Practice points:

- Whereas the gold standard in the therapy of Parkinson’s disease is dopamine supplementation, it fails to exert a disease-modifying effect and can be associated with severe motor complications.

- Alterations in the glutamatergic neurotransmission contribute to the neurodegenerative process and to the development of motor symptoms in Parkinson’s disease.

- Amantadine alone or in combination with AMPA receptor blockers ameliorates levodopa-induced dyskinesias.

- Memantine might be beneficial for the cognitive impairment and dementia in Parkinson’s disease patients. Moreover, some data point to its possible beneficial effect in motor symptoms and dyskinesias. Further studies are needed to assess its efficacy.

- In animal models, riluzole offered neuroprotection, but the clinical trials to date have not reproduced this beneficial effect. However, further randomized controlled trials with greater numbers of patients are worth considering.

- The kynurenine pathway of the tryptophan metabolism involves both neuroprotective and neurotoxic compounds, and alterations in their delicate balance may be connected with neurodegenerative processes. Elevation of the level of the NMDA antagonist kynurenic acid might be a possible novel disease-modifying therapeutic tool and also of use for the management of levodopa-induced dyskinesias.
**Summary:** Oral levodopa is the current baseline therapy in the management of Parkinson’s disease, but non-motor complications and therapy-related dyskinesias pose an important challenge for clinicians. Glutamate receptors have been implicated in the neurodegenerative process of Parkinson’s disease and also in the development of levodopa-induced dyskinesias. This article will discuss the role of NMDA receptors in Parkinson’s disease and their modulation as a possible therapeutic approach.

1. Introduction

Parkinson’s disease (PD), the second most common progressive neurodegenerative disorder, is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Dopamine replacement with oral levodopa, the gold standard in PD therapy, offers symptomatic relief to the patients, but it is associated with the development of dyskinesias and it also fails to exert a disease-modifying effect. Levodopa-induced dyskinesia (LID) is an important cause of disability in PD patients, thereby posing a major challenge in the clinical management. Although the current widespread use of dopamine receptor agonists may delay the onset of LID, it will occur at a later time point in consequence of the progressive loss of the nigrostriatal dopaminergic function. Dopamine receptor agonists are additionally associated with a higher risk of non-motor complications, including impulse-control disorders[1], and also fail to modify the disease progression, so that extensive research is still required to find neuroprotective strategies. Glutamate, the main excitatory neurotransmitter in the human brain, has been implicated in the pathophysiology of PD at multiple levels. Alterations in the glutamatergic neurotransmission may contribute to the neurodegenerative process and to the motor symptoms of PD, while evidence from animal models further supports a connection with the development of LID[2]. Glutamate receptors may therefore be a potential therapeutic target for drug development. A number of compounds that are capable of influencing the glutamatergic neurotransmission are already under investigation in clinical trials, while some potential molecules have as yet received less attention. The kynurenine pathway (KP) of the tryptophan metabolism produces both an
NMDA agonist and an antagonist, and influencing this metabolic route could therefore offer a valuable therapeutic strategy.

2. Glutamate and NMDA receptors in the pathogenesis of PD

Glutamate, the main excitatory neurotransmitter in the central nervous system (CNS), exerts its effects through ionotropic and metabotropic receptors. The ionotropic receptors comprise three distinct subtypes, each of which bears the name of its preferred agonists: N-methyl-D-aspartate (NMDA), kainate and \( \alpha \)-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA). NMDA receptors are involved in such physiological functions as cognition and memory processes. However, these receptor subtypes have gained considerable attention because of their key role in excitotoxic processes, as their overactivation results in an excessive calcium influx into the cells and finally leads to neuronal injury. Excitotoxic processes have been demonstrated to contribute to the pathomechanism of both acute and chronic neurological diseases (e.g. ischemic stroke, Alzheimer’s disease (AD) or Huntington’s disease (HD)). Glutamate excitotoxicity has been suggested to contribute to the pathogenic process in PD too, enhancing the effects of oxidative stress and a mitochondrial dysfunction[3]. Extensive research is therefore under way with the aim of finding neuroprotective strategies, and NMDA receptors are one of the main targets for drug development.

