

Kynurenines in cognitive functions: their possible role in depression

IMOLA PLANGAR¹, ZSOFIA MAJLATH¹ AND LASZLO VECSEI^{1,2}

¹ Department of Neurology, University of Szeged, Hungary

² Neurology Research Group of the Hungarian Academy of Sciences and University of Szeged, Hungary

Depression can originate from changes in tryptophan availability, caused by activation of the kynurenine pathway (KP) as a result of inflammation. Alterations in the KP and the changing levels of its metabolites have recently been considered to be factors contributing to the pathogenesis of depression. The key molecular mediator which induces the conversion of tryptophan into kynurenine is indoleamine-2,3-dioxygenase. Following its activation, both the production of neurotoxic compounds and the diminished peripheral accessibility of tryptophan are regarded as essential steps in the pathophysiological processes. The aim of this review is to survey the role of the KP in depression and its relationships with cognitive functions.

(Neuropsychopharmacol Hung 2012; 14(4): 239-244; doi: 10.5706/nph201212004)

Keywords: tryptophan metabolism, kynurenine pathway, cognitive deficit, depression

Stress, originally an engineering term, was introduced into the language of human physiology by Hans Selye in 1936. Selye put forward the view that stress is a condition which seriously perturbs the physiological and psychological homeostasis of an organism, and that chronic stress can lead to the development of mental disorders. He suggested that the hypothalamic-pituitary-adrenal (HPA) axis plays a central role in regulating the stress response. The disadvantages of chronic stress were at first thought to be due to hypersecretion of the glucocorticoids (cortisol and corticosterone), elevated levels of which can damage the hippocampal neurons, and particularly the pyramidal neurons in the CA3 region (Nestler et al., 2002).

Depression is a severe psychiatric disorder which affects up to 20% of the adult population throughout the world, accompanied by enormous mental suffering and one of the major causes of disability worldwide. One of the factors involved in the pathophysiology of depression is a dysfunction of the monoaminergic system, a system that exuberantly projects to the prefrontal cortical, limbic and striatal structures presumed to be responsible for the behavioural and visceral aspects of mood disorders (Nestler et al., 2002).

Obviously, the endocrine and immune systems also participate prominently in the pathology of these

diseases (Brambilla et al., 2000). The fundamental hormonal response to stress is activation of the HPA axis, including secretion of the corticotropin releasing hormone (CRH) and arginine-vasopressin from the hypothalamus, followed by release of the adrenocorticotrophic hormone from the pituitary, which stimulates the secretion of glucocorticoids from the adrenal cortex. It is known that chronic stress can lead to depression or depressive-like behaviour, and abnormalities of the HPA axis have been found in patients with major depression. Women with depression exhibit a higher degree of HPA axis activation than depressed men, and the extent of dysregulation of the HPA axis is greatest during the menopause, when women are exposed to the loss of oestrogens. A decline of the testosterone level in males can also cause depression. Concerning the HPA axis, both an increased level of CRH and the enhanced secretion and reactivity of cortisol can induce depression (Weizman et al., 2012).

There is a growing body of evidence which suggests that changes in the glutamatergic system and mainly in the function of N-methyl-D-aspartate (NMDA) receptors play a role in hippocampal synaptic plasticity deficiencies, and thereby in the loss or atrophy of cells, which results in the morphometric changes that can be observed in patients with severe, chronic mood

disorders (Maeng & Zarate, 2007). Imaging studies involving patients with major depressive disorders have revealed decreases of approximately 10% in the right hippocampal volume and of about 10-20% in the left hippocampal volume. This demonstrated the existence of a correlation between the total lifetime duration of depression and hippocampal shrinkage (Szakács et al., 2012). Inflammatory processes activate the kynurenine pathway (KP) which reduces the availability of tryptophan (TRP), thereby potentially contributing to the pathogenesis of depression.

TRYPTOPHAN METABOLISM

TRP is an essential amino acid, required for the biosynthesis of proteins, 5-hydroxytryptamine (5-HT, serotonin) and niacin. There are two major metabolic routes for TRP degradation in the brain: the methoxyindole pathway and the KP (Oxenkrug et al., 2010). A large variety of external and internal processes can induce the oxidative catabolism of TRP.

