REVIEW ARTICLE

Role of Kynurenine Pathway Metabolites in Depression-A Review

Priyadarshini Soni[1*], Prabhat Singh[2], Lubhan Singh[3], Sokindra Kumar[4]

Abstract

Today most common psychiatric problem across the world is depression and stress is main source of ailment. According to World health organization, it will be the main cause of morbidity by 2020 in the world. Depression can critically affects the quality of life as it is characterized by many symptoms like unhappy feeling, lack of interest and pleasure, down energy, inadequacy, regret feeling, slow-down of thoughts or reduction in physical movement, speech can affects, altered appetite or sleep, sad, and increase the risk of suicide. Human body is inadequate to produce tryptophan, which is a crucial amino acid; therefore it must be required from diet. After absorption, L-tryptophan crosses the BBB (Blood-brain barrier) by non-specific L-type amino acid transporter and act as a precursor to various metabolic pathways in the central nervous system (CNS). Kynurenine is an important pathway that is associated with tryptophan (TRP) metabolism, where it develops a lot of metabolites such as 3-hydroxykynurenine (3HK), anthranilic acid (AA), kynurenic acid (KYNA), 3-hydroxyanthranilic acid (3HAA) and quinolinic acid (QUIN) known as kynurenines. It is already reported previously that disturbance in neuroprotective and neurotoxic metabolites leads to many psychiatric disorders. This review summarizes the role of the kynurenine pathway metabolites in depression.

Keywords: 3-hydroxykynurenine, 3-hydroxyanthranilic acid, Anthranilic acid, Kynurenic acid, Kynurenine pathway, Tryptophan.

Journal of Applied Pharmaceutical Sciences and Research, (2020); DOI: 10.31069/japsr.v3i3.1

Introduction

Depression

Depression is a frequent brain disorder with a variety of symptoms such as unhappy feelings, lack of interest or joy, guilty feelings, lack of dignity or satisfaction, disturbance in sleep or appetite, and suicidal thoughts.[1,2] It has been recorded that suicidal behavior in depression is a serious social health issue, which correlates to mood disorder and leads to significant disability and psychological impairment.[3-6] As per the WHO (World Health Organization) depression affects more than 300 million of people of all ages in the world and furthermore, it is the prominent cause of disability in modern society, where people tolerate it and commit suicide every year.[7,8] Previous reports suggest that more than 60% of civil and economic prices are raised mainly by depression and anxiety like brain disorders among all psychiatric problems.[9,10] Alterations of neurotransmission in brain act crucially in the growth of many neuropsychiatric disorders. In stress and infection, kynurenine pathway (KP) metabolism is activated itself which is associated to big changes in behavior; because of this, kynurenine may play a major role in etiology of neurological disorders like depression.[11]

Role of Kynurenine pathways (KP) in depression (including different metabolites)

The KP is a large metabolic pathway for essential amino acid (EAA) L-tryptophan (TRP), which induced in stress condition or immune activation; also it is responsible for degeneration of tryptophan, which contains many neuroactive metabolites known as "kynurenines" that affects brain function.[12-17] Previously, it was found that an increased level of KP metabolites in plasma and cerebrospinal fluid (CSF) is related to the onset of depression.[18-20] It has been recorded that atypical concentration of kynurenine in many brain diseases affects the tryptophan and serotonin levels.[21] Kynurenine and serotonin are key signaling particles in the immune response.[22-25] Lots of kynurenine are generated on serotonin damage in the inflammatory response,[26,27] which ultimately result in behavioral alteration including constant sadness, lack of interest and low energy levels.[28] Glutamate is a simple amino acid act as an excitatory neurotransmitter in the central nervous system (CNS).[29,30] In a study, it is recorded that pyridine-2, 3-dicarboxylic acid produced during neuronal excitation is a major component of kynurine pathway. Quinolinic acid (QUIN) has been recognized as an endogenous, selective agonist of N-methyl-D-aspartate (NMDA) receptors and it is well known to generate axon-sparing excitotoxicity in CNS. Over-excitation of NMDA receptors plays a crucial role in the etiology of neurodegenerative disorders.[31,32] Thus, metabolic alteration in the KP may create numerous biological responses in depression. Increasing data has been gathered regarding activation of the KP and at the beginning of the depression.[33-35]

Role of tryptophan (TRP) metabolism in brain disorder (Depression)

Tryptophan (TRP) is one of 9 essential amino acid obtained from an external source (diet) as human body does not synthesize itself and its required dose is 3.5 mg per kg body weight per day, and

[1]Research Scholar, Kharvel Subharti College of Pharmacy, Swami Vivekanand, Subharti University, Meerut-250005

[2]Assistant Professor, Kharvel Subharti College of Pharmacy, Swami Vivekanand, Subharti University, Meerut-250005

[3]Associate Professor, Kharvel Subharti College of Pharmacy, Swami Vivekanand, Subharti University, Meerut-250005

[4]Professor, Kharvel Subharti College of Pharmacy, Swami Vivekanand, Subharti University, Meerut-250005

Corresponding Author: Ms. Priyadarshini Soni, Research Scholar, Kharvel Subharti college of Pharmacy, NH-58, Meerut (UP) 250005, INDIA, Email: priyadarshiniverma2013@gmail.com

