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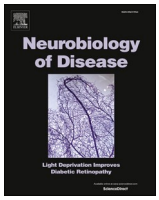

Review

Striatal glutamatergic hyperactivity in Parkinson's disease

F. Campanelli [a], G. Natale [a], G. Marino [a,b], V. Ghiglieri [c,d,**], P. Calabresi [a,d,*]

[a] Sezione di Neurologia, Dipartimento di Neuroscienze, Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Rome, Italy
[b] Dipartimento di Medicina, Università di Perugia, Perugia, Italy
[c] Università Telematica San Raffaele, Rome, Italy
[d] Clinica Neurologica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

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ABSTRACT

Glutamatergic hyperactivity in the nucleus striatum, the main basal ganglia input, has been involved in the progression of Parkinson's disease (PD) and the onset of L-Dopa-induced dyskinesias (LIDs). Abnormalities in the spiny projection neurons excitability and firing, and in the overactivity of glutamate transmission found in animal models of PD, pointed to the synaptic dysfunctions as a primary target to counteract alterations before overt neurodegeneration, conferring a key role to striatal glutamatergic transmission in the early phases of the disease. The present paper provides an overview of the evidence that glutamatergic overactivity is a critical mechanism underlying different PD-associated striatal alterations in early and advanced symptomatic stages of the disease. These aberrant changes, under L-Dopa therapy, lead to a more complex synaptopathy that involves other neurotransmitter systems and persistent modifications to generate LIDs. The review discusses the main changes in glutamatergic functions found in PD preclinical models and clinical studies and an update of the current pharmacological strategies to modulate the glutamatergic systems at the pre- and postsynaptic levels will be provided.

1. Introduction

Glutamate is the prevalent neurotransmitter in the excitatory synapses of the central nervous system (CNS). It plays a crucial role in fundamental brain functions, such as synaptic plasticity, formation of neural networks during development (Reiner and Levitz, 2018), and modulation of learning and memory processes, including motor cognition in the cortico-basal ganglia circuit.

Glutamate receptors subtypes, including ionotropic and metabotropic receptor families, are located on both pre- and postsynaptic neurons in virtually all the areas of the CNS.

Ionotropic glutamate receptors are ligand-gated non-selective cation channels that can be classified based on specific binding of the agonists *N*-methyl-D-aspartate (NMDA), kainic acid (KA), and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). These receptors have distinct roles in different forms of synaptic plasticity that are considered primary cellular mechanisms underlying specific learning and memory types (Calabresi et al., 1992).

Unlike the ionotropic glutamate receptors, which are ligand-gated ion channels and mediate fast excitatory synaptic responses, metabotropic glutamate receptors (mGluRs) provide a different level of response complexity through their association with the phosphoinositide (PI) and cyclic nucleotide (cAMP) second messenger systems. Three groups of mGluRs differ in their coupling to intracellular second messengers and their sensitivity to pharmacological agents (Mazzitelli et al., 2018). Group I, consisting of $mGluR_1$ and $mGluR_5$, is coupled to the heterotrimeric guanine nucleotide-binding protein $G_{q/11}$, whose activation leads to increased intracellular levels of inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) *via* stimulation of phospholipase C_β. This pathway is linked to the release of Ca^{2+} from intracellular stores.

As members of Group II receptor family, $mGluR_2$ and $mGluR_3$ are coupled to $G_{i/o}$ and promote the inhibition of adenylyl cyclase and voltage-dependent Ca^{2+} channels, together with the activation of voltage-dependent K^+ channels. Similarly, Group III receptors ($mGluR_4$, $mGluR_7$, and $mGluR_8$) are associated with $G_{i/0}$ type proteins, while $mGluR_6$, mainly expressed in retinal ON bipolar cells, initially thought to be linked to a cGMP phosphodiesterase, is linked to a G_0 (Nawy, 1999;

* Correspondence to: P Calabresi, Dipartimento di Neuroscienze, Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma, Italy.
** Correspondence to: V Ghiglieri, Università Telematica San Raffaele, via di Val Cannuta 247, 00166 Roma, Italy.
E-mail addresses: veronica.ghiglieri@uniroma5.it (V. Ghiglieri), paolo.calabresi@policlinicogemelli.it (P. Calabresi).

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Reiner and Levitz, 2018). With such an ample range of responses, which ensures an elaborate interplay with other neurotransmitter systems, glutamate-mediated excitatory signals play a pivotal role in shaping the actions of the basal ganglia circuitry. Thus, even small changes that bring to overstimulation of glutamate receptors may exert potential neurotoxic effects by triggering apoptotic cell death due to Ca^{2+} overload.

In Parkinson's disease (PD), the reduction of striatal dopamine (DA) release due to degeneration of dopaminergic afferents generates multiple alterations of the synaptic physiology, mainly affecting the striatal glutamatergic transmission, with subtle changes of the spiny projection neurons (SPNs) (Natale et al., 2021; Tozzi et al., 2021), which in turn, trigger compensative mechanisms within the striatal microcircuitry (Tozzi et al., 2016; Tozzi et al., 2011). As the dopaminergic cells damage continues, alterations of the quality control systems - operated by cellular organelles to prevent protein misfolding and control inflammatory and cell death pathways - advances (Lin et al., 2019) and excitotoxicity is observed in target neurons (Iovino et al., 2020) with the loss of corticostriatal plasticity and consequent inability to control voluntary movements.

2. The healthy basal ganglia

The basal ganglia refer to an interconnected group of subcortical nuclei located in the deep encephalon, responsible for motor control and higher cognitive functions (Fig. 1). The nuclei comprise the caudate nucleus, the putamen, the internal and external globus pallidus (GPi and GPe), the subthalamic nucleus (STN), and the substantia nigra, pars reticulata (SNpr) and pars compacta (SNpc). The caudate nucleus and the putamen, fused in the front part and generally referred to as a single structure, the neostriatum (or striatum), have cellular and functional homologies due to their embryological origin from the same telencephalic structure. The striatum is considered the primary nucleus of the input layer to the basal ganglia and, by receiving glutamatergic afferents from the cerebral cortex and the thalamus and dopaminergic inputs from the SNpc, acts as an integrative hub contributing to the selection of appropriate behaviors (Redgrave et al., 1999).

While glutamatergic afferents represent the primary inputs, in the nucleus striatum this excitatory command is re-elaborated under the modulatory actions of DA, as the striatal efferent projections use the inhibitory neurotransmitter gamma-amino-butyric acid (GABA). Differently, in the so-called “hyperdirect pathway”, cortical inputs to STN, engaged in reciprocal connections with GPe, maintain the excitatory signal to ensure an efficient driving on the activity of output nuclei (Polyakova et al., 2020). Besides cortical inputs, the striatum receives also abundant glutamatergic afferents from the intralaminar centrolateral nucleus (CLn) and parafascicular nucleus (PFn) (Smith et al., 2014) of the thalamus. Thalamo-striatal plastic adaptations are less characterized but play an essential role as thalamic neurons form synapses with SPNs and cholinergic interneurons (Cenci et al., 2018; Smith et al., 2014; Tritsch and Carter, 2016).

