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Endogenous neuroprotection in chronic neurodegenerative disorders: with particular regard to the kynurenines

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Abstract

Parkinson's disease (PD) and Huntington's disease (HD) are progressive chronic neurodegenerative disorders that are accompanied by a considerable impairment of the motor functions. PD may develop for familial or sporadic reasons, whereas HD is based on a definite genetic mutation. Nevertheless, the pathological processes involve oxidative stress and glutamate excitotoxicity in both cases. A number of metabolic routes are affected in these disorders. The decrease in antioxidant capacity and alterations in the kynurenine pathway, the main pathway of the tryptophan metabolism, are features that deserve particular interest, because the changes in levels of neuroactive kynurenine pathway compounds appear to be strongly related to the oxidative stress and glutamate excitotoxicity involved in the disease pathogenesis. Increase of the antioxidant capacity and pharmacological manipulation of the kynurenine pathway are therefore promising therapeutic targets in these devastating disorders.

Keywords: neurodegeneration • Parkinson's disease • Huntington's disease • kynurenine pathway • kynurenic acid • quinolinic acid • oxidative stress • glutamate excitotoxicity • neuroprotection

Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder [1] that exhibits increasing prevalence with aging. On average, it affects about 2 in 1000 people [2–4]. Only about 10% of the cases reveal a familial background; the remaining 90% are considered to be sporadic with uncertain aetiology, which draws attention to the role of possible environmental risk factors

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(reviewed in [5]). The main clinical features of PD, including resting tremor, rigidity, brady- and hypokinesia and postural instability, develop in consequence of the complex dysfunction of the motor network, with crucial roles for the alterations in the basal ganglia circuits (reviewed in [6]). The main underlying pathological hallmark is a preferential loss of brain stem catecholaminergic, and especially mesencephalic dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the development of intracellular inclusions called Lewy bodies [7]. The resulting dopamine deficiency, apparent mainly in the striatum, means that the brain is no longer capable of sufficient motor function control (reviewed in [6]).

Huntington's disease (HD) is likewise a chronic progressive neurodegenerative disease [8], observed in the middle-aged. In contrast with PD, it is genetically determined by an autosomal dominantly inherited definite single mutation in the IT15 gene coding for the huntingtin protein [9]. The prevalence of HD is rather low relative to that of PD; it affects only about 5 in 100,000 people [10–13]. The clinical features of HD are characterized by cognitive, psychiatric and motor symptoms (reviewed in [14, 15]). In view of the motor symptoms, the typical loss of coordination of the voluntary movements and the appearance of involuntary movements (such as chorea and dystonia) evolve. Further, a progressive gait impairment also develops, manifested in brady- and hypokinesia [16, 17]. The pathological alterations are mainly seen in the central nervous system (CNS), and especially in the caudate nucleus, the putamen and the deeper layers of the cerebral cortex [18]. The loss of γ-aminobutyric acidergic (GABAergic) medium-sized spiny neurons (MSNs) in the striatum (caudate nucleus + putamen) is the most pronounced feature [19–21], resulting in a dysfunction of the basal ganglia circuits, and leading to the development of the characteristic symptoms (reviewed in [22]).

The role of mitochondrial impairment and oxidative stress in neurodegeneration

Background

The mitochondria take part in both physiological and pathological processes, such as energy supply, signalling, Ca^{2+}-homeostasis, cell cycle regulation, apoptosis, free radical generation, thermogenesis, development and aging (reviewed in [23, 24]; Fig. 1). The electrons arising from the oxidation of the reduced coenzymes nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide reduce molecular oxygen (O_2) predominantly to H_2O, but 1–2% of the O_2 is incompletely reduced, producing the superoxide anion ($O_2^{\cdot -}$). In the event of the dysfunction of one or more respiratory chain complexes, the production of $O_2^{\cdot -}$ is enhanced. Although $O_2^{\cdot -}$ itself is only moderately damaging, it is highly reactive [25]. It can be transformed to hydrogen peroxide (H_2O_2), a process catalysed by manganese superoxide dismutase, or it can interact with nitric oxide, providing the highly toxic peroxynitrite anion. Under physiological conditions, H_2O_2 is broken down by glutathione peroxidase or catalase, but if H_2O_2 is present in excess amount, it can react with transition metal ions (*e.g.* Fe^{2+}) in the Fenton reaction, producing another highly toxic and reactive metabolite, the hydroxyl radical. Besides the mitochondria (the electron transport chain; ETC) as a major source of free radicals, other free radical-producing pathways involve participation of the enzymes xanthine oxidase, monoamine oxidase, cytochrome P450, myeloperoxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, etc. In contrast with other organs, the brain is more sensitive to lesion-provoking reactive oxygen species because its O_2 demand is high, it contains high concentrations of polyunsaturated lipids and its antioxidant capacity is relatively low (reviewed in [26]). There is evidence that the mitochondria play important roles in both necrotic and apoptotic cell death (reviewed in [27, 28]). It is important that the occurrence of necrosis or apoptosis depends on the severity of the pathological stimuli [29, 30]. These stimuli, such as oxidative stress, a Ca^{2+} overload, or ATP depletion, can lead to the formation of mitochondrial permeability transition (MPT) pores, a process strongly influenced by the Bcl-2 family proteins (reviewed in [31]). The presence of these pores allows the release of cytochrome-c into the cytosol, where it forms an essential part of the apoptosome, which is composed of cytochrome-c, apoptotic protease activating factor 1 and procaspase 9 [32]. The result is the activation of caspase-9, which then processes and activates other caspases, leading to the biochemical execution of the cells. It should be mentioned that caspase-independent cell death pathways also exist (reviewed in [33]).

