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Review article

Involvement of the kynurenine pathway in the pathogenesis of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by loss of dopaminergic neurons and localized neuroinflammation occurring in the midbrain several years before the actual onset of symptoms. Neuroinflammation leads to microglia activation and release of a large number of proinflammatory mediators. The kynurenine pathway (KP) of tryptophan catabolism is one of the major regulators of the immune response and is also likely to be implicated in the inflammatory and neurotoxic events in Parkinsonism. Several neuroactive compounds are produced through the KP that can be either a neurotoxic, neuroprotective or immunomodulator. Among these metabolites kynurenic acid (KYNA), produced by astrocytes, is considered as neuroprotective whereas quinolinic acid (QUIN), released by activated microglia, can activate the N-methyl-D-aspartate (NMDA) receptor-signalling pathway, leading to excitotoxicity and amplify the inflammatory response. Previous studies have shown that NMDA antagonists can ease symptoms and exert a neuroprotective effect in PD both *in vivo* and *in vitro*. There are to date several lines of evidence linking some of the KP intermediates and the neuropathogenesis of PD. Moreover, it is likely that some of the KP metabolites could be used as prognostic biomarkers and that pharmacological modulators of the KP enzymes could represent a new therapeutic strategy for PD.

Abbreviations: 3-HK, 3-hydroxykynurenine; 6-OHDA, 6-hydroxydopamine; A, Amygdala; ACMSD, 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase; AD, Alzheimer's disease; AD, Anterodorsal nucleus (Thalamus); α-syn, Alpha-synuclein; CCL2, Chemokine (C—C motif) ligand 2; CSF, Cerebrospinal fluid; DA, Dopaminergic neurons; DM, Dorsomedial nucleus (Thalamus); Glu, Glutamatergic pathway; GPe, external Globus Pallidus; GPi, internal Globus Pallidus; IDO-1, indoleamine 2,3 dioxygenase; IL1β, Interleukin-1β; IL8, Interleukin-8; INF-γ, Interferon-γ; KAT, Kynurenine aminotransferase; KMO, Kynurenine 3-monooxygenase; KP, Kynurenine pathway; KYN, Kynurenine; KYNA, Kynurenic acid; LBs, Lewy bodies; LID, (L-DOPA)-induced dyskinesia's; LPS, Lipopolysaccharides; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; NAD^+, Nicotinamide adenine dinucleotide; NF-κB, Nuclear factor kappa B; NMDA, N-methyl-D-aspartate; NMDA-R, NMDA Glutamatergic receptor; PD, Parkinson's disease; PYC, Pycnogenol; QPRT, Quinolinate phosphoribosyl transferase; QUIN, Quinolinic acid; REM, Rapid Eye Movement; RN, Reticular Nucleus; ROS, Reactive Oxygen Species; SN, Substantia Nigra; SNpc, Substantia Nigra, *pars compacta*; SNpr, Substantia Nigra, *pars reticulata*; SOD, Superoxide dismutase; STN, Subthalamic Nucleus; TH, Tyrosine Hydroxylase; TLR, Toll-Like Receptor; TNF-α, Tumour Necrosis Factor-alpha; TRP, Tryptophan; UCP, Uncoupling Protein; VA, Ventral Anterior nucleus (Thalamus); VL, Ventral Lateral nucleus (Thalamus); VM, Ventral Medial nucleus (Thalamus).

