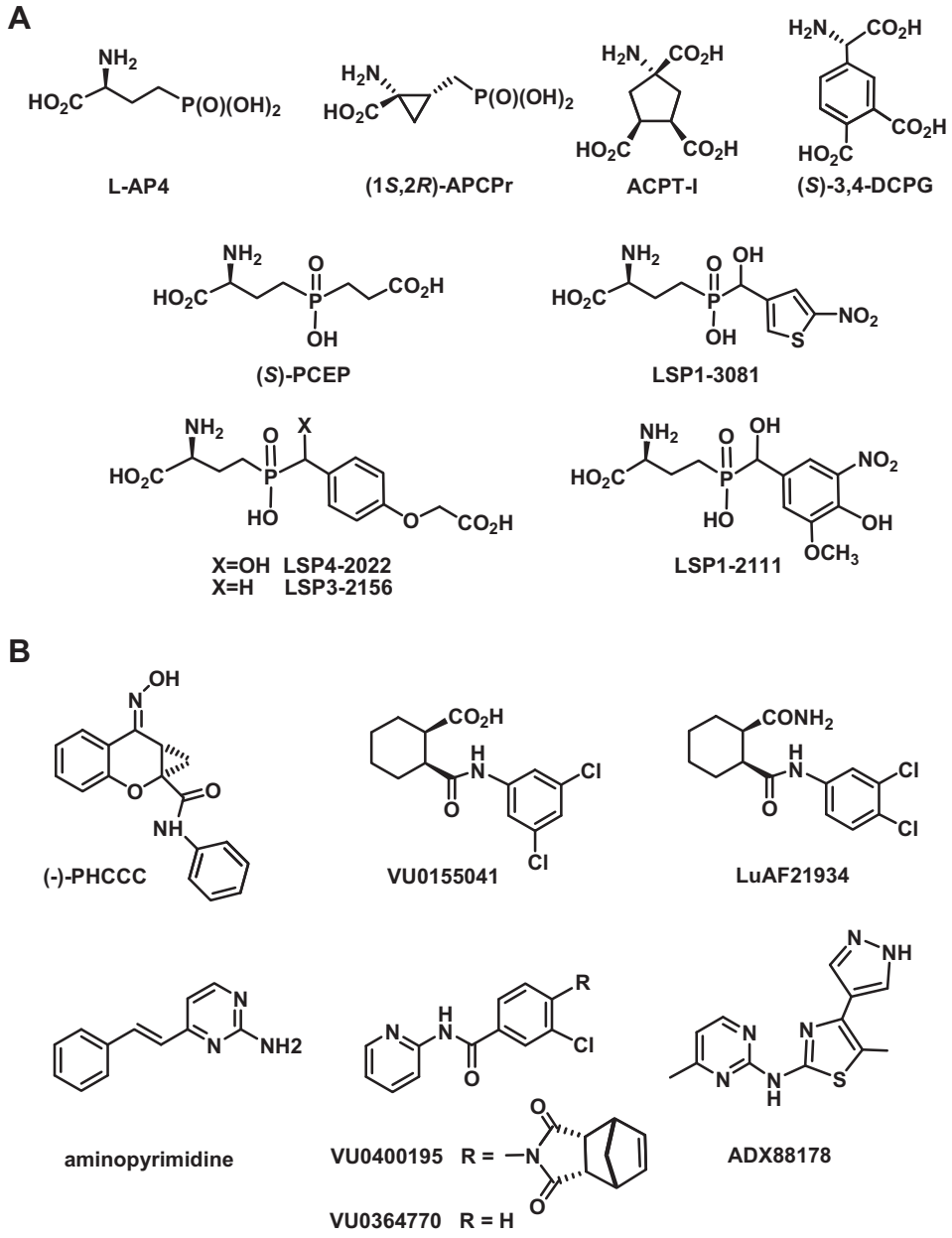

Fig. 2. Group-III mGlu receptor orthosteric agonists and mGlu4 receptor PAMs. A) Group-III mGlu receptor orthosteric agonists. B) Positive allosteric modulators of mGlu4 receptor.

glutamate where and when needed – appears somehow limited, and at least has to be taken with caution. Secondly, the binding pocket of the allosteric compounds located in the 7TM of mGlu receptors is highly hydrophobic, such that most PAMs developed so far are hydrophobic compounds. Although this largely facilitates their ability to penetrate the brain, this is also an important limitation for their development as therapeutic molecules. Indeed, hydrophobic molecules are difficult to dissolve and manipulate for *in vivo* studies, and they display a low effective fraction, most being trapped in lipid membranes. In addition, because most proteins have a central hydrophobic core, it is likely that such molecules will target additional proteins, not necessarily related to GPCRs, then increasing the probability of off target activities. Such a probability is even increased considering that some of these molecules may be cell permeant, then possibly targeting intracellular proteins. The metabolic instability and clearance of several of these compounds is another aspect to be considered (Lin et al., 2003). Indeed early developments of HTS hits resulting from mGlu4 and 7 receptor campaigns, suffered from limited stability and/or rapid clearance (East et al., 2010; Engers et al., 2010; Sukoff Rizzo et al., 2011).

