Kynurenine Pathway of Tryptophan Metabolism in Neuropsychiatric Disorders: Pathophysiologic and Therapeutic Considerations

Ather Muneer

Islamic International Medical College, Riphah International University, Rawalpindi, Pakistan

Under physiological conditions 95% of the ingested essential amino acid tryptophan is metabolized by the kynurenine pathway (KP) to yield the ubiquitous co-enzyme nicotinamide adenine dinucleotide, fulfilling cellular energy requirements. Importantly, the intermediaries of KP exert crucial effects throughout the body, including the central nervous system. Besides, KP metabolites are implicated in diverse disease processes such as inflammation/immune disorders, endocrine/metabolic conditions, cancers and neuropsychiatric diseases. A burgeoning body of research indicates that the KP plays a pathogenic role in major psychiatric diseases like mood disorders and schizophrenia. Triggered by inflammatory processes, the balance between neurotoxic and neuroprotective branches of the KP is disturbed. In preclinical models these discrepancies result in behaviors reminiscent of depression and psychosis. In clinical samples, recent studies are discovering key kynurenine pathway abnormalities which incriminate it in the pathogenesis of the main psychiatric disorders. Harnessing this knowledge has the potential to find disease biomarkers helpful in identifying and prognosticating neuropsychiatric disorders. Concurrently, earnest research efforts directed towards manipulating the KP hold the promise of discovering novel pharmacological agents that have therapeutic value. In this manuscript, an in-depth appraisal of the extant literature is done to understand the working of KP as this applies to neuropsychiatric disorders. It is concluded that this pathway plays an overarching role in the development of major psychiatric disorders, the KP metabolites have the potential to serve as disease markers and new medications based on KP modulation can bring lasting cures for patients suffering from these intractable conditions.

KEY WORDS: Inflammation; Kynurenine pathway; Kynurenic acid; Quinolinic acid; Mood Disorders; Schizophrenia.

INTRODUCTION

Psychiatric illnesses are highly prevalent conditions and major ailments like mood disorders and schizophrenia (SCZ) have devastating impact on the sufferers. About a century ago very little was known about the neurobiology of mental disorders, but now this aspect is being increasingly elucidated. In the last fifty years, careful observations have shown that a biological pathway, known as the kynurenine pathway (KP) is involved in the pathophysiology of principal psychiatric disorders [1]. Metabolism along the KP plays a key role in generating cellular energy in the form of the coenzyme, nicotinamide adenine dinucleotide (NAD^+), required for instance, in mounting immune response against pathogens. However, several KP metabolites play a vital role in physiological processes in the body, including the central nervous system (CNS) and their dysregulation is increasingly incriminated in disease states [2]. In this respect, some products like quinolinic acid (QA) induce neurotoxicity mediated, in part, through NMDA receptor (NMDAR) signaling and glutamatergic neurotransmission, whereas some other metabolites have neuroprotective properties [3]. Accordingly, preclinical studies reveal that in laboratory animals, KP metabolites induce phenotypic changes reminiscent of depression and schizophrenia like psychosis [4].

Current evidence shows that the KP is involved in the regulation of many bodily systems that are dysfunctional in psychiatric disorders such as CNS neurotransmission, immune-inflammatory, endocrine, and metabolic sys-

tems [5]. It is highly desirable to expound on the mechanisms through which the kynurenines (KYN) link with so many systems and ultimately influence domains such as emotion, cognition, pain, and ageing itself [6]. Whereas, the disrupted kynurenine pathway increases the risk of developing psychiatric disorders, certain treatments like electroconvulsive therapy, ketamine, physical exercise and some non-steroidal anti-inflammatories alter kynurenine metabolism [7]. This raises the possibility that kynurenine metabolites have value as treatment response or therapeutic monitoring biomarkers, and targeting the KP emerges as a unique opportunity in developing novel treatments for neuropsychiatric disorders [8,9].

The purpose of this review is to outline the metabolism of tryptophan along the kynurenine pathway in order to highlight the actions of various metabolites in the CNS. An earnest effort is made to investigate the current literature by referring to the PubMed electronic database and elucidate the role of KP in principal psychiatric disorders. The endeavor results in the recognition of the pathophysiologic role and the therapeutic potential that modulation of the KP holds in discovering novel pharmacological agents for refractory mental illnesses.

SEARCH STRATEGY

In January 2020 the PubMed electronic data was queried by a variety of search terms, for example 'kynurenine pathway—psychiatric', 'kynurenine pathway—neuropsychiatric', 'kynurenine—depression', 'kynurenine—mood disorders', 'kynurenine—schizophrenia', etc. A very large number of articles, in excess of 500 hundred were retrieved. The search was focused on papers published in English language during the last 10 years. This reduced the number of citations to 300 and included review articles, original papers consisting of human and animal studies. Surprisingly only a few systematic reviews and meta-analyses were found on the subject, as the majority comprised of narrative reviews. The abstracts of selected articles were read and those found to be particularly relevant (about 100) were read in full and their reference lists were also consulted. In this way a comprehensive appraisal of the current literature was performed. The views were formulated in a cohesive manner and the manuscript was created based on findings of the extant literature.

THE KYNURENINE PATHWAY—METABOLISM AND ACTIONS

In the human beings, tryptophan (TRP) is an essential amino acid wholly derived from dietary sources. It is converted into several bioactive molecules, most importantly the neurotransmitter serotonin and the hormone melatonin. However, only a small percentage of TRP goes into the synthesis of these molecules, since more than 95% is converted into kynurenine and its metabolic intermediaries, terminating in the generation of (NAD^+), an important cellular energy source [10]. In the body, many tissues produce kynurenines, for example the liver enzyme *tryptophan dioxygenase* (*TDO*) converts TRP into KYN, while in the cells of the immune system and brain, *indoleamine 2,3-dioxygenase* (*IDO*) catalyzes this step [11]. The KP has two main branches - under physiological conditions KYN is preferentially converted into 3-hydroxykynurenine (3HK) and then 3-hydroxyanthranilic acid (3HAA), quinolinic acid (QA), and ultimately NAD^+. The remaining balance of KYN is converted into kynurenic acid (KynA) by the enzyme, *kynurenine aminotransferase* (*KAT*) [12]. Figure 1 illustrates the key steps in the metabolism of TRP along the kynurenine pathway (Fig. 1). In the discussion that follows, two KP metabolites i.e. KynA and QA are further elaborated upon, since ostensibly they have important pathophysiological roles.

Kynurenic Acid

KynA is considered to have neuroprotective properties, and at high concentrations competitively inhibits ionotropic glutamate receptors. Additionally, it selectively decreases activity at the glycine co-agonist site of the NMDA receptor, and the administration of even low concentrations of KynA (nanomolar range) into the brain of laboratory animals reduces glutamate levels by 30—40% [13]. KynA also putatively acts as a negative allosteric modulator at the alpha7-nicotinic receptor (α7nACh). Lately, KynA has been shown to possess agonist activity at an orphan G-protein-coupled receptor (GPR35), modulating cAMP production and inhibiting the N-type Ca^{2+} channels of sympathetic neurons and astrocytes, eventually causing suppression of many inflammatory pathways [14]. Furthermore, KynA regulates the immune response through its agonistic effects on the aryl hydrocarbon receptor (AhR), a transcription factor involved in
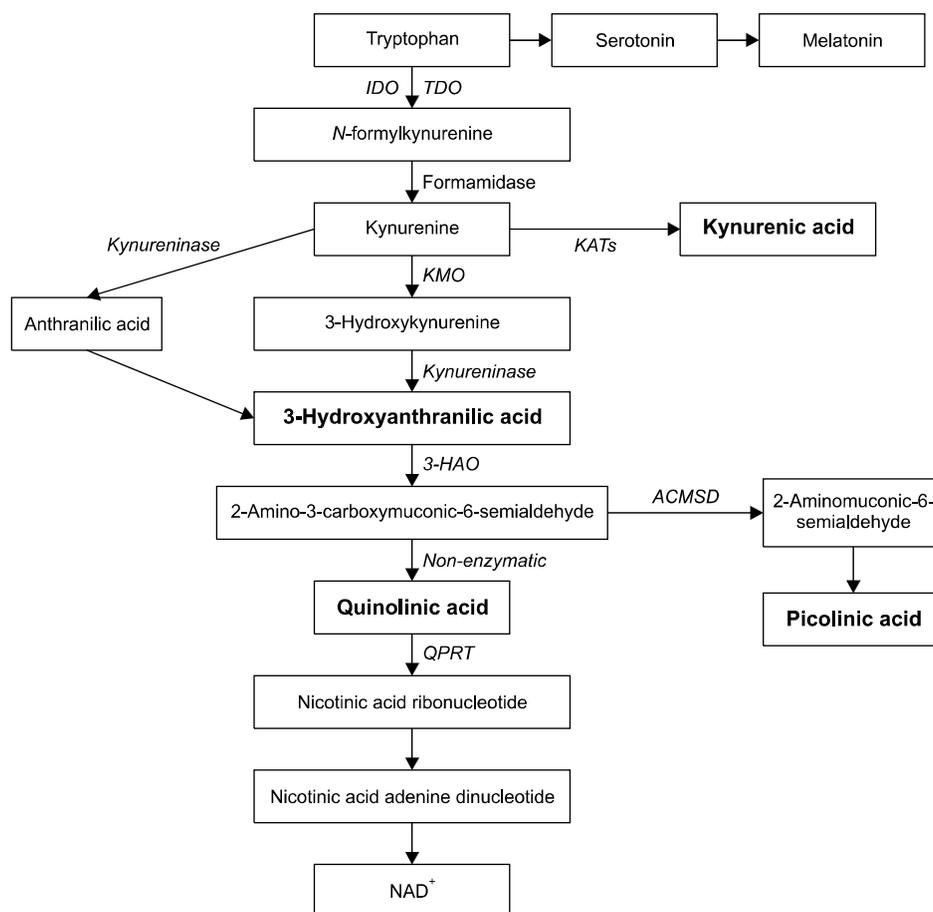
Fig. 1. Tryptophan metabolism along the kynurenine pathway. Tryptophan is an essential amino acid wholly derived from the diet. It is metabolized into active molecules, namely the neurotransmitter serotonin and the hormone melatonin. However, greater than 95% of tryptophan is metabolized along the kynurenine pathway to neuroactive metabolites like quinolinic acid and kynurenic acid. Here key metabolites and enzymes of the kynurenine pathway are illustrated. Refer to the text for a full description of the role of kynurenine pathway in neuropsychiatric disorders.

IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan dioxygenase; KAT, kynurenine aminotransferase; ACMSD, amino-β-carboxymuconate-semialdehyde-decarboxylase; QPRT, quinolinate phosphoribosyltransferase; NAD$^+$*, nicotinamide adenine dinucleotide; KMO, kynurenine 3-monooxygenase; 3-HAO, 3-hydroxyanthranilic acid oxidase.*

the metabolism of xenobiotics. Currently intense research efforts are underway to delineate the role of KynA and understand its actions on various receptors types in the pathogenesis of positive, negative and cognitive symptoms of schizophrenia [15].

Quinolinic Acid

Conversely, QA is an NMDAR agonist (synaptic action, neuroplasticity) and can also inhibit reuptake of glutamate by astrocytes, leading to excitotoxicity (extrasynaptic). Lately, the actions of QA have been further characterized and it is now believed to exert neurotoxic effects via at least nine different mechanisms including the generation of reactive oxygen species, disruption of the blood brain

barrier, destabilization of the cellular cytoskeleton, promotion of tau phosphorylation and disruption of autophagy. Moreover, QA intensifies the inflammatory response by stimulating the production of proinflammatory mediators in astrocytes. Supposedly, QA may also trigger microglia through the NMDAR, a pathway that has been incriminated in programmed neuronal cell death or apoptosis [16-18].

Blood Brain Barrier

TRP, KYN, and 3HK can be transported across the blood brain barrier (BBB). In fact, under physiological conditions 60−80% of KYN in the brain is thought to be of exogenous origin, being actively transported across the

BBB by the large neutral amino acid transporter (LAT1). This number may approach 100% following systemic immune activation, although if inflammation is limited to the brain, KYN can be produced centrally from TRP [19]. In contrast, the conventional view is that KynA and QA poorly cross the BBB and thus these metabolites are thought to be derived in situ from KYN in the brain. However, the issue of BBB permeability is complex and the orthodox version that peripheral QA and KynA do not enter the brain is perhaps too simplistic [20]. Experimentally, in small rodents, a significant correlation has been found between serum and brain QA and about 50−70% of subcutaneously-infused radiolabeled QA is eventually detected in the brain and CSF [21]. It is conceivable that in major psychiatric disorders secondary to inflammation BBB integrity is decreased, such that the entry of circulating KP metabolites into the CNS depends on the degree of underlying inflammation. In support of this argument, in patients with HIV and Hepatitis C who have been on interferon α therapy, a significant correlation is detected between circulating and CSF levels of QA [22,23].

KYNURENINE PATHWAY AND MOOD DISORDERS

Please refer to Table 1 while reading this sections which gives highlights of studies on major depressive disorder described here (Table 1).

IDO Induction by Pro-inflammatory Cytokines

Proinflammatory cytokines (PIC) upregulate brain *IDO* expression and divert the metabolism of TRP towards KYN. The stimulation of *IDO* is primarily via the interferon gamma receptor (IFN-γR), but other pathways particularly toll-like receptor 4 (TLR4), interleukin 1 beta receptor (IL-1βR) and tumor necrosis factor alpha receptor (TNFαR) also activate *IDO* [24,25]. When systemic inflammation is present, CNS concentration of KYN further increases via its enhanced transport through the BBB [26]. Looked at from the evolutionary perspective, triggered immune cells require large amounts of energy to put off an infection, and thus QA is needed to generate adequate amounts of NAD^+. Therefore, under inflammatory conditions increased metabolism is expected along the QA branch of the KP, and indeed this is borne out in the pre-clinical and human literature. In the rat brain, *KMO* but

not *KAT-II* expression is increased after systemic LPS administration and in human hippocampal progenitor cells, IL-1β (a pro-inflammatory cytokine) has been shown to increase *KMO* transcripts [27,28].

Inflammation Induced Production of QA

While most research has focused on the balance between the production of KynA and QA, it is also possible that neurotoxicity may result from a failure to adequately metabolize QA once it is formed. In human neurons, *quinolinate phosphoribosyltransferase* (*QPRT*), the enzyme that metabolizes QA into nicotinic acid mononucleotide and ultimately NAD^+, becomes saturated in the presence of high extracellular concentrations (300−500 nanomolar) of QA. Interestingly, investigations have shown that, *in vitro*, a comparable threshold of QA possesses neurotoxic properties [29,30]. Plausibly, when QA is produced at a faster rate than its conversion to NAD^+ this metabolite accumulates at toxic concentrations, raising the possibility that in the background of inflammatory illness increasing the expression of *QPRT* may have therapeutic benefits. When cellular bioenergetics are compromised, *KMO* activity is likely increased to compensate for this deficit by producing more NAD^+ from QA. This may become counter-productive during inflammation and infectious processes, as in the tissues hypoxic micro-environments prevail. Thus, in order to rapidly generate energy, triggered immune cells shift their metabolism away from NAD-dependent oxidative-phosphorylation to glycolysis and lactic acid production. Supposedly, this metabolic shift causes further exacerbation and accumulation of QA [31-33].

The Glutamate Model of Depression

As alluded to above, KynA is an NMDA receptor antagonist while QA is an agonist. The later has a similar potency to glutamate at the NMDAR, but QA remains in the synaptic cleft for a longer period of time due to less-efficient reuptake, and therefore its excitotoxic effects are stronger. Moreover, the competing actions of KynA and QA at the NMDAR have neuroplastic properties, and this credibly unifies the inflammation and glutamate models of depression [34]. Accordingly, one group of researchers demonstrated that LPS increases QA in the brain, but that the pro-depressive effects of LPS can be blocked by low-dose ketamine without altering the sickness behav-

Table 1. A selection of studies representing involvement of the kynurenine pathway in depression and suicidal behavior

Study	Methods	Results	Conclusion
Allen *et al.*, 2018 [7]	Drivers of KP metabolism (PIC, HPA-axis activity) were measured in MDD patients receiving multiple ketamine infusions and ECT.	MDD subjects at baseline had higher KYN and lower KnyA. Effective treatment with ketamine showed a trend towards reduction in KYN but this did not reach statistical significance.	There is evidence of disturbance in KP in treatment resistant depression but ketamine treatment is not statistically related to improvement in biomarkers.
Raison *et al.*, 2010 [22]	In hepatitis C patients treated with INF-α, both peripheral and CSF levels of KP metabolites downstream of IDO were measured and correlated with depressive symptomatology.	Patients who developed depression had ↑ peripheral and CSF concentrations of KYN and QA and these correlated with symptomatology and inflammatory mediators.	Systemic administration of INF-α resulted in central KP activation, along with cytokines and positively correlated with the severity of depressive symptomatology.
Al-Hakeim *et al.*, 2020 [24]	IDO, (IFN)-γ, IL-4 and TGF-β1 were measured in MDD patients before and after treatment with sertraline and add-on ketoprofen.	Prior to treatment all biomarkers were raised in cases compared to controls. Following treatment with sertraline there was significant reduction in biomarkers. Ketoprofen add on significantly decreased IDO levels.	MDD is associated with kynurenine and immune-inflammatory pathways activation. Antidepressants at least in part act by dampening the activated immune response. Adjunctive NSAID further ameliorates these abnormalities.
Zoga *et al.*, 2014 [25]	Serum IDO measured by ELISA in Female MDD patients (n = 40) and 40 HC. Other mediators measured were TNF-α, INF-γ, CRP and 5-HT.	Baseline values of IDO and immune mediators were higher, and with effective treatment all decreased except INF-γ.	KP enzyme IDO may play an Important role in depression and further elaboration of antidepressant induced reduction in IDO is warranted.
Borsini *et al.*, 2017 [28]	*In vitro*, neurogenesis in human hippocampal progenitor cells. Other parameters measured were IL-1β, mRNA transcripts of KMO and IDO and levels of QA.	Neurogenesis decreased in depression with raised IL-1β. This was reversed when progenitor cells incubated with standard antidepressants and ω-3 fatty acids. However, differential effects of antidepressants and ω-3 fatty acids were noted on KP.	Although there was the common effect of reversal of IL-1β induced inhibition of neurogenesis, venlafaxine, sertraline and ω-3 fatty acids had different effects on KP related mechanisms. Future efforts should be directed at elucidating these mechanisms.
Wichers *et al.*, 2005 [49]	Hepatitis C patients treated with INF-α were studied with repeated measurements of TRP, KYN, KynA and CAA (Competing amino acids for TRP)	During 24 weeks of study INF-α treatment was associated with depressive symptomatology, ↑ KYN/TRP reflecting ↑ IDO activity and ↑ KYN/kynA reflecting neurotoxic challenge but no increase was observed in TRP/CAA.	In INF-α induced depression there is evidence for increased IDO activity and neurotoxic challenge but TRP availability to brain did not change significantly.
Baranyi *et al.*, 2015 [50]	QA levels were measured prospectively in hepatitis C patients receiving INF-α during the entire course of treatment and 3 months after the end of treatment.	During treatment depressive symptoms increased significantly, ↑ IDO activity as measured by serum KYN levels and ↑ QA. The increase in QA was greater with more severity of depression.	Neurotoxic challenge by increased QA may be responsible for INF-α induced depression. These findings support the inflammatory hypothesis of depression.
Savitz *et al.*, 2015 [52]	Subjects with moderate to severe MDD were studied in comparison to HC. Hippocampal volume was measured with sMRI and serum levels of KYN, KynA and QA were determined with LC-MS/MS	KynA/QA trended lower in MDD but correlated positively with hippocampal and amygdalar volumes, whereas QA and KYN were higher in MDD.	Dendritic atrophy with resultant loss of hippocampal volume in MDD was probably secondary to immune-related imbalance in KynA and QA.
Young *et al.*, 2016 [55]	Un-medicated MDD subjects were compared with HC and hippocampal activity measured with fMRI during recall of autobiographical memory (AM) along with serum KP metabolites and cytokines.	In the MDD group, KynA/3HK was inversely associated with left hippocampal activity during AM recall. Further, in this group KynA/QA was positively correlated with percent negative specific memories recalled. Neither CRP nor the cytokines were significantly associated with AM recall or activity of the hippocampus.	In MDD, KynA (neuroprotective) versus QA (neurotoxic) have differential impact on AM recall and hippocampal activity. This effect was absent for inflammation-related mediators (CRP, cytokines).

