1-2024

The Neurochemistry of Depression: The Good, The Bad and The Ugly

Kami Pearson

Kimberley Beier

Thornton Mardis

Bryan Munoz

Asma Zaidi

The Neurochemistry of Depression: The Good, The Bad and The Ugly

by Kami Pearson, MS, Kimberley Beier, BS, Thornton Mardis, MA, Bryan Munoz, MS & Asma Zaidi, PhD

Kansas City University

This article reviews the various metabolites generated in the competing pathways of tryptophan metabolism including the kynurenine pathway.

Kami Pearson, MS, is a Research Associate, **Kimberley Beier, BS,** Thornton Mardis, MA, and Bryan Munoz, MS, are medical students, and Asma Zaidi, PhD, (pictured), is a Professor of Biochemistry. All are at Kansas City University, Kansas City, Missouri.

Abstract

A large constellation of experimental evidence suggests that neuroinflammation is involved in the onset of depression and neurodegenerative disorders. Many studies have shown impairments in tryptophan metabolism, the major pathway for the synthesis of serotonin, the mood regulating neurotransmitter. This article reviews the various metabolites generated in the competing pathways of tryptophan metabolism including the kynurenine pathway. Increased synthesis of the neurotoxic compound quinolinic acid occurs at the expense of the synthesis of the neuroprotective metabolite kynurenic acid. This shift in equilibrium plays a critical role in the induction of oxidative stress, neuroinflammation, and neurotoxicity. Sufficient protein intake with adequate amounts of tryptophan along with dietary antioxidants and flavonoids may offer protection against major depressive and neurodegenerative disorders.

Depression

Depression, aka major depressive disorder (MDD), is recognized as a leading cause of disability worldwide, with 350 million people affected as of 2019, an increase of 18% over the last decade.[1] Approximately one in five individuals will experience a major depressive episode during their lifetime. Women are affected by depression at rates nearly twice that of men.[2] The economic burden of MDD, estimated at $236 billion in 2010, showed a steep 40% increase to $326 billion in 2018.[3] Depression occurs on a spectrum and is a complex disorder with a wide array of symptoms and clinical features that may require unique treatments. Clinical presentations include depressed mood, anhedonia, insomnia, appetite or weight changes, anergia, psychomotor or neurocognitive dysfunction, and most notably, suicidal ideation.[2] Over the last decade, major advancements have been made in elucidating the etiology of depression. The role of serotonin continues to be studied, and inflammation is now understood as a major player in the development of depression. It is clear that depression is a heterogeneous disease, with distinct biochemical features underlying each subtype. Emerging new evidence challenges existing assumptions of the key players that contribute to the development of depression and the severity of symptoms.

Tryptophan Metabolism

Tryptophan, an essential amino acid, is critical in the synthesis of multiple bioactive metabolites including serotonin, kynurenine, melatonin, and vitamin B3.[4] It is important in both gastrointestinal and central nervous system (CNS) function and can be metabolized through multiple pathways.[5] In recent studies, the gut microbiota have shown significant effects on tryptophan metabolism.[6] Modulation of the gut-brain-axis is implicated in intestinal and neuropsychiatric disorders such as irritable bowel syndrome and depression.[7] Of the essential amino acids, tryptophan possesses the lowest reserve, making it vulnerable to deficiency.[8] Understanding the role of tryptophan metabolism in MDD may help uncover potential alternative therapeutic approaches for the treatment of depression. This review focuses primarily on the intricate components of tryptophan metabolism in relation to the CNS and depressive disorders, including the serotonin and kynurenine pathways. Through an analysis of novel evidence, the role of tryptophan metabolism in the biochemistry of depression can be better understood.

The Serotonin Pathway

The monoamine theory has been the leading theory of depression since the 1950s. Interestingly, a recent systematic review of serotonin's role in depression concluded that there is no consistent evidence of a direct association between depression and the famous neurotransmitter.[9] Furthermore, no evidence supports depression stemming from decreased activity or concentration of serotonin. The monoamine theory has still persisted in part due to the effectiveness of selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) in treating depression, which are effective in 70% of MDD patients. The partial effectiveness of anti-depressant medications in treating depression may indicate that serotonin does play a role, although not directly as previously believed. The monoamine theory alone is not enough to explain the heterogeneity of clinical symptoms in patients, or why symptoms can vary so much, even for a given patient.[2]

Serotonin (5-hydroxytryptamine, or 5-HT) is a well-known neurotransmitter, but still relatively poorly understood. It is a product of tryptophan metabolism, with 5-10% of tryptophan contributing to serotonin production.[10] The rate limiting enzymes in this pathway are tryptophan hydroxylase 1 (TPH1) and tryptophan hydroxylase 2 (TPH2) with the latter being found exclusively in the CNS. TPH1 and TPH2 function to convert tryptophan into 5-hydroxytryptophan which undergoes an enzymatic decarboxylation to form serotonin. Serotonin can be further metabolized to either melatonin or be converted to 5-hydroxyindoleacetic acid via the action of the enzyme monoamine oxidase (MAO), a target for monoamine oxidase inhibitors (MAOIs), therapeutic agents used to treat depression.[5]

