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Kynurenine pathway: the link between depressive disorders and inflammation

Szlak kinureninowy: związek między zaburzeniami depresyjnymi a stanem zapalnym

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Summary

Depression is highly prevalent worldwide and the leading cause of disability. It is believed that currently more than 300 million people of all ages suffer from depression. However, the unambiguous cause of the depression remains unknown. It is suggested that the occurrence of this disease is primarily affected by genetic factors, psychological factors and atypical brain structure or function. Recently, an increasingly important role is attributed to the inflammatory response, which is considered to be the main cause of depression. Activation of the kynurenine pathway (KP) is one of the described mechanisms by which inflammation can induce depression. Kynurenine pathway activation is associated with several neuropsychiatric diseases, including major depression disorder (MDD). The imbalance between the neuroprotective and neurotoxic metabolites in the kynurenine pathway and the associated serotonin and melatonin deficiency, may contribute to the manifestation of depressive symptoms. In this review we discuss the role of the major enzymes of the tryptophan KP: tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) and the role of selected kynurenic metabolites in the depressive disorders. Particular attention was also paid to the genetic basis of depressive disorders and to the summary of current knowledge on the effectiveness of treatment and supplementation with tryptophan and 5-hydroxytryptophan in depression.

Keywords: **tryptophan • kynurenine pathway • depressive disorders**

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INTRODUCTION

Depression is the most common mental disorder in the world [20]. Globally, over 300 million people of all ages suffer from depression [2]. Major depressive disorder (MDD; unipolar depression) is a relatively frequent mental illness with a lifetime prevalence of about 12% [16]. Depression disorders have been ranked as the fourth leading cause of disability worldwide by the World Health Organization [33].

Major depressive disorder (MDD) is a serious mental disorder that is associated with genetic factors, psychological factors and atypical brain structure or function [28, 34]. Depressive disorder is a brain disorder expressed by the interactions of various heterogeneous pathogenic mechanisms, mainly associated with inflammation. This hypothesis is based on the studies showing that patients with infectious or autoimmune diseases had a relatively high incidence of depression. Moreover, elevated concentration of inflammatory markers, such as CRP and pro-inflammatory cytokines (IL-1β, IL-6), have been observed in patients with depression [23, 66]. Inflammation is closely associated with the monoamine regulation, with increased levels of tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFNγ). IFNγ induces indoleamine 2,3-dioxygenase-1 (IDO), the enzyme responsible for the metabolism of tryptophan (TRP). IDO guides tryptophan down the kynurenine (KYN) pathway and away from serotonin and melatonin synthesis. The role of such processes has been shown in the emergence of depression in IFN-treated hepatitis C patients [5, 6].

Researchers have found that depressive behaviours induced by cytokines are probably related to the activation of the kynurenine pathway (KP). So far, a great deal of effort in studying tryptophan metabolites has been focused on serotonin. However, the synthesis of serotonin from tryptophan accounts for only 3% of non-protein tryptophan metabolism. In contrast, the kynurenine branch of tryptophan metabolism accounts for approximately 90% [53]. The studies based on animal models of the depressive symptoms have reported that IDO is likely to be a key metabolic enzyme in the KP [29].

In this review, we present the kynurenine pathway of tryptophan catabolism, which is most crucial for inflammation-induced depression. We analyse the role of the enzymes and metabolites in the KYN pathway and how it affects depression.

TRYPTOPHAN (TRP)

Tryptophan is an essential amino acid with an indole ring structure. Humans are not able to synthesize TRP and therefore, it must be obtained from nutrition sources e.g. chocolate, eggs, legumes, meat and fish. An average daily intake of TRP is 3.5 mg per kg of body weight and this amount is required in order to maintain the nitrogen balance in the human body [37]. About 50–85% of plasma TRP is bound to albumin, and this bound form is unstable and easily broken [64]. Tryptophan is required by all living organisms.

