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Targeting glutamatergic synapses in Parkinson's disease

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Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic neurons of the substantia nigra and dramatic motor and cognitive impairments. The current knowledge indicates that the strength of glutamatergic signals from the cortex to the striatum is regulated during the progression of the disease. The efficacy of ionotropic glutamate receptors to modulate synaptic transmission in the striatum indicates that modulation of the activity of these receptors may represent a key target to rescue the altered neurotransmission in PD. Preclinical and clinical studies suggest that agents targeting ionotropic glutamate receptors may ameliorate the motor symptoms of PD as well as to reduce the onset of levodopa-induced dyskinetic motor behaviour.

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Introduction

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorders. PD physiopathology is linked to a widespread process of degeneration of dopamine (DA) secreting-neurons in the *Substantia Nigra pars compacta* (SNpc), with the loss of the striatal projecting neurons. The natural history of PD is complex and involves differential mechanisms during its various preclinical and clinical phases. Early clinical symptoms of PD are detected when about 70–75% of DA neurons are lost [1].

Striatal medium spiny neurons (MSNs) represent the large majority of the striatal neuronal population. At dendritic spines of striatal MSNs, DAergic terminals from the substantia nigra pars compacta converge with glutamatergic terminals. The degeneration of the nigrostriatal DAergic pathway leads to significant morphological and functional changes in the striatal neuronal circuitry, including modifications of the corticostriatal glutamatergic synaptic architecture with consequent loss of striatal synaptic plasticity [2]. Accordingly, an integrated cross-talk between DA and glutamate receptors plays an essential role in driving a physiological motor behaviour. The crucial role of striatum in basal ganglia circuitry relies also on the functional interactions between MSNs and interneurons, including aspiny cholinergic interneurons (ChIs) that receive a strong input from cortex and play a modulatory action on striatal synaptic transmission influencing also the glutamatergic transmission.

Most of the knowledge acquired in the past decades on pathophysiological mechanisms associated to PD derives from studies performed in experimental animal models [3,4]. Such models have been classically based on the use of neurotoxins such as 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) that have been shown to induce most of the neuropathological aspects of PD in rodents or in non-human primates [3,4]. However, several transgenic models have been established more recently, based on the disease-causing mutations identified for monogenic forms of familial PD.

Most of the results obtained in the last decade by using these two types of PD animal models have clearly demonstrated that the subcellular localization and the activity of postsynaptic glutamate receptors in striatum represent a key event in PD pathogenesis [5]. Alterations of the levels and function of both ionotropic and metabotropic glutamate receptors in striatum have been described in several different experimental models of PD and in brain tissue from PD patients. Accordingly, it has been hypothesized that the rescue of a balanced glutamatergic transmission at striatal MSNs and ChIs could potentially restore functional alterations of the basal ganglia circuitry in the different phases of the disease [5].

Targeting NMDA receptors (NMDARs) in Parkinson's disease

It is known that in striatal MSNs, NMDARs are mainly composed by GluN2A and GluN2B regulatory subunits, being GluN2B the predominant GluN2-type subunit present in these neurons [6]. Early studies found a decrease of GluN1/GluN2B containing NMDARs in striatal membranes in the 6-OHDA-lesioned rat striatum [7,8]. Interestingly, DA depletion induces similar alterations in the levels of striatal GluN1/GluN2B NMDARs in the synaptic membrane fractions of MPTP-treated macaques [9]. More

recent studies found an increased expression of synaptic GluN2A but not GluN2B subunits in MSNs in a rat model characterized by a partial (about 75%) lesion of the nigrostriatal pathway and mild motor symptoms [10•], thus suggesting that different degrees of DA-denervation could lead to specific alterations of the NMDARs. Notably, the above-described alterations in NMDAR subunit composition at MSNs synapses correlated with the reduction of NMDAR-dependent corticostriatal synaptic plasticity [8,10•,11,12]. Changes of NMDARs localization at synapse are strictly correlated with modifications of GluN2-type subunits binding with members of the PSD-MAGUK family of scaffolding proteins, such as PSD-95 [8,10•,12]. In addition, other studies reported that experimental parkinsonism in rats is related to a decreased synaptic membrane localization PSD-MAGUK proteins [13] thus addressing a crucial role for PSD-MAGUK/NMDARs clustering in the observed aberrant localization of NMDAR subunits at the MSN synapse.