Although serotonin is involved in many peripheral processes such as peristalsis, mucus production, blood vessel dilation, etc., its role in the CNS has been the focus of most studies. In particular, its involvement in depression and schizophrenia are the subject of intense research.[11] The major functions of serotonin include involvement in movement, mood, learning and memory, sleep and circadian rhythm, anxiety, aggressiveness, and social status.[12] The vast diversity of effects induced by serotonin is due to simultaneous effects on multiple neuronal targets and the large number of receptors expressed on a variety of cells, with differing locations, affinities, and downstream signaling pathways. 5-HT neurons in the CNS are localized to the raphe nuclei in the midbrain. These are known as the B1-B9 cell groups and provide descending serotonergic innervation to the spinal cord and medulla.[12] 5-HT neurons terminate in several major CNS regions, including the cortex, limbic system, midbrain, and hindbrain.[13] However, the enterochromaffin cells of the enteric nervous system account for approximately 90% of serotonin production.[14]

After serotonin is released from a neuron, it binds to the serotonin receptors (5-HTR). There are seven 5-HTR classes, with various subgroups, based on their structures and functions. 5-HTR_{1A} and 5-HTR_{1B} are of particular interest because of their noted involvement in the pathophysiology of MDD, bipolar disorder, schizophrenia, and anxiety disorders.[15] Once in the neuronal synapse, serotonin is taken back up by the presynaptic neuron to terminate signaling. The serotonin transporter (SERT) drives the reuptake of 5-HT

from the synaptic cleft back into presynaptic neurons via utilization of sodium and chloride gradients. The SERT is the target of many widely used medications including SSRIs and SNRIs.[16] which target serotonin and norepinephrine. The proposed mechanism of action of SSRIs is inhibition of SERT, resulting in increased extracellular serotonin levels present in the synapse.[17] SNRIs achieve faster antidepressant effects by elevating concentrations of dopamine in the forebrain.[18] As mentioned before, there is insufficient evidence supporting a direct correlation between decreased serotonin levels and depression[9,15] suggesting that the observed beneficial effects of antidepressants may include other mechanisms.

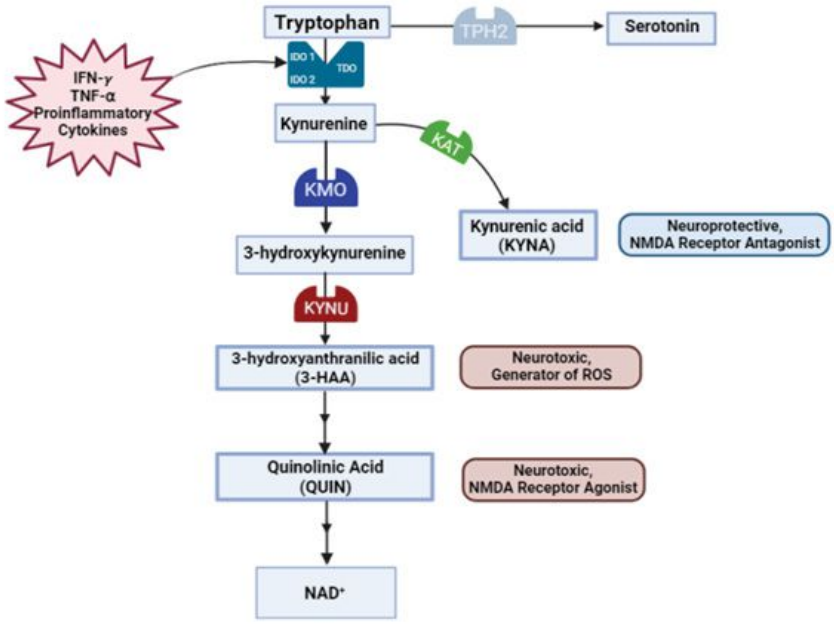

Figure 1. The Kynurenine Pathway.
The presence of pro-inflammatory cytokines results in the activation of the kynurenine pathway through the activation of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase 1 and 2 (IDO 1 and 2). Kynurenine aminotransferase (KAT) catalyzes the synthesis of kynurenic acid (KYNA) from kynurenine. Kynurenic acid is a neuroprotective agent and is an antagonist of NMDA receptors. This pathway is inhibited by IL-1β, TNF-α and IFN-γ. An alternative pathway utilizes the enzyme kynurenine 3-monooxygenase (KMO) to synthesize the intermediate 3-hydroxykynurenine. Kynureninase (KYNU) acts on 3-hydroxykynurenine to produce 3-hydroxyanthranilic acid (3-HAA), which promotes the production of hydroxyl radicals, directly causing oxidative stress. Quinolinic acid (QUIN) acts as an agonist of the NMDA receptor (NMDAR), activation of which leads to an influx of Ca^{2+} and Na^{+}. 3-HAA and QUIN are considered neurotoxic because they create excitotoxicity and induce apoptosis while decreasing synaptic plasticity.[21,22,35,41,69]
Created with BioRender.com