How to cite this article: Soni P., Singh P., Singh L., Kumar S.. Role of Kynurenine Pathway Metabolites in Depression-A Review. Journal of Applied Pharmaceutical Sciences and Research. 2020; 3(3):1-6

Source of support: Nil

Conflict of interest: None

the rich sources are chocolate, eggs, fish, dairy products, legumes, and meat.[36-38] Tryptophan is considered a substrate for producing different bioactive molecules with important physiological roles. Tryptophan is converted to serotonin (5-Hydroxytryptamine), which is a neurotransmitter contribute to adaptive response in central nervous system (CNS) also correlate to change in mood, anxiety etc. After this, serotonin is transformed into N-acetyl serotonin (NAS) and melatonin with biological activity for tryptophan metabolites.[39] Tryptophan has been recorded to metabolize through KP and produces various metabolites, which is responsible for inflammation, immune response and excitatory neurotransmission. 3-Hydroxykynurenine (3HK), anthranilic acid (AA), kynurenic acid (KYNA), 3-hydroxyanthranilic acid (3HAA) and quinolinic acid (QUIN) are the different metabolites produced by kynurenine pathway described as chemical identities mutually called as kynurenines, coordinated to so many psychological and mental illness like depression and schizophrenia.[40] Kynurenines declines in CNS in different cells as quinolinic acid (QUIN) and N-methyl-D aspartate receptor (NMDAR) agonist are produced by microglia and kynurenic acid (KYNA) is produced by astrocytes etc.[41] Dysregulation of these two metabolites lead to major depressive disorder.[42] It has been recorded that the tryptophan (TRP)-Kynurenine (KYN) pathway has been performing a crucial role in the beginning of depression.

Kynurenine Pathway

At first, in a catabolic step, tryptophan is oxidized by breaking of the indole-ring, by enzyme tryptophan 2,3- dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO-1 or IDO-2) to form kynurenine.[43] Hypothalamic pituitary adrenal (HPA) axis is activated by stress which causes the release of glucocorticoids from the adrenals which leads to introduction of TDO, simultaneously activate the intracellular glucocorticoid receptors (GR). Tryptophan is metabolized into kynurenine by TDO. It is further changed into kynurenic acid (KYNA) by the enzyme Kynurenine aminotransferase (KAT)/3-Hydroxykynurenine by kynurenine monooxygenase (KMO). Now by the enzyme kynureninase (KYNU), 3-Hydroxykynurenine is again metabolized to form anthranilic acid (AA) or 3-hydroxyanthanilic acid because of this acetyl CoA or unstable intermediate, 2-amino-3-carboxymuconate get accelerated by 3-hydroxyanthranilic acid 3, 4-dioxygenase (3-HAO) enzyme. A 2-Amino-3-carboxymuconate metabolite is again transformed to picolinic acid now it is nonenzymatically converted

