Kynurenines and other novel therapeutic strategies in the treatment of dementia

Zsófia Majláth, János Tajti and László Vécsei

Ther Adv Neurol Disord

[2013] 6(6) 386–397

DOI: 10.1177/

1756285613494989

© The Author(s), 2013.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Dementia is a common neuropsychological disorder with an increasing incidence. The most prevalent type 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 expectations of preventing disease progression, and 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. This pathway is also closely related to neuroinflammatory processes 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: Alzheimer's disease, dementia, kynurenine, neuroprotective agents

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 Deyn *et al.* 2011; De Ronchi *et al.* 2005; Mejia-Arango and Gutierrez, 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 [Honjo *et al.* 2012; Iadecola, 2010; Iadecola and Gorelick, 2003; Liu and Zhang, 2012].

There are a number of common features in the pathomechanisms of neurodegenerative processes,

including mitochondrial disturbances [Karbowski and Neutzner, 2012; Szalardy *et al.* 2012], neuroinflammation [Glass *et al.* 2010], glutamate excitotoxicity [Lau and Tymianski, 2010] and oxidative stress [Gandhi and Abramov, 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 [Birch *et al.* 1988; Kessler *et al.* 1989; Perkins and Stone, 1982].

There is currently no definite cure for dementia syndromes, although intensive research is under way with 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 patients. The KP offers a valuable target for neuroprotective therapies.

Correspondence to:

László Vécsei, MD, PhD, DSc

Neuroscience Research Group of the Hungarian Academy of Sciences and University of Szeged, Semmelweis u.6., H-6725 Szeged, Hungary and Department of Neurology, University of Szeged, Szeged, Hungary
vecsei.laszlo@med.u-szeged.hu

Zsófia Majláth, MD
János Tajti, MD, PhD
Department of Neurology, University of Szeged, Szeged, Hungary

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 body dementia
Frontotemporal dementias
Other dementia types:
AIDS–dementia complex
Normal pressure hydrocephalus
Prion diseases
AIDS, acquired immunodeficiency syndrome.

Dementia aetiology and diagnosis

The diagnosis of the dementia syndrome is usually based on the *Diagnostic and Statistical Manual of Mental Disorders fourth edition* (DSM-IV) criteria [American Psychiatric Association, 2000; Feldman *et al.* 2008].

The diagnostic criteria for dementia are the following:

- (1) an acquired memory decline and a severe impairment in one or more cognitive domains, including gnosis, executive function, praxis and language;
- (2) 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 [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, a 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).

The hallmark neuropathological features of the most common dementia form, AD, are amyloid- β

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 cognitive decline and a cerebrovascular disorder. Recent findings provided evidence that cerebrovascular dysfunction and neurodegenerative processes are strongly associated during the development of dementia [Iadecola and Gorelick, 2003]. Vascular risk factors may accelerate amyloid- β production and deposition, thereby contributing to disease progression in AD. Likewise, amyloid deposition causes cerebral amyloid angiopathy, which results in a disturbed cerebral perfusion [Honjo *et al.* 2012; Thal *et al.* 2008]. 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]. Cerebrovascular dysfunction may contribute markedly to the development of neurodegenerative processes. Other vascular dementia forms may develop as a result of the presence of vascular risk factors, such as atherosclerosis or small vessel disease, and in post-stroke cases [Battistin and Cagnin, 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 and Yu, 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]

The kynurenine pathway and the role of kynurenines in dementia

The kynurenine pathway

The KP, the main route of 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.* 2011a]. Kynurenines have been shown to play important roles in the regulation of neurotransmission and in immunological processes [Vécsei, 2005; Vécsei *et al.* 2013; Zadori *et al.* 2011a]. 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; Pardutz *et al.* 2012; Tajti *et al.* 2011, 2012], AIDS dementia complex (ADC) [Guillemin *et al.* 2005b] and several neurodegenerative disorders, including AD [Guillemin and Brew, 2002; Plangar *et al.* 2011; Zadori *et al.* 2011a].

