Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines

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ABSTRACT

The pathomechanism of Alzheimer's disease (AD) certainly involves mitochondrial disturbances, glutamate excitotoxicity, and neuroinflammation. The three main aspects of mitochondrial dysfunction in AD, i.e., the defects in dynamics, altered bioenergetics, and the deficient transport act synergistically. In addition, glutamatergic neurotransmission is affected in several ways. The balance between synaptic and extrasynaptic glutamatergic transmission is shifted toward the extrasynaptic site contributing to glutamate excitotoxicity, a phenomenon augmented by increased glutamate release and decreased glutamate uptake. Neuroinflammation in AD is predominantly linked to central players of the innate immune system, with central nervous system (CNS)-resident microglia, astroglia, and perivascular macrophages having been implicated at the cellular level. Several abnormalities have been described regarding the activation of certain steps of the kynurenine (KYN) pathway of tryptophan metabolism in AD. First of all, the activation of indolamine 2,3-dioxygenase, the first and rate-limiting step of the pathway, is well-demonstrated. 3-Hydroxy-L-KYN and its metabolite, 3-hydroxy-anthranilic acid have pro-oxidant, antioxidant, and potent immunomodulatory features, giving relevance to their alterations in AD. Another metabolite, quinolinic acid, has been demonstrated to be neurotoxic, promoting glutamate excitotoxicity, reactive oxygen species production, lipid peroxidation, and microglial neuroinflammation, and its abundant presence in AD pathologies has been demonstrated. Finally, the neuroprotective metabolite, kynurenic acid, has been associated with antagonistic effects at glutamate receptors, free radical scavenging, and immunomodulation, giving rise to potential therapeutic implications. This review presents the multiple connections of KYN pathway-related alterations to three main domains of AD pathomechanism, such as mitochondrial dysfunction, excitotoxicity, and neuroinflammation, implicating possible therapeutic options.

1. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent progressive neurodegenerative disorder, characterized by age-related memory impairments and personality changes, placing a significant burden not only on the families and caregivers, but on the global economy as well [1]. As a result of the great scientific effort which was made to reveal the complex pathomechanism of AD, the deleterious factors responsible for disease development are becoming better understood [2]. However, currently only symptomatic therapies are available for this insidious condition, and there is at present no curative treatment available [3]. Accordingly, there is a huge need for the identification of novel therapeutic targets via which a better symptomatic or causative care may be provided beside the more widely applied preventive measures. **A number of hypotheses exist with regard to the pathogenesis of AD. In addition to the probably most popular amyloid cascade and tau hypotheses, some alternative ones, such as those related to DNA damage, aberrant neuronal cell cycle re-entry, and demyelination, have been elaborated to explain certain discrepancies in the current models and the serial failure of clinical trials assessing drugs targeting amyloid- or tau-induced alterations, and to try to fill the remaining gaps [4]. However, the pathological hallmarks currently applied to establish the definite diagnosis of AD during autopsies are amyloid plaques and neurofibrillary tangles, keeping in mind that the exact initiating factor in AD pathogenesis still remains unknown. Despite the mostly unknown initiating factor, downstream mitochondrial disturbances, glutamate excitotoxicity, and neuroinflammation serve as probably the most important linking points in neurodegenerative disorders, being demonstrated in human and experimental studies in AD as well, in addition to the distinguishing proteinopathic features of neurodegenerative conditions. Some metabolites and enzymes of the kynurenine (KYN)**

pathway of tryptophan (TRP) metabolism have come into focus of recent research with regard to these three cardinal aspects of neurodegeneration [5].

The aim of this review is to highlight some aspects of mitochondrial disturbances, glutamate excitotoxicity, and neuroinflammation and their relations to the **multiple documented** alterations of the KYN pathway of the TRP metabolism (Fig. 1) in AD **and its experimental models**, with the delineation of some possible therapeutic targets, **without attempting an in-depth analysis of current leading and alternative hypotheses of AD, an effort exceeding the scope of this current paper.**

2. MITOCHONDRIAL DISTURBANCES IN ALZHEIMER'S DISEASE

There are three main aspects of mitochondrial dysfunction in AD: 1) defects in mitochondrial fission/fusion (i.e., dynamics); 2, altered mitochondrial bioenergetics; and 3) defects in mitochondrial transport [6-8].

Mitochondrial dynamics is a process consisting of fusion (a moving mitochondrion interacts with a passive one forming a tubular network) and consecutive fission (a segmentation resulting in two mitochondria) [9, 10]. Fusion is mediated by mitochondrial inner membrane GTPases optic atrophy 1 (Opa1) and mitofusin 1 and 2 (Mfn1 and Mfn2), whereas fission is regulated by mitochondrial outer membrane division proteins dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) amongst others. The analysis of brain samples of AD patients demonstrated fragmented and punctuated mitochondrial morphology resulting from dysfunctional mitochondrial dynamics [11, 12]. Accordingly, the mRNA levels of Fis1 were increased, whereas those of Opa1, Mfn1, Mfn2, and surprisingly Drp1 were decreased in AD brains [13]. *In vitro* studies, where M17 or N2a cells overexpressing the wild-type amyloid-beta (Aβ) precursor protein (AβPP) or that of comprising the Swedish mutation (AβPP^{sw}) were applied, demonstrated that Aβ accumulation resulted in decreased

Mfn1, Mfn2 and Opa1, whereas Fis1 levels were increased, accompanied with the fragmentation of mitochondria and reduction in their number [12, 14]. Alterations in the level of Drp1 are controversial, because it was demonstrated to be unchanged or interestingly decreased [12, 14]. The fragmentation of mitochondria was also confirmed in neuronal cell cultures obtained from a transgenic (Tg2576) mouse model of AD, where *Fis1* gene and protein were significantly upregulated, whereas *Mfn1* gene and protein were decreased [15]. Furthermore, the application of oligomeric Aβ-derived diffusible ligands (ADDL) induced the decrease of mitochondrial length and reduced mitochondrial density in neurites and axons via the impairment of their bidirectional transport [16-18]. The underlying reason for Aβ-induced mitochondrial alterations may be the presence of direct interaction of Aβ aggregates with these organelles, followed by their accumulation related to translocase of outer membrane 40 (TOM40) and translocase of inner membrane 23 (TIM23) [19-21]. This pathological Aβ accumulation blocks the import of cytoplasmic proteins into the mitochondria, interfering with their functionality, and its extent was linked to the degree of cognitive impairment of AD [21, 22]. One aspect of this impaired functionality may be the interaction of Aβ with Drp1 [23]. In a mouse model of AD, the observed association of Aβ with synaptic mitochondria may serve as one of the culprits for synaptic degeneration characteristic of AD [18]. In addition to Aβ-related impairment in mitochondrial dynamics, tau may also have a pathological influence on it [24, 25]. Accordingly, the co-localization of hyperphosphorylated tau protein with Drp1 was demonstrated as well with the presence of excessive mitochondrial fragmentation [26].

