

Review

Tryptophan Metabolism in Central Nervous System Diseases: Pathophysiology and Potential Therapeutic Strategies

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[Received March 19, 2022; Revised September 15, 2022; Accepted September 16, 2022]

ABSTRACT: The metabolism of L-tryptophan (TRP) regulates homeostasis, immunity, and neuronal function. Altered TRP metabolism has been implicated in the pathophysiology of various diseases of the central nervous system. TRP is metabolized through two main pathways, the kynurenine pathway and the methoxyindole pathway. First, TRP is metabolized to kynureneine, then kynurenic acid, quinolinic acid, anthranilic acid, 3-hydroxykynureneine, and finally 3-hydroxyanthranilic acid along the kynureneine pathway. Second, TRP is metabolized to serotonin and melatonin along the methoxyindole pathway. In this review, we summarize the biological properties of key metabolites and their pathogenic functions in 12 disorders of the central nervous system: schizophrenia, bipolar disorder, major depressive disorder, spinal cord injury, traumatic brain injury, ischemic stroke, intracerebral hemorrhage, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Furthermore, we summarize preclinical and clinical studies, mainly since 2015, that investigated the metabolic pathway of TRP, focusing on changes in biomarkers of these neurologic disorders, their pathogenic implications, and potential therapeutic strategies targeting this metabolic pathway. This critical, comprehensive, and up-to-date review helps identify promising directions for future preclinical, clinical, and translational research on neuropsychiatric disorders.

Key words: central nervous system disease, depression, kynureneine pathway, methoxyindole pathway, neuroinflammation, tryptophan

1. Introduction

L-tryptophan (TRP) is an essential amino acid that must be obtained from the diet. The TRP metabolites of the kynurenine pathway (KP) or the methoxyindole pathway (MP) are involved in the biosynthesis of proteins that are

essential for neuronal construction and maintenance. These metabolites are significantly associated with the appearance, development, and outcomes of various neuropsychiatric disorders [1]. The metabolism of TRP by KP and MP is described in Figure 1. We first review changes in TRP metabolism and its pathogenic role in

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psychiatric disorders, such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) [2], and in disorders of the central nervous system (CNS), such as spinal cord injury (SCI) [3], traumatic brain injury (TBI), ischemic stroke, and intracerebral hemorrhage (ICH) [4]. Next we review the role of TRP in multiple sclerosis (MS), an autoimmune disease [5], and neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) [6]. We

also review preclinical and clinical studies published mainly since 2015 that explore TRP metabolism, its downstream metabolic molecules, relevant biomarkers, and the potential therapeutic targets of this signaling pathway. This review is pivotal, comprehensive, and up to date and provides new ideas for exploring new treatment options and identifying promising directions for future research on drug discovery of neuropsychiatric disorders.

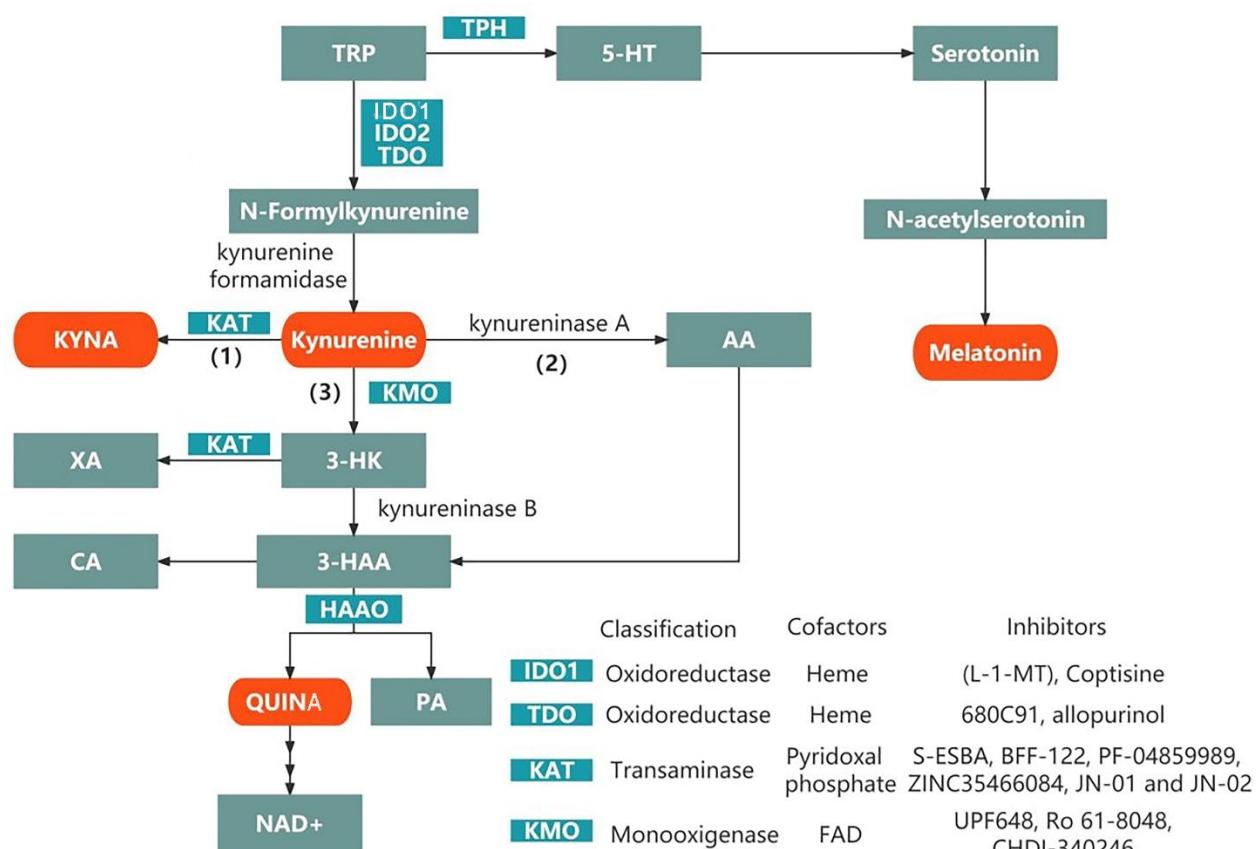


Figure 1. Tryptophan metabolism by the kynureneine and methoxyindole pathways. Kynureneine is a central KP metabolite capable of degradation through three specific pathways, shown in (1), (2) and (3) in the schematic diagram, to generate different neuroactive metabolites. Abbreviations: TRP, tryptophan; IDO, indoleamine-2,3-dioxygenase; TDO, tryptophan-2,3-dioxygenase; KAT, kynureneine aminotransferase I-III; AA, anthranilic acid; 3-HK, 3-hydroxykynureneine; 3-HAA, 3-hydroxyanthranilic acid; KMO, kynurene 3-monooxygenase; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; KP, kynureneine pathway; KYNA, kynurenic acid; PA, picolinic acid; QUINA, quinolinic acid; TPH, tryptophan hydroxylase; CA, cinnabarinic acid; XA, xanthurenic acid; NAD⁺, nicotinamide adenine dinucleotide; 5-HT, 5-hydroxytryptophan; TPH, tryptophan hydroxylase.

2. The KP

TRP is absorbed from the intestinal tract and transported to the CNS via neutral amino acid transporters on the blood-brain barrier (BBB) [7]. Under physiological conditions, more than 95% of free TRP is metabolized to kynureneine through the KP. In addition, a small portion is converted to serotonin and other metabolites [8]. The

main branches of the KP are described in Figure 2. In KP, L-kynureneine (L-KYN), anthranilic acid (AA), 3-hydroxykynureneine (3-HK), and kynurenic acid (KYNA) are formed in the brain and peripheral tissues. Peripheral kynureneine and other metabolites (excluding KYNA and 3-hydroxyanthranilic acid (3-HAA)) are involved in central KP metabolism by passing through the BBB [9, 10].