Parkinson's disease

The observation that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a product of meperidine analogue synthesis, can cause the development of chronic parkinsonism [34, 35] drew attention to the involvement of a mitochondrial dysfunction in PD, for 1-methyl-4-phenylpyridinium ion (MPP^+), the toxic metabolite of MPTP [36, 37], has been shown to be capable of the selective inhibition of complex I of the mitochondrial ETC [38, 39]. Later, a significant decrease in complex I activity was observed in the substantia nigra and platelets of patients with idiopathic PD [40, 41], though the currently available experimental data suggest some inconsistency (reviewed in [42]). Nevertheless, the possible role of exposure to pesticides (with consequent complex I inhibition and/or reactive oxygen intermediate (ROI) generation) in the development of idiopathic PD (reviewed in [43]) provides further evidence of the crucial role of a mitochondrial dysfunction in the disease pathogenesis. Indeed, the proved Fe^{2+} accumulation in PD SNpc appears to be a factor aggravating the oxidative damage (reviewed in [44–46]). In consequence of genetic mutations, the deteriorated function of several gene products (*e.g.* α-synuclein, parkin, phosphatase and tensin homologue induced putative kinase 1 [PINK1], high-temperature requirement protein A2

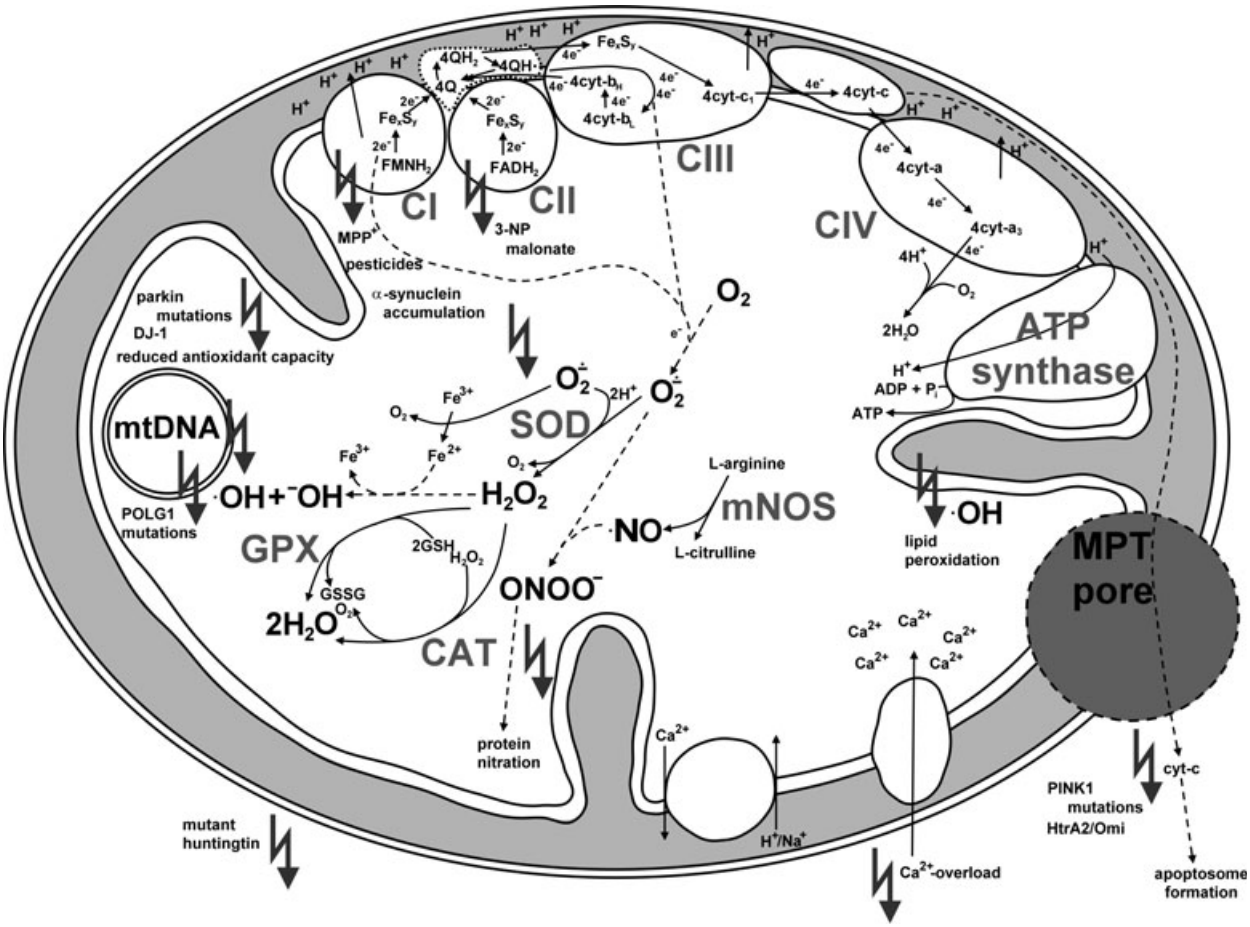

Fig. 1 Oxidative stress and mitochondrial impairment in PD and HD (for details see the text). 3-NP: 3-nitropropionic acid; ADP: adenosine diphosphate; ATP: adenosine triphosphate; CI-IV: mitochondrial ETC complexes I-IV; CAT: catalase; cyt: cytochrome; $FADH_2$: reduced flavin adenine dinucleotide; Fe_xS_y: iron-sulfur cluster; $FMNH_2$: reduced flavin mononucleotide; GPX: glutathione peroxidase; GSH: reduced glutathione; GSSG: oxidized glutathione; H_2O_2: hydrogen peroxide; HtrA2: high-temperature requirement protein A2; mNOS: mitochondrial nitric oxide synthase; MPT: mitochondrial permeability transition; mtDNA: mitochondrial deoxyribonucleic acid; MPP^+: 1-methyl-4-phenylpyridinium ion; · NO: nitric oxide; $O_2^{\cdot -}$: superoxide anion; ·OH: hydroxyl radical; $ONOO^-$: peroxynitrite anion; Q: oxidized coenzyme Q_{10}; ·QH: semiquinone coenzyme Q_{10}; QH_2: reduced coenzyme Q_{10}; PINK: phosphatase and tensin homologue-induced putative kinase 1; POLG1: mtDNA polymerase γ1; SOD: superoxide dismutase.