THE METHOXYINDOLE PATHWAY

The accessibility of TRP as a substrate is the first rate-limiting factor during the pathway because less than 5% of TRP is degraded through this route. The hydroxylation of TRP catalysed by tryptophan-hydroxylase, which results in 5-hydroxytryptophan, is a rate-determining step. The next step is decarboxylation, which leads to the formation of 5-HT. 5-HT functions as a neurotransmitter in the brain; after it is released from the synaptic nerve terminals, it binds to its receptors (5-HT₁₋₇) in the synaptic cleft. 5-HT is also a substrate of melatonin synthesis; its N-acetylation, followed by O-methylation, furnishes 5-methoxy-N-acetyltryptamine (melatonin). A lack or deficient production of 5-HT, N-acetyl-5-HT or melatonin contributes to mood disturbances and depression (Lewy et al., 1980), sleeping problems and disturbances in the circadian rhythm (Oxenkrug & Requintina, 2003).

THE KYNURENINE PATHWAY

The other major route of TRP metabolism is the KP, in which the central compound is kynurenine (KYN). KYN is generated from TRP by the action of indoleamine-2,3-dioxygenase (IDO) or tryptophan-2,3-dioxygenase (TDO). IDO is present in the periphery and also in the brain, while TDO is largely located in the liver. About 95% of the TRP is broken

down via this pathway. KYN can be metabolized in two distinct pathways, serving as a precursor of the neuroprotective kynurenic acid (KYNA) or the neurotoxic 3-hydroxy-L-kynurenine (3-OH-KYN) and quinolinic acid (QUIN). 40% of the KYN content of the mammalian brain is produced locally in the brain, and 60% is taken up from the blood by a large neutral amino acid carrier. KYN is converted to KYNA through irreversible transamination by kynurenine aminotransferases (KATs), the biosynthetic enzymes of KYNA formation in the brain (Guidetti et al., 2007).

KYNA is one of the main TRP metabolites produced by the neurons and astrocytes via the KP in the mammalian brain (Robotka et al., 2008). It has been shown that KYNA in nanomolar concentrations exerts a neuromodulatory effect, whereas in supra-physiological concentrations it has proved to be a broad-spectrum endogenous antagonist of ionotropic excitatory amino acid receptors, and inhibits the neuronal activity (Rozsa et al., 2008). In low micromolar concentrations, it blocks the NMDA receptor activity, displays high affinity for the glycine-binding site of the NMDA receptor, and is additionally a weak antagonist of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors (Sas et al., 2007). Consequently, an elevation in KYNA concentration under physiological conditions can result in a cognitive impairment (Potter et al., 2010). In contrast, under pathological conditions, the situation can be quite different. Overactivation of the NMDA receptors occurs following glutamate excitotoxicity and anti-glutamatergic drugs can help in the restoration of the basal level of activation, facilitating a memory recovery in a cognitive impairment.

The α 7-nicotinic acetylcholine (α 7-nACh) receptors are non-competitively inhibited by KYNA and it can increase the expression of non- α 7-nACh receptors (Pereira et al., 2002). It has been established that cross-talk exists between the cholinergic system and KYNA, a situation which has been surmised to play a role in the pathogenesis of several brain lesions (Alkondon et al., 2004). With regard to its pharmacological activity, KYNA appears to have a neuroprotective potential, but in very high concentrations it can exert adverse effects, as illustrated by the intracerebroventricular injection of KYNA into rats, which results in decreased exploratory activity, stereotypy, ataxia, sleeping and respiratory depression (Vécsei & Beal, 1990).

The process of neurodegeneration might be caused by glutamate or other endogenous excitotoxins, e.g. QUIN, which is a selective NMDA receptor agonist,

present in nanomolar concentrations in the brain. QUIN is one of the most important participants in the KP: it takes part in the final step of the KP leading to the synthesis of the essential co-enzyme nicotinamide adenine dinucleotide (NAD⁺) and NAD phosphate, which are essential for energy homeostasis and cellular mechanisms (Rozsa et al., 2008; Robotka et al., 2008). QUIN can exert pronounced effects on the NMDA-sensitive subpopulation of glutamate receptors. It is present in nanomolar concentrations in the brain and is a weak, but specific competitive agonist of the NR2A and NR2B NMDA receptor subtypes.

