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Alzheimer's disease, astrocytes and kynurenines

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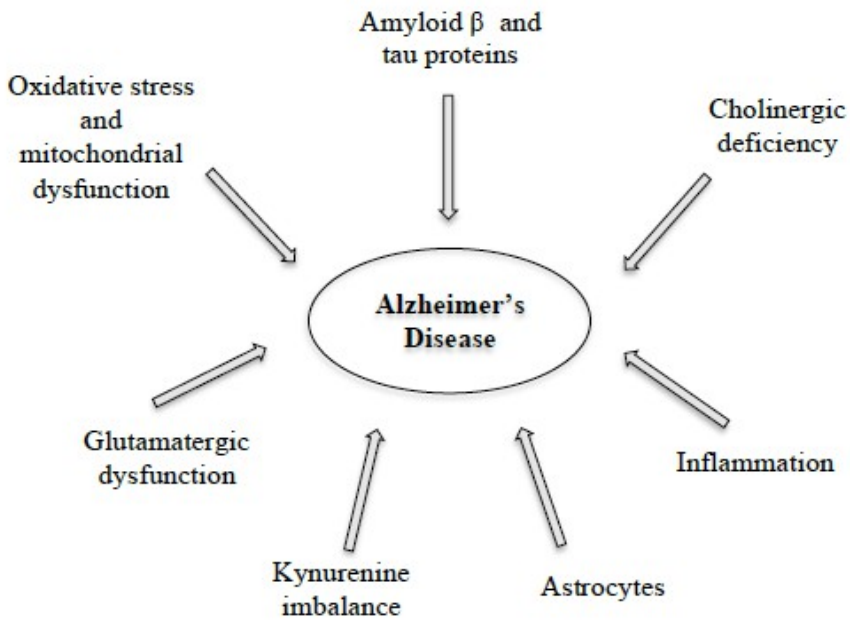
Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disease and the most common cause of dementia. The etiology of AD is not entirely clear and despite the increasing knowledge regarding the pathomechanism, no effective disease-modifying therapy is yet available. Astrocytes earlier presumed to serve merely supportive roles for the neuronal network, have recently been shown to play an active role in the synaptic dysfunction, impairment of homeostasis, inflammation as well as excitotoxicity in relation to AD pathology. This review focuses on the pathomechanism of AD with special attention to the role of the astrocytes, excitotoxicity and the alterations in the kynurenine metabolism in the development of the disease. The correction of the neuroprotective/neurotoxic imbalance in the kynurenine pathway may represent a novel target for pharmaceutical interventions in dementia related to neurodegenerative disorders.

Graphical abstract



Keywords

Alzheimer’s disease, amyloid, astrocytes, excitotoxicity, glutamate, kynurenines

Introduction

Alzheimer's disease (AD) is a chronic, progressive, age-related, irreversible neurodegenerative disease. It represents the most common cause of dementia in the elderly, affecting some 15-35.6 million people worldwide . Due to the aging of the population, AD represents a serious public health issue. By 2050, it is expected to affect as many as 13.2 million people in the US, 16.2 million in Europe and 115 million worldwide . The clinical features of AD include a gradual impairment of short-term memory at the beginning of the disease and of long-term memory thereafter and a decrease in learning ability and of language skills, accompanied by personality and behavioral changes, ultimately leading to the patient's inability to perform the activities of daily living and death . A familial, genetic form of the disease has been described; however, it represents only a minority of the total cases of AD . The cause and the mechanisms leading to neurodegeneration in AD have not been completely elucidated.

With regard to the pathologic alterations, AD is characterized by an excessive extracellular accumulation of amyloid-beta (Aβ) in the brain and an intracellular deposition of hyperphosphorylated tau protein that leads to the formation of neurofibrillary tangles (NFTs). Amyloid plaques are formed by of aggregated Aβ peptides, whereas NFTs are composed primarily of hyperphosphorylated tau protein . There is evidence of a gradual loss of neurons and of an altered synaptic structure and function in AD, leading to damage to the neuronal network . Pre- and postsynaptic changes, such as an impairment of neurotransmitter release or an altered expression of certain postsynaptic proteins occur across the entire brain, but the hippocampus is most critically involved . These alteration results in brain atrophy, with a significant reduction in size of some brain regions, mainly those involved in the memory processes, such as hippocampus, frontal cortex and limbic areas . There is also evidence of activation of the microglia and the astrocytes in the disease process, and more recently a highly expression of inflammatory cytokines has been revealed in human AD brain samples . No effective disease-modifying therapy, capable of preventing the progression of the neurodegenerative process is yet available. Efforts are continuing is done in order to elucidate the pathomechanisms of the disease and to find new targets for effective therapeutic interventions. In this respect, there is growing interest in understanding the mechanisms of Aβ production and clearance, the alterations in cellular homeostasis, the role of glial cells as well as the role of inflammation and excitotoxicity in AD. This review focuses on the pathomechanisms of AD, particularly the roles of astrocytes in the disease development and aims to reveal connections between amyloid deposition, an astrocyte dysfunction and excitotoxicity; the latter being an important component in the development of neurodegenerative diseases. We also discuss the anti-excitotoxic and hence the putative neuroprotective effects of the neuroactive kynurenines and their potential roles in AD therapy.

The pathomechanism of AD

The cause of AD is not yet known. Several hypotheses exist attempting to explain the pathomechanism of AD, these include the cholinergic deficiency hypothesis, the Aβ and tau hypothesis, the inflammation hypothesis, the oxidative stress and mitochondrial dysfunction hypothesis, as well as the glutamatergic hypothesis.

1. The cholinergic deficiency hypothesis

Based on the correlation observed between the loss of cholinergic neurons and the deterioration of memory in animal models of AD, the cholinergic hypothesis postulates that cholinergic neuronal loss could be the primary event in AD . This hypothesis is currently falling out of favor, in view of clinical and experimental results with medications targeting the improvement of cholinergic transmission .

The α7 nicotinic acetylcholine receptors (α7nAChRs), located presynaptically in the hippocampus and the cerebral cortex, and have been shown to play a role in the release of different neurotransmitters. They enhance excitatory glutamatergic neurotransmission and presumably regulate synaptic plasticity . In AD, the function of α7nAChRs is impaired; furthermore, these receptors can bind to the Aβ oligomers with high affinity . There is recent evidence of a consistent deficiency in the α7AChRs in patients with AD as well as of an increase in the number astrocytes expressing α7nAChRs. The latter involved in the production of nitric oxide (NO) and an alteration calcium homeostasis that might be related to the alterations in the metabolism of the amyloid precursor protein (APP) and to the inflammation that occurs in AD .

2. The amyloid and tau hypothesis

The Aβ and tau hypothesis postulates that the development of Aβ or tau protein deposits serve as the initiating step of AD . The Aβ aggregates are surrounded by dystrophic neurons and reactive glial cells, and the Aβ peptide therefore may presumably be the key neurotoxic agent that causes the alterations in the neurons and the activation of the glial cells . There is evidence suggesting that it is not the plaques but the Aβ oligomers represent the major cause of the synaptic dysfunction and synaptic failure , and that Aβ causes a mitochondrial dysfunction and impairs the energy homeostasis . It is presumed that the formation of NFT is a consequence of Aβ aggregation. Tau is a highly soluble cytoskeleton protein with a role in neuronal transport processes. Hyperphosphorylated and misfolded tau protein readily aggregates and is toxic to neurons, provoking neuronal dysfunction and apoptosis .

Aβ is a 37-49 peptide generated from APP. APP plays a role in the differentiation of the nervous system, signaling and cell adhesion. There are three APP cleaving enzymes (α-, β- and γ-secretases), which act differently and lead either to the amyloidogenic or non-amyloidogenic processing of APP (Fig. 1). The action of α- and γ-secretase leads to soluble αAPP (non-amyloidogenic pathway), whereas the action of β- and γ-secretase leads to soluble βAPP and the neurotoxic Aβ (amyloidogenic pathway) . Most of the generated Aβ is Aβ40 and only 10% is represented by Aβ42, which is able to form aggregates and presumed to be the causative agent of AD .

β-Secretase cleaves APP to give the membrane-bound C-terminal fragment β (CTFβ) and βAPP; the latter is located outside the cell. γ-Secretase cleaves CTFβ to furnish Aβ with an extracellular location and APP intracellular domain (AICD) with an intracellular location. The α-secretase cleaves APP to CTFα, which is subsequently cleaved by γ-secretase to form AICD and p3 peptide, both are soluble . The rate-limiting enzyme of Aβ production is the β-secretase, also named β-site APP cleaving enzyme (BACE 1 and 2). Therefore, BACE inhibition might be a possible therapeutic option in AD. BACE and APP genes are located on chromosome 21. BACE polymorphism has been shown to be responsible for the sporadic cases of AD that occur in Down's syndrome . Mutations in the genes responsible for the non-amyloidogenic processing of APP, such as the γ-secretase subunits presenilin (PSEN1 and 2), and the ADAM 9, 10 and/or 17 genes, cause increases in Aβ levels and can lead to early-onset AD . BACE inhibitors, α-secretase activators, and γ-secretase inhibitors and modulators are being investigated for their therapeutic effects in AD .