The Kynurenine Pathway

The predominant catabolic pathway for tryptophan in most tissues is the kynurenine pathway (KP), accounting for 90-95% of tryptophan metabolism.[5,7] Several metabolites are formed through the KP, including kynurenic acid (KYNA), quinolinic acid (QUIN), and 3-hydroxyanthranilic acid (3-HAA) (Figure 1). These molecules are the focus of ongoing research in our laboratory. The prevalence of this pathway is largely observed in the liver, brain, and in immune cells. The activation of KP is tightly regulated and dependent on tissue specific enzymes. In the liver, the prominent rate determining enzyme is tryptophan dioxygenase (TDO). While, in the brain and immune cells, the enzymes indoleamine 2-3-dioxygenase 1 (IDO1) and 2 (IDO2) are both utilized in the formation of kynurenine, the first important product in the metabolism of tryptophan.[19] Kynurenine can be further metabolized to form 3-hydroxykynurenine, anthranilic acid, or kynurenic acid through interactions with the enzymes kynurenine-3-monooxygenase (KMO), kynureninase (KYNU), and kynurenine aminotransferase (KAT), respectively. Of the possible fates of kynurenine, 3-hydroxykynurenine is the favored product. Further downstream, 3-HAA is formed from 3-hydroxykynurenine through interactions with KYNU. This product is then catabolized into QUIN, a known neurotoxin, and consequently into nicotinamide adenine dinucleotide (NAD^{+}), a molecule important for cellular energy and redox reactions.[20-22]

Inflammation

Inflammation is a biological process that allows the immune system to fight sources of infection and repair damaged tissues.[23] This is true especially in the case of chronic inflammation, where peripheral cytokines induce an array of depressive symptoms referred to as sickness behaviors.[24] The connection between chronic stress and the pathophysiology of many psychiatric disorders, including MDD, have been well documented. Clinical studies have discovered alterations in stress hormone levels, namely glucocorticoids, in depressed patients. Consequently, glucocorticoids and their receptors have been investigated as primary targets in depressive disorders.[25] Individuals diagnosed with MDD exhibit increased peripheral inflammatory biomarkers as measured in blood plasma or cerebrospinal fluid compared to healthy controls. One example of this is the positive correlation between elevated levels of a well-known multifactorial and non-specific pro-inflammatory marker, C-reactive protein (CRP) and suicide attempts in depressed patients.[26] Elevated CRP has also been shown to correlate with the severity of the depressive symptoms.[26,27] Additionally, there is a correlation between CRP and known central inflammatory biomarkers, including tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6.[26,28-30] Pro-inflammatory cytokines including TNF-α and IL-1β are known to induce neuronal serotonin reuptake.[31] Glutamate neurotransmission is greatly affected by inflammation. Glutamate secretion is increased under stress, with high levels inducing excitotoxicity; this can be exacerbated by synergistic activity between glutamate and QUIN, one of the metabolites generated in the KP.[10] This information suggests that during inflammatory states, inflammatory signaling can potentiate a depressive episode, via depleted serotonin levels and enhanced QUIN/glutamate induced excitotoxicity. Increased CRP has been associated with increased glutamate in the brain and is hypothesized to be connected to alterations in reward processing and dopamine neurotransmission. Inflammatory biomarkers mentioned above have the ability to cross the blood-brain barrier and are believed to contribute to oxidative stress, neurotoxicity, and dysregulation of glutamate levels within the brain.[30,32,33] Additionally, evidence exists that these depressive symptoms further promote the production of pro-inflammatory molecules, creating a cyclic feedback loop exacerbating symptom severity.[29]

The neuro-inflammatory hypothesis of depression emphasizes that elevated levels of inflammatory cytokines in the CNS resulting from stress-induced immune system changes contribute to depressive symptoms via neurotoxic effects and oxidative stress.[34] This newly proposed hypothesis, while still being investigated, shows promise in the field of depression research. Tissue injuries resulting from inflammation are often mediated by oxidative damage of cellular components. While reactive oxygen species (ROS) cause DNA and protein damage, antioxidants act as ROS scavengers and prevent this damage from occurring. One such compound capable of ROS scavenging is L-kynurenine. This compound not only scavenges the highly damaging hydroxyl free radicals and peroxynitrite, but also prevents DNA and protein degradation induced by oxidative stress.[35] This finding identifies the antioxidant properties of L-kynurenine as a potential target for the treatment of MDD symptoms. Conversely, studies have shown that other KP metabolites, such as 3-HAA, facilitate the formation of peroxyl free radicals which cause tissue damage. Another intermediate of this pathway, 3-hydroxykynurenine, has been shown to induce neuronal apoptosis in certain regions of the brain. It is unclear if these findings are representative of the effects of endogenous tryptophan metabolism in the pathophysiology of MDD. Several studies have shown that antidepressant medications reduce overall inflammation throughout the body. Additionally, behavioral interventions such as psychotherapy also appear to decrease inflammatory signaling.[10] While other non-pharmacological approaches, such as diet and exercise, have been recommended for years to treat symptoms of depression, the anti-inflammatory effects of such treatments are just now being understood.[36]

