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Review article

M. MAJEWSKI[1], A. KOZLOWSKA[2], M. THOENE[3], E. LEPIARCZYK[2], W.J. GRZEGORZEWSKI[1]

OVERVIEW OF THE ROLE OF VITAMINS AND MINERALS ON THE KYNURENINE PATHWAY IN HEALTH AND DISEASE

[1]Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Warmia and Mazury, Olsztyn, Poland;
[2]Department of Human Physiology, Faculty of Medical Sciences, University of Warmia and Mazury, Olsztyn, Poland;
[3]Department of Medical Biology, Faculty of Medical Sciences, University of Warmia and Mazury, Olsztyn, Poland

The kynurenine pathway (KP) of L-tryptophan metabolism produces several neuroactive metabolites with an amino acid structure. These metabolites may play an important role in the pathophysiology of irritable bowel syndrome, Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia, AIDS-dementia complex, depression, epilepsy and the aging process. Modulation of the KP through inhibition or stimulation of enzyme synthesis and activity can be an alternative approach to traditional therapy. Furthermore, it may be responsible for the altered functioning of the enteric nervous system and the central nervous system. There is evidence that the KP is sensitive to changes in the concentration of many vitamins and minerals that play a crucial role as coenzymes and cofactors in the *de novo* synthesis of nicotinamide adenine dinucleotide coenzyme. A reduction in the availability of the active form of vitamin B_6 (pyridoxal 5'-phosphate, PLP) is known to affect tryptophan hydroxylase, kynurenine aminotransferase and kynureninase (KYNU). Vitamin B_2 deficiencies result in a reduction in the activity of the flavin adenine dinucleotide dependent enzyme, kynurenine 3-monooxygenase. Minerals are also responsible for the proper functioning of enzymes engaged in L-tryptophan metabolism. Mn^{2+}, Zn^{2+}, Co^{2+} and Cu^{2+} influence KYNU activity, and Mg^{2+} regulates quinolinate phosphoribosyl transferase. Fe^{2+} is responsible for the proper functioning of both indoleamine 2,3-dioxygenase and 3-hydroxy-anthranilic acid dioxygenase. Changes in the concentration of KP metabolites and in enzymatic activity have been found in many pathological states. Therefore, it is justifiable to regulate the concentration of certain kynurenines or enzymes in the KP which may provide a potential therapeutic target for the treatment of various health impairments. This review demonstrates the role of vitamin and mineral activity on the KP, which may have an effect on the proper functioning of the human organism. Surplus administration of vitamins did not elicit any beneficial effects on L-tryptophan metabolism. Whether a mineral surplus influences L-tryptophan metabolism is still not established. It seems that cofactor deficiencies influence the KP far more than surpluses.

Key words: *central nervous system, coenzymes, enteric nervous system, iron, kynurenic acid, L-kynurenine, L-tryptophan, magnesium, neurological disorders, niacin, quinolinic acid, serotonin, vitamin B_6, vitamin B_2*

INTRODUCTION

The kynurenine pathway (KP) of L-tryptophan metabolism is increasingly recognised as a critical source of neuroactive metabolites with relevance for health and disease. There is mounting evidence that L-tryptophan metabolism depends on the adequate availability of both vitamins (1-10) and minerals (11-19) which work as cofactors and coenzymes in metabolic reactions. L-tryptophan is an "essential" amino acid for mammals, as they cannot make it themselves. Therefore, they must obtain it in the form of food. This aromatic substance can be utilized not only for protein synthesis, but also for the biosynthesis of nicotinamide adenine dinucleotide (NAD^+) through the KP, as well as the biosynthesis of serotonin and melatonin through the serotonin pathway (20).

L-tryptophan has been proven to modulate gene expression and nutrient metabolism with an impact on whole-body homeostasis. It has been demonstrated that a temporary L-tryptophan deficiency can cause memory failure in healthy humans; as well as dermatitis, depression, and anxiety (20, 21). A low dietary tryptophan intake during rat development produced lower rates of serotonin synthesis in the brain, affecting GABAergic cortical interneurons and contributing to an increased susceptibility to convulsions (22).

In a preclinical study of pregnant rats, an excess of L-tryptophan in the diet caused hyperserotonaemia in the rat foetus, which had an adverse effect on the development of serotonergic neurons, thus affecting the growth of new-born rats (23). On the other hand, Strasser *et al.* (24) point out that L-tryptophan supplementation while dieting could be highly useful in preventing neuropsychiatric symptoms or in treating uncontrolled weight gain in mammals.

Serotonin is an important neurotransmitter in the enteric nervous system (ENS) (25-28), in the central nervous system

(CNS) (29), as well as in the autonomic nervous system (ANS). In the ENS, serotonin regulates secretion, motility and sensation (*Table 2*), while in the CNS it modulates mood, cognition and sleep (20, 29). Serotonin also regulates the secretion of pituitary growth hormone, which in turn stimulates the liver to produce insulin-like growth factor-I, which is necessary for the development and growth of rat pups as well as other mammals (23). Neuropsychiatric problems have been attributed to too much or too little serotonin (27, 29, 30). Recent studies have proven, that changes in serotonin concentration play a crucial role in human gastrointestinal (GI) physiology, being a therapeutic target in irritable bowel syndrome (IBS) etiology (26, 27, 31).

The other product of L-tryptophan metabolism is melatonin. It has been shown in several studies to have free radical scavenging activity (55), antioxidant properties (56), anti-apoptotic activity (57), and enhancement of mitochondrial function (58).

In recent years, attention has increasingly focused on the medical significance of the enzymatic oxidation of L-tryptophan which is dependent on some B group vitamins and minerals to form compounds collectively known as "kynurenines". Segregated into at least two distinct branches, often termed as the "neurotoxic" and "neuroprotective" arms of the KP, they are regulated by the two key enzymes, flavin dependant (FAD) kynurenine 3-monooxygenase (KMO) and pyridoxal-5'-phosphate (PLP, vitamin B_6) dependent kynurenine aminotransferase (KAT), respectively (59). These enzymes are mainly located in the brain (being segregated into specific cell types) (60), in the liver and kidney (59) as well as throughout the body. Several of these enzymes are under the tight control of inflammatory mediators (59, 61) (*Table 3*).