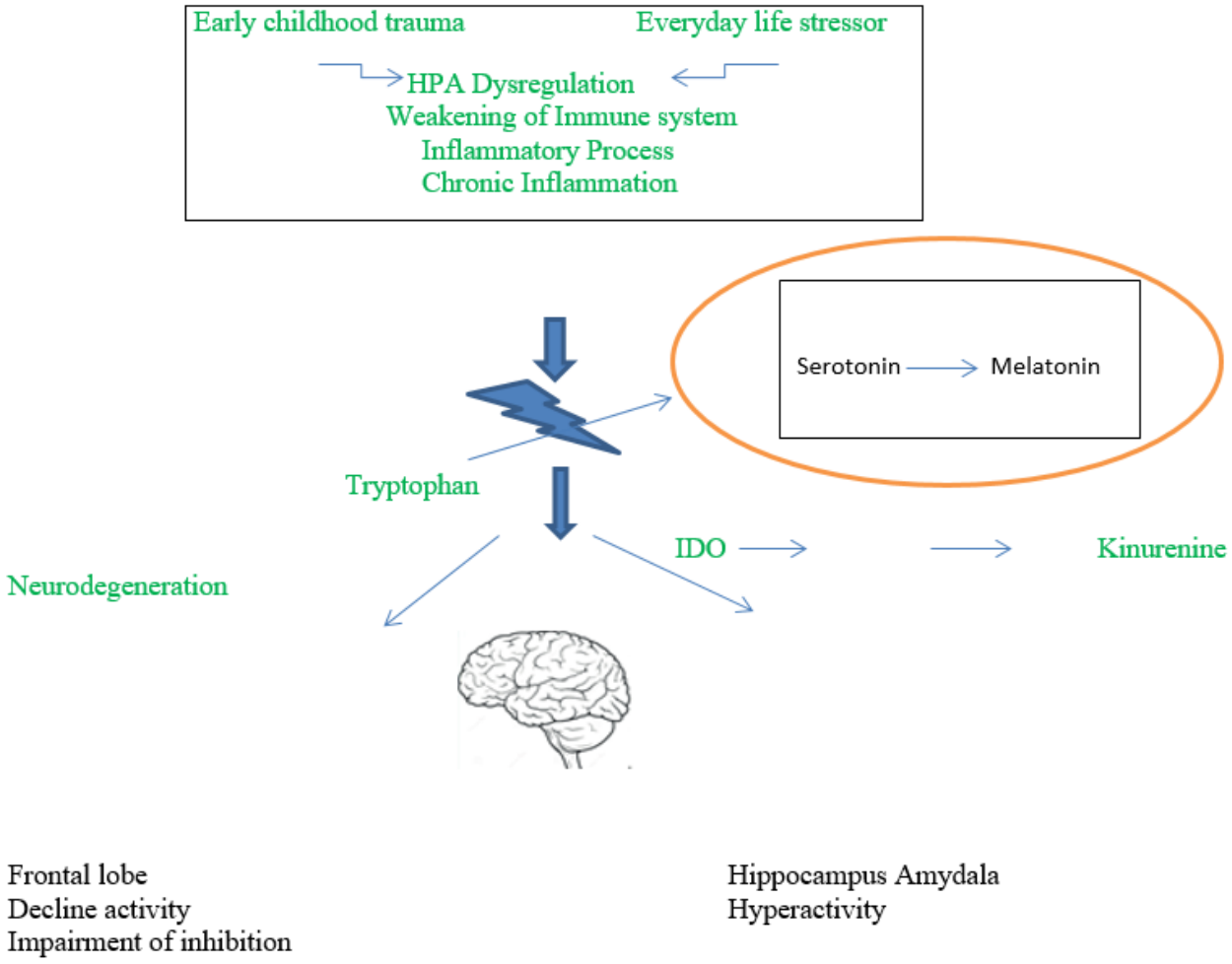

Figure 1: Neurodevelopmental theory of depression

to quinolinic acid for end-point metabolite nicotinamide adenine dinucleotide (NAD).[44-46] Sympathoadrenal medullary (SAM) arrangement with b-adrenergic receptor may activate the IDO to hit the stress, which results in the release of proinflammatory cytokines. Kynurenine pathway (KP) is sectioned in astrocytes and microglia in the brain; astrocytes produces KYNA, which have neuroprotective activity in the CNS. When tryptophan is metabolized in microglia it increases the reactive oxidative properties and contributes to excitotoxicity or neurotoxicity.[47-49]

Kynurenic Acid (KYNA)

Kynurenic acid (KYNA) is an internal tryptophan metabolite that is produced along with the KP and exerting anticonvulsant and neuroprotective activities in the brain.[50] KYNA strongly controls dopaminergic and glutamatergic neurotransmission and its high levels in brain correlated to memory impairments and psychotic symptoms.[51] KYN is changed into KYNA via transamination reaction in the presence of kynurenine aminotransferase enzyme. Mostly it is produced locally in the brain by neurons or certain glial cells like astrocytes/ oligodendrocytes after crossing the BBB.[52-54] At low concentration KYNA act upon the glycine modulatory site of the NMDA receptor and at higher concentrations, act upon glutamate site of NMDA receptors and act upon the a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors.[55,56] Previous reports suggest that KYNA stimulates orphan G protein-coupled receptor GPR35, which is expecting to lower the extracellular glutamate concentration in the brain and stop the release of pro-inflammatory cytokines by monocytes and macrophages.[57] As it increases in brain found to have sedative and anticonvulsant activity firstly and after that protect against brain ischemia.[58] Moreover, this some study reported that low level of KYNA produces serious psychiatric symptoms including suicidal and depression severity.[59-61]

Picolinic acid (PIC)

PIC is an internal metabolite[62] of L-tryptophan (TRP)[63] and a previous study reported its involvement as neuroprotective, immunological, and antiproliferative action in human body. Therefore its important physiological actions are unclear still. Chemically it is a six-member ring structure found in biological medium like cell culture supernatents, blood serum and cerebrospinal fluid (CSF), human milk, pancreatic juice etc.[64-66] PIC is produce by L-tryptophan through a secondary arm of kynurenine pathway. PIC pathway is very complicated and it is reported that change in KP metabolism participate in pathophysiology of neurodegenerative diseases of CNS.[67] A precursor metabolite, 2-amino3-carboxymuconic-6-semialdehyde (ACMS) forms picolinic acid (PIC) by the enzymatic reaction of 2-amino-3-carboxymuconic-6-semialdehyde decarboxylase (ACMSD) enzyme.[68,69] ACMSD is recognized in brain at very low rate, and PIC does not impair after formation in brain but as resulting component expelled in urine or bile in the kynurenine pathway.[70] As it is a monocarboxylic acid and it can naturally chelates iron, zinc and other metals,[71] so many clinical studies revealed the encouraging anti-depressant action of chromium picolinate complex in depression. Functions of PIC are unclear, but in general, it is recognized as nonactive