In addition to its effect on mitochondrial dynamics, the binding of Aβ to the mitochondria results in deficient energy production as well, considerably contributing to the pathogenesis of AD [27, 28]. The assessment of mitochondria isolated from brain specimens of AD patients demonstrated the reduced activity of cytochrome c oxidase (i.e., complex IV of the electron

transport chain (ETC)) and ATP synthase (i.e., complex V of the ETC), with a compensatory increased expression of the corresponding genes [29-33]. Furthermore, the reduced activity of key mitochondrial matrix enzymes, such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase was demonstrated as well [34-36]. The presence of alterations in mitochondrial bioenergetics was clearly detected in *in vitro* or *in vivo* models overexpressing AβPP or AβPP[sw] with or without mutations in the presenilin 1 (PS1) or presenilin 2 (PS2) or tau genes [12, 27, 37-47]. In addition to enzymatic dysfunction, oxidative stress-induced damage of mitochondrial DNA (mtDNA) is pronounced as well, and accordingly, the *post mortem* analysis of the brains of AD patients demonstrated increased rate of mtDNA mutations and decreased mtDNA copy number [48-51]. The exposure of mitochondria to different Aβ species and their accumulation resulted in impaired activity of the ETC with a consequent decrease in respiration rates and mitochondrial membrane potential and an increase in reactive oxygen species (ROS) production [39, 52-56]. The pathological interactions involve the inhibition of Aβ-binding alcohol dehydrogenase (ABAD), the decrease of the threshold of mitochondrial permeability transition pore (mPTP) formation by cyclophilin D, and the increased conductivity of the voltage-dependent anion-selective channel 1 as well, thereby considerably contributing to the further worsening of mitochondrial dysfunction [57-59]. The presence of apoptosis-related events (e.g., mitochondrial swelling, opening of the mPTP, cytochrome c release, and caspase-3 activation) was demonstrated as well [60-63]. The Aβ-induced ROS production may evoke a vicious cycle via the further enhancing Aβ formation [45, 64]. ROS generation resulted in the upregulation of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) activity and expression level, thereby increasing Aβ load [65-67]. Beside the deleterious effects of Aβ, the pathological forms of tau induce the disturbance of mitochondrial bioenergetics as well. Studies with cell lines or transgenic animals overexpressing mutant tau protein demonstrated mitochondrial

depolarization, impaired respiration, reduced ATP synthesis, increased oxidative stress, and lipid peroxidation [25, 27, 41, 44, 47, 68, 69]. Interestingly, mitochondrial energy disturbances probably precede Aβ-related pathology [27, 43]. In light of proteomic analyses, these abnormalities may be related to the alterations of complexes I and IV of the ETC; the impairment of the former one was related to tau, whereas the impairment of the latter one was related to Aβ [27]. This second aspect of mitochondrial disturbance in AD accompanies to synaptic dysfunction as well, as preserved bioenergetics are essential for the following functions: 1) the maintenance of ion gradients required for sustained membrane potential; 2) the mobilization and release of synaptic vesicles; and 3) the support of synaptic assembly and plasticity [8].

The presence of *APOE* ε4 genotype has been demonstrated to be associated with a considerably (i.e., four times) enhanced likelihood for the development of AD [70]. *APOE* ε4 contributes to the pathogenic processes by disrupting neurogenesis, cholesterol metabolism, AβPP processing, the degradation of Aβ, tau hyperphosphorylation, and other cellular pathways, including mitochondrial function and synaptic plasticity [70-73]. The decreased activity of α-ketoglutarate dehydrogenase in AD brain correlates with *APOE* ε4 genotype and it decreases the expression of complex I and IV and the activity of complex IV of the ETC as well [74, 75]. This impairment is presumably mediated by the interaction of *APOE ε4* with mitochondria [75, 76].

The transport of mitochondria is mediated by fast axonal transport [77]. Kinesin-1 heavy chain protein, encoded by the *KIF5B* gene is responsible for the anterograde transport of mitochondria with the aid of adaptors (trafficking kinesin-binding protein 1 and 2; Trak1 and Trak2) to mitochondrial Rho GTPase 1 and 2 (Miro1 and Miro2), whereas dynein protein performs their retrograde transport via the interaction with the dynactin complex [78]. The treatment of rodent hippocampal neurons with Aβ or the presence of a PS1 or AβPP mutation

resulted in the significant reduction of anterograde mitochondrial transport, thereby considerably accompanying to synaptic dysfunction characteristic of AD, which findings were confirmed in mouse model of AD and by the *post mortem* analysis of brains from AD patients [15, 79-86]. It was hypothesized that alterations in synaptic mitochondria develops earlier than in non-synaptic mitochondria [87]. It seems that tau is required for Aβ-induced impairment of axonal transport, which process is presumably initiated via the activation of NMDARs, glycogen synthase kinase 3β (GSK3β), and casein kinase 2 (CK2) [84, 88, 89].

Naturally, the above detailed three main aspects of mitochondrial dysfunction act synergistically: the activation of Drp1 and Fis1 by free radicals resulted in mitochondrial fragmentation, their altered synaptic transport, and consequentially reduced synaptic ATP levels and dysfunction [87]. Furthermore, in light of the downregulation of peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PGC-1α) and its target genes, the mitochondrial biogenesis signaling has been indicated to be impaired as well in AD [90, 91].

3. GLUTAMATE EXCITOTOXICITY IN ALZHEIMER'S DISEASE

Beside and in part in connection with mitochondrial dysfunction, Aβ can influence glutamatergic neurotransmission in several ways. Under physiological concentrations, Aβ takes part in the regulation of proper neurotransmitter release; however, the elevated concentrations of Aβ alters synaptic transmission via its deteriorating effects on synaptic vesicle pools [92, 93]. With regard to its effects on glutamatergic neurotransmitter receptors, the NMDAR may be the major site of Aβ action even in the early stages of AD; and furthermore, NMDAR activation increase the production of Aβ [94]. The composition of a conventional NMDAR is composed of two glycine or D-serine-binding GluN1 subunits, which are responsible for the formation of the ion channel, and two glutamate-binding GluN2

(A-D) subunits, having regulatory and refining roles. The available data suggest that the predominance of GluN2A subunit-containing NMDARs at the synaptic site promotes neuronal survival, involving the activation cyclic-AMP response element binding protein (CREB) and the suppression of forehead box protein O (FOXO)-mediated pathways [95-99]. Contrastingly, the predominance of GluN2B subunit-containing NMDARs at the extrasynaptic site, increased by the phosphorylation at Tyr1336 site, mediates neurotoxicity involving the opposite effects on the above mentioned pathways [95-99]. However, in light of some recent findings, the simultaneous activation of synaptic NMDARs may be also necessary for the initiation of cell death program [100]. So in brief, alterations in synaptic and extrasynaptic glutamatergic transmissions seem to synergistically contribute to the pathomechanism of AD. The alterations induced by oligomeric Aβ contributing to synaptic dysfunction involve the decrease of long-term potentiation (LTP; a form of synaptic strengthening following a brief, high-frequency stimulation), the enhancement of long-term depression (LTD; a form of synaptic weakening following low-frequency stimulation or synaptic inactivity), and the depotentiation of LTP [101-104]. The enhancement of LTD in AD is mediated by the internalization of synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors induced by oligomeric Aβ and non-apoptotic caspase activation [62, 105, 106]. *In vitro* studies suggest that the activation NMDARs by Aβ is mainly confined to those containing GluN2B subunit, i.e., with a preferential localization at the extrasynaptic site [107]. Furthermore, the experimental intracerebroventricular injection of Aβ in rats downregulated the ratio of GluN2A/GluN2B subunits, shifting the pathways toward excitotoxicity [99]. Some of the deleterious downstream excitotoxic effects of Aβ via the GluN2B subunit-containing NMDARs is mediated by the connection of the receptors to neuronal nitric oxide (NO) synthase (NOS) by a scaffolding protein PSD-95 (postsynaptic density protein of molecular weight 95 kDa),