3. Amyloid metabolism and clearance

Aβ accumulates in the extracellular space within the interstitial fluid (ISF), and forms senile plaques. This process is presumably facilitated by an altered microenvironment . The extent of the plaques, however, does not correlate with the severity of cognitive impairment, and it has been shown that it is not the plaques that are responsible for the neuronal damage, but rather the Aβ oligomers . It is presumed that Aβ accumulates in the intracellular compartment due to amyloidogenic APP processing and to an ineffective neuronal catabolism of Aβ .

4. Amyloid clearance and some factors influencing it (Fig. 2)

Several mechanisms play a role in the intracellular clearance of Aβ, for instance the Rab GTPase family members, and lysosomal enzymes such as the cathepsins, or the newly described neprilysin (NEP). Their altered function leads to the intracellular accumulation of Aβ and eventually cell death . Another source of intracellular Aβ is its reuptake from the extracellular space. The intracellular accumulation of Aβ is presumed to be responsible for the initial injury of the synapses and neurites in the early stages of AD . The glial cells play a fundamental role in the clearance of Aβ from the brain parenchyma. Besides they are phagocytic activity, they are also the source of apolipoprotein E (ApoE), the main chaperon of Aβ in the central nervous system. Among the isoforms described, the ApoEε4 variant is one of the most important risk factors for AD . Among the secondary chaperons, ApoJ, transthyretin and alfa2-macroglobulin play roles in the clearance Aβ. The Aβ is exported from the brain interstitial fluid (ISF) to the blood by specialized carriers through the blood-brain barrier (BBB), and to a lesser extent through the choroid plexus-cerebrospinal fluid (CSF) and the CSF-blood barrier at the Virchow-Robin spaces. The carriers involved in this transport include the low-density lipoprotein receptor-related proteins (LRP1 and 2) and the ATP-binding cassette. Genetic variations of these transporters influence disease progression in AD. Aβ is eliminated in the liver and to a lesser

extent in the kidney. Among the nuclear receptors, the peroxisomal proliferator-activated receptors (PPARs) have a relevant role in the brain Aβ clearance and it has been shown in experimental models that the activation of PPARs has a beneficial effect on the pathology of AD and the mitochondrial dysfunction .

It is presumed that the deposited Aβ peptides evoke neuronal dysfunction and neurodegeneration, on the one hand via toxic dendritic and synaptic injury and, on the other hand, through the activation of microglial cells and astrocytes .

It has been revealed that the Aβ-induced neuritic damage in AD is mediated by glycogen synthase kinase (GSK-3). This enzyme also regulates tau protein, it promotes tau phosphorylation, and can thereby cause destabilization of the microtubule network. Furthermore, GSK-3 interacts with the *N*-methyl-D-aspartate receptors (NMDARs) and hence the glutamatergic system. Additionally, inhibitors of GSK-3 interfere with the cleavage of APP and block the production and accumulation of Aβ .

Despite the sound evidence of the role of Aβ in the pathomechanism of AD, reduction of the Aβ levels in the brain has been shown in clinical trials, not to improve the cognitive function in AD patients, even though there was evidence indicating the clearance of Aβ plaques. This suggests that other factors might also be involved in the pathogenesis of AD .

5. The role of inflammation in the pathomechanism of AD

Chronic inflammation contributes to the pathogenesis of neurodegenerative diseases and is an established feature of AD as well . In contrast, hypotheses exist proposing that neuroinflammation might have a protective role and that microglial activation may diminish the pathologic changes by releasing immune suppressing and neurotrophic agents .

The microglia have a phagocytic capacity and are activated by a variety of inflammatory processes and diseases affecting the central nervous system (CNS). Activated microglia express cell surface molecules such as cytokine and chemokine receptors, CD11b, CD11c, CD14, MHC molecules, Fc receptors and scavenger receptors, they also have pattern recognition receptors of the Toll-like receptor (TLR)-type and acting as antigen-presenting cells (APCs). Aβ activates microglia and astrocytes through the TLRs as well , which induces a signaling cascade that further involves the activation of transcription factors (e.g. NF-kappaB, AP-1) . During the microglial neuroinflammatory response, inflammatory mediators, neurotoxic cytokines, proinflammatory chemokines and reactive oxygen species (ROS) are released . Some of these factors induce the chemotaxis of astrocytes around the plaques . As a result, activated microglial cells recruit astrocytes and induce their proliferation . Astrocytes have been shown to enhance the neuroinflammatory response. The aim of glial cell activation is the clearance of Aβ deposition; however, the chronic inflammatory conditions lead to damage to the surrounding neurons and promote further amyloidogenesis, as shown in animal models .

Notably, an elevation of inflammatory markers can be detected in the serum and CSF before any increase in Aβ or hyperphosphorylated tau could be noted . Accordingly, the plasma levels of certain the inflammatory markers, such as IL-6, TNF alfa, IL-10 and IL-13, have been shown to correlate inversely with the whole brain volume, the entorhinal cortex volume and the ventricular volume in AD .

A body of evidence from epidemiological studies suggests that medication with non-steroidal anti-inflammatory (NSAIDs) reduces the risk of development of AD and can delay the onset and reduce the severity of AD symptoms, thereby supporting the role of inflammation in the pathomechanism of AD . It has been shown that NSAIDs exert their protective role by modulating the activity of γ-secretase and by altering the β-sheet conformation of Aβ and hence its ability to aggregate . Despite the established role of inflammation in the pathology of AD, clinical trials with NSAIDs produced negative results . It has been suggested that these medications might be beneficial in the very early stages of the disease process .

There is recent interesting evidence that a high-fat diet is a significant risk factor for the development of AD and that long-chain fatty acids such as palmitic acid or lauric acid, stimulate inflammatory markers and processes involved in AD and modulate the amyloid processing. It is presumed that a high-fat diet increases the uptake of fatty acids from the plasma to the brain, predominantly into astrocytes located in the vicinity of the BBB . In experimental models, an increase in BACE 1 expression has been observed in astrocytes exposed to palmitic acid .

6. Oxidative stress and the role of a mitochondrial dysfunction in AD

APP and Aβ react with mitochondrial components and lead to a mitochondrial dysfunction, which increases the synaptic damage and causes neuron apoptosis . Mitochondrial dysfunction results in impaired ATP production and increased oxidative stress, which further enhances inflammatory processes. It has been shown that ApoE4 impairs mitochondrial trafficking and function, and promotes apoptosis .

7. The glutamatergic hypothesis

The NMDARs play an important role in learning and memory functions as well as in regulating synaptic plasticity; however, an overactivation of these receptors result in an excess calcium influx and induces neuronal damage and eventually neuronal death . The NMDARs are activated by the Aβ oligomers and they mediate the effects of tau protein in AD . Overactivation of the NMDARs induces the cleavage of the enzyme GSK-3 by activated calpain . On the other hand, a GSK-3 inhibitor exerts protective action against NMDAR-induced excitotoxicity by inducing a downregulation of the NMDARs, an effect that is compromised in the presence of Aβ. It is presumed that altered GSK-3 signaling may be a pathophysiological mechanism in AD .

Astrocytes

The astrocytes, the most abundant glial cells in the CNS, play an essential role in maintaining the brain structure and function. There is an emerging concept of glial cells contributing to the pathogenesis of neurological diseases due to their critical function in maintaining brain homeostasis (glio-centric view) . Indeed, astrocytes can contribute to neuropathological processes either by loss or pathological modification of their function (astroglial asthenia and astrocytopathology, respectively), or through astroglial reactivity. A central role of astrocytes in the pathomechanism of certain diseases, such as hepatic encephalopathy has been already been documented, where a reduced glutamate uptake, an enhanced glutamine production, and a reduced K^+ buffering have been described. Though not so clearly unraveled, the astrocytes play a fundamental role in the development of other neurodegenerative disorders as well, such as AD . The following sections further detail the functions of astrocytes and their impairments in AD (Fig. 3).

1. Maintenance of brain homeostasis

The astrocytes maintain the fluid, ion, neurotransmitter and pH balances (homeostasis) in the synaptic space. Experimental studies demonstrated that water exchange between the brain, the blood and the different brain compartments is regulated by astrocytes through aquaporin 4 (AQP4). Importantly, an altered AQP4 expression has been revealed in the astrocytes of AD patients and in AD models . During repolarization, when the extracellular potassium concentration increases, astrocytes take up the excess potassium through a potassium channel and are able to release it via gap junctions, thereby stabilizing the neuronal activity .

Ca^{2+} signaling in the astrocytes is essential for neuronal communication. It modulates neuronal activity and survival, and is involved in neuronal death following ischemia . Increases in intracellular calcium concentrations have been observed in astrocytes at the presence of relatively low Aβ concentrations. This has significance in intercellular communication; however, there is no propagation of an action potential along their processes. In the astrocytes, the presence of Aβ induces an increase in intracellular calcium concentrations, which can upregulate glial fibrillary acidic protein (GFAP) and S100β, stimulate the signaling pathways of BACE 1 expression, promote the formation of ROS, lead to cell dysfunction and ultimately cell death .

The extracellular pH is regulated by the transport of H^+ with a Na^+/H^+ exchanger and through the lactate and glutamate transporters in astrocytic membranes .