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] (Figure 1). The rate-limiting step of this metabolic route is the enzymatic degradation of TRP by indoleamine 2,3-dioxygenase (IDO) or TRP 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 [Guidetti *et al.* 2007; Guillemin *et al.* 2001; Han *et al.* 2010; Okuno *et al.* 1991; Yu *et al.* 2006]. 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 and Stone, 1982] and a non-competitive inhibitor of the $\alpha 7$ 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 KMO, resulting in the production of 3-hydroxy-kynurenine (3-HK) [Battie and Verity, 1981]. The continuing downstream metabolic cascade then produces the free radical generator 3-hydroxyanthranilic acid (3-HANA) and the N-methyl-D-aspartate (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 [De Carvalho *et al.* 1996; Stone and Perkins, 1981].

The enzymes participating in the KP are differently distributed among the different cells in the central nervous system (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].

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 patients with pathologically confirmed AD, 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 cerebrospinal fluid (CSF) of patients with AD were decreased, with no alterations in the serum KAT I or KAT II activity [Hartai *et al.* 2007; Heyes *et al.* 1992]. Moreover, an increased serum KYN/TRP ratio has been detected in patients with AD, 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 patients with AD [Widner *et al.*

Figure 1. The kynurenine pathway.

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

The kynurenine pathway in other conditions of cognitive decline

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 ADC. The significantly elevated levels of QUIN detected in the CSF of patients with ADC 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, 1991b; 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 postsurgical 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 patients with stroke, and recent data suggested that an increased IDO activity resulting in a higher kynurenine/TRP ratio is associated with poststroke 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 and colleagues demonstrated that KYNA levels are decreased in the striatum of HD patients [Beal *et al.* 1990]. Similarly, reduced

KAT activity has been demonstrated in several brain regions of patients with HD [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 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].

Future therapeutic possibilities by targeting the kynurenine pathway

The roles of the above-mentioned alterations in patients with AD 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 [Vécsei and Beal, 1990], and in another study KYNA level elevations caused spatial working memory deficits [Chess *et al.* 2007]. By contrast, one animal study demonstrated that the inhibition of KYNA formation may be associated with enhanced cognitive performance [Potter *et al.* 2010]. However, under the pathological conditions in neurodegenerative processes in which 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 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

Table 2. Possible targets for drug development in Alzheimer's disease [Potter, 2010].

Cholinergic receptor agonists Vaccines against amyloid β Antibodies against amyloid β Secretase inhibitors Anti-inflammatory drugs tau-targeting agents
--

acid transporter inhibitor; this concept has already been 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 7-chlorokynurenine acid. 4-Chlorokynurenine has already successfully completed a phase I clinical safety trial (for further information, see the press release on the Vista Gen website/Press releases: <http://www.vista-gen.com/?p=1061>) [Vécsei *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 [Gellert *et al.* 2012; Knyihar-Csillik *et al.* 2008; Vamos *et al.* 2010; Zadori *et al.* 2011b]. 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 an 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].

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 [Sorbi *et al.* 2012]. Intensive research is currently being carried out with a view to the development of novel therapeutic tools which could possibly slow disease progression besides providing symptomatic relief (Table 2) [Potter, 2010].

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 cyclooxygenase 1 inhibitors may be of therapeutic value in AD, but further studies are needed to assess their efficacy [Choi *et al.* 2013].

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- β protein production and clearance, and cerebrovascular effects [Marzolo and Bu, 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 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- β protein is produced from amyloid precursor protein as a result of the proteolytic activity of β -secretase β -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- β 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 patients with AD. 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 I clinical trial [Jeppsson *et al.* 2012].

Conclusion

The pathomechanisms of different types of dementias are still under investigation, and the therapeutic possibilities are therefore limited. Neuroinflammatory processes, lipid metabolism and secretase inhibitors are currently controversial fields in drug development, but further research may facilitate an understanding. 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.

Funding

This work was supported by the Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged, and by the project entitled TÁMOP 4.2.2.A-11/1/KONV-2012-0052.

Conflict of interest statement

The authors declare that there were no conflicts of interest in preparing this article.

