Targeting the kynurenine pathway-related alterations in Alzheimer's disease: a future therapeutic strategy

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Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disorder associated with dementia as a main feature. Despite decades of thorough research in the field of AD, the pathomechanism is still not fully understood. The development of novel experimental models can help us in the discovery of both genetic and non-genetic components of disease pathogenesis. As currently available therapies in AD can provide merely moderate or only temporary symptomatic relief, there is a great demand for the development of new drugs with higher therapeutic potential. Some of the candidates would be those of targeting the kynurenine pathway, the neuroactive metabolites of which are surely involved in both neurodegeneration and neuroprotection, mainly in relation with glutamate excitotoxicity and oxidative stress. Both analogs of the neuroprotective kynurenic acid and small molecule enzyme inhibitors preventing the formation of neurotoxic compounds may have potential therapeutic significance. However, there is a great need for new strategies via which to improve the efficacy, the transport across the blood-brain barrier and bioavailability, naturally with simultaneous minimization of the adverse side-effects.

Key words: Alzheimer's disease, kynurenine pathway, animal models, therapy

Alzheimer's disease

Alzheimer's disease (AD) is the most common age-related, progressive neurodegenerative disorder. It usually starts with a memory loss and leads to a cognitive deficit and dementia. There are many behavioral symptoms, *e.g.* aggression, agitation and psychosis, which are responsible for the distressing aspect of AD and pose a great emotional, physical and economic challenge [1-2]. AD selectively affects numerous neuronal populations involving glutamatergic neurons in the hippocampus and cortex, basal forebrain cholinergic neurons and brainstem monoaminergic neurons [3-5] and cortical synapses [6-7]. The disease is characterized by neuropathological changes such as amyloid-beta (Aβ) plaques and neurofibrillary tangles, in the regions responsible for memory formation consisting of glutamatergic circuits. A severe reduction in mitochondrial complex IV activity suggests that an energy deficit plays a key role in the development of AD [8]. Most AD cases are sporadic and numerous heritable mutations in the amyloid-β precursor protein (AβPP), which belongs to the type 1 transmembrane family of glycoproteins, have been linked to the disease. The AβPP has a Swedish mutation, in which Lys-595 and Met-596 are replaced by Asp and Lys, respectively. This enhances the early onset and propagation of AD, and leads to the cognitive impairments associated with AD [9]. The

expression of the Swedish mutation alters the overall gene expression, including AD-related kinases, phosphatases, presenilin-2, and glycogen synthase kinase-3β [10]. The cleavage of AβPP by β- and γ-secretases leads to the formation of Aβ peptides, which assemble into extracellular amyloid plaques [11]. Close correlations were reported in earlier studies between the severity of the different diseases and the degree of amyloid accumulation. It has recently become rather uncertain whether amyloid aggregates really are the basic toxic species amongst conformational forms. These may rather represent a protective mechanism by segregation of toxic intermediates in the amyloid assembly pathway [12]. Presenilin-1 is the most common gene in AD and 177 mutations have so far been identified in this gene. One of the up-to-date mutations in presenilin-1, I202F, occurs in exon 7 of the presenilin-1 gene and the fourth transmembrane domain of presenilin-1 protein. This new mutation fits the pattern, in accordance with previously defined presenilin-1 mutations, lining up along the helical transmembrane domains of presenilin-1 [13-14].

Insoluble fibrillar tau-protein deposits are typically observed within the cell bodies and dendrites of the neurons [15]. These neurofibrillary tangles are the other major pathogenic marker of AD. R406W is the unique tau mutation causing AD-like dementia and tauopathy in humans

and it has the special ability to reduce tau phosphorylation in cultured cells [16-18] or *in vitro* by recombinant glycogen synthase kinase-3β [19].