Although much efforts have been put in the development of mGlu receptor PAMs, and even though these molecules remain of major interest in drug development, mGlu receptor agonists still have proven efficacy in a number of preclinical and clinical studies (Niswender and Conn, 2010), and are still worth considering in drug development programs. For example, the mGlu2/3 receptor agonist LY2140023 is still under clinical trials for schizophrenia (Patil et al., 2007; Fell et al., 2012). Although originally considered as not brain permeant, a number of mGlu receptor agonists were shown to penetrate the brain significantly (Monn et al., 1996, 1997; Moldrich et al., 2001; Palucha-Poniewiera et al., 2008; Beurrier et al., 2009; Goudet et al., 2012) and their oral bioavailability can be improved through the generation of pro-drugs, as well illustrated by the LY2140023 compound (Mezler et al., 2010). The

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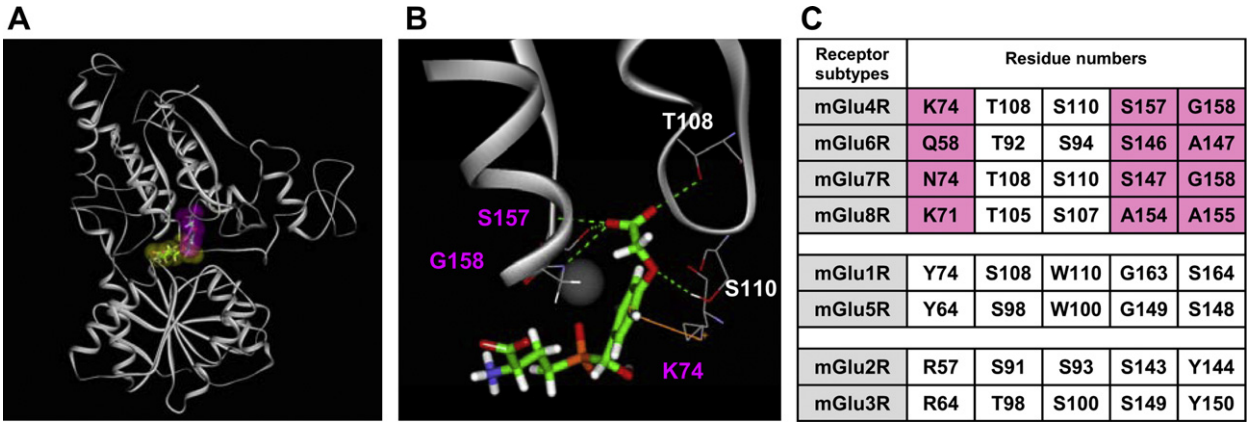

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Receptor subtypes	Residue numbers				
mGlu4R	K74	T108	S110	S157	G158
mGlu6R	Q58	T92	S94	S146	A147
mGlu7R	N74	T108	S110	S147	G158
mGlu8R	K71	T105	S107	A154	A155
mGlu1R	Y74	S108	W110	G163	S164
mGlu5R	Y64	S98	W100	G149	S148
mGlu2R	R57	S91	S93	S143	Y144
mGlu3R	R64	T98	S100	S149	Y150

Fig. 3. A) mGlu4 receptor VFT domain docked with LSP4-2022. The Van der Waals volumes of the glutamate part (yellow) and distal part (magenta) of LSP4-2022 are shown. B) Expanded view at binding site where distal residues interacting with the ligand are displayed. The three selective residues are indicated in magenta. The α-proton of G158 that is replaced by a methyl group in A155 of mGlu8 receptor, is shown as a gray Van der Waals sphere. C) Alignment of residues from the selective pocket that interact with the distal part of the agonists. The selective residues are highlighted in magenta.

polarity of such molecules will certainly limit their off-target activity, while also improving their soluble and effective fraction (Di and Kerns, 2003).