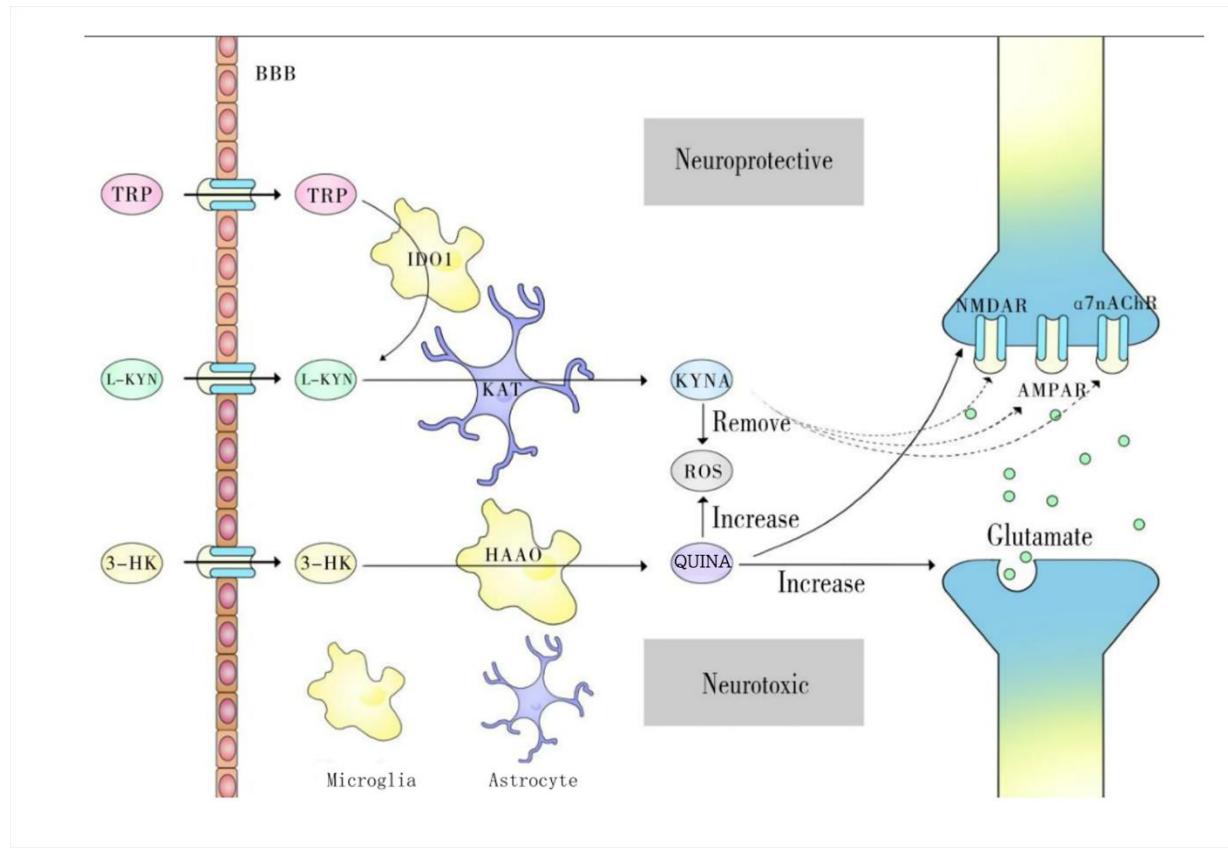


Figure 2. The main branches of the kynureneine pathway. TRP, L-KYN, and 3-HK can penetrate the BBB. Thus, they are converted to different intermediates in the extracellular space of brain tissue. TRP is converted to L-KYN by IDO1 in macrophages. L-KYN is converted to KYNA in astrocytes. 3-HK is converted to QUINA by HAAO in microglia. In diseases other than SCZ, KYNA is neuroprotective, as it can remove ROS and inhibit NMDARs, α 7nACh, and AMPARs. QUINA is neurotoxic, as it can increase ROS formation, increase glutamate production, and activate NMDARs. Abbreviations: TRP, tryptophan; 3-HK, 3-hydroxykynureneine; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; α 7nAChR: α 7 nicotinic acetylcholine receptor; AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; BBB: blood-brain barrier; IDO, indoleamine-2,3-dioxygenase; KAT, kynureine aminotransferases I-III; KMO, kynureneine 3-monooxygenase; KYNA, kynurenic acid; L-KYN, L-kynureneine; NMDAR: N-methyl-D-aspartic acid receptor; TRP, tryptophan; QUINA, quinolinic acid; SCZ, schizophrenia; ROS, reactive oxygen species

In KP, the first step is the conversion of TRP to N-formyl kynureneine by indoleamine 2,3-dioxygenase (IDO1 or IDO2) and tryptophan-2,3-dioxygenase (TDO) and then to L-KYN. IDO1 is expressed, in addition to the brain, in many other organs, such as the kidney, pancreas, and white blood cells [11]. IDO1 plays a critical pathogenic role in brain disorders when activated by proinflammatory cytokines [12], such as interferon γ (IFN- γ), interleukin-6 (IL-6), and tumor necrosis factor α (TNF- α) [13]. This effect is more prominent in women than in men [14]. Dendritic cells also express IDO1 under physiological conditions but are highly induced by traumatic, autoimmune, and neuroinflammatory diseases [15-17]. IDO1 expression has been reported to be upregulated 6 h after injury and remains elevated for up to 21 days in a controlled cortical impact model of pediatric TBI in rabbits [18]. Unlike IDO1, IDO2 is not active in TRP decomposition. Its physiological functions and roles

in disease conditions involving KP activity are not yet clear [19]. However, Lauren M F Merlo et al. showed that IDO2 plays a proinflammatory role in mediating B and T-cell activation in immune responses [20]. TDO is present mainly in the liver [21]. The peripheral system produces the majority of L-KYN (approximately 60%), but not all KYN metabolites are permeable to the brain. The rest is generated in the brain [22].

The KP pathway mainly produces two biologically active metabolites, quinolinic acid (QUINA) and KYNA. Kynureneine 3-monooxygenase (KMO) is predominantly expressed in microglia [23]. KMO converts KYN to 3-HK, which is metabolized into the potential neurotoxin QUINA [24]. These two products antagonize each other and reach a balance. Neuroprotective L-KYN has immunosuppressive properties that inhibit antigen-presenting cell (APC) activities, especially in dendritic cells [25]. Furthermore, L-KYN blocks T-cell

proliferation, upregulates programmed cell death-1, and leads to the generation of regulatory T cells [26]. Therefore, L-KYN exhibits neuroprotective and anti-inflammatory properties by regulating innate and adaptive immunity. In a model of inflammation-induced depression, KYN increased at 2 h, and KYN concentrations decreased back to baseline levels at 6 h [27]. The concentration of QUINA in the cerebrospinal fluid of adult patients with TBI increases significantly in the first 72–83 h after injury, reaching approximately 9 times the normal concentration of QUINA. KYN levels in cerebrospinal fluid from patients with severe TBI increases on Days 4 and 5 after injury, KYNA increases

on Days 2–5 after injury, and QUINA increases on Days 1–5 after injury [24]. Zakhary G et al. found that the expression of QUINA and KYNA increased at 24 and 72 h after partial frontal lobectomy in rats [28].