In addition to its indispensable role in the protein synthesis, tryptophan is the precursor of many physiologically important metabolites produced during the course of its degradation along four pathways, 3 of which are of quantitatively minor significance, with the fourth, the kynurenine pathway (KP), accounting for ~95% of overall TRP degradation. The pathways of little importance (and their important products) include:

- hydroxylation (serotonin, 5-hydroxytryptamine or 5-HT in the brain, and melatonin in the pineal);
- decarboxylation (tryptamine); and
- transamination (indolepyruvic acid [IPA]) [3].

The final product of the kynurenine pathway is nicotinamide adenine dinucleotide (NAD+), an important cofactor in cellular reactions linked to energy metabolism, which is emerging as an attractive therapeutic target for several diseases [8]. It was well documented that the enhancement of kynurenine pathway and the increase in KYN/TRP ratio along with the decrease in serotonin (the neurotransmitter of normal mood state), play a critical role in the pathophysiology of depressive disorders, including MDD patients [7, 39, 42].

KYNURENINE PATHWAY (KP) IN DEPRESSIVE DISORDERS

The KP exists mainly in the liver, where it is responsible for ~90% of overall TRP degradation under normal physiologic conditions. The KP also exists extrahepatically, but its contribution to TRP degradation is normally minimal (5–10%), however it becomes quantitatively more significant under conditions of immune system activation [2, 3]. The KP is regulated mainly by two enzymes: tryptophan 2,3-dioxygenase (TDO) in the liver and indoleamine 2,3-dioxygenase (IDO) in extrahepatic tissues [2]. Stress and immune activation can enhance the kynurenine pathway in depressive disorders [42]. In such a case, the metabolism of tryptophan through kynurenine pathway takes place mainly in the blood and lymphoid tissues [32]. The metabolism of TRP in kynurenine pathway is shown in figure 1. In this pathway, TRP is oxidized by TDO or IDO, while the product of this reaction (N′-formylkynurenine) is rapidly hydrolyzed to kynurenine. KYN is metabolized mainly by oxidation to 3-hydroxykynurenine (3-HK), followed by hydrolysis of 3-HK to 3-hydroxyanthranilic acid(3-HAA) or it is converted to anthranilic acid (AA). Subsequently, 3-HAA is oxidized to an unstable intermediate, 2-amino-3-carboxymuconic acid-6-semialdehyde (ACMS). The KP favors the non-enzymic cyclization of ACMS to quinolinic acid (QUIN), which undergoes further metabolism to nicotinamide and NAD [2]. This pathway is connected with neurotoxic branch. The second is a neuroprotective branch, where KYN is transformed into the kynurenic acid by kynurenine amino transferases [29].

In recent years, the tryptophan-kynurenine pathway has received greater attention, because new important metabolites were discovered, which may play a role in the health and the disease, as well as particularly in conditions associated with immune dysfunction and central nervous system disorders [3].

THE MAIN ENZYMES OF KP: TRYPTOPHAN 2,3-DIOXYGENASE (TDO) AND INDOLEAMINE 2,3-DIOXYGENASE (IDO1/IDO2)

Two major enzymatic pathways metabolize the TRP. One pathway utilizes TDO, while the second pathway is regulated by the ubiquitous IDO [1]. The TDO is expressed mainly in the liver and its expression is induced by tryptophan itself or by corticosteroids (e.g. cotrisol), secretion of which occurs in response to stress [57]. In the normal physiologic conditions, the activity of TDO is generally stabilized and it is mainly controlled by the TRP [59]. Under physiological conditions, about 99% of tryptophan is degraded by the TDO into kynurenine (KYN) in the liver. In contrast to the TDO, the IDO activity is weak in many extrahepatic tissues, about 5% of the hepatic activity TDO [11]. However, the stress and immune activation can enhance the kynurenine pathway through the induction of rate-limiting enzymes indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase.

The TDO influences systemic tryptophan levels by controlling tryptophan levels in the blood, whereas IDO acts locally to modulate tryptophan levels in response to inflammation. Moreover, enzymes of the kynurenine pathway (TDO or IDO) are also expressed in different cell and tissue types, and in result, they determine the presence and relative abundance of subsequent metabolites. Hepatocytes are the only cells in which all enzymes of the kynurenine pathway are found.

