International Journal of Tryptophan Research

CONCISE REVIEW

Kynurenic Acid in the Digestive System—New Facts, New Challenges

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Abstract: This review provides information on the most recent findings concerning presence, origin, and role of kynurenic acid (KYNA), a tryptophan metabolite, in the digestive system. KYNA is an antagonist of both the ionotropic glutamate receptors and the alpha7 nicotinic acetylcholine receptor, as well as an agonist of G-protein coupled GPR35 receptor. Since the GPR35 receptor is mainly present in the gastrointestinal tract, researchers have concentrated on the digestive system in recent years. They have found that KYNA content increases gradually and significantly along the gastrointestinal tract. Interestingly, the concentration of KYNA in the lumen is much higher than in the wall of intestine. It has been documented that KYNA may have a positive influence on the number of pathologies in the gastrointestinal tract, in particular ulcers, colon obstruction, or colitis. Future studies might determine whether it is advisable to supplement KYNA to a human organism.

Keywords: kynurenic acid, digestive system, pathophysiology, food, herb

International Journal of Tryptophan Research 2013:6 47–55

doi: 10.4137/IJTR.S12536

This article is available from http://www.la-press.com.

Introduction

Kynurenic acid (KYNA) is a metabolite of tryptophan formed enzymatically along the kynurenine pathway. The first step in the pathway is catalyzed by tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenase (IDO), enzymes responsible for tryptophan degradation to formylkynurenine. TDO is primarily expressed within the liver and IDO is an extrahepatic cytokine inducible enzyme. The next step in the synthesis of kynurenine is catalyzed by formylkynurenine formamidase. The main end product of kynurenine catabolism is nicotinamide adenosine dinucleotide (NAD^+). An another biologically active product, KYNA, is generated from kynurenine by kynurenine aminotransferase.[1,2]

KYNA presence was first demonstrated in urine by Liebig.[3] Nevertheless, the compound was not thoroughly analyzed until the 1980's and 1990's when researchers indicated that KYNA is an antagonist of ionotropic glutamate receptors.[4–8] Subsequently, researchers presumed that KYNA is present in the human brain.[9,10] Numerous studies were conducted to investigate the role of KYNA in the physiology and pathology of the central nervous system (CNS). Since both the concentration of KYNA in the human brain and penetration of KYNA through a blood-brain barrier are low, studies of peripheral KYNA gained popularity.

Mechanisms of Action

Table 1 presents a summary of receptors affected by KYNA, quantities of KYNA necessary to exert action, and further comments regarding its mechanism of action. KYNA is widely known as an antagonist of ionotropic glutamate receptors and the alpha7 nicotinic acetylcholine receptor,[4–8,11] receptors present mainly in the brain. Research conducted over the last two decades of the 20th century, therefore, focused on the role of KYNA in the physiology and pathology of the CNS. More recently, KYNA was found to be an agonist of the G-protein coupled GPR35 receptor.[12] The presence of such receptors predominantly on immune cells and the gastrointestinal tract[12] has led researchers to investigate KYNA action in periphery.

The detailed information on the effect of KYNA exerted by interaction with above mentioned receptors was a matter of several currently published review papers.[13–15]

Content of KYNA in the CNS and Periphery

The concentration of KYNA in cerebrospinal fluid and the brain lies within the range of 0.001–0.032 μM and 0.001–1.58 μM, respectively (Table 2), and is lower than the concentration necessary to affect glutamate or cholinergic receptors (Table 1). The concentration of KYNA in peripheral tissues ranges from 0.090 μM in the wall of the intestine to 0.815 μM in the kidney. The lowest concentration of KYNA in body fluids was found in saliva (0.003 μM) while the highest was found in mucous from ileum (16.1 μM). The content of KYNA in urine ranges from 4–40 μM (Table 2).