Kynurenines and their Clinical Relevance

Under multiple pathological states, tryptophan is catalyzed at a higher rate due to increased activation of the KP.[37] Multiple signaling molecules and pro-inflammatory cytokines activate the IDO enzymes in the brain. The major KP metabolites (kynurenic acid (KYNA), QUIN, and 3-HAA)

show a wide variety of effects on neuronal cells ranging from neuroprotective to neurotoxic. Over the last decade thanks to exciting advances in our understanding of tryptophan metabolism, numerous promising therapeutic avenues have been discovered for a wide array of pathologies including Parkinson's, Alzheimer's, tissue damage caused by ROS, MDD, HIV-related cognitive decline, and schizophrenia.[8,38,39]

Of the three compounds, KYNA and QUIN are the most widely studied and have been shown to exhibit an interesting dichotomy through direct and indirect neuroprotective and neurotoxic effects, respectively. Here we will explore the various mechanisms of action of KYNA, QUIN and 3-HAA, while discussing possible therapeutic avenues.

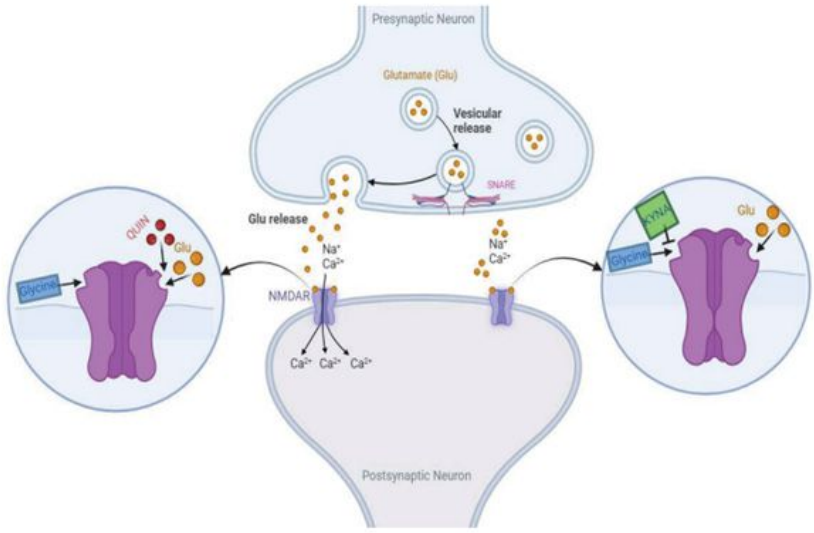

Figure 2. NMDA Receptor Activation and Inhibition by Kynurenic Acid and Quinolinic Acid.
Activation of the presynaptic neuron causes vesicular release of glutamate. Glutamate binds to the NMDA receptor (NMDAR) on a postsynaptic neuron. NMDARs are an ionotropic glutamate receptor, activation of which is responsible for an influx of Ca^{2+} and Na^{+}. Quinolinic acid (QUIN) is an NMDAR agonist and activates the receptor by binding directly to the glutamate binding site. Kynurenic acid (KYNA), an NMDAR antagonist, inhibits NMDA receptor activation by binding to the glycine-binding site. [8,39-45,49,61,64]
Created with BioRender.com.

Kynurenic Acid

Kynurenic acid (KYNA) interacts with multiple neuronal targets: the ionotropic glutamate receptors N-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR), kainate receptors (KAR), the α7 nicotinic acetylcholine receptor, the orphan G protein-coupled receptor GPR35, and the lesser known G protein-coupled receptor HCAR3.[40-43] As early as the 1980's, KYNA was discovered to act as a broad-spectrum competitive antagonist at the glutamate and glycine co-agonist binding sites on the NMDAR[44] (Figure 2). NMDARs are a ubiquitous ionotropic glutamate receptor present in all tissues but are exceptionally important in neuronal cells as they are a key player in calcium signaling. Dysregulation of the NMDA receptors result in excitotoxic effects on neurons, which has been a mechanism of cell injury implicated in many neurodegenerative diseases.[8,39,45]

KYNA also exhibits similar competitive antagonistic effects on the AMPAR, present in both pre– and post– synaptic plasma membranes and play a key role in neuronal plasticity and pathology.[46] KYNA exhibits a biphasic effect on AMPA receptors *in vitro*: low micromolar concentrations act as a positive modulator to increase AMPA activity, whereas higher millimolar concentrations exhibit antagonistic effects. Low micromolar concentration of KYNA has been proven to increase excitatory synaptic transmission, thereby providing a potential therapeutic target for learning and memory formation.[47] Less is known about the exact function of KAR but it is thought to play a role in pre– and post–synaptic signaling and plasticity.[48] More research needs to be conducted to elucidate the direct effects of KYNA–mediated antagonism of KAR.