The KP produces several neuroactive metabolites. The neurotoxic ones are: amino acid 3-hydroxy-L-kynurenine (3-OH-L-KYN), 3-hydroxy-anthranilic acid (3-OH-AA), and quinolinic acid (QUIN). The neuroprotective metabolite is kynurenic acid (KYNA) (60, 62). Moreover, the KP is the major route of L-tryptophan metabolism (95% of all ingested L-tryptophan) that leads to the formation of the active form of niacin (NAD^+) in the main chain (63). Meanwhile, the side-chains of this pathway generate KYNA and xanthurenic acid (XA) (64) (*Fig. 1*).

QUIN is considered to be an endogenous agonist of the N-methyl-D-aspartate (NMDA) receptor with strong excitotoxic properties (65). By contrast, KYNA possesses a neuroprotective action (in the CNS), and is an NMDA receptor antagonist as well as a non-competitive antagonist of the nicotinic receptor α-A7 subtype (66). What's more, QUIN, 3-OH-L-KYN and 3-OH-AA are responsible for the production of the extremely reactive free radical species, $O_2^{\bullet -}$ and H_2O_2 (62).

Some health related states may influence the proper functioning of the KP (*Table 4*). Excessive L-kynurenine (L-KYN) production and an accompanying deficiency of the substrate L-tryptophan, may be the cause of a number of pathological conditions. According to Sasaki *et al.* (104), insulin-dependent diabetes mellitus in rats may alter the activity

Table 1. Serotonin involvement in the enteric system.

Material and trial	**Receptor under investigation**	**Mechanism of action** (32)	**Localization** (25)
- guinea-pig ileum and stomach, *isolated*, - mouse and rat colon, *isolated*, - human jejunum, rabbit small intestine, *isolated*	5-HT $_{1p}$ "orphan"	unknown	neuronal (myenteric neurons and submucosal ganglia, gastric myenteric inhibitory motor neurons)
- rat stomach and fundus, *isolated*	5-HT $_{2B}$	$(Ca^{2+})i$	smooth muscles
- human ileum, *isolated*			
- human colon, *in vitro*			
- rat jejunum, *isolated*	5-HT $_3$	$(Ca^{2+})i$	neuronal
- rat small intestine, *in vivo*			
- guinea-pig ileum, *isolated*			
- human, *in vivo*			
- human small intestine, *in vivo*			
- human jejunum, *in vitro*	5-HT $_4$	$(Ca^{2+})i$	neuronal and smooth muscle
- mice stomach to colon, *in vitro* and *in vivo*			
- human			
- guinea pigs and rats small intestine, *in vivo*			
- rat jejunum, *isolated*	5-HT $_7$	cAMP	smooth muscle cells, enteric neurons, enterocytes, immune cells (26, 28)
- guinea-pig ileum, *isolated*			
- guinea-pig proximal colon, *in vitro*			
- humans small and large intestines, *in vitro*			
- human ascending, transverse, descending and sigmoid colon and rectum, *isolated*			

Abbreviations: 5-HT, serotonin receptor; $(Ca^{2+})i$, cytosolic free calcium concentration; cAMP, cyclic adenosine monophosphate; ENS, enteric nervous system.

of enzymes engaged in L-tryptophan metabolism, which may lead to changes in the production of different kynurenines. Matsuda *et al.* (105) recently found in rats that another KP enzyme - α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) - is also associated with proper cholesterol metabolism. This enzyme is dependent on proper concentrations of Fe^{2+}, Co^{2+} and Zn^{2+} (13).

L-tryptophan utilization as a fuel for energy production is dependent upon the adequate availability of both vitamins and minerals such as: pyridoxal 5'-phosphate (PLP, B_6), riboflavin (B_2), niacin (B_3), thiamine (B_1), pantothenic acid, lipoate, ubiquinone, Mg^{2+}, Fe^{2+}, Zn^{2+} and Co^{2+} (106). Consequently, a lack of certain vitamins and minerals may lead to the dysfunction of enzymes engaged in L-tryptophan metabolism and many health-related disorders (107) (*Table 4*).

ENZYMES ENGAGED IN TRYPTOPHAN METABOLISM ALONG THE KYNURENINE PATHWAY

L-kynurenine to L-tryptophan ratio as a tryptophan and indoleamine 2,3-dioxygenase indicator

The first and rate-limiting step of the KP is the oxidative cleavage of the 2,3-double bond of the indole ring of L-tryptophan to form an unstable product (N-formyl-L-kynurenine, NFK) which is further converted to L-KYN. This reaction is catalysed by two iron dependent dioxygenases (122, 123). They are tryptophan 2,3-dioxygenase (TDO), which is constitutively expressed in liver; and the inflammatory cytokine-induced indoleamine 2,3-dioxygenase-1 (IDO-1) which is located in the brain and in the intestine (124). The enzyme catalyses the oxidation of L-tryptophan to L-KYN in a reaction that produces peroxides and gives rise to highly reactive and potentially harmful oxygen and hydroxyl radicals (62). The heme prosthetic group of TDO-heme-Fe^{3+} must be reduced to the heme-Fe^{2+} form prior to mediating L-tryptophan oxidation (122, 125). Like other hemeproteins, IDO binds O_2 to the deoxy protein where it is involved in the oxidation of substrates (*Table 4*). It was proven that IDO activity is dependent on the proper concentration of Fe^{2+} and many inflammatory stimuli (*Table 2*).

The plasma (serum) ratio of L-KYN to L-tryptophan (K-TR ratio) is a generally accepted clinical marker of IDO activity (126). It is highly correlated to neopterin levels, which is a macrophage-derived metabolite that increases after interferon-gamma stimulation, and is a good reflection of inflammatory status (90). Considering that both IDO and TDO regulate the rate of L-tryptophan conversion into L-KYN, plasma concentrations of L-tryptophan and L-KYN might also be affected by the activity of TDO (21). However, the K-TR ratio

Table 2. Serotonin involvement in the enteric system.