Three branches are involved in the metabolism of kynureneine: (1) the KYNA pathway, (2) the AA pathway, and (3) the 3-HK pathway. Next, 3-HK is converted to 3-HAA, which merges with the second metabolic pathway. Finally, 3-HAA can be converted to QUINA and eventually nicotinamide adenine dinucleotide (NAD⁺) or picolinic acid (PA) [19]. The primary metabolites in the TRP pathway are described in Table 1.

Table 1. The primary metabolites in the tryptophan pathway.

Substances	Structural formula	Functions in the Kynureneine pathway
TRP		The metabolic substrate of KP pathway
L-KYN		<ul style="list-style-type: none"> 1. Neuroprotective effect 2. Immunosuppression, inhibition of the activity of natural killer cells, APC and DC [25] 3. Blocking T-cell proliferation and upregulation of regulatory T cells [43]
KYNA		<ul style="list-style-type: none"> 1. Neuroprotective effect 2. A competitive antagonist of NMDA and AMPA [30] 3. Anti-inflammatory effect by stimulating GPR35 [34] 4. Immunosuppressive effect by activating AhR [37] 5. An antioxidant to remove ROS [31]
QUINA		<ul style="list-style-type: none"> 1. Neural excitotoxicity [6] 2. Selective activation of NMDA receptors [8] 3. ROS formation and lipid peroxidation [29] 4. BBB disruption [47] 5. Upregulation of nitric oxide synthase and increases in neurotoxicity [93]
3-HK		<ul style="list-style-type: none"> 1. The metabolite of L-KYN catalyzed by KMO 2. Neurotoxic effect 3. Producing free radicals and participating in the metabolism of oxidative stress and fat peroxidation [22]
3-HAA		<ul style="list-style-type: none"> 1. The 3-HK metabolite catalyzed by Kynureinase 2. Neurotoxic effect
AA		<ul style="list-style-type: none"> 1. The metabolite of L-KYN catalyzed by Kynureinase 2. Inhibition of 3-HAA metabolism in QUINA and PA, thus exhibiting a neuroprotective effect [161]

Abbreviations: 3-HAA: 3-hydroxyanthrenilic acid; 3-HK: 3-hydroxykynureine; AA: anthranilic acid; AhR: aryl hydrocarbon receptor; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; APC: antigen-presenting cells; BBB: blood-brain barrier; DC: dendritic cells; GPR35: G protein-coupled receptor 35; KMO: kynureneine 3-monooxygenase; KP: kynureneine pathway; KYNA: kynurenic acid; L-KYN: L-kynureine; NMDA: N-methyl-D-aspartic acid; PA: picolinic acid; QUINA: quinolinic acid; ROS: reactive oxygen species; TRP: L-tryptophan.

The three branches ultimately generate two metabolites: KYNA and QUINA [29]. However, acute injuries or chronic neuroinflammation disrupt this equilibrium and cause neurotoxic metabolites to predominate. These toxic metabolites can damage the CNS and cause neurodegeneration. In contrast to previous research, recent studies have shown that KYNA might exert both neuroprotective and neurotoxic effects [19].

(1) L-KYN generates KYNA by kynurenine amino-transferase (KAT). KAT enzymes are believed to be expressed in brain astrocytes. KYNA inhibits endogenous broad-spectrum glutamate receptors, namely, N-methyl-D-aspartic acid receptors (NMDAR), kainite receptors, and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPAR) [30]. The most significant effect is an inhibition of the NMDAR glycine binding site at high micromolar concentrations [31]. KYNA is also a partial antagonist of the ionic glutamate receptor and the kainite receptor, inhibiting the effect of glutamate at high concentrations [30]. Significantly, nanomolar to micromolar levels of KYNA can facilitate AMPA receptor responses [32]. Furthermore, KYNA can function as a noncompetitive antagonist of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) [33]. It interferes with glutamate and nicotinic neurotransmission, reducing glutamate levels in neuronal synapses and thus preventing excessive glutamate excitement. Excess glutamate in the synaptic cleft dysregulates Ca^{2+} homeostasis, mitochondrial function, and reactive oxygen species (ROS) production [5]. KYNA also stimulates G protein coupled receptor (GPR) 35, which is expressed on the surface of various immune cells and exhibits an anti-inflammatory effect [34]. For example, the KYNA-GPR35 interaction can reduce the inflammatory response of mononuclear macrophages to lipopolysaccharide [35] and release cytokines from human invariant natural killer cells [36]. Similarly, KYNA activates the aryl hydrocarbon receptor (AhR), which may exert an immunosuppressive effect similar to that of KYN [37]. One recent study demonstrated that KYNA removes ROS as an antioxidant [31]. This data indicate that KYNA protects against neurotoxicity by inhibiting NMDAR. In addition, KYNA antagonism to NMDA and $\alpha 7$ nACh exacerbates cognitive dysfunction in SCZ [38].

(2) L-KYN is degraded by kynurenase to produce AA, which is further converted to 3-HAA by monohydroxylase. Serum AA levels may indicate the severity of depression, and brain AA concentrations are significantly associated with the appearance of depression during the treatment of patients with hepatitis C [9].

(3) L-KYN can be catalyzed by KMO to 3-HK and then converted to 3-HAA by KYNU, therefore merging with the second metabolic branch. A series of enzymes, such as 3-hydroxyanthranilate oxidase, metabolize 3-

HAA to QUINA and ultimately to NAD^+ or PA. In addition, 3-HK can be converted to xanthurenic acid (XA) by KAT. Finally, 3-HAA is oxidized to generate cinnabarinic acid (CA).

KMO is expressed in resident macrophages in adipose tissue [39] and predominantly in microglia [40] but not in neurons or astrocytes in the brain [41, 42]. In TBI or neurodegenerative conditions, the main rate-limiting enzyme in neurotoxicity, KMO, is activated by proinflammatory factors in microglia to generate neurotoxic products such as 3-HK, 3-HAA, and QUINA [12]. Therefore, KMO is considered a promising target for anti-inflammatory therapy to treat neuroinflammation, but modulation of the dual role of KMO remains to be studied.

3-HK is a product of L-KYN transformed through KMO, which has strong lipophilicity and can easily pass through the BBB [43]. 3-HK autoxidation converts it to 3-HAA and participates in fat peroxidation and other oxidative stress processes [22].

QUINA can mediate neural excitotoxicity by promoting glutamate production and inhibiting the uptake and conversion of glutamate into glutamine [44]. However, QUINA can also selectively activate NMDARs [8]. This effect is more pronounced in the hippocampus, neocortex, and striatum but not in the cerebellum or spinal cord neurons. Neurons in the former locations predominantly express the NR2B subunit of NMDAR, while neurons in the latter brain areas mainly contain the NR2C subunits, and QUINA has a higher affinity for the NR2B subunits [45]. In addition, QUINA can combine with iron to transfer electrons to oxygen to form ROS, which leads to lipid peroxidation [29]. This suggests the use of iron chelation to inhibit the binding of QUINA to iron and thus protect neurons [46]. QUINA also affects GFAP phosphorylation and decreases the stability of the astrocyte cytoskeleton, thus contributing to the breakdown of the BBB [47].

Furthermore, by activating NMDARs, QUINA induces astrocyte apoptosis and neuronal dysfunction [47]. QUINA also increases the expression of nitric oxide synthase and thus influences the production of nitric oxide ($\text{NO}\cdot$) as well as vasodilation [48]. The effects of QUINA and KYNA show a certain degree of antagonism, suggesting that the balance of these two metabolites may affect the development and prognosis of various neurological diseases. Furthermore, QUINA generates NAD^+ under physiological conditions (< 100 nm). It is also involved in energy metabolism within mitochondria [47]. The imbalance in the NAD^+/NADH ratio is associated with mitochondrial disorders and aging and age-related diseases [3].