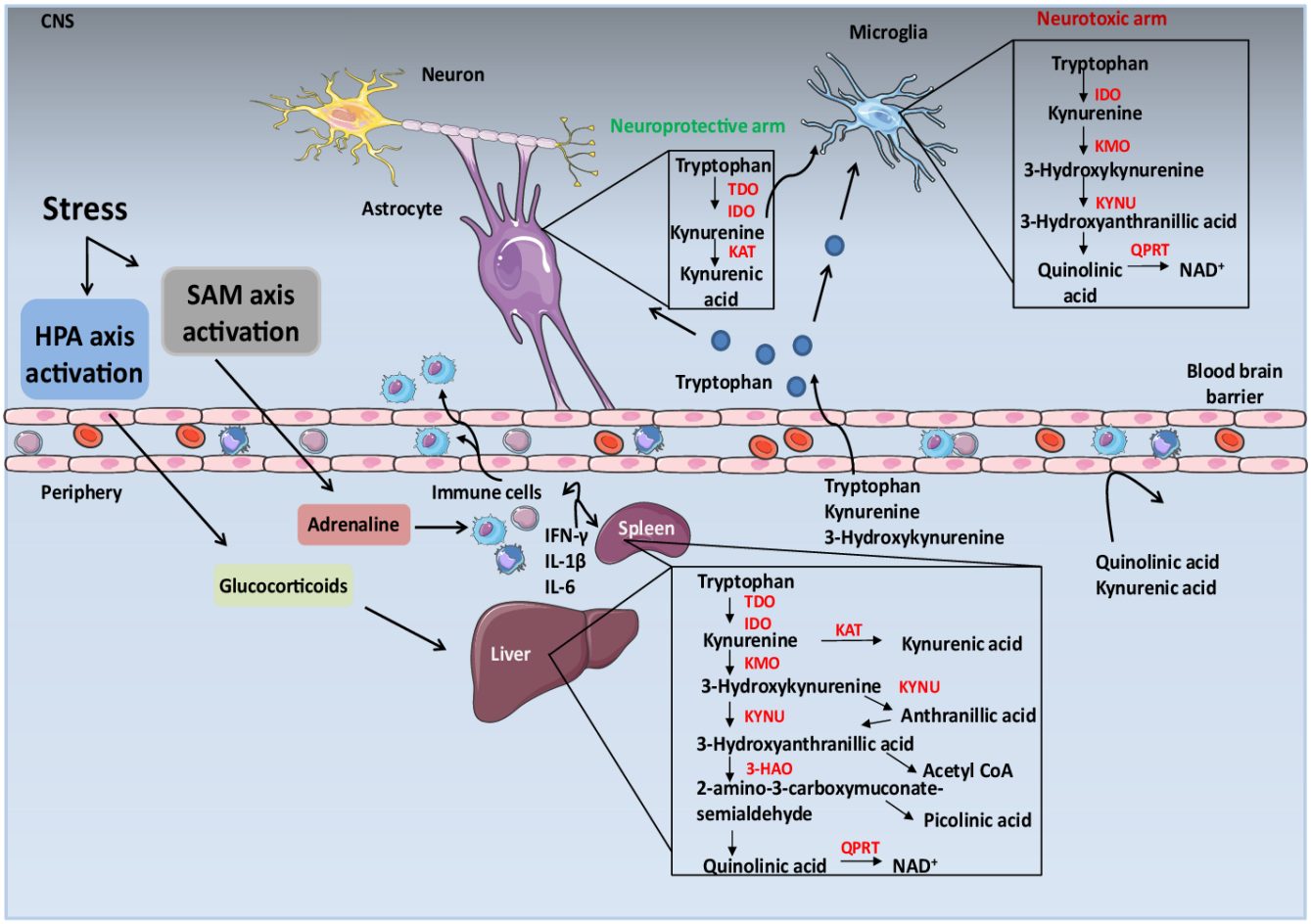

Figure 2: Role of Kynurenines in depression

component against QUIN toxicity and its decreased level found in suicide committers.

3-Hydroxyanthranilic Acid

3-Hydroxyanthranilic acid (3HAA) can be produce by the hydrolysis of 3-hydroxykyurenine (3-HK) or the oxidation of anthranilic acid in the brain. Anthranilic acid is a precursor of 3-HAA produced by kynurininase enzyme.[72] 3-HAA is very reactive molecule act as pro-oxidant or antioxidant. It is previously reported that only young patients having Major depressive disorder along with melancholic, highlighted the relation among 3-HAA/KYN.[73] In kynurenine pathway for the oxidative metabolism of TRP, there are two important compounds as QUIN and kynurenic acid, also redox-active compound 3-HAA having important activity on the nervous system and immune system, it is reported that altered level of this compound related to change in anthranilic acid level in chronic brain damage, hunting's disease, stroke and depression etc. in all these diseases there is reduce level of 3-HAA and rise in anthranilic acid level.[74]