thereby increasing the production of NO in an excessive amount [108-110]. The above mentioned increase in the production of Aβ via extrasynaptic NMDAR activation is probably mediated by the shift of AβPP production from AβPP695 to Kunitz protease inhibitory domain-containing isoforms with higher amyloidogenic potential and leads to the formation of a vicious cycle [111, 112]. GluN2B-mediated glutamatergic neurotransmission seems to be involved in tau-induced neurotoxicity as well, probably via the tyrosine kinase Fyn pathway [113, 114]. Tau increased targeting of Fyn sensitizes NMDARs to Aβ toxicity with a positive feedback, i.e., the Aβ-triggered hyperphosphorylation of tau enhance its affinity for Fyn [115]. The major downstream pathological effect evoked by Aβ in this way may be the disturbance of neuronal calcium homeostasis [116].

In addition to its receptorial effects, Aβ downregulates glutamate uptake capacity of astrocytes and thereby induces a dysfunctional glutamate clearance from the extracellular space [117-120]. Indeed, soluble Aβ oligomers were proved to be capable of inducing glutamate release from astrocytes [121]. The downregulation of the expression of excitatory amino acid transporter 2, one of the transporters responsible for glutamate uptake by astrocytes, was demonstrated in transgenic mouse models as well [122, 123]. However, the available data on human specimens with regard to this issue are controversial [124-127]. Additionally, some findings indicate that microglial upregulation of cystine/glutamate antiporter system x_c^- may also contribute to altered glutamate homeostasis [128]. The consequentially elevated glutamate levels in the extracellular space and the above delineated presence of energy impairment, as a consequence of mitochondrial dysfunction and oxidative stress, may interact to cause glutamate excitotoxicity, involving a partial membrane depolarization, which results in the relief of the Mg^{2+} blockade of the NMDAR channel and leads to subsequent calcium overload of the cell [129].

4. NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

Emerging evidence supports that neuroinflammation, i.e., the active presence of proinflammatory immunological processes within the CNS, contributes substantially to the pathogenesis of a number of neurodegenerative disorders, including AD, and is probably more relevant in terms of the pathogenesis as core neuropathological hallmarks of the disease [130]. Signs indicative of ongoing neuroinflammation during the course may be present before the dementia stage, opening possibilities for the identification of putative prognostic biomarkers as well as of potential therapeutic targets of the disease.

Pathogenic markers of neuroinflammation in AD include cellular and soluble factors as well. As compared with encephalitides and multiple sclerosis (MS) where the adaptive immune system with target-specific T and B lymphocytes are presumed to play key roles in disease pathogenesis (including the promotion of the degenerative alterations), neuroinflammation in neurodegenerative disorders including AD are predominantly linked to central players of the innate immune system, with CNS-resident microglia, astroglia, and perivascular macrophages having been heavily implicated at the cellular level [131]. This neuropathological dichotomy is reflected also by the findings of recent genome-wide association studies (GWASs) and an expression quantitative trait locus (eQTL) genetic study [132].

Microglia are resident myeloid cells of the CNS that, similarly to tissue macrophages, are responsible for screening their respective tissue region for pathogens and cellular debris in order to engage them in part via phagocytosis and degradation [133]. Furthermore, these cells are also involved in the development and maintenance of neuronal circuitry in part by releasing trophic factors such as brain-derived neurotrophic factor (BDNF) [134, 135]. There is a plethora of evidence for the crucial contribution of microglia to AD pathogenesis. Microglia are long known to be abundantly present around senile Aβ plaques in *post mortem* AD brain tissues [136]. These cells are phenotypically altered, suggestive of being reactive to

pathological stimuli. This increased microglial activation in the human brain with probable AD can now be reflected also by non-invasive imaging techniques taking advantage of radiotracers (such as microglial translocator protein (TSPO) ligands) used with positron emission tomography [137, 138]. Evidence suggests that brain parenchymal Aβ (especially in monomeric form) is capable of priming and thus aiding the activation of microglia in response to pathological stimuli, which in turn produce and release a number of proinflammatory cytokines and chemokines [131, 139-141]. This process is presumed to be aggravated by additional environmental and genetic components such as systemic inflammation and mutations affecting the innate immune system, respectively [131]. Though the *in vivo* relevance of microglial phagocytosis of Aβ is a matter of debate, microglia are known to express intra- and extracellular Aβ degrading enzymes (e.g., neprilysin and insulin-degrading enzyme, respectively), and their normal function plays crucial roles in the clearance of parenchymal Aβ from the brain, most probably as part of a self-limiting adaptive process [142, 143]. The sustained presence of Aβ in the brain, however (especially in more aggregated forms, such as oligomers, protofibrils, and fibrils), is presumed to lead to permanent neuroinflammation with a chronic activation of microglia through various receptor-dependent and -independent mechanisms, which is accompanied by different microglial phenotypic alterations and deficient microglial function in a self-sustaining process, supposedly contributing to neurodegeneration and the development tau pathology in the AD brain [131]. In line with this concept, deficient microglial function has been demonstrated in transgenic AD mice, whereas mutations affecting genes involved in microglial phagocytosis and function, including *TREM2*, *CD33*, *MS4A6A*, and *CR1*, have been associated with an increased risk of sporadic AD, and the levels of the autophagy protein Beclin 1, with crucial roles in microglial phagocytosis, have been shown to be decreased in microglia isolated from brains of sporadic AD patients [144-154]. Though the applicability of

the 'proinflammatory M1' versus 'anti-inflammatory M2' dichotomous phenotypical classification of macrophages for CNS-resident microglia is extensively debated, agonists of PPARγ, a transcription factor that drives anti-inflammatory processes including a switch toward an M2 phenotype and whose relevance is of increasing interest in MS as well, are under extensive preclinical and clinical investigation as potential disease-modifying therapies in AD, with a phase 3 trial called TOMORROW currently ongoing with the PPARγ agonist, pioglitazone [131, 155-160].