Quantitatively, the most of TRP is metabolized by TDO in the liver, however due to the fact that IDO is important in the brain, it is a key enzyme involved in the inflammation-induced depression [25]. According to Winder et al., the pro-inflammatory cytokines that activate the IDO mainly include IFN-γ and to a lesser extent IFN-α and TNF-α [60]. Moreover, the anti-inflammatory cytokines (e.g. IL-4) inhibit IDO [8, 35, 41]. The TRP metabolism shifts from the liver to the extrahepatic sides (mainly

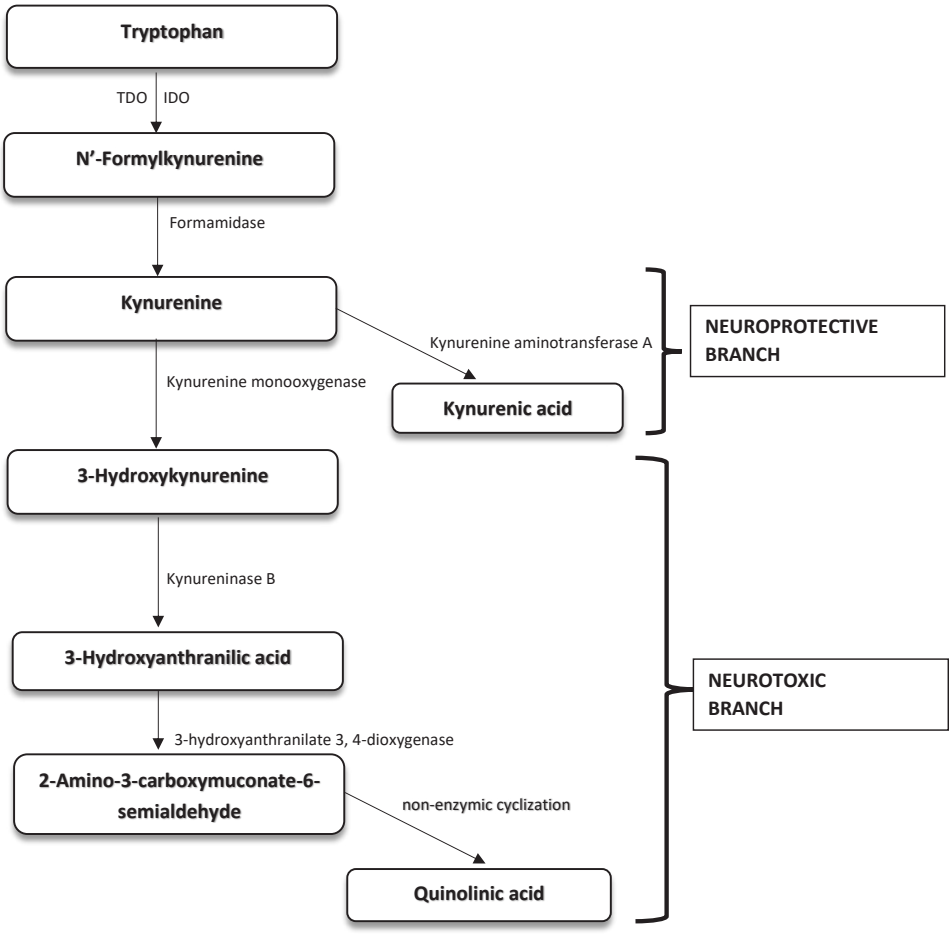

Fig. 1. Schematic representation of the kynurenine pathway of tryptophan metabolism

brain) in an inflammatory state or infectious condition. The activity of IDO can be evaluated by the ratio KYN/TRP and this marker is especially important in the inflammatory state [12].

As a precursor, the KYN is catabolised mainly into KYNA or quinolinic acid (QUIN). However, in the presence of inflammation, the KYN metabolism shifts to the QUIN arm and leads to a reduction in KYNA/KYN [36].