Quinolinic acid

QUIN is recognized as one of the influential kynurenine pathway metabolite that is neurotoxic and engage in neuro-progression of depression; the word neuro-progression executes with cell death, low neuro-genesis, loss of plasticity (neuronal and synaptic), rise in immunoreactivity.[75] QUIN works as an NMDA receptor agonist, which evolves excitotoxic damage by the glutamatergic activation of neurons and astrocytes.[76] QUIN in the brain initially formed by microglia cell and after that, it reaches to macrophagial cell and as said above it is neurotoxic because it is involved in many mechanisms, one of which is as activation of glutamate N-methyl-D-aspartic acid receptors (NMDARs).[77-78] Possibly, people would be much susceptible because of high expression of these (NMDRAs) receptors raises the level of QUIN. The next mechanism of QUIN neurotoxicity is developed by the rise of glutamate release from neurons and then blockage of its uptake. After that, deterioration occurs by astrocyte, leading to high up of extracellular glutamate level overstimulation of glutamatergic system.[79] A previous study has recorded the high level of QUIN and the neurotoxic effects of which may participate in structural alteration and functional modification in patients with brain disorders.[80] As said above QUIN is excitotoxic and act as modular of oxidative stress by raising the reactive oxygen species (ROS) which lead to excitotoxicity of NMDA receptor as it produces complex with iron and afterward high up the ROS level ultimately cause cell death.[81-83] Accordingly, overactivation of NMDAR plays a crucial role in the pathophysiology of depression.[84] And a recent study revealed that the high level of QUIN correlates to depressive patient.[85] Many studies strongly suggested that QUIN participates in producing neurodegenerative diseases like huntington's disease (HD).[86]

Regulation of the KP by IDO and TDO enzymes

Roles of IDO and TDO

TDO and IDO are the rate-limiting enzymes of the KP that regulate the production of active metabolites,[87] having identical functions only. Diversity lie in substrate specificity, tissue, and cellular localization.[88] IDO is a monomeric enzyme with a broader substrate specificity, extra-hepatically found in intestinal, lung, placenta, and brain tissue.[89,90] When KP activates in microglia cause large production of neurotoxic kynurenine catabolites as QUIN also, inflammatory mediators may affect the brain structure and neuronal functions by indoleamine 2,3 dioxygenase (IDO), so pathophysiology of depression may be linked with depression. TDO is the homotetrameric enzyme present in both astrocytes and neurons in the brain. In general, TDO actions are managed by tryptophan's availability. TDO expression is regulated by GR mediated induction; therefore, stress-associated changes in expression of TDO are determined by HPA-axis through glucocorticoids. The study indicates that in depression, TDO and IDO enzymes are activated, having similarities in targets for depression.[91]

Conclusion

There are several studies that target the role of stress-promoted KP activation in many brain disorders. The main role of KP imbalance emerges in depression and also in schizophrenia. Stress is the main cause of the pathophysiology of brain disorders as it activates the KP. KP produces biologically active metabolite as QUIN, KYNA, PIC, and 3-HAA, and imbalance of these metabolites results in development of many mental illnesses. One of the metabolites (QUIN) is responsible for suicidal behavior. Enzymes involved in KP also contribute in brain diseases as recorded in study that imbalance of these enzymes appears in suicidal cases. Kynurenine pathway plays an important role in the development of brain diseases like depression.

References

1. Xiao-Jie Liua,b,*, et al., Anti-depressant effects of Xiaoyaosan on rat model of chronic unpredictable mild stress: a plasma metabonomics study based on NMR spectroscopy, January 6, 2012.
2. Serretti A et al. Depressive syndrome in major psychoses: a study on 1351 subjects. Psychiatry Res 2004.
3. Gianluca Serafini 1,2,*, et al., A Specific Inflammatory Profile Underlying Suicide Risk? systematic Review of the Main Literature Findings, 1 April 2020.
4. Bachmann, S. Epidemiology of Suicide and the Psychiatric Perspective. Int. J. Environ. Res. Public Health 2018, 15, 1425.
5. Pompili, M.; Gibiino, S.; Innamorati, M.; Serafini, G.; Del Casale, A.; De Risio, L.; Palermo, M.; Montebovi, F.; Campi, S.; De Luca, V.; et al. Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients. Psychiatry Res. 2012, 200, 389–394.
6. Pompili, M.; Shrivastava, A.; Serafini, G.; Innamorati, M.; Milelli, M.; Erbuto, D.; Ricci, F.; Lamis, D.A.; Scocco, P.; Amore, M. Bereavement after the suicide of a significant other. Indian J. Psychiatry 2013, 55, 256–263.
7. Barbora Waclawiková, Role of Microbiota and Tryptophan Metabolites in the Remote Effect of Intestinal Inflammation on Brain and Depression, 25 June 2018.
8. World Health Organization. Depression. Available online: http://www.who.int/en/news-room/factsheets/detail/depression (accessed on 20 June 2018).
9. Piotr Gałecki, et al., Inflammatory theory of depression, 2018.
10. Sousa de RT, Zanetti MV, Brunoni AR, Machado-Vieira R. Challenging treatment-resistant major depressive disorder: A roadmap for improved therapeutics. Curr. Neuropharmacol. 2015; 13(5): 616–635.
11. Ludmila A. Kasatkina1, et al., Vitamin D deficiency induces the excitation/inhibition brain imbalance and the proinflammatory shift, 5 December 2019, Katherine O'Farrell a, 2 December 2015.
12. Michael D. Lovelace1,2, et al., Current evidence for a Role of the Kynurenine Pathway of Tryptophan Metabolism in Multiple Sclerosis. 4 August 2016.
13. Katherine O'Farrell a, Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders, 2015.
14. Reus, G.Z., Jansen, K., Titus, S., Carvalho, A.F., Gabbay, V., Quevedo, J., 2015. Kynurenine pathway dysfunction in the pathophysiology and treatment of depression: evidences from animal and human studies. J. Psychiatr. Res. 68, 316e328.

