# The potential role of kynureninesin Alzheimer's disease - pathomechanism and therapeuticpossibilitiesbyinfluencing the glutamate receptors

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**Abstract**: The pathomechanism of neurodegenerative disorders still poses a challenge to neuroscientists, and continuous research is under way with the aim of attaining an understanding of the exact background of these devastating diseases. The pathomechanism of Alzheimer's disease (AD) is associated with characteristic neuropathological features such as extracellular amyloid-β and intracellular tau deposition. Glutamate excitotoxicity and neuroinflammation are also factors that are known to contribute to the neurodegenerative process, but a cerebrovascular dysfunction has recently also been implicated in AD. Current therapeutic tools offer moderate symptomatic treatment, but fail to reduce disease progression. The kynurenine pathway (KP) has been implicated in the development of neurodegenerative processes, and alterations in the KP have been demonstrated in both acute and chronic neurological disorders. Kynurenines have been suggested to be involved in the regulation of neurotransmission and in immunological processes. Targeting the KP therefore offers a valuable strategic option for the attenuation of glutamatergic excitotoxicity, and for neuroprotection.

**Keywords**: neurodegeneration, Alzheimer's disease, dementia, kynurenine pathway, glutamate, excitotoxicity

## Introduction

Chronic progressive neurodegenerative diseases, such as AD and Parkinson's disease (PD) display an increasing prevalence in parallel with the aging of the population, and have therefore generated considerable recent research interest. Despite extensive studies on the background of neurodegenerative processes, the exact molecular basis remains still to be clarified. Although these devastating diseases have a serious impact on the quality of life of the patients, their management is often challenging. Current therapies offer mostly only symptomatic relief and no neuroprotective therapy is available. The pathomechanisms of different neurodegenerative disorders share a number of common features. Excitotoxicity, neuroinflammation, a mitochondrial disturbance and oxidative stress have been implicated in both acute and chronic neurological disorders(Zadori et al. 2012). Of these, excitotoxicity is of outstanding importance, as glutamate and N-methyl-D-aspartate (NMDA) receptors play a pivotal role in physiological processes in the human brain. This review sets out to discuss the importance of glutamate excitotoxicity in neurological disorders, with particular focus on AD. The role of the KP in AD and other neurological diseases, and its modulation as a potential therapeutic strategy are also presented.

## Glutamate excitotoxicity in the pathomechanism of AD and other neurological disorders

Neurodegenerative processes share some common features, which are not disease-specific. While there are still a number of details that await elucidation, there are several common mechanisms that are widely accepted; the role of mitochondrial disturbances, excitotoxicity, neuroinflammation and oxidative stress appear evident(Sas et al. 2007; Zadori et al. 2012) (Fig.1.). Glutamate is of outstanding importance in the normal brain function, but the excessive stimulation of excitatory receptors may induce a vicious cascade that finally results in neuronal damage; this process is called glutamate excitotoxicity. Glutamate excitotoxicity has been implicated in the pathomechanisms of ischaemic stroke, traumatic brain injury, and various neurodegenerative disorders (Palmer et al. 1993; Zadori et al. 2012). The extent of excitotoxic processes in the pathomechanism of these disorders contuse to be a topic of debate, but the beneficial effect of blood glutamate scavenging supports the paradigm that excitotoxic injuries contribute at least partly to the neuronal damage. Oxaloacetate, a blood glutamate scavenger, has been found to exert beneficial effects in ischaemic conditions (Marosi et al. 2009; Nagy et al. 2009; Nagy et al. 2010).

One of the most prevalent neurodegenerative disorders is AD, the most common type of dementia (Nestor et al. 2004). The characteristic neuropathological features of AD are the extracellular deposition of amyloid-β protein (Aβ) and the intracellular deposition of tau(Yankner 1996; Selkoe and Schenk 2003). AD was earlier thought to involve a distinct pathology which can be clearly distinguished from vascular dementia (VD). However, in recent years the role of a cerebrovascular dysfunction has been linked to the neurodegenerative process of AD, and vascular risk factors have attracted growing attention in connection with AD development and progression. Overlaps between VD and AD have long been recognized, but in recent years a complete paradigm shift has begun, and AD has been suggested to be a primarily vascular disease (de la Torre 2002). Only a small proportion of

