Kynurenines and other novel therapeutic strategies in the treatment of dementia

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Abstract:

Dementia is a common neuropsychological disorder with an increasing incidence. The most prevalent of the different types of dementia is Alzheimer's disease. The underlying pathophysiological features of the cognitive decline are neurodegenerative processes, a cerebrovascular dysfunction and immunological alterations. The therapeutic approaches are still limited, although intensive research is being conducted with the aim of finding neuroprotective strategies. The widely accepted cholinesterase inhibitors and glutamate antagonists did not meet the expectations that they would prevent disease progression, and the research is therefore currently focusing on novel targets. Nonsteroidal anti-inflammatory drugs, secretase inhibitors and statins are promising drug candidates for the prevention and management of different forms of dementia. The kynurenine pathway has been associated with various neurodegenerative disorders and cerebrovascular diseases, it is closely related to neuroinflammatory processes too, and it has been implicated in the pathomechanisms of certain kinds of dementia. Targeting the kynurenine system may be of therapeutic value in the future.

Keywords: dementia, Alzheimer's disease, kynurenine, neuroprotective agents

1. Introduction

Dementia is an acquired cognitive decline, beyond what might be attributed to normal aging. It is a general term referring to a clinical syndrome of multiple cognitive deficits with several different underlying pathologies. The classification of the various dementia types may be based on genetic, pathological or clinical features. The prevalence and incidence data reveal an increasing tendency in parallel with the aging of the population. The overall prevalence of dementia is around 6-8% [De Ronchi *et al.*, 2005, De Deyn *et al.*, 2011, Mejia-Arango *et al.*, 2011], with the most prevalent type being Alzheimer's disease (AD) [Nestor *et al.*, 2004].

The main pathogenic mechanisms involved in the development of dementia are neurodegeneration and a cerebrovascular dysfunction, which have been recognized to be closely associated [Iadecola *et al.*, 2003, Iadecola, 2010, Honjo *et al.*, 2012, Liu *et al.*, 2012].

There are a number of common features in the pathomechanisms of neurodegenerative processes, including mitochondrial disturbances [Karbowski *et al.*, 2012, Szalardy *et al.*, 2012], neuroinflammation [Glass *et al.*, 2010], glutamate excitotoxicity [Lau *et al.*, 2010] and oxidative stress [Gandhi *et al.*, 2012]. Excitotoxic damage to neuronal cells is caused by the overactivation of glutamate receptors, inhibition of which could therefore be a promising neuroprotective strategy. A valuable endogenous neuroprotective molecule is kynurenic acid (KYNA), a tryptophan (TRP) metabolite produced in the kynurenine pathway (KP), which exerts broad-spectrum endogenous excitatory amino acid receptor antagonistic properties [Perkins *et al.*, 1982, Birch *et al.*, 1988, Kessler *et al.*, 1989].

There is currently no definite cure for dementia syndromes, although intensive research is under way 2with a view to the development of novel therapeutic interventions that may be

able to prevent or slow down the progression of the disease, thereby improving the quality of life of the patients. The KP offers a valuable target for neuroprotective therapies.

2. Dementia aetiology and diagnosis

The diagnosis of the dementia syndrome is usually based on the DSM-IV criteria [American Psychiatric Association. *et al.*, 2000, Feldman *et al.*, 2008].

The diagnostic criteria for dementia are the following:

- An acquired memory decline and a severe impairment in one or more cognitive domains, including gnosis, executive function, praxis and language
- Cognitive impairments that interfere with work or social activities

A number of brief cognitive tests are available for the assessment of the overall cognitive performance, the most widely used being the highly sensitive and specific Mini-Mental State Examination (MMSE) [Folstein *et al.*, 1975], and the clock-drawing test [Shulman, 2000]. Other tests include the Montreal Cognitive Assessment [Nasreddine *et al.*, 2005], DemTect [Kalbe *et al.*, 2004], the 7-Minute Screen [Solomon *et al.*, 1998] and the Behavioural Neurology Assessment short form [Darvesh *et al.*, 2005], which are more accurate in cases of mild dementia. After recognition of a cognitive impairment, detailed clinical evaluation, specific laboratory tests and structural neuroimaging may help to identify the aetiology [Feldman *et al.*, 2008, Gauthier *et al.*, 2012]. The most common types of dementia are AD and vascular dementia, but there are multiple other pathologies which may lead to a cognitive decline (Table 1).