15. Francesca M., et al., Elevated kynurenine pathway metabolism during neurodevelopment: Implications for brain and behavior, January 2017.
16. Pocivavsek, A.; Notarangelo, FM.; Wu, HQ.; Bruno, JP.; Schwarcz, R. Astrocytes as Pharmacological Targets in the Treatment of Schizophrenia: Focus on Kynurenic Acid. In: Pletnikov, M.; Waddington, J., editors. Modeling the Psychopathological Dimensions of Schizophrenia. Elsevier; San Diego, CA, USA: 2015. p. 423-443.
17. Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 2012; 13:465–477.
18. Ebrahim Haroon 1, et at., Associations among peripheral and central kynurenine pathway metabolites and inflammation in depression, 2020.
19. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. Mol Psychiatry 2010;15:393–403.
20. Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. Biol Psychiatry 2003;54:906-14.
21. Robert Schwarcz1, et al., The kynurenine pathway and the brain: challenges, controversies and promises, January 2017.
22. BarboraWaclawiková, et al., Role of Microbiota and Tryptophan Metabolites in the Remote Effect of Intestinal Inflammation on Brain and Depression, 25 June 2018.
23. Le Floc'h, N.; Otten, W.; Merlot, E. Tryptophan Metabolism, from Nutrition to Potential Therapeutic Applications. Amino Acids 2011, 41, 1195–1205.
24. Nguyen, N.T.; Nakahama, T.; Le, D.H.; Van Son, L.; Chu, H.H.; Kishimoto, T. Aryl Hydrocarbon Receptor and Kynurenine: Recent Advances in Autoimmune Disease Research. Front. Immunol. 2014, 5, 551.
25. O'Mahony, S.M.; Clarke, G.; Borre, Y.E.; Dinan, T.G.; Cryan, J.F. Serotonin, Tryptophan Metabolism and the Brain-Gut-Microbiome Axis. Behav. Brain Res. 2015, 277, 32–48.
26. Keszthelyi, D.; Troost, F.J.; Jonkers, DM; van Donkelaar, E.L.; Dekker, J.; Buurman, W.A.; Masclee, A.A. Does Acute Tryptophan Depletion Affect Peripheral Serotonin Metabolism in the Intestine? Am. J. Clin. Nutr. 2012, 95, 603–608.
27. Gál, E.M.; Sherman, A.D. L-Kynurenine: Its Synthesis and Possible Regulatory Function in Brain. Neurochem. Res. 1980, 5, 223–239.
28. Catena-Dell'Osso, M.; Rotella, F.; Dell'Osso, A.; Fagiolini, A.; Marazziti, D. Inflammation, Serotonin and Major Depression. Curr. Drug Targets 2013, 14, 571–577.
29. Stone TW. Cortical pyramidal tract interneurones and their sensitivity to L-glutamic acid. J Physiol. 1973; 233:211–225. [PubMed: 4357199]
30. Stone TW. Blockade by amino acid antagonists of neuronal excitation mediated by the pyramidal tract. J Physiol. 1976; 257:187–198.
31. Perkins MN, Stone TW. Quinolinic acid: regional variations in neuronal sensitivity. Brain Res. 1983b; 259:172–176.
32. Stone TW, Perkins MN. Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. Eur J Pharmacol. 1981; 72:411–412.
33. Masashi Sakurai1, et al., Serum Metabolic Profiles of the Tryptophan-Kynurenine Pathway in the high risk subjects of major depressive disorder, 2020.
34. Gál, E. M. & Sherman, A. D. Synthesis and Metabolism Of L-Kynurenine In Rat Brain. Journal of Neurochemistry 30, 607–613.
35. Lapin, I. P. Kynurenines as probable participants of depression. Pharmakopsychiatrie und Neuropsychopharmakologie 6, 273–279 (1973).
36. Igor Cervenka, Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health, 11 March 2020.
37. T. Canli, K. P. Lesch, Long story short: The serotonin transporter in emotion regulation and social cognition. Nat. Neurosci. 10, 1103–1109 (2007).
38. N. R. Council, Recommended Dietary Allowances: 10th Edition (The National Academies Press, Washington, DC, 1989).
39. C. A. Yates, J. Herbert, Differential circadian rhythms in pineal and hypothalamic 5-HT induced by artificial photoperiods or melatonin. Nature 262, 219–220 (1976).
40. Y. Chen, G. J. Guillemin, Kynurenine pathway metabolites in humans: Disease and healthy states. Int. J. Tryptophan Res. 2, 1–19 (2009).