(HtrA2)/Omi, DJ-1, leucine-rich repeat kinase 2 [LRRK2] and mitochondrial DNA [mtDNA] polymerase γ1 [POLG1]) can additionally contribute to the development of PD by affecting the mitochondria too (Fig. 1), amongst other subcellular compartments (reviewed in [42, 47, 48]). The mitochondrial accumulation of α-synuclein under pathological conditions results in decreased complex I activity and the increased production of ROI in human dopaminergic neurons [49]. The decrease in parkin function may result in a reduced mitochondrial antioxidant capacity [50]. PINK1 is able reduce the cytochrome c release from the mitochondria by phosphorylating tumour necrosis factor receptor-associated protein 1, thereby inhibiting oxidative stress-induced apoptosis. Furthermore, PINK1 has been shown to be able to phosphorylate both parkin [51] and HtrA2/Omi [52]; the regulation of the proteolytic activity of the latter may result in resistance to mitochondrial stress. DJ-1 acts as an atypical peroxiredoxin-like peroxidase and its dysfunction results in impaired mitochondrial ROI scavenging [53]. The available data [54] support the possibility of LRRK2 action at the mitochondria, but the mechanism has not yet been clarified. Mutations in POLG1 render mtDNA more vulnerable to oxidative damage, resulting in a mitochondrial dysfunction, and thus these mutations may also be associated with the development of PD [55].

Huntington's disease

An early finding suggestive of the involvement of a mitochondrial dysfunction in the development of HD was a decreased activity of succinate dehydrogenase (complex II of the ETC) in post-mortem

HD brains [56]. It was later observed that a plant/fungal toxin, 3-nitropropionic acid (3-NP), which is capable of the irreversible inhibition of succinate dehydrogenase [57], causes extrapyramidal symptoms due to food poisoning [58]. This toxin and the reversible enzyme inhibitor malonate [59] were therefore widely applied in the animal modelling of HD [60–62]. Mutant huntingtin has been shown to be able to bind directly to mitochondria, thereby altering their normal function [63] (Fig. 1). The impaired mitochondrial Ca^{2+} handling [64] and the repression of transcription factors, *e.g.* that responsible for peroxisome proliferator-activated receptor γ coactivator 1-α (involved in the regulation of gene expression related to mitochondrial biogenesis and respiration) [65], are certainly associated with the mitochondrial dysfunction in HD.

Glutamate excitotoxicity in neurodegeneration

Background

The toxic effects of glutamate, the main excitatory amino acid in the brain, were first observed in 1957 [66], and the term glutamate-induced excitotoxicity was introduced by Olney in 1969 [67]. Besides their role in physiological signal transduction, the ionotropic and metabotropic glutamate receptors take part in pathological excitotoxic processes too (reviewed in [68]; Fig. 2). The N-methyl-D-aspartate (NMDA) receptors (NMDARs) seem to play the central role in excitotoxicity. The available data suggest that the activation of NMDARs (which facilitates the entry of cations, and in particular Ca^{2+}, into the neurons) at the extrasynaptic site is neurotoxic, whereas synaptic NMDAR activation promotes neuronal survival [69]. A conventional NMDAR is composed of 2 NMDAR subunit 1s (NR1s) and 2 NMDAR subunit 2s (NR2s), forming a heterotetramer. The NR1s form the ion channel, whereas the NR2s (NR2A-D) have more of a regulatory and refining role. It has been shown that the NR2B-containing NMDARs predominate at the extrasynaptic site [70], and there is accumulating evidence that glutamate-induced excitotoxicity is mainly mediated by these NR2B-containing NMDAR channels [71]. The α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs) are composed of a combination of GluR1–4 subunits, whereas the kainate receptors consist of subunits GluR5–7. The cation permeability profile shows Ca^{2+} permeability for the AMPARs too, with the exception of those containing the GluR2 subunit. Conversely, the kainate receptors are mostly impermeable to Ca^{2+}. The activation of AMPARs and kainate receptors can be associated with both NMDAR function and dysfunction by inducing relief of the Mg^{2+} blockade of the NMDAR channel. The metabotropic glutamate receptors (mGluR1–8) can be classified into three groups; their functions are mainly linked to G-proteins. The activation of group I mGluRs (mGluR1 and mGluR5) results in intracellular Ca^{2+} mobilization through inositol triphosphate (IP_3) production, leading to IP_3 receptor 1 (IP_3R1) activation on the endoplasmatic reticulum (ER) [72, 73]. This can accompany the pathological Ca^{2+} signalling characteristic of glutamate excitotoxicity. The activation of group II mGluRs (mGluR2–3) and group III mGluRs (mGluR4, mGluR6–8) leads to the downstream inhibition of voltage-dependent Ca^{2+} channels [74], thereby decreasing glutamate release. The dysfunction or down-regulation of these receptors may result in an enhanced release of glutamate. The alterations in glutamate uptake mediated by glutamate transporters (EAAT1–5: excitatory amino acid transporter 1–5), and especially EAAT1 [glutamate aspartate transporter (GLAST)] and EAAT2 [glutamate transporter-1 (GLT-1)], may also result in an elevation of extracellular glutamate concentration accompanying the excitotoxic process (reviewed in [75]; Fig. 2). However, this elevation is not absolutely necessary for excitotoxicity. An energy impairment due to a mitochondrial dysfunction and/or oxidative stress can also lead to partial membrane depolarization, resulting in relief of the Mg^{2+} blockade of the NMDAR channel (Fig. 2). Thus, even in physiological concentrations, glutamate can evoke downstream events such as a Ca^{2+} overload and free radical generation, inducing a self-propagating process [76]. The downstream events evoked by a Ca^{2+} overload certainly involve mitochondrial Ca^{2+} sequestration with a consequential impairment of the mitochondrial function, ER stress, pathological overactivation of several types of kinases and/or phosphatases, proteases (*e.g.* caspases and calpains), neuronal nitric oxide synthase (nNOS), endonucleases, phospholipases and transglutaminases, leading to detrimental effects (reviewed in [77]).