Some *in vivo* models of Alzheimer's disease

The most important task at present is to develop new disease-modifying modes of treatment. Before making effort to stop or at least slow neurodegenerative processes, a better understanding of the pathophysiology of diseases is needed, which demands on better animal models. With the aid of such animal models, new disease-modifying therapies can be tested and improved. The ideal animal model should meet many requirements. However, it must be borne in mind that animal models can never be perfect. Certain biochemical and physical differences have been demonstrated in the amyloid plaques in AD patients and in AD animal models. In one of the transgenic mouse models of AD, the ATP-gated P2X7 purinergic receptor cation channel is upregulated around amyloid peptide plaques and co-localizes to microglia and astrocytes. After ischemia in the cerebral cortex of rats and also following spinal cord injury, upregulation of the P2X7 receptor subtype on the microglia occurs, while the P2X7 receptor-like immunoreactivity is enhanced in the activated microglial cells of the MS

and ALS spinal cord [20]. As an *in vitro* model for neuroinflammation involving the application of neuron/microglia co-cultures, P2X7 receptor activation on microglia appears necessary for the microglial cell-mediated injury of neurons.

In recent years, a novel triple mutant mouse model of AD (3xTgAD mice) has been generated, in which the mice exhibit age-dependent Aβ deposition and tau-pathology in the hippocampus and cerebral cortex [21-22]. These mice express familial AD AβPP and presenilin-1 mutations, together with a tau mutation [21].

Non-mammalian organisms can also provide suitable information about the disease. In a nematode, a *Caenorhabditis elegans* screening mutation revealed a relationship between presenilins and the Notch signaling pathway [23]. In consequence of human Aβ expression in *Caenorhabditis elegans* [24] and *Drosophila melanogaster* [25], amyloid deposits in muscle and neurodegeneration can also be observed. With the help of yeast, Aβ toxicity can be studied well [26]. As a brief evasive as regards the use of yeast in modelling neurodegenerative disorders, it is important to mention here that Giorgini et al performed a genomic screen in yeast to identify gene deletions that suppress the toxicity of a mutant Htt fragment (Htt103Q). This study suggests that a conserved mechanism of polyQ toxicity might be observed in yeast and Huntington's disease

(HD) patients involving upregulation of the kynurenine pathway metabolites. The mitochondrial kynurenine 3-monooxygenase is activated in HD patients and also in animal model of HD. Pharmacological inhibition of this may revise mutant Htt-mediated toxicity [27]. Later they published that a histone deacetylase (HDAC) inhibitor entirely blocks increases in kynurenine pathway metabolites in microglia of HD mice. This suggests that transcription of the kynurenine pathway is regulated by HDAC activity in mammalian cells [28]. So the yeast genom screening might serve as a rapid testing tool to explore the involvement of kynurenine pathway alterations in the development of AD. Use of these organisms has provided a possibility for the screening of drug libraries with the aim of the discovery of new compounds that block Aβ toxicity [29]. Paquet et al. have created the transgenic expression of the human tau-P301L protein in zebrafish neurons, in a design involving a Gal4-upstream activating sequence-based vector system [30]. The pathology of the disease, the specific hyperphosphorylation and the conformational changes in tau, can be better monitored than earlier. This is the first demonstration of *in vivo* cell death imaging. Additionally, neurons can be observed in their natural environment, together with astroglia, oligodendrocytes and microglia [31]. Because of the rapid appearance of pathologic phenotypes,

transgenic zebrafish larvae can be utilized not only to monitor and understand processes of diseases *in vivo*, but also to test and validate drugs on a large scale [30] (Table 1).

Mitochondrial impairment and neurodegeneration

The key cytoplasmic organelles, the mitochondria, are vital for the function and survival of neurons. These are the energy powerhouse of the cells, because they provide energy from the aerobic metabolism. Mitochondria are both important sources and targets of reactive oxygen species (ROS). Damaged mitochondria demonstrate an increased level of generation of reactive oxidants, *e.g.* ROS. Healthy aging is associated with a decreased neuronal mitochondrial metabolism and recent studies suggested an altered glial mitochondrial metabolism [32]. High levels of ROS can induce mitochondria-impairing mechanisms, such as a mitochondrial permeability transition, and uncouple oxidative phosphorylation, leading eventually to cell death via apoptosis or necrosis. The mitochondrial damage can comprise a respiratory chain enzyme or mitochondrial DNA (mtDNA) impairment. Oxidative stress and damaged mtDNA in aging impair the ion homeostasis and mitochondrial energy metabolism in the neurons, thereby making them vulnerable to degeneration [33]. Dysfunctions of the mitochondrial

energy metabolism contribute to the generation of ROS, disturbed Ca^{2+} buffering and a reduced ATP metabolism [34].