Table 1. Continued

Study	Methods	Results	Conclusion
Bay-Richter *et al.*, 2015 [58]	KP metabolites, QA and KynA along with inflammatory cytokines were regularly measured in the CSF of repeated suicide attempters over a 2 year period.	Over time, in suicide attempters versus HC, QA was increased and KynA decreased in the CSF. There was a significant relationship between low KynA and severe depressive symptoms. Moreover high IL-6 was associated with more severe suicidal symptoms.	Long-term dysregulation of KP was demonstrated in the CSF. More severe inflammation was associated with greater severity of depressive and suicidal symptoms.
Brundin *et al.*, 2016 [60]	Picolinic acid (PA) is a neuroprotective KP metabolite and the enzyme amino-β-carboxymuconate-semialde hyde-decarboxylase (ACMSD) decreases QA by competitively increasing PA production. In the serum and CSF of suicide attempters QA and PA were measured over a 2 year period. Moreover, genotyping of ACMSD was done on cases and compared to population-based controls.	The ratio PA/QA was significantly decreased in both the serum and CSF of cases versus controls. On repeated measures CSF levels of PA were consistently decreased over 2 years. The minor C allele of the ACMSD SNP rs2121337 was more prevalent in suicide attempters and associated with increased CSF QA.	In subjects prone to suicidal behavior increased CSF QA levels were seen. In suicide attempters there was an imbalance in PA/QA due to an SNP in ACMSD. KP metabolites can serve as biomarkers of suicidal behavior and ACMSD is a potential therapeutic target.

CRP, C-reactive protein; CSF, cerebrospinal fluid; IDO, indoleamine 2,3-dioxygenase; KP, kynurenine pathway; KYN, kynurenine; KynA, kynurenic acid; QA, quinolinic acid; LC-MS/MS, liquid chromatography—tandem mass spectrometry; MDD, major depressive disorder; HC, healthy controls.

ior, inflammatory mediators or *IDO* activity [35]. Instead, the anti-depressant effects of ketamine are mediated through its antagonistic properties at the NMDAR and the promotion of AMPA receptor-mediated glutamatergic neurotransmission. This finding suggests that inflammation-induced activation of the NMDAR by QA is a key mechanistic pathway through which inflammation exerts its depressive effects [36].

Depression and Inflammation

There is now convincing data that inflammation plays a pathophysiological role in a sub-set of cases with depression. The evidence in this regard can be laid out as follows: (a) depressive episode-associated increases in circulating pro-inflammatory cytokines [37], (b) increased expression of inflammation-related genes in monocytes or peripheral blood mononuclear cells (PBMCs) of mood disorder patients [38], (c) the occurrence of depressive episodes in about 30% of patients receiving immune-stimulating treatments [39], (d) the development of depressive symptoms in some healthy individuals given low-dose endotoxin [40], (e) prospective studies demonstrating a positive association between the concentrations of inflammatory mediators at baseline and the development of *de novo* cases of major depressive disorder (MDD) [41], (f)

an epidemiological association between depression and diseases with an autoimmune or inflammatory component [42], (g) higher numbers and activation of microglial cells measured *in vivo* with positron emission tomography [43], and (h) increased number and activation of microglia in depressed suicide victims brains at postmortem [44]. See Table 2 for further information on the evidence presented here (Table 2).

Animal Models

The lesson that has been learnt from meticulously performed experiments is that the kynurenines wield pathophysiological and neuro-behavioral effects that extend beyond those of inflammatory mediators. In this vein, preclinical work in mice has revealed that the pro-depressive effects of lipopolysaccharide (LPS) can be blocked by the genetic deletion or pharmacological inhibition of *IDO* without affecting cytokine levels, implying that within the brain *IDO* activity is essential for the expression of the depressive phenotype [45,46]. Likewise, *KMO* knockout mice are protected from the pro-depressive effects of LPS, demonstrating that, at least in mice, neurotoxic kynurenine metabolites are principal mediators of inflammation induced depression-like behaviors [47,48].

Table 2. The relationship between inflammation and depression－The evidence base

Study	Parameter	Result	Conclusion
Wu *et al.*, 2017 [37]	Circulating cytokines	IL-6 levels increased in MDD and BDD.	Depressive episodes are associated with increased levels of proinflammatory cytokines.
Leday *et al.*, 2018 [38]	Examination of the transcriptome of the circulating mononuclear cells.	In MDD subjects proinflammatory genes were stimulated in a replicable manner.	Transcriptomic analysis of the messenger RNA was a more accurate measure as compared to serum cytokines and cell counts. This study showed the usefulness of transcriptional biomarkers, sub-classifying MDD patients along immunological parameters.
Małyszczak *et al.*, 2019 [39]	Depressive symptoms induced by interferon therapy in Hepatitis C patients	In hepatitis C patients, INF-α treatment for 24 weeks resulted in symptoms of depression. These were more severe in subjects having an underlying biological susceptibility.	Vulnerability that was biologically based and general immune activation, instead of psychological factors (neuroticism) were related to the severity of depression.
Maes *et al.*, 2012 [40]	Serum levels of IgM and IgA against the lipopolysaccharide (LPS) of gram negative enterobacteria	Serum antibodies against LPS of gut commensals were significantly higher in MDD versus controls. IgM levels were statistically higher in patients with chronic depression as compared to those without.	These findings show that increased translocation of gut bacteria along with immunological responses play a part in the development of chronic depression.
Huang *et al.*, 2019 [41]	To assess whether there was a time-based relationship between inflammation (IL-6, hsCRP) and depressive symptoms (BDI), and to evaluate the role of genetic factors on this association.	Eighty-three twin pairs (166 subjects) assessed at baseline and after 7 years. Examination showed a significant positive association from visit 1 IL-6 to visit 2 BDI. But, the opposite trajectory (visit 1 BDI to visit 2 IL-6) was statistically non-significant after correcting for confounding variables.	Elevated IL-6 likely to be a risk factor for depression rather than a consequence, while the opposite may be true for CRP. When taking into account twin factor, significant relationship from IL-6 to depression was only seen in monozygotic twins. This meant that genetic factors played a role in this association.
Vallerand *et al.*, 2019 [42]	The bidirectional association between MDD and alopecia areata (AA) was investigated in a population-based cohort study. The development of incident AA/MDD during follow-up were considered the main outcome measures.	Twenty-six years of follow up showed that MDD increased the risk of subsequently developing AA by 90%. Antidepressant use had a protective effect on the risk of AA. Conversely, AA was found to increase the risk of subsequently developing MDD by 34%.	These results suggested that patients with AA were at increased risk for the later development of MDD. However, having MDD also appeared to be a significant risk factor for AA, with antidepressants moderating this risk.
Li *et al.*, 2018 [43]	Microglia are chief immune mediators in the brain and are implicated in the pathophysiology of MDD. Fifty un-medicated patients with MDD and 30 HC were investigated with positron emission tomography (PET) to examine microglia activation. Cognitive functions were evaluated with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).	MDD patients showed microglia activation throughout fronto-limbic regions. The subjects showed impairment on the attention and delayed memory domains of RBANS. In the frontal cortex, increased microglia activation was associated with lower scores on the RBANS attention domain.	In MDD subjects, microglial activation was detected in significant brain regions. Moreover, attentional dysfunction may be associated with microglial pathology in the frontal cortex of untreated MDD subjects.
Suzuki *et al.*, 2019 [44]	Activated microglia may have a causal role in suicide and underline inflammatory processes including the triggering of the kynurenine pathway. Neuropathological studies of the human postmortem brain of suicide victims were reviewed in this study.	Review of original studies showed that there were increased numbers/activation of microglia in crucial areas like dorsolateral prefrontal cortex, anterior cingulate cortex and mediodorsal thalamus.	Firm evidence from post-mortem studies that the chief immune cells of the brain (microglia) were activated in suicide victims. This signified that inflammation played a contributory role in suicide.