Table 1. The most common dementia types

- Alzheimer's disease
- Vascular dementia and vascular cognitive impairment
- Dementia with extrapyramidal syndromes
    - Huntington's disease
    - Parkinson's disease
    - Lewy bodies dementia
- Frontotemporal dementias
- Other dementia types
    - AIDS-dementia complex
    - Normal pressure hydrocephalus
    - Prion diseases

The hallmark neuropathological features of the most common dementia form, AD, are amyloid-ß protein deposition in senile plaques and cerebral blood vessels, and tau deposition in the neurons forming neurofibrillary tangles. The other main form, vascular dementia, is defined as the common presence of a cognitive decline and a cerebrovascular disorder. Recent findings provided evidence that a cerebrovascular dysfunction and neurodegenerative processes are strongly associated during the development of dementia [Iadecola *et al.*, 2003]. Vascular risk factors may accelerate amyloid ß production and deposition, thereby contributing to disease progression in AD. Likevise, amyloid deposition causes cerebral amyloid angiopathy, which results in a disturbed cerebral perfusion [Thal *et al.*, 2008, Honjo *et al.*, 2012]. Neuroimaging studies have demonstrated that a reduced cerebral blood flow can be associated with early stages of AD, and cerebral hypoperfusion may precede the clinical symptoms of dementia and contribute to the development of AD [Rombouts *et al.*, 2005, Ruitenberg *et al.*, 2005]. A cerebrovascular dysfunction may contribute markedly to the development of neurodegenerative processes. Other vascular dementia forms may develop in consequence of the presence of vascular risk factors such as atherosclerosis or small vessel disease, and in post-stroke cases [Battistin *et al.*, 2010, Thal *et al.*, 2012].

Cognitive decline and dementia may present in several neurodegenerative disorders. Huntington's disease (HD) is a chronic progressive disorder of autosomal dominant inheritance, which involves characteristic motor disturbances and a remarkable cognitive decline. The genetic background of HD is the polyglutamine expansion of the huntingtin gene [Tan *et al.*, 2012] but recent genetic studies on yeasts have implicated several other genes which may influence the neurotoxic process, including kynurenine-3-monooxygenase (KMO) [Giorgini *et al.*, 2005, Tauber *et al.*, 2011]

3. The kynurenine pathway and the role of kynurenines in dementia

3.1. The kynurenine pathway

The KP, the main route of the TRP metabolism, is responsible for the breakdown of more than 90% of the TRP in the human brain [Wolf, 1974]. This metabolic cascade involves several neuroactive metabolites, collectively termed kynurenines [Lapin, 1978, Zadori *et al.*, 2011]. Kynurenines have been shown to play important roles in the regulation of neurotransmission and in immunological processes [Vécsei, 2005, Zadori *et al.*, 2011, Vecsei *et al.*, 2013]. Alterations in the KP have been implicated in the pathomechanism of cerebral ischaemia [Sas *et al.*, 2008, Stone *et al.*, 2012], migraine [Fejes *et al.*, 2011, Tajti *et al.*, 2011, Pardutz *et al.*, 2012, Tajti *et al.*, 2012], AIDS dementia complex (ADC) [Guillemin *et al.*, 2005] and several neurodegenerative disorders, including AD [Guillemin *et al.*, 2002, Plangar *et al.*, 2011, Zadori *et al.*, 2011].

The KP of the TRP catabolism comprises multiple enzymatic steps that result in the formation of the essential coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate [Beadle *et al.*, 1947] (Fig. 1). The rate-limiting step of this metabolic route is the enzymatic degradation of TRP by indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). The first stable intermediate in the KP is L-kynurenine (L-KYN), which can be converted in two different routes: either by the kynurenine aminotransferases (KATs) to form

the neuroprotective KYNA, or in a sequence of enzymatic steps which lead to the production of NAD [Beadle *et al.*, 1947]. The four subtypes of KATs identified so far are mainly localized in the astrocytes within the brain [Okuno *et al.*, 1991, Guillemin *et al.*, 2001, Yu *et al.*, 2006, Guidetti *et al.*, 2007, Han *et al.*, 2010]. In the human brain, KYNA production can be attributed mainly to the activity of KAT-II [Guidetti *et al.*, 2007]. KYNA is a broad-spectrum endogenous inhibitor of ionotropic excitatory amino acid receptors [Perkins *et al.*, 1982] and a non-competitive inhibitor of the α7 nicotinic acetylcholine receptor [Hilmas *et al.*, 2001], and it was recently discovered that it may also be a ligand for the previously orphan G protein-coupled receptor GPR35 [Wang *et al.*, 2006].