Such considerations prompt us to re-examine the possibility of developing orthosteric mGlu receptor agonists, and examine whether their main limitations – i.e. lack of subtype selectivity, and difficulties to pass the blood–brain barrier – can be overcome. Identifying such compounds will certainly allow an interesting comparison between the effect of agonists and PAMs in various animal studies. Indeed, by constantly activating the receptor, such compounds may have more pronounced effects than PAMs, especially when dealing with non desensitizing group-III mGlu receptors such as mGlu4 receptor that are not susceptible to homologous desensitization (Mathiesen and Ramirez, 2006). The mGlu4 receptor can however be internalized and desensitized upon protein kinase C activation (Mathiesen and Ramirez, 2006) but since it is located on pre-synaptic terminals, this kinase is not expected to be often activated (Iacovelli et al., 2004). Moreover, when situated on pre-synaptic GABA-ergic terminals, this receptor will be weakly activated, limiting the potential effect of PAMs. Consequently, constant activation of group-III mGlu4 receptors may have more pronounced neuroprotective effects.

3. Development of mGlu receptor group-III agonists

The first demonstration of *in vivo* benefits of group-III mGlu receptors in animal models of PD, was performed with icv injection of L-AP4 (Valenti et al., 2003). Since the initial expression of mGlu4 receptor, L-AP4 has been known as its most potent agonist (Tanabe et al., 1993). However L-AP4 is unselective among mGlu4, 6 and 8 receptors and poorly penetrates into the brain. Constrained L-AP4 analogues were designed in order to increase potency and/or selectivity (Johansen et al., 1995; Amori et al., 2000, 2006; Bessis et al., 2003; Sibille et al., 2007) (Fig. 2A). Yet only (1*S*,2*R*)-APCPr remained as potent as L-AP4. Although this compound did not display improved subtype selectivity it revealed a positive effect in an animal model of PD (Sibille et al., 2007). In another rational approach, dicarboxylic glutamate analogues ACPTs and DCPG were designed (Acher et al., 1997; Thomas et al., 2001) (Fig. 2A). Both these compounds were shown to cross the blood–brain barrier (Moldrich et al., 2001; Palucha-Poniewiera et al., 2008). Moreover (*S*)-DCPG is selective of the mGlu8 subtype (Thomas et al., 2001), but it failed to relieve Parkinsonian symptoms in rat models. At high concentration (100 mg/kg) the racemic mixture was even procataleptic (Ossowska et al., 2004). In contrast ACPT-I that activates mGlu4, 6 and 8 receptors with similar potencies, showed favorable effects following systemic injection (Lopez et al., 2008, 2012). In addition to its beneficial anti-parkinsonian actions, ACPT-I is also able to relieve hyperalgesia in inflammatory/neuropathic pain and produce antidepressant effects in rat models (Palucha et al., 2004; Goudet et al., 2008). This set of advantageous properties found with one single agonist opens promising possibilities of treating simultaneously motor and non-motor symptoms of PD (Chaudhuri et al., 2006; Aarsland et al., 2012; Wasner and Deuschl, 2012).

In the search for mGlu4 receptor agonists, a virtual high throughput screening approach was also developed (Triballeau et al., 2005) and led to the discovery of PCEP (Selvam et al., 2010). Interestingly this molecule is composed of an L-AP4 part and an additional chain. The L-AP4 part binds to the highly conserved glutamate-binding site (Acher and Bertrand, 2005) while the additional distal part binds into a new variable pocket (Selvam et al., 2010; Goudet et al., 2012) (Fig. 3). A series of derivatives was synthesized and demonstrated that binding to this additional site confers increased potency and selectivity to these ligands. This cavity is flanked with two loops that delimit its size and where 3 selective residues are found (Fig. 3). Mutant functional assays demonstrated that indeed the high mGlu4 receptor selectivity of LSP4-2022 versus mGlu8 is directly linked to two of these residues S157 G158 (Goudet et al., 2012). Specific interaction/repulsion with the third variable residue (K74 in mGlu4 receptor) of this site may lead to mGlu7 receptor selective ligands and provide the tools to investigate the role of mGlu7 receptors in PD. Thus it is now well demonstrated that subtype selective agonists may be discovered. Hence, with their high aqueous solubility, their ability to well penetrate the brain, their high free fraction in plasma, their metabolic stability because of their high polarity, these compounds should certainly be regarded as valuable drugs to be developed for PD symptomatic treatments.