2. Neurotransmitter regulation

Astrocytes perform the reuptake of neurotransmitters including glutamate. Within the astrocytes these transmitters are metabolized to precursors, which can reenter into neurons after astrocytic release and can be reconverted into active neurotransmitters. Furthermore, in response to certain changes in synaptic activity, the astrocytes are able to release purines and glutamate. These observations led to

the “tripartite synapse hypothesis”, according to which astrocytes constitute a functional synapse with the neuronal synaptic elements, and directly interact with them during synaptic activity . There is scientific evidence that in addition to an intracellular elevation of calcium levels, inflammatory molecules are also necessary for astrocytic gliotransmitter release. Astrocytes are presumed to be activated in neurodegenerative diseases during an early inflammatory process . The activation of astrocytes is characterized by proliferative and morphologic alterations and the upregulation of GFAP .

3. Role in inflammatory processes

There are increases in the number, the size and the motility of astrocytes surrounding amyloid plaques. Activated astrocytes express pro-inflammatory molecules and thereby participate in neuroinflammation and neurodegeneration. However, astrocytes can also provide neuroprotection through a release of neurotrophic factors. Molecules secreted by activated astrocytes include S100β, chemokines and cytokines such as IL-1β, IL-6, TNFα and TGFβ . The responses of the astrocytes to the progression of AD have not yet been completely unraveled ; however, substances released in result of cell death have been shown to activate both microglia and astrocytes, through the receptor for advanced glycation end-products . Figure 4 presents the role of activated astrocytes in the inflammatory processes in AD pathomechanism.

4. Signal transmission and synaptic connectivity

Besides providing metabolic and trophic support to the neurons, the astrocytes modulate information processing, synaptic transmission and signal transmission throughout the CNS, and regulate neural and synaptic plasticity. In this respect, the astrocytes secrete neural growth factors, such as the glial-derived growth factor (GDNF) and the brain-derived neurotrophic factor (BDNF). It has been demonstrated that the astrocytic function is crucial for memory formation .

The astrocytes are essential for synapse formation during astrogliogenesis, for synapse maturation and for the maintenance of synaptic connectivity throughout life. Increases in synaptic activity and in the number of synapses are mediated by thrombospondin, a matrix-associated protein generated by astrocytes . The astroglial membranes are very thin structures that cover synapses. Their perisynaptic processes are devoid of organelles and neurotransmitter vesicles, but contain molecules responsible for the transport of ions, neurotransmitters, glutamine and neurotransmitter receptors. These processes provide morphological plasticity and can change the synaptic coverage dynamically, and thereby regulate the neurotransmitter concentration and synaptic connectivity . In AD, signs of morphological atrophy of the astrocytes have been demonstrated. These morphological alterations may result in an insufficient synaptic coverage, which might impair the synaptic connectivity and contribute to neuronal death . In AD animal models, these morphological changes were shown very early in the most vulnerable brain regions, such as the entorhinal and prefrontal cortices .

5. Regulation of blood flow

Through the production of arachidonic acid, prostaglandins and NO, which increase or decrease the blood vessel diameter, astrocytes can regulate the local CNS blood flow in response to changes in neuronal activity . Through paravascular processes, the astrocytes ensheath 97% of the CNS vasculature and leave only small clefts between the blood vessels and the endfeet, thereby allowing the CSF from the subarachnoid space to flow along the blood vessels throughout the brain. This phenomenon was revealed by dynamic two-photon and contrast-enhanced MR imaging . In these paravascular spaces, its content of the CSF can exchange with the ISF of the brain parenchyma. The clearance of interstitial substances, including Aβ, is possible along the paravenous spaces . These paravascular CSF channels together with astrocytes compose the glymphatic system in the CNS . The change of substances through this system is facilitated by arterial pulsatility and is most active during sleep . Exchange of water within this system is supported by astrocytes as well via the expression of the AQP4 water channels .

Earlier studies indicate that a cerebrovascular dysregulation and damage to the BBB occur in AD, and that the risk of sporadic AD is increased by transient hypoxic or ischemic attacks, silent infarcts and stroke episodes . A connection has been discovered between AD and cardiovascular disease, suggesting that sporadic AD might in fact be a vascular disease characterized by an impaired neuronal perfusion and the accumulation of toxic metabolic products due to an altered permeability of the BBB . In this respect, areas of hypoperfusion and changes in cerebral blood flow have been revealed by imaging studies (PET and CT scans, respectively) in the parahippocampal gyrus, the frontal and the temporal cortex as well as in the hippocampus in AD patients . Amyloid angiopathy, present in up to 90% of AD patients , is presumed to be a result of a failure to eliminate Aβ from the cerebral blood vessels . Astrocytes together with the neurons, the pericytes and the microglia constitute the neurovascular unit (NVU), which has roles in maintaining the permeability of the BBB, the cerebral blood flow and hence the brain homeostasis. The astrocytic endfeet form a barrier between the neurons and the blood vessels and control the local blood flow in accordance with metabolic demands .

6. Role of the astrocytic glycolytic metabolism in AD

The astrocytes are the major glucose consumers in the brain, responsible for the utilization of about 85% of the total glucose, whereas the neurons consume only small amounts . This difference is explained by the higher expression of the glycolysis-promoting enzyme system 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB3) in the astrocytes than in the neurons. The astrocytes present a low activity of the ubiquitylation enzyme APC/C-Cdh1, which regulates the activity of PFKFB3. The result is a higher rate of glycolysis in the astrocytes than in the neurons and the sensitivity of neurons to depleted energy states. With aging, the uptake and the metabolism of glucose decline and a decrease in the rate of glycolysis occurs in astrocytes . This metabolic change can be an early phenomenon in the development of AD . Animal models of AD and the post-mortem analysis of

AD patient brains demonstrated a down-regulation of the genes related to the glycolytic pathway . In AD patients, changes in activity of the glycolytic enzymes have been observed, with a reduced activity of glucose-6-phosphate in the hippocampus and an increased activity of lactate dehydrogenase in the temporal and frontal cortices . The alterations in glucose metabolism in AD are linked to Aβ aggregation, internalization and an ineffective astrocytic clearance. The intracellular accumulation of Aβ impairs the astrocytic glucose metabolism and leads to decreased glutathione and lactate production, which increases the vulnerability of the neighboring neurons . The changes in the activity of glycolytic enzymes were observed to correlate with an increased GFAP expression in the astrocytes and with the spatial distribution of Aβ deposits in the human brain .

Astrocytes and amyloid deposition

There is an interconnection between reactive astrogliosis and amyloid deposition. The formation of Aβ is related to reactive astroglia while on the other hand, Aβ activates the astrocytes and induces morphologic and functional alterations within them. These include an increase in GFAP, S100β factor and IL1β . Activated astrocytes are present in animal models of AD and in the brains of AD patients and, as outlined above, in some studies reactive gliosis has been shown to even precede other morphological changes characteristic of AD or to be an early phenomenon in AD . It has also been suggested, that the progression of amyloid deposition is different from that of astrocytosis and that gliosis might continuously contribute to the ongoing neurodegeneration .

The reactive astroglial change in AD is predominantly focal in distribution, and the astrocytes surrounding the amyloid plaques are suggested to play several key roles in AD pathology, including amyloid uptake and amyloid clearance. Indeed, an overexpression of BACE 1 and an accumulation of intracellular Aβ have been documented in the astrocytes in AD . It has been shown more recently that an overexpression of BACE 1 occurs in reactive astrocytes located around the amyloid plaques, as a result of the action of proinflammatory cytokines, and the astrocytes may therefore become an important source of Aβ in AD . Subsequently a vicious circle may develop, in which the astrocytes around the amyloid plaques release proinflammatory molecules and cytokines, such as IFNγ, TNFαand IL-1β, which then stimulate other astrocytes, activate BACE 1 activity and lead to further Aβ production. The accumulations of Aβ42 species were demonstrated to correlate with the extent of local histopathological changes. The astrocytes preferably take up oligomeric Aβ. The uptake of Aβ42 were shown to be more pronounced during the early stages of the disease, but no impairment of the amyloid uptake by astrocytes could be proved in AD . Amyloid uptake is influenced by the amyloid plaque-associated proteins, such as α1-antichymotrypsin (ACT-1), ApoJ and ApoE, by the enzyme lipoprotein lipase and via the overexpression of the low-density lipoprotein receptor. Furthermore, astrocytes have been shown to overexpress ACT-1, which presumably inhibits Aβ breakdown and might induce the hyperphosphorylation of tau protein .

Notably, astrocytes are capable not only of the uptake, but also of the clearance of Aβ from the brain into the perivascular space and of the degradation of Aβ (Fig. 3). The degradation of the internalized amyloid occurs in the lysosomal pathway. Three enzymes are responsible for the degradation of Aβ: NEP, insulin-degrading enzyme and matrix metalloproteinase-9 (MMP-9) . NEP is regulated in a feedback manner directed by AICD released during amyloid cleavage, but it is only capable of degrading soluble forms of Aβ. The insoluble forms are degraded by glial cells and MPPs . Angiotensin-converting enzyme-1 and endothelin-converting enzyme-2 inhibit NEP, thereby reducing Aβ clearance . The upregulation of NEP in normal astrocytes and in astrocytes surrounding the amyloid deposits suggests a neuroprotective role of astrogliosis. Astrocytes derived from AD patients, however, show no increases in NEP, suggesting a functional deficit of astrocytes in AD .