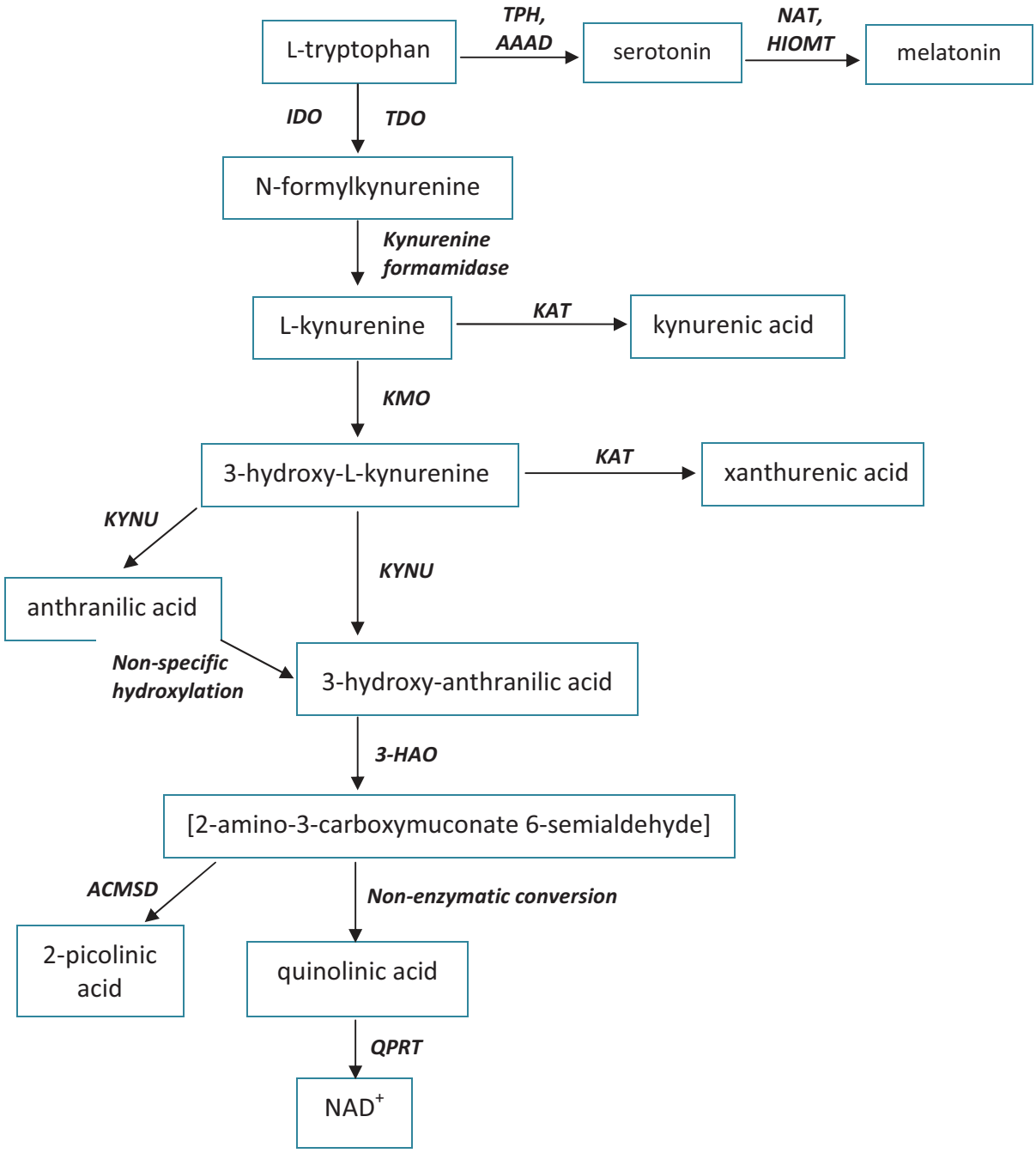
Material and trial	Effect	References
- guinea-pig ileum and stomach, *isolated*, - mouse and rat colon, *isolated*, - human jejunum, - rabbit small intestine, *isolated*	initiation of secretory and peristaltic reflexes	Michel *et al*. (33) Branchek *et al*. (34) Mawe *et al*. (35) Gershon *et al*. (36)
- rat stomach and fundus, *isolated*	smooth muscle contraction	Cohen *et al*. (37)
- human ileum, *isolated*	smooth muscle contraction	Borman *et al*. (38)
- human colon, *in vitro*	enhanced cholinergic-neuron-mediated contractions	Borman *et al*. (39)
- rat jejunum, *isolated*	smooth muscle contraction	McLean *et al*. (40)
- rat small intestine, *in vivo*	intestinal secretion	Beutler (41)
- guinea-pig ileum, *isolated*	neurogenic smooth muscle contraction	Buchheit *et al*. (42)
- human, *in vivo*	enhanced colonic transit	Gore *et al*. (43)
- human small intestine, *in vivo*	emetogenesis associated with anticancer chemotherapy ENS	Tyers *et al*. (44)
- human jejunum, *in vitro*	smooth muscle contraction or relaxation	Budhoo *et al*. (45) Kuemmerle *et al*. (46)
- mice stomach to colon, *in vitro* and *in vivo*	ENS growth and maintenance	Liu *et al*. (47)
- human	relief of chronic constipation	Del Tredici *et al*. (48)
- guinea pigs and rats small intestine, *in vivo*	generation of new enteric neurons	Takaki *et al*. (49)
- rat jejunum, *isolated*	smooth muscle contraction	McLean *et al*. (40)
- guinea-pig ileum, *isolated*	smooth muscle relaxation	Carter *et al*. (50)
- guinea-pig proximal colon, *in vitro*	neurogenic relaxation	Briejer *et al*. (51) Elswood *et al*. (52)
- humans small and large intestines, *in vitro*	expression	Krobert *et al*. (53)
- human ascending, transverse, descending and sigmoid colon and rectum, *isolated*	relaxation of isolated colon circular muscle	Prins *et al*. (54)

most accurately reflects IDO activity in conditions associated with inflammation (91).