Parkinson's disease

A recently published paper [78] dealing with the dysregulation of glutamate homeostasis in the mouse SNpc due to chronic MPTP treatment provided evidence of glutamate excitotoxicity involvement in PD pathogenesis secondary to a mitochondrial dysfunction (commented in [79]). Neurons in the SNpc possess glutamate receptors and receive glutamatergic input from the subthalamic nucleus (the main input), cerebral cortex, amygdala and pedunculopontine and laterodorsal tegmental nuclei (reviewed in [80]). The metabolic compromise leads to a decrease in striatal dopaminergic innervation, resulting in overactivation of the subthalamic nucleus. This causes an increase in glutamate release onto the compromised dopaminergic neurons in the SNpc (reviewed in [81]). Hence, the excitotoxic cascade further worsens the neurodegenerative process, inducing a vicious cycle.

Huntington's disease

The results of kainic acid experiments suggested that glutamate excitotoxicity may play an important role in the development of HD [82, 83]. Subsequent experiments with ibotenic acid [84] and quionolinic acid (QUIN) [85, 86] furnished evidence in support of this. To explain the selective impairment of the MSNs, it should be borne in mind that they receive a massive glutamatergic input from

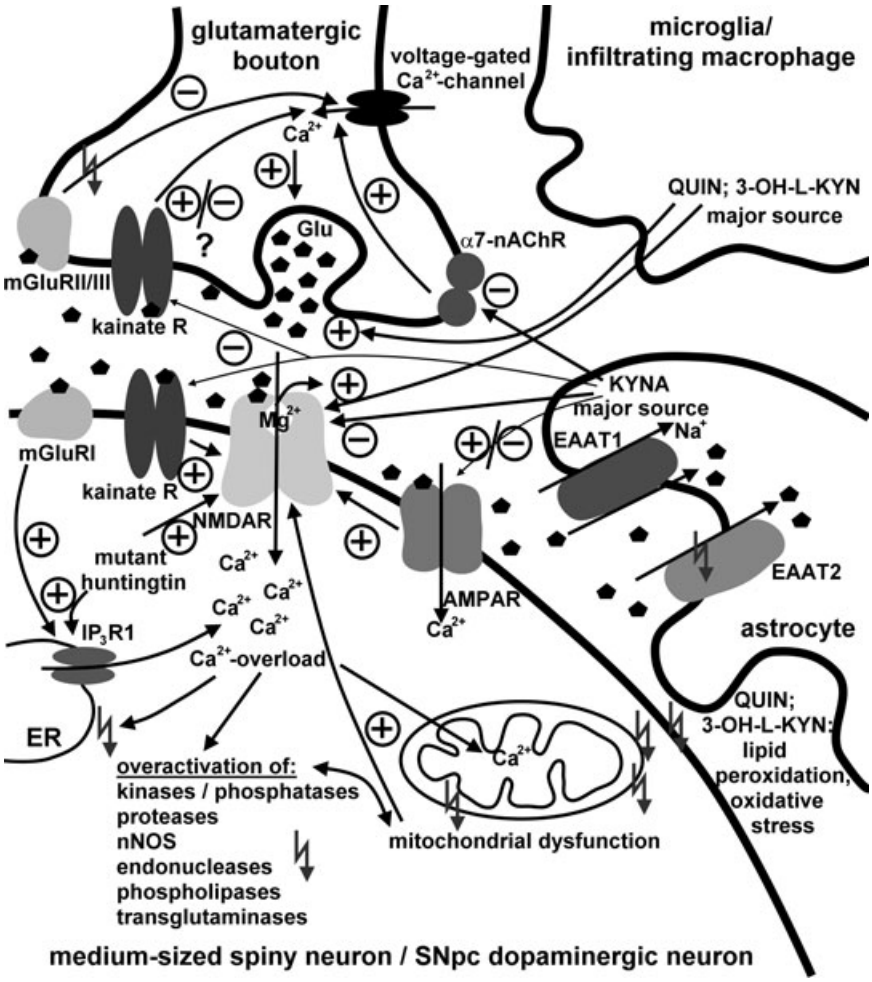

Fig. 2 The pathomechanism of glutamate excitotoxicity influenced by the neuroactive kynurenines (for details see the text). 3-OH-L-KYN: 3-hydroxy-L-kynurenine; α7-nAChR: α7-nicotinic acetylcholine receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; EAAT1–2: excitatory amino acid transporter 1–2; ER: endoplasmic reticulum; Glu: L-glutamate; IP_3R1: inositol triphosphate receptor 1; kainate R: kainate receptor; KYNA: kynurenic acid; mGluRI-III: group I-III metabotropic glutamate receptors; NMDAR: N-methyl-D-aspartate receptor; nNOS: neuronal nitric oxide synthase; QUIN: quinolinic acid.

the cortex [87] and the thalamus (reviewed in [88]). As the NMDA receptors are to be found in especially high amount on the spines of the MSNs [89], these neurons are rather sensitive to glutamate [90, 91], which explains the extremely extensive loss of striatal neurons expressing NMDARs [92]. Furthermore, the expression pattern of the receptor subunits differs from those of the other striatal neurons [89, 93], as the extrasynaptic NMDARs of MSNs preferentially contain the NR2Bs [94, 95]. The expression of mutant huntingtin can sensitize the NR2B-containing NMDARs [96, 97], thereby aggravating the excitotoxic process [98] (Fig. 2). Additionally, the polyglutamine expansion has been found to interfere with the ability of huntingtin to interact with the post-synaptic density protein of 95 kD (PSD95) [99], a structural link between nNOS and NMDARs [100], which also results in the sensitization of NMDARs. Indeed, the glutamate uptake is reduced in HD [101], and the experimental data suggest that the reduced expression of mGluR2s may lead to an increase in glutamate release [102], ensuring the possibility of enhanced activation through the sensitized NMDARs. Further, mutant huntingtin can increase Ca^{2+} release from the ER, by binding to the IP_3R1s [103].

