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A further update on the role of excitotoxicity in the pathogenesis of Parkinson's disease

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Abstract Increased levels of extracellular glutamate and hyperactivation of glutamatergic receptors in the basal ganglia trigger a critical cascade of events involving both intracellular pathways and cell-to-cell interactions that affect cell viability and promote neuronal death. The ensemble of these glutamate-triggered events is responsible for excitotoxicity, a phenomenon involved in several pathological conditions affecting the central nervous system, including a neurodegenerative disease such as Parkinson's disease (PD). PD is an age-related disorder caused by the degeneration of dopaminergic neurons within the substantia nigra pars compacta, with a miscellaneous pathogenic background. Glutamate-mediated excitotoxicity may be involved in a lethal vicious cycle, which critically contributes to the exacerbation of nigrostriatal degeneration in PD. Since excitotoxicity is a glutamate-receptor-mediated phenomenon, growing interest and work have been dedicated to the research for modulators of glutamate neurotransmission that might enable new therapeutic interventions to slow down the neurodegenerative process and ameliorate PD motor symptoms.

Keywords Glutamate receptors · Excitotoxicity · Calcium · Metabolic shift · NMDARs and mGluR5 antagonists

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Introduction

Excitotoxicity is the pathological process through which neurons are damaged and killed after excessive stimulation of glutamatergic receptors by glutamate, the main excitatory neurotransmitter in the central nervous system (CNS), or similar substrates. Excitotoxicity is due to intracellular processes, such as calcium overload and bioenergetic changes, which increase the oxidative burden and activate apoptosis. Notably, excitotoxic phenomena are involved in several brain diseases such as stroke, epilepsy and neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease (PD) (Mehta et al. 2013; Koutsilieri and Riederer 2007). PD is a very common age-related pathology affecting more than 1 % of the population over 60 years of age. The majority of cases (about 90 %) are sporadic and aging is the major risk factor, while only 10 % of cases show monogenic basis and are defined as familial (de Lau and Breteler 2006). PD pathogenesis is a complex and multifactorial process in which both genetic features and environmental stressors converge and compromise neuron viability by affecting the cellular systems dedicated to the maintenance of homeostasis: protein quality control systems and mitochondria. PD is caused by the degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNc), a mesencephalic nucleus included in the basal ganglia circuitry, which is responsible for the modulation of voluntary movement. Typical PD symptoms include resting tremor, bradykinesia, rigidity and postural instability. The pharmacological treatment currently available is purely symptomatic and is based on the restoration of dopamine levels in the brain by administration of its precursor, 3,4-hydroxyphenylalanine (L-Dopa), which significantly ameliorates PD motor deficit. However, chronic treatment with L-Dopa is frequently

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associated with progressive reduction of drug's efficacy and the development of motor complications culminating with involuntary movements known as L-Dopa-induced dyskinesias (LIDs) (Salat and Tolosa 2013).

Within the basal ganglia other neurotransmitter systems, such as GABAergic, cholinergic and glutamatergic, are present together with the dopaminergic system. In particular, glutamatergic stimulation in the basal ganglia has two major sources (Fig. 1): the projections from the subthalamic nucleus (STN), the only excitatory nucleus of the system, and the motor cortex. Secondary glutamatergic afferents to the SNc proceed from the amygdala, the peduncolopontine and laterodorsal tegmental nuclei (reviewed in Misgeld 2004). In PD, the altered neurotransmission observed within the basal ganglia affects the glutamatergic system, thereby suggesting a critical involvement of glutamate-mediated excitotoxicity in the pathogenesis as well as in the progression of the neurodegenerative process underlying the disease.