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Contents

1. Introduction

1.1. Parkinson's disease

Parkinson's disease (PD) is an age-related progressive neurodegenerative disorder with an age-adjusted incidence of 13.5–13.9 per 100,000 person per year, and a prevalence of 315 per 100.000 individuals (the second most common worldwide). The prevalence of PD increases with age being from 428 per 100,000 in 60–69 years old people to 1903 per 100,000 in 80 years old people (Pringsheim et al., 2014). PD is characterized by motor symptoms (bradykinesia, rigidity, resting tremor and gait disturbances), which are clinically symptomatic when 70–80% of nigrostriatal terminals have degenerated. However, a wide spectrum of non-motor clinical features including autonomic dysfunction, rapid eye movement (REM) sleep disturbances, anxiety and depression, cognitive impairment or falling are also associated with PD, being more debilitating than motor signs and worsening with disease progression (Berg et al., 2014). The neuropathological hallmarks of PD are chronic inflammation, oxidative stress and loss of dopaminergic neurons in ventral mesencephalon with presence of proteinaceous inclusions, or Lewy bodies (LBs) in remnant neurons. These oxidative mechanisms can be the primary cause or can be the consequence of mitochondrial failure. At the research level, a wide range of experimental models including primary cell cultures, rodents and monkeys have consolidated the involvement of a persistent chronic glia (Barcia et al., 2004). In the line of these evidence, microglia and astroglia activation have leaded to cytokines production (Barcia et al., 2012b), release of extracellular matrix metalloproteinases (Annese et al., 2015), microglial motility, gliapse formation (Barcia et al., 2013) and receptors modulation (Downer et al., 2013), implicating several molecular and cellular pathways (Wang et al., 2012) (Gratwicke et al., 2015)(Zecca et al., 2003).

1.2. Aetiology of PD: sporadic versus genetic forms and risk factors

The cause of PD and the underlying mechanisms remain elusive but recent studies pointed out that combined genetic, environmental factors and aging confer risk for developing sporadic PD rather than genetic or environmental factors alone. In fact, epidemiological studies have shown that up to 40% of PD patients with age at onset of less than 30 years, and 17% of those with age at onset of less than 50 years will probably present the familial form of the disease with either autosomal dominant or recessive mode of inheritance for which at least 19 genes and various loci have been identified so far. These genes include i) Mendelian genes, ii) highly-penetrant mutations in different genes, either autosomal dominant forms such as SNCA, LRRK2, EIF4G1, VPS35, or recessive mutations such as parkin/PARK2, PINK1, DJ1/PARK7 causing rare monogenic forms, and iii) more than 20 chromosomal loci able to modulate the risk for PD with low risk effects have been identified by genome-wide association studies; however the true significance of many of these loci is still unknown (Lill et al., 2012).

At present, there is still great expectation waiting for the results from the new DNA sequencing technologies (exome and whole-genome sequencing) or the NeuroX genotyping platform (Nalls et al., 2015). Up to now, the discovery of point mutations, duplication or triplication of *SNCA* gene coding for α-synuclein (α-syn) protein with demonstration that α-syn is a major component of LBs led Braak and co-workers (2003) to staging the disease progression (Braak et al., 2003) according to appearance of α-syn containing LBs and Lewy neuritis and disease severity (Goedert et al., 2013). Accordingly to Braak's hypothesis, PD progresses in neuronally-connected ascending manner to dorsal motor nucleus of the glossopharyngeal and vagus nerves likely from gut and/or olfactory mucosa (stage 1 & 2), then from lower brain stem to midbrain including nigral regions (stage 3 & 4) and lastly to the neocortical regions (stage 5 & 6). However, it has been suggested that LB pathology alone is not sufficient and that associated neuronal loss leads to Parkinsonism (Buchman et al., 2012). Additionally, it has been recently hypothesised that somatic mutations can develop in patients with PD (Kim and Jeon, 2014). In fact, somatic mosaicism has been associated with Alzheimer's disease (AD) (for a mutation in the presenilin-1 gene) (Beck et al., 2004) or with spastic paraplegia associated (for mutation in SPG4/SPAST) (Depienne et al., 2007; Godbolt et al., 2004). The somatic mosaicism in the SNpc can occur prior to the arrival of tyrosine hydroxylase-immunoreactive cells to the ventral midbrain from the ventricular zone of the mesencephalic aqueduct, and before they complete the final mitosis. Two or more genetically distinct cells would be present in one individual as some dopaminergic neurons would be mutated and others would not. This theory could explain the variability of PD in different individuals and the different evolution of the disease depending on the severity of the mutation. If a somatic mutation can be considered, the neuropathological changes and the clinical features in PD would depend on the extent of the somatic mosaicism, the proportion of dopaminergic (DA) neurons with the

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