AD cases have a genetic origin; the majority are sporadic. The most important risk factor for the development of AD is advancing age, the prevalence and incidence data demonstrating an increasing tendency with rising age (Hofman et al. 1991; Katz et al. 2012). However, a number of vascular risk factors have been associated with AD, and cerebrovascular abnormalities have also been revealed. Vascular risk factors, which are wellknown to be associated with cerebrovascular diseases, have also been linked to AD in recent years. Hypertension has been associated with an increased risk of stroke, VD and AD (Ruitenberg et al. 2001; Haag et al. 2009; Stewart et al. 2009). Untreated hypertension exhibits a correlation with hippocampal atrophy and a more pronounced AD pathology (Petrovitch et al. 2000; Korf et al. 2004). Diabetes, the most common metabolic disorder, poses an increased risk not only of stroke, but also of AD, especially in patients who are ApoE $\varepsilon_4$ -positive (Ott et al. 1999; Peila et al. 2002). One possible mechanism might involve the impaired insulin-degrading enzyme activity, which is also a factor in Aβ degradation (Qiu and Folstein 2006). AD has even been suggested to be "the brain type of diabetes mellitus", as an insulin-resistant state of the brain has been demonstrated (Hoyer 1998, 2004). Antibodies to the α1 adrenergic receptors have been associated with hypertension and diabetes, and these antibodies have also been detected in the serum of AD patients (Wenzel et al. 2008; Hempel et al. 2009; Karczewski et al. 2012a). The immunization of rats with these antibodies resulted in severe cerebrovascular impairments, which may explain the connections of these vascular risk factors with AD (Karczewski et al. 2012b).

Cerebral blood flow measurements in patients detected marked differences, which were predictive of AD even before the emergence of cognitive symptoms (Ishii et al. 2000; Varma et al. 2002). Multiple pathologies have also been detected at the level of the microvasculature (Farkas and Luiten 2001). Similarly, an impaired cerebral blood flow and autoregulation capacity has been observed in animal models of AD, this impairment proving to be associated with oxidative stress (Iadecola et al. 1999; Niwa et al. 2002b; Niwa et al. 2002a). These findings link the presence of Aβ to oxidative stress and neuroinflammation. On the other hand, focal cerebral hypoperfusion has been demonstrated to result in an altered expression of Aβ-degrading enzymes in parallel with enhanced Aβ formation (Hiltunen et al. 2009). These data also indicate the existence of chronic hypoperfusion in AD brains, accompanied by an elevated level of oxidative stress. Alterations in cerebral blood flow and Aβ synthesis conversely influence each other. In VD, neuroimaging and clinical signs of a cerebrovascular disease are more evident; a cognitive decline often develops after an acute ischaemic stroke or after multiple cortical infarcts (Kling et al. 2013).

As a consequence of a reduced blood flow, a hypoxic state arises in the neurones, and this could contribute to the development of an excitotoxic process. An energy impairment as a result of a mitochondrial dysfunction and the excessive activation of glutamate receptors together initiate downstream metabolic cascades, which finally converge in neuronal damage. In the event of an energy impairment, partial membrane depolarization may occur, and in this case even physiological glutamate concentrations may be capable of overstimulating the NMDA receptors, resulting in an excessive calcium influx into the cells and the production of free radicals (Novelli et al. 1988).

*Fig. 1 Converging pathways in neurodegenerative processes*

**The kynurenine pathway**

- **Neuroactivekynurenine metabolites**

The KP is the main metabolic route of tryptophan (TRP) degradation in mammals; it is responsible for more than 95% of the TRP catabolism in the human brain (Wolf 1974). The metabolites produced in this metabolic cascade, collectively termed kynurenines, are involved in a number of physiological processes, including neurotransmission and immune responses (Nemeth et al. 2005; Vecsei et al. 2013). The KP also involves neurotoxic and neuroprotective metabolites, and alterations in their delicate balance have been demonstrated in multiple pathological processes. The KP consists of a cascade of enzymatic steps which finally result in the formation of the essential coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate(Beadle et al. 1947). The first and rate-limiting step in this metabolic route is the enzymatic degradation of TRP by either indoleamine 2,3-dioxygenase (IDO) or

TRP 2,3-dioxygenase (TDO). The central intermediate of the KP is L-kynurenine (L-KYN), where the metabolic pathway divides into two different branches. L-KYN is transformed to either the neuroprotective kynurenic acid (KYNA) or 3-hydroxy-L-kynurenine (3-OH-KYN), which is further metabolized in a sequence of enzymatic steps to yield finally NAD (Fig.2). KYNA is synthetized in response to the action of kynurenine-aminotransferases (KATs), which have been identified as having 4 distinct isoforms, localized mainly in the astrocytes (Okuno et al. 1991; Guillemin et al. 2001; Han and Li 2004; Yu et al. 2006; Guidetti et al. 2007; Han et al. 2010). KYNA is a broad-spectrum endogenous inhibitor of ionotropic glutamate receptors, a non-competitive inhibitor of the α7 nicotinic acetylcholine receptor, and (according to more recent data) also a ligand for the previously orphan G-protein-coupled receptor GPR35(Perkins and Stone 1982; Hilmas et al. 2001; Wang et al. 2006). KYNA is a competitive agonist at the strychnine-insensitive glycine-binding site of the NMDA receptors (Kessler et al. 1989). Interestingly, on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, KYNA exerts a dual action in a concentration-dependent manner: in low concentrations it can facilitate, while in higher concentrations it antagonizes these receptors (Prescott et al. 2006; Rozsa et al. 2008). The neuroprotective effect of KYNA is mainly attributed to the inhibition of the NMDA receptors, e.g. by preventing glutamate excitotoxicity. However, inhibition of the α7 nicotinic acetylcholine receptors may contribute to this effect, because these receptors are involved in the regulation of presynaptic glutamate release (Marchi et al. 2002).