The kynurenine pathway

Historical overview

L-Kynurenine (L-KYN) is a central intermediate in the main pathway of the tryptophan (TRP) metabolism [104]; it was first identified in rabbit urine [105]. More than 95% of TRP is metabolized through kynurenines [106]. This pathway is responsible for the production of nicotinic acid [107], a major component of NAD^+ and nicotinamide adenine dinucleotide phosphate ($NADP^+$) coenzymes. L-KYN can be metabolized in three distinct ways to kynurenic acid (KYNA), anthranilic acid (ANA) and 3-hydroxy-L-kynurenine (3-OH-L-KYN). KYNA, which has been identified in dog urine [108], is a side-product of the main metabolic route [109], while ANA and 3-OH-L-KYN, first identified in 1941 and in 1949, respectively [110, 111], can be further metabolized in some steps through an important intermediate, QUIN [112, 113], to NAD^+ in a common pathway (Fig. 3). As regards the role of kynurenines in the CNS, it is important to highlight that L-KYN is present in the

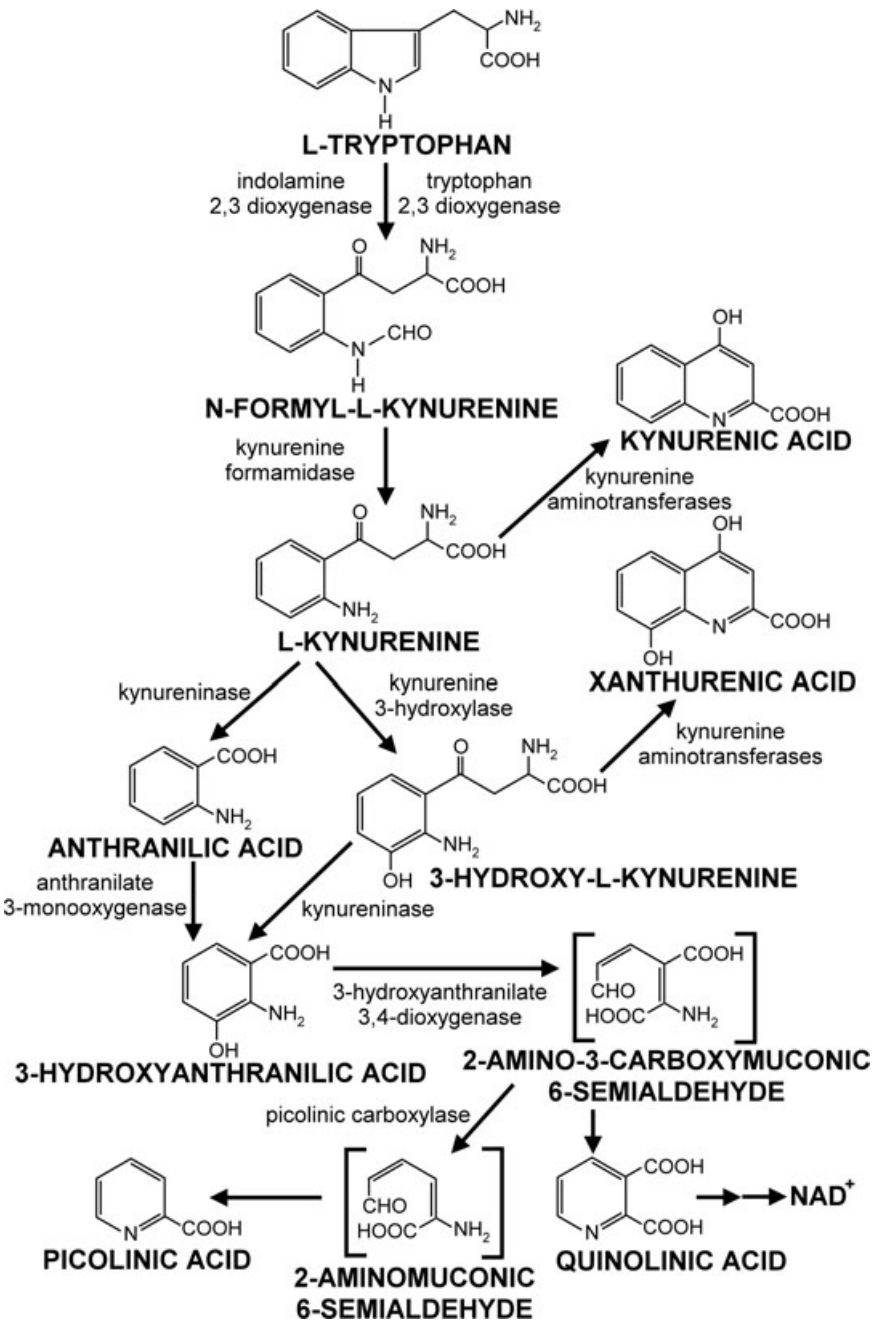

Fig. 3 The kynurenine pathway of the tryptophan metabolism. NAD^+: nicotinamide adenine dinucleotide.

mammalian brain tissue in a concentration of around 200 ng/g. A total of 40% of it is formed locally, and 60% is taken up from the periphery [114, 115] as a consequence of its being able to cross the blood–brain barrier [116, 117] by the large neutral amino acid carrier, a process studied in detail by Fukui *et al.* [118]. The metabolites have also been detected in the mammalian brain [115, 119], in which KYNA, 3-OH-L-KYN and QUIN are commonly referred to as neuroactive kynurenines (reviewed in [120–122]). The potential role of kynurenines in depression was suggested in 1973 [123], but the first direct evidence of neuroactive properties, such as convulsive and stimulatory effects, was demonstrated only in 1978 [124].

The biosynthesis of neuroactive kynurenines

KYNA is produced from its precursor, L-KYN, in an irreversible transamination by the action of four subtypes of kynurenine

aminotransferases (KATs; reviewed in [125]): KAT-I-II [126], KAT-III [127] and mitochondrial aspartate aminotransferase (mitAAT, also called KAT-IV) [128]. KAT-II has been demonstrated to be the main KYNA-producing enzyme in the rat and human brains, whereas in the mouse brain KAT-II surprisingly possesses the lowest activity and mitAAT the highest [128]. The KATs are abundantly expressed in the astrocytes [129], but only weak granular staining can be seen in the neurons [130]. The development of KAT-II-specific antibodies revealed that the expression of this enzyme subtype is confined entirely to the astrocytes [131]. 3-OH-L-KYN is formed by the action of kynurenine 3-hydroxylase [132], whereas QUIN is produced by 3-hydroxyanthranilate 3,4-dioxygenase [133]. This branch of the kynurenine pathway is mainly localized in the microglia and macrophages [134], whereas astrocytes do not express kynurenine 3-hydroxylase, but only 3-hydroxyanthranilate 3,4-dioxygenase [129].

