An update on the potential role of excitotoxicity in the pathogenesis of Parkinson’s disease

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Summary

The primary cause of the neurodegenerative process that underlies Parkinson’s disease (PD) is still unknown. Different mechanisms probably contribute to triggering neuronal death in the nigrostriatal pathway, including mitochondrial defects, oxidative stress and proteolytic stress. Glutamate-mediated excitotoxicity may be a further contributor. Glutamate is the predominant fast excitatory neurotransmitter in the central nervous system and, in the presence of specific conditions, a potential neurotoxin. Although excitotoxicity per se is unlikely to act as a major causative agent in PD pathogenesis, glutamate-mediated intracellular changes may contribute, in a more subtle way, to the mechanisms that trigger the neurodegenerative process in the substantia nigra pars compacta (SNc). It is, therefore, likely that synergistic interactions between mitochondrial defects, oxidative stress and glutamatergic stimulation take place at the SNc level. These interactions may create the conditions for the development of the nigrostriatal damage that characterizes PD.

KEY WORDS: glutamate, NMDA, mitochondria, oxidative stress, subthalamic nucleus, substantia nigra

Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the general population. Being an age-related disease, in the context of the progressive aging of the population that our society is witnessing, the incidence of PD is destined to increase. This will increase the social impact and cost of this condition, justifying the pressing need for the development of new therapeutic strategies.

The main pathological features of PD include degeneration of dopaminergic, melanized neurons of the substantia nigra pars compacta (SNc) projecting to the corpus striatum and the presence of intracytoplasmic, proteinaceous inclusions, termed Lewy bodies, in surviving neurons (1). The striatal dopaminergic denervation resulting from SNc cell loss triggers complex functional modifications within the basal ganglia circuitry, and these are the neural substrate of the typical motor symptoms of the disease (tremor, rigidity, bradykinesia) (2). Although PD is the prototypical movement disorder, PD patients manifest numerous non-motor symptoms, which include autonomic dysfunction, sleep disorders, psychiatric symptoms, gastrointestinal dysfunction and cognitive dysfunction (3).

The primary cause of the degenerative process underlying sporadic PD, which accounts for the vast majority of PD cases, is still unknown. Indeed, given the multifactorial nature of the disease, the process leading to nigral cell death likely originates from the reciprocal interactions of a restricted number of potentially contributing mechanisms. These mechanisms include mitochondrial defects, enhanced formation of reactive oxygen species — leading to oxidative damage — and aberrant protein aggregation (4). In addition to these mechanisms, there is another factor that may contribute to the neuronal loss underlying PD: excitotoxicity mediated by the excitatory amino acid glutamate (Fig. 1).

Figure 1 - Factors that contribute to the pathogenesis of Parkinson’s disease.
Mitochondrial defects, oxidative stress and protein aggregation due to cell protein mishandling are the major mechanisms involved in the pathogenesis of PD. These mechanisms, which reciprocally interact, may create conditions favoring the excitotoxic effects of glutamate on dopaminergic neurons of the substantia nigra pars compacta (SNc), thereby triggering the neurodegenerative process.
Glutamate-mediated neurotransmission and neurotoxicity

Glutamate is the predominant fast excitatory neurotransmitter in the central nervous system (CNS). Glutamate-mediated transmission plays a central role in numerous fundamental brain functions, such as synaptic plasticity phenomena involved in memory and learning, formation of neural networks during development, and repair of the CNS. Within the basal ganglia circuitry, glutamate mediates excitatory neurotransmission at crucial points, including the efferent excitatory projections that sensorimotor cortical areas send to the striatum and subthalamic nucleus (STN), and the projections that the STN, in turn, sends to its target nuclei (Fig. 2); glutamate, therefore, plays a central role in the neural mechanisms that underlie PD motor symptoms. In addition, under specific conditions glutamate can act as a neurotoxin; this latter mechanism – termed excitotoxicity – may contribute to the neurodegenerative process underlying PD pathogenesis.

Glutamate stimulates specific receptors that can be classified into two major families: receptors incorporating a cationic ion channel, known as ionotropic receptors, and receptors linked to G proteins, known as metabotropic receptors.