The increased QUIN level in astrocytes and neurons can activate NMDA receptors, thereby inducing excitotoxicity. It can provoke lipid peroxidation, potentiate oxidative stress (Sas et al., 2007) and induce astrocytes to generate various cytokines, such as interferon- γ (IFN- γ), interleukin-1 β and tumour necrosis factor- α (Braidy et al., 2009). It was thought that these inflammatory cytokines induce the activity of IDO, one of the first TRP metabolism enzymes. High expressions of QUIN and IDO have been observed in the human hippocampus and neocortex (Guillemin et al., 2005a). IDO is induced in various types of inflammation, and activation of the immune system, the accumulation of QUIN and the up-regulation of IDO are therefore considered to contribute to the pathophysiology of depression.

Stone and colleagues demonstrated that free radicals may contribute to the neurotoxic effects of QUIN (Stone et al., 2001). 3-OH-L-KYN generates reactive oxygen species and may therefore also cause neuronal death (Sas et al., 2007), but this effect is NMDA receptor-independent.

THE POSSIBLE ROLE OF THE KYNURENINE PATHWAY IN THE PATHOPHYSIOLOGY OF DEPRESSION

There appear to be no measured data on depressed patients as concerns the expression of enzymes responsible for the downstream metabolism of KYN (Hughes et al., 2012). The basis of the “neurodegeneration hypothesis of depression” ascribed to Myint and Kim (2003) is an imbalance in the production of KP components in depression. As compared with healthy controls, depressed subjects were found to exhibit decreased KYNA concentration and an elevated TRP/KYN ratio (Myint et al., 2007). Moreover, preclinical data indicated that KYN itself causes depressive behaviour in an animal model of depression (O'Connor et al., 2009).

Schwarcz and colleagues reported that the KP is closely controlled by the immune system (Schwarcz et al., 2012). Dysregulation of this pathway, with changes in the levels of its metabolites resulting in the hyper- or hypofunction of active compounds, is associated with psychiatric diseases such as depression and schizophrenia. With recently developed pharmacological agents, it is now possible to utilize novel therapeutic interventions and to achieve metabolic equilibrium.

IFN- α has been applied as an immunotherapeutic agent, but a decreased serum level of TRP was observed in patients who received this therapy, which was therefore associated with psychiatric side-effects such as depression (Bonaccorso et al., 2007). Coherency has been described between changes in the peripheral blood levels of TRP, KYN and KYNA during IFN- α management (Raison et al., 2010). The plasma KYN/KYNA ratio is increased during IFN- α treatment and this bears a relation to depressive symptoms (Wichers et al., 2005).

In experimental animals, increased levels of pro-inflammatory cytokines can induce behavioural changes (O'Connor et al., 2009). Raised levels of inflammatory cytokines have been observed in the brain and the periphery of depressive patients (Oxenkrug 2010). The various factors that can activate IDO in the brain include oxidative stress, inflammation and infection (Heyes et al., 1993). Pro-inflammatory cytokines activate IDO and kynurenine-3-monooxygenase, which converts KYN into 3-OH-KYN and shifts the KP towards the neurotoxic path.

O'Connor and colleagues have recently reinforced the fact that IDO, as a critical molecular mediator, has a crucial role in the development of inflammation-induced depressive-like behaviour. They demonstrated that the peripheral administration of lipopolysaccharide (LPS) to mice activated IDO, which increased the brain 5-HT turnover and generated a depressive-like behavioural syndrome. According to the monoamine hypothesis, the low levels of monoamine neurotransmitters in the brain e.g. 5-HT, dopamine and noradrenaline, can induce depression. The activation of IDO depresses the synthesis of 5-HT through the utilization of TRP which can contribute to the development of depression. In contrast, the inhibition of IDO activation, either directly with an IDO antagonist, or indirectly with an anti-inflammatory drug that extenuates the LPS-induced expression of pro-inflammatory cytokines, prevents the development of depressive-like behaviour. Interestingly, both an IDO antagonist and an anti-inflammatory drug are able to

restore the KYN/TRP ratio. Moreover, KYN administration to wild-type mice induced depressive-like behaviour dose-dependently (O'Connor et al., 2009).