Neuroactive kynurenines: sites of action

KYNA exerts broad-spectrum endogenous antagonism on ionotropic excitatory amino acid receptors [135] (Fig. 2). In micromolar concentrations, it acts as a competitive antagonist at the strychnine-insensitive glycine-binding site of the NMDAR [136] and displays weak antagonistic effects on the AMPARs and kainate receptors [137]. KYNA has been found to be capable of facilitating AMPAR responses in low (nanomolar to micromolar) concentrations [138], but the concentration range is controversial: KYNA in micromolar concentrations has recently been shown to have neuroinhibitory effects, whereas in nanomolar concentrations it was claimed to be a facilitator [139]. In addition to its direct effects on glutamate receptors, KYNA non-competitively blocks the α7-nicotinic acetylcholine receptors [140], presynaptic activation of which is involved in the regulation of glutamate release [141]. It has been reported that, through activation at the G protein-coupled receptor GPR35, KYNA can elicit IP_3 production and Ca^{2+} mobilization [142], but the role of this phenomenon is questionable as regards the CNS, because GPR35 exhibits a limited expression in the brain and a relatively high KYNA concentration is necessary for activation. With respect to the KATs, it is interesting that the neuronal expression of KAT-I appears to have effects on developmental processes, such as programmed cell death [143]. QUIN is a weak, but specific competitive agonist of the NMDAR subgroup containing the NR2A and NR2B subunits, with low receptor affinity [144]. There are 2 mechanisms *via* which it can cause excitotoxicity modulating the glutamatergic system: the direct activation of NMDARs [145] or the release and uptake inhibition of glutamate [146, 147] (Fig. 2). The production of ROI [148] and lipid peroxydation due to QUIN also contribute to its neurotoxic effects [149]. The deleterious effects of 3-OH-L-KYN are mediated by free radicals and not glutamate receptors [150, 151] (Fig. 2). Some of its detrimental actions may be due to its metabolite, 3-hydroxyanthranilic acid, which readily undergoes auto-oxidation with the production of O_2^- [152], and it has also been shown to be neurotoxic [153].

Neuroactive kynurenines in neurodegenerative disorders

Parkinson's disease

The involvement of kynurenine pathway abnormalities in the pathogenesis of PD is suggested by the findings that 3-OH-L-KYN concentrations have been found to be elevated in the frontal cortex, putamen and SNpc of patients with PD, probably contributing to the oxidative damage [154]. Conversely, KYNA concentrations are decreased. Accordingly, a reduction in KAT-I in the SNpc of mice has been observed after MPTP treatment [155]. Furthermore, administration of 6-hydroxydopamine (a free radical generator in catecholaminergic neurons) considerably diminishes not only tyrosine hydroxylase, but also KAT-I immunoreactivity in the remaining SNpc neurons [156]. In rat cerebral cortical slices, MPP^+ appreciably decreased KAT-II activity, with the resulting depletion of KYNA [157].

Huntington's disease

There is a seeming imbalance of the tryptophan metabolism in the striatum in different stages of the disease. A relative decrease in KYNA level and reduced activity of KATs have been demonstrated in the striatum of HD patients [158–160]. The cerebrospinal fluid level of KYNA has also been observed to be decreased in HD [161]. The elevation in QUIN concentration in the early stages correlates well with the increased activity of its producing enzyme, 3-hydroxyanthranilate 3,4-dioxygenase, in HD brains [162]. The fact that the intrastriatal injection of QUIN is highly applicable for the animal modelling of HD [85, 86, 163] well supports its pathogenetic role in HD development (reviewed in [164]). In correlation with the findings detailed above, young mice with the targeted deletion of KAT-II, showing decreased KYNA and normal 3-OH-L-KYN and QUIN concentrations, displayed an increased vulnerability to the intrastriatal injection of QUIN as compared with the wild-type controls, suggesting the importance of KYNA in controlling the neurotoxicity of QUIN [165]. The striatal concentration of 3-OH-L-KYN changes in parallel with the QUIN level in HD [160, 166], and it has been shown to potentiate the neurotoxic effects of QUIN in the rat striatum [167]. After 3-NP treatment, the activity of KAT-I is reduced most markedly in the striatum of the rat brain, suggesting a link between the metabolic disturbances and an altered tryptophan metabolism in HD [168]. Furthermore, the use of rat cerebral cortical slices proved that the activities of KAT-I and KAT-II were decreased [157]. The results of a yeast genomic screen indicated that deletion of the KYNA-producing enzyme enhances mutant huntingtin-mediated toxicity, whereas it is ameliorated mainly by the deletion of 3-OH-L-KYN, but also by that of the QUIN-producing enzyme [169].

Endogenous neuroprotection in Parkinson's and Huntington's diseases

Background

PD is one of the few neurodegenerative disorders for which effective symptomatic therapies are available, whereas in HD, the proposed symptomatic therapies are few and have limited effects. The main aim of preclinical and clinical studies in this field is to achieve neuroprotection (preservation of the neuronal structure and function) or at least to provide highly effective symptomatic treatment. Amongst the therapeutic strategies, a popular approach is to attain neuroprotection by the exogenous administration of endogenously occurring natural substances or their derivatives with slight modifications. L-3,4-dihydroxyphenylalanine (L-DOPA), the compound most widely used as symptomatic therapy in PD, is a good example of this approach. Although there have been numbers of preclinical and clinical studies on both PD and HD (reviewed in [170–173]), we mention here only the forms of endogenous neuroprotection confined to the prevention of oxidative stress, energy impairment and glutamate excitotoxicity.