Ionotropic receptors

Three families of ionotropic receptors were initially identified, on the basis of their preferred agonists: N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors. Molecular biology studies later clarified that ionotropic receptors are, in fact, composed of various subunits encoded by different genes. The subunit composition determines the biophysical properties of the receptor and, to a variable extent, its pharmacology. The heteromeric nature of ionotropic receptors has favored a certain degree of terminological confusion, due to the various nomenclatures coined by the laboratories that cloned the subunits. The International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) has therefore proposed a new nomenclature for glutamate ionotropic receptors (5), which is used in this review.

The NMDA receptor: three families of subunits, GluN1, GluN2 and GluN3 (formerly known as NR1, NR2 and NR3) have been identified (6). Two GluN1 and two GluN2 subunits combine to form the tetrameric structure of the NMDA receptor. Within the extra-cellular domain of the receptor, GluN1 subunits host a modulatory binding-site for glycine, while GluN2 subunits contain the binding-site for glutamate. The membrane domain hosts the channel pore associated with the receptor. The channel pore is permeable to calcium and is regulated by a voltage-dependent magnesium block, which limits the inward calcium flow elicited by receptor activation.

The AMPA receptor: four subunits, GluA1 through GluA4 (formerly known as GluR1 – GluR4 or GluRA – GluRD), have been cloned. The AMPA receptor has a tetrameric structure consisting of symmetric dimers of GluA2 and either GluA1, GluA3 or GluA4 (7). AMPA receptors in the CNS are mainly permeable to sodium and potassium ions; given the central role of calcium in the mechanisms of excitotoxicity, this explains why AMPA receptors play a minor role in this context.

The kainate receptor: molecular cloning has identified five subunits – GluK1 (ex GluR5), GluK2 (ex GluR6), GluK3 (ex GluR7), GluK4 (ex KA1) and GluK5 (ex KA2) (8). Compared to NMDA and AMPA receptors, understanding of the functions of kainate receptors is still limited. As in the AMPA receptor, the ion channel associated with the kainate receptor is permeable to sodium and potassium ions, with a low permeability to calcium (8). Distribution of kainate receptors in the brain appears to be more restricted, compared to the other two classes of ionotropic receptors.

Metabotropic receptors

Stimulation of metabotropic receptors (mGlurSs) activates intra-cellular second messenger pathways, through cyclic nucleotides or phosphoinositol metabo-
lism. Activation of mGlurRs can also modify ion channel function, through the release of G protein subunits within the membrane.

Eight genes have been identified, GRM1 through GRM8, which encode eight different mGlur subtypes, labeled mGlur1 to mGlur8. On the basis of their structure and physiological activity, three groups of mGlurRs have been recognized: groups I (mGlur1 and mGlur5), II (mGlur2 and mGlur3) and III (mGlur4, mGlur6, mGlur7, mGlur8).

Stimulation of mGlurRs in group I activates the enzyme phospholipase C, which leads to the formation of inositol 1,4,5-trisphosphate (IP3) and diacyl glycerol; IP3 increases the cytosolic concentration of calcium by stimulating its release from intra-cellular stores, whereas diacyl glycerol serves as co-factor for the activation of protein kinase C. Group I mGlurRs are also associated with cationic channels; in fact, mGlur1 and mGlur5 receptors can negatively modulate a variety of potassium channels, thereby activating inward cationic currents and increasing neuronal excitability (9).

The mGlurRs in group II and group III are negatively coupled to adenylyl cyclase; therefore, their activation prevents the formation of cyclic adenosine monophosphate from ATP. Group II and III mGlurRs are predominantly involved in pre-synaptic inhibition.

Glutamate as a neurotoxin

It was John Olney who first correlated the excitatory properties of various glutamate analogs with their ability to produce neurotoxic damage, thereby coining the term “excitotoxicity” (10). It was subsequently shown that excitotoxicity is a receptor-mediated event and that glutamate antagonists can prevent both excitation and toxicity (11). Ever since the studies of Olney, excitotoxicity has been considered a crucial component of the pathological pathways of many CNS diseases, such as stroke, epilepsy, and progressive neurodegenerative disorders. Virtually all glutamate receptor subtypes have been implicated in mediating neurotoxicity. However, excitotoxicity is mainly linked to glutamate-triggered changes in intracellular calcium levels. As a consequence, the NMDA receptor, being highly permeable to calcium, has been identified as the key player.