References

- Aisen, P. (2002) The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. *Lancet Neurol* 1: 279–284.
- American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*,

4th ed. Washington, DC: American Psychiatric Association

- Bahn, A., Ljubojevic, M., Lorenz, H., Schultz, C., Ghebremedhin, E., Ugele, B. *et al.* (2005) Murine renal organic anion transporters mOAT1 and mOAT3 facilitate the transport of neuroactive tryptophan metabolites. *Am J Physiol Cell Physiol* 289: C1075–C1084.
- Baran, H., Jellinger, K. and Deicke, L. (1999) Kynurenine metabolism in Alzheimer's disease. *J Neural Transm* 106: 165–181.
- Battie, C. and Verity, M. (1981) Presence of kynurenine hydroxylase in developing rat brain. *J Neurochem* 36: 1308–1310.
- Battistin, L. and Cagnin, A. (2010) Vascular cognitive disorder. A biological and clinical overview. *Neurochem Res* 35: 1933–1938.
- Beadle, G., Mitchell, H. and Nyc, J. (1947) Kynurenine as an intermediate in the formation of nicotinic acid from tryptophane by neurospora. *Proc Natl Acad Sci U S A* 33: 155–158.
- Beal, M., Matson, W., Swartz, K., Gamache, P. and Bird, E. (1990) Kynurenine pathway measurements in Huntington's disease striatum: evidence for reduced formation of kynurenic acid. *J Neurochem* 55: 1327–1339.
- Birch, P., Grossman, C. and Hayes, A. (1988) Kynurenate and FG9041 have both competitive and non-competitive antagonist actions at excitatory amino acid receptors. *Eur J Pharmacol* 151: 313–315.
- Burt, T., Agan, B., Marconi, V., He, W., Kulkarni, H., Mold, J. *et al.* (2008) Apolipoprotein (apo) E4 enhances HIV-1 cell entry in vitro, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. *Proc Natl Acad Sci U S A* 105: 8718–8723.
- Campesan, S., Green, E., Breda, C., Sathyaikumar, K., Muchowski, P., Schwarcz, R. *et al.* (2011) The kynurenine pathway modulates neurodegeneration in a Drosophila model of Huntington's disease. *Curr Biol* 21: 961–966.
- Chess, A., Simoni, M., Alling, T. and Bucci, D. (2007) Elevations of endogenous kynurenic acid produce spatial working memory deficits. *Schizophr Bull* 33: 797–804.
- Choi, S., Aid, S., Caracciolo, L., Minami, S., Niikura, T., Matsuoka, Y. *et al.* (2013) Cyclooxygenase-1 inhibition reduces amyloid pathology and improves memory deficits in a mouse model of Alzheimer's disease. *J Neurochem* 124: 59–68.
- Corder, E., Saunders, A., Strittmatter, W., Schmechel, D., Gaskell, P., Small, G. *et al.* (1993) Gene dose of apolipoprotein E type 4 allele and the

