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Kynurenines, neurodegeneration and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is one of the major causes of dementia. The pathogenesis of the disease is not entirely understood, but the amyloid β peptide (Aβ) and the formation of senile plaques seem to play pivotal roles. Oligomerization of the Aβ is thought to trigger a cascade of events, including oxidative stress, glutamate excitotoxicity and inflammation. The kynurenine (KYN) pathway is the major route for the metabolism of the essential amino acid tryptophan. Some of the metabolites of this pathway, such as 3-hydroxykynurenine and quinolinic acid, are known to have neurotoxic properties, whereas others, such as kynurenic acid, are putative neuroprotectants. Among other routes, the KYN pathway has been shown to be involved in AD pathogenesis, and connections to other known mechanisms have also been demonstrated. Oxidative stress, glutamate excitotoxicity and the neuroinflammation involved in AD pathogenesis have been revealed to be connected to the KYN pathway. Intervention at these key steps may serve as the aim of potential therapy.

Keywords: Alzheimer • kynurenine • oxidative stress • glutamate excitotoxicity • neuroinflammation

Alzheimer's disease

Alzheimer's disease (AD) is one of the most common causes of dementias. A recent report forecast that the prevalence of AD was set to rise to 35.6 million people globally by 2010 [1, 2], with the imposition of an enormous financial burden. The key feature of the disease is the progressive deficit in several cognitive domains [3–7], paralleled by regionally specific brain atrophy [8–11].

The first breakthrough towards an understanding of the pathomechanism of AD was the identification of amyloid β-peptide (Aβ) in the meningeal vessels of AD patients and later in the senile plaques [12–14]. Aβ is the product of the degradation of the amyloid precursor protein (APP), the gene of which is located on chromosome 21 [15–18]. The APP is cleaved by β- and γ-secretases. Mutations of the presenilin 1 and 2 (the subcomponents of γ-secretase), [19] and the APP [20–24] result in the accumulation of the amyloidogenic form of Aβ and the clinical picture of AD, but the genetically determined form of the disease is relatively rare. However, the oligomerization of Aβ seems to be the pivotal step in the pathogenesis of AD but the role of it was also questioned recently [25]. An intimate interaction between the oligomerization of Aβ and several other pathomechanistic mechanisms leads to the hyperphosphorylation of τ-proteins, the formation of neurofibrillary tangles, synaptic degeneration, oxidative stress, microglial and astrocytic activation, activation of the apoptotic cascade, cell death and transmitter deficiency (Figs 1 and 2). The aim of therapeutic approaches is to modify one or other of these individual steps, generally by anti-amyloid, neuroprotective or neurorestorative means.

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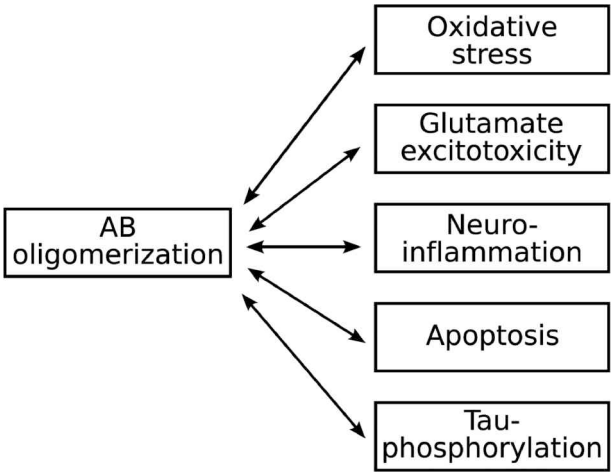

Fig. 1 Schematic outline of the pathomechanism of AD.