In the AD brain, the significantly enhanced oxidative damage may cause a mitochondrial dysfunction and abnormal dynamics, leading to an energy deficit in AD neurons [35]. The oligomeric Aβ peptide plays a crucial role in the formation of the mitochondrial permeability transition pore [36], thereby contributing to the mitochondrial dysfunction in the AD brain [37], including impaired ATP production and increased levels of oxidative stress. Impaired axonal transport with the proximal accumulation of mitochondria can lead to the loss of distal synapses [38]. Altered calcium homeostasis has also been reported in AD, related to Aβ production, presenilin mutations and tau phosphorylation [39-40].

The role of excitotoxins in neurodegeneration

One of the major causes of the development of neurodegenerative processes is excitotoxicity, first described by Olney in 1969 [41]. During this pathological phenomenon, neurons are damaged or killed by the overactivation of receptors of excitatory neurotransmitters, such as *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors. Classical excitotoxicity involves three connected steps of a cascade mechanism

that occur in parallel: a Na^+ influx, a Ca^{2+} influx and the exocytosis of glutamic acid, leading to persistent depolarization of the neurons. Glutamate is the major excitatory neurotransmitter in the mammalian CNS, and the principal example of an excitotoxin in the brain [42]. The abnormal function of glutamate receptors may result in an enhanced release of glutamate. The changes in glutamate uptake may elevate the extracellular concentration of glutamate accompanying the excitotoxic process [43]. Excitotoxicity can occur in consequence of endogenous excitotoxins. These substances, which can act on the receptors of cerebral excitatory amino acids, may also play important roles in the pathogenesis of certain brain disorders, *e.g.* AD, Parkinson's disease, HD, amyotrophic lateral sclerosis, stroke, multiple sclerosis (MS), epilepsy and migraine [44-45]. The activation of excitatory amino acid receptors results in the selective neuronal death characteristic of these diseases [46-48]. In the pathogenesis of AD, glutamate excitotoxicity plays a key role. Neurons exposed to Aβ demonstrate increased vulnerability to this phenomenon. Overstimulation of ion-channel glutamate receptors may result in oxidative events and these receptors are up-regulated following Aβ exposure. The glutamatergic tone and Aβ may act synergistically [49]. Some studies suggest that in specific brain areas glutamatergic signaling is compromised by Aβ-induced modulation of synaptic glutamate

receptors, resulting in an early cognitive deficit [50]. A Ca^{2+} overload can raise the level of kinase activation, with the formation of neurofibrillary tangles [51].

Drugs that block NMDA or other glutamate receptors, and also compounds that decrease glutamate release, attenuate some of the pathological symptoms in experimental models of acute and chronic neurodegenerative diseases [52]. As NMDA receptor antagonists, the glycine and polyamine site agents, NR2B subunit specific antagonists and ion channel blockers may come into consideration as they have acceptable side-effects [53]. Thus, the glycine site agent kynurenic acid (KYNA) might appear to be a good candidate, but from a pharmacological aspect, it has several disadvantages, mainly as regards the route of its administration, its elimination half-life and its penetration through the blood-brain barrier. In recent years, therefore, several new KYNA analogs or prodrugs have been designed in attempts to get round these disadvantages [54]. One of the most important groups of these compounds comprises the KYNA amides [55], which may selectively inhibit the NR2B subunit of NMDA receptors [56].

Summary of currently available therapies in Alzheimer's disease

Cholinesterase inhibitors can moderate AD. Through impeding of the action of acetylcholinesterase (AChE) with AChE inhibitors (AChEIs), the action of ACh and its interaction with cholinergic receptors and K^+ channels can be prolonged. AChEIs such as donepezil, rivastigmine and galantamine have moderate beneficial effects on memory and cognition [57]. *In vitro* studies have revealed that donepezil possesses a neuroprotective effect through decreasing glutamate excitotoxicity, reducing Aβ toxicity and increasing the survival of cells. In contrast, donepezil and rivastigmine offer only a symptomatic effect without neuroprotection [58-59].

An AChEI of natural origin, galantamine, provides protection for neurons and reduces cell death. Galantamine can increase dopaminergic neurotransmission in the hippocampus of mice [60]. In the human brain, galantamine either prevents or improves the decline of cognition and daily activities [61].