The activation of IDO may also reduce serotonin concentration. The behavioural and neural effects of IDO are believed to be primarily dependent on the formation of neuroactive kynurenine metabolites, rather than the reduction in serotonin [12, 38].

KYNURENINE PATHWAY METABOLITES (TRYCATS)

Recent studies reported that stress could increase the permeability of the blood brain barrier (BBB) in depression, thus the ability of kynurenine metabolites to cross the BBB is increased in the major depressive disorders [18, 31]. Kynurenine and its metabolites are known for their effects on the central nervous system (CNS) and they have been linked to several psychiatric and mental health disorders, such as depression and schizophrenia. The CNS receives about 60% of KYN from the periphery through the transport across the blood-brain barrier, while the rest is produced locally [8]. Individual kynurenines have neuroprotective and neurotoxic effects, and the imbalance between them is one of the causes of the manifestation of depressive symptoms. In the brain, most of the kynurenine pathway metabolites are formed in the microglia and astrocytes. The synthesis of 3-hydroxykynurenine and further downstream metabolites occurs in microglia, while the synthesis of kynurenic acid in the astrocytes [22]. In addition, there is evidence for interplay between tryptophan metabolites in the peripheral tissues and in the central nervous system, which are separated by the blood–brain barrier. Tryptophan, kynurenine, 3-hydroxykynurenine, and anthranillic acid can cross the blood–brain barrier easily. Due to that fact, the fluctuations in the blood levels of these metabolites can affect metabolism in the kynurenine pathway in the brain. Kynurenic acid, 3-hydroxyanthranilic acid and quinolinic acid cross the barrier poorly [18]. The imaging studies have also demonstrated that abnormal KYN metabolites (mainly: 3-HK, QUIN, 3-HAA) are correlated with volume loss in the hippocampus and reduced grey matter density in the prefrontal lobe, both critical areas for learning and memory function in the MDD and other psychiatric disorders [46].

KYNURENINE (KYN)

The kynurenine to tryptophan (KYN/TRP) ratio is elevated in the major depressive disorder (MDD) [19].A recent meta-analysis has evaluated KYN pathway and found a significant reduction in the concentrations of KYNA, KYN and ratios of KYNA/QUIN in the depressed patients, compared to the control subjects [40]. This imbalance in KYN pathway not only emerged in active depressed phase, but also persisted in patients with major depression in long-term remission [47].

KYNURENIC ACID (KYNA)

Kynurenic acid is an endogenous antagonist of ionotropic glutamate receptors, the alpha 7 nicotinic acetylcholine receptor and the N-methyl d-aspartate (NMDA) receptor, with anticonvulsant, neuroprotective and antidepressant activity [52]. KYNA concentration is decreased in the MDD [45].

Kynurenic acid possesses anti-inflammatory and antioxidant properties [20]. Out of all individual by-products of the KP, the KYNA has been mostly studied. It was originally discovered in canine urine, but higher concentrations of KYNA have been measured in the gut (increasing gradually along its length), bile, pancreatic juice of rats and pigs, as well as, to a lesser extent, in human saliva and synovial and amniotic fluid [55]. It has been shown that KYNA has hepatoprotective role in the rat's model, which may be potentially used in in the treatment of acute liver failure [20]. Its pharmacological role arouse the continuing interest of the researchers [54].

NEUROTOXIC BRANCH

Several metabolic factors in the KYN - QUIN branches have been corroborated to be neurotoxic and therefore, they are called the neurotoxic branch of the KP [29]. Both 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranilic acid (3-HAA) are accepted as pro-oxidant metabolites and free radical generators [10, 48]. Under the conditions of immune activation, the QUIN levels are considerably increased. The increased levels of QUIN are involved in neurodegenerative and neurological disorders, such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS-dementia, cerebral malaria, depression, and schizophrenia [21]. The ratio of neuroprotective factors to neurotoxic factors (KYNA/QUIN) could be used to estimate the imbalance of the KP metabolism, in order to assess the degree of nerve injury [26].