In the past decade, allosteric modulators were considered as more promising than orthosteric ligands, and large HTS campaigns were thus set up. They provided several mGlu4 receptor PAM hits and optimized series. The first one to be disclosed was *N*-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (-)-PHCCC (Maj et al., 2003; Marino et al., 2003) and later several others as VU0155041 (Niswender et al., 2008), styryl aminopyrimidine (East et al., 2010) and VU0400195 in the phenylpicolinamide series (Jones et al., 2011) (Fig. 2B). They were successfully tested in animal models of PD such as haloperidol-induced catalepsy and reserpine-

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induced akinesia in rats but many did not hold optimal PK until the recent discovery of VU0364770 (Jones et al., 2012), LuAF21934 (Bennouar et al., 2013) and ADX88178 (Célanire and Campo, 2012) (Fig. 2B). The more recent PAMs where tested in the haloperidol-induced catalepsy model but also in more elaborate assays as the forelimb asymmetry-induced by unilateral 6-OHDA lesions of the median forebrain bundle, and attentional deficits induced by bilateral 6-OHDA nigrostriatal lesions in rats (Célanire and Campo, 2012; Jones et al., 2012). In addition these compounds showed efficacy in rodent PD models in combination with L-DOPA and A_2A antagonists. Notably, ADX88178 enabled a reversal of forelimb akinesia in striatum 6-OHDA lesioned rats when administered with a low dose of L-DOPA but not alone (Célanire and Campo, 2012). PAMs of mGlu4 receptor have also shown a synergy when applied with orthosteric agonists (Valenti et al., 2005; Klak et al., 2007; Bennouar et al., 2013). Simultaneous administration of ACPT-I and PHCCC in a rat model of depression (forced swimming test) produced positive effects at doses that are inactive alone (Klak et al., 2007). When applying combined LSP1-2111 and LuAF21934 to corticostriatal brain slices, recorded postsynaptic glutamatergic currents were reduced at sub-threshold concentrations of each compound (Bennouar et al., 2013). The modulation of the glutamate hyperactivity in the basal ganglia has been shown to alleviate PD symptoms (see above). Thus a combination of the two types of ligands, orthosteric agonists and PAMs, may offer an optimal approach for treating motor symptoms of PD but also mood disorders that are associated (Aarsland et al., 2012).

4. Group III mGlu receptors in the basal ganglia and Parkinson's disease

Group III mGlu receptors are expressed presynaptically at multiple synapses within the basal ganglia suggesting that their activation may modulate transmission at these synapses (Fig. 4A). mGlu receptor subtypes 4, 7 and 8 are located at the corticostriatal glutamate synapse, in the pallidum and the SN pars reticulata (SNr), both at GABAergic and glutamatergic synapses (Pin and Duvoisin, 1995; Conn and Pin, 1997; Conn et al., 2005; Duty, 2010) while the mGlu6 receptor subtype is confined to the retina. The classical view of the pathophysiological model of the BG predicts that dopamine deficiency leads to opposite effects on the two main striatal efferent neurons, which project respectively to the globus pallidus pars externa (GP) ("indirect" pathway) or the entopeduncular nucleus EPN/SNr ("direct" pathway) (Fig. 4B). These output structures of the BG indirectly control the cortical motor area by modulating GABA transmission of the motor thalamic nuclei (Albin et al., 1989; DeLong, 1990).

The current model of the functional organization of the basal ganglia posits that increased activity of striatal GABA neurons projecting to the GP leads to the over-inhibition of the GP, which in turn results in the disinhibition of the STN (Albin et al., 1989; DeLong, 1990). Hyperactivity of the STN, leading to excessive inhibitory output from the EPN and SNr to the thalamus, thereby reducing thalamocortical input, is considered as the pathophysiological hallmark of PD (Blandini et al., 2000). Group III mGlu receptors, located presynaptically at corticostriatal glutamatergic synapses, in the striatopallidal GABAergic nerve terminals (first link of the indirect pathway) and on EPN/SNr afferents, may thus play a preponderant action in reducing these overactive pathways in Parkinsonian state (Conn et al., 2005; Duty, 2010; Broadstock et al., 2012). To date, there are only few compounds of a selective subtype of group III mGlu receptors that cross the blood–brain barrier. The recent development of new allosteric modulators as well as orthosteric agonists which are able to discriminate between group III mGlu receptor subtypes has provided a great help to better understand the role of the mGlu4, 7 and 8 subtypes in the physiopathology of PD.