Though these interactions are substantial, it appears the protective actions of KYNA are multifactorial, as inhibition of NMDAR and interaction with other bona fide KYNA receptors alone do not explain the metabolite's ability to protect against complex neurodegenerative and psychiatric diseases and ischemic injury.

Recent studies have shed light on many more protective effects of kynurenic acid, including a meta-analysis measuring peripheral KYNA, L-kynurenine, and QUIN levels in patients diagnosed with depression. The results revealed a statistically significant decrease in both KYNA and L-kynurenine, whereas QUIN remained stable in patients that were on antidepressants. It is still unknown whether this imbalance of the ratio between KYNA and QUIN is a causative or correlative nature of the disease. Further research is needed to determine the exact mechanism involved in the complex pathogenesis of depression.[49]

KYNA is also a potent antioxidant in the brain where it scavenges ROS that are generated in neonatal hypoxia-ischemia (HI), an unfortunate occurrence seen in approximately two to four in 1,000 live births in the US.[50] One study highlighted the possible therapeutic routes regarding this mechanism. The results of this research showed that treatment of rats with KYNA one hour post-HI significantly reduced ROS, glutathione (GSH) level, and antioxidant enzyme activity.[50] Not only is KYNA a direct antioxidant but it also acts indirectly via activation of GPR35, which in turn prevents ATP loss in post-ischemic attack via the remodeling of the mitochondrial ATP-synthase enzyme.[51]

Quinolinic Acid

Quinolinic acid (QUIN) is a biologically active intermediate of the KP, which ultimately serves as a precursor for the initiation of the NAD cycle and nicotinamide catabolism, producing niacin and NAD^+.[20,52] Interestingly, when compared with KYNA, QUIN exhibits opposite effects on cells; these effects become apparent in states of chronic inflammation. Most of the QUIN present in the CNS is produced by activated resident microglia and macrophages in response to an inflammatory extracellular environment.[53] Shifts in tryptophan metabolism leaning towards high QUIN:KYNA ratio has been correlated with many neurodegenerative and psychiatric diseases found in the US population[54].

One proposed mechanism for this is the metabolite's known effect as an NDMAR agonist (Figure 2), which has the potential to lead to increased intracellular calcium levels resulting in downstream damage of astrocytes and neurons with subsequent disruption of metabolism and induction of apoptosis.[55,56] Increased QUIN levels have also been linked to increased oxidative stress leading to lipid peroxidation. This membrane damage is modulated by interaction of QUIN with Fe^{2+} to form QUIN-Fe^{2+} complexes that mediate ROS generation.[57] Overall, it is clear that increased levels of QUIN production correlate to pathologic states. Whether this observation is completely correlative or if there is a causative effect is an exciting area of future investigation.

Disruption of tryptophan metabolism with increased activity of the KP and production of QUIN may result in deficiencies in tryptophan and the derived neurotransmitters. With the activation of microglia and macrophages in response to inflammation in the brain, QUIN may reach neurotoxic levels, which can lead to neuronal dysfunction, lipid peroxidation and cytoskeletal destabilization.[58,59] The toxicity of QUIN specifically affects neurons located in the hippocampus, striatum, and neocortex, due to the selectivity of QUIN toward NMDA receptors residing in these locations.[60]

3-Hydroxyanthranilic Acid (3-HAA)

3-Hydroxyanthranilic acid (3-HAA), a transient intermediate that contributes to the production of QUIN, has been generally overlooked when compared to other key players in the KP. Nevertheless, its acute cytotoxicity has been well documented. 3-HAA spontaneously oxidizes to form cinnabarinic acid, an unstable side product that reacts with GSH under physiologic conditions. Cinnabarinic acid is also a known agonist of both metabotropic glutamate receptor and the aryl hydrocarbon receptor.[61] 3-HAA itself has been directly implicated in apoptosis, likely due to decreased mitochondrial membrane potential and increased production of ROS.[62]

3-HAA plays a prominent role in the liver, kidneys, and brain.[20] In adolescents diagnosed with MDD, elevated levels of 3-HAA and striatal choline have been found in plasma, thus correlating neurobiological differences with clinical presentation.[63] Total striatal choline is a biomarker for cell membrane turnover, indicative of cell

death. 3-HAA has been proposed to contribute to the development of depressive symptoms via the overstimulation of NMDA receptors.[64] Additionally, neuronal atrophy resulting from free radical generation further promotes depressive symptoms. Studies have also shown that under pathological conditions, 3-HAA can induce apoptosis in neuronal cells in specific brain regions.[23] This is due to 3-HAA's ability to directly cause oxidative damage through the metabolism of 3-HAA to cinnabarinic acid and the resultant production of free radicals. Additionally, 3-HAA has been shown to decrease intracellular NAD^+ levels in human neurons and astrocytes.[65]

Conclusion

This review has summarized key aspects of the neuro-inflammatory hypothesis of depression and has highlighted the myriad of roles played by kynurenic acid (KYNA), quinolinic acid (QUIN) and 3-hydroxyanthranilic acid (3-HAA), metabolites generated in the kynurenine pathway (KP). The diverse effects of these compounds in the central nervous system, ranging from neuroprotective to neurotoxic, is indicative of a new direction in understanding the etiology of depression and identification and development of novel targets for its treatment.

