Kynurenines in Parkinson's disease: therapeutic perspectives

Dénes Zádori[1], Péter Klivényi[1], József Toldi[2], Ferenc Fülöp[3], László Vécsei[1*]

[1]*Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of Szeged, Semmelweis u. 6, H-6725 Szeged, Hungary*

[2]*Department of Physiology, Anatomy and Neuroscience, University of Szeged, Közép fasor 52, H-6726 Szeged, Hungary*

[3]*Department of Pharmaceutical Chemistry, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary*

[*]Author for correspondence: László Vécsei, MD, PhD, DSc, Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of Szeged, Semmelweis u. 6., H-6725 Szeged, Hungary; Phone: +36 62 545348; Fax: +36 62 545597; E-mail: vecsei.laszlo@med.u-szeged.hu

Run-in heading: Kynurenines and Parkinson's disease

Abstract

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder the pathomechanism of which is not yet fully known. As regards the molecular mechanism of development of the disease, oxidative stress/mitochondrial impairment, glutamate excitotoxicity and neuroinflammation are certainly involved. Alterations in the kynurenine pathway, the main pathway of the tryptophan metabolism, can contribute to the complex pathomechanism. There are several possibilities for therapeutic intervention involving targeting of this altered metabolic route. The development of synthetic molecules that would shift the altered balance towards the achievement of neuroprotective effects would be of great promise for future clinical studies on PD.

Keywords: Parkinson's disease, excitotoxicity, oxidative stress, neuroinflammation, kynurenines, neuroprotection, therapy

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder originally described by James Parkinson in 1817 (Parkinson, 1817), but the 4 cardinal symptoms were delineated over 120 years before in a Hungarian medical text by Ferenc Pápai Páriz (Papai Pariz, 1690; Bereczki, 2010). The disease affects approximately 0.2% of the population on average, but the prevalence rises steeply with increasing age, reaching more than 4% at 85 years of age (de Rijk *et al.*, 2000). Most of the cases are considered to be sporadic with uncertain aetiology, and attention is drawn to the possible role of environmental risk factors; and the underlying genetic mutation could recently be determined in only some 10% of the cases (reviewed by de Lau and Breteler, 2006). The deteriorated functioning of several genes and gene products has been identified (reviewed by Bekris *et al.*, 2010), e.g. that of α-synuclein (PARK1/PARK4; Polymeropoulos *et al.*, 1996, Farrer *et al.*, 1999), parkin (PARK2; Matsumine *et al.*, 1997), phosphatase and tensin homologue [PTEN]-induced putative kinase 1 [PINK1] (PARK6; Valente *et al.*, 2001), DJ-1 (PARK7; van Duijn *et al.*, 2001), leucine-rich repeat kinase 2 [LRRK2] (PARK8; Funayama *et al.*, 2002), high-temperature requirement protein A2 [HtrA2]/Omi (PARK13; Strauss *et al.*, 2005) and human leukocyte antigen [HLA]-DRA (PARK18; Hamza *et al.*, 2010). Clinically, PD can mainly be characterized by motor symptoms, such as resting tremor, rigidity, brady- and hypokinesia and postural instability, but cognitive, psychiatric, autonomic and sleep disturbances also develop (reviewed by Rodriguez-Oroz *et al.*, 2009). The main pathological hallmark of PD is a loss of brain stem catecholaminergic, and especially mesencephalic dopaminergic (DA-ergic) neurons in the substantia nigra pars compacta (SNpc), and the presence of Lewy bodies (intracytoplasmic inclusions, the main component of which is α-synuclein) and Lewy neurites in the vulnerable population of neurons (Braak *et al.*, 2003). The consequential decrease in DA content, mainly in the striatum, has the result that the brain is no longer capable of adequate control of the motor functions (reviewed by Rodriguez-Oroz *et al.*, 2009).