CA and XA act on metabotropic glutamate receptors (mGlu) [30]. CA can inhibit excitotoxic neuronal cell death by activating mGlu4 receptors, while XA has

antipsychotic-like effects by positively activating mGlu2 and mGlu3 receptors [49]. In addition, CA can serve as an AhR ligand to stimulate T cells to produce IL-22[50]. Changes caused by the combination of CA and AhR are not yet known. Xanthine may exhibit a neuroprotective effect by reducing 3-OH-kynurenine levels. It also induces cell apoptosis by altering mitochondrial function and increasing the concentration of intracellular calcium ions, thus playing an excitatory role in the brain [51]. Under physiological conditions, PA is rarely present in the brain, replacing NAD⁺ when enzymes such as 3-hydroxyanthranilate oxidases are present [34]. As a secondary signal for macrophages, PA causes the activation of IFN- γ -primed macrophages and triggers a cytokine-driven inflammatory response [52].

3. The MP

Another metabolic direction of TRP is through the MP. First, tryptophan-5-hydroxylase metabolizes TRP to 5-hydroxy tryptophan (5-HT). It is then converted to serotonin by the aromatic L-amino acid decarboxylase enzyme. Next, serotonin forms N-acetyl serotonin (NAS), also an agonist of BDNF receptors [53], and melatonin, by an alkylamine N-acetyltransferase.

Melatonin is neuroprotective against glutamate toxicity [54]. Previous studies have shown multiple anti-inflammatory effects, including inhibition of the expression of neuronal NO synthase and cyclooxygenase-2, reducing the BOX-1 signal of the high-mobility group and activating Toll-like receptor-4, negatively regulating NLRP3, inhibiting the activation of NF- κ B, and positively regulating nuclear factor erythroid 2-related factor 2 [55]. Melatonin penetrates the BBB [56] and thus binds to G protein-coupled receptors after secretion, namely, MT1 and MT2 [57]. As an antioxidant, it directly scavenges free radicals and indirectly stimulates antioxidant enzymes to inhibit oxidative enzymes and stabilize mitochondrial membranes [58, 59]. Furthermore, the cascade reaction products of melatonin have antioxidant properties. N(1)-acetyl-5-methoxykynuramine, for example, has an efficient antioxidant effect [60]. In the Fenton/Haber-Weiss reaction, melatonin chelates ferrous iron and copper, reducing toxic hydroxyl radicals and oxidative stress [61]. Melatonin is said to be an efficient antioxidant and protects against metal-induced oxidative stress; it also exhibits significant antineuroinflammatory properties and can protect against AD [62]. Melatonin has been investigated in several clinical trials for its antioxidant, anti-inflammatory, and antiapoptotic properties and the restoration of tissue function, with consistent protective effects observed [61].

4. Psychiatric disorders

4.1. SCZ

The pathophysiology of SCZ supports the hypothesis of hypofunction of NMDARs, which could be associated with metabolites of the KYN pathway that suppress NMDARs [30] and therefore decrease neurotransmitter activities. As an antagonist of NMDARs, KYNA plays a vital role in this process [38]. The KYN pathway plays various roles in the dysregulation of the SCZ immune system. Through a meta-analysis, Cao Bing et al. reported lower levels of TRP and higher KYN/TRP ratios in SCZ patients; lower KYN was associated with SCZ patients without medication, while higher levels of KYN were observed in patients after treatment [63]. Abbas F. Almulla et al. showed an increase in IDO activity in brain tissue and peripheral serum and a decrease in KMO activity and a reduction in KYNA production in the brains of SCZ patients [64]. Impaired KMO expression and activity were also observed in postmortem brain tissues of SCZ patients [65]. Subsequent elevation of KYNA levels was suggested to have a causal link with the psychopathology of SCZ, as in the so-called "KYNA hypothesis of SCZ" [66]. Elevated levels of KYNA in developing brain tissue or CSF [67] are related to cognitive deficits [68] and psychotic symptoms [69] in SCZ. The single nucleotide polymorphism of the KMO gene is related to SCZ, further supporting the notion that the decrease in the 3-HK branch in the KP pathway may cause L-KYN to convert to KYNA, which is one of the causes of SCZ [19].

In addition to KYNA, the newly discovered 3-HK metabolite XA may play a pathogenic role in SCZ. As an endogenous agonist of the mGlu2 receptor, XA exhibits antipsychotic therapeutic effects in mice [70]. Interestingly, blood levels of XA are markedly reduced in patients affected by SCZ, regardless of the stage of the disorder or drug status, suggesting that lower levels of XA in blood may serve as a potential trait marker for SCZ [70]. Another KYNA metabolite is CA, an activator of metabotropic glutamate receptors mGlu4, which may have a therapeutic role in SCZ. However, CA did not confer any therapeutic effects in mice with mGlu4 deficiency [71]. Furthermore, CA levels were low in brain tissues from SCZ patients [71]. In particular, circulating AA levels are elevated in SCZ patients simultaneously with KYNA [70, 72] and are positively correlated with the severity of symptoms [10].

4.2. BD

BD is a mental illness characterized by abnormalities in the structure and function of several areas of the brain

(e.g., the prefrontal cortex, anterior cingulate cortex, amygdala, and hippocampus) [73]. Although the pathomechanism of BD is not clearly understood, there is a wide range of evidence that inflammation and TRP metabolism contribute to the development of the disease [74]. The sorting nexin family is involved in the regulation of intracellular transport and signal transmission. A postmortem study of the brains of BD patients revealed that downregulation of sorting nexin 7 increased caspase-8-driven interleukin-1 β production, subsequently activating the KYN pathway and resulting in neurotoxicity [75]. Another MRI study showed that the L-KYN/TRP (K/T) ratio in the blood of patients with BD was negatively correlated with amygdala volume, corpus callosum integrity, and frontal-parietal cortex thickness as quantified by MRI [76]. KYNA is considered protective in BD, but in patients with lifelong psychotic characteristics, elevated KYNA levels in the CSF are correlated with genetic mutations in KMO [77]. Therefore, the accumulation of KYNA in the brain is related to the pathophysiology of BD. Changes in melatonin secretion are also correlated with the disease state. Patients with BD with altered circadian rhythms had reduced levels of melatonin during the euphoric, manic, and depressive phases [78]. There is evidence that the level of 5-hydroxyindoleacetic acid (5HIAA), the main serotonin metabolite, is reduced in the cortex of patients with BD. Decreases in central 5-HT activity in patients with BD might cause mania and depression [79].

4.3. MDD

MDD is related to elevated metabolism in the 3-HK branch of the KP. The process of enhanced degradation of TRP to KYN away from serotonin production is called a "KYN shunt". The TRP degradation pathway and the KYN shunt have been implicated in MDD [80]. The shutdown of TRP metabolism from the MP to KP, moving away from serotonin production to KYN production, leads to serotonin deficiency in MDD [81]. It also results in higher levels of the neurotoxic metabolite QUINA than the neuroprotective metabolite KYNA [23]. KP activation has been clinically observed in interferon-induced depression, and LPS-induced depression-like behavior in animals has been associated with activation of the KYN pathway [80]. A clinical study showed that the ratio of KYNA to 3HK or QUINA is positively associated with hippocampal volume, and decreased hippocampal volume is correlated with impaired autobiographical memory recall in patients with MDD [23]. The levels of L-KYN, 3-HK, and KYNA are elevated in the mouse model of chronic social defeat [82]. The body produces PA to limit the formation of quinoline and inhibit suicidal behavior [82]. Changes in IDO-1 expression were analyzed in

MDD patients, with higher baseline levels observed in patients than in normal controls, and the clinical efficacy of the antidepressant can be attributed at least partly to decreases in IDO1 expression. However, there are currently no reports on IDO2 expression in MDD [83]. Increased levels of IDO1 can lead to increased 3-HK production, which exerts a neurotoxic effect. The polymorphism of the IDO1 gene is related to susceptibility to cytokine-induced depression [84]. Consistent with our expectations, IDO knockout mice exhibit reduced depression-like behavior [85].