Excitotoxicity

Glutamate, the major excitatory neurotransmitter in the CNS, is involved in synaptic transmission and plasticity, neuronal growth, learning and memory. Glutamate excitotoxicity has been shown to contribute to neuronal death in ischemia, traumatic brain injury and several neurodegenerative diseases, including AD. Astrocytes have an essential role in maintaining extracellular glutamate concentration below a toxic level, by the use of the glutamate-glutamine cycle and excitatory amino acid transporters (EAAT). It has been suggested that cytokines are responsible for the changes induced in the glutamine-glutamate cycle in AD. In the presence of TNFα, EAAT1 is downregulated and the expression of glutamine synthetase (GS) is reduced. This results in a reduction in glutamate uptake together with a reduction in glutamine release by astrocytes; therefore astrocytes become unable to protect neurons from glutamate excitotoxicity .

1. Role of the glial cells in excitotoxicity. Glutamate synthesis

Activated microglia are capable of inducing excitotoxicity and neurodegeneration by an excessive release of glutamate . The astrocytes are essential for glutamatergic and gamma-aminobutyric acid (GABA)-ergic neurotransmission, and the glutamine-glutamate/GABA cycle requires interactions between the neurons and the astrocytes . The syntheses of these neurotransmitters from glucose take place within the astrocytes, since neurons lack the necessary enzymatic apparatus. As such, the astrocytes provide the neurotransmitter glutamine for neurons in the glutamine-glutamate/GABA cycle. On the other hand, glutamate from the extracellular space is partly taken up by the astrocytes, converted to glutamine and subsequently returned to the neurons. Within the neurons, glutamine is further metabolized to form GABA and glutamate (Fig. 5).

2. Glutamate synthesis

Within the astrocytes, glucose is transformed glycolytically into pyruvate. Pyruvate is degraded by pyruvate dehydrogenase to form acetyl coenzyme A (CoA). This condenses with oxaloacetate to form

citrate, which is a constituent of the tricarboxylic acid (TCA) cycle. Two molecules of pyruvate are necessary to form a *de novo* molecule of citric acid. During one TCA cycle, citrate loses carbon and is transformed into oxaloacetate, which condenses again with acetyl-CoA for energy production. Pyruvate can also be converted in the astrocytes to a *de novo* oxaloacetate by the action of pyruvate carboxylase, an enzyme not present in the neurons. Through this production of *de novo* citrate molecules, the TCA intermediate α-ketoglutarate becomes available for glutamate synthesis. It is not clear whether this process is catalyzed by glutamate dehydrogenase or by aspartate aminotransferase. The complex pathway of glutamate synthesis has been suggested to be directly coupled to the process of the astrocytic degradation of glutamate and GABA .

In the astrocytes, glutamate is converted into glutamine by glutamine synthetase (GS). Glutamine is released from the astrocytes through the system N 1 (SN1) transporter. From the extracellular space, glutamine enters the neurons through the system A transporter 1 and 2 (SAT1 and SAT2) transporters. Glutamine is then converted by phosphatase-activated glutaminase (PAG) into glutamate at the membrane of neuronal mitochondria . Subsequently, glutamate packed into vesicles via the vesicular glutamate transporters (VGLUTs). A small amount of the neurotransmitters released by the neurons are returned to the neurons themselves by a reuptake mechanism; however, the majority enters the astrocyte through transporters, where they are re-converted to glutamine. Recent research suggests that about 15% of the glutamate released from the neurons is oxidatively degraded in the astrocytes . Furthermore, it has been shown that the glutamine can move from one astrocyte to an other through a functional syncytium, and astrocytes might therefore be able to supply even neurons situated at some distance with glutamine, presumably in a regulated process .

One of the essential roles of the astrocytes is to maintain sufficiently low levels of glutamate in the extracellular space, thereby preventing excitotoxic neuronal injury. The uptake of glutamate into the astrocytes is achieved by two glutamate transporters: glutamate aspartate transporter (GLAST) (also known as excitatory amino-acid transporter 1 (EAAT1)) and glutamate transporter-1 (GLT-1) (also known as excitatory amino-acid transporter 2 (EAAT2)). The transport of glutamate is energy-dependent and requires the uptake of 3 Na^+ and one H^+ and the efflux of K^+. Mutations of the genes encoding these transporters lead to excitotoxicity and neurodegeneration, as demonstrated in animal models .

Astrocytes are a source of glutathione, superoxide dismutase and ascorbate, and thereby exert antioxidant properties, which act in order to prevent excitotoxic injury . Astrocytes may also possess neuroprotective properties through the production of neurotrophic factors, as mentioned above (i.e. BDNF, GDNF and insulin-like growth factor (ILGF)) .

Experimental models of AD revealed a decrease in glutamate uptake and a decreased expression of EAATs , which changes that have been linked to the deposition of Aβ . EAAT gene transcription has been demonstrated in experimental models to be modulated by the YY1 transcription factor under both

physiological and pathological conditions, and targeting such signaling pathways could offer therapeutic benefits in AD .

3. Excitotoxicity in AD - excitotoxins and amyloid

The neuropathological staging system introduced by Braak suggest that the entorhinal cortex is involved in the early progression of AD . The entorhinal cortex receives afferents from the fourth cortical layer, the association cortex, the hippocampus and other parts of the limbic cortex, and gives projections to the hippocampus and the association cortex. These afferents and some of the efferent of the entorhinal cortex, such as the perforant pathway, which originates predominantly from the second entorhinal layer and projects to the hippocampus, are glutamatergic. In preclinical and in mild cases of AD, a reduction in the number of neurons in the second and fourth layers of the entorhinal cortex has been detected . The conversion from the stage of mild cognitive impairment to dementia might be characterized by a synaptic loss in the outer molecular layer of the dentate gyrus . Synaptic loss has been revealed to be the strongest predictive factor for cognitive decline in AD, as indicated by a delay in memory recall or a decline in the results of the Mini-Mental State Examination test. In the advanced stages of the disease, a severe neuronal loss occurs in the neocortical association areas . Molecular markers of glutamatergic synaptic dysfunction can be detected even in the early stages of AD. Decreases in the expression of VGLUT1 and VGLUT2 and of synaptophysin as well as a co-localization of Aβ with VGLUT1 and 2 transporters in the presynaptic terminals were observed . The dysfunction of the glutamatergic network is presumably due to the neurotoxic Aβ peptide and tau protein. Aβ influences the glutamatergic neurotransmission in several ways. Aβ aggregates can induce tau hyperphosphorylation and aggregation, which results in further neurotoxicity . Aβ deposition affects the glutamatergic synaptic vesicular pool and impairs neurotransmitter release and synaptic transmission. The postsynaptic ionotropic glutamate receptors include the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, the NMDARs, and the G protein-coupled metabotropic glutamate receptors, which can be divided into three groups according to their functions . Aβ exerts its neurotoxic effects predominantly on the NMDARs, stimulation of which enhances Aβ production. The NMDAR is a tetramer composed of two glycine-binding units that form the ion channel and two glutamate-binding subunits with a modulating role. NMDARs that contain the phosphorylated GluN2B subunit are predominantly located extrasynaptically . Experimental data suggest that stimulation of the NMDARs at the extrasynaptic site is neurotoxic, whereas their activation at the synaptic site promotes cell survival . Notably, Aβ activates Fyn kinase that causes increased phosphorylation of the GluN2B subunit, which expands the spectrum of the NMDAR-mediated toxic effects of Aβ on neurons. Besides these morphological changes induced by Aβ oligomers in the synaptic transmission, functional changes have also been documented. Aβ causes synaptic dysfunction by impairing the long-term potentiation (LTP; which follows brief, high-

frequency stimulation) and by potentiating the long-term depression (LTD; which follows low-frequency stimulation) .

High-frequency stimulation of presynaptic glutamatergic neurons induces an increased release of glutamate in the synaptic cleft. First, the AMPARs and the metabotropic glutamate receptors are stimulated. Their sustained activation leads to activation of the NMDARs. The activation of NMDARs containing the GluN2A subunit evokes an increase in the postsynaptic Ca^{2+} concentration, which subsequently initiates a cascade of events involved in LTP induction. A decreased stimulation of the glutamatergic synapse leads to the internalization of the synaptic NMDARs and activation of the extrasynaptic NMDARs that contain GluN2B subunits, and induces a weaker increase in the postsynaptic Ca^{2+} concentration, a phenomenon referred to as LTD. In physiological conditions, this phenomenon is associated with the synapse remodeling, whereas in pathological conditions, with synaptic failure . Activation of the GluN2B subunits can induce apoptosis via caspase-8 and caspase-3, and might be responsible for synaptic dysfunction and neuronal death in AD .

Aβ also induces internalization of the AMPARs, an effect that requires the metabotropic activation of the NMDARs . A scaffolding protein that binds to the GluN2B subunit connects the NMDARs to NO synthase and may have an important role in excitotoxicity through excessive production of NO . GluN2B-mediated glutamatergic neurotransmission is involved in the neurotoxic effects exerted by tau protein on the synaptic function . As described above, Aβ causes an impairment of the astrocyte function, downregulating their glutamate uptake capacity. A revision of the importance of the kynurenine pathway (KP) in the elimination of glutamate excitoxicity in AD should be considered.

Kynurenines and their potential roles in AD

Since numerous data sources suggest that the KP is involved in the pathogenesis of various neurological disorders (pain syndromes, stroke and epilepsy), special emphasis is placed on reviewing its role in neurodegenerative processes, such as Huntington's disease (HD) , Parkinson's disease (PD) and AD .