It should be emphasized that the concentration of KYNA high enough to interact with glutamate, alpha-7 cholinergic, and GPR35 receptors in vitro was detected in lumen of ileum. Also of note, the GPR35 receptor is mainly present in gastrointestinal tissues.[12]

KYNA in CNS

Glutamate receptors are mainly located in the CNS. According to electrophysiological studies, KYNA exerts a modulatory effect on neurotransmission in the brain.[11,16] Several papers review the action and the potential role of KYNA in the brain.[17–19]

KYNA in Periphery

Initially, KYNA was found in urine in 1853.[3] More recently, presence of KYNA in urine was described in numerous papers (Table 2).[20–26]

It was evidenced that KYNA is present in serum where its concentration varied from 0.004–0.06 μM (Table 2). Additionally, KYNA was found in synovial[27] and amniotic fluid.[28]

Furthermore, numerous reports concentrate on KYNA content outside of the CNS, specifically focusing on its presence in the digestive system.

KYNA Content in Digestive System

Table 3 presents the most recent findings of KYNA concentration in the lumen of the digestive system. The lowest concentration of KYNA was found in human saliva (0.003 μM) and human gastric juice (0.01 μM), while the highest content of KYNA was detected in the rat's middle ileum mucus (8.08 μM) and the rat's distant ileum mucus (16.10 μM). It is worth noting that the concentration of KYNA increases gradually

Table 1. Receptors affected by kynurenic acid.

Receptor/binding site	Concentration [EC_{50}; μM]	Comment	Reference
NMDA autoreceptors	0.03	On glutamatergic nerve terminals	48
Strychnine insensitive glycine/NMDA receptor	8		5
	41		6
	15		7
	15		11
	24.4–195.4		8
NMDA	187		6
	200–500		7
	235		11
AMPA/kainate	101	AMPA	6
	400	GLUR6	4
	432.5–595.7		8
α7 nicotinic	7		11
	Ineffective	1000–3000 μM	8
GPR35	7	Rat	12
	11	Mouse	
	39	Human	
Sulfotransferases	2.9–4.9	Mouse Sult1b1	49
	18.8–22.0	Human SULT1A1	
	19.6–45.8	Human SULT1B1	
Aryl hydrocarbon receptor (AHR)	1.4	Human AHR-expressing mice	50
Organic anion transporting polypeptides (OATP1B1/3)	~20	Rat and human hepatocytes	51
Poly(ADP)ribose polymerase (PARP)	670		52
Arachidonic acid- induced platelets aggregation	900	Guinea pig	53
Adenosine diphosphate-induced platelets aggregation	1100	Guinea pig	
$GABA_A$	2900		8
Strychnine-sensitive glycine receptor	>3000	34% inhibition	
p75	up to 10 μM <25% inhibition	NGF binding to p75 receptor in PC12 cells	54

Abbreviations: AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; GABA, γ-aminobutyrate; GPR35, G protein-coupled receptor; NMDA, N-methyl-D-aspartate.

along the gastrointestinal tract, reaching its highest value at the very end of it. It is also noteworthy that KYNA content in the distant ileum of the rat mucus is nearly 5400 times higher than in human saliva. The physiological significance of such remarkable gradation of KYNA concentration in the digestive system is currently unknown.

Interestingly, a much lower concentration of KYNA was found in the wall of the gastrointestinal tract. According to Kuc et al, the concentration of KYNA in the wall of a rat's duodenum, jejunum, and ileum was 0.29 μM, 0.21 μM and 0.28 μM, respectively.[29] Pawlak et al reported a concentration of 0.09 μM of KYNA in rat intestine.[30] The content of KYNA in the wall of a rat's duodenum, jejunum, and ileum was, therefore, 19%, 6%, and 3% of the content of KYNA in the lumen of the appropriate part of a rat's intestine, respectively. As a result, the supposition that KYNA is produced in the wall of the intestine and then secreted to the intestinal fluid in such a high amount seems rather unlikely.