Astroglia, a resident cell-type of the CNS of neurodectodermal origin, has been strongly implicated in the pathogenesis of AD, though the information at present available about its exact roles in the pathogenesis is substantially less comprehensive than about those of microglia. Similarly to microglia, reactive astrocytes surround and engage Aβ senile plaques, contributing to neuroinflammation via releasing cytokines, chemokines, and nitric oxide [130, 161-163]. Just like microglia, astrocytes express intra- and extracellular Aβ-degrading enzymatic apparatus upon exposure to Aβ [164]. Furthermore, they also internalize and degrade Aβ, with astroglial ApoE playing crucial roles in both astroglia- and microglia-mediated Aβ clearance among experimental conditions [165-168]. Supporting a potential detrimental role of astrocytes upon chronic activation during AD pathogenesis, viral inactivation of astrocytes alleviated the pathology in a transgenic murine model of AD [169].

The potential roles of other cell types in the CNS in the modulation of neuroinflammation in AD, including those of perivascular macrophages, endothelial cells, neurons, and oligodendrocytes, are also under investigation, but the results are at present far less conclusive compared to those for microglia and astrocytes [131].

Alterations indicative of ongoing neuroinflammation in AD can be detected at the level of soluble macromolecules as well. The expression of a number of proinflammatory *cytokines*, major sources of which are astrocytes and microglia, have been revealed in human AD brains,

as well as in the brains of transgenic rodent AD models [170-181]. The most frequently reported cytokines include tumor necrosis factor alpha (TNFα), interleukin (IL)-1β, IL-6, IL-12, and IL-23 among many others. The possible biomarker value of the cerebrospinal fluid (CSF) or plasma levels of some of these cytokines have also been proposed in AD; however, the reports are extremely heterogeneous, which at present do not enable firm conclusions to be reached [182]. More intriguingly, the levels of some of the cytokines found elevated in the CSF of AD patients by some authors have also been reported to be increased even before the dementia phase of AD, i.e., during the stage of mild cognitive impairment (MCI) [182]. In particular, elevated levels of the proinflammatory cytokine, TNFα, and its soluble receptors, sTNFR1 and sTNFR2, in the CSF of patients with MCI were reported to predict more rapid conversion to AD dementia [183, 184]. Though these types of 'conversion studies' are associated with severe inherent limitations, they substantiate the potential diagnostic relevance of neuroinflammatory cytokine alterations in AD [185]. Despite the proposed and increasingly established roles of proinflammatory cytokine alterations in disease pathogenesis in AD, controversial results have also been published demonstrating deleterious effects of anti-inflammatory cytokines and beneficial effects of proinflammatory cytokines in terms of brain Aβ clearance *in vivo* [186-190]. Of note, generally disappointing results have been obtained from studies aiming at the modification of inflammatory response in AD with non-steroidal anti-inflammatory drugs (NSAIDs) or elective cyclooxygenase-2 (COX-2) inhibitors at the clinical level [191-195]. These molecules in part aim at reducing the production of the inflammatory arachidonate metabolite prostaglandin E2, the level of which was likewise found altered in the CSF of AD patients and whose microglial receptorial action appears to be crucial in the development of core pathological features in AD animal models, whereas another presumed mechanism of action of NSAIDs is related to the activation of PPARγ [196-200]. All these underlie the relevance of the double-edged nature of neuroinflammation in AD

and neurodegenerative conditions as a whole, a maladaptive chronification of an originally beneficial acute immune response, the suppression of which may result in adverse outcomes, and the exploitation of the therapeutic potential of which will definitely require further research and more sophisticated therapeutic approaches.

5. THE RELATION OF KYNURENINES TO MITOCHONDRIAL DYSFUNCTION, GLUTAMATE EXCITOTOXICITY, AND NEUROINFLAMMATION, AND THEIR INVOLVEMENT IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Approximately 95% of TRP is metabolized through its KYN pathway (Fig. 1) [201]. This metabolic route consists of several neuroactive compounds, including kynurenic acid (KYNA), 3-hydroxy-L-KYN (3-OH-L-KYN), 3-hydroxyanthranilic acid (3-OH-ANA), and quinolinic acid (QUIN). The detailed description of their physiological functions together with a historical overview of research on these metabolites have already been published, and are, accordingly, out of the scope of this current review [202]. Briefly, this pathway is predominantly responsible for the endogenous production of nicotinamide adenine dinucleotide, and is capable of influencing redox reactions and glutamatergic neurotransmission through its neuroactive intermediates, often in opposite directions. Although some other metabolites of the pathway may also have effects on neuronal function and dysfunction (especially in terms of redox reactions), their role in neuronal physiology and pathophysiology is at present less firmly established and are probably less important compared to the 'neuroactive' compounds [203]. A sustained balance between the concentrations of neuroactive intermediates of the KYN pathway may help to ensure the maintenance of normal neural function. By contrast, a number of abnormalities have been described as regards the activation of certain steps of the KYN pathway of TRP metabolism in various tissues and CNS regions in

neurodegenerative disorders, including AD (Figs. 2 and 3) [5, 202, 204-207]. Accordingly, therapeutic options may arise either via the application of drug analogs or via the modulation of the activity of their producing enzymes [5, 208-211].

Indolamine 2,3-dioxygenase

As regards the first and rate-limiting step of the pathway, a number of studies described increased activity of indolamine 2,3-dioxygenase (IDO) in AD [212-215]. A group demonstrating increased activity of IDO in the serum of AD patient reported an inverse correlation of IDO activity with cognitive performance, accompanied by a positive correlations with the levels of neopterin, a macrophage activity marker, as well as soluble receptors for TNF and IL-2 [212, 213]. Others reported increased IDO immunoreactivity in microglia, astrocytes, and neurons, with the glial expression of IDO being the highest surrounding senile plaques [214]. The preferential accumulation of IDO in senile plaques as well as neurofibrillary tangles have later been confirmed by another group as well [216]. In line with these results and the proposed ability of Aβ to activate microglia in AD brains, increased IDO expression has been demonstrated in microglia and human primary macrophages *in vitro* upon exposure to Aβ$_{1-42}$ [217]. These together indicate that the inflammatory milieu in AD, including elevated concentrations of TNFα, a potent activator of IDO, promotes the activation of TRP metabolism via the KYN pathway, leading to the production of multiple downstream effectors with various potential consequences relevant in terms of the pathogenesis of AD, as discussed below.