- risk of Alzheimer's disease in late onset families. *Science* 261: 921–923.
- Csillik, A., Knyihar, E., Okuno, E., Krisztin-Peva, B., Csillik, B. and Vécsei, L. (2002) Effect of 3-nitropropionic acid on kynurenine aminotransferase in the rat brain. *Exp Neurol* 177: 233–241.
- Darlington, L., Mackay, G., Forrest, C., Stoy, N., George, C. and Stone, T. (2007) Altered kynurenine metabolism correlates with infarct volume in stroke. *Eur J Neurosci* 26: 2211–2221.
- Darvesh, S., Leach, L., Black, S., Kaplan, E. and Freedman, M. (2005) The behavioural neurology assessment. *Can J Neurol Sci* 32: 167–177.
- De Carvalho, L., Bochet, P. and Rossier, J. (1996) The endogenous agonist quinolinic acid and the non endogenous homoquinolinic acid discriminate between NMDAR2 receptor subunits. *Neurochem Int* 28: 445–452.
- De Deyn, P., Goeman, J., Vervaet, A., Dourcy-Belle-Rose, B., Van Dam, D. and Geerts, E. (2011) Prevalence and incidence of dementia among 75–80-year-old community-dwelling elderly in different districts of Antwerp, Belgium: the Antwerp Cognition (ANCOG) Study. *Clin Neurol Neurosurg* 113: 736–745.
- De Ronchi, D., Berardi, D., Menchetti, M., Ferrari, G., Serretti, A., Dalmonte, E. *et al.* (2005) Occurrence of cognitive impairment and dementia after the age of 60: a population-based study from Northern Italy. *Dement Geriatr Cogn Disord* 19: 97–105.
- Espey, M., Chernyshev, O., Reinhard, J., Jr, Namboodiri, M. and Colton, C. (1997) Activated human microglia produce the excitotoxin quinolinic acid. *Neuroreport* 8: 431–434.
- Fejes, A., Pardutz, A., Toldi, J. and Vécsei, L. (2011) Kynurenine metabolites and migraine: experimental studies and therapeutic perspectives. *Curr Neuropharmacol* 9: 376–387.
- Feldman, H., Jacova, C., Robillard, A., Garcia, A., Chow, T., Borrie, M. *et al.* (2008) Diagnosis and treatment of dementia: 2. Diagnosis. *CMAJ* 178: 825–836.
- Folstein, M., Folstein, S. and McHugh, P. (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198.
- Forrest, C., Mackay, G., Oxford, L., Millar, K., Darlington, L., Higgins, M. *et al.* (2011) Kynurenine metabolism predicts cognitive function in patients following cardiac bypass and thoracic surgery. *J Neurochem* 119: 136–152.
- Foster, A., White, R. and Schwarcz, R. (1986) Synthesis of quinolinic acid by 3-hydroxyanthranilic acid oxygenase in rat brain tissue in vitro. *J Neurochem* 47: 23–30.
- Fukui, S., Schwarcz, R., Rapoport, S., Takada, Y. and Smith, Q. (1991) Blood-brain barrier transport of kynurenines: implications for brain synthesis and metabolism. *J Neurochem* 56: 2007–2017.
- Gandhi, S. and Abramov, A. (2012) Mechanism of oxidative stress in neurodegeneration. *Oxid Med Cell Longev* 2012: 428010.
- Gauthier, S., Patterson, C., Chertkow, H., Gordon, M., Herrmann, N., Rockwood, K. *et al.* (2012) Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). *Can Geriatr J* 15: 120–126.
- Gellert, L., Varga, D., Ruszka, M., Toldi, J., Farkas, T., Szatmari, I. *et al.* (2012) Behavioural studies with a newly developed neuroprotective KYNA-amide. *J Neural Transm* 119: 165–172.
- Gigler, G., Szenasi, G., Simo, A., Levay, G., Harsing, L., Jr, Sas, K. *et al.* (2007) Neuroprotective effect of L-kynurenine sulfate administered before focal cerebral ischemia in mice and global cerebral ischemia in gerbils. *Eur J Pharmacol* 564: 116–122.
- Giorgini, F., Guidetti, P., Nguyen, Q., Bennett, S. and Muchowski, P. (2005) A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease. *Nat Genet* 37: 526–531.
- Glass, C., Saijo, K., Winner, B., Marchetto, M. and Gage, F. (2010) Mechanisms underlying inflammation in neurodegeneration. *Cell* 140: 918–934.
- Gold, A., Herrmann, N., Swardfager, W., Black, S., Aviv, R., Tennen, G. *et al.* (2011) The relationship between indoleamine 2,3-dioxygenase activity and post-stroke cognitive impairment. *J Neuroinflammation* 8: 17.
- Greenberg, S., Rebeck, G., Vonsattel, J., Gomez-Isla, T. and Hyman, B. (1995) Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann Neurol* 38: 254–259.
- Guidetti, P., Amori, L., Sapko, M., Okuno, E. and Schwarcz, R. (2007) Mitochondrial aspartate aminotransferase: a third kynurenate-producing enzyme in the mammalian brain. *J Neurochem* 102: 103–111.
- Guidetti, P., Luthi-Carter, R., Augood, S. and Schwarcz, R. (2004) Neostriatal and cortical quinolinate levels are increased in early grade Huntington's disease. *Neurobiol Dis* 17: 455–461.