BD, bipolar disorder; BDD, bipolar depression; HC, healthy controls; hsCRP, high sensitivity C-reactive protein; LPS, lipopolysaccharide; MDD, major depressive disorder.

Clinical Studies

In clinical samples it has been shown that almost 30% of patients receiving immunotherapy e.g., IFNα for hepatitis C or cancer develop depressive episodes that overlap with KP activation. Furthermore, IFNα-induced depression corresponds with increase in the ratio of KYN to KynA, indicating a role for the activation of the neurotoxic QA pathway in the genesis of depression [49]. A current study demonstrated that those patients who had clinical depression (higher scores on HRSD) 6−9 months post IFNα-treatment, also had significantly greater plasma concentrations of QA at the corresponding time points [50]. In MDD with an inflammatory etiology, evidence points towards reduction in the peripheral concentration of KynA associated with a decrease in the ratio of KynA to QA, which is evident in the CSF as well [22].

Hippocampal Involvement in Mood Disorders

Interestingly, in the brain the balance between the KynA and QA pathway metabolism is correlated with specific regions, particularly the hippocampus. This relative anatomical specificity is consistent with the high density of NMDAR in the hippocampus, and preclinical data reveal a stronger shift towards the neurotoxic branch of KP in the hippocampus relative to other brain regions [51]. Correspondingly, in individuals with MDD a group of researchers found that lower "neuroprotective indices" or ratios (KynA:3HK, KynA:Qa) were associated with reduced hippocampal volumes [52]. The same investigators demonstrated comparable findings in concussed athletes with depression, and in subjects with bipolar disorder (BD) [53,54]. Also, a follow-up study in depressed patients showed an inverse relationship between peripheral KynA/3HK and left hippocampal activity during the recall of autobiographical memories, indicating a link between kynurenine metabolism and hippocampal function [55].

Suicide

Suicidal behavior cuts across diagnostic boundaries and an increasing body of research is indicative of a strong link between suicidality and inflammation [56]. In the case of suicide attempters, activation of the KP had been reported and the most significant finding in this regard was the relative increase in QA in suicide attempters versus controls [57]. Another study in patients prone to suicidal behavior revealed that symptoms of depression and suicidality varied in direct relation to the degree of inflammation and kynurenine metabolite levels in the CSF. It also demonstrated a long-term dysregulation of the kynurenine pathway over a period of 2 years in the CNS of suicide attempters [58]. Considering postmortem samples, a study in depressed suicide victims demonstrated increased numbers of microglia immunoreactive for QA within sub-regions of the anterior cingulate cortex [59]. Extending these findings further, a group of researchers showed that suicide attempters had reduced levels of the neuroprotective metabolite, picolinic acid (PIC), and a decreased PIC/QA ratio in both the CSF and plasma [60]. Intriguingly, a metabolite in the kynurenine pathway 2-amino-3-carboxymuconic-6-semialdehyde (ACMS) is spontaneously degraded to form QA but can also be converted to PIC by the enzyme *amino-β-carboxymuconate-semialdehyde-decarboxylase* (*ACMSD*). Thus, the demonstrated decrease in PIC supports the likelihood that in the context of suicidal behavior a deficiency in *ACMSD* activity exists. However, more generally it can be assumed that in suicidal behavior aberrant QA-mediated glutamate signaling is driven by altered enzymatic activity at several different points in the KP [61].

Cognition

It is widely accepted that cognitive deficits occur in mood disorders, while impairments like amotivation, alogia and flattening of affect are recognized as negative symptoms of schizophrenia. Cognitive deficits are amongst the most debilitating symptoms of depression and are poorly responsive to the currently available antidepressants [62]. Concerning the role of KP, two contending versions are put forward; in mood disorders, neurotoxic metabolites such as QA have been shown to damage the brain and lead to cognitive deficits [63]. As already mentioned earlier, in MDD subjects there was an association between lower serum KynA to 3HK concentrations and greater hippocampal activity (indicating more effortful recall) during an autobiographical memory task [55]. Although the subject of cognitive deficits and KP metabolism was not widely studied in mood disorders, emerging evidence indicates that KP metabolites are involved in the pathogenesis of these symptoms and could serve as potential targets of treatment [64].

Conversely, in schizophrenia elevated KynA is considered to underlie the cognitive deficits such as executive

dysfunction, impairments in set shifting and abstract thinking. In preclinical studies, elevation of brain KynA through the genetic or pharmacological knockdown of *KMO* was shown to induce cognitive abnormalities evocative of schizophrenia, whereas a recent human study found that plasma KynA levels were significantly higher in SCZ patients than in healthy controls (HC) and that these correlated negatively with attention/vigilance and social cognition [65]. On the other hand, reducing brain KynA through pharmacological inhibition or genetic knockdown of *KAT*-II improved cognitive functioning possibly through modulation of α7nAChRs and glycine co-agonist site of NMDAR [66]. Kynurenic acid is now considered a main player in many aspects of mammalian physiology, including the control of glutamatergic and cholinergic synaptic transmission and immunomodulation (through AhR and GPR35). The new understanding of KynA and *KAT* isoenzymes is likely to foster the identification and rational design of brain penetrant small molecules to attenuate KynA synthesis, without the harmful withdrawal of KynA-dependent neuroprotective actions [67].

Pain

Whereas PIC alone might induce pain, preclinical work demonstrates that *IDO* activation plays a key role in inflammation-related pain and associated depression-like behavior. With respect to latter, the hippocampus appears to play a central role as a study in rats showed that the induction of chronic pain with Freund's adjuvant induced depression like behavior together with hippocampal *IDO* upregulation via IL-6 signaling. Both the nociceptive and depression-like behavior was attenuated in *IDO* gene knockouts or by pharmacological inhibition of *IDO* [68]. In line with these data, acute influenza A virus infections induced robust *IDO* expression in the lungs and lymphoid tissue and also resulted in pain hypersensitivity. This effect was absent in *IDO* knockouts but could be revived by intravenously-administered KYN [69]. Neurotoxic KP metabolites have been implicated in pain-related behavior and spared nerve injury in a murine model increased *KMO* expression and QA concentration along with decreased KynA in the contralateral hippocampus via an IL-1-dependent mechanism. Pharmacological inhibition of *KMO* abolished the depression-like behavior but not the mechanical allodynia, supposedly because inhibition of spinal cord NMDAR was required for analgesia

[70]. It is worth mentioning that chronic pain is a significant risk factor for depression as 30−60% of individuals with clinically severe pain have comorbid major depression, and conversely idiopathic pain is common in MDD [71]. In this regard, a recently published study showed abnormalities of KP metabolite profile in high risk individuals with major depression. Specifically, anthranilic acid emerged as a possible biomarker for depression-related symptoms, since the metabolite's profile in the chronic pain disorder group and chronic unpredictable mild stress mice model were similar to those in the study subjects [72].

KYNURENINE PATHWAY IN SCHIZOPHRENIA

Please refer to Figure 2 to get a pictorial perspective of KP involvement in mood disorders and schizophrenia (Fig. 2).