Intrinsic mechanisms underlying glutamate-mediated neuronal death

Glutamate receptor-mediated overload of calcium can trigger either necrotic or apoptotic cell death. Necrotic cell death is mainly due to the activation of calcium-dependent enzymes involved in the catabolism of proteins, phospholipids and nucleic acid and is generally associated with intense stimulation of the NMDA receptor. Unlike necrosis, apoptosis can be triggered by mild or chronic overstimulation of the NMDA receptor. In this framework, mitochondria have been recognized to play a major role. These organelles, which play a critical role in maintaining low levels of cytosolic calcium, can determine a cell’s fate by activating either survival or death signaling pathways. Low-intensity stimuli may cause mitochondrial depolarization leading to the induction of autophagy, a cytoprotective mechanism particularly important in neurons, while more intense stress signals can directly activate the apoptotic cascade. This happens, in particular, when the NMDA receptor-mediated increase in intracellular calcium exceeds the mitochondrial buffering capacity (12).

Another mechanism subserving NMDA-mediated cytotoxicity is oxidative stress, resulting from the imbalance between the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) and the ability of the cell to neutralize these molecules. Again, mitochondria are directly involved: oxidative stress causes the mitochondrial permeability transition pore to open, thereby prompting further mitochondrial production of free radicals and release of apoptogenic factors. Overstimulation of the NMDA receptor causes, in particular, formation of RNS; the NMDA-mediated calcium influx, in fact, activates the neuronal isoform of nitric oxide synthase to form NO, which reacts with superoxide anion formed during mitochondrial respiration. This reaction yields the highly reactive free radical peroxynitrite (ONOO̅), which can induce DNA fragmentation by oxidative damage, and block protein phosphorylation by tyrosine nitration (13).

Source specificity of calcium-induced neurotoxicity and post-synaptic mechanisms of glutamate-mediated excitotoxicity

Calcium-mediated neurotoxicity is strictly linked to the entry point of the ion. In fact, if calcium enters the cell through the L-type voltage-sensitive calcium channels, there is no cell damage. Conversely, if equivalent increases in intracellular calcium are caused by glutamate-induced stimulation of the NMDA receptor, remarkable neurotoxicity is observed (14). This observation has led to the “source-specificity” hypothesis, which proposes that rate-limiting enzymes or substrates responsible for excitotoxicity must be co-localized with NMDA receptors. This initial intuition was subsequently developed, showing that NMDA receptors are linked to downstream molecular complexes located beneath the post-synaptic membrane, termed post-synaptic densities (PSDs). PSDs incorporate numerous scaffolding and cytoskeletal proteins, as well as modulatory enzymes; this assembly of “mediators” physically couples the NMDA receptor to downstream signaling enzymes, ultimately mediating the specific cellular responses to calcium ions (15). A major role, in this framework, is played by protein PSD-95, which connects GluN2 sub-units of the NMDA receptor to intracellular proteins and signaling enzymes. Through this interaction with PSD-95, GluN2 subunits can regulate the intracellular pathways involved in neuronal survival or death (16).

Glutamate excitotoxicity in the pathogenesis of Parkinson’s disease

Excessive stimulation of glutamate receptors – due to either increased release or decreased removal of glutamate – may play a role in neurological conditions, such as stroke and brain trauma. This form of direct excitotoxicity was initially proposed as a causative factor in neurodegenerative disorders, too. However, it soon became apparent that this mechanism is unlikely to play a major role.
role in chronic disorders such as PD. The brain is remarkably resistant to the potential toxicity of glutamate, thanks to a highly efficient uptake system, which rapidly removes any excess amino acid from the synaptic cleft. Rapid and massive increases in glutamate levels are, therefore, required to overcome the adaptive defenses of the brain and cause neuronal damage. This may be what occurs in hypoxic/ischemic brain damage, which is associated with large increases in extracellular glutamate and marked depression of the glutamate uptake system (17), but not in PD. Nevertheless, it has been repeatedly proposed that glutamate-mediated excitotoxicity may contribute to PD pathogenesis (18); this issue has been addressed in innumerable experimental studies, some of which have also proposed neuroprotective properties for compounds acting on glutamate receptors (Table I); these results, however, have not been confirmed in the clinical setting. If massive increases in glutamate can be ruled out in PD, alternative mechanisms of excitotoxicity must intervene; as discussed below, these mechanisms may trigger neuronal damage in the presence of enhanced susceptibility of nigrostriatal neurons to the potential toxicity of glutamate.