3-OH-KYN is produced by the action of kynurenine-3-monooxygenase (KMO). The downstream metabolic cascade includes other neuroactive metabolites, such as the free radical generator 3-hydroxyanthranilic acid (3-HANA) and the NMDA receptor agonist quinolinic acid (QUIN). 3-OH-KYN, QUIN and 3-HANA all act as potent free radical generators, while QUIN also displays NMDA agonistic properties (Stone and Perkins 1981; de Carvalho et al. 1996). Furthermore, QUIN induces lipid peroxidation, and results in an elevation of the

extracellular glutamate level, thereby enhancing the excitotoxic process (Connick and Stone 1988; Rios and Santamaria 1991; Tavares et al. 2002).

*Fig. 2 The kynurenine pathway of the tryptophan metabolism*

- **The role of kynurenines in neurological disorders**

Alterations in the KP have been demonstrated in a number of neurological disorders; the most important data are summarized in Table 1.

**Table 1. Alterations in the kynurenine pathway in neurodegenerative disorders**

| | |
|---|---|
| Parkinson's disease | • decreased KYNA and increased 3-OH-KYN levels in the putamen and the substantianigra pars compacta(Ogawa et al. 1992)<br>• elevated IDO level in the serum and cerebrospinal fluid (CSF) (Widner et al. 2002)<br>• MPTP treatment decreases KAT-expression in mice (Knyihar-Csillik et al. 2004) |
| Huntington's disease | • elevated levels of QUIN and 3-OH-KYN in the striatum at early stages (Guidetti et al. 2004)<br>• increased 3-OH-KYN levels (Pearson and Reynolds 1992)<br>• decreased level of KYNA in the striatum and cortex (Beal et al. 1990; Beal et al. 1992)<br>• decreased activity of KAT in the striatum (Beal et al. 1990; Beal et al. 1992) |
| Amyotrophic lateral sclerosis | • elevated L-KYN and QUIN levels in the CSF and serum, increased IDO activity in the CSF (Chen et al. 2010)<br>• elevated level of KYNA in the CSF, decreased level of KYNA in the serum in advanced stage of the disease (Ilzecka et al. 2003) |

Imbalances in the KP have been demonstrated not only in AD, but also in other disorders in which there is a cognitive decline, and influencing this delicate balance may be of therapeutic value (Majlath et al. 2013). Changes in kynurenine metabolites have additionally been suggested to correlate with the infarct volume, the mortality of stroke patients and the post-stroke cognitive impairment (Darlington et al. 2007; Gold et al. 2011). In another study, serum kynurenine levels and inflammatory markers were measured in patients undergoing cardiac surgery; the results indicated an association of several kynurenine metabolite levels with the post-surgical cognitive performance (Forrest et al. 2011). KP metabolites have also been implicated in vascular cognitive impairment (Oxenkrug 2007). As concerns AD, a substantial amount of evidence demonstrates an altered TRP metabolism. In the brain of pathologically confirmed AD patients, decreased levels of L-KYN and 3-OH-KYN have been detected, while the level of KYNA in the striatum and caudate nucleus was significantly elevated. In parallel with the increased KYNA level, a higher KAT-I activity was measured (Baran et al. 1999). From the aspect of the peripheral kynurenine metabolism, decreased KYNA levels were measured in the serum, red blood cells and CSF of AD patients, (Heyes et al. 1992; Hartai et al. 2007). Additionally, enhanced IDO activity was demonstrated in the serum of AD patients, as reflected by an increased KYN/TRP ratio, this elevation exhibiting inverse correlation with the rate of cognitive decline (Widner et al. 1999, 2000). IDO activation was also correlated with several immune markers in the blood, thereby indicating an immune activation, which lends further support to the role of neuroinflammation in the pathomechanism of AD. An increased IDO activity was also confirmed by immunohistochemistry in the hippocampus of AD patients, together with an enhanced QUIN immunoreactivity(Guillemin et al. 2005). Interestingly, $A\beta_{1-42}$ induced IDO expression and QUIN production in human macrophages and microglia (Guillemin et al. 2003). A further finding confirming the role of QUIN in the pathomechanism of AD was the fact that QUIN was not only co-localized with hyperphosphorylated tau in the AD cortex, but also capable of inducing tau phosphorylation in primary neurone cultures (Rahman et al. 2009).