CONNECTION BETWEEN THE KYNURENINE PATHWAY AND COGNITIVE FUNCTIONS

Structural changes caused by depression can be observed in several brain regions, and especially in the hippocampus (Sheline, 2003). Several studies have suggested that KYNA can modulate hippocampus-related cognitive functions and endogenously regulate the extracellular level of glutamate in the hippocampus. An increased KYNA level can aggravate, whereas a reduced KYNA level can improve the cognitive functions (Pocivavsek et al., 2011). Increased KYNA concentrations, which cause excessive NMDA inhibition and produce spatial working memory deficits, may deteriorate learning processes and reveal the influence of glia-derived molecules on cognitive functions (Chess et al., 2007).

Neuroimaging studies in particular have demonstrated a decreased hippocampal volume in patients with depression, who display severe impairments in selective attention, cognitive flexibility, executive function and working and verbal memory. There was no significant difference between depressed patients and healthy controls in the visual recall test. These results confirm observations of an intact short and long-term visual memory with an impaired executive function and attention in remission, findings suggestive of an intact hippocampal function during remission (Sarosi, 2011).

Alterations in the kynurenine metabolism have been detected in the serum and also in post mortem studies of the brain in Alzheimer's disease patients, and the changes in the kynurenine metabolite levels have proved to be associated with an impaired cognitive function (Sas et al., 2007; Gulaj et al., 2010). It has also been observed that increased KP activation and changes in the levels of kynurenine metabolites correlate significantly with the cognitive performance in patients undergoing cardiac surgery (Forrest et al., 2011). Alterations in the KP have been observed in other dementia disorders, e.g. Huntington's disease and the AIDS dementia complex (Leblhuber et al., 1998; Guillemin et al., 2005b).

CONCLUSIONS

It has emerged that the KP is involved in the pathophysiology of depression, variations in the concen-

trations of the KP metabolites contributing to the pathogenesis of this psychiatric disorder. Imbalances in the KP and TRP depletion are closely related with learning processes and may contribute to the development of cognitive deficits.

The involvement of KP imbalances in these pathophysiological processes is evident and may be a promising target for the development of novel therapeutic strategies.

Acknowledgements. This work was supported by the "Neuroscience Research Group of the Hungarian Academy of Sciences and the University of Szeged", TÁMOP-4.2.1/B-09/1/KONV-2010-0005 and ETT 026-04. The Project named "TÁMOP-4.2.1/B-09/1/KONV-2010-0005 – Creating the Center of Excellence at the University of Szeged" is supported by the European Union and is co-financed by the European Regional Development Fund.

Corresponding author: Laszlo Vecsei, Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Centre, University of Szeged, H-6725 Szeged, Semmelweis u. 6., Hungary. Tel.: 00 36 62 545348
e-mail: vecsei.laszlo@med.u-szeged.hu