3-Hydroxy-L-kynurenine and 3-hydroxyanthranilic acid

According to some early studies, the proposed deleterious effects of 3-OH-L-KYN, a metabolite produced by kynurenine 3-monooxygenase (KMO), are mediated by free radicals

and not glutamate receptors, and some of its detrimental actions may be due to its metabolite, 3-OH-ANA, via its auto-oxidation, leading to the production of superoxide anion [218-221]. In contrast, there is a body of evidence calling for antioxidant and free radical scavenging properties inherent to 3-OH-L-KYN as well; therefore, a dual action in the CNS may be proposed in this respect [222]. Indeed, in studies on striatal slices, 3-OH-L-KYN exerted a concentration- and time-dependent dual effect on lipid peroxidation, inducing pro-oxidant actions at low (5-20 μM) and antioxidant activity at higher (100 μM) micromolar concentrations [223]. The proposed protective actions were related to the stimulation of glutathione S-transferase and superoxide dismutase activities and to the elevations in the protein contents of the transcription factor and antioxidant regulator nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and some of its related proteins [223]. It is important to mention that the basal extracellular concentrations of 3-OH-L-KYN in the rat brain (2 nM) are far below the above mentioned levels [224]. A recent study assessing the effects of 3-OH-L-KYN and 3-OH-ANA with regard to mitochondrial dysfunction demonstrated that both compounds decreased 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction in a concentration-dependent manner in association with an impairment of mitochondrial membrane potential [225]. However, these findings were not related to alterations in ROS production or lipid peroxidation, probably due to the demonstrated hydroxyl radical and peroxynitrite scavenging activities of both compounds [225]. Summarily, the concentration- and time-dependent toxic effects of 3-OH-L-KYN and 3-OH-ANA include the impairment of cellular energy metabolism, but the accompanying role of early ROS production is controversial. Nevertheless, these findings demonstrate that the KMO branch of the kynurenine pathway, i.e., which gives rise to the metabolites 3-OH-L-KYN and 3-OH-ANA among others, may represent a direct relationship between neuroinflammation and oxidative stress/mitochondrial dysfunction in AD, as this branch is preferentially active in

microglia/macrophages, which respond with IDO overexpression and subsequently increased KYN metabolism upon exposure to Aβ [217, 226-229].

With regard to the levels of these metabolites in AD tissues, though early studies demonstrated non-significant alterations in 3-OH-L-KYN levels in AD brains, recent immunohistochemical studies proved that 3-OH-L-KYN may considerably accompany to the damage of neuronal tissues, with its levels found to be significantly elevated in hippocampal neurons in AD compared to controls [216, 230, 231]. With regard to the periphery, markedly increased levels of 3-OH-L-KYN [232] as well as elevated levels of circulating IgA directed against 3-OH-L-KYN [233] were found in serum samples of AD patients, though a study found only a trend for 3-OH-L-KYN to be increased in the plasma of AD patients [234]. This elevation in the periphery may at least in part underlie the elevated concentrations of 3-OH-L-KYN and its metabolite QUIN in AD brain tissues, as 3-OH-L-KYN can pass through the BBB via an active transport. In contrast, the CSF content of 3-OH-L-KYN in AD patients was found decreased by 81% [235].

The potential alteration of 3-OH-L-KYN and 3-OH-ANA levels in the brain may also be relevant in terms of neuroinflammation in AD, since both molecules have been associated with potent immunosuppressive features, as being among the most potent effectors of IDO-mediated endogenous immunosuppression, an effect relevant in immunological phenomena such as allograft acceptance, tumor camouflage, and maternofetal tolerance [5]. Of note, these effects are generally attributed to the suppression of target-specific immunity, especially of Th1/Th17 cell proliferation, which is a response rather characteristic of MS than of AD where natural immunity is presumed to take leading roles. However, a recent report revealed that infiltrating Th1 and Th17 cells are present in the brain of transgenic AD mice (AβPP/PS1), and that Aβ-specific Th1 cells transferred to these murine brains could elicit marked microglial activation, Aβ deposition, and cognitive dysfunction [236]. Similar lymphocytic

engagement of deposited Aβ can be seen in a clinical and pathological subtype of cerebral Aβ angiopathy (CAA) in humans, that is CAA-related inflammation (CAA-RI) [237]. These findings indicate the potential role of target-specific immunity as well in the early events of AD pathogenesis, giving further potential relevance of altered 3-OH-L-KYN and 3-OH-ANA levels in the brain of AD patients. On the other hand, this potentially relevant feature further complicates the interpretation of the possible roles of these molecules in AD, especially of 3-OH-L-KYN, a molecule that has pro-oxidant, antioxidant, as well as potent immunomodulatory features, all being of plausible relevance in AD.

Quinolinic acid

QUIN, which is produced by 3-hydroxyanthranilate 3,4-dioxygenase (HAAO), is a weak but specific competitive agonist of the NMDAR subgroup containing the GluN2A and GluN2B subunits, with low receptor affinity [238]. QUIN has been demonstrated to be a neurotoxic compound in several paradigms [5, 210]. On the one hand, it can cause glutamate excitotoxicity via the following mechanisms: it can directly activate NMDARs and, in addition to its receptorial effect, it is capable of modulating glutamate release and inhibiting the uptake of glutamate by astrocytes [239-241]. Accordingly, the hyperphosphorylation of tau proteins via the overactivation of NMDAR is augmented by QUIN, further contributing to glutamate excitotoxicity in AD [242]. On the other hand, QUIN has been demonstrated to be involved in ROS production and lipid peroxidation as well, **in an NMDAR-dependent or -independent manner,** thereby further contributing to the pathogenesis of AD [243-246]. **QUIN is capable of inducing NOS activity in astrocytes and neurons, generating ROS via the formation of QUIN-Fe^{2+} complexes, and reducing antioxidant defenses, thereby leading to oxidative stress and diminished mitochondrial function [247-252].**

As regards the expression of QUIN in AD brains, early studies demonstrated no alterations in various regions of the brain of AD patients [253-255]. However, Guillemin et al. reported increased QUIN immunoreactivity in neurons and glial cells in AD brains, with the microglial expression being the highest surrounding senile plaques, but also uniformly labeling neurofibrillary tangles, which is in line with the ability of QUIN to increase tau hyperphosphorylation [214, 215]. This increase of QUIN in AD plaques have been confirmed by further quantitative methods by the same group [256]. This increase corresponds to elevated QUIN levels observed in the plasma of AD patients correlating inversely with cognitive functions [234]. However, this finding as regards increased blood QUIN levels in AD could not be replicated by others from serum [232]. Likewise, no difference could be detected in the CSF levels of QUIN by multiple groups [255, 257]. Data regarding the potential of QUIN to contribute to IDO-mediated immunosuppression is contradictory [258-260]. Contrastingly, QUIN has been shown to promote astrocytes to produce large amounts of the potent monocyte chemoattractant protein-1 (MCP-1), and has the ability to induce astroglial production of IL-1β (a key mediator of neuroinflammation in AD), and dose-dependently promotes astroglial proliferation, dysfunction, or cell death [261-263]. Together with the data evidencing that QUIN is preferentially expressed in microglia/macrophages and also does so in AD brains, these data may indicate that QUIN does not only represent a direct link between microglial neuroinflammation and oxidative damage/NMDAR-mediated excitotoxicity/mitochondrial dysfunction as relevant pathogenic factors in AD, but it may serve as a direct mediator of a positive feedback loop in microglial neuroinflammation [214, 226-229]. With regard to the therapeutic targeting of QUIN-related alterations in AD, the application of 4-chlorokynurenine (4-Cl-KYN), the BBB-penetrant pro-drug of the selective glycine site NMDAR antagonist, 7-Cl-kynurenic acid (7-Cl-KYNA), was demonstrated to ameliorate QUIN-induced hippocampal toxicity [264]. The explanation for this finding may

involve the powerful inhibition of QUIN synthesis by 4-chloro-3-hydroxyanthranilate, another metabolite of 4-Cl-KYN, in addition to the formation of 7-Cl-KYNA [265, 266].