Dopamine versus Glutamate Hypothesis

First proposed in the 1960's, the dopamine hypothesis specified that increased dopamine neurotransmission in the mesolimbic pathway was responsible for the psychotic symptoms of schizophrenia. Over time, this proposition was amended to account for the psychotomimetic effects of phencyclidine (PCP), a dissociative anesthetic agent and a non-competitive NMDAR antagonist [73]. In rodent models, PCP induced psychotic symptoms and neurocognitive deficits reminiscent of those in schizophrenia, whereas in healthy human subjects its administration resulted in positive, negative and a range of cognitive symptoms. It was postulated that antagonism at the NMDAR and its glycine co-agonist site were responsible for these manifestations [74]. The astrocyte-derived kynurenic acid was the only known endogenous NMDAR and α7nACh antagonist in the brain, and it was hypothesized that in schizophrenia elevated brain KynA altered glutamatergic and cholinergic neurotransmission with indirect increases in dopaminergic signaling [75]. Consistent with this supposition, in animal models, experimentally elevating central KynA levels were shown to increase the burst-firing of midbrain dopaminergic neurons. In line with these results, patients with schizophrenia were shown to have increased KynA in the CSF, while the same abnormality was detected in the brain at postmortem [76].
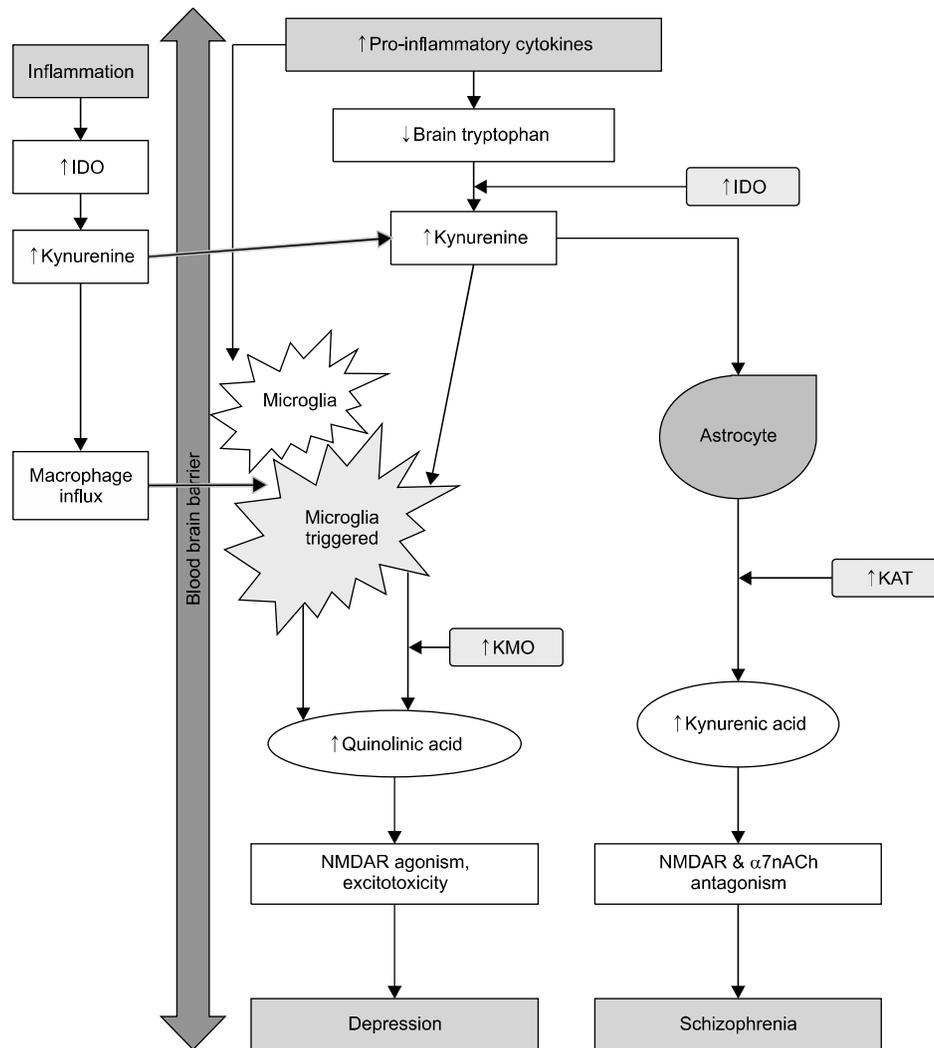
Fig. 2. Kynurenine pathway abnormalities in depression and schizophrenia. An illustration of main biochemical abnormalities in two major psychiatric disorders, i.e., depression and schizophrenia. In the brain, proinflammatory cytokines and other inflammatory mediators cause induction of indoleamine 2,3-dioxygenase and triggering of microglia with increased production of quinolinic acid which is an agonist at the *N*-methyl-D-aspartate receptor and also acts as an excitotoxin. This mechanism is thought to underlie the expression of the depressive phenotype during inflammatory processes. On the contrary in schizophrenia, kynurenine amino transferase, another key kynurenine pathway enzyme is expressed which increases the formation of kynurenic acid. The latter is the only known endogenous NMDAR antagonist and acting through intermediary mechanisms, indirectly increases dopaminergic neurotransmission in the mesolimbic pathway, which is the chief abnormality in schizophrenia. See also text for a full description of KP abnormalities in neuropsychiatric disorders.

NMDAR, NMDA receptor; KP, kynurenine pathway; *IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase.*

Neuroinflammation

It was likely that in psychosis the given increase in KynA was due to inflammation related rise in KYN. In this vein, there was evidence that as in mood disorders, inflammation might play a mechanistic role in schizophrenia. For instance, *in vivo* PET studies reported increased microglial activation in patients with schizophrenia, indicating brain inflammation [77,78]. The neurotoxic branch of

the kynurenine pathway seemed to be unaffected since quinolinic acid was found at normal levels in the CSF and 3-hydroxykynurenine levels were unaltered in the post-mortem brain [79]. Studies investigating peripheral levels of 3-HK detected no difference in serum levels between first-episode neuroleptic-naive patients and controls, whereas other studies suggested that serum levels of 3-HK were decreased following antipsychotic therapy and

could predict the severity of clinical symptoms in neuro-leptic-naive patients with first-episode of schizophrenia [80]. In line with data from the CSF and post mortem studies, cultured human dermal fibroblasts obtained from patients with BD or schizophrenia were shown to release significantly more KynA than cells obtained from controls [81]. Yet another study reported increased plasma levels of KynA in schizophrenia, whereas two studies described decreased plasma levels in patients with either schizophrenia or BD. A recent study examined kynurenic acid in the saliva of patients with schizophrenia and found no basal differences in KynA levels, but tested the hypothesis that the concentrations would change following a psychological stress challenge. The investigators found a higher rate of stress intolerance in patients with schizophrenia, and that the salivary concentration of KynA increased more in patients who did not tolerate the stressful tasks. In the latter group, the increase in kynurenic acid concentration correlated with more severe psychiatric symptoms [82]. Importantly, under normal conditions KynA did not pass the BBB, and the relationship between concentrations of KynA in plasma, CSF, saliva or other tissues had not been comprehensively evaluated.

KAT as a Therapeutic Target

Taken together, these data suggested that a reduction in brain concentrations of kynurenic acid was a novel therapeutic approach for psychotic and cognitive disorders. In this regard it had been proposed that inhibition of *KATs* (*kynurenine amino transferase*), enzymes catalyzing the final step in the production of KynA, could be a feasible option. Although, so far four *KATs* (*KAT I—IV*) had been characterized, *KAT II* appeared to account for ~75% of the production of KynA in the mammalian brain under normal conditions [12]. It had been emphasized that specific inhibition of *KAT II* significantly reduced brain concentrations of KynA. Indeed, mice with a targeted deletion of *KAT II* exhibited decreased brain KynA levels that were associated with enhanced performance in cognitive paradigms [83]. Interestingly, administration of PF-04859989, a selective brain-penetrant *KAT II* inhibitor, decreased midbrain dopamine firing and prevented amphetamine- or ketamine-induced disruption of sensory processing and improved cognitive function in rodents and non-human primates [84].

IMMUNE RESPONSE

Regulation of the Immune Reaction

The KP metabolites play an important role in the regulation of the immune response, and stimulated KP acts as a key negative feedback loop that short-circuits the inflammatory reaction. Currently, it is considered that decreased substrate availability i.e., tryptophan is because of its increased utilization to provide the energy needed for the immune response via conversion of QA to NAD^+. Furthermore, triggering of the KP results in increased concentrations of KYN, 3HK, and 3-HAA which suppress the immune response by inducing the apoptosis of Th1 and natural killer cells (NKC). In addition, TGF β production and regulatory T-cell (T reg) numbers are increased, leading to an environment characterized by immune tolerance or tolerogenicity [85]. This is required to resolve the inflammatory response, however, in the case of pregnancy tolerogenicity protects the allogenic fetus from the mother's immune response [86]. In this vein, a study demonstrated that pregnant mice given an *IDO* inhibitor rejected semiallogenic but not syngenic fetuses, suggesting that the maternal T-cell response against paternal MHC antigens might occur through an *IDO*-dependent mechanism. Nonetheless, the applicability of this model to humans was doubtful, since blocking *IDO in vitro* did not completely inhibit T-cell function and TRP was required by the fetus for normal development. Some researchers construed that, in the context of pregnancy, the putative depletion of TRP was either highly localized or increased TRP utilization had a more modest effect on immune-tolerance [87,88].

Immune Dysregulation in Mood Disorders

As alluded to above, persistent stimulation of the KP leads to a state of immune tolerance with increased vulnerability to infections and malignancies. This phenomenon is relevant to psychiatry, since in a sub-group of patients with severe mood disorders impairment in adaptive immunity was demonstrated. This manifested as reduced numbers and functioning of lymphocytes, fewer NKC with decreased cytotoxicity and increased Treg cells. These findings were significant since depressed individuals ostensibly had increased vulnerability to infections, acutely showed reduced immunogenic responses to vaccines and lost humoral immunity more rapidly in the

years after vaccination [89].

Postpartum Disorders

Given their alleged role in fetal tolerance, it is likely that the kynurenines play a part in the development of postpartum psychiatric disorders. Conceivably, increased KYN, 3HK, and 3-HAA which suppress Th1 and NKC protect against fetal rejection at the expense of increasing the risk of depression. In women without depressive symptoms TRP levels increased within two days of birth, whereas this rise was absent in participants with mild depressive symptoms (postpartum blues) [90]. In line with this result, it was found that in a general population sample of women during the first 3 days after birth, an increase in KYN as well as amino acids that competed with TRP for transport across the BBB, occurred. Possibly this reflected a decrease in the brain availability of TRP, which in turn resulted in "postpartum blues" [91]. A group of investigators observed a shift towards the QA pathway in the first two months postpartum but this phenomenon happened in both women with mood disorders and healthy controls. However, a recent study in women who underwent delivery through cesarean section reported increased serum concentrations of 3HK and 3HK/KYN (putatively reflecting increased *KMO* activity) only in cases with postpartum depression, versus those without this condition [92].