As compared with donepezil and galantamine, rivastigmine is more effective because it can inhibit both AChE and butyrylcholinesterase. It can reduce the cortical atrophy and slow the rate of decline for as long as 5 years [62-63].

Memantine is an NMDA receptor antagonist [64] which inhibits the influx of Ca^{2+}, thereby reducing cell damage and resulting in moderate improvements in behavior and cognition [65]. This is the only well-tolerated and safe drug in clinical use for AD that targets the glutamatergic system. There are reports that memantine can inhibit the abnormal phosphorylation of tau [66-67]. A comparative study has indicated that neither donepezil nor memantine furnishes a significant improvement in mild AD [68].

The kynurenine pathway and its alterations in Alzheimer's disease

L-Kynurenine (L-KYN) is one of the major intermediates of the tryptophan metabolism, in which L-tryptophan is transformed into nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate, these two co-enzymes being essential for cellular mechanisms [54; 69-70] (Figure 1). L-KYN, the central compound of the kynurenine pathway, can be metabolized in two distinct pathways, to KYNA or to 3-hydroxy-L-kynurenine (3-OH-L-KYN) and quinolinic acid (QUIN). Under both physiological and pathological conditions, these neuroactive kynurenines play pivotal roles [71] (Table 2).

60% of the mammalian brain L-KYN content is taken up from the blood by a neutral amino acid carrier, and the remaining 40% is produced

locally in the brain [72]. The rate of cerebral L-KYN production has been reported to be 0.29 nmol/g/h [73]. Its key role is to serve as a precursor of neuroprotective KYNA and the neurotoxic 3-OH-L-KYN (Figure 2). The level of L-KYN in the cerebrospinal fluid (CSF) does not change in AD. L-KYN is transformed to KYNA by irreversible transamination on the action of kynurenine aminotransferases (KATs). In high, nonphysiological concentrations, KYNA has proved to be a broad-spectrum endogenous antagonist of ionotropic excitatory amino acid receptors [74]. It exhibits a high affinity for the glycine-binding site of the NMDA receptor, blocking its activity in low micromolar concentrations [75] and it is additionally a weak antagonist of the AMPA/kainate receptors [76]. It has recently been demonstrated that KYNA in nanomolar concentrations displays a neuromodulatory effect, whereas in micromolar concentrations, above the physiological range, it inhibits the neuronal activity [77-78]. Moreover, KYNA noncompetitively blocks the α7-nicotinic acetylcholine (α7-nACh) receptors and can increase the expression of non-α7-nACh receptors [79-80]. It has been concluded that cross-talk occurs between KYNA and the cholinergic system, a situation which has been presumed to play a role in the pathogenesis of numerous brain impairments [81]. In view of its pharmacological activity, it seems to possess a neuroprotective potential,

but in very high concentrations it can exert adverse effects, as exemplified by the intracerebroventricular injection of KYNA into rats, which results in reduced exploratory activity, ataxia, stereotypy, sleeping and respiratory depression [82]. Under physiological conditions, elevation in KYNA concentration can result in cognitive impairment [83-84]. However, under pathological conditions, the situation can be different. Due to glutamate excitotoxicity, a receptor overactivation occurs, where anti-glutamatergic agents can help in setting up again the basal level of activation, promoting a memory regain in cognitive impairment.

QUIN participates in the kynurenine pathway, leading to the synthesis of the essential co-enzyme NAD^+. It is present in nanomolar concentrations in the brain and exerts pronounced effects on the NMDA-sensitive subpopulation of glutamate receptors [85]. It is a weak, but specific competitive agonist of the NR2A and NR2B NMDA receptor subtypes [86-87]. When the level of QUIN in the brain becomes elevated, it exhibits an excitatory effect at the NMDA receptors. It can provoke lipid peroxidation [88], produce toxic free radicals [89] and induce astrocytes to generate various chemokines, such as IFN-γ, IL-1β and TNF-α [90-92]. Interesting results are manifested by AD patients as concerns the immunoreactivity of QUIN and one of the first tryptophan metabolism