Dopaminergic fibers innervate different nuclei, but their main action, in the dorsal striatum, is to operate a fine regulation on the two GABAergic pathways to control motor activity: the direct and indirect striatofugal pathways (Graybiel, 2000; Kandel et al., 2003). The release of DA in the striatum has opposite effects on the activity of the direct and indirect pathways; DA favors excitement in striatonigral neurons due to their enrichment in DA D_1 receptors (D_1Rs), whereas it inhibits striatopallidal neurons through the activation of the DA D_2 receptors (D_2Rs), mainly expressed in these cells. Thus, the activation of these two receptors produces different biochemical responses, being associated with distinct G proteins (Gerfen and Surmeier, 2011).

D_1Rs are coupled to $G_{s/olf}$, which increases intrinsic excitability and promotes long-term potentiation (LTP) of glutamatergic synapses (Calabresi et al., 2000), facilitating signaling through the direct pathway (Gerfen and Surmeier, 2011; Grace et al., 2007). On the contrary, activation of D_2Rs involves $G_{i/0}$ proteins, resulting in decreased intrinsic excitability and induction of long-term depression (LTD) (Calabresi et al., 1997; Surmeier et al., 2014).

Based on these neuroanatomical characteristics, direct and indirect pathways were initially believed to have competing effects on motor command. Recent evidence, however, highlights that i) the distinction between these two pathways is not as straightforward as previously reported, ii) a number of striatal neurons co-express D_1 and D_2Rs, iii)

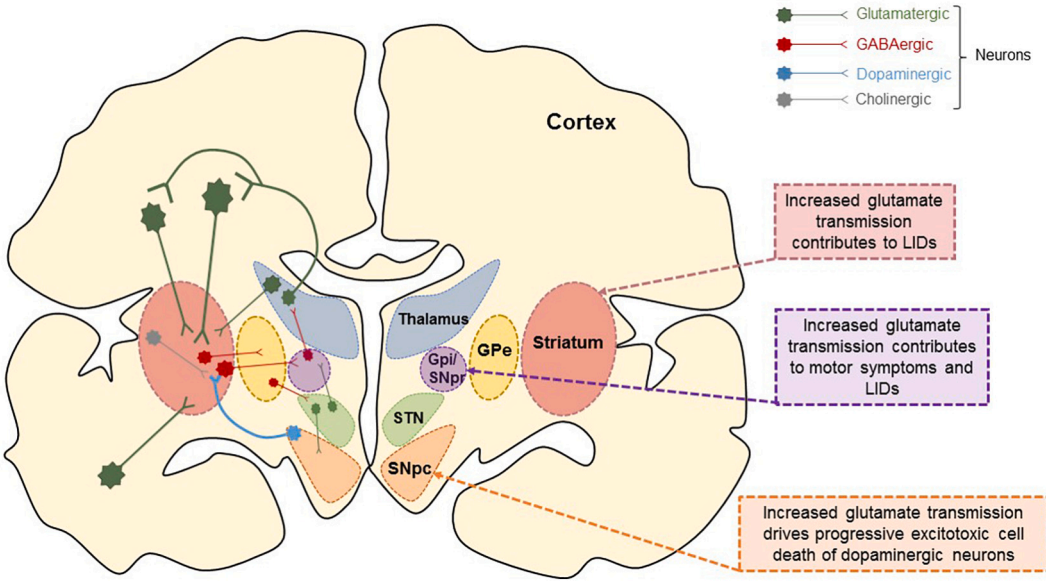

Fig. 1. Schematic representation of the basal ganglia motor circuit, showing the direct/indirect pathway in Parkinson's disease. Excitatory glutamatergic connections are depicted in green, inhibitory GABAergic connections are depicted in red. Blue connections indicate degeneration of the dopaminergic nigrostriatal tract that induces downstream modifications in activity in the motor circuits. Glutamatergic overactivity following DA denervation is believed to be implicated in the appearance of motor complications, development of L-Dopa-induced dyskinesia (LIDs), and excitotoxic cell death of dopaminergic neurons in SNpc.
SNpc/SNpr substantia nigra pars compacta/pars reticulata, STN subthalamic nucleus, GPe/GPi globus pallidus external/internal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

both the striatopallidal and the striatonigral neurons are enrolled to finely regulate the execution, and ensure the fluidity and sequencing of the voluntary movements, and iv) a balance between these systems is necessary to establish and control motor coordination and gait (Calabresi et al., 2014; Cui et al., 2013). By acting through its receptors on both pathways and based on the conditions generated by the glutamatergic afferents, DA determines the adjustment of a motor program, facilitating movements. Here we focus on the parkinsonian state, in which this striatal DA-glutamate interplay is disrupted, and the activation of these two pathways is also dysregulated, accounting for the onset of the clinical PD.

3. Glutamate hyperactivity in Parkinson's Disease and L-Dopa-induced dyskinesias

3.1. Parkinsonian state

PD is the third most common neurological disorder causing disability after stroke and Alzheimer's disease (Deuschl et al., 2020), and is characterized by a neuronal loss in the SNpc, leading to profound changes in the functional organization of the entire basal ganglia network.

The dopaminergic neurons have an essential role in determining the striatal ability to receive motor information from the cortex and return it, through the output nuclei and the thalamus, back to the cortex (Calabresi et al., 2014). In PD, the deficiency of DA within the striatum and the abnormalities in basal ganglia function progressively lead to the development of bradykinesia, tremor, rigidity, and gait difficulties (Galvan and Wichmann, 2008).

As a consequence of the nigrostriatal denervation, the modulation of events mediated by glutamate receptors is impaired in the striatum, resulting in a net overactive signal from the output nuclei. Besides these effects, the excessive glutamate neurotransmission leads to molecular alterations in glutamatergic synapses, with the functional loss of dopaminergic targets priming the overwhelming progression of PD symptoms. Such a state may persist for years and evolve in unpredictable trajectories, with a functional reorganization of neuronal and non-neuronal activity, conditioning the responses to classical therapies based on DA replacement. The corticostriatal synapses may not be able to manage unphysiological levels of DA, which, in turn, would enhance the risk of oxidative stress due to the resumed DA metabolism.

Relevant to thalamo-striatal pathway alterations, it has been reported that DA depletion selectively reduces thalamo-striatal drive in direct SPNs (dSPNs) with an action mediated mainly by AMPA receptors (Parker et al., 2016).

3.2. Dyskinetic state

In this pathological frame, replacing DA levels with chronic l-3,4-dihydroxyphenylalanine (L-Dopa) treatment (Lang and Lozano, 1998; Mercuri and Bernardi, 2005) causes a further reorganization of receptors expression on the postsynaptic membranes in synapses that already show a heavy dysregulation of glutamatergic neurotransmission.