LID is considered to be the most important therapy-related complication of PD, as it has a deteriorating effect on the quality of life of PD patients. The main pathogenic factors in the development of LID are the progressive decrease of the nigrostriatal dopamine storage capacity related to the disease severity, and the discontinuous stimulation of neurons by levodopa[4]. These factors result in downstream changes in gene expression and protein...
synthesis, alterations in the mean neuronal firing rate, and reduced activity in specific brain regions, finally leading to an abnormal motor cortex activity underlying LID [4-6]. Another important feature in the pathogenesis of LID is the altered glutamatergic neurotransmission. The increased activity of glutamate receptors, and the hyperphosphorylation of NMDA receptors have been confirmed in several animal studies [7, 8]. A growing body of evidence supports the notion that in PD and LID synaptic alterations occur in the distribution, subunit composition and phosphorylation of NMDA receptors [9-11]. A study involving a rat model of PD has demonstrated that the extracellular glutamate level and the gene expression of the glial glutamate transporter GLT1 are significantly increased after chronic levodopa administration[12]. Human PET investigations have provided evidence of enhanced NMDA receptor activity in specific motor cortical areas of the brain of dyskinetic PD patients after levodopa administration[13]. All these findings point to the role of a relatively enhanced glutamatergic activity in LID, thereby giving a rationale for the use of glutamate receptor inhibitors in the management of PD and LID.

3. NMDA receptors as potential therapeutic targets

Targeting NMDA receptors might offer multiple benefits in the clinical management of PD, as a substantial amount of evidence suggests that alterations in the glutamatergic neurotransmission and in the glutamate receptor function may be involved in the neurodegenerative process and in the development of the motor complications of PD. Preclinical studies have indicated that different selective and non-selective glutamate receptor inhibitors may improve the motor symptoms and dyskinesia in PD. As glutamatergic alterations have been implicated in the development of levodopa-induced motor complications, the idea of glutamatergic inhibition emerged early, and a number of glutamate
antagonists have been investigated. However, to date only the weak NMDA antagonist amantadine has become widely applied for the treatment of dyskinesias; the use of other NMDA antagonists in PD is limited.

3.1. Amantadine

Amantadine has been demonstrated to improve LID symptoms both in the form of acute intravenous administration, and also as chronic treatment [14-16]. Earlier authors debated the achievement of a sustained effect of amantadine for LID, but a recent study provided evidence that the beneficial effect of amantadine treatment for motor complications in PD remains even after 1 year of continuous therapy, while drug withdrawal results in a worsening of the dyskinesia [17].

NMDA antagonists may cause adverse side-effects, and determination of the minimal effective and tolerable dose is therefore an important question in the clinical management. Combination therapies may offer a solution, and result in even better symptom relief. Bibbiani et al. demonstrated in different animal models that combination therapy with amantadine and an AMPA receptor blocker led to a significant reduction in levodopa-induced motor complications. They also concluded that through the use of combination therapy, lower doses may be sufficient to relieve the symptoms [18]. The benefits of the combination therapy of LID with amantadine and an AMPA-receptor antagonist were likewise demonstrated by another animal study: topiramate exerted a synergistic effect with amantadine, and their combination attenuated the dyskinesia more effectively than did either drug alone [19].

3.2. Memantine

Memantine, another well-known NMDA antagonist, is generally recognized as effective for the therapy of AD. The presumption of the beneficial effects of memantine for the dementia associated with PD has been confirmed by several randomized controlled studies [20-22].
Moreover, memantine therapy may improve not only the cognitive impairment, but also the motor symptoms of PD. Interestingly, the impact of memantine correlated with the serum homocysteine level [23]. Another surprising observation from case reports was that memantine was also able to improve levodopa-induced motor complications [24, 25]. This observation related to only a small number of patients, and therefore far-reaching consequences cannot be drawn. However, this observation is in accordance with the preclinical data concerning the glutamatergic alterations in the pathomechanism of LID. Further randomized-controlled studies on larger populations will assess the efficacy of memantine for the management of levodopa-induced motor complications.

3.3. Riluzole
Riluzole, an inhibitor of glutamate release, has been investigated in both preclinical and clinical studies. In a primate model of PD, riluzole treatment proved to be neuroprotective and to reduce behavioral changes [26]. In other animal models, riluzole was capable of slowing down the disease progression and delaying the onset of motor abnormalities [27]. Unfortunately, the results of clinical studies did not reflect the promising preclinical results [28]. Certain beneficial effects relating to the disease progression and the duration of the „ON“ state were observed in riluzole-treated patients, but these changes did not reach the level of statistical significance [29, 30]. This could probably be attributed to the small numbers of patients enrolled in those studies, and further randomized trials on larger populations therefore appear reasonable for a further assessment of the efficacy of riluzole in PD.