- Guillemin, G. and Brew, B. (2002) Implications of the kynurenine pathway and quinolinic acid in Alzheimer's disease. *Redox Rep* 7: 199–206.
- Guillemin, G., Brew, B., Noonan, C., Takikawa, O. and Cullen, K. (2005a) Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. *Neuropathol Appl Neurobiol* 31: 395–404.
- Guillemin, G., Kerr, S. and Brew, B. (2005b) Involvement of quinolinic acid in AIDS dementia complex. *Neurotox Res* 7: 103–123.
- Guillemin, G., Kerr, S., Smythe, G., Smith, D., Kapoor, V., Armati, P. *et al.* (2001) Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. *J Neurochem* 78: 842–853.
- Han, Q., Cai, T., Tagle, D. and Li, J. (2010) Structure, expression, and function of kynurenine aminotransferases in human and rodent brains. *Cell Mol Life Sci* 67: 353–368.
- Harris, C., Miranda, A., Tanguay, J., Boegman, R., Beninger, R. and Jhamandas, K. (1998) Modulation of striatal quinolinic neurotoxicity by elevation of endogenous brain kynurenic acid. *Br J Pharmacol* 124: 391–399.
- Hartai, Z., Juhasz, A., Rimanoczy, A., Janaky, T., Donko, T., Dux, L. *et al.* (2007) Decreased serum and red blood cell kynurenic acid levels in Alzheimer's disease. *Neurochem Int* 50: 308–313.
- Heyes, M., Brew, B., Martin, A., Markey, S., Price, R., Bhalla, R. *et al.* (1991a) Cerebrospinal fluid quinolinic acid concentrations are increased in acquired immune deficiency syndrome. *Adv Exp Med Biol* 294: 687–690.
- Heyes, M., Brew, B., Martin, A., Price, R., Salazar, A., Sidtis, J. *et al.* (1991b) Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status. *Ann Neurol* 29: 202–209.
- Heyes, M., Saito, K., Crowley, J., Davis, L., Demitrack, M., Der, M. *et al.* (1992) Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. *Brain* 115: 1249–1273.
- Hilmas, C., Pereira, E., Alkondon, M., Rassoulpour, A., Schwarcz, R. and Albuquerque, E. (2001) The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. *J Neurosci* 21: 7463–7473.
- Honjo, K., Black, S. and Verhoeff, N. (2012) Alzheimer's disease, cerebrovascular disease, and the beta-amyloid cascade. *Can J Neurol Sci* 39: 712–728.
- Hosaka, A., Araki, W., Oda, A., Tomidokoro, Y. and Tamaoka, A. (2013) Statins reduce amyloid beta-peptide production by modulating amyloid precursor protein maturation and phosphorylation through a cholesterol-independent mechanism in cultured neurons. *Neurochem Res* 38: 589–600.
- Iadecola, C. (2010) The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol* 120: 287–296.
- Iadecola, C. and Gorelick, P. (2003) Converging pathogenic mechanisms in vascular and neurodegenerative dementia. *Stroke* 34: 335–337.
- Jauch, D., Urbanska, E., Guidetti, P., Bird, E., Vonsattel, J., Whetsell, W., Jr. *et al.* (1995) Dysfunction of brain kynurenic acid metabolism in Huntington's disease: focus on kynurenine aminotransferases. *J Neurol Sci* 130: 39–47.
- Jeppsson, F., Eketjall, S., Janson, J., Karlstrom, S., Gustavsson, S., Olsson, L. *et al.* (2012) Discovery of AZD3839, a potent and selective BACE1 inhibitor clinical candidate for the treatment of Alzheimer disease. *J Biol Chem* 287: 41245–41257.
- Kalbe, E., Kessler, J., Calabrese, P., Smith, R., Passmore, A., Brand, M. *et al.* (2004) DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *Int J Geriatr Psychiatry* 19: 136–143.
- Karbowski, M. and Neutzner, A. (2012) Neurodegeneration as a consequence of failed mitochondrial maintenance. *Acta Neuropathol* 123: 157–171.
- Kaul, M., Garden, G. and Lipton, S. (2001) Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* 410: 988–994.
- Kessler, M., Terramani, T., Lynch, G. and Baudry, M. (1989) A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists. *J Neurochem* 52: 1319–1328.
- Knyihar-Csillik, E., Mihaly, A., Krisztin-Peva, B., Robotka, H., Szatmari, I., Fulop, F. *et al.* (2008) The kynurenate analog SZR-72 prevents the nitroglycerol-induced increase of c-fos immunoreactivity in the rat caudal trigeminal nucleus: comparative studies of the effects of SZR-72 and kynurenic acid. *Neurosci Res* 61: 429–432.
- Lapin, I. (1978) Stimulant and convulsive effects of kynurenines injected into brain ventricles in mice. *J Neural Transm* 42: 37–43.