This recovery of DARs stimulation may lead to excessive glutamatergic transmission resulting in failure of a rapid glutamate removal from the synaptic cleft that may bring to compensative redistribution of extrasynaptic glutamatergic receptors, setting the stage for L-Dopa-induced alterations (Calabresi et al., 2010; Cenci and Lundblad, 2006; Gardoni et al., 2006; Sgambato-Faure and Cenci, 2012). These findings support the concept that, in the striatum, a link exists between abnormalities of glutamate transmission, receptor function, and the pathogenesis of L-Dopa-induced dyskinesias (LIDs). While overactivity of glutamatergic signaling enhances the direct striatonigral pathway, parallel changes in the indirect pathway are made complex by the multiple alterations occurring at the single pathway and circuit levels. For example, in control conditions, the oscillatory and synchronized neuronal activity of the pallido-subthalamic system tightly depends on their reciprocal interactions (Bevan et al., 2002; Plenz and Kital, 1999), which are shaped by the frontal motor cortices, whose neurons project to both striatum and STN (Bevan et al., 2002; Cenci et al., 2018; Mallet et al., 2008). In PD, a range of dysfunctional changes in the striatum concurs to the unbalance between direct and indirect pathways that, under L-Dopa treatment, evolves into distinct patterns of alterations of synaptic plasticity, resulting in a net disinhibition of the thalamo-cortical pathway (Yang et al., 2021).

Results from animal models of PD demonstrated that increases in glutamate levels after chronic L-Dopa treatment could be selectively observed in dyskinetic animals (Robelet et al., 2004), supporting the concept that the hyperactivity of glutamate transmission is implicated in the development and maintenance of these motor complications (Nash and Brotchie, 2002; Robelet et al., 2004). Early molecular studies established that hyperphosphorylation of striatal NMDAR subunits and upregulation of both NMDA and AMPA receptors could be observed following L-Dopa treatment in experimental PD models (Calon et al., 2002; Chase and Oh, 2000). A series of studies then confirmed these findings, demonstrating that aberrant NMDAR subunit composition and function at SPNs favor the pathophysiology of LIDs. Specifically, synaptic localization of $GluN_{2A}$ was found increased in postsynaptic densities in association with abnormal redistribution of $GluN_{2B}$ to the extrasynaptic membranes, with a consequent alteration of synaptic $GluN_{2A}/GluN_{2B}$ ratio (Gardoni et al., 2006; Gardoni et al., 2012; Mellone et al., 2015). This specific pattern of molecular changes correlates with the motor abnormalities observed in L-Dopa-treated dyskinetic rats.

Further cell-type- and NMDAR subunit-specific changes have been recently reported, showing that chronic treatment with L-Dopa leads to increased levels of $GluN_{2D}$ subunit expression at the striatal postsynaptic densities in physiological conditions, while the SPNs of the adult striatum tipically express $GluN_{2A}$-containing NMDARs and a small amount of $GluN_{2B}$ subunits. Indeed, in control conditions, few or null $GluN_{2D}$-containing NMDARs are found in SPNs, as they are almost exclusively present in striatal cholinergic interneurons, also known as “tonically-active neurons” (TANs), that receive glutamatergic inputs from the frontal cortex and the thalamic nuclei (Tozzi et al., 2016). Although TANs are deeply involved in shaping the direction of corticostriatal plasticity, thalamic inputs have been less explored in relation to LIDs, and it has not been fully clarified, if an altered pattern of thalamic neurons is reflected in striatal changes and through which neuronal subtypes. According to an early view, the thalamo-striatal projections are not involved in the pathogenesis of LIDs (Zhang et al., 2013). More recent evidence, however, demonstrates that under L-Dopa the functional connectivity between parafascicular neurons and indirect SPNs (iSPNs) is selectively enhanced through the action of TANs (Tanimura et al., 2019).

3.3. Preclinical research: animal models

The link between DA neurotransmitter system alterations and glutamatergic hyperactivity has been explored, and the glutamatergic system has been challenged with different therapeutic approaches in animal models and in clinical settings.

The most significant contribution to the explanation of the functional changes occurring in PD has been provided by modeling the disease in rodents and non-human primates (NHP) (Fig. 2).

3.3.1. 6-hydroxydopamine (6-OHDA) rodent model

In rodents, the principal experimental paradigm that offered mechanistic insights of PD was based on the intracerebral injection of neurotoxin 6-OHDA (Ungerstedt, 1968). This toxin enters dopaminergic and noradrenergic neurons through the monoamine transporters. Unilateral or bilateral injection either into the SNpc or in the proximity of the nigrostriatal fibers (“medial forebrain bundle, MFB”) induces the cell death of mesencephalic SNpc neurons due to the acute oxidative stress