More recently, it has been found that mammals possess a third dioxygenase enzyme, in addition to TDO and IDO-1. IDO-2's active site contains a heme moiety for L-tryptophan binding and catabolism (127). This enzyme is capable of catalysing the oxidative cleavage of L-tryptophan, and is subsequently named indoleamine-2,3-dioxygenase type 2 (IDO-2) with a role in immunity (128). The discovery of a third initiating protein of the KP has attracted considerable research interest due to the established roles of IDO-2 in L-tryptophan metabolism (129) and TDO/IDO-1 dysfunction in numerous pathological conditions, including malaria (123, 130) and cancer (131).

An overexpression of IDO activity is connected with human cancer development (109, 110), IFN-α-induced depression (132) and IBS development (111, 112). Cytokines up-regulate IDO

Fig. 1. Tryptophan metabolism along the kynurenine pathway and serotonin pathway.



Abbreviations: 3-HAO, 3-hydroxy-anthranilate 3,4-dioxidase; AAAD, aromatic L-amino acid decarboxylase; ACMSD, α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase; HIOMT, hydroxyindole-O-methyltransferase; IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine amino transferases I-III; KMO, kynurenine 3-monooxygenase; KYNU, kynureninase; NAT, N-acetyltransferase; TDO, tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase; QPRT, quinolinic acid phosphoribosyl transferase.

Table 3. The expression of enzymes on the kynurenine pathway by inflammatory mediators (59, 61).

Enzyme	Inflammatory mediators	
	Up-regulation	**Down-regulation**
IDO	LPS, BCG, IFNs, TNF-alpha, IL-1beta, IL-6	
KMO	LPS, IFN-gamma, IL-1beta	
KYNU	LPS, IL-1beta, IFN-gamma	
KAT		IL-1beta, IFN-gamma (KAT-I)
3-HAO	LPS	
ACMSD		IFN-gamma

Abbreviations: LPS, lipopolysaccharide; BCG, *bacillus Calmette-Guerin*; IFN, interferon; TNF, tumour necrosis factor; IL, interleukin.

expression (132), causing a decrease in extracellular serotonin (*Table 3*). This can induce an increase in sleep, reduce locomotor activity, and decrease social exploration with co-existing anhedonia in animal models. These symptoms resemble the vegetative symptoms of depression in humans (133). Furthermore, dysregulation of L-tryptophan metabolism together with vitamin B_6 insufficiency influences serotonin and melatonin formation, with an impact on motility and perception in the ENS (124).

In IBS patients, plasma kynurenine levels are significantly elevated as is the K-TR ratio, an index of IDO activity, in comparison to control levels (134).

The inhibition of IDO activity with L-tryptophan loading, exerts protective effects by suppressing the formation of neurotoxic QUIN, 3-OH-L-KYN, 3-OH-AA, and nitric oxide synthase (135), and increases melatonin formation. Therefore this could be a new therapeutic approach in the treatment of many CNS and ENS disorders. Moreover, down-regulation of IDO, leads to a reduction of proinflammatory cytokine activity (59).

Kynurenine-3-monooxygenase (kynurenine 3-hydroxylase)

KMO catalyses the specific hydroxylation of L-KYN at the third position of its phenol ring to generate 3-OH-L-KYN, an endogenous oxidative stress generator, which causes neuronal cell death with apoptotic features and regional selectivity (136). The mechanism of toxicity to the cells is through the generation of reactive oxygen species in the respiratory chain (137).

KMO is up-regulated by FAD coenzyme (a form of vitamin B_2) and its monomeric protein is non-covalently and very tightly bound to FAD with the ability to slow chemical dissociation (1). NADPH, NADH, FAD and inflammatory stimuli up-regulate enzyme activity, whereas AA, XA and most likely vitamin B_6 are the negative regulators of the enzyme activity (62) (*Table 3* and *Table 5*). In vitamin B_6 deficiency, KMO activity is decreased, which may further lead to the development of other neurological disorders (10, 108).

Physiologically, high KMO levels are found in the liver and kidney, as well as within macrophage and microglial cells, whereas low KMO levels are distributed throughout all regions of the brain (136). More thorough studies further indicate that the enzyme is localized upon the outer mitochondrial membrane (138-140).

Recently, KMO has been proven to be involved in the pathogenesis of Huntington's disease (113), post-traumatic sepsis (138), Alzheimer's disease (141), and is considered to be an important pharmaceutical target for the development of drugs against neurodegenerative diseases (142, 143). Increased concentrations of 3-OH-L-KYN have been found in the disorders described above. Thus, KMO inhibition can be a potential therapeutic target for the treatment of neurodegenerative diseases (1, 114).

Kynureninase (L-kynurenine hydrolase)

KYNU is a vitamin B_6 dependent enzyme which lies on the main pathway towards acetyl-CoA or NAD^+ synthesis. Both L-KYN and 3-OH-L-KYN can be oxidized to AA or 3-OH-AA, respectively (144). L-KYN to AA and 3-OH-L-KYN to 3-OH-AA ratios are considered to be the KYNU indicators (*Table 4*). The role of 3-OH-L-KYN in health and disease is controversial as there have been reports regarding its pro-oxidant and antioxidant properties (62).

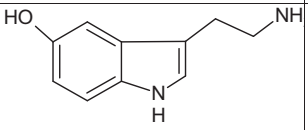
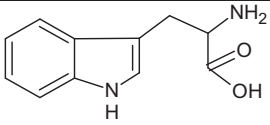
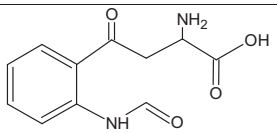
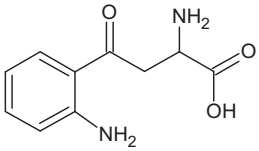
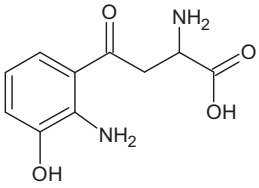
In parallel with KYNU, another vitamin B_6 dependent enzyme, KAT, utilizes the same reactants but obtains XA and KYNA as products instead (116).