The remarkable content of KYNA amounting to 0.31–0.83 μM and 1.11 μM was found in bile of human and pig, respectively.[29] Unexpectedly, KYNA was detected in the pancreatic juice of pigs with a relatively high concentration (0.76 μM).[29] However, the distribution and activity of kynurenine transaminases in pancreatic tissue, and thus the mechanism

Table 2. KYNA content in tissues and body fluids.

Tissue	KYNA content [μM]*	Comment	References
Brain	0.14–1.58	Human	9,55,56
	0.001–0.05	Rat	57–59
	~0.002	Hamster	60
	0.16	Gerbil	61
Kidney	0.815	Rat	30
Liver	0.161	Rat	30
Lung	0.172	Rat	30
Intestine	0.090–0.29	Rat	29,30
Ileum (lumen)	8.08–16.1	Rat	29
Spleen	0.129	Rat	30
Muscle	0.197	Rat	30
Plasma	0.004–0.060	Human	62–66
	0.016	Human, pregnant women	23
	0.066	Human, umbilical cord blood	28
	0.122	Monkey	67
	0.028–0.065	Rat	68
	~0.02	Hamster	60
Cerebrospinal fluid	0.001–0.005	Human	63,64,69–72
	~0.005	Human, 7 months old	73
	0.006	Monkey	67
	0.032	Gerbil	61
Saliva	0.003	Human	44
Amniotic fluid	1.132	Human	28
Synovial fluid	0.016	Human; rheumatoid arthritis	27
Urine	4–40	Human	20–25
	11.7	Human, pregnant women	23

Notes: *For the sake of a comparison, the content of KYNA in wet tissue was calculated as follows: ηmol/g = μM.

of KYNA formation in exocrine acinar cells of the pancreas, have not been elucidated to date.

Based on the data concerning the KYNA absorption in the intestine[31,32] and its presence in bile and pancreatic juice,[29] the hepatic-pancreatic-intestinal secretion-absorption functional cycle creating a high concentration of KYNA in intestinal fluid can be suggested. Furthermore, it is highly probable that activity of colon microbiota participates in the maintaining of KYNA in the gastrointestinal content especially in their distal part as well.[29]

Table 3. Content of KYNA in the lumen of digestive system.

	Species	KYNA content [μM]	Reference
Saliva	Human	0.003	44
Gastric juice	Human	0.01	74
Bile	Human	0.31–0.84	74
Bile	Pig	1.11	74
Pancreatic juice	Pig	0.76	74
Jejunum—mucus	Rat	1.49	29
Proximal ileum—mucus	Rat	3.30	29
Middle ileum—mucus	Rat	8.08	29
Distal ileum—mucus	Rat	16.10	29

Properties of KYNA in Pathological States of the Gastrointestinal Tract

Numerous researchers have analyzed properties of KYNA in the pathology of the gastrointestinal tract. According to Glavin et al, KYNA protects against gastric and duodenal ulceration caused by a poisonous Atlantic shellfish.[33] Furthermore, Glavin and Pinsky found that KYNA attenuates stress- and ethanol-induced ulcers in rats.[34] KYNA was also found to inhibit intestinal hypermotility and xanthine oxidase activity during experimental colon obstruction in dogs.[35] Moreover, Varga et al pointed out that KYNA decreases motility and inflammatory activation in the early phase of acute experimental colitis in rats.[36]

Interestingly, the KYNA level in serum was found to be higher in inflammatory bowel disease patients[37] while it was found to be lower in irritable bowel syndrome patients, in comparison with healthy subjects.[38] The second finding was confirmed by Christmas et al who found that KYNA levels in serum tends to decrease in irritable bowel syndrome patients.[39] Finally, a high concentration of KYNA was detected in mucus aspirated from the coecum or ascending colon of patients suffering from colorectal cancer adenomas.[40] A summary of the findings is presented in Table 4.