enzymes, indoleamine-2,3-dioxygenase-1 (IDO-1). High expressions of QUIN and IDO-1 have been observed in the human hippocampus and neocortex and in senile plaques [93]. In the hippocampus of the AD brain, which is one of the most vulnerable regions in AD, both IDO-1 expression and QUIN accumulation have been detected in the cortical microglia, astrocytes and neurons [93]. IDO is induced in various types of inflammation, and complex and multiple inflammation occurs in AD progression [94]. The observed up-regulation of IDO and the accumulation of QUIN are thus considered to be feasible. It has been shown that a soluble oligomer of Aβ peptide activates the microglia *in vitro*, while inducing QUIN production and IDO expression in the cells [95]. Stone et al. reported that free radicals may be involved in the neurotoxic effects of QUIN and considered the possibility that QUIN may play a role in AD [96].

3-OH-L-KYN may also cause neuronal death because it generates ROS [97]. Bonda et al. used immunocytochemical methods to demonstrate the roles of some intermediates of the kynurenine pathway in the pathogenesis of AD. They observed that 3-OH-L-KYN and its cleaved product 3-hydroxyanthranilic acid (3-HAA) significantly damage the neuronal tissues and presumably participate in neurodegeneration through glial activation, consequent Aβ activation and upregulation of

the kynurenine pathway. Elevated levels of 3-OH-L-KYN and the rate-limiting enzyme IDO-1 were observed; this latter was shown to be specifically localized in conjunction with neurofibrillary tangles, and the association of IDO-1 with senile plaques was confirmed [98].

Pharmacological manipulation of the kynurenine pathway with a view to the treatment of Alzheimer's disease

Abnormalities of the kynurenine pathway clearly play a crucial role in the neurodegeneration involved in various neurological and psychiatric disorders [71]. Subsequent to the availability of novel pharmacological agents, a number of interesting features of L-KYN biology have recently been discovered [54]. In another animal model, L-KYN combined with probenecid rescued the Schaffer collateral-CA1 synapses from impaired long-term potentiation induction after transient global ischemia [99]. One of the most important treatment possibilities is the modulation of kynurenergic compounds because this can furnish one of the greatest biochemical armaments [100]. Effective inhibitors of mammalian kynurenine 3-hydroxylase, 4-chloro-3-hydroxyanthranilic acid (4-Cl-3-HAA) oxygenase and IDO have been available for years. The targeting of other pathway enzymes has lagged behind. Most of the original enzyme inhibitors were simple derivatives or structural analogs of the

naturally occurring substrates, e.g. for 3-HANA oxygenase and 1-methyltryptophan (for IDO).

With regard to the pharmacological features of the kynurenines, an elevated level of KYNA in the CNS seems to be a potential therapeutic possibility. Fortunately, KYNA behaves as an endogenous neuroprotective agent and can prevent neuronal loss following excitotoxic, infectious or ischemia-induced neuronal injuries [101-103]. 5,7-Dichlorokynurenic acid and 7-chlorokynurenic acid (7-Cl-KYNA) are well-known KYNA analog NMDA glycine site antagonists [104]. 5,7-Dichlorokynurenic acid did not reverse the phosphatase inhibitor okaidic acid-induced AD-type abnormal hyperphosphorylation of tau in hippocampal organotypic cultures [105]. The *in situ* production of 7-Cl-KYNA can be achieved through use of the blood-brain penetrable pro-drug 4-chlorokynurenine (4-Cl-KYN), which is preferentially metabolized in brain areas where neurodegeneration takes place, allowing administration of a lower dosage of the drug [106]. The systemic administration of 4-Cl-KYN did prevent quinolinate-induced neurotoxicity in the hippocampus of the rat [107]. Further, 4-Cl-KYN can be transformed into 4-Cl-3-HAA, a potent, selective inhibitor of 3-HAA oxygenase [108], and thus it can inhibit QUIN synthesis too, besides blocking the NMDA receptors. Hence, modification of the

kynurenine pathway through pharmacological inhibition of the enzymes of QUIN synthesis is a rational approach via which to divert the kynurenine metabolism toward the neuroprotective KYNA [109]. Novel chemical structures have been identified by further rational design or by screening chemical libraries (*e.g.* the discovery of *N*-(4-phenylthiazol-2-yl)benzenesulfonamides as potent kynurenine 3-hydroxylase inhibitors) [110]. Potent and specific kynureninase blockers which preferentially inhibit the mammalian enzyme were recently synthesized [111-112]. These enzyme inhibitors have so far not been examined *in vivo*, but can be expected to play a crucial part in the dynamics of the kynurenine pathway metabolism [54].