TNF, IL-6, and other inflammatory genes in peripheral blood mononuclear cells are upregulated in patients with MDD. The expression level of these genes is associated with the amygdala response to fear [82]. For a long time, evidence has linked 5-HT to the etiology of MDD. The classic antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs), including sertraline and fluoxetine, exert their effects by increasing serotonin levels in the synaptic cleft [86]. Furthermore, previous studies have shown TRP depletion in the brains of MDD patients with decreased availability of the serotonin-1A receptor and the -2A receptor [87]. However, serotonin levels are increased in multiple depressive phenotypes, indicating the involvement of other mechanisms in MDD [88].

4.4. Therapeutic Perspectives

Targeting the TRP mechanism is an ongoing research direction to treat the psychiatric disorders mentioned above. Long-term SCZ could be controlled by blocking KYN transport to the brain or inhibiting KYNA production in the brain [19]. For example, for the treatment of SCZ, the enzyme KATII is one of the targets. The KATII inhibitor (S)-4-(ethylsulfonyl) benzoylalanine (S-ESBA) has been shown to reduce KYNA levels in the rat brain and thus enhance cognition [89]. However, the selective difference between species and the toxicity of KAT inhibitors limits their potential use [19]. Given that XA production also depends on KAT, it remains unclear whether inhibiting KAT is a worthwhile treatment option. A new direction in BD therapy is the modulation of biological rhythms. As an agonist of MT1 and MT2, agomelatine has been shown in clinical trials to be beneficial for 81% of patients with bipolar I disorder. However, it has side effects, such as mania, when combined with lithium, and other studies have shown that it has no apparent therapeutic effect [90]. Elevating endogenous melatonin levels in the brains of patients with BD is a feasible solution. Reducing KP while increasing MP may be a promising treatment prospect, such as inhibiting IDO1 with subsequent decreases in neurotoxic products. For MDD patients, two feasible treatment options include the use of KYNA competitive inhibitors,

such as AV-101, and inhibiting transport of L-KYN to the brain. For example, leucine can compete with L-KYN for LAT1, thus reducing the concentration of KYNA in the brain [8]. Furthermore, previous studies have shown that 10 of the 19 amino acids can reduce L-KYN synthesis [91], suggesting that diet therapy can help in the management of mental illness. The specific pathophysiology that underlies psychiatric disorders remains unclear. Compounds targeting KP hold promise as novel treatments. Well-designed preclinical and clinical studies with KP-targeted treatment are needed to advance our understanding and the treatment of psychiatric disorders.

5. Acute spinal cord and brain injury

5.1. SCI

SCI damages the spinal cord and results in spinal cord shock. After an initial mechanical injury, damaged cells release neurotoxic glutamate [92]. Glutamate acts on the glutamate receptor AMPA, causing the death of oligodendrocytes and demyelinating nerve cells. KYNA exhibits a neuroprotective effect due to its inhibition of glutamate release, while QUINA exerts the opposite effect [93]. Previous studies have also shown that an increase in QUINA levels after SCI is related to suicidal ideation. Administration of inhibitors to reduce the production of QUINA without affecting the levels of other neuroactive substances can significantly increase the area of white matter that survives within the injured site. Administration of KYNA derivatives can improve recovery of motor function in adult male Wistar rats 1–4 weeks after SCI [93]. Furthermore, 5-HT promotes the regeneration of damaged axons [93].

5.2. TBI

A TBI is caused by an external force that injures the brain. Its pathogenesis involves primary and secondary injury. Inflammation leads to secondary brain damage and promotes ROS formation [94, 95]. The generation of inflammatory cytokines, such as IFN- γ and IL-6, increases the expression level of IDO. Elevated levels of IDO and QUINA are present in young rabbit models of TBI [18]. In human TBI, it has been confirmed that QUINA, L-KYN, and KYNA levels increase in the CSF. The concentration of QUINA and IDO1 expression is correlated with the worsening condition and mortality of a patient, suggesting the harmful effects of KP [15]. Acute early activation of the KYNA pathway can prevent the development of depressive symptoms after mild TBI, and QUINA in serum can potentially be a biomarker of repetitive TBI [96]. Targeting TRP metabolism can help

to elucidate its pathogenic role in various emotional changes induced by TBI [97].

5.3. Ischemic and hemorrhagic stroke

Stroke can be classified as ischemic or hemorrhagic stroke. Ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery. In contrast, hemorrhagic stroke (e.g., ICH) refers to the accumulation of intracerebral bleeding caused by the rupture of a penetrating artery. The pathogenesis of ischemic or hemorrhagic stroke can be divided into primary and secondary brain injury. Direct damage to ischemic stroke is due to the initial interruption of cerebral blood flow, causing a local brain infarction. The primary injury to ICH is due to increased intracranial pressure caused by physical compression of a hematoma. Secondary brain injury caused by ischemic stroke or ICH involves excitotoxicity, inflammation, and oxidative stress [98–100]. Excitotoxicity induced by TRP metabolites could be one of the mechanisms of the secondary injury. Animal experiments show that the QUINA/KYNA ratio increases in mice and gerbils, which is related to immune cell infiltration and the severity of ischemic stroke [101]. One study showed that IDO activity increases in ischemic stroke and correlates with prognosis; simultaneously, TRP levels decreased, suggesting that TRP metabolism improved [102]. The 3-HAA/AA ratio decreases when the KYNA level increases, indicating a compensatory protection mechanism against secondary brain damage [103]. Serum melatonin concentration decreases after stroke. As a neuroprotective agent, melatonin improves prognosis when administered exogenously [104]. ICH is a common and serious cerebrovascular disease with high mortality [105]. Similar to ischemic stroke, TRP metabolism may play a role in the pathophysiology of ICH. However, very few studies have investigated the effects of TRP metabolism in preclinical and clinical ICH studies [106], indicating a new direction of research.

5.4. Therapeutic Perspectives

Modulation of KP production is significant in the treatment of traumatic disorders, and KMO may be a new pharmacological target for the treatment of traumatic disorders [107]. Furthermore, KMO inhibitors can reduce the impact of chronic inflammation and potentially mitigate neuropathic pain and psychological disturbances after SCI [93]. TDO and KMO inhibitors also improve the prognosis of stroke patients, while IDO inhibitors do not show protection [103].

In preclinical studies, the NMDAR inhibitor memantine has improved the prognosis of ischemic stroke [108]. Furthermore, as an endogenous ligand for

NMDAR, KYNA is a promising drug candidate with fewer CNS side effects. For example, N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride, a KYNA analog, has shown therapeutic efficacy [109].

5-HT and melatonin are also drug candidates for drugs for traumatic disorders. Potential treatment strategies for SCI include the regulation of neuroinflammation and the transplantation of mesenchymal stem cells and neural precursors to create a preregeneration environment and increase the preregeneration capacity of damaged neurons. 5-HT can promote the regeneration of damaged axons. Increased 5-HT axon density at the injured site is a good indicator of improved functional recovery [110]. Furthermore, melatonin reduces oxidative stress and inflammation by activating the signaling pathway of nuclear factor erythroid 2-related factor 2 and alleviates secondary damage to TBI [94]. Oral melatonin can reduce the severity of stroke patients and improve cognitive decline [104].