2. Some of the main aspects of the pathogenesis in Parkinson's disease

2.1. Oxidative stress and mitochondrial dysfunction

The development of animal models of toxin-induced parkinsonism drew attention to the roles of oxidative stress and a mitochondrial dysfunction in PD and to the pathogenetic potency of environmental risk factors (reviewed by Beal, 2001; Bove *et al.*, 2005). The neurotoxic effects of 6-hydroxy-DA (6-OHDA) on central nervous system (CNS) catecholaminergic neurons were described in 1968 (Ungerstedt, 1968). As 6-OHDA crosses the blood-brain barrier (BBB) only poorly, specific damage to the nigrostriatal DA-ergic pathway is achieved by stereotaxic injection of the toxin into the SN, the medial forebrain bundle or the striatum (Javoy *et al.*, 1976). It destroys catecholaminergic structures through the combined action of reactive oxygen intermediates (ROI) and quinones (Cohen, 1984). Shortly after the observation in humans of the parkinsonism-inducing effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a product of meperidine analogue synthesis (Langston *et al.*, 1983; Langston and Ballard, 1983), it became the most widely used animal model of PD (Hallman *et al.*, 1984). As this compound readily penetrates the BBB, its systemic administration is most common. It exerts its toxic effects through its metabolite, 1-methyl-4-phenylpyridinium ion (MPP^+; Chiba *et al.*, 1984; Langston *et al.*, 1984), which has been shown to be capable of the selective inhibition of complex I of the mitochondrial electron transport chain (ETC; Nicklas *et al.*, 1985; Mizuno *et al.*, 1987). After freely penetrating cellular membranes, the natural cytotoxic compound rotenone, widely used as a commercial pesticide and insecticide, can accumulate in the mitochondria; like MPP^+, it also inhibits complex I of the ETC (Betarbet *et al.*, 2000; Schuler and Casida, 2001). In contrast with the previously described two models, proteinaceous inclusions, immunoreactive for α-synuclein, can be detected in the remaining SNpc neurons in rotenone-infused rats (Betarbet *et al.*, 2000). The potent herbicide paraquat, which is structurally somewhat similar to MPP^+, can also be used in animal modelling of PD, due to its ROI-producing action (Brooks *et al.*, 1999; McCormack *et al.*, 2002). These findings are consistent with the observation that a decrease in complex I activity has been

described in the SN and platelets of PD patients (Reichmann and Riederer, 1989; Schapira *et al.*, 1989). However, there are some inconsistencies in the currently available experimental data (reviewed by Banerjee *et al.*, 2009). As concerns the role of underlying genetic PD mutations in oxidative stress, some of them have a proved effect on the mitochondrial function under normal or pathological conditions. The mitochondrial accumulation of α-synuclein in human DA-ergic neurons can result in increased ROI generation (Devi *et al.*, 2008), while a parkin dysfunction can lead to a decreased mitochondrial antioxidant capacity (Yang *et al.*, 2007). PINK1 can inhibit oxidative stress-induced apoptosis by reducing cytochrome release from the mitochondria (Kim *et al.*, 2008). Regulation of the proteolytic activity of HtrA2/Omi (e.g. due to phosphorylation by PINK1) may result in resistance to mitochondrial stress (Plun-Favreau *et al.*, 2007). The dysfunction of DJ-1, which exhibits atypical peroxiredoxin-like peroxidase activity, may result in impaired mitochondrial ROI scavenging (Andres-Mateos *et al.*, 2007). It has also been demonstrated that the LRRK2(G2019S) mutation, which is the most common identifiable cause of PD, results in decreases in both mitochondrial membrane potential and total intracellular adenosine-triphosphate level in mutation carriers (Mortiboys *et al.*, 2010).

2.2. Glutamate excitotoxicity

DA-ergic neurons in the SNpc possess glutamate receptors and they receive extensive glutamatergic innervation from the subthalamic nucleus (the main input), cerebral cortex, amygdala and pedunculopontine and laterodorsal tegmental nuclei (reviewed by Misgeld, 2004). Although oxidative stress and mitochondrial impairment seem to be the predominant causative factors in the development of PD, glutamate excitotoxicity also has an important role in the pathogenesis of the disease. There are synergistic interactions between mitochondrial defects, oxidative stress and glutamatergic stimulation (reviewed by Blandini, 2010). The latter may be secondary to the former, because evidence has recently been provided that chronic MPTP treatment results in the dysregulation of glutamate homeostasis (Meredith *et al.*, 2009; commented on by Caudle and Zhang, 2009). The striatal hypo-DA-ergic status due to the metabolic compromise leads to overactivation of the subthalamic nucleus. This may result in increased glutamate release onto the compromised DA-ergic neurons in the SNpc

(Rodriguez *et al.*, 1998), setting up an excitotoxic cascade that further worsens the neurodegenerative process. One of the main events during glutamate excitotoxicity is a cytosolic calcium overload, which results in calmodulin activation and nitric oxide ($NO^{\cdot}$) production through neuronal $NO^{\cdot}$ synthase (nNOS; reviewed by Bredt, 1999). When produced in excess, $NO^{\cdot}$ is capable of inhibiting the ETC in a concentration-dependent manner (reviewed by Brown, 2010). There is a mitochondrial isoform of NOS (i-mtNOS) in the SNpc, which can be rapidly induced during the inflammation accompanying the pathologic cascade events (Escames *et al.*, 2003).