GENES REGULATION

Experimental animal models have shown that genetic or pharmacological inhibition of the KYN pathway reduces the induction of depression-like behaviour caused by lipopolysaccharide (LPS) administration [36].

The identification of a single gene, which will be associated with major depression, is difficult, because the psychiatric illnesses are under polygenic influence and they are associated with the interactions between genetic variants and environmental exposures [56].

Major depressive disorder has been associated with polymorphisms in the glucocorticoid receptor gene NR3C1, the monoamine oxidase A gene, the gene for glycogen synthase kinase-3β and a group-2 metabotropic glutamate receptor gene (GRM3). Bieliński et al. have shown the relation between polymorphisms in the DAT1 and COMPT, as well as the intensity of depression symptoms in obese subjects [4]. Whereas, the most recent study has found an increased expression of 15 genomic regions in the subjects with MDD from European population (n=75 607) [24].

It is estimated that the heredity of depressive disorders reaches 50%. This means that genes alone are not enough to explain all the cases of mood disorders. Genetic predisposition increases the risk, which in combination with environmental stressors, may ultimately result in the occurrence of the disease. Many of these genes are associated with decreased neuroplasticity of the brain and inflammation, which reduce ability of the brain to respond to external stressors factors [49].

ANTIDEPRESSANT TREATMENT – THE ROLE OF THE KYNURENINE PATHWAY

The largest group of antidepressant is related to the monoamine hypothesis (an imbalance or a deficiency of the monoamine neurotransmitters like: serotonin in depressive patients). Another group of antidepressants is ketamine, an antagonist of NMDA receptors. Recent studies have found that selective serotonin reuptake inhibitors (SSRIs) or a serotonin modulator and stimulators (SMSs) are linked to KYN pathway regulation. Animals studies have showed that SSRIs impact TRP metabolism by limiting the production of KYN metabolites via regulation on TDO or IDO or shift the KYN catabolism away from the neurotoxic KMO pathway towards the potential neuroprotective KYNA by regulating relevant enzymes [44, 51]. The antidepressant sertraline (SSRI group) caused a reduction in the KYN/MEL (melatonin) ratio and 3-hydroxykynurenine (3-HK)/MEL ratio in MDD patients, compared to pretreatment. Patients who showed poor response to sertraline treatment did not experience changes in these pathways [65]. Mackay et al. showed a positive correlation between KYN metabolite concentrations and psychiatric rating scores in depressive patients treated for 18 weeks with fluoxetine (SSRI group) [30]. Eskelund et al. in the recent study have shown that chronic vortioxetine (SMS group) or fluoxetine (SSRI group) treatment was associated with reduction in levels of the QUIN in various brain regions and plasma of animals with depression-like phenotype. Contrary, ketamine had no effect on the metabolites levels of KP pathway [15]. The decreases in QUIN with antidepressants is particular interesting as QUIN is a potential neurotoxin, which is increased in depression and its level correlates positively with the severity of depressive symptoms [78, 79]. Another study has observed that ketamine had no effect on IDO activity or pro-inflammatory cytokines in mice with LPS-induced anhedonic behavior [58]. In rats with combined exposure of LPS and chronic mild stress (CMS), treatment with the antidepressants imipramine was effective in reversing depressive-like behavior and the elevated KYN/TRP ratio and TNF-α gene expression [14]. Chen et al. suggest that classical antidepressants act on the KYN pathway and that KYN pathway modulators produce antidepressant effects in rodents. Rats subjected to unpredictable chronic mild stress (UCMS), and QUIN microinjection into the hippocampus exhibited depressive-like behavior and increased levels of glutamate [9]. In an animal model of depression induced by TRP diet depletion, the depressive-like behavior was associated with increased levels of KYN and reduced levels of KYNA. Treatment with the paroxetine (SSRI group) reversed these alterations in KYN pathway, but not the depressive behavior [17].

The effect of drugs on kynurenine metabolites is not fully characterized. The evidences presented above suggest that classical antidepressants cause a general reduction in concentrations of metabolites downstream TRP or shift the metabolism from the neurotoxic to neuroprotective pathway.