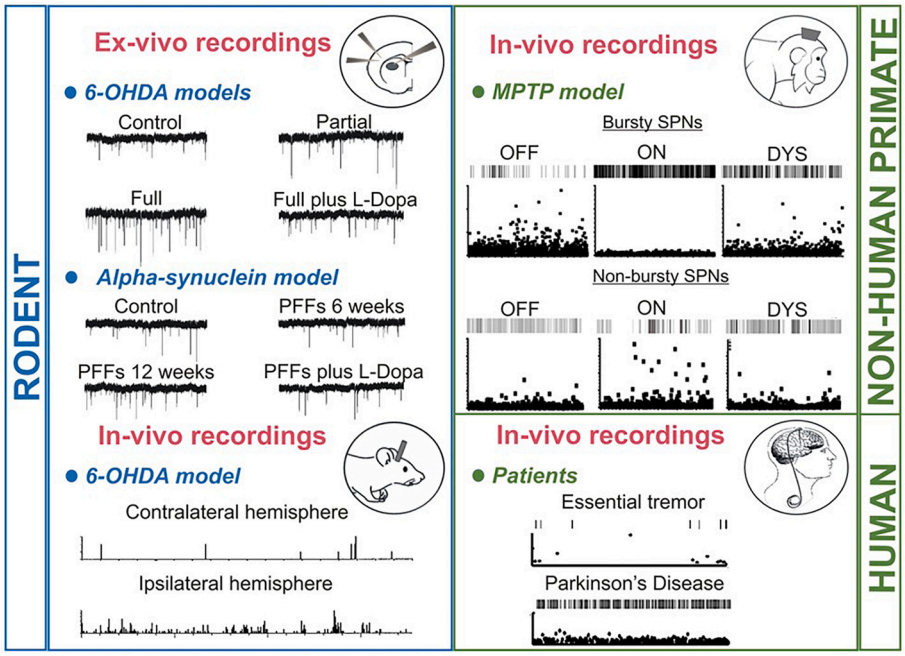

Fig. 2. Glutamatergic abnormalities in striatal SPNs in preclinical and clinical PD and LIDs. (Left upper panel) Representative traces from *ex vivo* whole-cell patch-clamp experiments showing glutamatergic sEPSCs recorded from SPNs in 6-OHDA and α-*syn*-PFF models of PD. 6-OHDA models: Partial-denervated rats present a higher amplitude of spontaneous glutamatergic activity than control animals. Full-denervated rats exhibit an increase in both frequency and amplitude of the glutamatergic sEPSCs, that return to control values after L-Dopa administration. α-syn-PFF model: rats 6-weeks post-injection display a glutamatergic activity similar to control animals, whereas at 12-weeks after α-syn-PFF injection, this transmission is increased with an augmented frequency and no variance in sEPSC amplitude. After a sub-chronic L-Dopa treatment, this abnormal glutamatergic hyperactivity is normalized. (Left lower panel) Strip chart of *in vivo* electrophysiological recording shows firing rates of SPNs from the striatum contralateral and ipsilateral of a unilateral 6-OHDA lesioned rat. The firing frequencies and burst rates of the ipsilateral hemisphere are higher than those recorded from the contralateral hemisphere *(Modified from (*Chen et al., 2001*)*.
(Right upper panel) Examples of firing patterns in bursty and non-bursty SPNs in the off (baseline parkinsonian disability), on (reversal of parkinsonism after levodopa injection), and dyskinesias states. Representative rasters and ISI distributions over time are shown from each motor state. The bursty SPNs increase the firing frequency (see the raster) and decrease in pausing (see ISI distributions) in the on and dyskinetic states. In non-bursty SPNs, the firing frequency decreased, pausing increased in the on-state, but this is reversed during dyskinesias *(Modified from (*Singh et al., 2015*)*.
(Right lower panel) Representative SPNs activity in patients with essential tremor (control) and PD. Raster and ISI distribution over time showed overactivity of SPNs in patients with PD, with increased firing frequencies and spike bursts *(Modified from (*Singh et al., 2016*)*.

generated by the inhibition of the mitochondrial complex I and the massive production of reactive oxygen species (ROS), such as superoxide and hydroxyl radicals, and hydrogen peroxide (Schober, 2004). Although dated, implementing the 6-OHDA lesion paradigm over time has allowed preclinical researchers to model distinct degrees of nigrostriatal denervation (Blandini et al., 2008; Paille et al., 2010), as a proper use of this model allows to obtain partial or full lesions of dopaminergic fibers, thus mimicking early and advanced symptomatic stages of PD. If 6-OHDA is injected into the striatum, the lesion induces a slower and less severe loss of dopaminergic nigrostriatal neurons (≈60–70%), modeling a more progressive neuronal degeneration (Kirik et al., 1998).

This modular paradigm is widely used to evaluate antiparkinsonian effects of pharmacological treatments and for neuroprotection studies to develop new drug therapies (Ilijic et al., 2011; Jiang et al., 1993), or surgical approaches with cell transplantation (Bjorklund et al., 2002; Roy et al., 2006).

3.3.1.1. Parkinsonian state. 6-OHDA fully-lesioned rats show increased neuronal excitability of striatal neurons that results from a more robust glutamatergic cortical input to the striatum, as confirmed by electrophysiology, electron microscopy, and *in vivo* microdialysis studies (Calabresi et al., 1993; Ingham et al., 1998; Lindefors and Ungerstedt, 1990; Meshul et al., 1999).

Accordingly, compelling evidence supports the concept that an increased glutamatergic transmission in the striatum occurs following DA denervation. Seminal studies using extracellular single-unit recordings in rats with unilateral 6-OHDA lesions showed that DA depletion induces changes in striatal SPNs activity, with a shift from a regular pattern to a rhythmic burst firing mode (MacLeod et al., 1990; Murer et al., 1997; Pan and Walters, 1988). Interestingly the firing frequencies of SPNs after nigrostriatal lesion increased from below 2 Hz, a typical value of healthy adult animals, to 5–12 Hz (Kita and Kita, 2011; Tseng et al., 2001).

Initial observations showed a characteristic association between D_2R hypersensitivity and an increase in NMDA-mediated neuronal excitability in brain slices of parkinsonian rats (Calabresi et al., 1993). As further support of the dopaminergic control of glutamate neurotransmission, nigrostriatal degeneration causes an abnormal increase in the spontaneous excitatory post-synaptic currents (sEPSCs) (Bagetta et al., 2012; Natale et al., 2021; Picconi et al., 2004; Tang et al., 2001). Other studies that found changes in glutamatergic spontaneous activity and differences between dSPNs and iSPNs offer an alternative view. Day and co-authors, in 2006, demonstrated that DA depletion produces a decrease in miniature EPSCs (mEPSCs) frequency in iSPNs with no change in the dSPNs (Day et al., 2006). A different insight was provided by Warre and collaborators, who observed no change in either frequency or amplitude of sEPSCs at the indirect pathway but a reduced frequency in the dSPNs, which suggests a decrease in neurotransmitter release probability (Warre et al., 2011).

Other studies investigated the specific electrophysiological changes in membrane excitability, expressed as evoked firing rate, in both types of SPNs. Notably, DA loss increases the intrinsic excitability of both dSPNs and iSPNs, as suggested by the enhanced evoked firing rates (Suarez et al., 2016; Suárez et al., 2014) found after 6-OHDA injection.

Interestingly, the extent of glutamatergic alterations observed in striatal neurons seems to depend on the degree of dopaminergic denervation. Besides being associated with mild motor symptoms, a partial nigrostriatal lesion is also linked to an incomplete alteration of the spontaneous glutamatergic activity (Natale et al., 2021). Partially lesioned rats exhibits an increase in the amplitude, but not in the frequency, of sEPSCs compared to fully lesioned animals, which show an increase in both the frequency and the amplitude of spontaneous glutamatergic activity (Bagetta et al., 2012; Natale et al., 2021).

Besides the extensive investigations conducted in *in vitro* and *ex vivo*

preparations, *in vivo* approaches have also been done using the 6-OHDA model to analyze the role of glutamatergic abnormalities in PDto provide information on the spontaneous firing of striatal neurons.

SPNs firing is controlled by excitatory input from cortical neurons during plateau depolarizations called UP states, which are preserved in *in vivo* experimental settings. Striatal NMDARs directly drive SPNs to threshold during UP states (Pomata et al., 2008), together with a bidirectional striatal compartment-specific control exerted by DAR signaling (Plotkin et al., 2011; Prager et al., 2020).

Chen and colleagues performed a chronic extracellular recording of SPNs in awake rats, 5 weeks after 6-OHDA lesion in the MFB. Neurons recorded in the dorsal striatum of the hemisphere ipsilateral to the lesion exhibits higher spontaneous firing frequencies and burst discharge patterns than those in the contralateral hemisphere (Chen et al., 2001). These findings indicate that unilateral DA depletion enhances spontaneous firing rate in the SPNs, in accordance with data from the *in vitro* studies described above.

3.3.1.2. Dyskinetic state. When antiparkinsonian drug L-Dopa is administered at therapeutic regimens in fully symptomatic rats, the hypersensitivity of DA D_2Rs is reversed, and glutamatergic overactivity induced by DA denervation decreases. These cellular effects are associated with improved motor coordination and a reduced akinesia of the limb contralateral to the lesion side (Picconi et al., 2004).

Previous studies also highlighted that activating DA D_2Rs by quinpirole leads to presynaptic inhibition of glutamatergic transmission in slices obtained from parkinsonian rats but not in control slices (Calabresi et al., 1993). Similar results were observed in parkinsonian rats that display dyskinetic behavior in response to L-Dopa treatment (Picconi et al., 2004). Accordingly, both L-Dopa and DA agonists are able to rescue these synaptic abnormalities, with the return of both frequency and amplitude of the glutamatergic sEPSCs to control values. However, the reduced NMDA/AMPA ratio (the parameter is used as an index of postsynaptic responsiveness) and alterations in these receptors' subunit composition observed in SPNs of experimental parkinsonism are not re-established after L-Dopa administration. Surprisingly, these glutamatergic synaptic abnormalities were restored after chronic treatment with a DA D_2/D_3 agonist in a dose-dependent manner (Bagetta et al., 2012).