- Lau, A. and Tymianski, M. (2010) Glutamate receptors, neurotoxicity and neurodegeneration. *Pflugers Arch* 460: 525–542.
- Lehrmann, E., Molinari, A., Speciale, C. and Schwarcz, R. (2001) Immunohistochemical visualization of newly formed quinolinate in the normal and excitotoxically lesioned rat striatum. *Exp Brain Res* 141: 389–397.
- Liu, H. and Zhang, J. (2012) Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. *Int J Neurosci* 122: 494–499.
- Mahley, R. (1988) Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 240: 622–630.
- Marzolo, M. and Bu, G. (2009) Lipoprotein receptors and cholesterol in APP trafficking and proteolytic processing, implications for Alzheimer's disease. *Semin Cell Dev Biol* 20: 191–200.
- Mejia-Arango, S. and Gutierrez, L. (2011) Prevalence and incidence rates of dementia and cognitive impairment no dementia in the Mexican population: data from the Mexican Health and Aging Study. *J Aging Health* 23: 1050–1074.
- Nasreddine, Z., Phillips, N., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I. *et al.* (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53: 695–699.
- Nestor, P., Scheltens, P. and Hodges, J. (2004) Advances in the early detection of Alzheimer's disease. *Nat Med* 10(Suppl.): S34–S41.
- Ohno, M., Sametsky, E., Younkin, L., Oakley, H., Younkin, S., Citron, M. *et al.* (2004) BACE1 deficiency rescues memory deficits and cholinergic dysfunction in a mouse model of Alzheimer's disease. *Neuron* 41: 27–33.
- Okuno, E., Nakamura, M. and Schwarcz, R. (1991) Two kynurenine aminotransferases in human brain. *Brain Res* 542: 307–312.
- Oxenkrug, G. (2007) Genetic and hormonal regulation of tryptophan kynurenine metabolism: implications for vascular cognitive impairment, major depressive disorder, and aging. *Ann N Y Acad Sci* 1122: 35–49.
- Pardutz, A., Fejes, A., Bohar, Z., Tar, L., Toldi, J. and Vécsei, L. (2012) Kynurenines and headache. *J Neural Transm* 119: 285–296.
- Perkins, M. and Stone, T. (1982) An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. *Brain Res* 247: 184–187.
- Plangar, I., Zadori, D., Klivenyi, P., Toldi, J. and Vécsei, L. (2011) Targeting the kynurenine pathway-related alterations in Alzheimer's disease: a future therapeutic strategy. *J Alzheimers Dis* 24(Suppl. 2): 199–209.
- Potter, M., Elmer, G., Bergeron, R., Albuquerque, E., Guidetti, P., Wu, H. *et al.* (2010) Reduction of endogenous kynurenic acid formation enhances extracellular glutamate, hippocampal plasticity, and cognitive behavior. *Neuropsychopharmacology* 35: 1734–1742.
- Potter, P. (2010) Investigational medications for treatment of patients with Alzheimer disease. *J Am Osteopath Assoc* 110(9 Suppl. 8): S27–S36.
- Rahman, A., Ting, K., Cullen, K., Braid, N., Brew, B. and Guillemin, G. (2009) The excitotoxin quinolinic acid induces tau phosphorylation in human neurons. *PLoS One* 4: e6344.
- Robotka, H., Sas, K., Agoston, M., Rozsa, E., Szenasi, G., Gigler, G. *et al.* (2008) Neuroprotection achieved in the ischaemic rat cortex with L-kynurenine sulphate. *Life Sci* 82: 915–919.
- Rombouts, S., Goekoop, R., Stam, C., Barkhof, F. and Scheltens, P. (2005) Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease. *Neuroimage* 26: 1078–1085.
- Ruitenbergh, A., den Heijer, T., Bakker, S., van Swieten, J., Koudstaal, P., Hofman, A. *et al.* (2005) Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol* 57: 789–794.
- Sapko, M., Guidetti, P., Yu, P., Tagle, D., Pellicciari, R. and Schwarcz, R. (2006) Endogenous kynurenate controls the vulnerability of striatal neurons to quinolinate: Implications for Huntington's disease. *Exp Neurol* 197: 31–40.
- Sas, K., Robotka, H., Rozsa, E., Agoston, M., Szenasi, G., Gigler, G. *et al.* (2008) Kynurenine diminishes the ischemia-induced histological and electrophysiological deficits in the rat hippocampus. *Neurobiol Dis* 32: 302–308.
- Shulman, K. (2000) Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry* 15: 548–561.
- Solomon, P., Hirschhoff, A., Kelly, B., Relin, M., Brush, M., DeVaux, R. *et al.* (1998) A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. *Arch Neurol* 55: 349–355.
- Sorbi, S., Hort, J., Erkinjuntti, T., Fladby, T., Gainotti, G., Gurvit, H. *et al.* (2012) EFNS-ENS Guidelines on the diagnosis and management of