TRYPTOPHAN AND 5-HYDROXYTRYPTOPHAN SUPPLEMENTATION

L-tryptophan is the precursor – via the intermediate 5-hydroxytryptophan (5-HTP) – of serotonin (5-HT). Some metabolic changes that are observed in depression may suggest that a dysfunction in the serotonergic neurotransmission is one of possible mechanisms of depression. These changes include: decreased serotonin (5-HT) uptake by the platelets; diminished levels of tryptophan in the plasma; changes in 5HT1A receptor density in different brain areas; decreased prolactin release in response to acute administration of 5-HT-reuptake inhibitors. Moreover, the efficacy of antidepressant medications (such as tricyclic antidepressants (TCAs), SSRIs) may be altered by the decreased potential to inhibit the serotonin transporter. The inhibition of serotonin synthesis by an administration of parachlorophenylalanine decreases the efficacy of antidepressants. Moreover, the use of a special diet containing various amino acids, except for tryptophan (resulting in the decrease of 5-HT synthesis in the brain) may lower mood mainly among recovered depressed patients withdrawn from antidepressants (but not among the healthy volunteers) [20, 59]. An increase in the extracellular level of 5-HT is associated with antidepressant effects [60, 61]. 5-HT is unable to penetrate through the blood-brain barrier (BBB), so if we intend to elevate the level of 5-HT in the central nervous system (CNS), we should administer either tryptophan or 5-HTP, which are able to cross the BBB. It should be noted, however, that the pharmacokinetic features of tryptophan and 5-HTP, due to their short half-life, are not optimal, so various modifications have been used to overcome these limitations (e.g. the co-administration of peripheral amino acid decarboxylase inhibitors). Others have proposed the development

of a slow-release form of 5-HTP to improve its pharmacokinetic efficacy. [60]. Several clinical investigations with various settings have been carried out to assess the antidepressive properties of 5-HTP and tryptophan. Unfortunately, these studies had usually small sample size and included not only patients with MDD, but also patients with bipolar depression or with schizoaffective disorder (moreover, some studies exclusively enrolled patients with diagnoses other than classic MDD). 5HTP and tryptophan as the supplements were compared to the placebo groups or to the patients with various antidepressants (i.e. active comparators, such as tranylcypromine; clomipramine; imipramine; fluvoxamine; fluoxetine). In addition, a few studies were conducted to assess the efficacy of L-tryptophan and 5-HTP as an adjunctive treatment to antidepressants [60, 63, 64]. However, all these preclinical studies did not support a hypothesis that tryptophan and 5-HTP are able to augment the effect of standard antidepressants either [66]. In addition, supplementation with both tryptophan and 5-HTP may cause side effects [50, 61]. Supplementation of tryptophan and 5-HTP is not included in the recommendations for the treatment of depressive disorders. Further studies are needed to determine whether tryptophan and 5-HTP are valuable factors in the adjuvant treatment of depression.

CONCLUSIONS

The inflammatory processes may play a causal role in the development of depressive illness, including MDD. The studies of hepatitis C or cancer patients receiving treatment with inflammation-inducing medications, show increased activation of the kynurenine pathway and decreased levels of tryptophan, which correlate with the inflammation-induced depression. Evidence from patients with inflammatory diseases or patients treated with interferon-α also demonstrated a strong correlation between the depressive symptoms and the production of neurotoxic kynurenine metabolites [43].

Initially, activation of the kynurenine pathway was believed to cause depressive symptoms as a result of serotonin depletion in the brain. However, the weight of the evidences suggests that an imbalance between neurotoxic and neuroprotective metabolites in the KP may be the principal driver of depression. Inflammation plays the main role in the deregulation of KP, however the enhanced immune response is not sufficient to develop depressive disorders. Many literature sources provide evidence that tryptophan metabolism is involved in the pathophysiology of depression (Table 1).