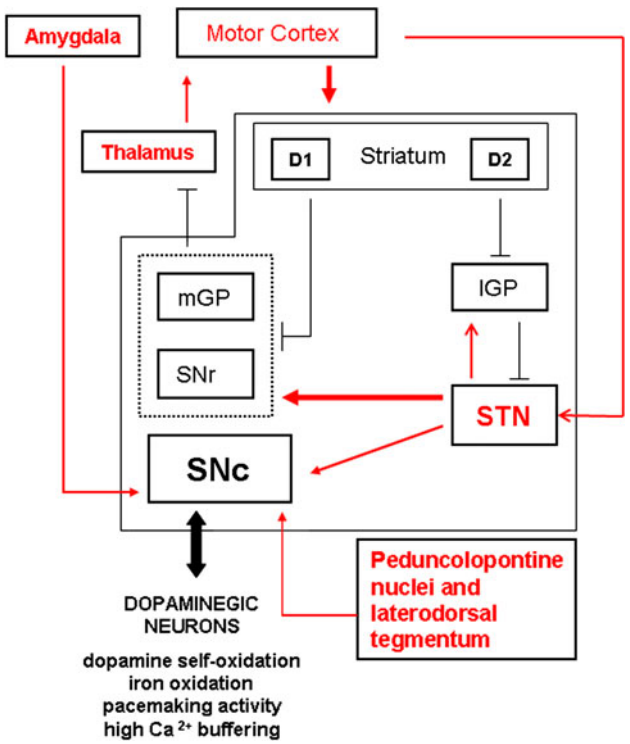

Fig. 1 Schematic representation of the basal ganglia circuitry and the glutamatergic nuclei projecting (*red titles* and *arrows*) to the striatum and the SNc. The cortex and the STN are the main sources of glutamate as indicated by the *thickness of the arrows*. Excitotoxic phenomena in PD are associated with and accelerate the progressive neurodegeneration in the SNc, according to the intrinsic properties and selective vulnerability of dopaminergic neurons. *D1/D2* dopaminergic receptors type 1 or 2 (on striatal neurons), *mGP/lGP* medial/lateral Globus Pallidus, *STN* subthalamic nucleus, *SNr/SNc* substantia nigra pars reticulata/pars compacta)

Glutamate and glutamatergic synapses

At excitatory synapses, glutamate is stored in vesicles and can be found in both pre- and post-synaptic neurons, as well as in glial cells, astrocytes in particular. Intracellular glutamate is relatively inactive and its concentration is 10,000 times higher than outside the cell, since extracellular glutamate concentration is tightly regulated to be maintained within a tolerable range. Astrocytes contribute to buffer most of the extracellular glutamate by promoting its uptake through high affinity protein carriers named Excitatory Amino Acid Transporters (EAATs) and by performing the intracellular conversion of glutamate into the inactive metabolite glutamine (Rothstein et al. 1996). Glutamate per se is not toxic, but can exert toxic effects by persistently and excessively stimulating glutamatergic receptors, which can be classified into two major families: (a) ionotropic receptors that incorporate a cationic ion channel and (b) metabotropic receptors linked to G proteins.

Ionotropic receptors

Glutamate can activate three types of ionotropic receptors: *N*-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and kainate receptors. Ionotropic glutamate receptors are ligand-gated ion channels permeable to positive ions, expressed in several areas of the CNS where they mediate depolarization of neuronal membrane potential and fast excitatory transmission. More critically, they are involved in the induction of phenomena of short- and long-term synaptic plasticity such as long-term potentiation (LTP) and depression (LTD), the molecular basis of memory formation (Rebola et al. 2010).

NMDARs are heteromeric complexes incorporating different subunits within a repertoire of three subtypes: NR1, NR2 and NR3 (Paoletti et al. 2013). These receptors are permeable to positive ions, calcium (Ca^{2+}) in particular, and they can have either synaptic or extrasynaptic localization. The current prevailing theory on NMDAR-mediated toxicity indicates that extrasynaptic rather than synaptic receptors contribute to excitotoxicity, according to their different subunit composition (Hardingham and Bading 2010). In fact, the presence of the NR2B subunit in the extrasynaptic NMDARs is thought to be responsible for excitotoxic phenomena; while the presence of NR2A subunit in the synaptic ones has been shown to activate neurotrophic pathways (Kaufman et al. 2012). Differently, Zhou and collaborators recently demonstrated that selective activation of extrasynaptic NMDARs alone is not toxic in neuron primary cultures and suggest that the onset of

excitotoxic processes is rather dependent on the magnitude and duration of synaptic and extrasynaptic NMDARs co-activation (Zhou et al. 2013).

AMPARs are tetramers and their composition can vary and include different combinations of four different subunit types. AMPARs are permeable to sodium, potassium and also to Ca^{2+}, depending on their subunit composition, and mediate fast synaptic transmission. Their structure and distribution in the brain is extremely heterogeneous and their activity at the synapse is dynamic and dependent on multiple factors, such as phosphorylation or associated transmembrane regulatory proteins. AMPARs may play a critical role in several brain diseases, ranging from ischemia to neurodegeneration (Chang et al. 2012).