- disorders associated with dementia. *Eur J Neurol* 19: 1159–1179.
- Stamford, A., Scott, J., Li, S., Babu, S., Tadesse, D., Hunter, R. *et al.* (2012) Discovery of an orally available, brain penetrant BACE1 inhibitor that affords robust CNS A β reduction. *ACS Med Chem Lett* 3: 897–902.
- Stone, T., Forrest, C., Stoy, N. and Darlington, L. (2012) Involvement of kynurenines in Huntington's disease and stroke-induced brain damage. *J Neural Transm* 119: 261–274.
- Stone, T. and Perkins, M. (1981) Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. *Eur J Pharmacol* 72: 411–412.
- Stoy, N., Mackay, G., Forrest, C., Christofides, J., Egerton, M., Stone, T. *et al.* (2005) Tryptophan metabolism and oxidative stress in patients with Huntington's disease. *J Neurochem* 93: 611–623.
- Szalardy, L., Klivenyi, P., Zadori, D., Fulop, F., Toldi, J. and Vécsei, L. (2012) Mitochondrial disturbances, tryptophan metabolites and neurodegeneration: medicinal chemistry aspects. *Curr Med Chem* 19: 1899–1920.
- Szekely, C., Thorne, J., Zandi, P., Ek, M., Messias, E., Breitner, J. *et al.* (2004) Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. *Neuroepidemiology* 23: 159–169.
- Tajti, J., Pardutz, A., Vamos, E., Tuka, B., Kuris, A., Bohar, Z. *et al.* (2011) Migraine is a neuronal disease. *J Neural Transm* 118: 511–524.
- Tajti, J., Szok, D., Pardutz, A., Tuka, B., Csati, A., Kuris, A. *et al.* (2012) Where does a migraine attack originate? In the brainstem. *J Neural Transm* 119: 557–568.
- Tan, L. and Yu, J. (2012) The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations. *J Neurol Sci* 323: 1–8.
- Tauber, E., Miller-Fleming, L., Mason, R., Kwan, W., Clapp, J., Butler, N. *et al.* (2011) Functional gene expression profiling in yeast implicates translational dysfunction in mutant huntingtin toxicity. *J Biol Chem* 286: 410–419.
- Thal, D., Griffin, W., de Vos, R. and Ghebremedhin, E. (2008) Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. *Acta Neuropathol* 115: 599–609.
- Thal, D., Grinberg, L. and Attems, J. (2012) Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. *Exp Gerontol* 47: 816–824.
- Valle, M., Price, R., Nilsson, A., Heyes, M. and Verotta, D. (2004) CSF quinolinic acid levels are determined by local HIV infection: cross-sectional analysis and modelling of dynamics following antiretroviral therapy. *Brain* 127: 1047–1060.
- Vamos, E., Fejes, A., Koch, J., Tajti, J., Fulop, F., Toldi, J. *et al.* (2010) Kynurenate derivative attenuates the nitroglycerin-induced CamKII α and CGRP expression changes. *Headache* 50: 834–843.