Table 1. Current state of knowledge about the importance of kynurenine pathway in depressive disorders

Study	Year	Sample type	Sample size	Main conclusions
Gabbay et al. [19]	2010	Human Blood samples	Adolescents with M-MDD (MDD with melancholic features; n = 20) Adolescents with Non M-MDD (MDD without melancholic features; n = 30) Healthy adolescents n = 22	KYN/TRP ratios were elevated and TRP concentrations were reduced in adolescents with M-MDD compared to Non M-MDD adolescents and to healthy controls. Adolescents with M-MDD may represent a biologically distinct clinical syndrome with increased activation of the KP
Wurfel et al. [62]	2017	Human Blood samples	Patients with MDD n = 35 Bipolar disorders (BD) n = 53 Healthy controls (HC) n = 92	In multiple analysis, MDD and BD patients had significantly reduced serum values of KYNA and/or KYNA/QUIN in comparison to control. There were positive correlations between CRP and KYN/TRP, 3HK, QUIN, 3HK/KYN (surrogate marker of KMO activity). Inflammation upregulates the enzyme, kynurenine mono-oxygenase (KMO), which converts KYN into 3-HK and QUIN (neurotoxic pathway)
Liu et al. [29]	2018	Human Blood samples	Patients with MDD n = 33 Bipolar depression (BD) n = 20 healthy control (HC) n = 20	Both MDD and BD groups showed significantly lower values of KYNA, QUIN, KYNA/QUIN and KYNA/KYN in comparison to HC. MDD and BD groups did not differ. Depression scale was negatively correlated with TRP, KYN, KYNA/QUIN values in the MDD. KYNA levels may be a potential biomarker for depression. Metabolites of KP have a crucial role in the occurrence and development of MDD
Duda et al. [13]	2019	Rat brain and spleen tissues	5 weeks administration of imipramine (IMI) to rats subjected to chronic mild stress (CMS). 80% of animals respond to IMI (CMS IMI-R). 20% of animals did not respond to IMI (CMS IMI-NR).	CMS increased IFN-γ, IL-6 and IDO mRNA and decreased KAT II (KP neuroprotective enzyme) mRNA expression in the cortex. CMS increased production of IFN-γ and IL-6 proteins in the spleen (this synthesis was decreased in CMS IMI-R). Chronic IMI administration to CMS rats decreased IDO and KMO mRNA and protein expression and increased KAT II/KMO mRNA and protein ratio in CMS IMI-R. CMS IMI-NR rats had higher IDO mRNA expression and protein level in comparison to IMI responders The antidepressant activity of IMI may be explained by modulatory activities on the KAT II/KMO ratio in brain areas

Study	Year	Sample type	Sample size	Main conclusions
Kruse et al. [27]	2019	Human Blood samples	Healthy participants 61 received endotoxin (inflammation-induced depressed mood) 54 received placebo	Endotoxin -induced inflammation leads to rapid changes in levels of kynurenine, tryptophan, and kynurenic acid, (QUIN change was not significant). Endotoxin-induced cytokines concentrations were positively associated with KYN and KYNA, and negatively with TRP. Changes in KYN and QUIN among endotoxin-exposed participants were positively associated with changes in depressed mood (according to the authors, this association would not survive in the multiple analysis)
Colle et al. [62]	2019	Human Blood samples	Current major depressive episode (MDE) patients (n = 173) Healthy control (n = 214).	Tryptophan levels did not differ between MDE patients and healthy control. Serotonin, kynurenine and kynurenine pathways metabolites with neuroprotective effects were lower in MDE patients
Arnone D. et al. [1]	2018	Human	Meta-Analysis of 21 clinical studies (14 investigating MDD and 7 BD).	Meta-analysis supports a role of KP in the pathogenesis of mood disorders. Imbalance between neuroprotective and neurotoxic kynurenine metabolites could play a role in mood disorders. A reduction in kynurenine metabolites (but not tryptophan) in major depression is a main observation
Ogyu K. et al. [40]	2018	Human	Meta-Analysis of 45 clinical studies	Individuals with depression had decreased level of KYNA, KYN and KYNA/QUIN. Antidepressant-free patients showed decreased KYNA levels and increased QUIN levels

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