Kainate receptors are permeable to sodium and potassium. They have tetrameric structure and their final composition is determined by selecting out of five different subunit types. Kainate receptors are ubiquitously distributed in the CNS, where they are found mainly in the hippocampus, lateral amygdala, cerebral cortex, globus pallidus and cerebellum. Post-synaptic kainate receptors mediate synaptic transmission, whereas pre-synaptic modulate neurotransmitter release at several synapses, thereby affecting short and long-term plasticity (Huettner 2003). Recent evidence shows that kainate receptors contribute to neurodegeneration by promoting not only excitotoxicity, but also microglial activation and neuroinflammation (Zhang and Zhu 2011).

Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGluRs) modulate glutamatergic neurotransmission and synergistically interact with ionotropic receptors; mGluR subtypes have been classified into three groups according to sequence similarity, signal transduction mechanism, and pharmacological properties. Group I (mGlu1 and 5) receptors are coupled to activation of phospholipase C and mediate post-synaptic excitatory effects. They are mainly located post-synaptically and modulate glutamate transmission through, respectively, negative and positive regulation of potassium and Ca^{2+} ion channels. Group II (mGlu2 and 3) and Group III (mGlu4, 6, 7, and 8) receptors are negatively coupled to adenyl cyclase and inhibit cAMP formation. Both groups are generally located pre-synaptically and inhibit glutamate release from axon terminals, thereby reducing glutamate-mediated excitotoxicity and preventing further activation of NMDARs. Also, mGluRs might exert their downstream action by functionally and/or physically interacting with other receptor types, such as dopamine and adenosine receptors (Ferré et al. 2007). Finally, mGluRs are involved in the activation of signaling pathways that modulate cell viability and stress responses, such as mitogen-activated protein kinase/extracellular receptor kinase (MAPK/ERK) pathway (Niswender and Conn 2010).

Excitotoxicity and the (in)direct role of glutamate

Excitotoxicity is mediated by glutamatergic receptor over-stimulation and can be either directly or indirectly triggered by glutamate. Excitotoxicity directly mediated by glutamate is highly dependent on the neurotransmitter concentration. In fact, excessive glutamate levels in the synaptic cleft cause hyperactivity of glutamatergic systems and eventually neurotoxicity, mostly through over-stimulation of NMDARs. In line with this affirmation, agonists of NMDARs such as quinolinic acid (QUIN) are responsible for excitotoxic effects. QUIN, a metabolite of the kynurenine pathway, the main pathway of tryptophan (TRP) metabolism, was shown to both increase neurotransmitter release at glutamatergic pre-synaptic terminals (Tavares et al. 2002) and directly act as a competitive agonist on post-synaptic NMDARs (de Carvalho et al. 1996). Furthermore, it was shown that persistently high concentrations of glutamate at striatal synapses lead to self-accumulation of glutamate in astrocytes. This phenomenon activates gliosis, saturates astrocyte capacity of buffering glutamate by reducing glutamine synthetase activity, and further promotes excitotoxicity (Morales and Rodriguez 2012).

Differently, indirect (or slow) excitotoxicity is mediated by stimulation of glutamatergic receptors in the absence of elevated extracellular levels of glutamate and is associated with any process that may compromise a neuron's ability to maintain normal membrane potential, such as intrinsic or toxin-induced mitochondrial deficits. This concept was at the root of the indirect excitotoxic hypothesis postulated in the early'90s by Albin and Greenamyre (Albin and Greenamyre 1992). In fact, membrane depolarization increases the opening rate of calcium-permeable, voltage-dependent channels, including NMDARs (Perez-Pinzon et al. 2012; Mehta et al. 2013), thereby activating the downstream pathways associated with excitotoxicity. Being an energy-dependent process, maintenance of membrane potential requires normal mitochondrial efficiency; it ensues that, for example, a powerful complex I inhibitor such as rotenone can increase the excitotoxic potential of glutamate by enhancing the vulnerability of dopaminergic neurons even to low concentrations of the neurotransmitter (Wu and Johnson 2009). More recently, Nguyen et al. (2011) reported that imbalance in mitochondrial fission/fusion leads to NMDAR up-regulation and oxidative stress, thereby proposing an additional link between bioenergetic defects and increased susceptibility to glutamate-mediated cytotoxicity.