6. Autoimmune diseases

6.1. MS

MS is an autoimmune-mediated disorder characterized by the formation of sclerotic plaques, inflammation, and demyelination [111]. There is an apparent KP imbalance in MS, although the exact role of KP is not fully clear. Preclinical studies have shown that IDO1 activity decreases in the brain and spinal cord of mice with experimental autoimmune encephalomyelitis (EAE), leading to increased Th1 and Th17-cell activity and reduced Treg cell activity, worsening the severity of the disease [112, 113]. Another study showed that after increasing IDO1 activity, 3-HAA in KP increased, resulting in an immunosuppressive effect [114]. Furthermore, the results of an in vitro study indicated that QUINA can alter oligodendrocytes, thus expanding its pathogenic effects in MS [22].

Clinical trials have shown that enhancing IDO1 suppresses immune responses, suggesting that IDO1 exerts anti-inflammatory and neuroprotective effects [44]. The CSF level of TRP decreases in MS patients [22]. The accumulation of QUINA is related to the severity of the disease [111]. The level of KYNA in the CSF of MS patients is significantly reduced in remission. In contrast, KYNA levels in plasma and CSF increase during acute relapse and decrease during chronic remission [22]. These findings indicate that KYNA may be involved in the relapse-remission phase of the disease. In the CSF, the PA level decreases while the QUINA level increases, which implies that KP metabolism switches to the neurotoxic

pathway [111]. 5-HT may play a pathogenic role in MS as its expression level in the CSF is decreased in MS patients [115]. NAS, the 5-HT metabolite, interacts directly with IDO1 and functions as a positive allosteric modulator to elevate the level of L-KYN [116]. It also activates AhR, thus exerting anti-inflammatory and immunoregulatory effects [116].

6.2. Therapeutic Perspectives

In summary, TRP metabolites and enzymes play a significant role in the pathogenesis of MS. The data suggest that by regulating the production or activity of these enzymes or metabolites or using synthetic analogs, MS can be managed or treated. Previous studies suggest that increasing IDO activity and inhibiting the production of downstream catabolic products hinder the progression of EAE and may be a new therapeutic strategy [117]. The KYNA analog laquinimod has been used as a disease-modifying therapy to treat MS in multiple stages [118]. In addition to anti-inflammatory and immune regulation, laquinimod protects astrocytes and oligodendrocytes [119]. It also reduces axon damage and promotes remyelination [120]. However, due to its severe adverse effects, it cannot be used currently as a drug in clinical practice [120]. Therefore, more studies are needed to investigate drug candidates with better and superior curative effects with fewer side effects [44].

Increasing the level of 5-HT can provide therapeutic benefits. Phenelzine can increase the content of 5-HT between axons and has also been shown to improve behavioral performance in a mouse model of EAE [121]. However, clinical trials have shown that fluoxetine, another drug that can increase the 5-HT concentration in the brain, did not benefit MS patients significantly [122]. The reason may be the small sample size, the baseline imbalance, or confounding bias [115]. These two contrasting results suggest that alternative mechanisms that regulate 5-HT may need to be investigated.

7. Neurodegeneration

7.1. AD

AD is the most common form of dementia, with continuous cognitive impairment and progressive memory loss [123]. Deposition of misfolded proteins such as amyloid beta-protein (A β) and hyperphosphorylated tau, loss of synaptic transmission, and neuroinflammation are characteristics of AD [124]. Tryptophan metabolites, QUINA and KYNA, together with other intermediates, show elevated concentrations associated with A β and tau in the CSF of AD patients, which are neurodegeneration biomarkers, suggesting that TRP is closely related to the

core pathology of AD [125]. One study showed that CSF levels of A β 40 and A β 42 correlated with those of K/T, KYNA, L-KYN, QUINA, and AA in AD patients with a high neocortical A β load [125]. Furthermore, high levels of QUINA are associated with neuronal damage in AD [126]. An increased K/T ratio in serum and CSF indicates that TRP metabolism is enhanced, and IDO activation increases in AD [5].

KYNA activation increases NAD $^+$ production, promotes DNA repair, strengthens genomic signaling, and generates more energy [127]. Therefore, it plays an important role in antioxidant defense and protection against AD [128]. Neurotoxic QUINA, mainly produced by activated microglia, can induce tau phosphorylation [129]. Interestingly, IDO-1 is colocalized with extracellular A β plaques [130]. KYNA levels are elevated in the CSF [131] but decreased in serum [132]. A recent study demonstrated that 3-HK and 3-HAA increase Cu $^{++}$ -induced neurotoxicity in rat astrocyte cultures [133]. However, the mechanism behind the neuronal death induced by TRP metabolites is not fully understood. Melatonin is a branch of TRP metabolism. As an antioxidant, free radical scavenger, protein aggregation inhibitor, anti-inflammatory agent, and regulator of various enzymes, melatonin exerts a neuroprotective role in delaying the development of AD [134]. The available evidence suggests that TRP metabolism is involved in the pathogenesis of AD. Therefore, targeting TRP metabolism will help to elucidate the pathomechanism of AD.

7.2. PD

PD is another common age-related neurodegenerative disease. Degeneration of dopaminergic neurons in the substantia nigra pars compacta produces characteristic motor symptoms [5]. Alpha-synuclein and dopamine metabolites in the CSF are considered biomarkers of PD [135]. Serum levels of TRP, L-KYN, and KYNA are lower in PD patients than in controls [136]. The KP of TRP catabolism can regulate inflammatory and neurotoxic processes in PD. The K/T ratio and 3-HK levels in the putamen, frontal cortex, and hippocampus of PD patients is significantly increased, indicating an increase in IDO/TDO activity in PD patients [137]. The KYNA level is decreased in the striatum and CSF of patients with PD and correlated with an increase in excitotoxicity, while the QUINA level is increased in the striatum and cortex [138]. QUINA and 3-HK are involved in the pathogenesis of PD. Related underlying mechanisms include NMDAR activation, ROS production [139], lipid peroxidation, and increased levels of nitric oxide synthase [136]. There is a significant correlation between increased neopterin levels and the

K/T ratio in the serum and CSF of patients with PD [137], with high cell-mediated immunity (e.g., CD4 $^+$ T cells and CD8 $^+$ T cells) in patients with advanced PD.

7.3. ALS

ALS is a progressive neurodegenerative disease characterized by selective death of motor neurons in the cerebral cortex, brainstem, and spinal cord, leading to atrophy of voluntary muscles, weakness, paralysis, and premature death [140]. In the brain, the level of TRP regulates serotonin production. Depression is related to decreased serotonin levels caused by TRP depletion [141] and sleep disturbances caused by decreased melatonin, both of which are symptoms in patients with ALS. The most commonly measured KPMs are L-KYN, TRP, KYNA, XA, and AA, and their levels are stable in ALS [142]. Astrocytosis is a feature of neuroinflammation in ALS. Activated microglia and activated KP are present in the motor cortex of patients with ALS, and the levels of TRP, L-KYN and QUINA in the CSF and serum are increased [143]. When the disease worsens, the high KYNA level is proportional to the severity and is neuroprotective. One study showed no significant differences in KYNA levels in serum or CSF between patients and control subjects [142]. However, the level of KYNA in CSF was higher in patients with severe clinical conditions than in control subjects, and the KYNA concentrations in serum and CSF are not related [142]. CSF levels of QUINA and IDO increased significantly in patients with ALS [6]. Activated voluminous microglia, reactive astrocytes, infiltrating macrophages, and T cells are present in the brain and spinal cord of ALS patients, suggesting that these inflammatory cells play a role in the pathogenesis of ALS [144], particularly glutamate excitotoxicity, oxidative stress, mitochondrial metabolic dysfunction, neuroinflammation, protein aggregation, and autophagy [144]. These data suggest that QUINA contributes to the pathophysiology of ALS.