In the other main branch of the KP, L-KYN serves as a substrate for kynurenine-3-monooxygenase (KMO), resulting in the production of 3-hydroxy-kynurenine (3-HK) [Battie *et al.*, 1981]. The continuing downstream metabolic cascade then produces the free radical generator 3-hydroxyanthranilic acid (3-HANA) and the NMDA receptor agonist quinolinic acid (QUIN) [Foster *et al.*, 1986]. 3-HK and 3-HANA are potent free radical generators, while QUIN displays neurotoxic properties, not only through the production of free radicals, but also by NMDA-receptor agonism [Stone *et al.*, 1981, De Carvalho *et al.*, 1996].

The enzymes participating in the KP are differently distributed among the different cells in the CNS: the microglial cells harbour little KAT, and the astrocytes contain hardly any KMO. KYNA production can therefore be attributed mainly to astrocytes, while microglial cells are primarily responsible for the synthesis of QUIN [Espey *et al.*, 1997, Guillemin *et al.*, 2001, Lehrmann *et al.*, 2001].

[Fig. 1. The kynurenine pathway]

3.2. Kynurenine pathway alterations in Alzheimer's disease

An increasing body of evidence supports the notion that alterations in the KP are involved in the pathogenesis of AD [Baran *et al.*, 1999, Widner *et al.*, 2000]. As long ago as 1998, Baran demonstrated that the levels of 3-OH-KYN and L-KYN were slightly decreased in the brain of pathologically confirmed AD patients, while the level of KYNA exhibited a significant increase in the putamen and caudate nucleus. This elevation in KYNA correlated strongly with an increased KAT-I enzyme activity [Baran *et al.*, 1999]. As concerns the peripheral kynurenine metabolism, the KYNA levels in the serum, red blood cells and CSF of AD patients were decreased, with no alterations in the serum KAT-I or KAT-II activity [Heyes *et al.*, 1992, Hartai *et al.*, 2007]. Moreover, an increased serum KYN/TRP ratio has been detected in AD patients, indicating an enhanced IDO activity, which may be explained by the role of inflammatory processes in the pathogenesis of AD [Widner *et al.*, 2000]. Conversely, an increased IDO activity was correlated with several immune markers in the serum of AD patients [Widner *et al.*, 2000]. Interestingly, an increased level of TRP degradation correlated with a reduced cognitive performance [Widner *et al.*, 2000]. An increased QUIN and IDO

immunoreactivity has been detected in the hippocampus of AD patients [Guillemin *et al.*, 2005], pointing to the role of QUIN in the neurodegenerative process. This concept was further supported by the observation that QUIN is co-localized with hyperphosphorylated tau in the AD cortex, and QUIN also proved to induce tau phosphorylation in *in vitro* studies [Rahman *et al.*, 2009].

3.3. Kynurenine pathway in other conditions of cognitive decline

The ADC is a characteristic dementia syndrome associated with human immunodeficiency virus type 1 infection. The neurotoxic kynurenine metabolite QUIN has been demonstrated to be involved in the development of the ADC. The significantly elevated levels of QUIN detected in the CSF of ADC patients correlated with the cognitive deficits, while zidovudine therapy resulted in a decreased QUIN level in parallel with a clinical improvement. These data raised the possibility that the neurotoxic properties of this metabolite contribute to disease progression [Heyes *et al.*, 1991a, Heyes *et al.*, 1991, Kaul *et al.*, 2001]. Experimental data indicated that an elevated QUIN production reflected local macrophage activation in the CNS [Valle *et al.*, 2004].