**Selective vulnerability of the SNc to glutamate-mediated excitotoxicity**

Nigral dopaminergic neurons are selectively vulnerable to excitotoxicity, even in the absence of any major increase in glutamate levels. Various mechanisms may underlie this vulnerability. It has long been known, for example, that bioenergetic defects and excitotoxicity are strictly correlated. Maintenance of membrane polarity requires continuous energy supplementation; therefore, impaired mitochondrial function can cause depolarization (19); under these conditions, the gating function exerted by magnesium is compromised and even non-toxic levels of glutamate become lethal by generating a large calcium influx (20). In the early '90s, these observations formed the basis of the indirect excitotoxic hypothesis (21,22), which postulated that any process impairing a neuron’s ability to maintain normal membrane potential enhances its vulnerability to glutamate toxicity. Substantial experimental evidence supported this hypothesis showing, for example, that inhibition of mitochondrial respiration, both in vitro and in vivo, causes excitotoxic lesions that can be prevented by NMDA antagonists (23). Interesting insights into these mechanisms have been provided, more recently, by studies conducted on rotenone, a fairly common pesticide and the most potent inhibitor of mitochondrial complex I, which causes, in rodents, nigrostriatal degeneration associated with Lewy body-like cytoplasmic inclusions (24). Due to its inhibitory effect on complex I, rotenone is believed to produce most of its damage by generating ROS at mitochondrial level. However, various studies have shown that rotenone can potentiate the cellular responses to glutamate in the SNc, even at low concentrations, thereby increasing the vulnerability of dopaminergic neurons to excitotoxicity (25). In the same way, another environmental toxicant associated with increased risk of developing PD, namely the herbicide paraquat, proved able to increase glutamate toxicity by stimulating glutamate efflux from neurons and thereby increasing calcium influx and formation of nitric oxide (26).

Finally, vulnerability of SNc neurons to glutamate may be enhanced by the presence of dopamine itself, which may amplify glutamate-mediated signal transduction (27).

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**Table I - Neuroprotective effects shown by some compounds acting on ionotropic or metabotropic glutamate receptors in animal models of Parkinson’s disease**

<table>
<thead>
<tr>
<th>Ionotropic receptors</th>
<th>Metabotropic receptors</th>
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<tr>
<td><strong>NMDA antagonists</strong></td>
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<tr>
<td>• Intranigral administra-</td>
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<td>tion of AP7, CPP or MK-801 counteracts both MPTP and 6-OHDA toxicity (42).</td>
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<td>• MK-801 attenuates MPTP-induced dopamine depletion in the striatum and protects nigral dopaminergic neurons (43).</td>
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<td>• Both systemic (44) and intra-subthalamic (37) administration of MK-801 counteract 6-OHDA toxicity on the nigrostriatal pathway.</td>
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<td><strong>Group I antagonists</strong></td>
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<td>• Intracerebroventricular injection of mGluR1 antagonist AIDA [(RS)-1-aminoindan-1,5-dicarboxylic acid] counteracts nigral dopaminergic nerve cell loss induced by MPTP (45).</td>
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<tr>
<td>• Systemic administration of mGluR5 antagonist MPEP [2-methyl-6-(phenylethynyl)-pyridine] counteracts both SNc cell loss and STN metabolic hyperactivity caused by 6-OHDA (44).</td>
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<tr>
<td>• MPEP protects nigrostriatal neurons against MPTP neurotoxicity (46,47).</td>
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<td><strong>Group II agonists</strong></td>
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<tr>
<td>• LY379268 (mGluR2/3 receptor agonists) protects nigrostriatal neurons against MPTP (48) and 6-OHDA (49).</td>
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<tr>
<td><strong>Group III agonists</strong></td>
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<tr>
<td>• Group III agonist L-AP4 (mGluR4/6/7/8) protects the nigrostriatal tract against 6-OHDA toxicity (50).</td>
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<td>• Treatment with PHCCC, a positive allosteric modulator selective for mGluR4, protects against MPTP toxicity (51).</td>
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<tr>
<td>• Co-administration of L-AP4 and MPEP results in robust nigrostriatal neuroprotection against 6-OHDA (52).</td>
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Excitotoxicity may also play a role in the pathogenesis of familial PD, which accounts for 10 to 15% of all PD cases. The most frequent form of early-onset, autosomal recessive PD (PARK2) is characterized by mutations in the parkin gene. Parkin is an E3 ubiquitin ligase that mediates the transfer of ubiquitin tails onto proteins to be eliminated by the ubiquitin-proteasome system. Parkin is also involved in other important cellular functions. For example, in combination with PINK-1, a kinase involved in another form of familial PD (PARK6), parkin plays a major role in the maintenance of mitochondrial integrity and morphology (28). Another role of parkin, recently recognized, is its regulation of the function and stability of excitatory glutamatergic synapses. In the presence of mutated parkin, glutamatergic synapses tend to proliferate, thereby enhancing the synaptic efficacy of glutamate. This inevitably increases neuronal vulnerability to glutamate-mediated excitotoxicity (29). At the nigral level, this phenomenon would generate a state of hypersensitivity to glutamate that, combined with other biochemical defects, such as mitochondrial impairment or proteolytic stress, may trigger the neurodegenerative process.