2.3. Neuroinflammation

The observation that reactive microglia expressing HLA-DR and cluster of differentiation (CD) 11b are present in PD patients (McGeer *et al.*, 1988) drew attention to the possible role of neuroinflammation in the development of the disease (reviewed by Chung *et al.*, 2010; Glass *et al.*, 2010). Furthermore, increased levels of cytokines have been observed in the nigrostriatal region of post-mortem brains and/or cerebrospinal fluid of patients with sporadic PD and in both 6-OHDA and MPTP models of PD (Mogi *et al.*, 1994; Mogi *et al.*, 1996; reviewed by Nagatsu and Sawada, 2005). Aggregated, nitrated and oxidized forms of α-synuclein have been found to accentuate microglial activation, and the α-synuclein leaving the cells is phagocytosed by microglia and leads to the release of proinflammatory cytokines (Zhang *et al.*, 2005; Reynolds *et al.*, 2008). Thus, there are strong connections between oxidative stress and glutamate excitotoxicity, and between oxidative stress and neuroinflammation (Fig. 1). It has been observed, for instance, that the internalization of α-synuclein is followed by ROI production (Zhang *et al.*, 2005). As regards the possible role of other immune cells in the development of the disease, it was recently reported that $CD4^{+}$ and $CD8^{+}$ T lymphocytes are present in post-mortem PD brains (Brochard *et al.*, 2009). Indeed, $CD4^{+}$-deficient mice were resistant to MPTP toxicity.

3. The possible contribution of alterations in the kynurenine pathway to the development of Parkinson's disease

3.1. Background

The kynurenine pathway is the main pathway of the tryptophan (TRP) metabolism, serving as a route to nicotinamide adenine dinucleotide (NAD^+) production (reviewed by Schwarcz, 1993; Stone, 1993; Vecsei, 2005). More than 95% of the TRP is metabolized through this pathway (Wolf, 1974). The central intermediate of the pathway is L-kynurenine (L-KYN), which can be metabolized to neuroactive compounds such as kynurenic acid (KYNA) and 3-hydroxy-L-kynurenine (3-OH-L-KYN), and in further steps to quinolinic acid (QUIN). In the CNS, 40% of the L-KYN is formed locally, while 60% is taken up from the periphery (Gal and Sherman, 1978), as it can readily cross the BBB (Fukui *et al.*, 1991). KYNA is formed by the irreversible action of four subtypes of kynurenine aminotransferases (KATs; Okuno *et al.*, 1991; Yu *et al.*, 2006; Guidetti *et al.*, 2007; reviewed by Han *et al.*, 2010). The main KYNA-producing enzyme in the rat and human brains is KAT-II, while in the mouse brain it is the mitochondrial aspartate aminotransferase (mitAAT, also called KAT-IV; Guidetti *et al.*, 2007). The KATs are mainly expressed in the astrocytes (Guillemin *et al.*, 2001); in fact, the expression of KAT-II is entirely confined to this cell type, while the neurons display only weak granular staining (Roberts *et al.*, 1992). The neuronal expression of KAT-I appears to have effects on developmental processes, such as programmed cell death (Csillik *et al.*, 2002). 3-OH-L-KYN is produced through the action of kynurenine 3-hydroxylase (Battie and Verity, 1981), while the formation of QUIN is mediated by 3-hydroxyanthranilate 3,4-dioxygenase (Foster *et al.*, 1986). The branch responsible for the production of the above metabolites is mainly localized in the microglia and macrophages (Espey *et al.*, 1997). Of these two enzymes, the astrocytes express only 3-hydroxyanthranilate 3,4-dioxygenase (Guillemin *et al.*, 2001). As regards the action of neuroactive kynurenines, KYNA has been demonstrated to be a glutamate antagonist (Perkins and Stone, 1982). In micromolar concentrations it acts as an antagonist at the strychnine-insensitive glycine-binding site of the N-methyl-D-aspartate (NMDA)