Other approaches suggested a role for GluN2A-containing NMDARs in PD. A genome-wide study identified GRIN2A gene, encoding the GluN2A subunit, as a genetic modifier of the inverse association of coffee with the risk of developing PD [14]. In addition, a recent study indicated that vertebrate motor behaviour and synaptic signalling acquired depend upon the duplication and diversification of ancestral GluN2-type genes [15].

Even if striatal ChIs represent less than 2% of the total neuronal population in the striatum, they are major players in striatal neurotransmission thanks to their extensive axonal branching. ChIs receive DAergic inputs from SNpc and, in turn, their synchronized activity triggers DA release from nigral terminals. They also receive and integrate glutamatergic inputs from both cortex and thalamic nuclei [16]. Furthermore, ChIs respond to sensory stimuli during reward-related learning, including a pause and subsequent rebound in spiking [17]. Accordingly, ChIs play a key function in controlling the striatal network and a possible alteration of their physiological activity in PD might have dramatic consequences on cognition and motor behaviour. However, the modifications of ChIs potentially induced by either complete or partial DA denervation have not been fully investigated and only few reports are available about NMDAR subunits composition in ChIs [18]. Very recently, Zhang and co-workers [19••] identified an important role for GluN2D-containing NMDARs expressed in ChIs in the control of DAergic and glutamatergic neurotransmission in the dorsal striatum, and demonstrated an abnormal functioning of these receptors in a mouse model of PD [19••]. GluN2D-containing NMDARs inhibit both DA and glutamate release through the action of acetylcholine released by ChIs in the intact striatum. Notably, the inhibitory role of GluN2D-containing NMDARs on glutamatergic neurotransmission is impaired in the 6-OHDA lesioned striatum, standing for a role of this NMDARs subtype in adaptive changes occurring in experimental Parkinsonism [20••].

Several preclinical and clinical studies addressed the efficacy of different types of NMDAR subunits antagonists in improving motor behaviour both in PD and in levodopa induced dyskinesia (LID; see Table 1). Overall, studies performed in animal models of PD demonstrated that NMDAR blockade ameliorate parkinsonian motor symptoms and improves DAergic therapy [5]. However, classical NMDA receptor antagonists are not well tolerated by primates because of numerous side effects [21–24]. GluN2B-selective antagonists such as ifenprodil and its derivatives (i.e. CP-101,606) reduced parkinsonian symptoms in both rats and non-human primates models of PD [21,25,26]. Unfortunately, other reports describe contradictory results on the effects of GluN2B-selective antagonists on the onset of LID in animal models of PD [24,27]. However, a randomized, double-blind, placebo-controlled clinical trial showed that CP-101,606 was able to reduce the severity of

Table 1

Agents targeting ionotropic glutamate receptors evaluated in preclinical studies in experimental animal models and in clinical trials.

Ionotropic glutamate receptors	Preclinical studies		Clinical trials
	Symptomatic efficacy	Antidyskinetic efficacy	
NMDA receptors			
Broad spectrum low-affinity antagonists			Amantadine [30,31•,33] Memantine [34••,35,36,49]
GluN2B antagonists	Ro 25-6981 [22] Ifenprodil [23] CP-101,606 [25] Ro631908 [27]	CI-1041 [21] CP-101,606 [24]	CP-101,606 [28]
GluN2A-interfering peptides		TAT-2A [29•]	
AMPA receptors			
Broad spectrum antagonists	CPP [40] NBQX [40,41]	Telampanel [42] LY-293558 [43] Topiramate [48,49]	Perampanel [44–46] Topiramate [49,50]