Molecular mechanisms underlying glutamate-mediated excitotoxicity

Calcium and the "source specificity" hypothesis

According to the literature, excitotoxicity is mainly due to glutamate-triggered changes in intracellular Ca^{2+} levels. Ca^{2+}-mediated neurotoxicity is strictly linked to the entry point of the ion. In fact, if Ca^{2+} enters the cell through the L-type voltage-sensitive calcium channels, no cell damage occurs. Conversely, if similar increase in intracellular Ca^{2+} is caused by glutamate-induced stimulation of NMDARs, remarkable neurotoxicity is observed (Sattler et al. 1998; Koutsilieri and Riederer 2007). After glutamatergic stimulation, NMDARs are immediately activated and Ca^{2+} can directly enter the cell through them. The initial Ca^{2+} internalization is followed by a delayed Ca^{2+} overload caused by the release from endoplasmic reticulum (ER) and mitochondrial stores. This phenomenon is modulated also by transmembrane mGluRs and is responsible for secondary cascades involving calpains and activation of pathways leading to either necrotic or apoptotic cell death. Usually, intense stimulation of the NMDARs causes a downstream process of macromolecules degradation finally inducing necrotic cell death. Differently, mild or chronic stimulation of the NMDARs activate apoptotic pathways and eventually cell death when the increase in intracellular Ca^{2+} exceeds the mitochondrial buffering capacity (Nicholls 2008). These observations have led to the "source-specificity" hypothesis, which suggests that enzymes or mediators of downstream pathways responsible for excitotoxicity co-localize with NMDARs at post-synaptic densities (Kennedy 1997; Hardingham and Bading 2003).

Ca^{2+} overload is responsible for inducing the activity of nitric oxide synthases (NOS) and affecting mitochondrial integrity and functions. Ca^{2+} directly enhances reactive oxygen and nitrogen species (ROS and RNS) production. Increased levels of ROS inhibit mitochondrial complex I activity, pyruvate dehydrogenase and critical enzymes involved in the tricarboxylic acid cycle, thereby leading to impaired ATP production and energetic crisis. Moreover, glutamate-induced oxidative stress leads to mitochondrial fragmentation, which promotes NMDARs up-regulation and further contributes to the vicious cycle of excitotoxicity and neuronal death (Nguyen et al. 2011). Finally, Ca^{2+} overload directly triggers the opening of the mitochondrial permeability transition (MPT) pore and cytochrome c release, further concurring to the damage of cellular macromolecules and the activation of apoptogenic pathways (Fig. 2).