Subthalamic hyperactivity, excitotoxicity and nigrostriatal damage

PD-related nigrostriatal degeneration triggers a cascade of functional alterations in the basal ganglia circuitry that alters the neuromotor sequences subserving voluntary movements (30). These changes culminate in hyperactivity of the STN, the only glutamatergic driving force within the basal ganglia circuitry (31). Recognition of the central role of STN has led to the development of a surgical approach to PD based on electrical stimulation, at high frequency, of this nucleus (deep brain stimulation or DBS) (32). DBS is now an established procedure in the framework of modern functional neurosurgery (33) and is currently considered a main therapeutic option in selected PD patients.

The primary targets of STN glutamatergic projections are the two segments of the globus pallidus (medial and lateral) and the substantia nigra pars reticulata (2); however, STN projections also target SNc neurons (34) (Fig. 3). Through this latter pathway, in the initial phase of the disease, increased STN activity may enhance the activity of surviving dopaminergic neurons, thereby compensating for the nigral cell loss (35). With disease progression, however, continuous glutamatergic overstimulation of residual SNc neurons may turn into an additional neurotoxic stimulus, further contributing to the underlying neurodegenerative process. On the basis of this premise, earlier studies suggested that reducing or abolishing STN overactivity has neuroprotective effects in animal models of PD (36,37). More recently, it has been demonstrated that silencing of hyperactive STN by chronic DBS increases survival of SNc neurons in 6-OHDA lesioned rats (38). Similar results have been obtained in primates by Wallace et al., who showed that subacute SNc cell loss (~50%) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can be prevented either by kainic acid lesion or high frequency stimulation of the STN (39). The protective effect of STN ablation, however, may be related to the extent of the nigral lesion; indeed, in another study on MPTP-treated monkeys, STN ablation failed to protect the SNc in the presence of a more profound loss of dopaminergic neurons (85%) (40).

The issue becomes more controversial when transposed to the clinical setting. It is well established that DBS induces prolonged, substantial amelioration of motor symptoms, although the intrinsic mechanisms underlying the beneficial effects of DBS are still incompletely understood; on the other hand, the results of studies evaluating medium- to long-term follow ups of operated patients, including a recent study reporting results of a five-year follow up (41), indicate that, notwithstanding the symptomatic effects of the procedure, the disease continues to progress. Thus, the neuroprotective effects shown by DBS in the animal model of PD have not been confirmed, at least so far, in humans.

Concluding remarks

Although excitotoxicity is unlikely to act as a single causative agent in PD pathogenesis, glutamate-mediated effects may contribute, in a more subtle way, to the mechanisms that trigger the neurodegenerative process in the SNc. Nigral dopaminergic neurons are particularly sensitive to the neurotoxic potential of glutamate, as...
they are selectively sensitive to other agents, such as rotenone or paraquat, which act as mitochondrial toxins or pro-oxidant agents. It is, therefore, likely that syner-
gistic interactions – between mitochondrial defects, ox-
idative stress and glutamatergic stimulation – take place at the SNc level. These interactions may create the con-
itions for the development of the nigrostriatal damage that characterizes PD.

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