References

1. Wang H, Tian X, Wang X, Wang Y. Evolution and Emerging Trends in Depression Research From 2004 to 2019: A Literature Visualization Analysis. Front Psychiatry. 2021;12:705749. doi:10.3389/fpsyt.2021.705749
2. Malhi GS, Mann JJ. Depression. Lancet. Nov 24 2018;392(10161):2299-2312. doi:10.1016/S0140-6736(18)31948-2
3. Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH, Kessler RC. The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). Pharmacoeconomics. Jun 2021;39(6):653-665. doi:10.1007/s40273-021-01019-4
4. Friedman M. Analysis, Nutrition, and Health Benefits of Tryptophan. Int J Tryptophan Res. 2018;11:1178646918802282. doi:10.1177/1178646918802282
5. Correia AS, Vale N. Tryptophan Metabolism in Depression: A Narrative Review with a Focus on Serotonin and Kynurenine Pathways. Int J Mol Sci. Jul 31 2022;23(15)doi:10.3390/ijms23158493
6. Hsu C-N, Tain Y-L. Developmental Programming and Reprogramming of Hypertension and Kidney Disease: Impact of Tryptophan Metabolism. International Journal of Molecular Sciences. 2020;21(22):8705. doi:10.3390/ijms21228705
7. Gao K, Mu CL, Farzi A, Zhu WY. Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. Adv Nutr. May 1 2020;11(3):709-723. doi:10.1093/advances/nmz127
8. Hestad K, Alexander J, Rootwelt H, Aaseth JO. The Role of Tryptophan Dysmetabolism and Quinolinic Acid in Depressive and Neurodegenerative Diseases. Biomolecules. Jul 18 2022;12(7) doi:10.3390/biom12070998
9. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular Psychiatry. 2022;doi:10.1038/s41380-022-01661-0
10. Dooley LN, Kuhlman KR, Robles TF, Eisenberger NI, Craske MG, Bower JE. The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation. Neurosci Biobehav Rev. Nov 2018;94:219-237. doi:10.1016/j.neubiorev.2018.09.006
11. De Deurwaerdere P, Di Giovanni G. Serotonin in Health and Disease. Int J Mol Sci. May 15 2020;21(10)doi:10.3390/ijms21103500
12. Bacque-Cazenave J, Bharatiya R, Barriere G, et al. Serotonin in Animal Cognition and Behavior. Int J Mol Sci. Feb 28 2020;21(5) doi:10.3390/ijms21051649
13. Berger M, Gray JA, Roth BL. The Expanded Biology of Serotonin. Annual Review of Medicine. 2009;60(1):355-366. doi:10.1146/annurev.med.60.042307.110802
14. Yano JM, Yu K, Donaldson GP, et al. Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell. 2015;161(2):264-276. doi:10.1016/j.cell.2015.02.047
15. Nautiyal KM, Hen R. Serotonin receptors in depression: from A to B. F1000Res. 2017;6:123. doi:10.12688/f1000research.9736.1
16. Yang DG, E. Illumination of serotonin transporter mechanism and role of the allosteric site. Science Advances. 2021;7:11.
17. Rudnick G, Sandtner W. Serotonin transport in the 21st century. J Gen Physiol. Nov 4 2019;151(11):1248-1264. doi:10.1085/jgp.201812066
18. Li J, Lu C, Gao Z, et al. SNRIs achieve faster antidepressant effects than SSRIs by elevating the concentrations of dopamine in the forebrain. Neuropharmacology. 2020;15(177)doi:10.1016/j.neuropharm.2020.108237
19. Savitz J. The kynurenine pathway: a finger in every pie. Mol Psychiatry. Jan 2020;25(1):131-147. doi:10.1038/s41380-019-0414-4
20. Badawy AA. Kynurenine Pathway of Tryptophan Metabolism: Regulatory and Functional Aspects. Int J Tryptophan Res. 2017;10:1178646917691938. doi:10.1177/1178646917691938
21. Braidy N, Grant R. Kynurenine pathway metabolism and neuroinflammatory disease. Neural Regen Res. Jan 2017;12(1):39-42. doi:10.4103/1673-5374.198971
22. Fallarino F, Grohmann U, Vacca C, et al. T cell apoptosis by tryptophan catabolism. Cell Death Differ. Oct 2002;9(10):1069-77. doi:10.1038/sj.cdd.4401073
23. Morita T, Saito K, Takemura M, et al. 3-Hydroxyanthranilic acid, an L-tryptophan metabolite, induces apoptosis in monocyte-derived cells stimulated by interferon-g. Ann Clin Biochem. 2001;2001(38):10.
24. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. Jan 2008;9(1):46-56. doi:10.1038/nrn2297
25. Pariante CM. Glucocorticoid receptor function *in vitro* in patients with major depression. Stress. Dec 2004;7(4):209-19. doi:10.1080/10253890500069650
26. Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. Jun 2020;25(6):1301-1311. doi:10.1038/s41380-018-0096-3
27. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: A meta-analysis. J Affect Disord. Dec 1 2020;277:940-948. doi:10.1016/j.jad.2020.09.025

28. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. Jan 2006;27(1):24-31. doi:10.1016/j.it.2005.11.006
29. Irwin MR, Wang M, Ribeiro D, et al. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry. Sep 15 2008;64(6):538-40. doi:10.1016/j.biopsych.2008.05.004
30. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. May 1 2009;65(9):732-41. doi:10.1016/j.biopsych.2008.11.029
31. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology. Oct 2006;31(10):2121-31. doi:10.1038/sj.npp.1301029
32. Ida T, Hara M, Nakamura Y, Kozaki S, Tsunoda S, Ihara H. Cytokine-induced enhancement of calcium-dependent glutamate release from astrocytes mediated by nitric oxide. Neurosci Lett. Feb 27 2008;432(3):232-6. doi:10.1016/j.neulet.2007.12.047
33. Pitt D, Nagelmeier IE, Wilson HC, Raine CS. Glutamate uptake by oligodendrocytes: Implications for excitotoxicity in multiple sclerosis. Neurology. Oct 28 2003;61(8):1113-20. doi:10.1212/01.wnl.0000090564.88719.37
34. Han KM, Ham BJ. How Inflammation Affects the Brain in Depression: A Review of Functional and Structural MRI Studies. J Clin Neurol. Oct 2021;17(4):503-515. doi:10.3988/jcn.2021.17.4.503
35. Ramirez Ortega D, Ugalde Muniz PE, Blanco Ayala T, et al. On the Antioxidant Properties of L-Kynurenine: An Efficient ROS Scavenger and Enhancer of Rat Brain Antioxidant Defense. Antioxidants (Basel). Dec 24 2021;11(1)doi:10.3390/antiox11010031
36. Kim HH, Jeong SH, Ha SE, et al. Cellular Regulation of Kynurenic Acid-Induced Cell Apoptosis Pathways in AGS Cells. Int J Mol Sci. Aug 10 2022;23(16)doi:10.3390/ijms23168894
37. Chen Y, Stankovic R, Cullen KM, et al. The kynurenine pathway and inflammation in amyotrophic lateral sclerosis. Neurotox Res. Aug 2010;18(2):132-42. doi:10.1007/s12640-009-9129-7
38. Nobis A, Zalewski D, Waszkiewicz N. Peripheral Markers of Depression. Journal of Clinical Medicine. 2020;9(12):3793. doi:10.3390/jcm9123793
39. Schwarcz R, Bruno JP, Muchowski PJ, Wu H-Q. Kynurenines in the mammalian brain: when physiology meets pathology. Nature Reviews Neuroscience. 2012;13(7):465-477. doi:10.1038/nrn3257
40. Hilmas C, Pereira EFR, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX. The Brain Metabolite Kynurenic Acid Inhibits α7 Nicotinic Receptor Activity and Increases Non-α7 Nicotinic Receptor Expression: Physiopathological Implications. J Neurosci. 2001;21(9):10.
41. Wang J, Simonavicius N, Wu X, Swaminath G, Reagan J, Tian H, Ling L. Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. J Biol Chem. Aug 4 2006;281(31):22021-22028. doi:10.1074/jbc.M603503200
42. Kapolka NJ, Isom DG. HCAR3: an underexplored metabolite sensor. Nat Rev Drug Discov. Nov 2020;19(11):745. doi:10.1038/d41573-020-00173-2
43. Elmslie KS, Yoshikami D. Effects of kynurenate on root potentials evoked by synaptic activity and amino acids in the frog spinal cord. Brain Research. 1985;330(2):7. doi:https://doi.org/10.1016/0006-8993(85)90685-7
44. Perkins MN, Stone TW. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. Brain Research. 1982;247(1):4. doi:https://doi.org/10.1016/0006-8993(82)91048-4
45. Babaei P. NMDA and AMPA receptors dysregulation in Alzheimer's disease. Eur J Pharmacol. Oct 5 2021;908:174310. doi:10.1016/j.ejphar.2021.174310
46. Zanetti L, Regoni M, Ratti E, Valtorta F, Sassone J. Presynaptic AMPA Receptors in Health and Disease. Cells. Aug 31 2021;10(9)doi:10.3390/cells10092260
47. Prescott C, Weeks AM, Staley KJ, Partin KM. Kynurenic acid has a dual action on AMPA receptor responses. Neuroscience Letters. 2006;402(1-2):4. doi:https://doi.org/10.1016/j.neulet.2006.03.051