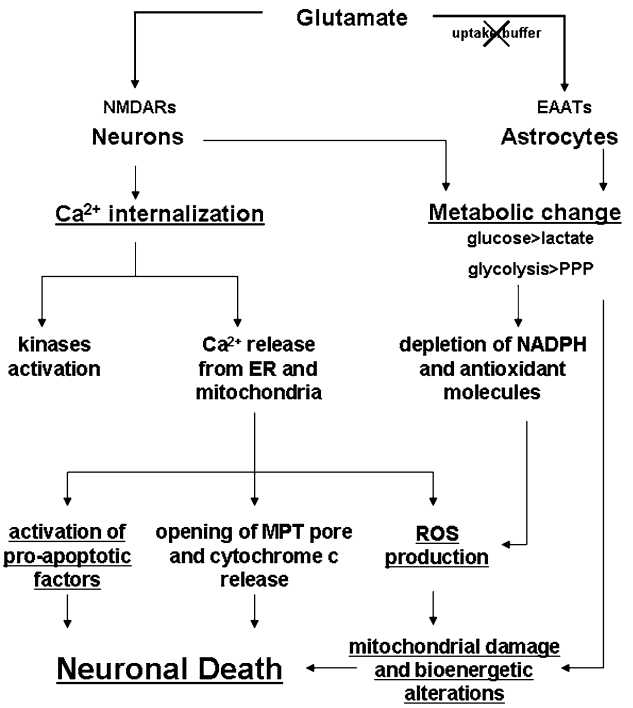

Fig. 2 Cellular mechanisms underlying glutamate-dependent excitotoxicity. To maintain optimal extracellular concentration, glutamate released at synapses is promptly internalized through EAATs and the buffering process is mainly mediated by astrocytes. Excitotoxic phenomena usually happen when glutamate cannot be properly buffered and very high levels of neurotransmitter are present in the synaptic cleft. There are two parallel intracellular mechanisms that mediate glutamate-mediated neurotoxicity: one is dependent on the raise of intracellular Ca^{2+} levels and another is dependent on metabolic changes in the neurons and, to a lesser extent, in the astrocytes. Both pathways impact on mitochondrial functions and eventually converge on the same downstream effects such as increase of oxidative stress, activation of pro-apoptotic factors, opening of MPT pore and cytochrome c release in the neurons, which eventually cause cell death. *EAATs* excitatory amino acid transporters, *ER* endoplasmic reticulum, *PPP* pentose phosphate pathway, nicotinamide adenine dinucleotide phosphate or *NADPH*, *MPT* mitochondrial permeability transition, *ROS* reactive oxygen species)

Glucose metabolism and astrocyte-neuron interactions

In the previous paragraph we stressed the concept that all of the intracellular oxidative changes and pro-apoptotic signals associated with glutamate-induced excitotoxicity are simply a consequence of intracellular Ca^{2+} overload. Recently, Bolaños and his collaborators (Rodriguez-Rodriguez et al. 2012) presented different, intriguing mechanisms that would parallel and reinforce Ca^{2+}-induced excitotoxicity, involving both neuron-astrocyte interactions and metabolic changes during glutamatergic neurotransmission. They suggest that glutamate receptor activation is coupled with signaling cascade pathways regulating glucose metabolism in both astrocytes and

neurons. As already mentioned, astrocytes are in charge of glutamate uptake from the synaptic cleft at the expenses of the intracellular ATP reservoir. Energy consumption in the astrocytes promotes glucose internalization and compensatory activation of glycolysis (Pellerin and Magistretti 1994). Concomitantly, in the neurons, glutamate-mediated NMDARs stimulation increases oxidative metabolism as well as glycolysis. In fact, NMDARs activation induces a critical metabolic change by shifting the substrate preference from lactate to glucose (Bak et al. 2006) and redirecting glucose utilization from the pentose phosphate to the glycolytic pathway (Rodriguez-Rodriguez et al. 2012). Altogether these conditions lead to increased energy metabolism and ATP synthesis and, most importantly, to depletion of antioxidant molecules in the neurons. In fact, one of the main functions of the pentose phosphate pathway is obtaining reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate (NADPH) from glucose oxidation. Thus, in physiological conditions, neurons tend to favor the activation of the pentose phosphate pathway over glycolysis to continuously regenerate NADPH, which is essential to maintain the pool of glutathione and other antioxidant molecules in a reduced state (Yin et al. 2012). The "metabolic reprogramming" induced by NMDARs ultimately leads to impaired neuronal capacity of detoxifying ROS and RNS and, after persistent stimulation, to the activation of pro-apoptotic factors (Rodriguez-Rodriguez et al. 2012). Therefore, the association between Ca^{2+}-induced dynamics and dysregulation of glucose metabolism critically interact and synergistically contribute to the neurodegenerative process triggered by glutamate excitotoxicity (Fig. 2).

PD and glutamate-mediated excitotoxicity

According to the literature, glutamate-mediated neurotoxicity is not responsible for the initial insult and neuronal loss in the SNc, but is rather a secondary effect of dopaminergic neurons susceptibility, molecular/bioenergetic defects as well as altered neurotransmission associated with cell death in this nucleus. The intrinsic vulnerability of dopaminergic neurons, associated with mitochondrial impairment, inefficient antioxidant defenses and deranged proteolytic machinery, represents the perfect background for the activation of Ca^{2+}-mediated excitotoxic phenomena and nigrostriatal death progression. Complex I inhibition was shown to trigger accumulation of glutamate in astrocyte primary cultures (McNaught and Jenner 2000). Also, aggregated α-synuclein, the main pathological hallmark in PD, was shown to increase the frequency of spontaneous miniature synaptic currents mediated by glutamate receptors and to augment both pre- and post-synaptic transmission, thereby aggravating the perturbation of intracellular Ca^{2+} homeostasis in neuronal cultures (Hüls et al. 2011). Despite its physiological role is not clearly understood, α-synuclein is thought to play a critical role in the maintenance of the pool of synaptic vesicles and neurotransmitter release (Marques and Outeiro 2012; Lundblad et al. 2012). Furthermore, in a transgenic mouse model of PD, Price et al. (2010) reported that α-synuclein overexpression interferes with mGluR5 trafficking, by up-regulating their (expression) levels and enhancing their excitotoxic action in the striatum, possibly as a result of a concomitant increase in downstream signaling. Interestingly, in the same paper the authors also demonstrated increased mGluR5 expression in the striatum of PD patients (Price et al. 2010).