METABOLISM

Gut Microbiota

Accumulating evidence points to the importance of the intestinal microbes in maintaining health. Tryptophan, an essential aromatic amino acid is converted by the commensal gut bacteria into indole derivatives such as indolic acid, skatole, and tryptamine which have profound effects on gut microbial composition, the host's immune system and the host-microbial interface. Lately, the notion of "leaky gut" has been proposed which suggests that bacterial endotoxin finds its way into the systemic circulation because of disturbed gut microbial balance or "dysbiosis". This leads to immune activation with attendant metabolic abnormalities and expression of neuropsychiatric disorders. Further details can be found in the excellent reviews cited here [93,94].

Immune Activation in the Metabolic Syndrome

In the adipose tissue immune cells are key regulators of metabolism modulating lipid storage, glucose homeostasis, and energy expenditure. However, as lipid levels increase the gathered macrophages shift to a pro-inflammatory state, and the neurotoxic branch of the KP is preferentially activated. Emerging evidence indicates that the kynurenines play a mechanistic role in the evolution of metabolic dysfunction. A high-fat diet in mice increased *IDO* expression in the plasma, adipose tissue, and muscle. However, *IDO* knockout animals were protected from the obesity promoting, inflammatory and anti-insulin effects of the administered regimen, although this was dependent on the maintenance of a healthy microbiome through the production of sufficient indole derivatives from TRP [95,96].

Relevance to Psychiatry

Given the research data linking kynurenines with metabolic function and the robust evidence for decreased KynA in depression, it is likely that dysregulation of the KP is part of the shared biology between the two conditions. Existing evidence reflects that patients with type 2 diabetes (T2D) exhibit the same pattern of reduced KynA versus QA as in depression. Additionally, in T2D there are reports of reduced expression of *KAT1* and *KAT2* in the skeletal muscle, with progressive increases in QA elevating the risk of the disorder. Likewise, in obese women it has been shown that pro-inflammatory macrophages in the adipose tissue are shifted towards the neurotoxic branch of the KP, and *KMO* expression is directly correlated with hemoglobin A1c levels [97,98].

AGING

Mechanistic Considerations

Perturbations in the KP have been linked to ageing and various age-related diseases including neurodegenerative disorders, diabetes, depression, cancer and cardiovascular diseases (CVD). The majority of CVD are believed to be associated with insulin resistance, whose pathogenesis also involves an altered KP metabolism. During ageing, and in many age-related disorders a low-grade, Th-1-type sustained inflammation has been reported which results in an activated immune system and the release of PIC. In this vein, IFN γ is able to induce *IDO* expression in peripheral

blood monocytes with a marked increase in neurotoxic QA concentrations, and also elevated is neopterin, a marker of Th1 immune response. Moreover, there is increased expression of *KMO* and the levels of 3-hydroxy anthranilic acid and anthranilic acid are persistently elevated. The former metabolite possesses ROS generating, inflammatory and neurotoxic effects. Age-associated cortisol production upregulates *TDO*, the other TRP metabolizing enzyme, resulting in elevated blood KYN and activation of the pathway [99,100].

Neurodegenerative Disorders

Alzheimer's disease (AD), the most common type of dementia is characterized by the targeted atrophy of the hippocampal gyri where NMDA receptors are abundant as glutamate neurotransmission constitutes the basis of memory acquisition. In AD, the accumulation of amyloid-β has several pathogenic effects including the generation of ROS, mitochondrial dysfunction, endoplasmic reticulum stress and *IDO* induction [101]. In the brain of AD patients there is upregulation of *IDO 1* and enhanced production of QA and, interestingly, elevated KynA concentrations in putamen and caudate nuclei have also been reported. The latter may be a compensatory mechanism for counteracting QA effects and may contribute to cognitive decline via the KynA inhibitory action at the NMDAR [102].

In Parkinson's disease (PD) there is degeneration of neurons in the substantia nigra and a consequent decrease in dopaminergic neurotransmission in the nigrostriatal tracts along with the presence of the hallmark Lewy bodies containing the aggregated protein, α-synuclein. Decreased KynA levels and increased 3-hydroxy kynurenine levels were found in PD brains allegedly leading to mitochondrial energy failure and exaggerated ROS production. Deficiencies in the activities of complex I in PD and complex IV in AD are supposed to contribute to mitochondrial disturbances [103].

Therapeutic Prospects

Recent years have seen an increase in research interest in the manifold changes in kynurenine metabolism in ageing and age-related conditions. The broad actions of KP intermediaries in the brain and their role in regulating the immune response give rise to the possibility of interfering with the pathological processes in an array of age-asso-

ciated diseases. Increasing knowledge about the KP is likely to lead to fresh approaches in treating these devastating diseases, while hopefully also prolonging the lifespan of the sufferers [91].

THERAPEUTIC CONSIDERATIONS

As discussed above, preclinical studies show that KP metabolites play an etiologic role in animal equivalents of depression and schizophrenia. Equally, the clinical literature while mostly cross-sectional is generally consistent with the animal data, although it cannot demonstrate causality. Accordingly, at least in theory, manipulation of the KP holds therapeutic potential. The activity of enzymes in the KP is subject to modification by pharmacological agents and in this respect, for the treatment of cancer, *IDO* inhibitors are in various stages of development. Additionally, clinical trials are underway with agents that act on various nodes in the metabolic pathway. The KP is at the crossroads for diverse physiological processes dysregulated in major psychiatric disorders including immunological, endocrine, metabolic and stress-response systems. Therefore, modulation of the KP could supposedly ameliorate varied manifestations and comorbidities of these conditions [104,105].

New Pharmacological Approaches

In mood disorders there is proof that neurotoxic metabolites are produced at the expense of KynA, such that inhibiting *KMO* or augmenting the activity of *KAT* could have anti-depressant and neuroprotective effects. In this regard, *KMO* inhibitors have shown some efficacy in preclinical models of neuropathic pain, HD, and AD. Since KP is alleged to have a regulatory role in the brain, a disproportionate reduction in QA together with an unbalanced elevation in KynA may be an undesirable outcome of therapeutic approaches involving *KMO* inhibition. Further, since peripheral *KMO* inhibition may cause a surge in circulating KYN concentrations which can then be converted into QA in the CNS, for therapeutic efficacy, sufficient brain penetration of the novel pharmacological agents is needed. Therefore, to circumvent the obstacles, modified approaches are in the offing and are likely to result in the discovery of new medications [106,107].

Preliminary clinical trials for MDD are currently underway with the KynA analogue, 4-chlorokynurenine or

AV-101. Like KynA, AV-101 is a selective antagonist at the glycine-binding site of the NMDAR and recently received fast track designation by the Food and Drug Administration, the US regulator [108]. Another promising strategy is based on the mechanics of KYN transport across the BBB. Under inflammatory conditions KYN, transported across the BBB by the large amino acid transporter LAT1, is preferentially metabolized into neurotoxic metabolites. Therefore, reducing the access of circulating KYN to the brain should, in theory, have therapeutic effects. In this vein, a group of investigators recently demonstrated that leucine treatment is a potential method of competitively blocking the LAT1 to prevent systemic KYN from entering into the brain. Moreover, they reported that leucine blocked LPS-induced depression-like behavior in mice without affecting levels of inflammation or sickness behavior [109]. Accordingly, in individuals with MDD even without evidence of inflammation, a phase 2 clinical trial is in progress to test the anti-depressant effects of leucine.

Currently Available Treatments

Electroconvulsive therapy

While novel compounds are under investigation, the literature suggests that several current treatments for depression alter KP metabolism. In this regard, a recent study showed that prior to treatment with electroconvulsive therapy (ECT) depressed patients had significantly lower levels of serum KynA/QA than controls, but this increased significantly after three ECT treatments performed over two weeks. In yet another study, increases in KynA and KynA/3HK were seen in depressed patients receiving twice-weekly ECT for an average of three weeks [110,111].

Ketamine

A group of investigators showed that in mice ketamine was able to abolish LPS-induced depressive behavior, possibly by blocking QA-mediated activation of NMDAR. The link between ketamine and KP has also been investigated in clinical populations, since in one study ketamine treatment was shown to acutely decrease circulating KYN and the KYN/TRP ratio, with a greater magnitude of reduction in treatment responders versus non-responders. Partially consistent with this result, a non-significant re-

duction in KYN and KYN/TRP was reported in ketamine responders versus non-responders at two hours and 24 hours post initial infusion. While these two studies did not report significant ketamine-induced changes in downstream KP metabolites, in another study, ketamine was shown to increase KynA concentrations from 24 hours after the first infusion until at least two weeks post initiation of treatment. Further, the elevation in KynA was greater in treatment responders versus non-responders. Metabolites down the neurotoxic branch were not measured, but increase in the ratio of KynA to KYN suggested that ketamine may shunt the metabolism of kynurenine towards KynA [112].