48. Contractor A, Swanson GT, Sailer A, O'Gorman S, Heinemann SF. Identification of the Kainate Receptor Subunits Underlying Modulation of Excitatory Synaptic Transmission in the CA3 Region of the Hippocampus. The Journal of Neuroscience. 2000;20(22):9.
49. Ogyu K, Kubo K, Noda Y, et al. Kynurenine pathway in depression: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2018;90:9. doi:https://doi.org/10.1016/j.neubiorev.2018.03.023
50. Bratek-Gerej E, Ziembowicz A, Godlewski J, Salinska E. The Mechanism of the Neuroprotective Effect of Kynurenic Acid in the Experimental Model of Neonatal Hypoxia-Ischemia: The Link to Oxidative Stress. Antioxidants (Basel). Nov 5 2021;10(11)doi:10.3390/antiox10111775
51. Wyant GA, Yu W, Doulamis IP, et al. Mitochondrial remodeling and ischemic protection by G protein-coupled receptor 35 agonists. Science. Aug 5 2022;377(6606):621-629. doi:10.1126/science.abm1638
52. Fukuwatari T, Shibata K. Nutritional Aspect of Tryptophan Metabolism. International Journal of Tryptophan Research. 2013;6s1:IJTR.S11588. doi:10.4137/ijtr.s11588
53. Heyes MP, Achim CL, Wiley CA, Major EO, Saito K, Markey SP. Human microglia convert L-tryptophan into the neurotoxin quinolinic acid. Biochem J. 1996;1996(320):2.
54. Ostapiuk A, Urbanska EM. Kynurenic acid in neurodegenerative disorders-unique neuroprotection or double-edged sword? CNS Neurosci Ther. Jan 2022;28(1):19-35. doi:10.1111/cns.13768
55. Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. FEBS J. Apr 2012;279(8):1356-65. doi:10.1111/j.1742-4658.2012.08485.x
56. Lugo-Huitron R, Ugalde Muniz P, Pineda B, Pedraza-Chaverri J, Rios C, Perez-de la Cruz V. Quinolinic acid: an endogenous neurotoxin with multiple targets. Oxid Med Cell Longev. 2013;2013:104024. doi:10.1155/2013/104024
57. Sˇtípek S, Sˇtastný F, Pláteník J, Crkovská J, Zima T. The effect of quinolinate on rat brain lipid peroxidation is dependent on iron. Neurochemistry International. 1997;30(2):5. doi:https://doi.org/10.1016/S0197-0186(97)90002-4
58. Verma MK, Goel R, Nandakumar K, Nemmani KV. Bilateral quinolinic acid-induced lipid peroxidation, decreased striatal monoamine levels and neurobehavioral deficits are ameliorated by G1P receptor agonist D-Ala (2) G1P in rat model of Huntington's disease. Eur J Pharmacol. 2018;828:10.
59. Pierozan P, Pessoa-Pureur R. Cytoskeleton as a target of quinolinic acid neurotoxicity:Insight from animal models. Mol Neurobiol. 2018;55
60. Zhou Q, Sheng M. NMDA receptors in nervous system diseases. Neuropharmacology. 2013;74:6.
61. Gómez-Piñeiroa RJ, Dali M, Mansuy D, Boucher J. Unstability of cinnabarinic acid, an endogenous metabolite of tryptophan, under situations mimicking physiological conditions. Biochimie. 2022;199:7.
62. Hiramatsu R, Hara T, Akimoto H, Takikawa O, Kawabe T, Isobe K, Nagase F. Cinnabarinic acid generated from 3-hydroxyanthranilic acid strongly induces apoptosis in thymocytes through the generation of reactive oxygen species and the induction of caspase. J Cell Biochem. Jan 1 2008;103(1):42-53. doi:10.1002/jcb.21384
63. Gabbay V, Liebes L, Katz Y, et al. The Kynurenine Pathway in Adolescent Depression: Preliminary Findings from a Proton MR Spectroscopy Study. Prog Neuropsychopharmacol Biol Psychiatry. 2010 34(1):19. doi:10.1016/j.pnpbp
64. Gabbay V, Klein RG, Katz Y, et al. The possible role of the kynurenine pathway in adolescent depression with melancholic features. J Child Psychol Psychiatry. Aug 2010;51(8):935-43. doi:10.1111/j.1469-7610.2010.02245.x
65. Braidy N, Grant R, Brew BJ, Adams S, Jayasena T, Guillemin GJ. Effects of Kynurenine Pathway Metabolites on Intracellular NAD+ Synthesis and Cell Death in Human Primary Astrocytes and Neurons. International Journal of Tryptophan Research. 2009;2:9.

Disclosure

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript. **MM**