Kynurenic acid

KYNA is another product of the KYN pathway of TRP metabolism. It is produced by kynurenine aminotransferases (KATs) and can influence glutamatergic neurotransmission at several levels and have exerted neuroprotective effects in several paradigms [5, 202, 210, 267, 268]. KYNA is capable of exerting a wide-spectrum of endogenous antagonistic effects at ionotropic excitatory amino acid receptors [269]. Its major action related to such receptors is mediated via the strychnine-insensitive glycine-binding site on the GluN1 subunit of the NMDAR [270]. However, the basal extracellular concentration of KYNA in rats (15–23 nM) is far below the required level, i.e., ~10–20 μM concentrations, to directly interfere with NMDAR functions under physiological concentrations [208, 271, 272]. Of note, KYNA has been demonstrated to have a dose-dependent dual action on AMPA receptors, as in low (nM to μM) concentrations, KYNA is capable of facilitating AMPA receptor responses with a potential positive effect on LTP, whereas in higher concentrations it has inhibitory effects, which may interfere with LTP formation and may be associated with cognitive dysfunctions [273, 274]. Though the most widely recognized and generally hypothesized neuroprotective mechanism of KYNA is linked to its anti-glutamatergic effects, predominantly on NMDARs, recent experimental findings associate KYNA with various additional actions counteracting processes relevant in mitochondrial dysfunction and neuroinflammation involved in AD.

The connection between altered KYNA levels and mitochondrial dysfunction is represented by the following observations. 1) As a free radical scavenger, KYNA can be regarded as an endogenous neuroprotectant in conditions with mitochondrial dysfunction, where excessive free radical production is present as a general feature [275-

277]. 2) Its potent NMDAR inhibitor functions can indirectly alleviate the downstream deleterious effects of excitotoxicity on mitochondrial function (i.e., by decreasing intracellular Ca^{2+} overload) [278]. 3) The expression/function of KATs has been reported to be downregulated in models/conditions with mitochondrial dysfunction [279, 280].

The effects of KYNA with direct implications in neuroinflammation in AD include the inhibition of TNFα expression via an agonistic effect on orphan receptor GPR35 on monocytes, and more recently by increasing the expression of neprilysin, an Aβ-degrading metallopeptidase expressed by astrocytes and microglia, the proper function of which has been found to substantially influence the severity of AD-like phenotype in experimental models *in vivo* [277, 281-284]. Regarding the proposed Aβ-degrading effect, however, it is to be mentioned that a previous study did not found KYNA to be able to modulate Aβ aggregation in their experiments [285]. In terms of immunomodulation, although KYNA did not influence Aβ-induced cell death in BV-2 microglial cell culture, it exerted an anti-inflammatory action by means of the reduction of the levels of proinflammatory cytokines TNFα and IL-6, and, intriguingly, decreasing the phagocytosis of Aβ [286]. As regards IL-6, another study likewise found a downregulation of this cytokine in stimulated mast cells [287]. However, a study on MCF-7 breast tumor cells reported the ability of KYNA to promote of IL-6 expression/secretion by activating aryl hydrocarbon receptor (AhR), which the authors discussed to potentially contribute to tumor camouflage by leading to a consequent increase in IDO expression in dendritic cells with various immunosuppressive downstream effects [288]. The relevance or presence of this mechanism in a neurodegenerative/neuroinflammatory setting in the brain, however, has not been established.

With regard to *post mortem* analyses of the brains of AD patients, the levels of KYNA were found to be non-significantly elevated in the hippocampus with no apparent changes in the

activities of either KAT-I or KAT-II [231]. Consistently, no significant alterations in KYNA levels in various brain regions were detected by another group in AD brains [289]. However, increased KAT-I activity in the caudate nucleus and putamen (together with a non-significant alterations in KAT-II activity) with a consequent significant elevations in KYNA concentrations in the respective regions have been described [231]. The role and relevance of this phenomenon in the striatum are of question, but the presence of a compensatory mechanism against the pronounced degeneration of the corticostriatal pathway with increased glutamate binding in the striatum in AD may be a suitable explanation [290, 291]. The cellular distribution of the observed alterations in KAT activity and/or expression may have a special importance, because it was demonstrated that treatment of rats with sodium azide (an inhibitor of mitochondrial complex IV) altered the pattern of the expression of KAT-I in various relevant brain regions: the astroglial immunoreactivity was found to be decreased, whereas neurons started to express KAT-I [292]. With regard to the alterations of KYNA levels in human biological fluids with a possible biomarker value, decreased concentrations have been detected in the serum, plasma, and CSF of AD patients; however, recent studies have reported unaltered serum and CSF KYNA levels [232, 234, 257, 293, 294]. In one of these recent studies that did not find significant alteration in CSF KYNA level between AD patients and age-matched controls and revealed no associations between CSF KYNA level and cognitive dysfunctions in AD patients, CSF KYNA levels were, however, found to be significantly correlated with the AD-biomarker p-tau (hyperphosphorylated tau) and the inflammatory marker soluble intercellular adhesion molecule-1 [294]. Furthermore, a gender difference was also demonstrated in this study, i.e., female AD patients had significantly higher CSF KYNA levels compared to the males, a difference not revealed in the control group. Interestingly, however, increased levels of circulating immunoglobulin A (IgA) against

conjugated KYNA were detected in the serum of AD patients, adding to the spectrum of controversial findings in the field [233].

On the basis of the well-established contribution of glutamate excitotoxicity (including the elevation of hippocampal QUIN levels), mitochondrial dysfunction (including ROS accumulation), and neuroinflammation (including glial IDO activation) to AD pathogenesis, the accumulating data supports that KYNA has multiple potential beneficial actions that involve all these three major pathogenic domains. Indeed, the inclusion of KYNA during the preparation process of hippocampal slices from $A\beta PP^{sw}$ transgenic animals exerted an age-dependent protective effect against the development of altered synaptic transmission, presumably by limiting the extent of excitotoxicity [295]. Furthermore, the systemic administration of L-KYN (the common precursor of KYNA, the probably neurotoxic metabolites 3-OH-L-KYN and anthranilic acid (ANA), and the 'proglutamatergic' excitotoxin QUIN) together with probenecid (an organic acid transporter inhibitor targeting the mechanisms eliminating KYNA from the brain) exerted protective effects against the intrahippocampal administration of $A\beta_{25-35}$, with a significant improvement in spatial memory. This effect was most probably attributed to NMDAR inhibition, as demonstrated by comparable effect of the specific NMDAR inhibitor, MK-801 [296]. A possible way to enhance the bioavailability of KYNA may be achieved by its improved transport through the blood-brain barrier (BBB) via its pharmaceutical modulation [297]. Most recently, the neuroprotective effect of a novel BBB-permeable KYNA analog with multiple pharmacological actions relevant in AD pathogenesis, including NMDAR binding, free radical scavenging, and also interference with $A\beta$ fibril evolution, has been reported in a Caenorhabditis elegans model of AD [298]. The potential neuroprotective/immunomodulatory features of KYNA relevant in AD highlight the importance of astrocytes in AD pathogenesis, as they lack functional KMO therefore

preferentially metabolizing L-KYN toward KYNA, and they readily expressed IDO in AD hippocampi [214, 228]. Interestingly, another KYNA analog, 5,7-dichlorokynurenic acid with a preferential action at the glycine-binding site of the NMDAR, was unable to recapitulate the protective effect of memantine, a partial antagonist at the NMDAR channel, on the abnormal hyperphosphorylation and accumulation of tau in organotypic cultures of rat hippocampal slices [299].