1. Metabolism, receptors and main effects of kynurenines

The KP is expressed in astrocytes, neurons, macrophages, and glial, endothelial and dendritic cells, and the largest amounts of kynurenine metabolites are utilized in the CNS . The KP is the major route of the catabolism of tryptophan (Trp). Approximately 95% of this essential amino acid may be converted to "kynurenines" by special enzymes (Trp and/or indoleamine 2,3-dioxygenases; i.e. TDO and/or IDO-1, IDO-2) . This conversion results in L-kynurenine (L-KYN), via the N-formylkynurenine transition product in the plasma. L-KYN is synthesized in the brain at the rate of 0.29 nmol/g/h and serves as a key molecule between the neurotoxic and neuroprotective directions of the pathway. Quinolinic acid (pyridine-2,3-dicarboxylic acid, QUIN), a neurotoxic compound is produced from L-KYN in the microglia cells, catalyzed by kynurenine 3-monooxygenase (KMO), via

additional toxic metabolites (3-hydroxykynurenine, 3-HK and 3-hydroxyanthranilic acid). These agents can generate toxic free radicals, oxidative stress, lipid peroxidation and glutamate excitotoxicity through activation of the essential amino-acid receptors (EAARs). In contrast, the characteristically neuroprotective kynurenic acid (4-hydroxyquinoline-2-carboxylic acid; KYNA) is formed directly from L-KYN in the astrocytes, catalyzed by kynurenine aminotransferases (KATs) (Fig. 6) and is an endogenous inhibitor of the EAARs .

KYNA is primarily a nonselective antagonist of the strychnine-insensitive glycine-binding site of the NMDARs . Furthermore, it can noncompetitively block the nicotinergic processes at the α7nAChRs, and it has the ability to inhibit the effects of AMPARs and kainate receptors only in mM doses . It takes part in neuronal and glial glutamatergic neurotransmission, intracellular Ca^{2+} concentration and mitochondrial membrane damage-induced neuronal cell death and neurodegeneration in the CNS . Most of the effects of KYNA (neuroprotective, antinociceptive and anti-inflammatory) are explained by inhibition of the EAARs, but other interactional partners have recently been also identified . KYNA is able to interact with the orphan G protein-coupled receptor 35 (GPR35), which is expressed in the neurons and glial cells (in the brain and dorsal root ganglia) and in the macrophages and monocytes (in the immune system) . As an agonist, KYNA Presumably activates the GPR35Rs, which decreases the level of cyclic adenosine monophosphate, the intracellular Ca^{2+} concentration, and hence the release of glutamate and proinflammatory mediators . KYNA can also act as an agonist on the aryl hydrocarbon receptor, which is essential in fundamental cell biology, maturation of the immune and nervous systems and carcinogenesis . Certain results concerning the relationship between the opioid and the kynurenine systems , suggest that the opioid receptors may also be a targets for kynurenine metabolites.

In healthy subjects under normal conditions the concentration of KYNA is nanomolar in the brain and micromolar in the blood plasma , but significant changes have been observed in the concentrations of kynurenine metabolites in different diseases. Research has revealed that a shift in the QUIN/KYNA rate toward the formation of toxic QUIN induces epileptic seizures and HD-like symptoms via neurotoxicity and lipid peroxidation .

2. Roles of kynurenines in neurodegenerative disorders

2.1 Huntington's disease

Relative decreases in the level of KYNA and a reduced activity of KAT have been demonstrated in the striatum of HD patients . Elevated concentrations of 3-HK can also contribute to the formation of neurodegenerative diseases such as HD . A preclinical rat model of HD revealed a severe reduction in KAT-I immunopositivity in the striatum after chronic (3-nitropropionic acid) treatment . The intrastriatal administration of QUIN, a possible endogenous neurotoxin in HD, provoked increased neuronal vulnerability in KAT-II-deficient mice , which suggests the importance of KYNA in controlling the effects of QUIN . Zádori and co-workers demonstrated that the systemic administration

of a novel KYNA derivative prolonged the survival of the animals, ameliorated the hypolocomotion and prevented weight-loss and the atrophy of the striatal neurons in a transgenic mouse model of HD . These data illustrated that alterations in the KP can contribute to the development of HD and increased KYNA concentration may prove protective against neurodegeneration .

2.2 Parkinson's disease

There is evidence that PD is accompanied by a shift in the KP . Ogawa and co-workers found that the concentrations of KYNA were decreased in the frontal cortex, putamen and pars compacta of the substantia nigra of patients with PD, whereas the 3-HK levels were increased in the putamen, indicating oxidative damage . It emerged from animal models of PD that mitochondrial neurotoxins cause decreased KAT immunoreactivity and subsequently a diminished KYNA levels in the brain affected by PD . Attenuated KAT-1 and KAT-2 activity and KYNA levels that were measured in the blood plasma of PD patients, but increased expressions of both these enzyme isoforms and the KYNA levels were observed in the red blood cells, suggesting a protective response against neurotoxic effects . A clinical study revealed increased 3-HK levels in the cerebrospinal fluid of PD patients, confirming the relevance of the KP in mechanisms of neurodegeneration .

2.3 Alzheimer's disease

An ever increasing amount of evidence indicates that an altered kynurenine metabolism is also implicated in the pathology of AD, but the mechanisms have not been identified in detail, and the influence of the KP in the development of the disease is rather controversial. There are two conceptions as concerns the role of an elevated KYNA levels in AD: it may be a causative factor in the development of AD or it may take part in a compensatory repair mechanism.

Kynurenines as provoking/damaging or compensatory/repair factors of AD

Widner and co-workers found that the concentration of Trp still tended to be lower in AD patients due to the enhanced degradation of Trp reflecting the significantly increased KYN/Trp ratio . Although KYNA inhibits the excessive release of glutamate during excitotoxicity, massive increase in the KYNA concentration in healthy subjects can trigger neuronal death. These processes may take place in AD, where the level of L-KYN rises in the brain and the plasma resulting in an elevated systemic KYNA content . KYNA-induced EAAR inhibition may be responsible for the impaired learning, memory and cognition in AD patients. An increased serum KYN/Trp ratio was observed in AD patients, indicating an enhanced IDO activity, which may be associated with the reduced cognitive performance . An elevated IDO activity can be elicited and/or aggravated by inflammatory processes .
An elevated L-KYN level additionally provides a possibility to increase the concentration of QUIN, a potent neurotoxic factor implicated in the pathogenesis of AD . Markedly increased serum levels of 3-HK were reported in AD patients as compared with patients with major depression and a cognitive

impairment. There were no significant differences between the groups in the levels of the other plasma kynurenine metabolites, which indicates that 3-HK produced in large quantities can easily be transported across the BBB, resulting in a higher production of the downstream metabolite QUIN in the brain of AD patients . Wu and co-workers demonstrated that the KP is overactivated by TDO-mediated mechanisms in AD. In a triple transgenic mouse model of AD, the production of QUIN proved to be strongly increased in the hippocampus, and TDO was highly expressed in the brain of mice. Furthermore, significantly higher TDO and IDO-1 immunoreactivity and the co-localization of TDO, QUIN, deposits of tau and amyloid protein were observed in the hippocampus of AD patients . Nevertheless, the lack of an elevated central QUIN concentration in AD has also been described .

There is evidence that the L-KYN and 3-HK contents are slightly decreased in the frontal cortex, caudate nucleus, putamen, hippocampus and cerebellum, while the concentrations of KYNA are significantly increased in the caudate nucleus and putamen in AD patients as compared with healthy controls. Moreover, the levels of KYNA are moderately elevated in other brain areas, and significantly higher reaction kinetics (Vmax and Km) and activities of KATs have been observed, correlating with the level of KYNA in the striatal areas .

Others have found significantly reduced KYNA levels in the serum, the erythrocytes and the CSF in AD patients, but the concentration of L-KYN and the activity of the KATs remained unchanged . As regards the relationship between the KP and CSF in dementia, a clinical study recently revealed a gender difference between AD patients . Significantly higher KYNA levels in the CSF were detected only in female AD patients, which suggest that this alteration is dependent on estrogen production. The concentration of KYNA revealed a significant association between phospho-tau and an inflammation marker (soluble adhesion molecule-1) in the whole AD group. Correlations were not detected from the aspect of the KYNA level and cognitive decline. These studies suggest that there is a huge imbalance in the KP in the context of AD .

A shift in the KP toward the formation of QUIN in the microglia can presumably contribute to the development of AD, which may be supplemented by the concomitant presence of QUIN, Aβ and inflammatory mediators. These compounds are potent generators of reactive oxygen species, lipid peroxidation and excessive neurotoxic glutamate release. Subsequently, neuronal death and tau hyperphosphorylation can provoke the development of AD-specific changes . It is possible that the marked increases in KYNA in the caudate nucleus and putamen may compensate the hyperactivity of the striato-frontal loop in AD . The blockade of NMDA receptors by KYNA may be a response to the neurotoxicity of QUIN, this mechanism being the only currently available therapeutic solution for the treatment of AD by drugs such as the NMDA antagonist memantine . In the future, regulation of the KP through enhancement the activities of TDO, IDO and KAT and/or reduction of the activity of KMO as specific enzymes appear to be a possible target in the therapy of AD. However, the negative

effects of high doses of KYNA on the cognitive functions, and especially its schizophrenia-inducing features, cannot be ignored .