The kynurenine pathway

Neuroactive kynurenines

The kynurenine (KYN) pathway is the major route for the metabolism of the essential amino acid tryptophan (TRP) [26], the final product of which is nicotinamide adenosine dinucleotide (NAD) (Fig. 3). The first stable metabolite of the pathway is KYN, which is transformed either by KYN aminotransferase (KAT) to kynurenic acid (KYNA) or by KYN hydroxylase to 3-hydroxykynurenine (3-OH-KYN), which is further metabolized to quinolinic acid (QUINA), the precursor of NAD (Fig. 3). These metabolites are usually referred to as neuroactive KYNs [27, 28]. KYNA is an antagonist of the strychnine-insensitive glycine-binding site of the N-methyl-D-aspartate (NMDA) receptor [29, 30], a weak antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainite receptors [31] and also an inhibitor of the α_7 nicotinic receptor [32], which is involved in the pre-synaptic regulation of glutamate (L-Glu) release. Conversely, the neuroinhibitory effect of KYNA is concentration dependent: in nanomolar concentrations, it facilitates field excitatory postsynaptic potentials (EPSPs) [33]. QUINA is neurotoxic [34], and has been shown to be a direct activator of NMDA receptors [35], to modulate the release or reuptake inhibition of L-Glu [36] and to be involved in lipid peroxidation [37, 38] and the production of reactive oxygen species (ROS) [38, 39]. 3-OH-KYN also leads to cell death involving apoptotic features by generating ROS [39–42].

Enzymes of the kynurenine pathway

The rate-limiting step of the KYN pathway is TRP–KYN transformation, which is catalysed by indoleamine 2,3-dioxygenase (IDO) (Fig. 3.). IDO is known to be expressed by activated astrocytes, microglia and infiltrating macrophages [43], but neuronal expression has also been demonstrated [44].

The key enzyme in the production of putative neuroprotective KYNA is a transaminase. Four isoforms of KAT have been identified in the mammalian brain [45], which contribute differently to

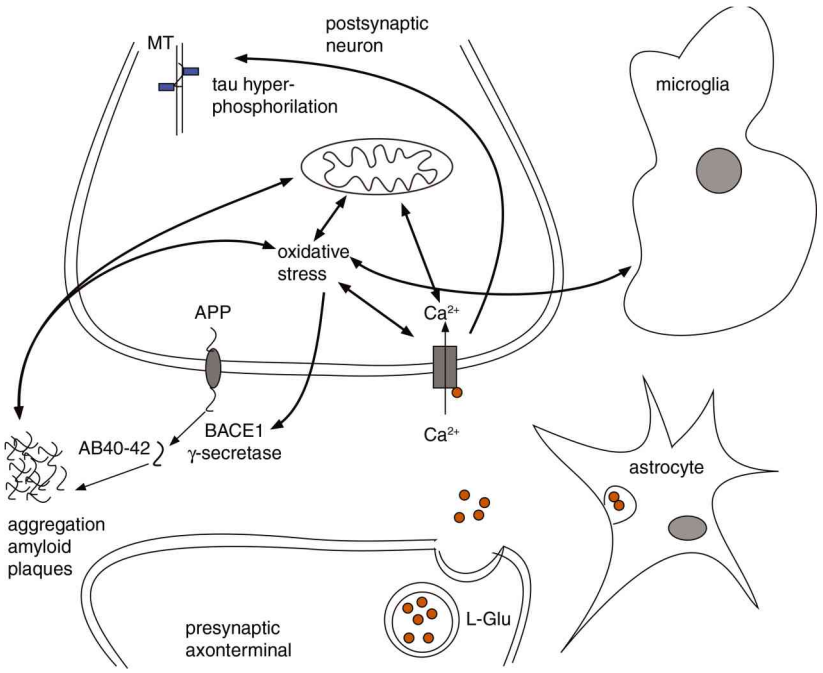

Fig. 2 Interactions of the major routes of the AD pathomechanism. The three main cellular components – the neuron, astrocyte and the microglia – are depicted in the figure. The central mechanism in the pathomechanism of AD is the aggregation of Aβ, which in turn activates several parallel but interacting pathomechanistic pathways: oxidative stress, neuroinflammation, τ-hyperphosphorylation, glutamate excitotoxicity.