All in all, scientific reports suggest that KYNA may have a positive influence on the number of pathologies of the gastrointestinal tract, especially regarding ulcers, colon obstruction or colitis. There is some dispute as to whether KYNA exerts a positive or negative action in bowel diseases since an increased level of KYNA in colon neoplasia cannot be interpreted either in favor of or against KYNA, as its mechanism of action in the mentioned diseases is yet unknown. Recently, KYNA's enhancement of the expression of cyclin-dependent kinase inhibitor, p21 Waf1/Cip1, and inhibition of cell proliferation and DNA synthesis in colon adenocarcinoma HT-29 cell line were described.[41]

Table 4. KYNA and pathology of gastrointestinal tract.

Pathology	Effect of KYNA	Reference
Gastroduodenal ulceration	KYNA protects against gastric and duodenal ulceration induced by extract from poisonous Atlantic shellfish in mice.	33
Gastroduodenal ulceration	KYNA blocks restraint-cold stress ulcers, ethanol ulcers and basal, non-stimulated gastric acid secretion in rats.	34
Experimental colon obstruction	KYNA inhibits intestinal hypermotility and xanthine oxidase activity during experimental colon obstruction in dogs.	35
Colitis	KYNA decreases motility and inflammatory activation in the early phase of acute experimental colitis in rats.	36
Inflammatory bowel disease	Serum level of KYNA is elevated in inflammatory bowel disease patients.	37
Irritable bowel syndrome	Serum level of KYNA is reduced in irritable bowel syndrome patients.	38
Diarrhea-predominant irritable bowel syndrome	Trend to decrease in KYNA content in serum of diarrhea-predominant irritable bowel syndrome patients.	39
Colon carcinoma, Adenoma tubulovillosum, Adenoma tubulare	High KYNA concentration is detected in mucus aspirated from caecum or colon ascendens of patients diagnosed with colon carcinoma, Adenoma tubulovillosum or Adenoma tubulare.	40

KYNA and the Gut Flora

Most recently, it was indicated that *Escherichia coli* is able to produce KYNA and liberate it to extracellular milieu.[29] Similarly, KYNA production was shown in cell-free extracts of *E. coli*.[42] Furthermore, there is allusion to positive correlation between microflora concentration and KYNA content in jejunum and ileum.[29] These findings suggest that gut flora may participate in forming the common pool of intestinal KYNA.

On the other hand, it has also been demonstrated that KYNA affects bacterial growth. Interestingly, low and medium concentrations of KYNA stimulate growth of certain probiotics while KYNA in high concentrations possesses antibacterial properties.[43,44]

Metabolism of KYNA

KYNA is present in the lumen of rat small intestine in micromolar concentrations,[29] which is sufficient to affect the GPR35 receptor. The sources of KYNA in the gastrointestinal tract are not known, although it seems that, in this instance, KYNA was either produced from tryptophan or delivered with food and other dietary products.

The pathway for KYNA creation in humans was most recently investigated by Hiratsuka et al in young Japanese women who consumed tryptophan in amount of 0.7 g (3328 μmol) per day with subsequent analyzes of various tryptophan metabolites.[20] KYNA production was reported near 10 μmol/day, indicating that transformation of tryptophan to KYNA occurs with an effectiveness of 0.3%.[20] Leklem reported a slightly higher effectiveness of the reaction at 0.42%.[26]

The expert report created by the World Health Organization (WHO), Food and Agriculture Organization

(FAO), and United Nations University (UNU) recommends a tryptophan dose of 4 mg/kg/day.[45] Therefore, assuming an adult's weight to be 70 kg, a recommended dose of tryptophan per person is 280 mg/day. It can be estimated that either 0.84 mg (effectiveness of 0.3%) or 1.18 mg (effectiveness of 0.42%) of KYNA is created in the human body along the kynurenine pathway from tryptophan.

Therefore, the research suggests that KYNA might be synthesized in the human body along the kynurenine pathway from its precursor, tryptophan. However, there was no analogous research on KYNA synthesis from its immediate precursor, kynurenine, and there is no data regarding the presence of kynurenine in either food or herbs.