It is worthwhile to look more closely at the two-sided (Janus's face) effects and properties of KYNA. Rózsa and her co-workers demonstrated that KYNA can act as an agonist in a nanomolar doses, and as an antagonist in a micromolar doses in an electrophysiological setup . Determination of the effective neuroprotective dose of KYNA without accompanying undesired side effects could lead to an alternative solution through which to diminishing the neurodegenerative and enhancing the cognitive processes.

3. Kynurenines as possible therapeutical perspectives

The literature reveals that KYNA is definitely involved in neuroprotective mechanisms through its inhibition of glutamate-induced excitotoxicity, but its impact on cognitive performance is doubtful. Although a detailed evaluation of the role of the KP in the pathogenesis of AD necessitates further studies, we presume that a shift in the kynurenine metabolism toward neurotoxic compounds leads to a relative KYNA deficiency. This raises the possibility that a well-controlled, slight increase in the concentration of neuroprotective KYNA would be beneficial from a therapeutic aspect .

However, there are several counter-arguments to the systemic administration of KYNA: its solubility is a limiting factor in higher doses, it is barely able to cross the BBB , and its clearance mediated by organic anion transporters is rapid in the brain and the body . New and specific structural analogs of KYNA have been designed in an attempt to overcome these disadvantages . If these promising neuroprotective agents could be endowed with enhanced water-solubility and BBB penetration, and if their application in appropriate doses not accompanied by side-effects, they may furnish new perspectives in the elimination of neurodegenerative processes .

It is interesting that there are natural sources of KYNA, such as *Gingko biloba* , fresh vegetables (broccoli, potatoes, carrots and cauliflower), and bee products (honey, propolis and bee pollen), which contain approximately 1-10 nmol/g KYNA. Their bio-absorption is presumably relatively low and most of them contain higher KYNA content without heat-setting treatment , and they are frequent components of the daily diet. Experiments have been conducted to determine the relevance and utilization of these foods in the human organism. Turski and co-workers studied the absorption processes of KYNA in the gastrointestinal system. When two doses of KYNA (25 mg/kg and 250 mg/kg) were administered to rats, and 5-100-fold or micromolar increases in KYNA concentration were observed in the serum 120 minutes after the treatment. The liver and the kidneys exhibited 10-fold elevated KYNA levels 30 minutes after the treatment .

An *in vitro* study revealed that both acute and chronic administration of the anti-parkinsonian drug zonisamide enhanced the release of L-KYN and KYNA in cultured astrocytes, whereas the level of QUIN was unaltered. These alterations may influence the transmission in direct and indirect pathways of basal ganglia, which indicates that the release of neuroprotective kynurenine metabolites as an

adjuvant mechanism can contribute to the effectiveness of monotherapy. It appears crucial to apply combined or supplemented therapy in the treatment of PD and to develop drugs, which can indirectly elevate the concentration of KYNA . As a therapeutic strategy, shifting the neurotoxic/neuroprotective imbalance toward the formation of KYNA or a reducing of the level of QUIN may come into consideration.

Conclusions

Various factors contribute to the initiation and progression of AD, such as Aβ, tau, inflammation, apoE, excitotoxicity, mitochondrial damage and oxidative stress. The astrocytes not only play the role of structural and metabolic support for the neurons, but also form an interactive network with them, providing an appropriate microenvironment for their normal function, and influencing neurotransmitter release and synaptic activity. In AD, the astrocytes have been shown to play a part in excitotoxicity, amyloidogenesis and the chronic inflammation characteristic of the disease. One of the first events to occur in AD is the synaptic dysfunction, and inflammatory changes linked to the astrocytes may ensue even before the typical neurodegenerative changes. As the neurons and astrocytes are both deeply involved in the various phatogenic processes leading to AD. A medication targeting only one component of this complicated network would therefore probably not work. Focus should be placed on multi-target approaches to the therapy, and on the attainment of a better understanding of the role of the astrocytes in the disease course, which might offer new insight into the pathomechanism of the disease and new therapeutic targets. In view of the part played by excitotoxicity in the development of AD, the putative neuroprotective role of neuroactive kynurenines in the therapy of AD should be further explored.

List of abbreviations

Aβ	amyloid-beta
AAT	aspartate aminotransferase
ACT	α1-antichymotrypsin
AD	Alzheimer's disease
ADAM	A-disintegrin and metalloproteinase genes
AICD	amyloid precursor protein intracellular domain
A-KG	α-ketoglutarate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
AP-1	activated protein-1 transcription factor
ApoE	apolipoprotein E
APC	antigen-presenting cell
APC/C-Cdh1	anaphase-promoting complex/cyclosome (APC/C)–Cdh1
APP	amyloid precursor protein
βAPP	β amyloid precursor protein
AQP4	aquaporin 4
BACE	β-site amyloid precursor protein cleaving enzyme
BBB	blood-brain barrier
BDNF	brain-derived growth factor
ChP	choroid plexus
CoA	acetyl coenzyme
CT	computed tomography
CTFα	C-terminal fragment α
CTFβ	C-terminal fragment β
CTK	cytokine
EAAT	excitatory aminoacid transporters
GABA	γ-aminobutyric acid
GDH	glutamate dehydrogenase
GDNF	glial-derived growth factor
GFAP	glial fibrillary acidic protein
GLAST	glutamate aspartate transporter
Gln	glutamine
GLT-1	glutamate transporter-1
Glu	glutamate
GluN2B	glutamate-binding subunits 2B

GS	glutamine synthetase
GSK-3	glycogen synthase kinase
IDE	insulin-degrading enzyme
IFNγ	γ interferon
IL-6	interleukin-6
ILGF	insulin-like growth factor
ISF	interstitial fluid
LDLR	low-density lipoprotein receptor
LRP	low-density lipoprotein receptor-related protein
LTP	long-term-potentiation
LTD	long-term depression
MMP-9	matrix metalloproteinase-9
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
α7nAChR	α7 nicotinic acetylcholine receptor
NEP	neprilysin
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NFT	neurofibrillary tangles
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NO	nitric oxide
NR	nuclear receptor
NSAID	non-steroidal anti-inflammatory medication
NVU	neurovascular unit
OAA	oxaloacetate
PAG	phosphatase-activated glutaminase
PC	pyruvate carboxylase
PET	positron emission tomography
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase
PPAR	peroxisomal proliferator-activated receptor
PSEN	presenilin
PYR	pyruvate
Rab GTPase	Rab guanosine-5'-triphosphatase
RAGE	receptor for advanced glycation end products
S100β	astroglial marker protein S100β
SAT1	system A transporter 1
SAT2	system A transporter 2

SN1	glutamine transporter, isoforms of system N
TCA	tricarboxylic acid cycle
TGFβ	transforming growth factor beta
TLR	Toll-like receptor
TNFα	tumor necrosis factor
VGLUT	vesicular glutamate transporters

Conflict of interest

The authors declare that they have no conflict of interest and have received no payment in preparation of their manuscript.

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Figures

Figure 1.

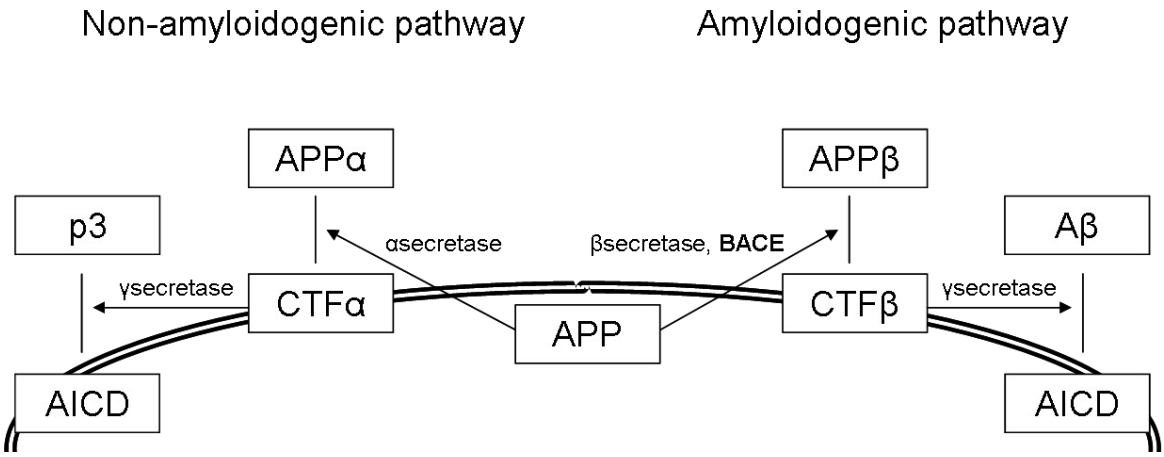


Figure 2.