- Vassar, R. (2004) BACE1: the beta-secretase enzyme in Alzheimer's disease. *J Mol Neurosci* 23: 105–114.
- Vécsei, L. (2005) *Kynurenines in the Brain: From Experiments to Clinics*. New York: Nova Biomedical Books.
- Vécsei, L. and Beal, M. (1990) Intracerebroventricular injection of kynurenic acid, but not kynurenine, induces ataxia and stereotyped behavior in rats. *Brain Res Bull* 25: 623–627.
- Vécsei, L., Szalardy, L., Fulop, F. and Toldi, J. (2013) Kynurenines in the CNS: recent advances and new questions. *Nat Rev Drug Discov* 12: 64–82.
- Wang, J., Simonavicius, N., Wu, X., Swaminath, G., Reagan, J., Tian, H. *et al.* (2006) Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. *J Biol Chem* 281: 22021–22028.
- Weggen, S., Eriksen, J., Das, P., Sagi, S., Wang, R., Pietrzik, C. *et al.* (2001) A subset of NSAIDs lower amyloidogenic A β 42 independently of cyclooxygenase activity. *Nature* 414: 212–216.
- Widner, B., Leblhuber, F., Walli, J., Tilz, G., Demel, U. and Fuchs, D. (2000) Tryptophan degradation and immune activation in Alzheimer's disease. *J Neural Transm* 107: 343–353.
- Wolf, H. (1974) The effect of hormones and vitamin B6 on urinary excretion of metabolites of the kynurenine pathway. *Scand J Clin Lab Invest Suppl* 136: 1–186.
- Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. and Siegel, G. (2000) Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 57: 1439–1443.
- Yan, Q., Zhang, J., Liu, H., Babu-Khan, S., Vassar, R., Biere, A. *et al.* (2003) Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. *J Neurosci* 23: 7504–7509.
- Yu, P., Li, Z., Zhang, L., Tagle, D. and Cai, T. (2006) Characterization of kynurenine aminotransferase III, a novel member of a phylogenetically conserved KAT family. *Gene* 365: 111–118.
- Zadori, D., Klivenyi, P., Plangar, I., Toldi, J. and Vécsei, L. (2011a) Endogenous neuroprotection in chronic neurodegenerative disorders: with particular

regard to the kynurenines. *J Cell Mol Med* 15: 701–717.

Zadori, D., Nyiri, G., Szonyi, A., Szatmari, I., Fulop, F., Toldi, J. *et al.* (2011b) Neuroprotective effects of a novel kynurenic acid analogue in a transgenic mouse model of Huntington's disease. *J Neural Transm* 118: 865–875.

Zlokovic, B. (2013) Cerebrovascular Effects of Apolipoprotein E: Implications for Alzheimer Disease. *JAMA Neurol* 70: 440–444.

Zwilling, D., Huang, S., Sathyaikumar, K., Notarangelo, F., Guidetti, P., Wu, H. *et al.* (2011) Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* 145: 863–874.

Visit SAGE journals online
<http://tan.sagepub.com>

SAGE journals