KP metabolites have been associated with a post-surgical cognitive impairment and the alterations observed in this patient population additionally correlated with inflammatory markers [Forrest *et al.*, 2011]. An enhanced kynurenine metabolism has been demonstrated to correlate with the infarct volume and mortality in stroke patients, and recent data suggested that an increased IDO activity resulting in a higher kynurenine/tryptophan ratio is associated with post-stroke cognitive impairment [Darlington *et al.*, 2007, Gold *et al.*, 2011]. Other studies have implicated kynurenine metabolites in vascular cognitive impairment and other neuropsychiatric conditions [Oxenkrug, 2007].

Experimental data indicate a correlation between KP alterations and HD pathomechanism. In early stages of HD, increased levels of QUIN and 3-OH-KYN have been measured [Guidetti *et al.*, 2004]. Beal et al. demonstrated in 1990 that KYNA levels are decreased in the striatum of HD patients [Beal *et al.*, 1990]. Similarly, a reduced KAT activity has been demonstrated in several brain regions of HD patients [Jauch *et al.*, 1995]. The results of a clinical study revealed an increased IDO and a decreased KAT activity, in parallel with an elevated level of oxidative stress [Stoy *et al.*, 2005]. These alterations have been assumed to contribute to the disease development. Similar changes in KAT activity have been observed in an animal model of HD [Csillik *et al.*, 2002]. Another animal study provided evidence of an increased vulnerability to the neurotoxicity of QUIN after KAT deletion, while elevation of the KYNA concentration proved to be protective [Harris *et al.*, 1998, Sapko *et al.*, 2006].

3.4. Future therapeutic possibilities by targeting the kynurenine pathway

The roles of the above-mentioned alterations in AD patients are still under investigation; the most feasible concept is that an accelerated kynurenine metabolism contributes to the neurodegenerative process through the overproduction of neurotoxic metabolites.

KYNA displays neuroprotective properties, but at concentrations above physiological it can exert adverse effects. The intracerebroventricular administration of KYNA resulted in behavioural abnormalities in rats, including stereotypy and ataxia [Vecsei *et al.*, 1990], and in another study KYNA level elevations caused spatial working memory deficits [Chess *et al.*, 2007]. On the other hand, one animal study demonstrated that the inhibition of KYNA formation may be associated with an enhanced cognitive performance [Potter *et al.*, 2010]. However, under the pathological conditions in neurodegenerative processes where glutamatergic excitotoxicity is present, inhibition of the overactivated glutamate receptors may restore the normal level of activation and improve the cognitive function. From this perspective, KYNA analogues may be a promising therapeutic tool in different pathologies relating to a cognitive impairment, by exerting a neuroprotective effect and restoring normal glutamatergic neurotransmission.

KYNA itself can cross the blood-brain barrier only poorly [Fukui *et al.*, 1991], and its systemic administration as a therapeutic tool is therefore not feasible. Furthermore, it is rapidly excreted from the brain by organic acid transporters [Bahn *et al.*, 2005]. One therapeutic possibility would be the administration of L-KYN together with probenecid, an organic acid transporter inhibitor; this concept has been already tested under ischaemic conditions with good results [Gigler *et al.*, 2007, Robotka *et al.*, 2008]. Another possibility could be the administration of the halogenated L-KYN derivative 4-chlorokynurenine, which produces the KYNA analogue 6-chlorokynurenic acid. 4-chlorokynurenine has already successfully completed a Phase I clinical safety trial (for further information, see the press release on the VistaGen website) [Vecsei *et al.*, 2013]. Other synthetic KYNA analogues have proved to be neuroprotective in different animal experiments including HD, and recent data provided evidence that this novel KYNA-amide does not exert cognitive side-effects [Knyihar-Csillik *et al.*, 2008, Vamos *et al.*, 2010, Zadori *et al.*, 2011, Gellert *et al.*, 2012]. Another approach could be the use of KMO inhibitors, which may shift the kynurenine metabolism towards KYNA production. KMO inhibition has been demonstrated to increase the brain KYNA concentration, improve spatial memory and anxiety deficits and prevent synaptic loss in a transgenic mouse model of AD [Zwilling *et al.*, 2011]. The same compound tested in a HD animal model was able to slow down neurodegeneration and increase survival time [Zwilling *et al.*, 2011]. Inhibition of KMO and TDO resulted in a shift of the KP towards KYNA formation and additionally ameliorated the neurodegenerative process in other animal models [Campesan *et al.*, 2011].