receptor (Kessler *et al.*, 1989), and it also seems to be capable of facilitating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor responses (Prescott *et al.*, 2006; Rozsa *et al.*, 2008). In contrast with this finding, it was earlier demonstrated that KYNA can exert weak antagonistic effects on the AMPA and kainate receptors (Birch *et al.*, 1988). It can also exert non-competitive blockade on the α7-nicotinic acetylcholine receptors (Hilmas *et al.*, 2001), presynaptic activation of which can accentuate glutamate release (Marchi *et al.*, 2002). It was also described that KYNA can activate G protein-coupled receptor GPR35, inducing the production of inositol triphosphate and Ca^{2+} mobilization, however the expression of GPR35 in the brain is very low, so its role in CNS processes is questionable (Wang *et al.*, 2006). Furthermore, it was also demonstrated that KYNA additionally reduces inflammatory responses at the periphery (Varga *et al.*, 2010) or in human leukocytes (Tiszlavicz *et al.*, 2011). As concerns the toxic effects of QUIN, besides its direct activation on NMDA receptors (Stone and Perkins, 1981), or the release and uptake inhibition of glutamate (Connick and Stone, 1988; Tavares *et al.*, 2002), it has neurotoxic effects through lipid peroxidation (Rios and Santamaria, 1991) or ROI production (Behan *et al.*, 1999). The toxic effects of 3-OH-L-KYN are solely mediated through free radical production (Eastman and Guilarte, 1990; Okuda *et al.*, 1998).

3.2. Alterations in the kynurenine system in Parkinson's disease

Alterations in the kynurenine metabolism may be involved in the development of PD (Fig. 1; reviewed by Nemeth *et al.*, 2006; Zadori *et al.*, 2009). KYNA levels have been demonstrated to be decreased in the frontal cortex, putamen and SNpc of patients with PD (Ogawa *et al.*, 1992) and, accordingly, both MPTP (Knyihar-Csillik *et al.*, 2004) and 6-OHDA treatments (Knyihar-Csillik *et al.*, 2006) resulted in diminished KAT-I immunoreactivity in the SNpc of mice. Furthermore, MPP^+ treatment decreased the KAT-II activity considerably in rat cerebral cortical slices, with a resulting decrease in KYNA concentration (Luchowski *et al.*, 2002). In contrast, 3-OH-L-KYN levels have been found to be elevated in human post-mortem brain samples, probably contributing to the oxidative damage (Ogawa *et al.*, 1992). A disturbance of the kynurenine metabolism in the periphery has also been demonstrated in PD (Hartai *et al.*, 2005).

4. Possibility of therapeutic intervention by modulation of the kynurenine system

There are several possibilities for restoration of the altered kynurenine metabolism in neurological disorders, including PD (reviewed by Stone and Darlington, 2002; Kincses and Vecsei, 2010; Zadori *et al.*, 2011b). One therapeutic strategy would be to increase the level of endogenous KYNA. Pretreatment with KYNA attenuated MPP^+-induced neuronal cell death *in vitro* in a human dopaminergic neuroblastoma cell line (Lee do *et al.*, 2008). In *in vivo* experiments, the co-infusion of exogenous KYNA with either NMDA or QUIN into the SNpc preserved the activity of striatal tyrosine hydroxylase (probably the most important and rate-limiting enzyme in DA production) (Miranda *et al.*, 1997). The direct injection of KYNA into the globus pallidus internus also resulted in beneficial effects against the toxic effects of MPTP (Graham *et al.*, 1990; Butler *et al.*, 1997). However, the systemic administration of KYNA cannot be selected for therapeutic purposes, as it crosses the BBB poorly (Fukui *et al.*, 1991). Furthermore, it undergoes rapid clearance from the brain and the body, mediated by organic anion transporters (Bahn *et al.*, 2005). Through use of the natural BBB-penetrable prodrug L-KYN, the former limiting factor might be overcome. However, the KYNA produced can easily be cleared from the brain. Accordingly, L-KYN did not afford any protection in the MPTP model of PD in our experiments (unpublished data). However, when combined with probenecid, an inhibitor of organic acid transport, L-KYN was able to exert protective effects in the 6-OHDA model of PD (Silva-Adaya *et al.*, 2011). Furthermore, when the administration of L-KYN and probenecid was supplemented with nicotinylalanine, an agent that inhibits the activity of both kynurenine 3-hydroxylase and kynureninase (thereby decreasing the formation of toxic metabolites), beneficial effects could also be seen against the NMDA and QUIN-induced excitotoxicity in the SNpc, through elevated KYNA levels (Miranda *et al.*, 1997). Numerous synthetic derivatives of both L-KYN and KYNA have been designed to achieve improved pharmacological properties (reviewed by Stone, 2000; Schwarcz, 2004; Fulop *et al.*, 2009). Synthetic kynurenines capable of reducing glutamate release, NMDA activation and NOS activity (Leon *et al.*, 1998a; Leon *et al.*, 1998b; Leon *et al.*, 2000; Camacho *et al.*, 2002) exhibited