REFERENCES

- Alkondon, M., Pereira, E.F., Yu, P., Arruda, E.Z., Almeida, L.E., Guidetti, P., Fawcett, W.P., Sapko, M.T., Randall, W.R., Schwarcz, R., Tagle, D.A., Albuquerque, E.X. (2004) Targeted deletion of the kynurenine aminotransferase ii gene reveals a critical role of endogenous kynurenic acid in the regulation of synaptic transmission via alpha 7 nicotinic receptors in the hippocampus. *J Neurosci* 24: 4635-4648.
- Bonaccorso, S., Marino, V., Biondi, M., Grimaldi, F., Ippoliti, F., Maes, M. (2002) Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J Affect Disord* 72: 237-241.
- Braidy, N., Grant, R., Adams, S., Brew, B.J., Guillemin, G.J. (2009) Mechanism for quinolinic acid cytotoxicity in human astrocytes and neurons. *Neurotox Res* 16: 77-86.
- Brambilla, F. (2000) Psychoneuroendocrinology: research on the pituitary-adrenal-cortical system. *Psychosomat Med* 62: 576-607.
- Chess, A.C., Simoni, M.K., Alling, T.E., Bucci, D.J. (2007) Elevations of endogenous kynurenic acid produce spatial working memory deficits. *Schizophr Bull* 33: 797-804.
- Forrest, C.M., Mackay, G.M., Oxford, L., Millar, K., Darlington, L.G., Higgins, M.J., Stone, T.W. (2011) Kynurenine metabolism predicts cognitive function in patients following cardiac bypass and thoracic surgery. *J Neurochem* 119: 136-152.
- Guillemin, G.J., Brew, B.J., Noonan, C.E., Takikawa, O., Cullen, K.M. (2005a) Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. *Neuropathol Appl Neurobiol* 31: 395-404.
- Guillemin, G.J., Kerr, S.J., Brew, B.J. (2005b) Involvement of quinolinic acid in AIDS dementia complex. *Neurotox Res* 7: 103-123.