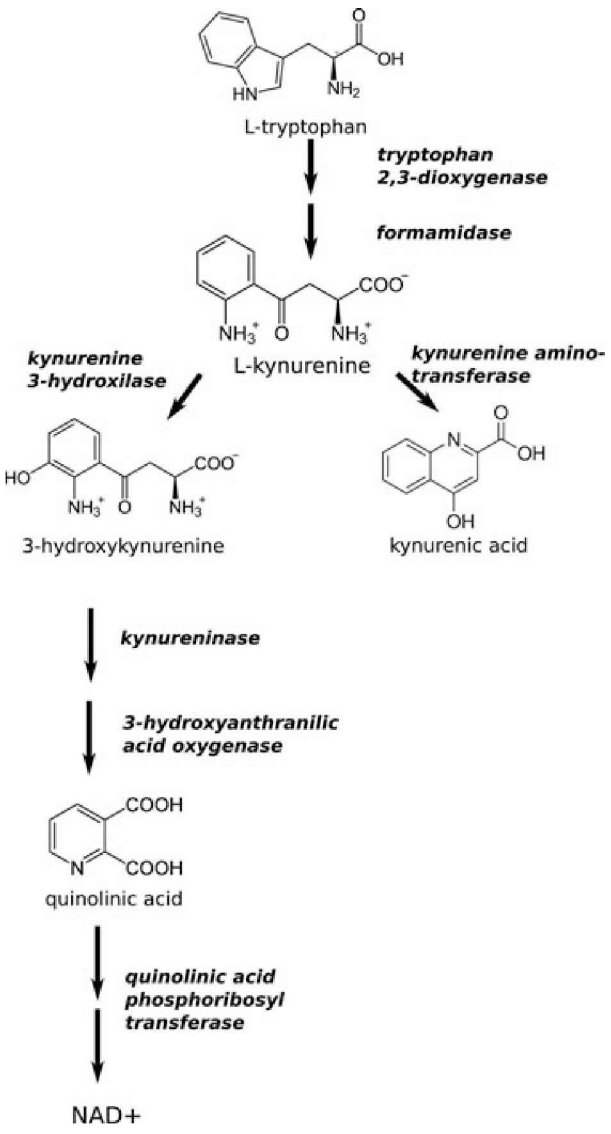

Fig. 3 The KYN pathway of the tryptophan metabolism. International Classification Number of the depicted enzymes: tryptophan 2,3-dioxygenase: EC 1.13.11.11; formamidase: EC 3.5.1.9; kynurenine-3-hydroxylase: EC 1.14.13.9; kynurenine aminotransferase: EC 2.6.1.7; kynureninase: EC 3.7.1.3; 3-hydroxyanthranilic acid oxidase: EC 1.13.11.6; quinolinic phosphoribosyltransferase: EC 2.4.2.19.

KYNA production in the different species [46]. The substrate profile, pH optimum and localization are different for the four isoforms. The pH optimum of KAT I and KAT III is relatively high, at around 9.5 to 10.0, whereas KAT II operates best at physiological pH and has a relative substrate specificity for KYN. KAT II is therefore the major biosynthetic enzyme of KYNA production in the brain. However, recent results indicated that the higher pH optimum of KAT I may well be due to methodological issues [47, 48]. Immunohistochemical studies indicated that KAT I and II are localized preferentially in the astrocytes [49, 50], whereas KAT IV (mitochondrial aspartate aminotransferase) is also present in neurons [51].

Importantly, downstream enzymes of the KYN pathway, such as 3-hydroxyanthranilate oxygenase, which leads to QUINA production, are expressed in the microglia, macrophages and astrocytes, but not in the neurons [52–54]. KYN hydroxylase seems to be an exception as it is not expressed in the astrocytes [55].