7.4. HD

HD is an autosomal dominant neurogenetic disorder. Its pathogenesis involves the repeat expansion of CAG in the first exon of the huntingtin gene (HTT), which encodes a polyglutamine stretch in the HTT protein [145]. Preclinical studies have shown that melatonin is significantly increased in presymptomatic HD sheep [146], and a self-protective response to the toxicity of the mutant huntingtin protein could be the cause [146]. Experiments with human samples and animal genetic models of HD have demonstrated that neuroactive metabolites in KP play a role in the development of HD [147]. Clinical studies have shown that the level of 3-HK

increases in the brains of patients [148], which has a toxic effect on the striatum, thus increasing the production of toxic QUINA. Increased QUINA causes a certain degree of excitotoxicity or oxidative stress, leading to striatal neuronal dysfunction [6]. A clinical study showed that the K/T ratio in the CSF is higher in HD patients than in control subjects at baseline and after TRP depletion, which can be caused by eating an amino acid mixture containing all essential amino acids except TRP [149].

The results suggested an increase in IDO activity in the HD brain.

Furthermore, HD patients exhibit abnormal TRP metabolism and increased oxidative stress. These factors contribute to continued brain dysfunction. Plasma levels of KYNA, 3-HK, and 3-HAA and KAT activity are decreased in HD [149]. Inhibition of KMO activity reduces QUINA production in HD brain tissues [77], suggesting that the KP inhibitor can reduce huntingtin-induced abnormal cytotoxicity.

Table 2. Changes in the kynurenine pathway in psychiatric disorders, acute brain and spinal cord disorders, and multiple sclerosis.

Brain (CSF)	SCZ	BD	MDD	TBI	SCI	Stroke	MS
TRP	↓ [70]	↓ [162]	↓ [163]	N [15]	-	↓ [103]	↓ [22]
QUINA	↓ [70]	N [162]	↑ [23]	↑ [15]	↑ [93]	↑ [103]	N or ↑ #
KYNA	↑ [65]	↓ [162]	↓ [163]	↑ [15]	-	↓ [102]	↑ or ↓ *
K/T	↑ [65]	N [162]	↑ [163]	↑ [15]	↑ [164]	↑ [165]	↑ [44]
Melatonin	↓ [166]	↓ [167]	↓ [168]	↓ [18]	↓ [169]	↓ [104]	↓ [170]
IDO	↑ [65]	↑ [171]	↑ [172]	↑ [18]	↑ [107]	↑ [102]	↑ [173]
5-HT	↑ [174]	↓ [79]	↑ [88]	↓ [18]	↓ [110]	↓ [175]	↓ [115]
L-KYN	↑ [63]	N [162]	N [163]	↑ [15]	↑ [93]	↑ [176]	↑ [116]
3-HK	↑ [8]	↑ [177]	↑ [82]	↑ [96]	↑ [93]	↑ [178]	↑ [44]
3-HAA	↑ [70]	-	N [179]	N [15]	↑ [93]	↓ [161]	↑ [44]

↑: increase; ↓: decrease; N: nonsignificant difference; -: uncertainty

There was no difference in the CSF level of QUINA between MS patients and normal subjects, but QUINA was increased in patients with relapsing-remitting MS (RRMS) in the relapse stage [180].

* KYNA increases during acute relapse and decreases during chronic remission [22].

Abbreviations: 3-HAA: 3-hydroxyanthrenille acid; 3-HK: 3-hydroxykynurenone; 5-HT: 5-hydroxy tryptophan; BD: bipolar disorder; CSF: cerebrospinal fluid; IDO: indoleamine 2,3-dioxygenase; K/T: L-KYN/TRP; KYNA: kynurenic acid; L-KYN: L-kynurene; MDD: major depressive disorder; MS: multiple sclerosis; QUINA: quinolinic acid; SCI: spinal cord injury; SCZ: schizophrenia; TBI: traumatic brain injury; TRP: L-tryptophan.

7.5. Therapeutic Perspectives

In general, inhibitors of the key enzymes in KP are believed to be therapeutic candidates for neurodegenerative diseases. KMO is located at the point of branch of QUINA and KYNA production. Therefore, drugs that specifically inhibit KMO activity, such as JM6 and Ro61-8048, can change metabolism to increase KYNA levels and reduce extracellular glutamate in the brain, providing neuroprotection [150]. Metabolites of the KP of TRP degradation, such as QUINA, induce cerebral oxidative stress and trigger the inflammatory response in several neurodegenerative diseases. As a phytochemical with antioxidant and anti-inflammatory activities, phenolic compounds can treat neurodegenerative diseases [151]. With similar biological properties, melatonin could also be a candidate drug [134].

Targeting TRP metabolism can help in the development of disease-modifying therapies for AD. The serotonin receptor (a G protein-coupled receptor) 5-HT4 and 5-HT6 receptors are new potential drug targets [152]. One of the main effects of 5-HT6R activation is to reduce

cholinergic transmission. Therefore, receptor antagonists can increase ACh production and stimulate cholinergic transmission. KYNA functions on the Ach receptor as a noncompetitive antagonist since the Ach concentration is decreased in AD [33]. The drugs available today exert only a symptomatic effect. Therefore, acetylcholinesterase and butyrylcholinesterase inhibitors remain FDA-approved drugs for the treatment of AD [153], including rivastigmine and galantamine [154]. TRP metabolites have tremendous therapeutic potential in AD, KYNA, and 5-HIAA and can reduce the accumulation of Aβ in the brain [155]. Exploring 5-HIAA analogs or precursors using KMO combined with KYNA may become a new research direction.

Although dopaminergic agonists (e.g., ropinirole, pramipexole, rotigotine), L-DOPA, and carbidopa are widely used to treat PD, they provide symptomatic relief but not a cure. Furthermore, the pathomechanism of the progression of metabolite-mediated disease of these drugs remains elusive [156]. However, inhibition of KMOs such as Ro 61-8048 can increase KYNA levels in PD brain tissue [157], which could be a potential drug candidate for

the treatment of PD [156]. Treatment targeting TRP includes probenecid, L-KYN + probenecid, and nicotinylalanine + L-KYN, which have been shown to increase KYNA levels in the brain and delay the neurodegeneration process of PD under in vitro and in vivo conditions [157].

There are three possible ways to treat ALS. The first is inhibition of the enzyme in KP. The second target is the precursors of NAD or KYNA, such as nicotinamide mononucleotide, which have been used to treat aging and neurodegeneration [158]. The third is synthetic drugs with high bioavailability and affinity for excitatory receptor binding sites [119]. Although Riluzole was the first drug

approved by the FDA to treat ALS in 1995 [144], there is still a lack of effective treatments for ALS today. Therefore, joint efforts of basic scientists and physician scientists in preclinical and clinical studies are needed.

Reducing presynaptic dopamine or blocking the D2 dopamine receptor is the current therapeutic strategy for treating chorea. Tetrabenazine is the only approved drug for treating chorea caused by HD [159]. IDO1 could be a new therapeutic target for HD by regulating inflammatory processes and neurodegeneration and inducing depressive symptoms in HD [145]. Similar to other neurodegenerative diseases, KMO inhibitors could also be a new therapeutic target for HD [160].

Table 3. Changes in the kynurenine pathway in neurodegenerative diseases.