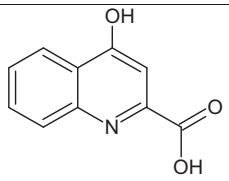
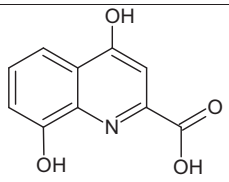
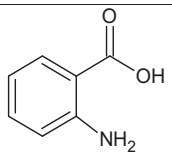
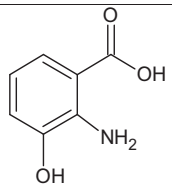
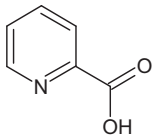
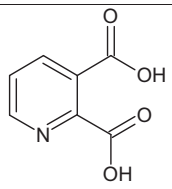
In vitamin B_6 deficiency states and in pregnancy, L-KYN and 3-OH-L-KYN predominate, suggesting a block in the pathway at the level of KYNU (76, 77). What is more, the KAT metabolites also exist, suggesting that although both enzymes require vitamin B_6, KYNU has been shown to be more sensitive to vitamin B_6 depletion than KAT (*Table 7*). Thus, depletion in vitamin B_6 concentration shifts the pathway towards the formation of KYNA and XA (84). Pregnancy exerts a more pronounced effect on KYNU activity than vitamin B_6 restrictions, and the effects of pregnancy and diet are additive (76, 77). In another study of vitamin B_6 deficiency, KYNU activity in the kidneys was significantly reduced, while KAT was increased (145). Moderate deficiency of vitamin B_6 causes an increase in the concentration of 3-OH-L-KYN whereas KYNA and AA concentration are decreased (146). According to Takeuchi *et al.* (145), the quantity of KYNA was highly increased. More serious deficiencies lead to an increase in the concentration of L-KYN and XA in blood and urine (146-149). The increase in the concentration of 3-OH-L-KYN is an important indicator of abnormalities occurring in the metabolism of vitamin B_6. Vitamin B_6 deficient animals excrete more XA and 3-OH-L-KYN, and less of the niacin metabolites (N-1-methyl nicotinamide and methyl-2-pyridone-4-carboxamide), when compared to the control group after L-tryptophan loading (84, 150). The 3-OH-L-KYN : 3-OH-AA ratio, which is a substrate-product ratio of KYNU, was proposed as the most sensitive and specific indicator of increased vitamin B_6 dependency (151).

A recent study shows that minerals can also exert an influence on KYNU activity. According to studies conducted by El-Sewedy *et al.* (2), Mn^{2+} can activate the enzymes, whereas Zn^{2+}, Co^{2+} and Cu^{2+} inhibit enzymatic activity. This inhibition is attributed to the blocking and inactivation of the sulfhydryl groups of the enzyme. The decreasing order by which these metal ions inhibit KYNU is $Cu^{2+} > Co^{2+} > Zn^{2+}$.

Additionally, KYNU is inactivated by incubation with a reaction product, L-alanine, and its function is restored by the addition of vitamin B_6 (153). The inhibition of KYNU is associated with sedative and anticonvulsant actions (154) (*Table 4*). On the other hand, interferon-gamma stimulation significantly

Table 4. Kynurenines and precursors in health and disease.

Compound	**Structure***	**Medical case and the sample**	
		Increased (reference)	Decreased (reference)
5-HT		- IBS, inflammatory diseases of the gastrointestinal tract, celiac disease, gastrointestinal infections, appendicitis (27) - schizophrenia, psychosis, Parkinson's disease, insomnia and generalized anxiety (30)	- depression (29)
L-TRP		- hyperserotonaemia (23)	- memory failure (21) - Alzheimer's disease - *plasma* (67) - Huntington's disease - *serum* (67) - depression - *plasma* (68-71) - Tourette's syndrome - *blood* (72)
NFK			
L-KYN		- Alzheimer's disease - *plasma* (67) - depression - *plasma* (68–71) - Tourette's syndrome - *blood* (72) - schizophrenia (73, 74) - development of sepsis (73) - vitamin B_6 deficiency (76, 77) - pregnancy (76, 77) - traumatic brain injury – *humans cerebrospinal fluid* (79) - acute coronary events (80) - inflammation (62, 90, 91)	
3-OH-L-KYN		- pregnancy (76, 77) - Alzheimer's disease - *serum* (78) - acute coronary events (80) - early phases of Huntington's disease (81) - Parkinson's disease (82, 83) - vitamin B_6 deficiency - *hepatocytes* (84)	- advanced phase of Huntington's disease (85) - users of vitamin B_6 supplements (86)

KYNA		- schizophrenia (73, 74) - traumatic brain injury - *humans cerebrospinal fluid* (79) - Alzheimer's disease - *putamen and caudate nucleus* (87) - type 2 diabetes (88) - vitamin B_6 deficiency (89)	- amyotrophic lateral sclerosis (64) - HIV dementia (64) - chronic brain injury (64) - multiple sclerosis (64) - Parkinson's disease (82, 83) - Alzheimer's disease - *cerebrospinal fluid* and *plasma* (92, 93) - Huntington's disease - *brain tissue* (94)
XA		- vitamin B_6 deficiency (84, 89, 90) - type 2 diabetes (88, 90) - insulin production and release impairment (90, 91)	
AA (vitamin L1)			
3-OH-AA		- bladder cancer - *urine* (95, 96)	- early-stage of Huntington's disease - *neostriatum* and *cortex* (85, 97)
PA		- development of murine cerebral malaria (98)	
QUIN		- traumatic brain injury - *humans cerebrospinal fluid* (79) - early phase of Huntington's disease (81, 100) - Alzheimer's disease (99) - aging process (101, 102)	- symptomatology of Tourette's syndrome (103)

*The chemical structures were built with the program ACD/ChemSketch Freeware (http://www.acdlabs.com/resources/freeware/chemsketch/).

Abbreviations: 3-OH-AA, 3-hydroxy-antranilic acid; 3-OH-L-KYN, 3-hydroxy-L-kynurenine; 5-HT, serotonin; AA, anthranilic acid; IBS, irritable bowel syndrome; KYNA, kynurenic acid; L-KYN, L-kynurenine; L-TRP, L-tryptophan; PA, picolinic acid; QUIN, quinolinic acid; XA, xanthurenic acid.

potentiates the expression of KYNU in cultured human glioma cells (61) (*Table 3*).