41. G. J. Guillemin, G. Smythe, O. Takikawa, B. J. Brew, Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. Glia 49, 15–23 (2005).
42. N. Müller, M. J. Schwarz, The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. Mol. Psychiatry 12, 988–1000 (2007).
43. Mándi Y, Vécsei L. The kynurenine system and immunoregulation. J Neural Transm. 2012;119:197–209.
44. Abdulla A.-B. Badawy, Kynurenine pathway and human systems, 2020.
45. Vecsei, L., Szalardy, L., Fulop, F., Toldi, J., 2013. Kynurenines in the CNS: recent advances and new questions. Nat. Rev. Drug Discov. 12, 64e82.
46. Lugo-Huitron, R., Ugalde Muniz, P., Pineda, B., Pedraza-Chaverri, J., Rios, C., Perez-de la Cruz, V., 2013.Quinolinic acid: an endogenous neurotoxin with multiple targets. Oxid. Med. Cell. Longev. 2013, 104024.
47. Elenkov, I.J., Wilder, R.L., Chrousos, G.P., Vizi, E.S., 2000. The sympathetic nerveean integrative interface between two supersystems: the brain and the immune system. Pharmacol. Rev. 52, 595e638.
48. Guillemin, G.J., Smith, D.G., Smythe, G.A., Armati, P.J., Brew, B.J., 2003a. Expression of the kynurenine pathway enzymes in human microglia and macrophages.
49. Guillemin, G.J., Kerr, S.J., Smythe, G.A., Smith, D.G., Kapoor, V., Armati, P.J., Croitoru, J., Brew, B.J., 2001. Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. J. Neurochem. 78, 842e853.
50. Carpenedo R, Chiarugi A, Russi P, et al. Inhibitors of kynurenine hydroxylase and kynureninase increase cerebral formation of kynurenate and have sedative and anticonvulsant activities. Neuro Science. 1994;61:237–43.
51. Erhardt, S., Olsson, S.K., Engberg, G., 2009. Pharmacological manipulation of kynurenic acid: potential in the treatment of psychiatric disorders.
52. Du, F., Schmidt, W., Okuno, E., Kido, R., Kohler, C., Schwarcz, R., 1992. Localization of kynurenine aminotransferase immunoreactivity in the rat hippocampus. J. Comp. Neurol. 321, 477e487.
53. Wejksza, K., Rzeski, W., Okuno, E., Kandefer-Szerszen, M., Albrecht, J., Turski, W.A., 2005. Demonstration of kynurenine aminotransferases I and II and characterization of kynurenic acid synthesis in oligodendrocyte cell line (OLN-93). Neurochem. Res. 30, 963e968.
54. Elena Y, et al., Kynurenine pathway metabolites and suicidality, 2015.
55. Stone TW. Neuropharmacology of quinolinic and kynurenic acids. Pharmacol Rev. 1993;45:309–79.
56. Stone TW, Addae JI. The pharmacological manipulation of glutamate receptors and neuroprotection. Eur J Pharmacol. 2002;447:285–96.
57. Stone, T.W., Stoy, N., Darlington, L.G., 2013. An expanding range of targets for kynurenine metabolites of tryptophan. Trends Pharmacol. Sci. 34, 136e143.
58. Moroni, F., Cozzi, A., Sili, M., Mannaioni, G., 2012. Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery. J. Neural Transm. 119, 133e139.
59. Carpenedo R, Chiarugi A, Russi P, et al. Inhibitors of kynurenine hydroxylase and kynureninase increase cerebral formation of kynurenate and have sedative and anticonvulsant activities. Neuro Science. 1994;61:237–43.
60. Bay-Richter, C., Linderholm, K.R., Lim, C.K., Samuelsson, M., Traskman-Bendz, L., Guillemin, G.J., Erhardt, S., Brundin, L., 2015. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. Brain Behav. Immun. 43, 110e117.
61. Yiquan Chen1, et al., Kynurenine Pathway Metabolites in Humans: Disease and Healthy States, 2010.
62. Jhamandas K, Boegman RJ, Beninger RJ, Bialik M. Quinolinateinduced cortical cholinergic damage: modulation by tryptophan metabolites. Brain Res. 1990;529:185–91.
63. R.S. Grant1,2, et al., The Physiological Action of Picolinic Acid in the Human Brain, 2009.
64. Dazzi, C, Candiano G, Massazza S, Ponzetto A, Varesio L. New highperformance liquid chromatographic method for the detection of picolinic acid in biological fl uids. J Chromatogr. 2001;751:61–8.