Relations of kynurenines to the pathomechanism of AD

Altered activation of the kynurenine pathway in AD

Alterations in the KYN pathway has been identified in several neurological and more specifically neurodegenerative diseases [56, 57], such as Huntington chorea [58], Parkinson's disease [59–62], multiple sclerosis [63, 64], focal dystonia [65] and migraine [66–69]. An increasing body of evidence indicates that the KYN pathway is involved in the pathogenesis of AD [70, 71]. Baran found slight decreases in the KYN and 3-OH-KYN levels in patients with pathologically confirmed AD [71]. A markedly increased content of KYNA was found selectively in the caudate nucleus and the putamen, which was correlated with increased KAT I activity. The level of aspartate aminotransferase in the cerebrospinal fluid (CSF) was found to be elevated in AD patients [72]. The mitochondrial form of the enzyme was identified as KAT IV [46]. The serum and red blood cell KYNA levels were decreased in AD patients, but there was no alteration in the KAT I or II activity [73]. Furthermore, the serum KYN/TRP ratio was found to be increased in AD patients, indicating and enhanced activity of IDO, the first key enzyme of the pathway [70]. Interestingly the TRP/KYN ratio also proved to be correlated with the cognitive performance of the patients [70]. Another study demonstrated lower KYNA concentration in the lumbar CSF in AD patients [74]. No alteration in QUINA was found either in the CSF [74] or in the examined cortical, subcortical or cerebellar structures [75]. $A\beta_{1-42}$ induced the expression of IDO and a significant increase in QUINA in human macrophages and microglia [76], but no similar effect of $A\beta_{1-40}$ was found [77]. A human AD brain preparation involving a subset of senile plaques displayed IDO and QUINA immunoreactivity, and these plaques were characterized by high microglia and reactive astrocytic contents [44].

Connection of oxidative stress and kynurenines

The central nervous system (CNS) is prone to oxidative stress-caused damage as it is rich in polysulphated fatty acids, has a high metabolic oxidative activity, has a high content of transition

metals and also exhibits relatively little antioxidant mechanism. Several lines of evidence indicate that oxidative stress has a key role in the pathogenesis of AD and especially in the initiation of pathological processes in sporadic AD [78–80]. *In vitro* studies have shown that Aβ in aqueous solution fragments and generates free radicals [81]. Post-mortem and animal model studies have confirmed the oxidative stress hypothesis by revealing signs of oxidative damage: changes in antioxidants (Cu/Zn superoxide dismutase [SOD] and glutathione reductase) [82], lipid peroxidation [83], free carbonyls [81] and peroxynitration [84]. A direct connection between Aβ and free radicals was proved by McLellan *et al.*, who demonstrated the co-localization of free radical-induced fluorescent staining with dense core plaques, but not with diffuse plaques in an *in vivo* transgenic mouse model and in *ex vivo* human AD tissue [85].

A close connection between APP/Aβ and the mitochondria had already been established. The APP and Aβ were found to be associated with the mithochondrial membrane [86, 87] and to bind to the mitochondrial matrix protein [88]. $A\beta_{1-42}$ inhibits cytochrome oxidase activity in a Cu-dependent manner [89]. Devi *et al.* found that the APP accumulates in the protein import channels of the mitochondria of AD patients and inhibits entry of the nuclearly encoded cytochrome c oxidase subunits in association with a decreased cytochrome activity and increased H_2O_2 production [90]. Similarly, Sirk *et al.* showed that $A\beta_{25-35}$ in a sublethal dose can inhibit the import of nuclearly encoded proteins to the mitochondria and that a sustained period of inhibited protein import leads to a reduced mitochondrial membrane potential and an increased level of ROS production [91]. Furthermore, Aβ promotes permeability transition pores in mitochondria [92], this effect seeming to be dependent on cyclophilin D as cyclophilin-deficient mitochondria are resistant to Aβ and Ca^{2+}-induced mitochondrial swelling and permeability transition [93].