Studies performed in dopamine depleted rats by means of reserpine treatment, show that activation of group III mGlu receptors decreases glutamatergic transmission in the SNr (Wittmann et al., 2002). It has also been shown that the group III mGlu receptor-selective agonists L(+)-2-amino-4-phosphonobutyric acid

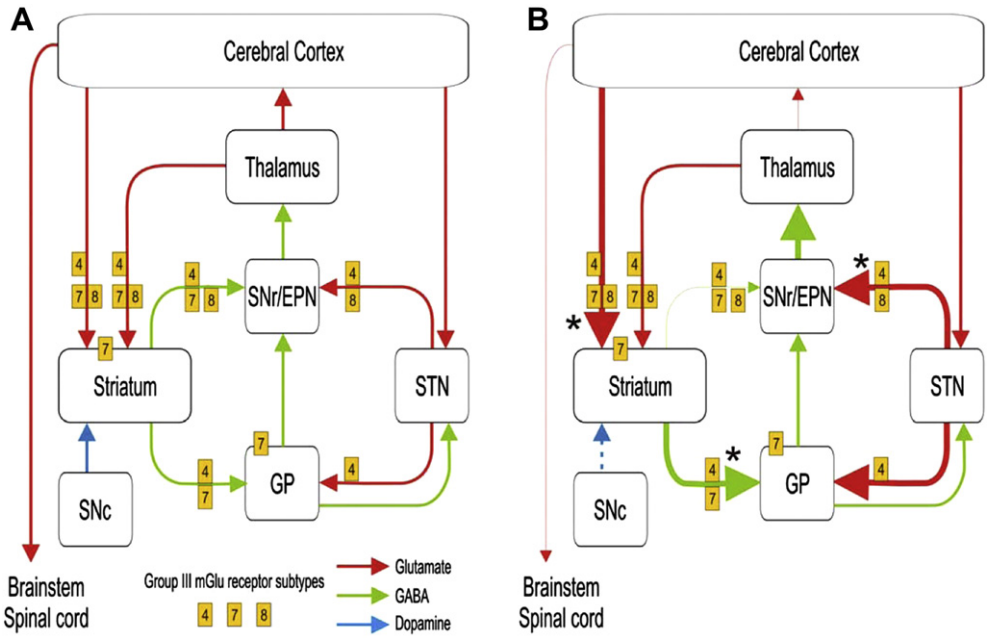

Fig. 4. Schematic representation showing the confirmed immunoreactivity of group III mGlu receptor subtypes in rodent's basal ganglia motor circuit in normal (A.) and parkinsonian state (B.). Numbers in the nuclei boxes represent postsynaptic localization of those subtypes in that nucleus, whereas numbers in the arrows represent pre-synaptic localization in that projection. The stars show synapses where activation of mGlu4 receptor subtypes may provide therapeutic benefit in Parkinson's disease. For further details, see Conn et al. (2005), Duty (2010), Galvan et al. (2006). EPN: entopeduncular nucleus; GP: globus pallidus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus.

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(L-AP4) and L-serine-O-phosphate (L-SOP) reduce KCl-evoked GABA release in the rat globus pallidus (Valenti et al., 2003; Macinnes and Duty, 2008). Physiological studies in rat brain slices have shown that L-AP4 or PHCCC, a positive allosteric modulator that selectively potentiates mGlu4 receptor signaling, reduces synaptic transmission at both the striatopallidal and STN-SNr synapses by presynaptic mechanisms. Notably, the same effect on the striatopallidal synapse has been described using the mGlu4 receptor orthosteric agonists, LSP1-3081 and LSP1-2111 (Cuomo et al., 2009). These findings suggest that targeting group III mGlu receptors may be highly efficacious in treating PD symptoms by either reducing the overall activity of the indirect pathway or by directly reducing STN activity.