New evidence extended these findings, examining the intrinsic excitability and evoked firing rate in each type of SPNs after chronic L-Dopa treatment. Interestingly, in dyskinetic animals, the authors found an imbalance between direct and indirect striatal SPNs. In effect, whereas in iSPNs of dyskinetic animals, L-Dopa restores the evoked firing rate and the intrinsic excitability (Fieblinger et al., 2014; Suarez et al., 2020), this treatment does not affect dSPNs, in which the hyperexcitability persisted (Suarez et al., 2020), or is partially restored (Fieblinger et al., 2014). These opposite mechanisms suggest that D_1 receptors hypersensitization is related to LIDs.

A series of studies provided further clarification of the DA control of glutamate release showing that striatal TANs are also affected by DA denervation and involved in LIDs. Although few in number, this local neuronal population acts as a crucial regulator of the SPNs activity through the activation, among others, of the DA D_2 and D_5 receptors, providing a strong modulation of glutamatergic release from corticostriatal terminals through the regulation of the endocannabinoid system (Tozzi et al., 2011).

Moreover, this control exerted by TANs over SPNs and other cellular subtypes is also mediated in the striatum by the vesicular glutamate transporter type 3 (VGLUT3), that, co-localizing with vesicular acetylcholine transporter (VAChT), stores in the same synaptic vesicles ACh and glutamate. Hence, this transporter represents a specific marker of glutamatergic excitatory neurotransmission and its lack may perturb the physiological activity of TANs and SPNs, thus impacting striatal transmission (Nelson et al., 2014). Recent studies report that VGLUT3-dependent glutamate transmission plays an important role in determining striatal dysfunctions in PD, and mostly in LIDs. Indeed, in 6-OHDA-injected animals, levels of this vesicular transporter are increased, and, following L-Dopa administration, VGLUT3 expression is normalized in TANs (Divito et al., 2015). In line with this evidence, results from another research group demonstrated a reduction of LIDs consequent to VGLUT3 genetic deletion and a decrease of the phosphorylation of molecular markers altered in this model (Gangarossa et al., 2016). Thus, these observations reveal the important role of VGLUT3 in glutamate transmission, TANs modulation and in the mechanisms that underlie motor deficits and LIDs in PD.

This and other discoveries opened a new perspective on the complexity of the striatal microcircuit and the interactions between the direct and the indirect pathways.

Recent *in vivo* studies demonstrated that chronic DA loss and L-dopa treatment modulate the spontaneous firing rate of direct and indirect pathway SPNs. Using optogenetically-labeled single-unit and Ca^{2+} imaging recordings in the dorsal striatum, researchers found that DA loss causes an increase in iSPNs firing and a considerable reduction in dSPNs activity only during periods of immobility. Interestingly, in freely moving parkinsonian mice, L-Dopa evokes abnormally high firing rates in a subset of dSPNs, which correlate with the dyskinesia severity and restoration of regular firing in the remaining dSPNs (Parker et al., 2018; Ryan et al., 2018). These results identify an imbalance in dSPNs and iSPNs activity specific to the lesioned hemisphere, demonstrating how the recovery or enhancement of firing rates can mediate DA replacement therapeutic effects and dyskinesia, respectively.

These data are consistent with the breakthrough finding of Costa and co-workers using *in vivo* optogenetics in mice, establishing that dSPNs and iSPNs are co-activated during preparation and initiation of movements or both inactive during immobility (Cui et al., 2013).

This series of evidence provides relevant pathophysiological information concerning the role of an altered glutamatergic transmission in response to DA level reduction in toxin models of disease.

3.3.2. Alpha-synuclein (α-syn) rodent models

Other recent toxin models that replicate more complex aspects of the human disease present the advantage of reproducing subtle synaptic alterations in a pre-neurodegenerative stage of PD. Aggregated α-syn, since its discovery as a major component of the Lewy bodies (LBs) and recognized hallmark of synucleinopathies, has gained increasing attention as a new target for PD therapy (Calabresi et al., 2014; Ghiglieri et al., 2018; Marino et al., 2022; Polymeropoulos et al., 1997; Spillantini et al., 1997; Vekrellis et al., 2011). The development of animal models characterized by the accumulation of this protein in aggregated forms, represents an ideal approach to investigate the mechanisms underlying early cellular and molecular alterations in PD.

Preclinical findings support the hypothesis that exogenous oligomeric forms, able to generate fibrils, induce aggregation of endogenous α-syn into pathogenic inclusions (Luk et al., 2009), which spread throughout the brain after being released from neurons (Hijaz and Volpicelli-Daley, 2020).

Recently developed experimental models show that intrastriatal injection of α-syn pre-formed fibrils (α-*syn*-PFF) in rodents induces Lewy-like pathology in dopaminergic neurons of the SNpc, followed by neuronal loss and motor behavior features similar to early PD (Cremades et al., 2012; Durante et al., 2019; Ghiglieri et al., 2018).

Interestingly, intrastriatal α-syn-PFF also lead to glutamatergic system overactivity and striatal alterations. In particular, by analyzing spontaneous synaptic currents in SPNs, in α-syn-PFF-injected rats 12 weeks after the surgery, it is possible to detect an increase of glutamate-mediated activity resulting in an augmented frequency without any variance of sEPSC amplitude. This finding emphasizes that, at this time point, the glutamatergic transmission is enhanced by a presynaptic mechanism. Conversely, at 6-weeks after the α-syn-PFF injection, this glutamatergic hyperactivity was not yet detectable (Tozzi et al., 2021).

However, at this early time point, a previous study reveals that SPNs exhibit, compared to control animals, a decrease in $GluN_{2A}$-NMDA currents (Durante et al., 2019), supporting the concept that striatal glutamatergic alterations are severely affected by the accumulation of α-syn aggregates even at pre-degenerative stages. As previously mentioned, the TANs are involved in this physiological control of glutamate release (Tozzi et al., 2011). Interestingly, *in vitro* application of low doses of exogenous human α-syn oligomers, modeling very early phases of the disease, causes reduction NMDA-mediated currents selectively in striatal TANs, due to a negative modulation of $GluN_{2D}$-expressing NMDARs (Tozzi et al., 2016). On the other hand, higher doses can also impair SPNs neuronal activity by reducing $GluN_{2A}$-dependent NMDAR functions (Durante et al., 2019).

Notably, this abnormal excitatory activity, observed in the pre-neurodegenerative stage of PD, is normalized after a sub-chronic L-Dopa treatment (Tozzi et al., 2021), showing a modulatory action of striatal DA on glutamate release, likely *via* retrograde signaling as previously reported (Yin and Lovinger, 2006). D_2Rs activation leads to the decrease of glutamate release through the synthesis of eCB anandamide and the retrograde activation of the CB1Rs, presynaptically located at the corticostriatal terminals (Wu et al., 2015). An interesting work established a new postsynaptic role of endogenous α-syn, revealing that this protein promotes the release of eCBs and controls synaptic plasticity through an α-syn-dependent vesicular exocytosis. (Ding et al., 2021, doi: 10.21203/rs.3.rs-953,724/v1, preprint).