In contrast, BACE an aspartyl protease with β-secretase activity [94, 95] can be induced by oxidative stress [96], which in turn leads to a proportional elevation of the carboxyl-terminal fragments of APP. This draws attention to the possible initiating role of oxidative stress in the pathogenesis of sporadic AD.

QUINA is known to cause an increased level of lipid peroxidation [37, 97], an effect that seems to be NMDA receptor dependent: MK-801, an NMDA receptor antagonist, can completely abolish QUINA-induced lipid peroxidation [97]. Another study raised the possibility that the lipid peroxidation effect of QUINA depends on iron and is likely to involve iron chelation by QUINA [98]. QUINA not only induces oxidative stress through the production of ROS, but also appears to influence the antioxidative mechanisms. The concentrations of reduced (GSH) and oxidized (GSSG) glutathione were decreased and increased, respectively, whereas the level of glutathione peroxidase remained stable, indicating a non-enzymatic conversion of GSH to GSSG [99]. The same study also showed that the cytosolic Cu/Zn SOD activity decreased, whereas the mitochondrial Mn SOD was unchanged after intrastriatal QUINA treatment [99], signifying the immediate cytoplasmatic effects of QUINA. Although ROS production seems to be a general feature of QUINA treatment, the lipid peroxidation effect is regionally specific in rat synaptosomes: the striatum and hippocampus displayed increased production of peroxidized lipids after QUINA treatment [38]. Furthermore, lipid peroxidation and oxidative stress could be antagonized by Nω-nitro-L-arginine, a selective antagonist of nitrogen monoxide synthase [100]. Nω-nitro-L-arginine was further shown to diminish KYNA synthesis by reducing the activities of KAT I and II [101, 102].

The importance of ROS production in QUINA toxicity was also demonstrated by the finding that free radical scavengers are able to attenuate the functional structural and behavioural effect of QUINA toxicity [103, 104].

Glutamatergic excitotoxicity

The key feature of glutamatergic neurotransmission is the rapid and efficient removal of L-Glu from the synaptic cleft with high-affinity transporters to prevent receptor over stimulation. L-Glu is taken up by the astrocytes, converted to L-glutamine, transported to the neurons and then recycled to L-Glu and finally packed into synaptic vesicles for reuse. Pathological accumulation of L-Glu leads to prolonged, tonic activation, sustained local depolarization and the influx of cations that trigger the further release of L-Glu. This vicious circle triggers intracellular events [105], primarily swelling of the neurons because of the increased cation concentration and consequent water influx, and secondly a delayed Ca^{2+}-dependent neuronal degeneration [106]. Neuronal degeneration is mediated by calpain I, which brings about cytoskeletal breakdown [107]. Phospholipases break down the cell membranes and generate arachnoidal acid [108], the metabolism of which generates free oxygen radicals and initiates apoptosis [109]. It has been shown that the NMDA receptor is closely linked to protein phosphatase 2A (PP2A), and stimulation of the NMDA receptor leads to the dissociation of PP2A and a reduction of the phosphatase activity [110]. This NMDA receptor-mediated mechanism may be involved in τ-hyperphosphorylation, a key step in the formation of neurofibrillary tangles [111].

As mentioned above, QUINA is the direct activator of NMDA receptors [35] and the neurotoxicity of the compound in sub-physiological concentrations is blocked by the NMDA receptor blockers MK-801 and memantine [112]. The neurotoxicity of QUINA was related in this experiment to the depletion of NAD^+, the activation of poly(ADP-ribose) polymerase, extracellular lactate dehydrogenase release and the induction of inducible and neuronal nitric oxide synthase [112]. The other possible mechanism by which QUINA induces AD pathology is PPA2-mediated τ-phosphorylation, which can be abrogated by memantine [111]. Interestingly, this effect of memantine seems to be unrelated to the glycine or L-Glu binding site of the NMDA receptor as PP2A inhibition-induced hyperphosphorylation could not be prevented by the NMDA antagonist 5,7-dichlorokynurenic acid or by D(-)-2-amino-5-phosphopentanoic acid [113].