Conclusion

The search for effective treatments for neurodegenerative disorders [113], especially for AD, is currently one of the most important topics of research relating to healthcare. Drug screening can be carried out through the use of different animal models and new biochemical targets. Following reassuring preclinical results, the design of clinical studies might be considered. The pharmacological manipulation of the kynurenine pathway, either using analogs of the pathway compounds or small molecule enzyme inhibitors would serve as promiseful therapeutic

approaches. However, the synthetic compounds should match several criteria. For example, prolonged absorption into the circulation, increased plasma half-life, better penetration through the blood-brain barrier and rather selective pharmacodynamic actions should be aimed at. Furthermore, the designed compounds should have as few side-effects as possible at the protective dose. In relation to AD, none of the drugs, targeting the kynurenine pathway, has ever been tested in clinical trials. Although there are numerous reassuring preclinical experiments, it is hard to set up well-designed clinical trials for several reasons. Firstly, it would be hard to carry out the testing of kynurenine pathway targeting compounds, especially the KYNA analogues, in normal subjects, because under normal conditions, these may induce cognitive dysfunction. Secondly, it would be to risky to test these compounds alone in patients with AD, lacking the currently used therapeutic agents. However, the set up of well-designed treatment regimes, using promising kynurenine pathway targeting compounds as a part of combination therapies with currently available therapeutic agents in AD may exert additional beneficial effects in that devastating disease. Hopefully, drugs targeting the kynurenine pathway would serve as an alternate choice amongst anti-glutamatergic agents in addition to the currently available memantine in the future treatment of AD.

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Figure 1.

A schematic outline of the kynurenine pathway

The kynurenine pathway is involved in the metabolism of tryptophan, in which L-tryptophan is transformed into NAD^+ and neuroactive intermediates, such as KYNA and QUIN.

Figure 2.

The role of kynurenine pathway in the neuronal function

L-TRP: L-tryptophan; L-KYN: L-kynurenine; 3-OH-L-KYN: 3-hydroxy-L-kynurenine; KYNA: kynurenic acid; 3-HAA: 3-hydroxyanthranilic acid; QUIN, quinolinic acid; NMDA-R: NMDA receptor; α7-nACh-R, α7 nicotinic acetylcholine receptor

Disease	Model	Results	References
Alzheimer's disease	transgenic AD mice, rats	P2X7 receptor antagonist improves recovery after spinal cord injury	[20]
	3xTgAD mice	preserved learning and memory	[21-22]
	human presenilin-1 mutant C. elegans	relationship between presenilins and Notch signalling	[23]
	human Aβ expression in tg C. elegans	in vivo investigation of factors that modulate amyloid formation	[24]
	Drosophila model of AD	reduction of Aβ aggregation	[25]
	Aβ in yeast	fibrillar Aβ has low toxicity	[26]
	human tau-P301L protein in zebrafish	hyperphosphorylation can be monitored well	[30]

Table 1. Some *in vivo* models of Alzheimer's disease

AD: Alzheimer's disease; Aβ: amyloid-beta; C. elegans: Caenorhabditis elegans

Metabolite	Level	Function	Dysfunction	Reference
L-KYN	Normal	precursor of KYNA and 3-OH-L-KYN		[73-74]
KYNA	High	it has proved to be a broad spectrum endogenous antagonist of ionotropic EAARs	it inhibits physiological neuronal activity	[74] [77-78]
	Low	it has neuromodulatory effect; non-competitively blocks the α7-nACh receptors and increases the expression of it		[77] [79-81]
QUIN	Normal	It is a specific agonist of NMDA receptor subtypes		[86-87]
	high		it can provoke lipid peroxidation, produce toxic free radicals and induce astrocytes to	[88-92]

		generate chemokines	
3-OH-L-KYN	Normal	causes neuronal death	[97]
	high	damages neuronal tissues, participates in neurodegeneration through glial activation and Aβ activation	[98]

Table 2.
Biochemical implications of kynurenine metabolites in neuronal function