Finally, neuroinflammation and activated microglia, which play a major role in the progression of SNc neurodegeneration, also contribute to glutamate release and potentiate glutamate receptor-mediated responses (in particular NMDARs), thereby leading to the exacerbation of excitotoxic phenomena (Barger et al. 2007; Noda and Beppu 2013). On the other hand, increased levels of glutamate can activate microglia and sustain inflammatory processes. In fact, it has been shown in the rat brain that glutamate receptors, in particular AMPARs, Kainate receptors and mGluRs (group I and III), are expressed on microglia cells and their activation is responsible for modulating the release of pro-inflammatory cytokines (Lee 2013). This evidence clearly suggests that neuroinflammation and glutamate-mediated excitotoxicity reciprocally sustain each others and create a vicious cycle, which eventually worsen nigrostriatal degeneration in PD.

In parallel, the loss of dopaminergic nigrostriatal terminals and the resulting dopamine depletion contribute to the re-arrangement of synaptic connectivity in the striatum, which accounts for the development of PD pathology and clinical features. Growing body of evidence indicates that, in particular for glutamatergic neurotransmission, significant changes occur during the progression of the disease. Changes in the levels of glutamate transporters (Salvatore et al. 2012; Raju et al. 2008), as well as in the subunit composition and phosphorylation pattern of NMDARs (Dunah et al. 2000), were observed in the basal ganglia of different animal models of PD; these changes varied according to the degree of striatal denervation and loss of endogenous dopamine. Both in animal models of PD (Picconi et al. 2012; Gao et al. 2013) and in the brains of PD patients (di Michele et al. 2013), loss of nigral dopaminergic neurons and striatal dopamine depletion locally affect the balance between excitatory and inhibitory neurotransmitters and synaptic plasticity (Fig. 1). These changes are likely to affect the threshold for the induction of glutamate and Ca^{2+}-dependent synaptic plasticity in the

striatum. For example, a partial nigrostriatal denervation, causing mild motor deficits in rats, affects NMDA-dependent LTP but not LTD and alters NMDAR composition in the post-synaptic density, thereby compromising the optimal nigrostriatal circuitry organization and neurotransmission (Paillé et al. 2010).

Modulation of glutamate receptors in PD offers beneficial effects on neuronal integrity, clinical motor symptoms and L-Dopa-induced side effects

Several studies have shown that modulation of glutamate receptors can prevent excitation and toxicity, thereby protecting neuronal viability and function (Santangelo et al. 2012; Hovelsø et al. 2012) (Table 1). Indeed, competitive NMDAR antagonists have shown neuroprotective properties, though they cannot be adopted in the clinical practice because of the severity of side effects associated with their administration, in particular at the cognitive level (Lipton 2007). Therefore, weak antagonists of NMDARs have been investigated. Kynurenic acid (KYNA), another intermediate of the kynurenine pathway, displays weak antagonistic action on NMDARs and, to a lesser extent, on AMPA/kainate receptors. Furthermore, KYNA was shown to reduce glutamate release at synapses by inhibiting α7-nicotinic cholinergic receptors, whose activation promotes glutamate release at glutamatergic pre-synaptic terminals (Zádori et al. 2011). On the same line, new strategies are currently under investigation to develop neuroprotective NMDAR antagonists (Koutsilieri and Riederer 2007). These molecules would target specific NMDAR subunits associated with excitotoxicity (e.g. NR2B) (Paoletti et al. 2013) or would be able to selectively interact with the pathways downstream of NMDARs activation,to prevent the intracellular responses that mediate excitotoxicity and eventually neuronal death (i.e. calcium overload, ROS production, bioenergetic changes and pro-apoptotic factor release) (Paillé et al. 2010).