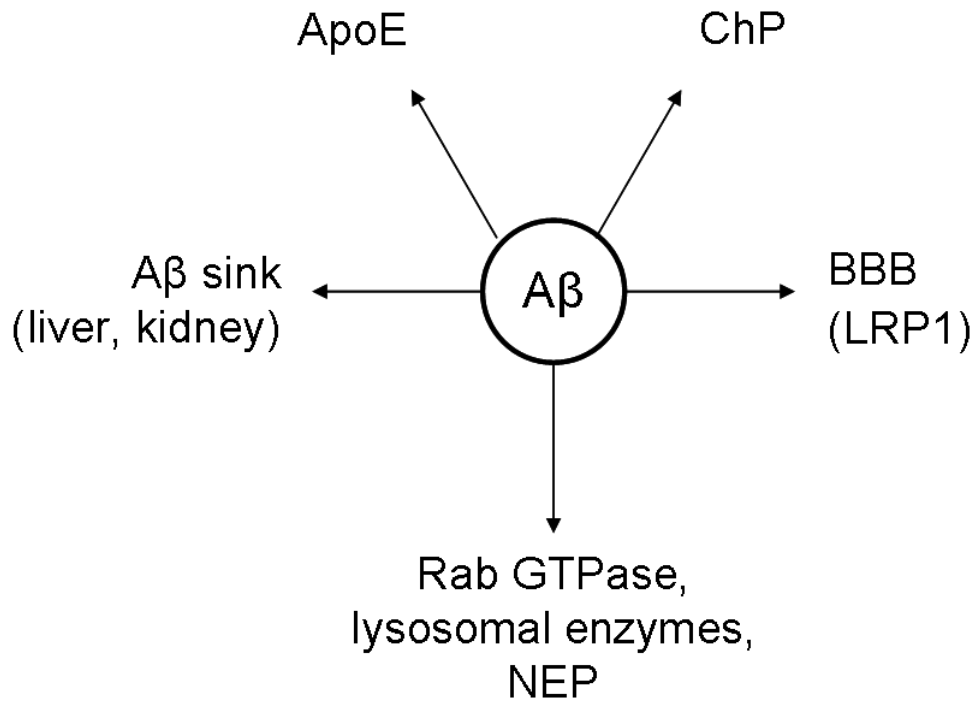


Figure 3.

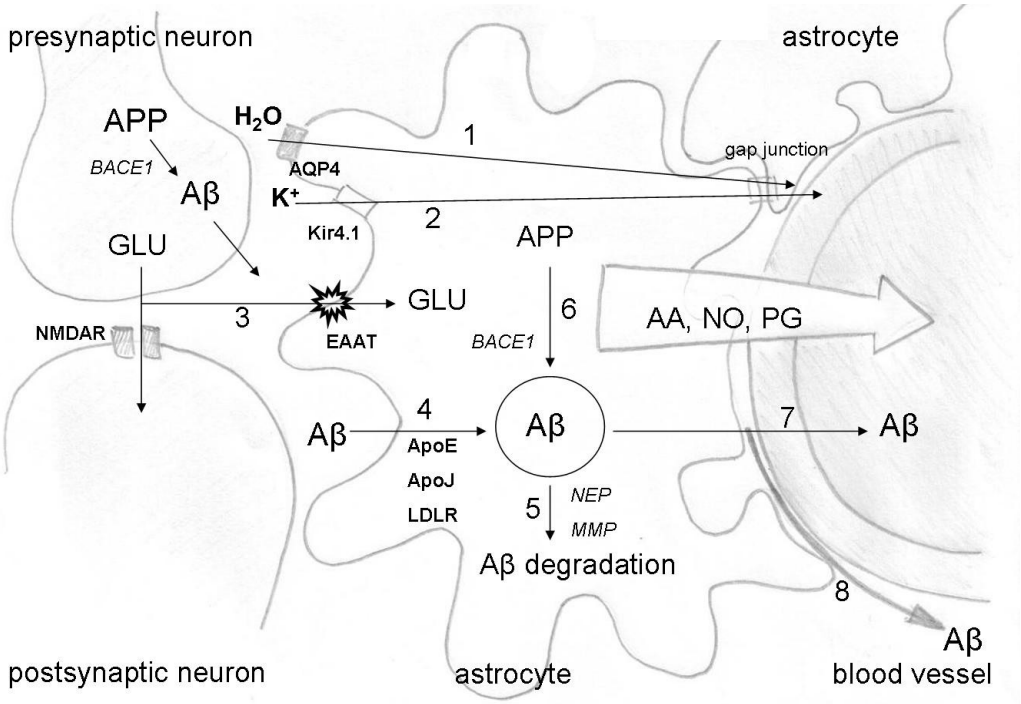
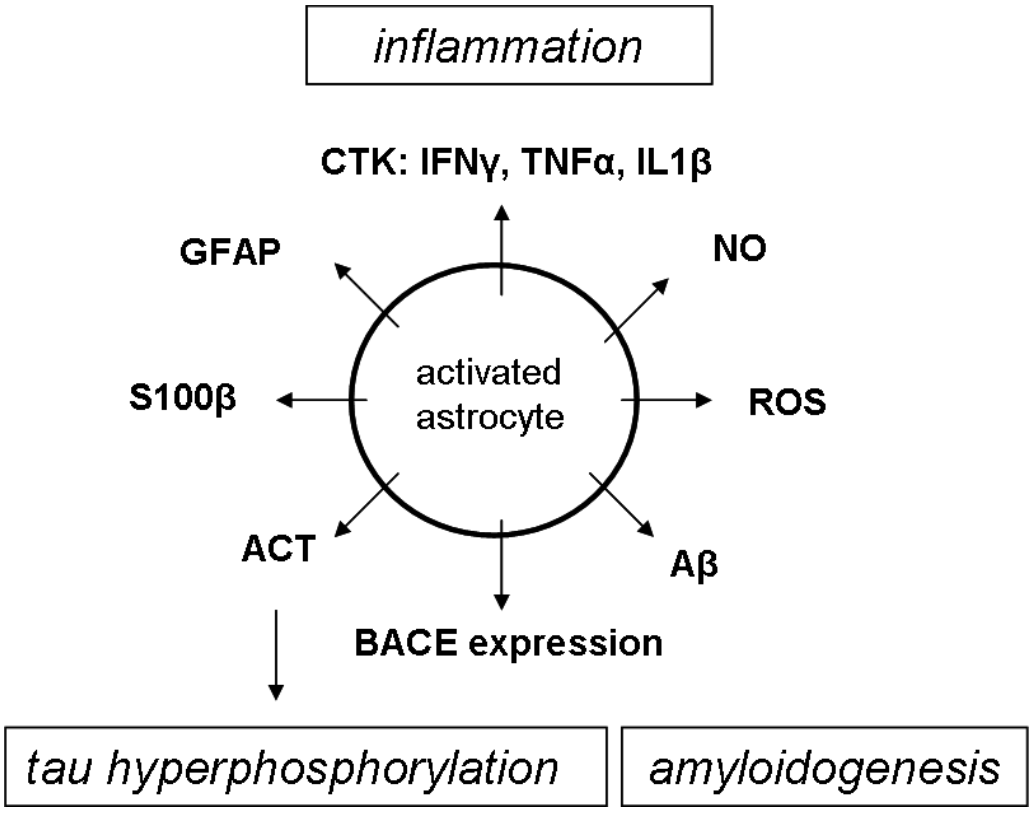


Figure 4.



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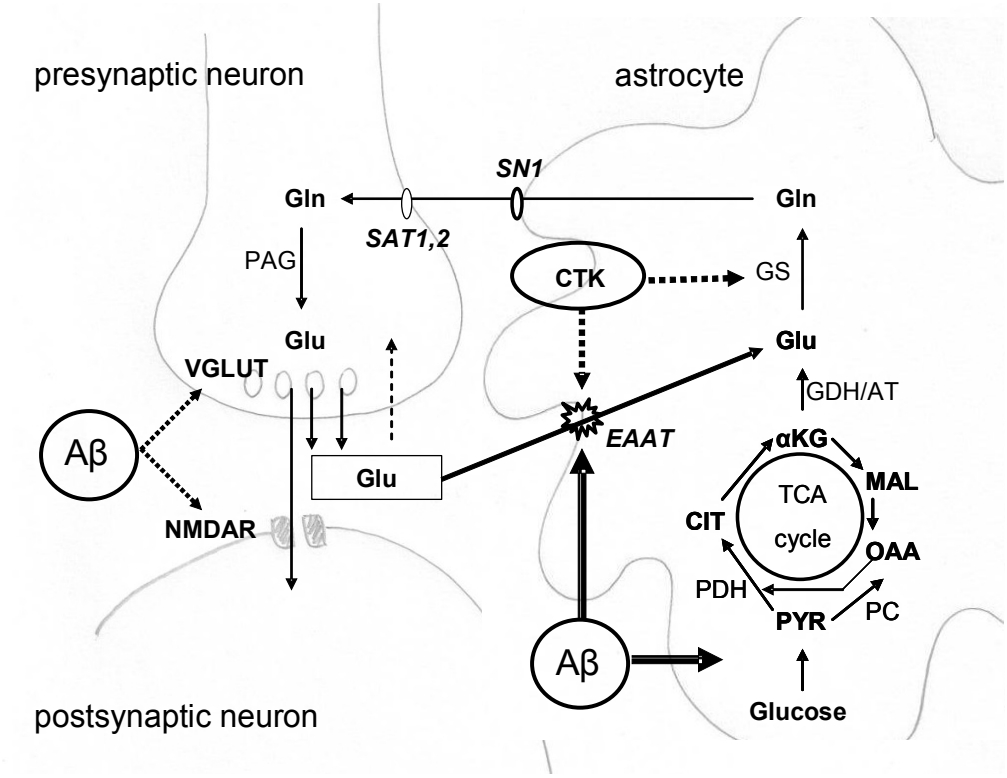

Figure. 6.