beneficial effects in the MPTP model of PD (Acuna-Castroviejo *et al.*, 2011). Another promising L-KYN derivative is 4-Cl-L-KYN, the BBB-penetrable prodrug of a 7-Cl-KYNA, a more selective glycine/NMDA inhibitor than KYNA (Reggiani *et al.*, 1989). Somewhat surprisingly, however KYNA, but not 7-Cl-KYNA, afforded protection against the toxic effects of MPP^+ in the rat striatum (Merino *et al.*, 1999). This might be explained in that KYNA perhaps exerts broader anti-excitotoxic action than 7-Cl-KYNA. However, in addition to 7-Cl-KYNA formation, 4-Cl-L-KYN can also be metabolized to 4-Cl-hydroxyanthranilate, a powerful inhibitor of QUIN synthesis (Parli *et al.*, 1980), extending the modes of neuroprotective action, with resultant prevention of QUIN-induced neurotoxicity in the rat hippocampus (Wu *et al.*, 2000) and rat striatum (Guidetti *et al.*, 2000). Nevertheless, it should be mentioned that the inhibition of kynurenine 3-hydroxylase would rather selected, as the blockade of 3-hydroxyanthranilate 3,4-dioxygenase activity may result in the accumulation of 3-hydroxyanthranilate, which has neurotoxic properties (Fornstedt-Wallin *et al.*, 1999). Accordingly, several small-molecule enzyme inhibitors have been designed (reviewed by Schwarcz and Pellicciari, 2002; Kiss and Vecsei, 2009). In MPTP-treated non-human primates, the kynurenine 3-hydroxylase inhibitor 3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide (Ro 61-8048) increased the serum L-KYN and KYNA levels and decreased the incidence of L-DOPA-induced dyskinesias, but did not affect the antiparkinsonian effect of L-DOPA (Gregoire *et al.*, 2008; Ouattara *et al.*, 2009). Various KYNA derivatives have also been designed to achieve neuroprotection. One group of these compounds comprises the KYNA amides (reviewed by Fulop *et al.*, 2009). Some KYNA amides are capable of the selective inhibition of the NR2B subunit-containing NMDA receptors (Borza *et al.*, 2007), which play an important role in glutamate excitotoxicity (Liu *et al.*, 2007). One KYNA amide, *N*-(2-*N*,*N*-dimethylaminoethyl)-4-oxo-1*H*-quinoline-2-carboxamide hydrochloride, has considerable *in vivo* stability (Zadori *et al.*, 2011a). When its effects were compared those of KYNA in an *in vitro* electrophysiological study, it proved to behave similarly to KYNA (Marosi *et al.*, 2010), while in experimental models of inflammation it displayed greater anti-inflammatory effects than those of KYNA (Varga *et al.*, 2010; Tiszlavicz *et al.*, 2011). It appears to be a promising candidate for drug development in neurodegenerative disorders, and it has already been

found protective in a transgenic animal model of Huntington's disease (Zadori *et al.*, 2011c).

5. Conclusions

The underlying pathomechanism in PD is currently undergoing thorough investigation. Although the exact genetic basis can be identified in only a small proportion of the cases, there are a number of environmental risk factors which are presumed to contribute to the development of PD. Recent research advances relating to pathogenetic factors in PD have confirmed close interactions between oxidative stress/mitochondrial dysfunction, glutamate excitotoxicity and neuroinflammation. Alterations in the kynurenine metabolism are surely involved in this complex pathogenetic circuitry. Drug development targeting this altered metabolic route may therefore deserve special attention. The recently available preclinical results are reasonably promising, and the time appears to be approaching for consideration of the design of well-planned clinical studies.

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Figure captions

Fig.1 The connection between the main aspects of PD pathogenesis. Neuroactive metabolites of the kynurenine pathway may have influence on all of these aspects. (3-OH-L-KYN: 3-hydroxy-L-kynurenine, ATP: adenosine triphosphate, KYNA: kynurenic acid, NO·: nitric oxide, QUIN: quinolinic acid, ROI: reactive oxygen intermediates; solid lines: activation, dashed lines: inhibition)