Together with a marked cell type-specificity, these time- and dose-dependent alterations highlight the importance of understanding the effects of hyperactive glutamatergic transmission on the different striatal populations to track the progressive changes leading to the onset of PD symptoms.

3.3.3. MPTP-based rodent and NHP models

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a mitochondrial complex I inhibitor whose effects were discovered in accidentally exposed humans (Langston et al., 1983). Once this lipophilic compound is converted to its metabolite, 1-methyl-4-phenylpyridinium (MPP^+) ion by the enzyme monoamine oxidase-B (MAO-B), it becomes toxic and is transported into DA neurons through the DA active transporter (DAT).

Systemic MPTP-induced PD model is mainly used in NHP because its administration is able to reproduce most of the clinical signs and pathological hallmarks of PD (Porras et al., 2012), and long-term L-Dopa treatment induces typical motor complications, including dyskinesias, making this model suitable for studying late-stage parkinsonism (Cao et al., 2007; Papa et al., 1999; Potts et al., 2014).

Different from NHP, rodents are less sensitive to MPTP toxicity. Among these species, mice are the most used since rats fail to reproduce parkinsonian features due to a species-specific metabolism of MPTP and/or efficient sequestration of MPP^+ (Blandini and Armentero, 2012). While monkeys show LB-like intraneuronal inclusions (Kowall et al., 2000), a major limit of the mouse model is the lack of LB pathology (Shimoji et al., 2005), although some studies demonstrated that the expression, regulation or pattern of α-syn can be observed after MPTP intoxication (Dauer et al., 2002; Vila et al., 2000). Phenotypic aspects of disease are also an issue, as motor features in mice are transient or difficult to measure (Schober, 2004).

3.3.3.1. Parkinsonian state. NHP models of PD closely mimic the motor and cognitive symptoms of the human disease associated with a widespread progressive dopaminergic cell loss (Vermilyea and Emborg, 2018). *In vivo* SPNs recordings provide unique and critical information to understand striatal neurons dysfunctions during behavioral tasks in conditions that are more similar to clinical PD. Recently, using NHP models, electrophysiological studies demonstrated that DA depletion leads to striatal SPNs hyperactivity.

In monkeys with DA lesion, single-cell recordings show alterations in glutamatergic neurotransmission resulting in a robust and broad increase of SPNs spontaneous firing that contributes to secondary dysregulation of striatal activity (Liang et al., 2008). In line with this evidence, Singh and collaborators, using single-cell striatal recordings in MPTP-treated primates with parkinsonism, also found changes in firing patterns associated with the advanced state. In such conditions, SPNs exhibit an altered firing pattern with bursting and pausing changes. Further, these abnormalities are differentially and inefficiently regulated by DA and correlated with motor responses (Singh et al., 2015). Moreover, by analyzing spontaneous activity of SPNs, the authors were also able to detect a specific enhancement of firing frequencies in the striatum of advanced parkinsonian primates, with a 10-fold increase in the alert state, averaging 28 ± 1.5 Hz in the putamen and 23.5 ± 1 Hz in the caudate (Liang et al., 2008; Singh et al., 2015).

This robust SPNs hyperactivity, found in advanced parkinsonian NHP, supports the progression of glutamate dysregulation over DA loss and demonstrates the primary role of glutamate in the SPNs firing changes and in their abnormal response to DA (Singh et al., 2018).

Interestingly, changes in activity pattern found in MPTP-treated mice displayed an increase in sEPSC amplitude in corticostriatal synapses of striatal SPNs, and no significant differences in the frequency of sEPSCs (VanLeeuwen et al., 2010).

3.3.3.2. Dyskinetic state. In SPNs of MPTP-based NHP models, where spontaneous firing pattern alterations in bursting and pausing are observed in the "off" state, L-Dopa administration exerts distinct effects based on their prevalent expression of DARs. In detail, Singh and co-workers demonstrated that in the "off" state, DA D_1-SPNs display a bursty firing pattern with prolonged pauses in spiking. Conversely, in the "on" state in most of these neurons, this pathological pattern almost disappeared, although this led to higher firing rates. On the other hand, non-bursty DA D_2-SPNs show an irregular firing pattern with marked pausing that increased in the "on" state, leading to a normalization of the pattern. With prolonged treatments, the appearance of dyskinesias is associated with the return of the "off" state synaptic condition in non-bursty SPNs, with a reversal of the pause rate and an inversion of the firing frequency changes. By contrast, in D_1-SPNs no further changes are observed after the occurrence of dyskinesias (Singh et al., 2015). These data suggest that exogenous DA inputs in advanced parkinsonism have an asymmetrical effect on SPNs subpopulations and an inefficient restoration of physiological firing activity patterns. The key role played by glutamate in SPNs alterations is further supported by results showing that local microinjection of glutamatergic antagonists significantly reduces these abnormalities in advanced parkinsonian primates. In addition, NMDAR or AMPAR blockade, able to dampen SPNs activity in the "off" state, also stabilizes activity changes in the "on" state induced by L-Dopa. These important data demonstrated that either NMDAR or AMPAR signaling blockade, effectively controls the SPNs response to DA, thus shaping DA-dependent striatal plasticity. Besides reducing SPNs activity, the infusion of NMDAR antagonist over an extended region of the putamen reduces dyskinesia, restoring the response to L-Dopa (Singh et al., 2018). These results provide compelling evidence that the SPNs hyperactivity is linked to the increase in glutamatergic signaling in the striatum, which can be considered a full-fledged functional target for motor control in the PD and LID states.

These findings are significant as NHP models provide insights on issues that have clinical impact (Capitanio and Emborg, 2008) and present motor and cognitive skills and neuroanatomical complexity that closely resemble those of humans, allowing to study the comparative neuroanatomy of the striatum. Compared to rodent models, NHPs can be subjected to a battery of more complex behavioral tests that assess different aspects of the syndrome and become a tool for clinical prediction of therapy responses to in PD patients at selected time points (Emborg, 2007).

3.4. Clinical research: PD patients

Currently, profoundly dysregulated SPNs activity has been found in human PD studies and supports a pivotal role of striatal glutamatergic excitation and hyperactivity in the response to DA replacement therapies (Fig. 2). After a reduction of striatal DA, the irreversible loss of the DA-mediated control of striatal function leads to motor symptoms such as hypokinesia, bradykinesia, and rigidity of the extremities and neck (Obeso et al., 2000). Consequently, movements are difficult to start and, once initiated, they are slow and may be difficult to stop. These complications may, in part, be due to the overactivity of glutamatergic projections from the STN to the basal ganglia output nuclei that inhibit the thalamus and subsequently reduce input to motor areas in the frontal cortex (Ambrosi et al., 2014).