Kynurenine aminotransferases

Kynurenine aminotransferases, as implied by their names, are the primary enzymes involved in the irreversible transamination of KYNA from L-KYN in human brain tissue, and are referred to as KATs. KATs are homodimeric pyridoxal proteins that mediate this catalytic conversion (4). Although four isoforms (KAT-I to -IV) of this enzyme have been hitherto identified, KAT-II is the enzymatic isoform that mainly accounts for the synthesis of cerebral KYNA (155). KAT is also involved in the biosynthesis of glutamic (156, 157) and aspartic acid (4), which function as neurotransmitters for the NMDA receptors in mammals (158) (*Table 5*). Moreover, KAT is responsible for the

Table 5. Vitamins and minerals regulation on the kynurenine pathway.

Enzyme	**Reaction catalysed**	**Up-regulation** (reference)	**Down-regulation** (reference)
Indoleamine 2,3-dioxygenase (IDO)	L-Trp + O_2 → N-formyl-L-kynurenine	Fe^{3+} (19)	
Tryptophan 2,3-dioxygenase (TDO)	L-Trp + O_2 → N-formyl-L-kynurenine	Fe^{3+} (19)	Cu^{2+} (11)
Kynurenine formamidase	N-formyl-L-kynurenine → L-KYN		Mn^{2+} (12)
Kynurenine 3-monooxygenase (KMO)	L-KYN + NADPH + H^+ + O_2 → 3-OH-L-KYN + $NADP^+$ + H_2O	vitamin B_2 (1, 9)	vitamin B_6 (62)
Kynureninase (L-kynurenine hydrolase, KYNU)	L-KYN + H_2O → AA + L-alanine	vitamin B_6 (8)	Zn^{2+}, Co^{2+}, Cu^{2+} (2)
	3-OH-L-KYN + H_2O → 3-OH-AA	Mn^{2+} (2)	
Kynurenine aminotransferases (KATs)	L-KYN + 2-oxoglutarate/pyruvate → KYNA + L-glutamate	vitamin B_6 (4-6)	
3-hydroxy-anthranilic acid 3,4-dioxygenase (3-HAO)	3-OH-AA + O_2 → 2-amino-3-carboxymuconate-6-semialdehyde	Fe^{2+} (3, 7)	Zn^{2+} (7)
α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD)	2-amino-3-carboxymuconate -6-semialdehyde → PA + CO_2	Fe^{2+}, Co^{2+} (13) Zn^{2+} (14, 18)	
Quinolinate phosphoribosyl transferase (QPRT)	QUIN + 5-phospho-α-D-ribose 1-diphosphate → NAD^+ + diphosphate + CO_2	Mg^{2+} (15, 16)	Cu^{2+}, Fe^{2+}, Fe^{3+}, Zn^{2+} (17)

transamination of 3-OH-L-KYN to XA in the competing, major branch of the metabolic cascade. However, this function of KAT has been rarely highlighted in the published literature as of yet (159). KATs are not sensitive to changes in minerals; however, there are some reports suggesting its sensitivity to vitamin B_6 fluctuations (*Table 7*). The data as of present have shown little effect of dietary vitamin B_6 on KATs' activity (76, 77).

KAT-I is potently inhibited by glutamine, whereas KAT-II is not sensitive to glutamine. KAT-I that is located in the brain is inhibited by competing substrates, like L-tryptophan, L-phenylalanine and L-glutamine, which are present in the human body under physiological conditions (160). On the other hand, KAT-I that is located in the heart is not inhibited by the afore-mentioned compounds (161).

Table 6. Vitamins and minerals on the kynurenine pathway in health and disease.

Enzyme	**Concentration** (reference)	
	Increased	Decreased
Indoleamine 2,3-dioxygenase (IDO)	- human glioma cells cultures (61) - depression (68 – 71) - development of sepsis (75) - human cancer (109, 110) - IBS development (111, 112)	- Alzheimer's disease (67)
Tryptophan 2,3-dioxygenase (TDO)		
Kynurenine formamidase		
Kynurenine 3-monooxygenase (KMO)	- Parkinson's diseases (1) - human glioma cells cultures (61) - post-traumatic sepsis (75) - Huntington's disease (85, 113, 114) - Alzheimer's disease (99) - human hepatocellular carcinoma (115)	- schizophrenia (73, 74)
Kynureninase (L-kynurenine hydrolase, KYNU)	- human glioma cells cultures (61)	- vitamin B_6 deficiency (76, 77) - pregnancy (76, 77)
Kynurenine aminotransferases (KATs)	- schizophrenia (116, 117)	- human glioma cells cultures (61) - Huntington's disease (94)
3-hydroxy-anthranilic acid 3,4-dioxygenase (3-HAO)		- schizophrenia (73, 74) - Huntington's disease (85) - chronic brain injury (118) - stroke (119) - depression (120) - osteoporosis (121)
α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD)		- human glioma cells cultures (61)
Quinolinate phosphoribosyl transferase (QPRT)		

It was reported that selective inhibitors of KAT-II restore nicotine-evoked glutamatergic activity in the cortex, being a possible treatment target for such cognitive impairments (162), as KAT-II is responsible for most of the KYNA synthesis in the brain. Notably, compounds targeting KAT-II selectively may provide clinical benefits in a host of psychiatric and neurological disorders by normalizing the function of brain KYNA and its receptors (116, 163).

The product of KAT activity - KYNA is known to be a highly neuroactive metabolite whose impairment is associated with a number of severe brain disorders such as Alzheimer's disease (164), schizophrenia (165) ischemic stroke (166), and with type 2 diabetes (88) (*Table 6*). High levels of KYNA have been identified in human urine during marked vitamin B_6 deficiency. Kocki *et al.* (167) has proven that the amino acid L-cysteine can down-regulate KYNA formation in the brain. A study among acute ischemic stroke patients revealed decreased activity of KAT, KYNA, L-tryptophan, and apolipoprotein A1 (166). Pregnancy results in an overall reduction of enzyme activity; however, the degree of reduction is minimal, and pregnancy does not enhance the effect of vitamin B_6 restriction.