Physical exercise

Physical exercise protects against the future onset of depression and is an important factor in the overall management of MDD. In a revealing study in mice, skeletal muscle exercise was shown to protect against depression-like behavior. This was accompanied by increased expression of *KAT* enzymes in the muscle, thus reducing peripheral KYN concentrations and, by inference, resulting in decreased cerebral levels of KYN and neurotoxic metabolites. Further, human volunteers undergoing a three-week endurance exercise program demonstrated increased expression of the *KAT* gene in the muscle [113]. In a continuation study, vigorous exercise was found to increase plasma concentrations of KynA and KynA/QA, and well-conditioned subjects showed a compensatory increase in *KAT* expression in the muscle tissue [114]. However, conflicting results were reported in other studies probably because of such factors as variations in trial designs, forms of exercise and length of employed regimens. In this vein, at least three ongoing clinical trials of exercise proposed alterations in the KP as a secondary outcome measure.

Nonsteroidal anti-inflammatory agents

In view of the assumed role of peripheral and neuro-inflammation in mood disorders, there is much interest in employing anti-inflammatory medications in the subgroup of MDD patients who have concomitant inflammation. In this respect cyclooxygenase (COX) inhibitors have shown therapeutic potential, in particular COX-1 inhibitors. A recently completed trial in bipolar depression showed that patients receiving low-dose aspirin, a COX-1 inhibitor, were significantly more likely to respond to

treatment than placebo-treated subjects, signifying that aspirin may be a useful adjunctive treatment for this condition [115]. Intriguingly, the COX-1 inhibitors indomethacin and diclofenac increased brain levels of KynA in rodents, and in these models levels of kynurenic acid were significantly increased in both the plasma and the hippocampus one hour after a single dose of ibuprofen. Whether the impact of COX inhibition on KynA was independent of NSAID's general anti-inflammatory effects remained to be seen, nonetheless, these data raised the prospect that modifications in KP metabolism might contribute to the alleged anti-depressant effects of COX inhibitors.

FUTURE DIRECTIONS

The kynurenine pathway has a key role in immune function and energy metabolism and any aberration would resonate through the system, ultimately bearing on neural function. This involvement is manifested in the form of neuropsychiatric disorders and associated medical comorbidities. Whereas preclinical studies have demonstrated that, independently of inflammatory processes, the KP plays an etiologic role in animal models of psychiatric illnesses, for example through neuroplasticity at the NMDAR, one challenge for the scientific community is to translate this work to humans. To achieve this objective, novel experimental methods with the necessary degree of specificity need to be developed to manipulate KP activity, so that causality is determined. It is clear that beyond the immune system the KP interacts with other biological systems and, in influencing this pathway, clarifying how inflammation, stress, pain, metabolic, and endocrine systems interconnect or diverge from one other will result in advancement of the field. Moreover, exploration of the role that genetic or epigenetic factors play in influencing the activity of key KP enzymes such as *IDO, KMO* and the *KATs* will further inform this area of research.

As a final note, the biomarker potential of kynurenines needs to be investigated. The KP metabolites have the potential to be utilized as biomarkers of response to existing treatments. Since dysregulation of the KP may weaken the capacity for neuroplasticity, the kynurenines can also be utilized as prognostic markers for neuroprogressive conditions such as mood disorders and schizophrenia.

PERSPECTIVE

Psychiatric disorders are severe conditions which seriously impair functioning in all areas of life. Major mental illnesses have a devastating impact on psychosocial functioning and relationships, however, in spite of these caveats no curative treatments are available and the sufferers face repeated failures in aspects of day to day living. Hence, it is imperative that urgent attention is given to this matter and new avenues of treatment found which can alleviate the suffering of patients with major mental disorders. In this respect, the kynurenine pathway of tryptophan metabolism holds particular promise as decades of research has endorsed its contribution to neuropsychiatric disorders and associated comorbidities. In these conditions, new findings consistently show the involvement of KP and point to potential targets whose manipulation can halt the progress of the disease process and bring lasting cures. In the manuscript, by highlighting the latest discoveries, an effort has been made to increase understanding in this regard and it is hoped that professionals involved in the field will find it useful.

CONCLUSION

In this manuscript a sincere effort has been made to bring to light abnormalities of kynurenine metabolism, as related to neuropsychiatric disorders. The new concept underlines that these conditions are systemic in nature, and their pathogenesis involves several bodily systems. The kynurenines play a crucial role in homeostasis, and ongoing research has compellingly demonstrated their involvement in psychiatric disorders. Since kynurenines have a regulating role in essential biological systems, their association with mental ailments could explain numerous comorbidities associated with these conditions. As the understanding regarding the neurobiological basis of psychiatric disorders evolves, it is hoped that the acquired knowledge will lead to better treatments for innumerable sufferers of these devastating illnesses.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Schwarcz R, Stone TW. *The kynurenine pathway and the brain: challenges, controversies and promises. Neuropharmacology 2017;112(Pt B):237-247.*

2. Kim YK, Jeon SW. *Neuroinflammation and the immune-kynurenine pathway in anxiety disorders. Curr Neuropharmacol 2018;16:574-582.*

3. da Silveira TL, Zamberlan DC, Arantes LP, Machado ML, da Silva TC, Câmara DF, et al. *Quinolinic acid and glutamatergic neurodegeneration in caenorhabditis elegans. Neurotoxicology 2018;67:94-101.*

4. Tufvesson-Alm M, Schwieler L, Schwarcz R, Goiny M, Erhardt S, Engberg G. *Importance of kynurenine 3-monooxygenase for spontaneous firing and pharmacological responses of midbrain dopamine neurons: relevance for schizophrenia. Neuropharmacology 2018;138:130-139.*

5. Majewski M, Kozlowska A, Thoene M, Lepiarczyk E, Grzegorzewski WJ. *Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease. J Physiol Pharmacol 2016;67:3-19.*

6. Sas K, Szabó E, Vécsei L. *Mitochondria, oxidative stress and the kynurenine system, with a focus on ageing and neuroprotection. Molecules 2018;23:191.*

7. Allen AP, Naughton M, Dowling J, Walsh A, O'Shea R, Shorten G, et al. *Kynurenine pathway metabolism and the neurobiology of treatment-resistant depression: comparison of multiple ketamine infusions and electroconvulsive therapy. J Psychiatr Res 2018;100:24-32.*

8. Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. *Neuroinflammation in bipolar depression. Front Psychiatry 2020; 11:71.*

9. Price JB, Bronars C, Erhardt S, Cullen KR, Schwieler L, Berk M, et al. *Bioenergetics and synaptic plasticity as potential targets for individualizing treatment for depression. Neurosci Biobehav Rev 2018;90:212-220.*

10. Cervenka I, Agudelo LZ, Ruas JL. *Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. Science 2017;357:eaaf9794.*

11. Qin Y, Wang N, Zhang X, Han X, Zhai X, Lu Y. *IDO and TDO as a potential therapeutic target in different types of depression. Metab Brain Dis 2018;33:1787-1800.*

12. Erhardt S, Schwieler L, Imbeault S, Engberg G. *The kynurenine pathway in schizophrenia and bipolar disorder. Neuropharmacology 2017;112(Pt B):297-306.*

13. Zakrocka I, Targowska-Duda KM, Wnorowski A, Kocki T, Jóźwiak K, Turski WA. *Influence of cyclooxygenase-2 inhibitors on kynurenic acid production in rat brain in vitro. Neurotox Res 2019;35:244-254.*

14. Fallarini S, Magliulo L, Paoletti T, de Lalla C, Lombardi G. *Expression of functional GPR35 in human iNKT cells. Biochem Biophys Res Commun 2010;398:420-425.*

15. Flis M, Szymona K, Morylowska-Topolska J, Urbańska A,

16. Krukow P, Kandefer-Szerszeń M, et al. *[The kynurenic acid hypothesis - a new look at etiopathogenesis and treatment of schizophrenia]. Pol Merkur Lekarski 2016;41:160-164. Polish.*

16. Pierozan P, Pessoa-Pureur R. *Cytoskeleton as a target of quinolinic acid neurotoxicity: insight from animal models. Mol Neurobiol 2018;55:4362-4372.*

17. Santana-Martínez RA, Silva-Islas CA, Fernández-Orihuela YY, Barrera-Oviedo D, Pedraza-Chaverri J, Hernández-Pando R, et al. *The therapeutic effect of curcumin in quinolinic acid-induced neurotoxicity in rats is associated with BDNF, ERK1/2, Nrf2, and antioxidant enzymes. Antioxidants (Basel) 2019;8:388.*

18. Jacobs KR, Lovejoy DB. *Inhibiting the kynurenine pathway in spinal cord injury: multiple therapeutic potentials? Neural Regen Res 2018;13:2073-2076.*

19. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, et al. *Neuroinflammation and depression: a review. Eur J Neurosci 2020. doi: 10.1111/ejn.14720. [Epub ahead of print]*

20. Pedersen BK. *Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol 2019;15:383-392.*

21. Guillemin GJ. *Quinolinic acid, the inescapable neurotoxin. FEBS J 2012;279:1356-1365.*

22. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, et al. *CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. Mol Psychiatry 2010;15:393-403.*

23. Baranyi A, Amouzadeh-Ghadikolai O, Lewinski DV, Breitenecker RJ, Stojakovic T, März W, et al. *Beta-trace protein as a new non-invasive immunological marker for quinolinic acid-induced impaired blood-brain barrier integrity. Sci Rep 2017;7:43642.*