4.1. Symptomatic effects of group-III agonists in PD

The first behavioral studies examined the effects of L-AP4 or L-SOP intracerebroventricular administration and demonstrated their anti-parkinsonian action in the reserpine-model of parkinsonism (Wittmann et al., 2001; Valenti et al., 2003; Austin et al., 2010). Using the same rodent model of PD and consistent with the physiological and neurochemical data, intrapallidal infusion of L-SOP has been shown to alleviate reserpine-induced akinesia, supporting the hypothesis that reducing activity at this synapse may have therapeutic efficacy (MacInnes et al., 2004). In the unilateral lesion model of PD induced by 6-OHDA injection in the medial forebrain bundle, L-AP4 was found to reduce the forelimb use asymmetry (Valenti et al., 2003). Interestingly, intrapallidal infusions of L-AP4 and the group III mGlu receptor agonist ACPT-I (Acher et al., 1997) were shown to reverse the akinetic symptoms in a reaction time task caused by partial bilateral 6-OHDA lesion, a model representing the early stages of PD (Lopez et al., 2007). Intrapallidal infusion of ACPT-I or (1*S*,2*R*)-(APCPr) and the derivatives of the hit compound (PCEP) identified following a virtual screening approach (see above) : LSP1-2111, LSP4-2022, or LSP3-2156 also reversed haloperidol-induced catalepsy in rats, providing further support for reducing transmission at the striatopallidal synapse as therapeutic strategy for the symptomatic treatment of PD (Konieczny et al., 2007; Lopez et al., 2007, 2008; Sibille et al., 2007; Beurrier et al., 2009; Goudet et al., 2012). Interestingly, these orthosteric mGlu receptor agonists have a clear advantage over allosteric compounds in terms of solubility. Recent studies have shown that both ACPT-I, LSP1-2111 and LSP4-2022 have anti-parkinsonian action on the haloperidol-induced catalepsy when administered systemically (Beurrier et al., 2009; Goudet et al., 2012; Lopez et al., 2012). In the early model of PD (rats with partial bilateral nigrostriatal 6-OHDA lesions), increased metabolic activity in the STN and the lateral motor part of the SNr is reduced by chronic ACPT-I administration for two weeks, suggesting that group III mGlu receptor activation may reverse the increased activity of these nuclei and contribute to the alleviation of motor symptoms achieved with chronic administration of group III orthosteric agonists (Lopez et al., 2012). Interestingly, according to the model of PD used (i.e. pharmacological acute or degenerative chronic 6-OHDA model) the involvement of Group III mGlu receptors in the SNr may be different. In rats, while some studies show that intranigral infusion of group III mGlu receptor agonists (L-SOP, L-AP4) reverses reserpine-induced akinesia and haloperidol-induced catalepsy (MacInnes et al., 2004; Konieczny et al., 2007; Austin et al., 2010), other show that intranigral ACPT-I or L-AP4 worsened akinetic deficits caused by partial 6-OHDA lesions and failed to markedly reverse catalepsy (Lopez et al., 2007), The reasons for such discrepancies among studies remain to be investigated, but they ultimately question the fact that directly targeting SNr activity may contribute to the anti-parkinsonian effects of systemic administration of orthosteric group III mGlu receptor agonists.

Most of the group III mGlu agonists such as L-AP4, L-SOP and ACPT-I show similar affinities at all group III mGlu cloned receptors except for mGlu7 for which binding affinities are always weaker. Therefore, their paradoxical effects on the motor symptoms of control and parkinsonian animals after intranigral administration may involve differential action on mGlu4 versus mGlu7 or 8 subtypes. As previously evidenced, mGlu4 receptors are believed to underlie most of group III anti-parkinsonian effects (Conn et al., 2005; Duty, 2010) while mGlu7 receptor activation in selective basal ganglia nuclei (i.e. the SNr) may account for adverse effects on parkinsonian symptoms (Greco et al., 2010). Both mGlu4 and mGlu7 receptors have been found on terminals of the glutamatergic corticostriatal pathway, on terminals of the GABAergic striatopallidal and striatonigral pathways (Bradley et al., 1999; Kosinski et al., 1999; Corti et al., 2002) as well as on glutamatergic terminals in the SNr originating from the subthalamic nucleus (Kosinski et al., 1999; Corti et al., 2002), all of which are found to be overactive in PD conditions. The distribution of mGlu8 receptors in the basal ganglia is the least well characterized of all, with expression of mRNA encoding mGlu8 receptors reported in the cortex, striatum and STN (Messenger et al., 2002; Broadstock et al., 2012) and moderate to high levels of mGlu8 immunoreactivity in the striatum and SNr (Duty, 2010). Interestingly, intrapallidal or intranigral injection of the a mixed mGlu8 receptor agonist/AMPA receptor antagonist (*R*,*S*)-3,4-DCPG was ineffective in the catalepsy or 6-OHDA models of PD (Lopez et al., 2007; Beurrier et al., 2009) thus ruling out any involvement of mGlu8 receptors in the anti-parkinsonian action of nondiscriminative group III mGlu receptor subtypes such as L-AP4 or ACPT-I. The new orthosteric agonist (LSP4-2022 and derivatives) that can discriminate between mGlu4 (nanomolar affinity) and mGlu8 subtypes, has recently been found to potently reverse haloperidol-induced catalepsy after either systemic or intracerebroventricular injection (Goudet et al., 2012), consistent with the implication of mGlu4 subtypes in its anti-parkinsonian action. A clear role of mGlu7 receptor as potential targets in animal models of PD still remains to be determined due to the lack of selective ligands. The mGlu7 receptor allosteric agonist AMN082 shows some relief of reserpine-induced akinesia (Broadstock et al., 2012), haloperidol-induced akinesia and motor asymmetry or prolonged RTS produced by 6-OHDA lesions at a low dose-range only (Greco et al., 2010) suggesting off-target action at higher concentration (Sukoff Rizzo et al., 2011). Although selectivity of orthosteric ligands among receptor subtypes is generally difficult to achieve, the existence of the second binding pocket that was recently highlighted in mGlu receptors VFT (Selvam et al., 2010; Goudet et al., 2012) could be crucial to the development of new series of extended orthosteric ligands able to discriminate between the different mGlu receptors subtypes. LSP4-2022 as well as other group III orthosteric agonists may thus offer most promise from a therapeutic perspective because of their high solubility and effectiveness after systemic administration.