9. Gulaj, E., Pawlak, K., Bien, B., Pawlak, D. (2010) Kynurenine and its metabolites in Alzheimer's disease patients. *Adv Med Sci* 55: 204-211.
10. Heyes, M.P., Saito, K., Major, E.O., Milstien, S., Markey, S.P., Vickers, J.H. (1993) A mechanism of quinolinic acid formation by brain in inflammatory neurological disease. Attenuation of synthesis from L-tryptophan by 6-chlorotryptophan and 4-chloro-3-hydroxyanthranilate. *Brain* 116: 1425-1450.
11. Hughes, M.M., Carballedo, A., McLoughlin, D.M., Amico, F., Harkin, A., Frodl, T., Connor, T.J. (2012) Tryptophan depletion in depressed patients occurs independent of kynurenine pathway activation. *Brain Behav Immun dx.doi.org/10.1016/j.bbi.2012.05.010*.
12. Leblhuber, F., Walli, J., Jellinger, K., Tilz, G.P., Widner, B., Laccione, F., Fuchs, D. (1998) Activated immune system in patients with Huntington's disease. *Clin Chem Lab Med* 36: 747-750.
13. Lewy, A.J., Wehr, T.A., Goodwin, F.K., Newsome, D.A., Markey, S.P. (1980) Light suppresses melatonin secretion in humans. *Science* 210: 1267-1269.
14. Maeng, S., Zarate, C.A. Jr. (2007) The role of glutamate in mood disorders: Results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. *Curr Psychiatry Rep* 9: 467-474.
15. Myint, A.M., Kim, Y.K. (2003) Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression. *Med Hypotheses* 61: 519-525.
16. Myint, A.M., Kim, Y.K., Verkerk, R., Scharpe, S., Steinbusch, H., Leonard, B. (2007) Kynurenine pathway in major depression: evidence of impaired neuroprotection. *J Affect Disord* 98: 143-151.
17. Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M. (2002) Neurobiology of depression. *Neuron* 34: 13-25.
18. O'Connor, J.C., Lawson, M.A., Andre, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R. (2009) Lipopolysaccharide-induced depressive-like behaviour is mediated by indoleamine-2,3-dioxygenase activation in mice. *Mol Psychiatry* 14: 511-522.
19. Oxenkrug, G.F., Requintina, P.J. (2003) Melatonin and jet lag syndrome: Experimental model and clinical implications. *CNS Spectrums* 8: 139-148.
20. Oxenkrug, G.F. (2010) Tryptophan-kynurenine metabolism as a common mediator of genetic and environmental impacts in major depressive disorder: the serotonin hypothesis revisited 40 years later. *Isr J Psychiatry Relat Sci* 47: 56-63.
21. Pereira, E.F., Hilmas, C., Santos, M.D., Alkondon, M., Maelicke, A., Albuquerque, E.X. (2002) Unconventional ligands and modulators of nicotinic receptors. *J Neurobiol* 53: 479-500.
22. Pocivavsek, A., Wu, H.Q., Potter, M.C., Elmer, G.I., Pellicciari, R., Schwarcz, R. (2011) Fluctuations in endogenous kynurenine acid control hippocampal glutamate and memory. *Neuropsychopharmacology* 36: 2357-2367.
23. Potter, M.C., Elmer, G.I., Bergeron, R., Albuquerque, E.X., Guidetti, P., Wu, H.Q., Schwarcz, R. (2010) Reduction of endogenous kynurenine acid formation enhances extracellular glutamate, hippocampal plasticity, and cognitive behaviour. *Neuropsychopharmacology* 35: 1734-1742.
24. Raison, C.L., Dantzer, R., Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., Miller, A.H. (2010) CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN- α : relationship to CNS immune responses and depression. *Mol Psychiatry* 15: 393-403.
25. Robotka, H., Toldi, J., Vecsei, L. (2008) L-Kynurenine: metabolism and mechanism of neuroprotection. *Future Neurol* 3: 169-188.
26. Rozsa, E., Robotka, H., Vecsei, L., Toldi, J. (2008) The Janus-face kynurenine acid. *J Neural Transm* 115: 1087-1091.
27. Sarosi, A. (2011) Neurocognition and psychogenetic vulnerability in depression. *Neuropsychopharmacol Hung* 13: 25-31.
28. Sas, K., Robotka, H., Toldi, J., Vecsei, L. (2007) Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders. *J Neurol Sci* 257: 221-239.
29. Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q. (2012) Kynurenines in the mammalian brain: when physiology meets pathology. *Nat Rev Neurosci* doi: 10.1038/nrn3257.
30. Sheline, Y.I. (2003) Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 54: 338-352.
31. Stone, T.W., Behan, W.M., Jones, P.A., Darlington, L.G., Smith, R.A. (2001) The role of kynurenines in the production of neuronal death, and the neuroprotective effect of purines. *J Alzheimers Dis* 3: 355-366.
32. Szakács, R., Janka, Z., Kálmán, J. (2012) The "blue" side of glutamatergic neurotransmission: NMDA receptor antagonists as possible novel therapeutics for major depression. *Neuropsychopharmacol Hung* 14: 29-40.
33. Vecsei, L., Beal, M.F. (1990) Intracerebroventricular injection of kynurenine acid, but not kynurenine, induces ataxia and stereotyped behaviour in rats. *Brain Res Bull* 25: 623-627.
34. Weizman, S., Gonda, X., Dome, P., Faludi, G. (2012) Pharmacogenetics of antidepressive drugs: a way towards personalized treatment of major depressive disorder. *Neuropsychopharmacol Hung* 14: 87-101.
35. Wichers, M.C., Koek, G.H., Robaey, G., Verkerk, R., Scharpe, S., Maes, M. (2005) IDO and interferon- α -induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Mol Psychiatry* 10: 538-544.

A kinureninek és a kognitív funkció összefüggései, és lehetséges szerepük a depresszió kialakulásában

A triptofán (TRP) szint változása, amelyet gyulladáscsökkentő folyamat eredményeként a kinurenin útvonal aktiválódása okozhat, depresszió kialakulásához vezethet. A kinurenin útvonal, illetve a benne részt vevő metabolitok szintjének változásai valószínűsíthetően hozzájárulnak a depresszió patogeneziséhez. Az indolamin-2,3-dioxigenáz (IDO) az a kulcsmolekula, amely indukálja a TRP átalakulását kinureninné (KYN). Aktiválódását követően mind a neurotoxikus komponensek termelődése, mind pedig a csökkent perifériás TRP szint egyértelműen elősegíti a patofiziológiai folyamatokat. Összefoglalónk célja az, hogy áttekintést nyújtson a kinureninmetabolizmus depresszióban betöltött szerepéről, illetve a kognitív funkciókkal való kapcsolatáról.

Kulcsszavak: triptofán metabolizmus, kinurenin útvonal, kognitív deficit, depresszió