QUINA was shown to increase the basal L-Glu release in an NMDA receptor-mediated manner [36, 114].

QUINA not only modulates the release of L-Glu but also inhibits the uptake of L-Glu to the astrocytes, which is considered to be one of the major processes in maintaining the L-Glu concentration below toxic levels [36]. A recent experiment demonstrating that KYN pre-treatment, which presumably leads to the production of KYNA in the astrocytes, is able to prevent the neurotoxic effect of L-Glu is indicative of the potential beneficial effect of KYN in neurodegenerative diseases [115].

Inflammation

An increased amount of reactive microglia is commonly found in the brain of AD patients [116, 117]. Most of them are around the Aβ-containing compact plaques [118–120]. Both immunohistochemical and *in vivo* imaging studies have revealed microgliosis-related signal changes in AD [121]. Furthermore, Edison *et al.* found that PET detected microglia activation, but not the amyloid burden correlated with the cognitive performance of the patients [122]. A role of the microglia has been proposed in the degradation of Aβ [123], but microglial activation also leads to activation of the complement system and the release of cytokines, chemokines and acute phase proteins (for reviews see [124–126]), which might also play a role in AD pathogenesis.

The KYN pathway is known to be involved in inflammatory processes with various mechanisms. Inflammation due to focal poliovirus is accompanied by the up-regulation of IDO, the rate-limiting step in the KYN pathway that results in increased levels of QUINA, KYN and KYNA [127, 128]. It has also been demonstrated that the sources of QUINA are the macrophages and to a lesser degree microglia. A human foetal brain culture consisting of neurons and astrocytes transformed TRP to KYN when stimulated by γ-interferon, but QUINA was formed only when macrophages were added to the culture [127, 129]. The abilities of macrophages and microglia to produce QUINA differ [130]; this is related to the lower expressions of three key enzymes of the KYN pathway in the microglia: IDO, kynureninase and KYN hydroxylase [131]. Aβ is known to induce phenotypic activation of the microglia and also to modulate the acute and chronic expression of pro-inflammatory genes [132, 133] that may produce potentially toxic products. Interestingly, besides many other pro-inflammatory genes, the expressions of the enzymes of the KYN pathway are also significantly altered by Aβ [124, 132]. Importantly, only $A\beta_{1-42}$, but not $A\beta_{1-40}$ or $A\beta_{25-35}$ activated THP-1 cells (a human monocytic cell line) [134]. Administration of γ-interferon after $A\beta_{1-42}$ pre-treatment, but not interleukin-1b, tumour necrosis factor-α or interleukin-6, induced the expression of IDO [134]. Microarray analysis of the gene expression profile of the Aβ stimulated microglia indicated an average increase of more than 40-fold (278-fold by real-time PCR) in IDO production at 24 hrs, which remained significantly elevated at 96 hrs [132]. Similarly, the expression of kynureninase was elevated (3.6-fold), but not that of KAT II. These data show that Aβ stimulation of the microglia shifts the KYN pathway in the direction of the production of neurotoxic QUINA relative to the putative neuroprotectant KYNA. In a recent study by Guillemin *et al.*, IDO and QUINA were overproduced in human AD hippocampus preparations [44]. Immunoreactivity of IDO and QUINA was detected in the microglia and astrocytes and also in the neurons. The intracytoplasmatic vesicular neuronal QUINA immunoreactivity is thought to be a result of the uptake rather than the *de novo* neuronal synthesis of QUINA as it was earlier shown that the neurons produce IDO, but not QUINA [135]. Further, the astrocytes lack KYN hydroxylase and consequently the uptake of QUINA might be part of the neuroprotective mechanism [43]. Additionally, QUINA induces astrogliosis and the production of chemokines such as interleukin 1β, MCP-1 (CCL2), RANTES (CCL5) and interleukine-8 (CXCL8) [136–139].