4.2. L-DOPA-induced dyskinesia

One of the major limitations to the use of L-DOPA is the emergence of dystonic and choreic movements in response to prolonged administration. These motor complications, which are generally referred to as L-DOPA-induced dyskinesia (LID) are particularly problematic, since they manifest in concomitance with the therapeutic action of L-DOPA (Obeso et al., 2000a; Fabbrini et al., 2007) and affect up to 90% of patients within 10 years from the beginning of L-DOPA therapy (Schrag and Quinn, 2000). The clinical relevance of LID, particularly in the advanced stages of PD, has prompted considerable attention with regard to the mechanisms at the basis

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of this disorder. At present, amantadine, an antagonist at NMDA glutamate receptors, is the drug most often used for the treatment of LID (Goetz et al., 2005). LID is also counteracted by pharmacological blockade of glutamate AMPA receptors (Konitsiotis et al., 2000) suggesting that augmented glutamatergic transmission in the basal ganglia may represent a critical factor for the development and expression of dyskinesia.

The above observations, in combination with the idea that activation of mGlu4 receptors depresses glutamatergic transmission (Pisani et al., 1997; Wittmann et al., 2002; Cuomo et al., 2009) suggest that mGlu4 receptors agonists may represent potential candidate drugs for the treatment of LID. In support of this possibility it has been recently reported that administration of LSP1-2111 in combination with L-DOPA reduces the development of dyskinesia in 6-OHDA-lesioned mice (Lopez et al., 2011). This effect appears to occur only when the mGlu4 receptor agonist is administered chronically in combination with L-DOPA, since acute treatment with LSP1-2111 does not reduce LID once this condition has been established (Lopez et al., 2011).

The results of this study suggest that mGlu4 receptor agonists may attenuate LID by reducing excitatory glutamatergic transmission in the basal ganglia. LSP1-2111 may also act by modulating GABA transmission. It has been shown that dyskinesia is accompanied by increased release of GABA in the substantia nigra pars reticulata (Rangel-Barajas et al., 2011). Interestingly, activation of group III mGlu receptors reduces GABAergic transmission in the same brain region (Wittmann et al., 2001). This effect disappears following dopamine depletion (Wittmann et al., 2002), but it may be rescued when the levels of neurotransmitter are normalized by L-DOPA. In this case, activation of mGlu4 receptors may help to control dyskinesia by reducing abnormal GABAergic function in the substantia nigra pars reticulata.

Previous work showed that LID is accompanied by pathologically elevated signaling along the cAMP and extracellular signal-regulated protein kinase (ERK) cascades (Santini et al., 2007, 2009; Westin et al., 2007; Lebel et al., 2010). These aberrant responses are produced by L-DOPA via activation of dopamine D1 receptors and occur specifically in the striatonigral medium spiny neurons of the direct pathway (Darmopil et al., 2009; Santini et al., 2009). Although these signaling abnormalities have been implicated in the development and expression of dyskinetic behavior (Feyder et al., 2011), they are not affected by administration of LSP1-2111. Thus, it is unlikely that the effect of LSP1-2111 is exerted by normalizing dopamine D1 receptor-mediated transmission in striatonigral medium spiny neurons. Further studies will be necessary to elucidate the mechanisms of action of LSP1-2111 with regard to its potential anti-dyskinetic properties.