The role of a second product, XA, and the influence of vitamins and minerals on its production is not well known. XA accumulates in pre-synaptic terminals and is intensively produced and excreted in urine after the ingestion of L-tryptophan during vitamin B_6 deficiency (145). Copeland (168) suggests that XA may be the first potential endogenous allosteric agonist (termed "endocoid") for the metabotropic glutamate receptors. Additionally, XA may participate in apoptotic events in vascular smooth muscle and retinal pigment epithelium cells with modifications in mitochondrial Ca^{2+} transport and oxygen consumption (169).

3-hydroxy-anthranilic acid 3,4-dioxygenase

3-HAO is an iron dependent enzyme requiring O_2, Fe^{2+} and sulfhydryl groups for its activation (3, 170, 171). This enzyme is mainly localized to hepatic tissue in the mitochondrial

Table 7. Vitamins and minerals on the kynurenine pathway.

Enzyme	Microelements					Macroelements	Vitamins	
	Fe^{2+}	Cu^{2+}	Mn^{2+}	Zn^{2+}	Co^{2+}	Mg^{2+}	B_2	B_6
IDO	+							
TDO	+	-						
KF			-					
KMO							+	-
KYNU		-	+	-	-			+++
KAT								+
3-HAO	+			-				
ACMSD	+			+	+			
QPRT	-	-		-		+		

Abbreviations: 3-HAO, 3-hydroxy-anthranilic acid dioxygenase; ACMSD, α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase; IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KF, kynurenine formamidase; KMO, kynurenine 3-monooxygenase; KYNU, kynureninase or L-kynurenine hydrolase; QPRT, quinolinate phosphoribosyl transferase; TDO, tryptophan 2,3-dioxygenase.
"+" up-regulation; "-" down-regulation

membrane, but is also expressed in the brain, mainly in astrocytes (172), in the liver, and in the inflammatory cells (65). There are no structural differences between the enzyme from the brain and the liver, except that higher amounts of 3-HAO have been observed in the liver (173).

3-HAO activity may normally be restrained by certain factors such as the availability of Fe^{2+} ions and O_2. The addition of Fe^{2+} stimulates the enzyme's activity 4- to 6-fold in striatal homogenates of mouse, rat, and human; and can be inhibited by ferritin (176). Iron released during neuronal damage stimulates 3-HAO and inhibits QPRT, thus significantly elevating the production of QUIN, which thereby causes more damage to the CNS. On the other hand, Zn^{2+} was described as having a negative impact on enzyme activity (7). Moreover iron ions are responsible for 3-OH-L-KYN induced neuronal cell death either by catalysing the oxidation of 3-OH-L-KYN or in promoting the production of highly reactive hydroxyl radicals (136, 152).

The role of 3-HAO in proper CNS functioning is still unclear and controversial. The activity of 3-HAO is significantly reduced in schizophrenia (73, 74), Huntington's disease (85), chronic brain injury (118), stroke (119), depression (120), and osteoporosis (121) (*Table 6*). In pathology, the normal ratio between 3-OH-AA and AA is also changed, with lower levels of 3-OH-AA and higher levels of AA than normal (175). There are also reports suggesting that 3-HAO plays anti-inflammatory and neuroprotective roles during inflammation, and thus may have implications for future therapeutic approaches for neuroinflammatory disorders (174). Thus, it is justifiable that reducing levels of toxic QUIN by administering such inhibitors of the enzymes of the KP, particularly 3-HAO, may be a reasonable approach for the treatment of such cognitive impairments (7).

2-amino 3-carboxymuconate 6-semialdehyde decarboxylase

ACMSD diverts 2-amino-3-carboxymuconate semialdehyde from QUIN production, towards picolinic acid (PA) formation, and thus is responsible for the proper homeostasis between PA, QUIN and NAD^+ (*Fig. 1*). ACMSD is a Zn-dependent amidohydrolase (14) and is activated slightly by Fe^{2+} and Co^{2+} (13) (*Table 7*). On the other hand, QUIN, PA and KYNA inhibit ACMSD activity (13). Furthermore, interferon-gamma significantly down-regulates the expression of both ACMSD and KAT-I in cultured human glioma cells (61); however, it significantly potentiates the expression of IDO-1, IDO-2, KYNU, and KMO (*Table 3*). ACMSD is present in kidney and liver, with its highest expression occurring in kidney (13). As the relative concentrations of PA and QUIN must be tightly controlled, modulation of ACMSD may be another key to the treatment of neurological disorders (*Table 4*). Therefore, ACMSD is an attractive therapeutic target for treating disorders associated with increased levels of neurotoxic QUIN, and factors which directly influence enzyme activity may be an interesting approach to modulate L-tryptophan metabolism.

An increased concentration of bivalent metals such as Fe^{2+}, Co^{2+} and Zn^{2+} may increase the concentration of PA, thereby decreasing QUIN formation.

Interestingly, PA may inhibit QPRT activity through Zn^{2+} chelation, thus reducing QUIN induced neurotoxicity (177).

Quinolinate phosphoribosyl transferase

QPRT has been identified in the CNS of both rats and humans (178, 179). The role of QPRT is to catabolize QUIN to NAD^+ with carbon dioxide as a by-product. QUIN is often implicated in the pathogenesis of a variety of human neurological diseases, as it is an agonist of the NMDA receptor (158), and has a high *in vivo* potency as an excitotoxin (177). NAD^+ is an important enzymatic cofactor that is vital to ongoing cell viability and maintenance of mechanisms such as the DNA repair protein poly(ADP-ribose) polymerases (180). Under physiological conditions, Mg^{2+} is required for QPRT activation with further evidence that a cysteine residue at the active site is required for reaction catalysis (178) (*Table 7*). The proper functioning of QPRT, which is dependent on Mg^{2+} intake, prevents the accumulation of toxic QUIN (*Table 5*). Mg^{2+} insufficiency may lead to the inhibition of enzyme, thus promoting accumulation of neurotoxic reactants. Grimaldi *et al.* (103) point out that Mg^{2+} deficiency may be the central precipitating event resulting in the symptomatology of Tourette's syndrome and several reported comorbid conditions. As of now, it is not known if Mg^{2+} supplementation influences enzymatic activity during the development of QUIN-induced toxicity of neurological processes, as free radical generation and oxidative stress are involved in this process.