A recent study, using single-cell recordings in the striatum of patients during surgery for STN or GPi deep-brain stimulation, provided the first insights into the electrophysiological activity in the human striatum (Singh et al., 2016). In this work, the authors compared striatal recordings across patients with PD and other neurological disorders, dystonia and essential tremor, and correlative evidence in NHP, showing that SPNs fire with an enhanced increase in frequency and abundant spike bursts. The mean rate of spontaneous firing frequency of SPNs in both putamen and caudate areas had a value between 13.5 and 47.9 Hz, averaging 30.2 ± 1.2 Hz in advanced PD patients. In addition, these neurons fired faster and frequently at rest with brief spike bursts composed of 10.5 ± 1 spikes, 7 ± 0.3 ms intraburst interspike intervals (ISIs), and 72 ± 9 ms duration (Singh et al., 2016) compared with the other conditions. Previous data described similar changes in neuronal activity in the STN and GPi of patients with PD (Rodriguez-Oroz et al., 2001). SPNs of patients with PD were overactive at baseline, firing at 10-fold and 3-fold higher than in patients with essential tremor and dystonia, respectively, thus determining a distinct level of hyperactivity in PD. Consistently, they showed that the very low SPNs spontaneous firing activity found in patients with essential tremor matched that of the classic normal state in NHP (low, irregular single spiking below 2–3 Hz) and other animal models. Therefore, the essential tremor could represent a control condition for the human SPNs activity. Furthermore, increased firing frequencies and spike bursts observed in patients with PD reproduce the changes found in the NHP MPTP model (Liang et al., 2008; Singh et al., 2015), revealing parallelism between normal-to-DA lesion animal states and essential tremor-to-PD human disorders.

Taken together, these findings indicate that alterations in the SPNs activity could be correlated to the extensive increase of burst firing, synchronization, and oscillatory activity in the cortico-basal ganglia circuit that arise after DA loss (Hammond et al., 2007; Obeso et al., 2008; Raz et al., 2000).

4. Therapeutic strategies targeting glutamate-mediated synaptic plasticity in Parkinson's Disease

The use of numerous approaches aimed at modulating glutamate signaling through pharmacological interventions represents the key avenue that leads to the development of nondopaminergic agents for PD and LIDs treatment. Among these, blunting excessive glutamate transmission by decreasing its downstream signaling pathways or its release may be a therapeutic strategy to normalize physiological neurotransmitter synaptic levels and allow for a more efficient replacement approach. An exhaustive review of the available drugs that counteract glutamatergic dysfunctions is beyond the scope of this paper (Akaike et al., 2018; Cerri et al., 2017). Here we review the studies conducted in the last decade that focused on identifying pre- and postsynaptic pharmacological targets to counteract PD-associated alterations of glutamatergic transmission.

Safinamide represents a strategy to ameliorate the efficacy of L-Dopa in PD's altered balance between glutamate and DA. It has a dual-mode of action. It selectively inhibits MAO-B, which catalyzes the oxidative deamination of biogenic and xenobiotic amines, including DA in the glial cells, thus contributing to maintaining the dopaminergic tone in the striatum (Strolin Benedetti et al., 1994). Interestingly, Safinamide can also block sodium channels in a state and use-dependent manner, thus preventing the calcium channel opening and then the release of glutamate in hyperactive synapses. Hence, through its primary sodium channel blockade, this drug can control neuronal glutamatergic hyperexcitability (Fig. 3). A research group has demonstrated, in two different studies, that its co-administration with L-Dopa, in PD patients with motor fluctuations involves a wearing-off reduction with no worsening of dyskinesia, probably due to its anti-glutamatergic action (Borgohain et al., 2014a; Borgohain et al., 2014b). A recent study, performed in fluctuating PD patients, proves that Safinamide, administered as an add-on to standard therapy, ameliorated motor symptoms and clinical fluctuations, moreover improving quality of life and activities of daily living, thus maintaining the efficacy in the long-term (Cattaneo et al., 2020).

Accordingly, results from experimental studies established that chronic *in vivo* administration of Safinamide, in add-on L-Dopa, ameliorated motor deficits and delayed the onset of LIDs in a 6-OHDA rodent model of PD (Sciaccaluga et al., 2020). Also when applied *in vitro*, Safinamide can modulate glutamatergic activity, reducing both the firing rate and synaptic currents of striatal SPNs in a dose-dependent manner without affecting synaptic plasticity. The reduction of sEPSCs in frequency but not in amplitude suggests that this drug exerts its action mostly presynaptically, confirming the inhibitory effect on glutamate release from cortical glutamatergic terminals. This effect is due to its reversible use-dependent inhibitory action on voltage-gated sodium channels, a function already recognized by previous studies in the striatum and in other brain areas (Gardoni et al., 2018; Morari et al., 2018; Müller and Foley, 2017).

It is well established that dysregulated striatal overactivity by glutamate in LIDs is partly due to enhanced levels of NMDARs. In effect, elevated phosphorylation of NMDAR subunits, resulting from D_1Rs activation after chronic L-Dopa treatment, causes overstimulation of the signaling pathways, including sequential phosphorylation of secondary messengers (Gardoni et al., 2006; Gardoni et al., 2012; Mellone et al., 2015; Mellone et al., 2019). Amantadine, a non-selective NMDA antagonist, causes an upregulation of brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase B (TrkB) expression, *via* the extracellular signal-regulated kinases (ERK) signaling cascade, able to block the phosphorylation of eEF2, which in turn silences BDNF translation (Autry et al., 2011). For these characteristics, Amantadine has been used in clinical studies to treat LIDs in PD patients (Elmer et al., 2018; Freitas and Fox, 2016) (Fig. 3). Essentially, longer-acting formulations, in addition to L-Dopa, have been suggested to improve the side-effect profile by reducing night-time drug levels and LIDs, supporting the use of this drug as an adjunct therapy for both dyskinesia and off-state in PD patients (Perez-Lloret and Rascol, 2018). However, an alternative view proposes that rather than decreasing glutamatergic currents by blocking synaptic NMDARs, Amantadine antagonizes inward-rectifier potassium subfamily 2 (Kir2) channels, thus enhancing the intrinsic excitability of SPNs (Shen et al., 2020). This study critically contributes to build the emerging concept that diminishing the difference in excitability of iSPNs and dSPNs is a more sustainable approach than disrupting NMDA-mediated function. Additionally, other NMDAR antagonists, like Memantine and Dextromethorphan combined with inhibition of cytochrome P450 2D enzyme (which has a recognized ability to catalyze the synthesis of the monoaminergic neurotransmitters DA and serotonin) show clinical efficacy and benefits on LIDs, reducing time and severity/peak of dyskinesia. The latter approach is used by administering Dextromethorphan/Quinidine in PD to treat LIDs in a small Phase IIa study (Fox et al., 2017; Freitas and Fox, 2016; Wictorin and Widner, 2016).