Furthermore, metabotropic glutamate receptors, in particular mGluR5, have been considered as alternative targets for modulating glutamate hyperactivity in PD, primarily because of the high expression of mGluRs in the basal ganglia and their diverse modulatory roles (Duty 2012). Indeed, mGluR5 and NMDAR are functionally coupled: mGluR5 activate NMDAR by relieving Mg^{2+} blockade (Bruno et al. 2001) and NMDAR, in turn, amplifies the activity of mGluR5 by preventing its desensitization

Table 1 Classification of ionotropic and metabotropic glutamate receptors and pharmacological impact on PD

Ionotropic	Subunit types	Studies in animal models of PD
NMDA	NR1 (8 variants) NR2 (A-D) NR3 (A, B)	Memantine administration reduces dopaminergic neuron excitability and cell loss in rat brain slices (Wild et al. 2013) Administration of MK-801 counteracts neurotoxicity in different animal models of PD (Turski et al. 1991; Dall'Olio et al. 1995; Blandini et al. 2001; Armentero et al. 2006) Administration of kynurenic acid (KYNA) is neuroprotective against MPP + in vitro (Lee et al. 2008) and against 6-OHDA in vivo when combined with probenecid (Silva-Adaya et al. 2011)
AMPA/Kainate	GluR1–4	Administration of 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoxaline (NBQX) shows neuroprotection against MPTP toxicity (Merino et al. 1999)
Metabotropic	**Coupled G-protein**	**Studies in animal models of PD**
Class I mGluR1 mGluR5	Phospholipase C post-synaptic	Treatment with MPEP ameliorates motor impairment (Breysse et al. 2002; Ambrosi et al. 2010) and L-dopa-induced dyskinesias (Levandis et al. 2008) in a rodent 6-OHDA model Treatment with MPEP show anti-parkinsonian properties in MPTP-lesioned mice (Battaglia et al. 2004) and monkeys (Morin et al. 2010) as well as neuroprotection in 6-OHDA lesioned rats (Armentero et al. 2006; Hsieh et al. 2012)
Class II mGluR2 mGluR3	Adenyl Cyclase pre-synaptic and post-synaptic	Treatment with positive allosteric modulators (PAMs) of Class II mGluRs such as LY379268 and 2R,4R-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) shows neuroprotective effects in different animal models of PD (Battaglia et al. 2003; Chan et al. 2010; Murray et al. 2002)
Class III mGluR4 mGluR6 mGluR7 mGluR8	Adenyl Cyclase pre-synaptic	Treatment with *N*-phenyl-7-(hydroxyimino)cyclopropa(b)-chromen-la-carboxamide (PHCCC) reduces striatal neurodegeneration in MPTP-treated mice (Battaglia et al. 2006) Administration of PAMs such as *N*,*N*′-dibenzhydrylethane-1,2-diamine dihydrochloride (AMN082), (*S*)-3,4-dicarboxyphenylglycine (DCPG) and -Methyl-*N*-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine (ADX88178) reverse parkinsonian symptoms in rodent models of PD (Greco et al. 2010; Johnson et al. 2013; Le Poul et al. 2012) More information on group III mGluR antagonists in different animal models of PD are reviewed in (Amalric et al. 2013) and (Duty 2010)

(Alagarsamy et al. 1999). Several studies in animal models of PD have demonstrated that the use of antagonists of mGluR5 such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]pyridine (MTEP) represent a very interesting therapeutic strategy in PD, in terms of neuroprotection and mostly in the clinical management of symptoms and LIDs (Ossowska et al. 2005; Armentero et al. 2006; Levandis et al. 2008; Ambrosi et al. 2010).

Alternatively, the combined administration of glutamate receptors modulators with molecules targeting other receptors is also under investigation. For instance, the administration of mGluR5 antagonist MPEP together with antagonists of adenosine A_{2A} receptors showed disease-modifying properties in different rodent models of PD (Coccurello et al. 2004; Kachroo et al. 2005). Also, agonists of cannabinoid receptors have been shown to interfere with the glutamatergic neurotransmission in the striatum (Huang et al. 2001), thereby suggesting a possible employment of these molecules in PD-related drug discovery.