Despite some previous research indicating that KYNA might be metabolized to quinaldic acid,[46] we did not observe its formation from KYNA in rat brain slices and liver homogenates (unpublished observation). Nevertheless, there is no data on KYNA accumulation in the body. Numerous scientific papers report that KYNA is present in human urine and hence excreted with it.[20–26] Reports of excreted KYNA concentrations vary from 1143.9 µg per day to 5376.6 µg per day (Table 5). Based on the results shown in Table 5, and bearing in mind the fact that estimated production of KYNA from tryptophan in human organism is either 840 µg per day or 1160 µg per day, it could be assumed that KYNA is also absorbed from the digestive system. In fact, there is indication that KYNA can be absorbed from the digestive system into blood circulation.[31]

Literature data suggests that the majority of KYNA content in human organisms likely comes from exogenous sources. Therefore, it is important to review the studies of KYNA content in food and herbs.

Table 5. Excretion of KYNA in urine.

KYNA content in urine	Reference	KYNA excretion [µg/day]*
9.97 µmol/day	20	1884.3
4.035 µmol/L	21	1143.9
2.54 µg/mL	22	3810
11.7 µmol/L	23	3317
18.965 µmol/L	24	5376.6
13 µmol/L	25	3685.5
15.9 µmol/day	26	3005.1

Note: *The assumption behind the calculations is that a human being excretes 1.5 liters of urine on a daily basis.[75]

KYNA in Food

According to research by Turski et al, KYNA is present in various kinds of food and, therefore, is a constituent of a human diet.[31,32] Interestingly, the concentration of KYNA varies significantly among analyzed food products. As can be seen in Table 6, content of KYNA in a majority of analyzed vegetables is higher in comparison to content of KYNA in various kinds of meat. Nevertheless, it is honey that contains the highest concentration of KYNA among all analyzed food products. It is also worth noting that KYNA content in broccoli is very high. Both honey and broccoli are believed to possess pro-health properties. On the other hand, high concentration of KYNA was found in potato and potato related food products, such as French fries or crisps, which are not commonly thought of as healthy food. Further research by Turski et al[27] indicated that the content of KYNA in potatoes may depend on variety of a potato.

Table 6. Content of KYNA in food products.

Food products	KYNA [µg/g wet weight]	Average consumption* [g wet weight]	KYNA intake [µg/day]
Red paprika	0.001	100	0.1
Apple	0.002	150	0.3
Sunflower oil	0.003	100	0.3
Beef	0.003	100	0.3
Pork	0.004	100	0.4
Cucumber	0.004	100	0.4
Sweet potato	0.005	100	0.5
Egg	0.005	70	0.35
Rice	0.006	100	0.6
Tomato	0.006	150	0.9
Carrot	0.007	50	0.35
Wheat flour	0.007–0.008	100	0.7–0.8
Hard cheese	0.008	50	0.4
Pea	0.009	100	0.9
Corn (maize)	0.016	100	1.6
Milk	0.017	200	3.4
Onion	0.023	50	1.15
Cauliflower	0.047	100	4.7
Crisps	0.060–0.157	30	1.8–4.7
French fries	0.035–0.160	100	3.5–16.0
Broccoli	0.418	100	41.8
Potato	0.040–0.648	100	4.0–64.8
Honey	0.179–0.877	10	1.79–8.77

Notes: All data on KYNA content in food products are from ref.[31,32] *Average consumption stands for a hypothetical quantity of a certain product that an average human being consumes in one day.

An average KYNA intake from food was calculated based on KYNA content in a gram of wet weight of a certain food product multiplied by an average consumption of a certain food product. The summary of results is shown in Table 6. Based on our estimation, the highest amount of KYNA delivered to the human body with food comes from broccoli. It should be noted, however, that the boiling procedure lowered KYNA content in broccoli by 88%.[31] High amounts of KYNA can be delivered with potatoes. This depends mainly on variety of potato and amount of consumed vegetable as boiling does not significantly affect KYNA content in potatoes.[31] Conversely, consumption of rice and maize delivers remarkably lower amounts of KYNA.