A future therapeutic approach: modulating the kynurenine pathway

The foregoing data indicate the significant involvement of the KYN pathway in the pathogenesis of AD. The key seems to be the shift in the TRP metabolism in the direction of neurotoxic agents and the relative reduction of neuroprotectant products. This shift has profound, but surely not independent effects on different pathomechanistic pathways in AD: oxidative stress, L-Glu neurotransmission and inflammation. Re-establishment of the physiological metabolite ratios, or even a shift of the TRP metabolism in the neuroprotectant direction may serve as a potential therapeutic approach [27, 140]. Synthetic KYNs such as KYNA are of limited therapeutic use as they penetrate the blood–brain barrier only poorly [141], an exception being 4-Cl-KYN that readily enters the brain and is transformed to 7-Cl-KYN by KAT [142]. The systemic administration of 4-Cl-KYN increased the level of 7-Cl-KYN in the hippocampus and reduced the kainite-induced seizure activity [142]. Similarly, 4-Cl-KYN reduced the neurotoxic effect of QUINA in the rat hippocampus and striatum [143, 144]. In contrast, the synthetic KYN derivative, NMDA antagonist 5,7-dichlorokynurenic acid did not attenuate PP2A inhibition-induced τ-hyperphospory-lation [113]. A substantial effort is being made to develop new KYNA derivatives that cross the blood–brain barrier [145]. We recently demonstrated that a novel KYN analogue, 2-(2-N,N-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride, exhibits features similar to those of KYNA [146]. In the micromolar range, its administration decreased the amplitude of the field EPSPs in the CA1 region of the hippocampus. Preclinical and subsequent clinical investigations of the compound are needed to evaluate its usefulness in neurodegenerative diseases such as AD.

Another possibility via which to increase the level of neuroprotectant KYNA is to modulate the activities of the individual enzymes of the KYN pathway. Nicotinylalanine, an agent that inhibits kynureninase and KYN hydroxylase activity, administered together with KYN and probenicid (an inhibitor of organic acid transport), increased the brain KYNA level and inhibited QUINA-induced neurotoxicity [147, 148]. Another such enzyme is KYN

hydroxylase, loss of function mutation of which in yeast reduces mutant huntingtin fragment toxicity [149]. Ro 61–8048, a high-affinity inhibitor of KYN hydroxylase significantly reduced the mutant huntingtin-induced production of 3-OH-KYN, but not that of QUINA production, and did not ameliorated ROS production [149]. In a recent study Amori *et al.* selectively inhibited KAT or KYN hydroxylase and reported the reduction of 3-OH-KYN – QUINA and KYNA production, respectively [150]. Interestingly pre-treatment with intrastriatal QUINA UPF 648 not only decreased the levels of 3-OH-KYN and QUINA, but also moderately elevated KYNA production [150].

Concluding remarks

There is appreciable evidence that the neurodegeneration in AD is mediated, at least partly, by neurotoxic products of the KYN pathway. Possible therapeutic approaches could be to reduce the expression of these neurotoxic agents or to increase the production of putative neuroprotectant KYNA or make use of its analogues. However, the specific involvement of the KYN pathway in AD, it also has to be emphasized that neurodegenerative diseases share several common features. Among other common mechanisms the shift in the KYN pathway seems to be general over different neurodegenerative diseases [27, 56, 58, 62–65] and such, neuroprotective therapies influencing the KYN pathway may be beneficial in several neurological pathologies.

Further research is needed to elucidate the exact role of the KYN pathway in the pathomechanism of these neurodegenerative processes in an effort to promote the development of novel therapeutic agents.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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