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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.

This article is part of a Special Issue entitled 'Metabotropic Glutamate Receptors'.

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