4.3. Neuroprotective effect on DA neurons

Current therapies provide an effective control of motor symptoms in the early stages of PD, but have little or no disease-modifying effect, with the possible exception of type-B monoamine oxidase (MAO_B) inhibitors. The development of a neuroprotective therapy that slows or reverses neurodegeneration is the most important unresolved issue in the treatment of PD. Neurodegeneration associated with PD depends on multiple mechanisms that accelerate and amplify the age-dependent loss of dopaminergic neurons in the SNc. These mechanisms include an increased formation of reactive oxygen species, abnormalities in protein folding and proteasomal degradation, autophagy, mitochondrial dysfunction, neuroinflammation, and excitotoxic neuronal death (Jenner and Olanow, 2006; Gupta et al., 2008; Hirsch and Hunot, 2009; Tansey and Goldberg, 2010; Harris and Rubinsztein, 2011; Vekrellis et al., 2011; Hoozemans et al., 2012). Nigral dopaminergic neurons express both AMPA and NMDA receptors (Counihan et al., 1998; Wang et al., 2005), and are particularly vulnerable to increases in extracellular glutamate concentrations (Nafia et al., 2008). The role of NMDA receptors in nigrostriatal degeneration has been widely examined using the MPTP mouse model of parkinsonism. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a prodrug that is converted into the toxic metabolite, 1-methyl-4-phenyl-pyridinium ion (MPP^+) by MAO_B. MPP^+ is taken up by the high affinity dopamine transporter, and kills nigral dopaminergic neurons mainly by inhibiting complex I of the mitochondrial respiratory chain (reviewed by (Przedborski and Jackson-Lewis, 1998)). Turski et al. (1991) have shown for the first time that pharmacological blockade of NMDA receptors protects nigral dopaminergic neurons against toxicity induced by local microinfusion of MPP^+. However, there are several reports showing no efficacy of MK-801 or other NMDA receptor antagonists as neuroprotective agents against MPTP or MPP^+ toxicity (Sonsalla et al., 1989, 1992; Kupsch et al., 1992; Michel and Agid, 1992; Araki et al., 2000). A more promising neuroprotective strategy consists of limiting the excitatory drive to the pars compacta of the substantia nigra without restraining the trophic activity of synaptic NMDA receptors. In this context, mGlu receptors have been considered as potential targets for neuroprotective agents in PD.

mGlu4 receptors in particular are strategically positioned to restrain the overactivity of the indirect pathway and reduce the excitatory drive to the SNc. Hence, it is easy to predict that activation of mGlu4 receptors protects nigral dopaminergic neurons in models of parkinsonism. This prediction has been fully confirmed using the mGlu4 receptor PAM, PHCCC, in mice challenged with MPTP. PHCCC injected i.p. 30 min before MPTP attenuated nigrostriatal degeneration, as shown by measurements of dopamine and its metabolites in the striatum, and number of TH^+ neurons in the SNc. PHCCC failed to induce neuroprotection in mGlu4 receptor knockout mice, which eliminates the bias of potential off-target effects of the drug (Battaglia et al., 2006). Interestingly, PHCCC was protective in wt mice when microinfused into the GP, suggesting that the drug acts by inhibiting the first synapse of the indirect pathway (Battaglia et al., 2006). To our knowledge, other mGlu4 receptor PAMs have not been tested in the MPTP model. However, VU0155041, a potent, selective mGlu4 receptor PAM, showed protective activity in the 6-OHDA model of parkinsonism (Betts et al., 2012). An important question is whether the simultaneous recruitment of either mGlu7 or mGlu8 receptors (or both), which can be achieved with the use of orthosteric agonists, is advantageous or detrimental for neuroprotection. Subchronic treatment with L-AP4, which activates all group-III mGlu receptor subtypes, affords neuroprotection in the 6-OHDA model (Vernon et al., 2005, 2007; Austin et al., 2010). Interestingly, LSP1-2111, a brain-permeant orthosteric agonist which displays a 30-fold greater affinity for mGlu4 vs. mGlu7 and mGlu8 receptors, showed protective activity in the MPTP model when injected systemically (15 mg/kg, i.p.) 30 min before, and then every 12 h for 7 days after a single dose of MPTP (30 mg/kg, i.p.) (Authors' unpublished observation). It will be extremely interesting to dissect the individual contribution of mGlu4, mGlu7, and mGlu8 receptors to mechanisms of neurodegeneration/neuroprotection by screening orthosteric agonists in the MPTP model, using, for example, mGlu4, mGlu7 and mGlu8 knockout mice and/or subtype-selective group-III mGlu receptor antagonists or NAMs, if available.

5. Conclusion

Numerous studies on *in vivo* models of PD have now clearly demonstrated that the group-III and more specifically the mGlu4 subtype receptors are highly promising targets for the symptomatic treatment of the disease. PAMs of mGlu4 receptors as well as

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orthosteric agonists alleviate motor symptoms e.g. rigidity, akinesia and L-DOPA induced dyskinesia but they also provide a neuroprotective effect that may slow the dopaminergic neuron degeneratoion that is the core of the pathology. Orthosteric agonists display advantageous properties such as solubility and low metabolism that are complementary to those of allosteric modulators (e.g. sub-type selectivity, membrane passage), thus both types of ligands present advantages and disadvantages for further development. Although they both need to be further improved, sub-type selectivity and slower clearance for orthosteric drugs, PK and off-target effects for modulators, they show great promise. Moreover the combination of an orthosteric agonist with an allosteric positive modulator may be the treatment of choice since a synergy between the two has been observed *in vivo*.

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