65. Smythe GA, Braga O, Brew BJ, et al. Concurrent Quantifi cation of Quinolinic, Picolinic, and Nicotinic Acids Using Electron-Capture Negative-Ion Gas Chromatography Mass Spectrometry. Anal Biochem. 2002;301:21–6.
66. Rebello T, Lonnerdal B, Hurley LS. Picolinic acid in milk, pancreatic juice, and intestine: inadequate for role in zinc absorption. Am J Clin Nutr. 1982;35:1–5.
67. Peters JC. Tryptophan nutrition and metabolism: an overview. Adv Exp Med Biol. 1991;294:345–58.
68. Coggan, S.E., Smythe, G.A., Bilgin, A., Grant, R.S., 2009. Age and circadian influences on picolinic acid concentrations in human cerebrospinal fluid. J. Neurochem. 108, 1220e1225.
69. Wang, X., Davis, I., Liu, A., Miller, A., Shamsi, SA, 2013. Improved separation and detection of picolinic acid and quinolinic acid by capillary electrophoresis-mass spectrometry: application to analysis of human cerebrospinal fluid. J. Chromatogr. A 1316, 147e153.
70. Guillemin, G.J., Cullen, K.M., Lim, C.K., Smythe, G.A., Garner, B., Kapoor, V., Takikawa, O., Brew, B.J., 2007. Characterization of the kynurenine pathway in human neurons. J. Neurosci. Off. J. Soc. Neurosci. 27, 12884e12892.
71. Jhamandas K, Boegman RJ, Beninger RJ, Bialik M. Quinolinateinduced cortical cholinergic damage: modulation by tryptophan metabolites. Brain Res. 1990;529:185–91.
72. Baran, H., Schwarcz, R., 1990. Presence of 3-hydroxyanthranilic acid in rat tissues and evidence for its production from anthranilic acid in the brain. J. Neurochem. 55, 738e744.
73. Goldstein, L.E., Leopold, M.C., Huang, X., Atwood, C.S., Saunders, A.J., Hartshorn, M., Lim, J.T., Faget, K.Y., Muffat, J.A., Scarpa, R.C., Chylack Jr., L.T., Bowden, E.F., Tanzi, R.E., Bush, A.I., 2000. 3-Hydroxykynurenine and 3-hydroxyanthranilic acid generate hydrogen peroxide and promote alpha-crystallin cross-linking by metal ion reduction. Biochemistry 39, 7266e7275.
74. L. Gail Darlington1, et al., On the Biological Importance of the 3-hydroxyanthranilic Acid: Anthranilic Acid Ratio
75. Berk.N, Kapczinski, F., Andreazza, A. C., Dean, O. M., Giorlando, F., Maes, M., et al. (2011). Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 35, 804–817.
76. Zhou, X., Hollern, D., Liao, J., Andrechek, E., and Wang, H. (2013). NMDA receptor-mediated excitotoxicity depends on the coactivation of synaptic and extrasynaptic receptors. Cell Death Dis. 4, 1–11.
77. Espey, M.G., Chernyshev, O.N., Reinhard Jr., J.F., Namboodiri, M.A., Colton, C.A., 1997. Activated human microglia produce the excitotoxin quinolinic acid. Neuroreport 8, 431e434.
78. Heyes, M.P., Achim, C.L., Wiley, C.A., Major, E.O., Saito, K., Markey, S.P., 1996. Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. Biochem. J.320 (Pt 2), 595e597.
79. Guillemin, G.J., 2012b. Quinolinic acid: neurotoxicity. FEBS J. 279, 1355.
80. van Heeringen, K., Bijttebier, S., Desmyter, S., Vervaet, M., Baeken, C., 2014. Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinatebased meta-analysis of structural and functional MRI studies. Front. Hum. Neurosci. 8, 824.
81. Kubicova, L., Hadacek, F., and Chobot, V. (2013). Quinolinic acid: neurotoxin or oxidative stress modulator? Int. J. Mol. Sci. 14, 21328–21338.
82. Stipek, S., Stastny, F., Platenik, J., Crkovska, J., Zima, T., 1997. The effect of quinolinate on rat brain lipid peroxidation is dependent on iron. Neurochem. Int. 30, 233e237.
83. Goda, K., Kishimoto, R., Shimizu, S., Hamane, Y., Ueda, M., 1996. Quinolinic acid and active oxygens. Possible contribution of active oxygens during cell death in the brain. Adv. Exp. Med. Biol. 398, 247e254.
84. Abdallah, C.G., Sanacora, G., Duman, R.S., Krystal, J.H., 2015. Ketamine and rapidacting anti-depressants: a window into a new neurobiology for mood disorder therapeutics. Annu. Rev. Med. 66, 509e523.
85. Steiner, J., Walter, M., Gos, T., Guillemin, G. J., Bernstein, H. G., Sarnyai, Z., et al. (2011). Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? Neuroinflammation 8, 1–9.
86. Whetsell WO Jr, Schwarcz R. Prolonged exposure to submicromolar concentrations of quinolinic acid causes excitotoxic damage in organotypic cultures of rat corticostriatal system. Neurosci Lett. 1989;97:271–5.
87. Badawy, A.A.-B., Evans, M., 1976b. Animal liver tryptophan pyrrolases – absence of apoenzyme and of hormonal induction mechanism from species sensitive to tryptophan toxicity. Biochem. J. 158, 79–88.
88. Ball, H.J., Jusof, F.F., Bakmiwewa, S.M., Hunt, N.H., Yuasa, HJ, 2014. Tryptophancatabolizing enzymes e party of three. Front. Immunol. 5, 485.
89. Forouhar, F., Anderson, J.L., Mowat, C.G., Vorobiev, S.M., Hussain, A., Abashidze, M., Bruckmann, C., Thackray, S.J., Seetharaman, J., Tucker, T., Xiao, R., Ma, L.C., Zhao, L., Acton, T.B., Montelione, G.T., Chapman, S.K., Tong, L., 2007. Molecular insights into substrate recognition and catalysis by tryptophan 2,3-dioxygenase. Proc. Natl. Acad. Sci. U. S. A. 104, 473e478.
90. Stone, T.W., 1993. Neuropharmacology of quinolinic and kynurenic acids. Pharmacol. Rev. 45, 309e379.
91. Yanjie Qin1, et al., IDO and TDO as a potential therapeutic target in different types of depression, 2018