Despite the promising experimental data, manipulations resulting in elevated levels of KYNA in the brain may inherently harbor effects associated with cognitive impairments and behavioral alterations [300-306]. Accordingly, knocking out one of its producing enzyme (KAT-II) resulted in the improvement of cognitive functions in mice [305]. Of note, achieving a selective inhibition of GluN2B subunit-containing extrasynaptic NMDARs may be a successful strategy in the amelioration of neurodegenerative processes [307]. Indeed, reaching an extracellular concentration that is capable of inhibiting the tonic extrasynaptic NMDAR currents and thereby reducing glutamate excitotoxicity in AD without impairing synaptic glutamatergic neurotransmission may yield a possible therapeutic option [308]. KYNA amides are synthesized by the amidation of KYNA at the carboxyl moiety and the resulting substances may preferentially act on GluN2B subunit-containing extrasynaptic NMDARs [209, 309]. Accordingly, one of the KYNA amide compounds synthesized by our group, N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride exerted protective effects both in the N171-82Q transgenic mouse model of Huntington's disease and the four-vessel occlusion model of cerebral ischemia in rats [310, 311]. At the dose capable of exerting these neuroprotective effects, the KYNA analog did not demonstrate any significant systemic side effects, i.e., it did not alter locomotor activity, working memory performance, and long-lasting, consolidated reference memory in contrast to the observed indirect side-effects following KYN administration [312-314]. These results are supported by

the findings that instead of decreasing LTP as it might be expected from its potential NMDAR antagonistic properties, it rather facilitated the potentiation of field excitatory postsynaptic potentials [315].

These data together strongly support the therapeutic potential of certain approaches related to the elevation of the levels of KYNA or its analogs in the brain in AD, with carefully keeping in mind the potential cognitive deleterious effects of the inhibition of synaptic NMDA/AMPA receptor-mediated currents during rational drug design.

6. CONCLUSIONS

Although more and more details are being revealed regarding the pathomechanism of AD, including mitochondrial dysfunction, glutamate excitotoxicity (Fig. 2), and neuroinflammation (Fig. 3), current therapeutic strategies are restricted only to few pharmaceutical agents. These three aspects of the pathomechanism certainly demonstrate relations to specific alterations in the KYN pathway of TRP metabolism (Fig. 2) [316-318]. Accordingly, the treatment of AD via the modulation of TRP metabolism appears to be a reasonable target of investigation; however, the complexity of the observed alterations and the seemingly narrow therapeutic window necessitate the development of sophisticated pharmaceutical approaches.

7. ACKNOWLEDGEMENT

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9. FIGURE CAPTIONS

Figure 1. The schematic depiction of the kynurenine pathway of tryptophan metabolism.

Figure 2. The possible implications of kynurenine pathway metabolites in mitochondrial dysfunction and glutamate excitotoxicity. 3-OH-ANA: 3-hydroxy-anthranilic acid, 3-OH-L-

KYN: 3-hydroxy-L-kynurenine, cc.: concentration, KYNA: kynurenic acid, LTD: long-term depression, LTP: long-term potentiation, QUIN: quinolinic acid