L-carnitine

L-carnitine plays a role in the mitochondrial exchange of fatty acids; it has direct or indirect antioxidant properties (reviewed in [174]). It has proved to be protective in cell culture against MPP^+ [175], and its derivative, acetyl-L-carnitine, also exerts beneficial effects in the MPTP model of PD in primates [176], and in a cellular toxin model of PD [177]. Although L-carnitine suppresses 3-NP-induced MPT [178], and is neuroprotective in a transgenic mouse model of HD [179], low-dose acetyl-L-carnitine administration in a double-blind, placebo-controlled study showed no benefit [180].

L-carnosine

L-carnosine (β-alanyl-L-histidine) is a dipeptide with demonstrated antioxidant, antiglycator and metal chelator properties (reviewed in [181]). In a pilot study, L-carnosine increased the efficacy of L-DOPA treatment in PD patients [182]. In a transgenic mouse model of HD, L-carnosine was unable to improve the survival or the motor performance of mice significantly (our unpublished data).

Coenzyme Q_{10}

Coenzyme Q_{10} is a lipid-soluble benzoquinone that functions as an electron transporter in the ETC and as an antioxidant. Coenzyme Q_{10} has also been demonstrated to be effective in the MPTP model of PD [183] and in the transgenic mouse models of HD [184, 185]. Whereas low-dose administration was ineffective [186], higher doses of coenzyme Q_{10} exerted beneficial effects in early PD patients in a phase II, multicentre, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging clinical trial [187] and in a monocentre, parallel-group, placebo-controlled, double-blind trial [188]. Surprisingly, a later multicentre, randomized, parallel-group, placebo-controlled, double-blind, stratified, single-dose trial in mid-stage PD did not indicate any significant amelioration [189]. A randomized, placebo-controlled, phase III trial was recently initiated. A multicentre, randomized, parallel-group, double-blind trial [Coenzyme Q10 And Remacemide Evaluation in Huntington's Disease (CARE-HD)] was unable to prove any significant effect on the functional decline in early HD, in contrast with an apparent amelioration tendency [190]. This might be due to underdosing; the Pre2CARE study has revealed that higher doses of coenzyme Q_{10} are reasonably well tolerated [191]. A larger study (2CARE) is currently ongoing for the re-evaluation of coenzyme Q_{10} in HD.

Creatine

Creatine kinase and its substrates creatine and phosphocreatine take part in the buffering of intracellular energy reserves (reviewed in [192]) and in the inhibition of MPT activation [193]. The exogenous administration of creatine proved effective in the MPTP model of PD [194] and the 3-NP, malonate [195] and transgenic mouse models [196, 197] of HD. Nevertheless, a randomized, double-blind phase II trial in early PD [198, 199] and a placebo-controlled randomized pilot trial [200] did not indicate any robust clinical benefit. A phase III, long-term (5 year follow-up), multicentre, double-blind, placebo-controlled study [The National Institutes of Health Exploratory Trials in Parkinson Disease Long-term Study 1 (NET-PD LS1)] is currently ongoing. As regards HD, creatine was not found to be significantly effective either in a 2 year open label pilot study [201, 202] or in a placebo-controlled pilot trial [203], likewise in PD. A high-dose phase III creatine trial started in 2008.

Cysteamine/cystamine

Cysteamine, an antioxidant, is capable of the prevention of lipid peroxidation and can exert beneficial effects through its action on enzymes responsible for the maintenance of an antioxidant milieu or energy preservation [204, 205]. Its oxidized form, cystamine, exerts a transglutaminase inhibitory effect (reviewed in [206]). An early study was unable to detect any protective effect of cysteamine in the MPTP model [207], but it has recently been proved that lower doses of both cysteamine and cystamine show efficacy [208, 209]. Treatment with cystamine afforded neuroprotection in transgenic mouse models of HD [210–212]. A phase I dose finding and tolerability study [Phase I dose finding and tolerability study of cysteamine (Cystagon) in Huntington's disease (CYTE-I-HD)] has already been carried out with cysteamine in HD patients [213].

Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is an essential n-3 polyunsaturated fatty acid that targets the mitochondrial function, especially by

acting on peroxisome proliferator activated receptors (reviewed in [214]). It has been shown that the administration of polyunsaturated fatty acid mixtures containing EPA improves dyskinesias and reverses weight loss in HD patients [215] and is beneficial in a transgenic mouse model of HD [216]. A randomized, double-blind, placebo-controlled study also demonstrated beneficial effects [217]. Although treatment with the ethyl ester of EPA (ethyl-EPA) improved the motor dysfunction in a transgenic mouse model of HD [218], and also led to an MRI and neuropsychological improvement [219] and a significant reduction in brain atrophy, particularly in the caudate and thalamus [220], a randomized, double-blind, placebo-controlled study indicated no benefit [221]. At present, The Huntington Study Group is conducting a multicentre, randomized, double-blind, placebo-controlled trial with ethyl-EPA [randomized controlled trial of ethyl-eicosapentaenoic acid in Huntington disease (TREND-HD)]. The preliminary data revealed no efficacy after 6 months [222].

α-lipoic acid

α-lipoic acid is a disulfide compound that serves as a coenzyme for mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. It exerted beneficial effects in the transgenic mouse model of HD [223] and in a cellular toxin model of PD [177].

Pyruvate

Pyruvate is the end-metabolite of glycolysis and serves as an energy substrate. Pyruvate and its simple derivative ethyl-pyruvate provided protection against MPP^+ toxicity *in vitro* [224, 225], but we did not observe any protection against MPTP in mice. Pyruvate also exerted neuroprotective effects in the QUIN rat model of HD [226].

Taurine

Taurine is a β-amino acid with antioxidant properties (reviewed in [227]). Although it has been found to be protective in the 3-NP model of HD [228], we did not observe any beneficial effects either in the MPTP model of PD, or in a transgenic mouse model of HD (our unpublished data).