4. Other possible novel therapeutic approaches in dementia

The therapies currently available for AD have the aim of restoring the cholinergic and glutamatergic dysfunction; cholinesterase inhibitors and the glutamate-antagonist memantine are well-known and widely-used drugs. However, for other dementia types the recommendations are not so clear. The evidence supports the use of cholinesterase inhibitors and memantine in Lewy body disease and Parkinson's disease dementia, with particular concern for side-effects; for other dementia types, there is currently no robust evidence in favour of any pharmacological approach [EFNS-ENS guideline-2012]. Intensive research is currently being carried out with a view to the development of novel therapeutic tools which

could possibly slow the disease progression besides providing symptomatic relief (Table 2) [Potter, 2010].

Table 2. Possible targets for drug development in Alzheimer's disease [Potter, 2010]
➢ cholinergic receptor agonists ➢ vaccines against amyloid-ß ➢ antibodies against amyloid-ß ➢ secretase inhibitors ➢ antiinflammatory drugs ➢ tau-targeting agents

Neuroinflammation is considered to be an important aspect in the pathomechanism of AD, and the observation from epidemiologic studies that nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with a lower risk of AD gave rise to the concept of using anti-inflammatory drugs for the treatment of dementia [Szekely *et al.*, 2004]. *In vitro* studies yielded evidence that some NSAIDs were able to decrease the level of the amyloid*β*-42 peptide in cultured cells [Weggen *et al.*, 2001], while ibuprofen treatment in an animal model of AD resulted in a reduction of the amyloid plaque load and microglial activation [Yan *et al.*, 2003]. Unfortunately, clinical trials have so far been disappointing [Aisen, 2002]. However, recently published data have suggested that selective COX-1 inhibitors may be of therapeutic value in AD, but further studies are needed to assess their efficacy [Choi *et al.*, 2013].

The lipid metabolism was linked with AD when the apolipoprotein E (ApoE) allele 4 was identified as a major genetic risk factor for AD [Corder *et al.*, 1993]. ApoE is a major cholesterol transport protein in the brain [Mahley, 1988]. The ApoE ε allele has been associated with an increased risk of cerebral amyloid angiopathy [Greenberg *et al.*, 1995] and HIV disease progression [Burt *et al.*, 2008], among others. ApoE, cholesterol and lipid metabolism alterations have been implicated in various stages of the pathogenesis of AD, including amyloid-ß protein production and clearance and cerebrovascular effects [Marzolo *et al.*, 2009, Zlokovic, 2013]. Statins have been associated with a lower risk of AD in large epidemiological studies [Wolozin *et al.*, 2000]. This can be explained in part by the fact that hyperlipidaemia is one of the major vascular risk factors and a cerebrovascular dysfunction may contribute to the development of AD. Moreover, statins have been reported to decrease amyloid-β peptide production in a cholesterol-independent mechanism [Hosaka *et al.*, 2013].

The amyloid-ß protein is produced from amyloid precursor protein in consequence of the proteolytic activity of β-secretase beta-site APP cleavage enzyme 1 (BACE1) and the γ-secretase complex [Vassar, 2004]. Inhibition of BACE1 has been demonstrated to result in a

lower amyloid-ß protein level and to enhance cognitive impairment in an animal model of AD [Ohno *et al.*, 2004]; BACE1 inhibitors may therefore be of therapeutic value in AD patients. The development of an orally available brain-penetrant BACE1 inhibitor was recently reported, which resulted in a reduced level of amyloid β protein formation in rats [Stamford *et al.*, 2012], while another recently developed BACE1-inhibitor has already progressed to a Phase 1 clinical trial [Jeppsson *et al.*, 2012].

5. Conclusions

The pathomechanisms of different types of dementias are still under investigation, and the therapeutic possibilities are therefore limited. Neuroinflammatory processes, the lipid metabolism and secretase inhibitors are currently controversial fields as concerns drug development, but further research may facilitate an understanding. The alterations in the KP are common features in the neurodegenerative, cerebrovascular and immunological aspects of dementias. This may therefore lead to a promising novel therapeutic approach for all types of dementia.

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