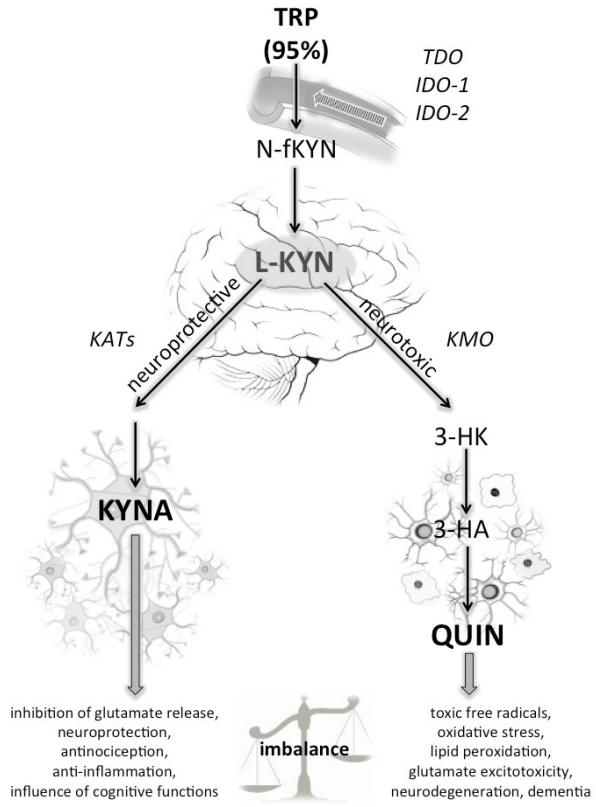

Figure legends

Figure 1. Amyloid precursor protein processing

The image shows the non-amyloidogenic processing of APP through the action of α- and γ-secretases leading soluble end products. The α-secretase cleaves APP to CTFα and the soluble αAPP, whereas γ-secretase cleaves CTFα to AICD and p3 peptide, both soluble. In the amyloidogenic-processing pathway, β-secretase (BACE) cleaves APP to the membrane-bound CTFβ and to βAPP, the latter located outside the cell. The γ-secretase cleaves CTFβ to the insoluble and neurotoxic Aβ with an extracellular location and to AICD with an intracellular location.

Abbreviations: AICD: APP intracellular domain, APP: amyloid precursor protein, αAPP: α amyloid precursor protein, βAPP: β amyloid precursor protein, CTFα: C-terminal fragment α, CTFβ: C-terminal fragment β

Figure 2. Amyloid clearance

The Rab GTPase family members, the lysosomal enzymes and neprilysin play a role in the intracellular clearance of amyloid. ApoE is the main chaperon of Aβ in the central nervous system. Aβ is exported to the blood from the brain interstitial fluid through the BBB and a lesser extent through the choroid plexus. The main carriers involved are the LRPs 1 and 2. Finally Aβ is eliminated in the liver and a lesser extent in the kidney.

Abbreviations: Aβ: β amyloid, ApoE: apolipoprotein E, BBB: blood-brain barrier, ChP: choroid plexus, LRP 1,2: low-density lipoprotein receptor-related proteins

Figure 3. The functions of astrocytes

Astrocytes maintain fluid, ion and neurotransmitter homeostasis of the synaptic space. Water exchange is regulated through the AQP4 receptors (arrow 1), whereas the excess K^+ is taken up by the Kir 4.1 K^+ channels (arrow 2) and released through gap junctions. Astrocytes release arachidonic acid, nitric oxide and prostaglandins and are able to regulate local CNS blood flow. Astrocytes take up excess glutamate and prevent neurotoxic injury (arrow 3). Astrocytes take up Aβ through amyloid plaque associated proteins, such as ApoE, ApoJ and the low-density lipoprotein receptor (arrow 4). Astrocytes degrade amyloid through neprilysin and matrix metalloproteinases (arrow 5). Overexpression of BACE and amyloid products occur in the activated astrocytes (arrow 6). Astrocytes dispose the Aβ into the blood through the BBB (arrow 7) and also through the paravenous spaces (arrow 8).

Abbreviations: Aβ: β amyloid, AA: arachidonic acid, ApoE: apolipoprotein E, ApoJ: apolipoprotein J, APP: amyloid precursor protein, AQP4: aquaporin 4, BACE: β-site amyloid precursor protein cleaving enzyme, EAAT: excitatory amino acid transporter, GLU: glutamate, LDLR: low-density lipoprotein receptor, MMP: matrix metalloproteinase, NEP: neprilysin, NO: nitric oxide, PG: prostaglandins

Figure 4. Activated astrocytes in the pathomechanism of AD.

Activated astrocytes release inflammatory mediators and maintain a chronic inflammatory state. The release of nitric oxide and reactive oxygen species causes oxidative stress. The overexpression of BACE occurs in activated astrocytes and leads to further amyloidogenesis. The overexpression of α1-antichymotrypsin might induce tau hyperphosphorylation and inhibit Aβ breakdown. Astrocyte activation is marked by the upregulation of glial fibrillary acidic protein and S100β protein.

Abbreviations: Aβ: β amyloid, ACT: α1-antichymotrypsin, CTK: cytokines, GFAP: glial fibrillary acidic protein, IFNγ: γ interferon, IL1β: β1 interleukin, NO: nitric oxide, ROS: reactive oxygen species, S100β: astroglial marker protein S100β, TNFα: tumor necrosis factor α.

Figure 5. The role of astrocytes in glutamate metabolism and excitotoxicity.

In astrocytes, glucose is glycolytically transformed into pyruvate. Pyruvate is degraded to acetyl coenzyme that condenses with oxaloacetate to form citrate, which is a component of the tricarboxylic acid cycle. During one cycle, citrate is transformed into oxaloacetate, which condenses again with acetyl-CoA for energy production. Pyruvate carboxylase converts pyruvate to *de novo* oxaloacetate. This enzyme is present in astrocytes, but absent in neurons. Two molecules of pyruvate form a *de novo* molecule of citric acid. Through the production of *de novo* citrate molecules, α-ketoglutarate becomes available for glutamate synthesis. In the astrocytes glutamate is converted to glutamine by

glutamine synthetase. Glutamine is released from astrocytes through the SN1 transporter. From the extracellular space glutamine enters the neurons through the SAT1 and SAT2 transporters. In the neurons glutamine is converted to glutamate, which returns to vesicles via the vesicular glutamate transporters. A small amount of neurotransmitters are released by neurons and returned by reuptake (discontinuous arrow), but the majority enters the astrocyte through the glutamate transporters (continuous thick arrow). Consequently astrocytes maintain low levels of glutamate in the extracellular space and might prevent excitotoxic neuronal injury. In AD the deposition of Aβ affects the glutamatergic vesicular pool, which might cause decreases in the expression of the vesicular glutamate transporters and exerts its neurotoxic effects mainly on the NMDARs resulting synaptic dysfunction (thin dotted arrow). Aβ deposition decreases astrocytic glutamate uptake by the downregulation of EAATs and impairs the metabolism of astrocytes. CTKs downregulate EAATs and reduce the expression of glutamine synthetase (thick dotted arrow). The result is a diminished glutamate uptake to astrocytes and a reduced glutamine release from astrocytes that impairs their ability to protect neurons from excitotoxic injury.

Abbreviations: Aβ: amyloid β, AAT: aspartate aminotransferase, CIT: citrate, CoA: acetyl coenzyme, CTK: cytokines, EAAT1, 2: excitatory amino acid transporter 1 and 2, GDH: glutamate dehydrogenase, Gln: glutamine, Glu: glutamate, GS: glutamine synthetase, αKG: α-ketoglutarate, NMDAR: N methyl-D aspartate receptor, OAA: oxaloacetate, PC: pyruvate carboxylase, PYR: pyruvate, SAT1, 2: system A transporter 1 and 2, SN1: glutamine transporter, isoforms of system N, TCA: tricarboxylic acid cycle, VGLU: vesicular glutamate transporters.

Figure. 6. Neuroprotective and neurotoxic pathways of kynurenines

Most of the TRP may convert to N-fKYN in the plasma by special enzymes TDO and/or IDO-1, IDO-2. L-KYN is synthesized in the brain and serves as a key molecule between the neurotoxic and neuroprotective directions of the pathway. QUIN, a neurotoxic compound is produced from L-KYN in the microglia cells, catalyzed by KMO, via additional toxic metabolites (3-HK and 3-HA). These agents can generate toxic free radicals, oxidative stress, lipid peroxidation and glutamate excitotoxicity. Subsequently it contributes to the development of neurodegeneration and dementia. In contrast, the characteristically neuroprotective KYNA is formed directly from L-KYN in the astrocytes, catalyzed by KATs. KYNA is an endogenous inhibitor of the glutamate release, thereby it has neuroprotective, antinociceptive, anti-inflammatory effects and influences the cognitive functions.

Abbreviations: 3-HA: 3-hydroxyanthranillic acid, 3-HK: 3-hydroxykynurenine, IDO-1: indoleamine 2,3-dioxygenase 1, IDO-2: indoleamine 2,3-dioxygenase 2, KATs: kynurenine aminotransferases, KMO: kynurenine 3-monooxygenase, KYNA: kynurenic acid, L-KYN: L-kynurenine, N-fKYN: N-formylkynurenine, QUIN: quinolinic acid, TDO: tryptophan 2,3-dioxygenase, TRP: tryptophan

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