Tocopherol

α-tocopherol (the predominant form of vitamin E in the tissues and in supplements) is a lipid-soluble antioxidant which, despite the great expectations, was reported to be ineffective both in animal MPTP models of PD [207, 229], and in PD patients in the large, randomized, placebo-controlled Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) study [230]. However, it has also been shown that α-tocopherol is capable of attenuating 6-hydroxydopamine lesions [231] and iron-induced nigral neuron loss [232]. Furthermore, a pilot trial of high-dose α-tocopherol and ascorbate demonstrated beneficial effects in PD patients [233]. Nevertheless, a double-blind, placebo-controlled study did not confirm the efficacy of high-dose α-tocopherol in HD patients, though it would be beneficial for patients early in the course [234]. Interestingly, γ-tocopherol (the predominant form of vitamin E in the diet) effected a considerably larger attenuation than the statistically ineffective α-tocopherol as concerns MPTP-induced dopamine loss [235].

L-KYN/KYNA

From a therapeutic aspect, enhancement of the effects of KYNA would be a successful therapeutic strategy providing protection against the effects of neurotoxic 3-OH-L-KYN and QUIN. This may be achieved by administration of the KYNA precursor L-KYN. Thus, a combination of the blood–brain barrier-penetrable L-KYN with nicotinylalanine, an agent that inhibits both kynurenine 3-hydroxylase and kynureninase activity, and with probenecid, an inhibitor of organic acid transport for enhancement of the brain KYNA concentration, exerted protective effects in the SNpc against both NMDA and QUIN-induced excitotoxicity [236], and in the striatum against QUIN-mediated neurotoxicity [237], possibly *via* the elevated level of KYNA. However, the co-administration of probenecid seems necessary to achieve a considerably elevated KYNA level in the field of interest. Although L-KYN alone was able to induce amelioration in animal models of cerebral ischemia [238, 239], it is mainly used in combination with probenecid to achieve neuroprotection (*e.g.* in a migraine model: [240]). However, it has recently been shown that probenecid alone can mitigate the alterations in that migraine model [241]. Further, probenecid is protective in a transgenic mouse model of HD [242], whereas L-KYN alone is ineffective (our unpublished data). In an MPTP model of PD, we did not find any protection with pure L-KYN either. Nevertheless, the available data suggest that L-KYN in combination with probenecid is perhaps capable of enhancing neuroprotection in chronic neurodegenerative disorders.

Although the direct injection of KYNA into the globus pallidus internus [243, 244], or its co-infusion with either QUIN or NMDA into the SNpc [236], resulted in beneficial effects in PD models, the systemic administration of KYNA does not seem to be a good therapeutic approach in CNS disorders for several reasons. It penetrates the blood–brain barrier poorly [118], and it undergoes rapid clearance from the brain and the body, mediated by organic anion transporters [245]. To overcome these disadvantages, numbers of KYNA derivatives have been synthetized with preserved or enhanced pharmacodynamic properties (reviewed in [246–248]). Although 7-chlorokynurenic acid (7-Cl-KYNA), which has enhanced antagonism at glycine/NMDA receptors, did not exert any protection against the intrastriatal neurotoxic effect of MPP^+ in rats, whereas KYNA did [249], the systemic administration of 4-chlorokynurenine (4-Cl-KYN), the blood–brain barrier-penetrable pro-drug of 7-Cl-KYNA, did prevent QUIN- and malonate-induced neurotoxicity

in the rat striatum [250]. The apparent contradiction between these experimental findings may be resolved in that 4-Cl-KYN can be metabolized to 4-chloro-3-hydroxyanthranilate, a powerful inhibitor of QUIN synthesis [251], which broadens the modes of neuroprotective action. Furthermore, the divergence between the KYNA and 7-Cl-KYNA effects can be explained in that the halogenation of KYNA results in compounds that are highly selective for the glycine site of NMDARs [252] and can mainly prevent NMDAR-mediated excitotoxicity, whereas a wider spectra of neurotransmitter receptors are involved in neurodegenerative processes. The KYNA amides seem to be excellent candidates, as they may be capable of the selective inhibition of the NR2B subunit-containing NMDARs too [253]. A newly synthesized KYNA amide, previously proved to be beneficial in migraine [254] and epilepsy [255] models, exerts neuroprotection in a transgenic mouse model of HD [256].

Concluding remarks

Although PD and HD are different clinical entities, their pathomechanisms reveal several common features. The main characteristic symptoms involve disturbances in motion in both cases, with an underlying dysfunction of the very complex motor system, mainly the basal ganglia. Oxidative stress with mitochondrial impairment and glutamate excitotoxicity are definitely involved in the disease development. Although these pathogenetic factors are closely connected to each other, and each can be evoked by the other, oxidative stress and mitochondrial impairment appear to play the predominant role in PD pathogenesis, whereas glutamate excitotoxicity does so in HD pathogenesis. Accordingly, the therapeutic strategies mainly target these two possibilities. As concerns endogenous neuroprotection, the main modes involve naturally occurring agents and their slightly modified derivatives, and in particular substances for the achievement of antioxidant protection and the preservation of the mitochondrial function and energy stores. These agents, such as L-carnitine, L-carnosine, coenzyme Q_{10}, creatine, cysteamine/cystamine, EPA, α-lipoic acid, pyruvate, taurine and tocopherol, all serve as potential therapeutics. However, in contrast with the promising preclinical findings, most of them did not exhibit unequivocal significant efficacy in clinical trials. This could be due to the lack of optimum dosing or an improper study design, but it is very important to pay special attention to the validity of the experimental models and to the heterogeneity of the human population and of the disease development. There is still a major need for further studies with natural or newly designed agents in order to achieve a significant level of neuroprotection, or at least a certain symptomatic benefit. As concerns the kynurenines, KYNA would serve as a good anti-excitotoxic agent by virtue of its wide-spectrum pharmacodynamic profile and low potency of inducing side-effects. However, there is a major need to improve the pharmacokinetic profile in order to attain an acceptable half-life and a better blood–brain penetrance. Thanks to a systematic molecule design, KYNA derivatives will hopefully exhibit therapeutic potency in both preclinical and clinical studies.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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