On the other side of the coin, Cu^{2+} Fe^{2+}, Fe^{3+}, Zn^{2+} deficiencies are considered to up-regulate QPRT activity, and thus may inhibit QUIN accumulation (17, 62). Moreover, the complex formation between QUIN and excess Fe^{2+} can produce oxidative cell damage through lipid peroxidation and can inhibit the auto-oxidation of the Fe^{2+} complex which is responsible for *in vitro* DNA chain breakage (181). Thus, an excess of Fe^{2+} plays an etiologically

significant role in neurodegenerative disorders (176). Pathologic accumulation of QUIN has been found in neurodegenerative disorders including Alzheimer's (99) and Huntington's disease (100) and has also been connected with the aging process (101, 102) (*Table 4*). Moreover, Sahm *et al.* (172) identifies QPRT as a potential therapeutic target in malignant gliomas. Sasaki *et al.* (104) suggest that the immune and neuronal systems of insulin dependent diabetes mellitus would be influenced by the increased amounts of QUIN and L-KYN, but not by those of PA and NAD^+ as diabetes mellitus does not augment the latter species. Treatment with metal chelates such as PA demonstrate significant neuroprotection against QUIN-formation, responsible for excitotoxic damage to the brain, towards NAD^+ formation (177).

CONCLUSIONS

Under pathological conditions, the concentrations of L-tryptophan, vasoactive L-kynurenine, neuroactive KYNA, QUIN, 3-OH-L-KYN, 3-OH-AA, and enzymes responsible for their formation (IDO, KMO, KAT, KYNU, 3-HAO) are significantly changed in blood, in urine and in the brain (182) (*Table 4*). Several of these enzymes are under the tight control of inflammatory mediators (59, 61). Also, the concentration of the essential amino acid L-tryptophan was reported to be decreased by the pro-inflammatory cytokines (59, 61). In septic shock patients, the concentration of L-tryptophan is decreased, as opposed to L-KYN which is intensively produced (75). Studies performed by Celinski *et al.* (183) demonstrate the protective effect of melatonin and L-tryptophan by reducing concentrations of pro-inflammatory Il-1, Il-6 and TNF-α. Also the concentrations of B group vitamins (76, 77, 86, 89, 107, 126, 146, 150, 151) and minerals are significantly altered (*Table 5*).

The evidence presented in this paper suggests that the KP is highly sensitive to changes in the concentration of B group vitamins (B_2, B_6) as well as micro- (Fe^{3+}, Mn^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}) and macro-elements (Mg^{2+}). Both vitamins and minerals can work as coenzymes and cofactors in *de novo* synthesis of another B-vitamin niacin. Another pathway of L-tryptophan metabolism, the serotonin pathway, is also dependent on proper diet and vitamin B_6 status (184-186), which suggests that any alterations to L-tryptophan metabolism might also influence the production and activity of both serotonin and melatonin (187).

Minerals and B group vitamins at physiological concentrations can either directly up-regulate and/or down-regulate the activity of enzymes engaged in L-tryptophan metabolism (*Table 7*). Vitamin B_6 was found to be the most crucial vitamin engaged in L-tryptophan metabolism, since it is involved in the proper functioning of the serotonin pathway enzyme tryptophan hydroxylase, and the kynurenine pathway enzymes KYNU and KAT.

However, surplus administration of B-group vitamins did not elicit beneficial effects on L-tryptophan metabolism, since deficiencies rather than surpluses seem to influence the KP (107). The administration of minerals in a normally balanced diet is not known to influence the KP.

Nutrient deficiencies plus coexisting physiological processes may have hyper-additive effects on biological systems, therefore causing increased harmful effects (76, 77). In other words, in alcoholics, people experiencing decreased food intake, and during high physical activity when the needs are increased (188), the concentration of L-tryptophan in the diet is not sufficient. Any diseases to the GI-tract influence both proper food absorption and GI synthesis of many organic compounds such as melatonin, serotonin or kynurenines in the gut (185). Thus, it is crucial to maintain proper functioning of the GI-tract, which will also accelerate the healing processes (189).

Pharmacological down-regulation of the L-tryptophan - L-KYN - NAD^+ pathway together with a tryptophan-rich diet and maintenance of adequate B vitamins and minerals is important for patients susceptible to depression, diabetes, post-traumatic stress disorder, chronic pain, cancer, and drug addiction (186). It is likely that this regulation can also influence the progression of epilepsy, Parkinson's disease, Alzheimer's disease or schizophrenia (141). Other conditions associated with inflammation and stress-induced excess of L-KYN production that coincide with vitamin B_6 deficiency are obesity, cardiovascular diseases, aging, pre-and postmenstrual phase in certain females, pregnancy, and hepatitis C virus infection (91).

It is therefore reasonable to assume that nutrients that affect the enzymes involved in the formation or metabolism of the "kynurenines" are useful tools that may improve our understanding of the role of those enzymes in physiology and pathology. However, much more diversified research is still needed to fully understand the complex interaction between enzymes and B group vitamins and minerals, how they react with each other, how they react within the nervous systems, as well as how they react on the periphery.

Abbreviations: 3-HAO, 3-hydroxy-anthranilic acid dioxygenase; 3-OH-AA, 3-hydroxy-antranilic acid; 3-OH-L-KYN, 3-hydroxy-L-kynurenine; 5-HT, serotonin; AA, anthranilic acid; CNS, central nervous system; ENS, enteric nervous system; FAD, flavin adenine dinucleotide; IBS, irritable bowel syndrome; IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KF, kynurenine formamidase; KMO, kynurenine 3-monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; KYNU, kynureninase or L-kynurenine hydrolase; L-KYN, L-kynurenine; L-TRP, L-tryptophan; NAD^+, nicotinamide adenine dinucleotide; NMDA, N-methyl-D-aspartate; PA, picolinic acid; QPRT, quinolinate phosphoribosyl transferase; QUIN, quinolinic acid; TDO, tryptophan 2,3-dioxygenase; XA, xanthurenic acid.

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Author's address: Dr. Michal Majewski, Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Warmia and Mazury, 14C Zolnierska Street, 10-561 Olsztyn, Poland
E-mail: michal.majewski@uwm.edu.pl