KYNA in Herbs

Research conducted by Turski et al indicates that analyzed herbs contain significant amounts of KYNA.[47] Interestingly, herbs seem to contain more KYNA than ordinary food products (Tables 6 and 7). Bearing in mind the fact that the use of herbs is beneficial for health, it might be suggested that KYNA may be partially responsible for their beneficial effects. As can be seen in Table 7, St. John's wort, nettle leaf, birch leaf, elderberry flower, and peppermint leaf contain the highest concentrations of KYNA among all analyzed herbs. All of them are regarded as herbal medicines when it comes to the digestive system. They are believed to possess protective and healing properties.

Table 7. Content of KYNA in herbs.

Herb	KYNA [μg/g dry weight]	KYNA intake [μg/day]*	References
Dandelion root	0.05	0.46	27,76
Willow bark	0.26	0.78	27,76
Nettle root	nd	1.08	47
Mullein flower	nd	2.44	47
Lime flower	nd	4.24	47
Common mallow flower	nd	5.98	47
Bean pericarp	0.57	8.51	27,76
Matricaria flower	nd	10.17	47
Strawflower	nd	10.74	47
Meadowsweet herb	nd	13.27	47
Horsetail herb	2.27	13.61	27,76
Peppermint leaf	3.82	19.50–22.91	27,47,76
Elderberry flower	1.73	20.74–31.1	27,47,76
Birch leaf	2.68	24.15	27,76
Nettle leaf	2.71	24.37–32.50	47
St. John's wort	nd	32.60	47

Notes: *KYNA intake stands for a maximum recommended daily dose according to producers' guidelines multiplied by KYNA content in a g wet weight of a certain herb.
Abbreviation: nd, no data.

Summary

Reviews of available data suggest that KYNA is present in the lumen of the digestive system in high concentration. Furthermore, KYNA is both produced in the human body from tryptophan as well as absorbed by it from various food and herbs. It can be also produced by gut flora. Numerous researchers suggest that KYNA may play a significant role in the functioning of the digestive system. Interestingly, recent studies indicate that KYNA may possess therapeutic properties when used to treat diseases of the gastrointestinal tract.

Nevertheless, numerous questions still need to be answered. No scientific data exists detailing KYNA excretion levels with feces. Furthermore, the ability of intestinal bacteria to produce KYNA and its subsequent production levels must be investigated. Moreover, existence of KYNA enterohepatic circulation also requires study as KYNA is excreted in bile and can be absorbed from the intestine. Specifically, the effectiveness of absorption in various parts of the digestive system deserves further elucidation.

There is no clear data concerning an optimal daily intake of KYNA by humans and their daily demand for it. Consequently, no data details whether there is the possibility of KYNA shortage in the human organism and, if so, the outcome generated by such shortage. We recommend gastrointestinal tract diseases and states of malnutrition be thoroughly analyzed, as daily exogenous KYNA supply may not be sufficient to cover its losses through, for example, urine.

KYNA's influence on enterocytes also warrants further investigation. And finally, the role of KYNA in tumor development needs be studied.

Future studies may determine whether it is advisable to supplement KYNA to a human organism.

Acknowledgements

M.P. Turski and M. Turska are students, volunteers in the Department of Toxicology, Institute of Rural Health and the Department of Experimental and Clinical Pharmacology, Medical University, respectively.

Author Contributions

Analyzed the data: MPT, MT. Wrote the first draft of the manuscript: MPT. Contributed to the writing of the manuscript: MT, PP, JPT, GO. Agree with manuscript results and conclusions: MPT, MT, PP, JPT, GO. Jointly developed the structure and arguments for the paper: MPT, MT, PP, JPT, GO. Made critical revisions and approved final version: MPT, MT, PP, JPT, GO. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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