Finally, other therapeutical approaches linked to the glutamatergic system in PD have been reported in recent studies showing that down-regulation or changes in the composition of NMDARs and/or AMPARs in the basal ganglia can be obtained after rasagiline and estrogens administration suggesting that their neuroprotective potential might rely on the suppression of glutamate-mediated excitotoxicity (Gardoni et al. 2011; Al-Sweidi et al. 2012; Liu and Zhao 2013). All these pre-clinical studies opened the path to trials performed on PD patients. These clinical trials were focused on the evaluation of the effects of glutamate receptor antagonists on PD motor symptoms and LIDs (Table 2). According to the results collected so far, not many molecules succeeded in ameliorating PD motor symptoms, while some of them were able to produce beneficial effects on the treatment of LIDs.

Concluding remarks

Nigrostriatal neurodegeneration that characterizes PD is primarily due to the selective vulnerability of dopaminergic neurons, nevertheless glutamate-mediated excitotoxicity critically contribute to worsen neuronal loss in the SNc because of the multiple afferents projecting onto this nucleus and the distribution of both ionotropic and metabotropic glutamate receptors within the basal ganglia circuitry. The ultimate effect of excitotoxic phenomena is activating apoptotic pathways through the disruption of mitochondrial and bioenergetic homeostasis, as well as the increase of intracellular Ca^{2+} levels and oxidative burden.

Table 2 Glutamate receptors antagonists adopted in clinical trials on parkinsonian patients

Molecules	Target glutamate receptor	Effects and references
Amantadine	NMDA	The drug shows beneficial effects on the treatment of LIDs (Wolf et al. 2010; Sawada et al. 2010; Elahi et al. 2012)
Memantine	NMDA	The drug shows beneficial effects on axial symptoms in PD and LIDs (Varanese et al. 2010; Moreau et al. 2013; Vidal et al. 2013)
Remacemide	NMDA (low affinity) Sodium channel blocking properties	The drug has no significant effects on motor symptoms and LIDs in PD patients (Shoulson et al. 2001; Clarke et al. 2001)
Budipine	NMDA (low affinity non-competitive)	The drug shows tremorlytic effects (Spieker et al. 1999) and ameliorates the execution of complex movements in PD patients (Müller et al. 2005)
MK-0657	NMDA (NR2B-selective)	The drug has no significant effects on PD motor function (Addy et al. 2009)
Traxoprodil (CP-101,606)	NMDA (NR2B-selective)	The drug ameliorates LIDs with no other beneficial effects (Nutt et al. 2008)
Perampanel	AMPA	The drug has no effects on either motor symptoms associated with the disease or LIDs (Eggert et al. 2010; Rascol et al. 2012; Lees et al. 2012)
AFQ-056	mGluR5 (NAM)	The drug shows clinically relevant amelioration of LIDs without negative effects on PD symptoms (Berg et al. 2011; Stocchi et al. 2013)
Dipraglurant	mGluR5 (NAM)	The drug significantly ameliorates LIDs (Addex Therapeutics, Geneva, Switzerland, NCT01336088 http://www.addextherapeutics.com/investors/press-releases/news-details/article/addex-reports-positive-top-line-phase-iia-data-for-dipraglurant-in-parkinsons-disease-levodopa-indu/)

Further information and details are reviewed in Meissner et al. (2011), Duty (2012), Johnson et al. (2009) and Gasparini et al. (2013). Clinical trials with molecules not directly modulating glutamate receptors, but acting as inhibitors of glutamate release (e.g. safinamide and zonisamide) are also reviewed in Meissner et al. (2011)

LID levodopa induced dyskinesias, *NAM* negative allosteric modulators

Interestingly, these same features are typical of PD pathogenesis, suggesting that glutamate-induced neurotoxicity originates from and participate to a vicious cycle of neuronal death that lies on a generalized alteration of both neuronal homeostasis and, on a larger scale, synaptic connections in the nigrostriatal pathway.

The drug discovery process is being oriented toward the development of new molecules and/or pharmacological strategies targeting glutamate receptors, with the idea of both slowing down the neurodegenerative process and (re)establish a synaptic and neurotransmitter balance in the basal ganglia circuitry. The future of this research might have significant impact on the clinical management of the disease and on patient quality of life.

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