		AD	PD	ALS	HD
Brain	TRP	↓ [125]	↓ [181]	↑ [143]	↓ [182]
	QUIN	↑ [29]	↑ [138]	↑ [142]	↑ [6]
	KYNA	↑ [29]	↓ [138]	N [142]	N [145]
	K/T	↑ [5]	↑ [137]	↑ [142]	↑ [182]
	Melatonin	↓ [134]	↓ [134]	↓ [134]	↓ [146]
	IDO	↑ [183]	↑ [137]	↑ [184]	↑ [145]
	3-HK	↑ [130]	↑ [137]	↑ [142]	↑ [148]
	L-KYN	↑ [125]	↑ [186]	↑ [143]	↑ [6]
Serum	TRP	↓ [125]	↓ [50]	↑ [143]	↓ [182]
	QUINA	↑ [29]	↑ [137]	↑ [142]	↑ [145]
	KYNA	↓ [132]	↓ [136]	↓ [142]	↓ [149]
	K/T	↑ [5]	↑ [185]	↑ [142]	↑ [182]
	3-HK	↓ [185]	N [185]	-	↓ [149]
	3-HAA	↑ [133]	↓ [138]	-	↓ [149]
	L-KYN	↑ [125]	↑ [186]	↑ [143]	↑ [6]

↑: increase; ↓: decrease; N: nonsignificant difference; -: uncertainty.

Abbreviations: 3-HAA: 3-hydroxyanthrenic acid; 3-HK: 3-hydroxykynurene; 5-HT: 5-hydroxy tryptophan; AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; IDO: indoleamine 2,3-dioxygenase; K/T: L-KYN/TRP; KYNA: kynurenic acid; L-KYN: L-kynurene; PD: Parkinson's disease; QUINA: quinolinic acid; TRP: L-tryptophan.

8. Conclusion

In this review, we summarized and discussed the latest research on the TRP metabolic pathway and its primary metabolites, elucidated its pathogenic role in 12 types of CNS disease, and noted that KP-targeted drugs have therapeutic potential to treat CNS diseases. When the CNS is injured, the metabolic pathway of TRP switches to KP. Inhibition of MP reduces the release of melatonin accordingly (Tables 2 and 3). L-KYN has two metabolic pathways, the neurotoxic QUINA pathway and the neuroprotective KYNA pathway. In general, the activities of the metabolites of these two pathways antagonize each other. The QUINA pathway is overactivated in various CNS diseases, whereas the KYNA branch is inhibited. Therefore, therapeutic strategies that inhibit the QUINA pathway and promote the KYNA pathway can modulate TRP metabolism and improve the histological and functional outcomes of CNS diseases. Research on specific enzyme inhibitors in the KP pathway has much

room for exploration, and we summarize relevant studies related to CNS diseases mainly in 2015-2022 in Table 4.

Meanwhile, MP metabolites also have tremendous therapeutic potential for CNS diseases, and it is essential to investigate treatment options and administration routes related to 5-HT and melatonin. Continuous advances in preclinical and clinical research in this area can bring hope to the fight against various CNS diseases. Above all, relevant translational research is essential to identify therapeutic strategies for the treatment of traumatic conditions. Furthermore, exploring therapeutic options that simultaneously regulate KP and MP can maximize benefits, supporting the potential of targeting TRP metabolism.

9. Search strategy and selection criteria

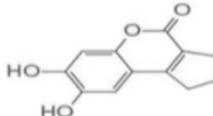
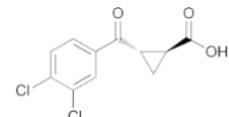
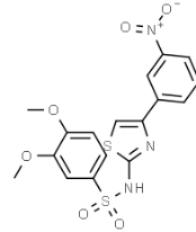
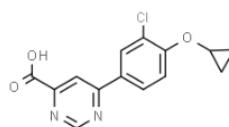
We used major scientific databases, such as PubMed, Web of Science, Home Springer, and ScienceDirect, for literature searches, mainly from 2015. We searched

through different combinations of the following keywords: TRP metabolism or TRP or kynurenine pathway or methoxyindole pathway, KYNA or QUINA or 3-HK or 3-HAA or IDO or 5-HT or melatonin, CNS disease or neurodegenerative disease or mental disorder or CNS or brain injury, biomarkers, targets, or treatment. References to related articles, bibliographies of articles, and relevant book chapters were also included in the scope

of our literature search. We only selected published articles in English and focused mainly on studies published since 2015. A total of 285 articles were reviewed, 90 articles were excluded, and we finally discussed 195 articles. The articles were shortlisted according to the title and abstract, and we chose articles that described TRP metabolism in CNS diseases. We also discuss relevant biomarkers and therapeutic strategies.

Table 4. Inhibitors of KP enzymes tested in preclinical models of brain disorders.

Inhibitors	Names	Structural Formula	Indications	Comments
IDO inhibitors	1-methyl-L-tryptophan (L-1-MT)		Depression/Preclinical [187]	Poor pharmacokinetics [188]; Competitive inhibitor [189].
	Coptisine		AD/Preclinical	Noncompetitive inhibitor. Potent inhibitor of recombinant human IDO [183].
TDO inhibitors	68OC91		Cognitive deficits and anxiety/Preclinical	Potent inhibitor without influencing 5-HT reuptake. Poor solubility and bioavailability [190].
	Allopurinol		Stress/Preclinical	Uncertain about structure and lack of clinical trials [190].
KATII inhibitors	(S)-4-(ethylsulfonyl)benzoyl Alanine (S-ESBA)		Neurodegenerative and Cognitive disorders/Preclinical [191]	KATII selective. Lowers the KYNA level in the rat brain [192]; Low activity against human KATII [19].
	BFF-122		Neurodegenerative and Cognitive disorders/Preclinical [191]	Irreversible KATII inhibitor. Irreversible PLP deactivators [191].
	PF-04859989		Neurodegenerative and Cognitive disorders/Preclinical [191]	Strong therapeutic effect in the rat. BBB permeable [192].

	ZINC354660 84		Experimental/laboratory phase	Potent inhibitor [193].
	JN-01 and JN-02	No information	Experimental/laboratory phase	Potent inhibitor [194]
KMO inhibitors	UPF-648		Neuropathy/Preclinical [107]	Acts as an effector molecule of KMO. Reduction of flavin by NADPH. Generating the cytotoxic H2O2 [195].
	Ro 61-8048		Neurodegenerative or neurologic disorders/Preclinical [196]	Competitive inhibitor [197]; Poor penetration of BBB in rats [195].
	CHDI-340246		HD/Preclinical	No therapeutic efficacy in a mouse model of HD [198].

Abbreviations: 5-HT, 5-hydroxytryptophan; AD, Alzheimer's disease; BBB: blood-brain barrier; CNS, central nervous system; HD, Huntington disease; IDO, indoleamine-2,3-dioxygenase; KAT, kynureine aminotransferase I-III; KMO, kynureine 3-monooxygenase; KP, kynureine pathway; KYNA, kynurenic acid; PPP, pyridoxal-51-phosphate; TDO, tryptophan-2,3-dioxygenase.

Acknowledgments

Junmin Wang was supported by Zhengzhou University Education and Teaching Reform Research and Practice project (2021ZZUJGLX219).

Competing interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Y.R. H, M.K. Z and X.M. C: initial draft preparation, production of the tables and schematic diagrams, and manuscript revision; R.Y. Z, A. L and M. H: reviewed and edited the manuscript; Y.F. Z and L. J: corrected the grammar and spelling of the manuscript; W.D. Z and C. J: reviewed the manuscript; J.M. W, X.C. F and J. W: conceptualization, review, and critically revised manuscript; all authors: literature search, review, commentary, and final approval of the manuscript.

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