3.4. Kynurenines
The KP is the main metabolic route of tryptophan degradation. The intermediates produced in this enzymatic cascade, collectively termed kynurenines, include several neuroactive metabolites (Fig. 1). The first step in the KP is the enzymatic degradation of tryptophan by
tryptophan 2,3-dioxygenase or indoleamine 2,3-dioxygenase. The key molecule in this pathway is L-kynurenine (KYN), which can be metabolized in two alternative ways. The first branch in the KP involves the formation of kynurenine acid (KYNA) by different subtypes of kynurenine-aminotransferases (KATs). Four types of KATs have been identified so far, each with slightly different biochemical properties[31]. The other main pathway of KYN degradation is catalyzed by kynurenine-3-monooxygenase (KMO) to form 3-hydroxykynurenine (3-OH-KYN), which is then further degraded in multiple enzymatic steps to form the neurotoxic quinolinic acid (QUIN). KYNA displays broad-spectrum endogenous antagonistic properties on ionotropic excitatory amino acid receptors of NMDA, AMPA and kainate types, and it is also a non-competitive inhibitor of 7-nicotinic acetylcholine receptors[32-34]. More recent studies have provided evidence that KYNA exerts a dose-dependent effect on the AMPA receptors: in low concentrations it facilitates these receptors, while in a higher concentration range it antagonizes them[35]. KYNA has also been described as a ligand of the G-protein-coupled receptor GPR35[36]. The multiple modes of action highlight the complex roles of KYNA in the CNS, suggesting an important regulatory function in neurotransmission, and it has been also implicated in the modulation of excitotoxic processes and neurodegeneration. On the other hand, the metabolites produced in the other branch of the KP contribute to free radical production and glutamate excitotoxicity.

Alterations in the KP are thought to play an important role in the pathogenesis of neurodegenerative disorders, such as HD or PD[37, 38]. KYNA, so far the only known endogenous neuroprotective agent, exerts its effects by inhibiting NMDA receptors and it
attenuates glutamate-mediated excitotoxicity. Another important effect is the inhibition of 7-
icotinic acetylcholine receptors, which results in a decrease in the extracellular glutamate
level, and secondarily in a reduced extracellular dopamine concentration [39, 40]. Animal
models of PD have demonstrated decreased KAT activity and lower KYNA levels in specific
brain regions, which may be linked to the neurodegenerative process [41-43]. Likewise,
human post-mortem studies have revealed decreased KYNA levels in the frontal cortex,
putamen and SNpc of PD patients, whereas the 3-OH-KYN level was elevated[44]. These
observations may lead to the assumption that a shift in the KP toward the formation of toxic
compounds and the lower availability of the neuroprotective KYNA may contribute to the
neurodegenerative process underlying the pathomechanism of PD. In accordance with this,
injection of the NMDA antagonist KYNA in an experimental PD model alleviated the 1-
methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonian symptoms[45].
However, the systemic administration of KYNA is limited because of its poor ability to cross
the blood-barin barrier[46]. In contrast, coadministration of KYN, the prodrug of KYNA,
together with the organic acid transport inhibitor probenecid resulted in an elevation of the
KYNA level and offered neuroprotection in a 6-hydroxydopamine (6-OHDA) model of PD
[47]. Another possible method is the synthesis of KYNA derivatives with better
pharmacological properties. Acuña-Castroviejo et al. demonstrated the neuroprotective effects
of synthetic kynurenines capable of NMDA antagonism in a MPTP-induced PD model [48].
Another synthetic KYNA-derivative, N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-
carboxamide hydrochloride, offered neuroprotection and ameliorated the symptoms in a HD
animal model, suggesting that its effects in other neurodegenerative disorders would also be
worthy of further investigation[49].

The inhibition of KMO causes a shift in the KP toward the formation of the NMDA antagonist
KYNA, while the production of neurotoxic metabolites is decreased. KMO inhibitors resulted
in elevated KYNA level and gave rise to beneficial effects in the prevention or reduction of LID, while they did not attenuate the antiparkinsonian effect of levodopa; these effects were associated with the modulation of NMDA receptors [50, 51].

Conclusions and future perspectives

The clinical management of PD patients is often challenging, because the symptoms arising from progression of the disease from the therapy-induced complications have to be addressed in parallel. At present there is no effective therapeutic strategy with which to modify the disease progression. Dementia (an important non-motor complication of PD) and LID are important features which exert a deteriorating effect on the quality of life of PD patients. Glutamate-mediated excitotoxicity is suggested to be involved both in the neurodegenerative process, and in the pathomechanism of the motor and non-motor complications. NMDA receptor inhibitors might therefore be a valuable target for the development of neuroprotective strategies, and the amelioration of the motor and non-motor complications. Some of the well-known NMDA inhibitors have already been shown to display beneficial effects in preclinical and clinical studies; however, the clinical data are in many cases controversial. Further large clinical trials are therefore needed to assess the efficacy of these drugs. Targeting the KP might offer promising candidates for drug development.


23. Litvinenko Iv, Odinak Mm, Mogil'naya Vi, Perstnev Sv: Use of memantine (akatinol) for the correction of cognitive impairments in Parkinson's disease complicated by dementia. *Neurosci Behav Physiol* 40(2), 149-155 (2010).


Fig. 1. The kynurenine pathway