**Future neuroprotective strategies in neurodegenerative diseases by targeting the KP**

Attenuation of glutamate excitototoxicity appears to be of promise as a therapeutic intervention for various neurological disorders. However, one potential disadvantage of NMDA antagonists might be the development of intolerable side-effects as a result of complete glutamate antagonism. Several NMDA antagonists which had given promising preclinical results failed in clinical trials. Among the reasons for these failures were the presence of side-effects or the lack of efficacy. These results, however, promoted a better understanding of the importance of the NMDA receptors in the normal brain functioning. Glutamatergic neurotransmission is crucial in maintaining the physiological brain function,

and cognitive processes and memory are of outstanding importance among these functions. However, in pathological cases, where overactivation of excitatory receptors is present, NMDA antagonism may be beneficial by restoring the physiological glutamatergic balance, and preventing the excitotoxic neuronal damage without impairing the normal functions (Parsons et al. 2007). Memantine was the first NMDA antagonist drug authorized for the therapy of AD (Lipton 2004). At present, no other NMDA antagonist is available in clinical practice, although there is still a great need for effective neuroprotective therapies.

The above experimental data suggest that interventions through the KP may offer novel therapeutic strategies with the aim of neuroprotection. Enhancement of the neuroprotective effects of KYNA or attenuation of the levels of neurotoxic metabolites might be a reasonable strategy. Unfortunately, KYNA crosses the blood-brain barrier (BBB) only poorly, and its systemic administration is therefore not feasible (Fukui et al. 1991). A possible approach may be the use of prodrugs which can penetrate the BBB or the application of synthetic KYNA analogues (Stone 2000). A third possible intervention might be modulation of the enzymatic machinery of the KP, to achieve a metabolic shift towards production of the neuroprotective KYNA and decreased synthesis of the neurotoxic metabolites. All these attempts have already been tested in multiple preclinical models of different diseases, including PD, HD, cerebral ischaemia and migraine (reviewed by Vecsei et al. 2013) . There is evidence of the beneficial effects of these methods in AD.  L-KYN administered together with probenecid, an inhibitor of the transport of  KYNA in the brain, prevented the morphological alteration and cellular damage induced by soluble Aβ. Moreover, this treatment resulted in a significant improvement of the spatial memory (Carrillo-Mora et al. 2010). 4-Chlorokynurenine, a halogenated derivative of L-KYN, also prevented neuronal damage in a toxic animal model (Wu et al. 2000). A synthetic KMO inhibitor has been demonstrated to exert beneficial effects in animal models of AD and HD,  not only by preventing neuronal damage, but (in the AD model) also preventing spatial memory deficits (Zwilling et al. 2011). The favourable results in these studies can be attributed mainly to the prevention of glutamate excitotoxicity, but other possible mechanisms may also be involved. In an *in vitro* study, KYNA increased the neuronal cell survival; this effect was associated with the induction of the gene expression and activity of neprilysin, an enzyme participating in the degradation of Aβ (Klein et al. 2013). These data suggest the possibility that KYNA may exert its neuroprotective effect, at least partly, by inducing amyloid degradation.

A further important aspect of KP modulation that must be taken into consideration is the development of potential side-effects because of the NMDA antagonism. Another synthetic KYNA analogue, N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride, whichexerted neuroprotective effects in animal models of both cerebral ischaemia and HD, was therefore tested in behavioural studies (Gellert et al. 2011; Zadori et al. 2011). The results clearly demonstrated, that in the dose in which it exerted its neuroprotective effect, this novel KYNA amide did not induce any significant systemic side-effect (Nagy et al. 2011; Gellert et al. 2012). Furthermore, in the same dosage, KYNA and its derivative did not reduce, but rather increased the induceability of long-term potentiation. This result might indicate that KYNA and its derivative may exert their neuroprotective effects by preferentially inhibiting extrasynaptic NMDA and α7 nicotinic acetylcholine

receptors, while sparing the synaptic NMDA-mediated currents (Demeter et al. 2013). Further investigations involving AD animal models are under way, but in the light of the results already available, further investigations are definitely justified.

## Conclusion

Glutamate excitotoxicity mediated by NMDA receptors is one of the most important factors in the development of neurodegenerative disorders, the pharmacological modulation of this process might therefore offer a valuable therapeutic strategy. Neuroprotective therapies are currently not available, and even the symptomatic treatment of these diseases is often challenging. Alterations of the KP have been clearly demonstrated in both acute and chronic neurological disorders, and imbalances between its neurotoxic and neuroprotective components may contribute to the pathomechanism of these diseases. Further investigations are needed in order to attain a better understanding of the possibilities of modulating the KP with the aim of developing novel therapeutic tools for neurodegenerative diseases.

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## Conflict of Interest

The authors have no conflict of interest to report.

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