Figure 3. The possible implications of kynurenine pathway metabolites in neuroinflammation in AD. Aβ triggers IDO induction in microglia/macrophages and astrocytes, with consequent activation of the kynurenine pathway. Microglia/macrophages preferentially metabolize L-KYN through the KMO branch, giving rise to 3-OH-ANA, 3-OH-L-KYN, and QUIN. 3-OH-ANA and 3-OH-L-KYN are implicated in oxidative stress and suppression of target-specific immune response, and their exact role in AD pathogenesis is not well established. QUIN is a neurotoxic metabolite abundantly present in hallmark pathologies such as amyloid plaques and neurofibrillary tangles, and can contribute to AD pathology by promoting neurodegeneration, tau hyperphosphorylation, lipid peroxidation, astrocyte dysfunction, and monocyte recruitment. Astrocytes preferentially metabolize L-KYN through the transaminase branch, giving rise to KYNA. KYNA may act as an endogenous neuroprotectant due to its anti-excitotoxic, antioxidant, Aβ degradation-promoting, and anti-inflammatory properties, with the latter being attributable to its ability to downregulate TNFα and IL-6 production in microglia/macrophages. 3-OH-ANA: 3-hydroxy-anthranilic acid, 3-OH-L-KYN: 3-hydroxy-L-kynurenine, Aβ: Amyloid-beta, IL-6: interleukin-6, KATs: kynurenine aminotransferases, KMO: kynurenine 3-monooxygenase, KYNA: kynurenic acid, IDO: indolamine 2,3-dioxygenase, TNFα: tumor necrosis factor alpha QUIN: quinolinic acid
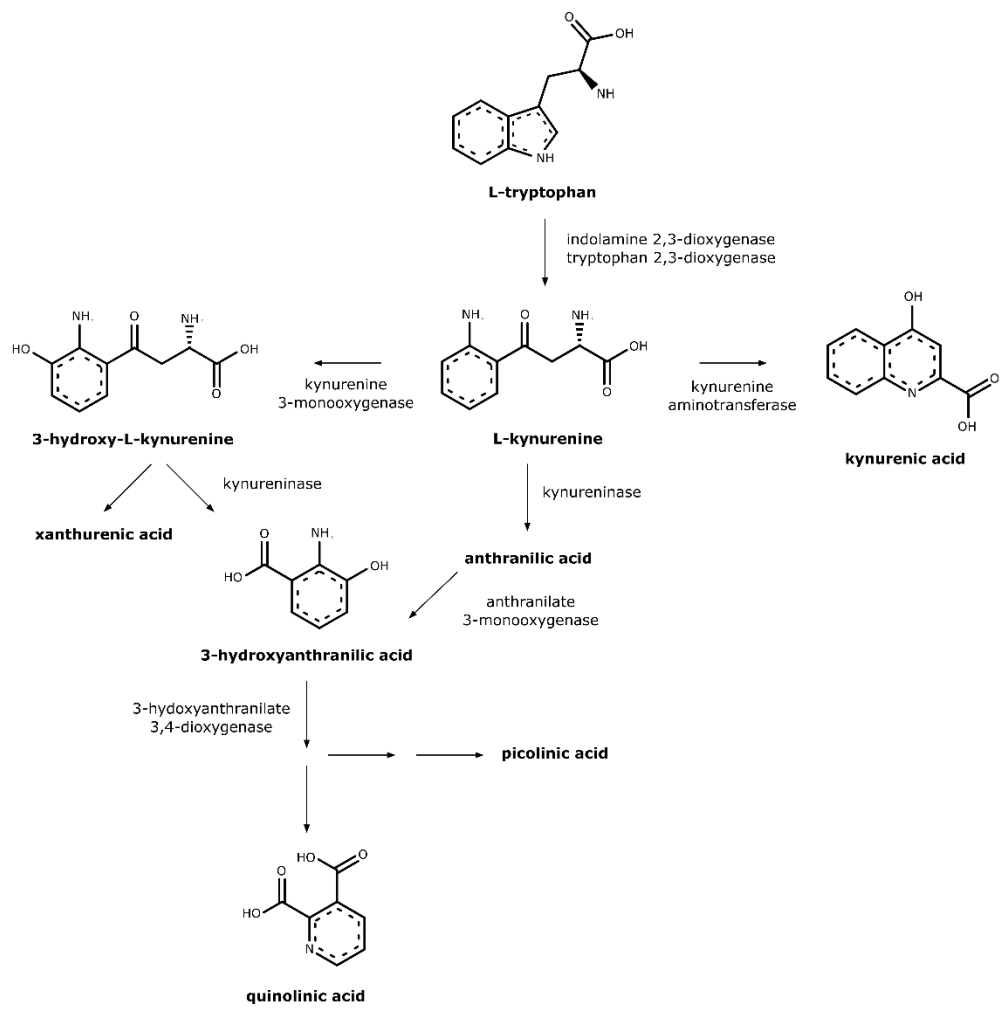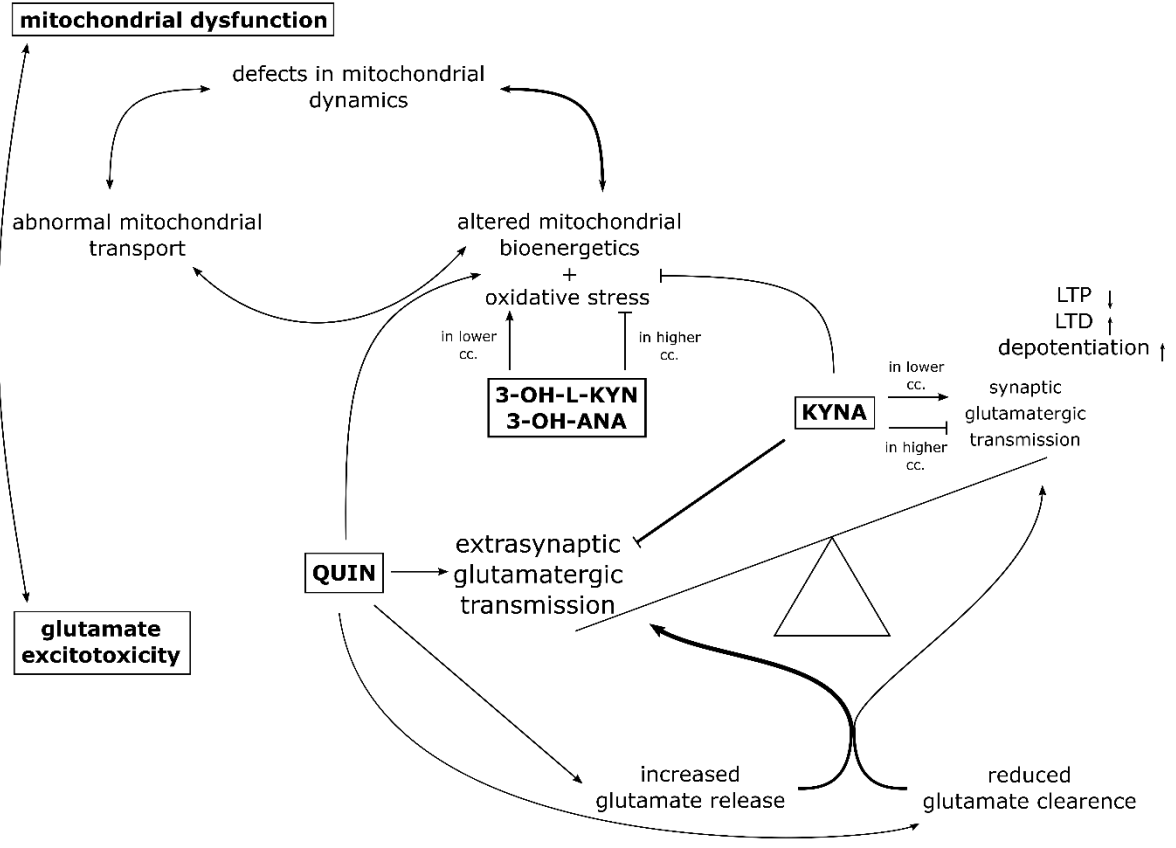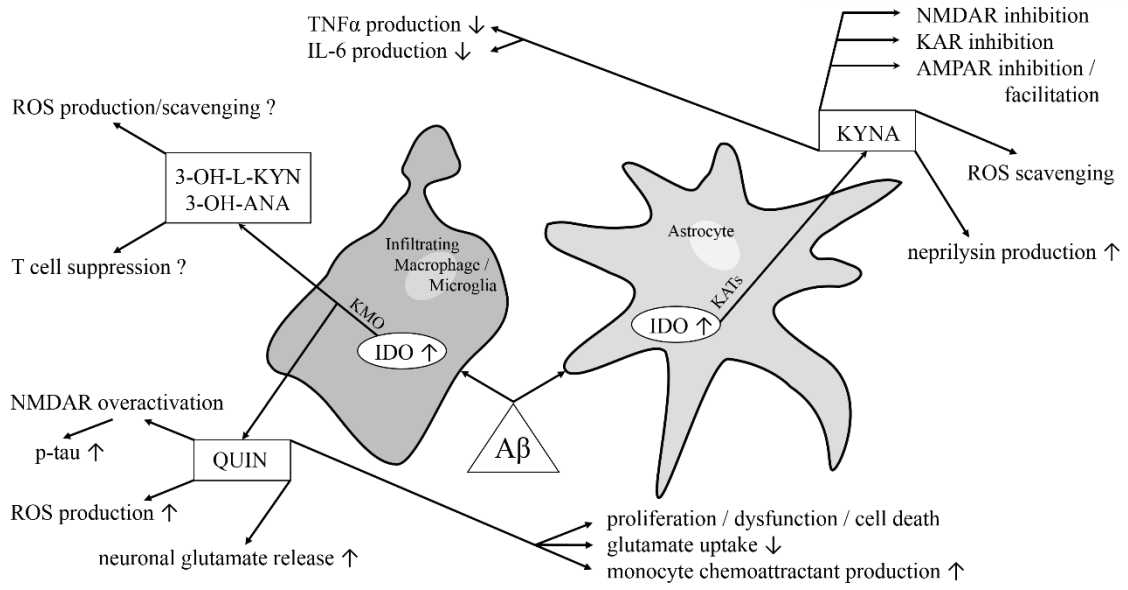
Figure 1

Figure 2

Figure 3