Relevant to receptor-targeted approaches, manipulations of the activity of specific mGluRs subtypes by selective drugs have increasingly

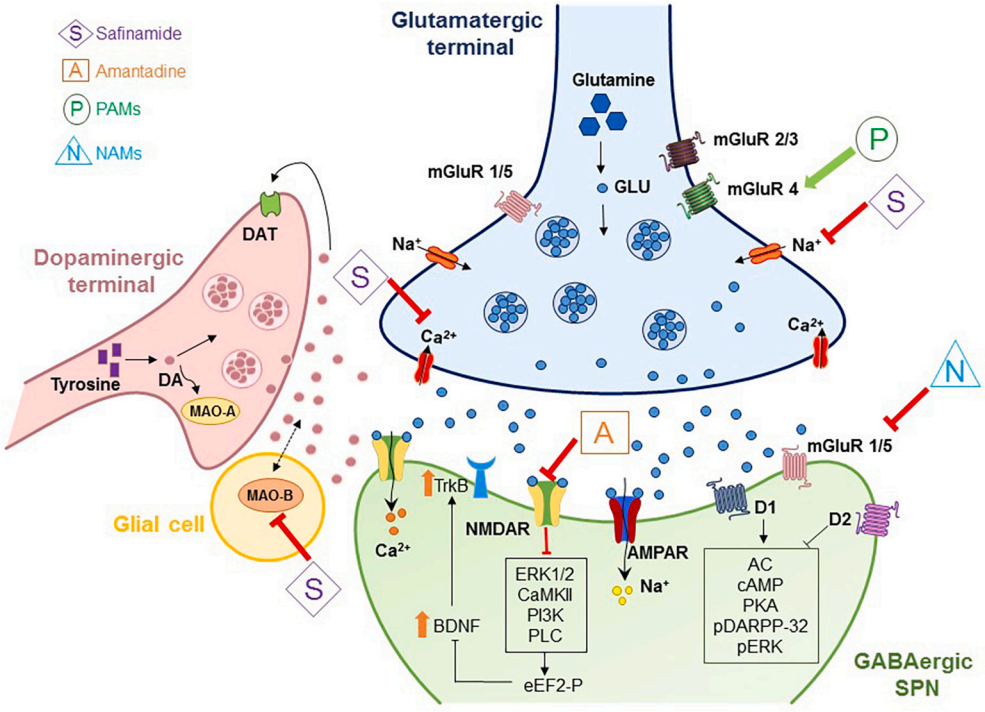

Fig. 3. The arsenal of pharmacotherapies targeting pre- and postsynaptic glutamate transmission in PD and LIDs.
Safinamide, an active drug with a dual mechanism of action, increases extracellular levels of dopamine in the striatum by MAO-B inhibition and controls the excessive glutamate release through state-dependent blocking of voltage-gated Na^+ channels and modulation of Ca^{2+} channels.
Amantadine, a non-selective NMDA antagonist, blocks NMDAR function and causes an upregulation of BDNF and TrkB expression through inhibition of ERK1/2, CaMKII, PI3K, and PLC signaling cascade that blocks the phosphorylation of eEF2, which in turn silences BDNF translation.
PAMs and NAMs, mGlu positive and negative allosteric modulators, acting on specific mGluRs subtypes reduce the glutamatergic overactivity at the corticostriatal neurons and limit the overactive indirect pathway.
Dopamine (DA); *N*-methyl-D-aspartate (NMDA); α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA); Dopamine transporter (DAT); monoamine oxidase-B (MAO-B); monoamine oxidase-A (MAO-A); phospholipase C (PLC); tyrosine receptor kinase B (TrkB); extracellular signal-regulated kinases 1/2 (ERK1/2); brain derived neurotrophic factor (BDNF); phosphoinositide 3-kinase (PI3K); calcium/calmodulin-dependent protein kinase II (CaMKII); eukaryotic elongation factor 2 (eEF2).

gained attention and interest in the search for efficient alternative treatment of PD aimed at reestablishing normal synaptic function and neuronal activity in the basal ganglia circuit. Among these, mGlu positive (PAMs) and negative (NAMs) allosteric modulators have displayed great benefits in various preclinical models of PD. These drugs show efficacy in reducing the incidence and severity of LIDs, as a L-Dopa-sparing therapy and neuroprotective agents, and have been included in clinical trials for the first time in 2017 and in 2014, respectively (Amalric, 2015; Amalric et al., 2013; Finlay and Duty, 2014; Litim et al., 2017; Rascol et al., 2014). Studies in MPTP-based NHP model and post-mortem brain tissue from PD patients demonstrated an increase of striatal expression of $mGluR_5$ after dyskinesias development (Sebastianutto and Cenci, 2018) and mGluR5 antagonists have been clinically tested for reducing LIDs symptoms in PD patients (Wang et al., 2018). Thus, this metabotropic receptor subtype is an interesting and potential target for treating LIDs and PD (Fig. 3).

$mGlu_4$ receptor has shown much promise as a therapeutic target for L-Dopa-sparing in PD (Fig. 3). Given the presynaptic localization of this receptor at the striatopallidal and subthalamopallidal synapses, where it controls GABA and glutamate release, it has been proposed that it may exert a series of actions that results in reducing the glutamatergic overactivity at the corticostriatal neurons and operating a control on the overactive indirect pathway (Beurrier et al., 2009; Cuomo et al., 2009; Marino et al., 2003; Valenti et al., 2003).

In this context, Foliglurax, a selective $mGlu_4$ PAM, is the first compound of its class to enter phase IIa clinical trials. A research group has recently provided evidence on its capability to relieve the motor symptoms and the complications induced by L-Dopa in rodent and primate models of PD. In particular, this drug, as an adjunct to L-Dopa, strongly decreased dyskinesia severity, inducing a dose-dependent reversal of parkinsonian motor symptoms in a macaque model of early-stage parkinsonism (Charvin et al., 2018). These data argue that it restores the physiological status of the striatum and, in addition to L-Dopa, improves the function of basal ganglia motor control in a rodent model of parkinsonism. In summary, the greater efficacy of these PAMs might be referred to their presynaptic action, which consists in decreasing glutamate neurotransmission by stabilizing glutamate release at the corticostriatal synapses.

Nonetheless, failure to meet the primary and secondary endpoints in a Phase II study led the company to interrupt the clinical development of Foliglurax. Understanding the reasons for this failure will be of great importance to establish the proper assessment of the therapeutic potential of $mGluR_4$ PAMs in PD (Doller et al., 2020).

5. Concluding remarks

Nigrostriatal denervation in PD leads to chain reactions that result in increased glutamatergic transmission in the striatum. In the healthy condition, an intact control of glutamate neurotransmission by modulatory systems of DA is crucial to regulating information processing through the basal ganglia, controlling action selection and execution. Many studies cited above demonstrate that glutamatergic hyperfunction in the striatum is a distinctive aspect of both parkinsonian syndrome and LIDs, although with substantial differences. An interesting aspect is that SPNs firing alterations and glutamatergic overactivity found in parkinsonian rodents, NHP, and in patients with PD vary with the extent of striatal denervation, giving unique insights into the understanding of the mechanisms underlying the steps to neurodegeneration underlying the emergence of symptoms. Based on these findings, research targeting specific time-dependent glutamatergic signaling alterations may improve the development of non-dopaminergic agents for PD that can optimize striatal responses, leading to innovative therapies for PD and, as a result, limiting the emergence of dyskinesias.

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