24. Al-Hakeim HK, Twayej AJ, Al-Dujaili AH, Maes M. *Plasma indoleamine-2,3-dioxygenase (IDO) is increased in drug-naïve major depressed patients and treatment with sertraline and ketoprofen normalizes IDO in association with pro-inflammatory and immune- regulatory cytokines. CNS Neurol Disord Drug Targets 2020;19:44-54.*

25. Zoga M, Oulis P, Chatzipanagiotou S, Masdrakis VG, Pliatsika P, Boufidou F, et al. *Indoleamine 2,3-dioxygenase and immune changes under antidepressive treatment in major depression in females. In Vivo 2014;28:633-638.*

26. Martín-Hernández D, Tendilla-Beltrán H, Madrigal JLM, García-Bueno B, Leza JC, Caso JR. *Chronic mild stress alters kynurenine pathways changing the glutamate neurotransmission in frontal cortex of rats. Mol Neurobiol 2019;56: 490-501.*

27. Connor TJ, Starr N, O'Sullivan JB, Harkin A. *Induction of indolamine 2,3-dioxygenase and kynurenine 3-monooxygenase in rat brain following a systemic inflammatory challenge: a role for IFN-gamma? Neurosci Lett 2008;441:29-34.*

28. Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su

KP, et al. Rescue of IL-1β-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav Immun 2017;65:230-238.

29. Myint AM, Kim YK. Network beyond IDO in psychiatric disorders: revisiting neurodegeneration hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 2014;48:304-313.

30. Adams S, Teo C, McDonald KL, Zinger A, Bustamante S, Lim CK, et al. Involvement of the kynurenine pathway in human glioma pathophysiology. PLoS One 2014;9:e112945.

31. Dantzer R. Role of the kynurenine metabolism pathway in inflammation-induced depression: preclinical approaches. Curr Top Behav Neurosci 2017;31:117-138.

32. Kanchanatawan B, Sirivichayakul S, Ruxrungtham K, Carvalho AF, Geffard M, Ormstad H, et al. Deficit, but not nondeficit, schizophrenia is characterized by mucosa-associated activation of the tryptophan catabolite (TRYCAT) pathway with highly specific increases in IgA responses directed to picolinic, xanthurenic, and quinolinic acid. Mol Neurobiol 2018;55:1524-1536.

33. Braidy N, Grant R. Kynurenine pathway metabolism and neuroinflammatory disease. Neural Regen Res 2017;12:39-42.

34. Savitz J. The kynurenine pathway: a finger in every pie. Mol Psychiatry 2020;25:131-147.

35. Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, et al. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology 2013;38: 1609-1616.

36. Sayson LV, Botanas CJ, Custodio RJP, Abiero A, Kim M, Lee HJ, et al. The novel methoxetamine analogs N-ethylnorketamine hydrochloride (NENK), 2-MeO-N-ethylketamine hydrochloride (2-MeO-NEK), and 4-MeO-N-ethylketamine hydrochloride (4-MeO-NEK) elicit rapid antidepressant effects via activation of AMPA and 5-HT$_2$ receptors. Psychopharmacology (Berl) 2019;236:2201-2210.

37. Wu W, Zheng YL, Tian LP, Lai JB, Hu CC, Zhang P, et al. Circulating T lymphocyte subsets, cytokines, and immune checkpoint inhibitors in patients with bipolar II or major depression: a preliminary study. Sci Rep 2017;7:40530.

38. Leday GGR, Vértes PE, Richardson S, Greene JR, Regan T, Khan S, et al. Replicable and coupled changes in innate and adaptive immune gene expression in two case-control studies of blood microarrays in major depressive disorder. Biol Psychiatry 2018;83:70-80.

39. Małyszczak K, Inglot M, Frydecka D, Hadryś T, Pawłowski T. Biological and psychological components of depression in patients receiving IFN-alpha therapy for hepatitis C. Adv Clin Exp Med 2019;28:1217-1222.

40. Maes M, Kubera M, Leunis JC, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J Affect Disord 2012;141:55-62.

41. Huang M, Su S, Goldberg J, Miller AH, Levantsevych OM,

Shallenberger L, et al. Longitudinal association of inflammation with depressive symptoms: a 7-year cross-lagged twin difference study. Brain Behav Immun 2019;75:200-207.

42. Vallerand IA, Lewinson RT, Parsons LM, Hardin J, Haber RM, Lowerison MW, et al. Assessment of a bidirectional association between major depressive disorder and alopecia areata. JAMA Dermatol 2019;155:475-479.

43. Li H, Sagar AP, Kéri S. Microglial markers in the frontal cortex are related to cognitive dysfunctions in major depressive disorder. J Affect Disord 2018;241:305-310.

44. Suzuki H, Ohgidani M, Kuwano N, Chrétien F, Lorin de la Grandmaison G, Onaya M, et al. Suicide and microglia: recent findings and future perspectives based on human studies. Front Cell Neurosci 2019;13:31.

45. Lawson MA, Parrott JM, McCusker RH, Dantzer R, Kelley KW, O'Connor JC. Intracerebroventricular administration of lipopolysaccharide induces indoleamine-2,3-dioxygenase-dependent depression-like behaviors. J Neuroinflammation 2013;10:87.

46. Salazar A, Gonzalez-Rivera BL, Redus L, Parrott JM, O'Connor JC. Indoleamine 2,3-dioxygenase mediates anhedonia and anxiety-like behaviors caused by peripheral lipopolysaccharide immune challenge. Horm Behav 2012;62:202-209.

47. Parrott JM, Redus L, Santana-Coelho D, Morales J, Gao X, O'Connor JC. Neurotoxic kynurenine metabolism is increased in the dorsal hippocampus and drives distinct depressive behaviors during inflammation. Transl Psychiatry 2016;6:e918.

48. Garrison AM, Parrott JM, Tuñon A, Delgado J, Redus L, O'Connor JC. Kynurenine pathway metabolic balance influences microglia activity: targeting kynurenine monooxygenase to dampen neuroinflammation. Psychoneuroendocrinology 2018;94:1-10.

49. Wichers MC, Koek GH, Robaeys G, Verkerk R, Scharpé S, Maes M. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Mol Psychiatry 2005;10:538-544.

50. Baranyi A, Meinitzer A, Breitenecker RJ, Amouzadeh-Ghadikolai O, Stauber R, Rothenhäusler HB. Quinolinic acid responses during interferon-α-induced depressive symptomatology in patients with chronic hepatitis c infection - a novel aspect for depression and inflammatory hypothesis. PLoS One 2015;10:e0137022.

51. Parrott JM, Redus L, O'Connor JC. Kynurenine metabolic balance is disrupted in the hippocampus following peripheral lipopolysaccharide challenge. J Neuroinflammation 2016;13:124.

52. Savitz J, Drevets WC, Smith CM, Victor TA, Wurfel BE, Bellgowan PS, et al. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. Neuropsychopharmacology 2015; 40:463-471.

53. Meier TB, Savitz J, Singh R, Teague TK, Bellgowan PS. *Smaller dentate gyrus and CA2 and CA3 volumes are associated with kynurenine metabolites in collegiate football athletes. J Neurotrauma 2016;33:1349-1357.*

54. Savitz J, Dantzer R, Wurfel BE, Victor TA, Ford BN, Bodurka J, et al. *Neuroprotective kynurenine metabolite indices are abnormally reduced and positively associated with hippocampal and amygdalar volume in bipolar disorder. Psychoneuroendocrinology 2015;52:200-211.*

55. Young KD, Drevets WC, Dantzer R, Teague TK, Bodurka J, Savitz J. *Kynurenine pathway metabolites are associated with hippocampal activity during autobiographical memory recall in patients with depression. Brain Behav Immun 2016; 56:335-342.*

56. Brundin L, Bryleva EY, Thirtamara Rajamani K. *Role of inflammation in suicide: from mechanisms to treatment. Neuropsychopharmacology 2017;42:271-283.*

57. Serafini G, Adavastro G, Canepa G, Capobianco L, Conigliaro C, Pittaluga F, et al. *Abnormalities in kynurenine pathway metabolism in treatment-resistant depression and suicidality: a systematic review. CNS Neurol Disord Drug Targets 2017;16:440-453.*

58. Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Träskman-Bendz L, Guillemin GJ, et al. *A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. Brain Behav Immun 2015;43:110-117.*

59. Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, et al. *Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation 2011;8:94.*

60. Brundin L, Sellgren CM, Lim CK, Grit J, Pålsson E, Landén M, et al. *An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. Transl Psychiatry 2016;6:e865.*

61. Bryleva EY, Brundin L. *Kynurenine pathway metabolites and suicidality. Neuropharmacology 2017;112(Pt B):324-330.*

62. Listunova L, Roth C, Bartolovic M, Kienzle J, Bach C, Weisbrod M, et al. *Cognitive impairment along the course of depression: non-pharmacological treatment options. Psychopathology 2018;51:295-305.*

63. Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, et al. *Cross-sectional relationship between kynurenine pathway metabolites and cognitive function in major depressive disorder. Psychoneuroendocrinology 2019;101:72-79.*

64. Konstantinou G, Papageorgiou CC, Angelopoulos E. *[Kynurenine pathway in bipolar disorder]. Psychiatriki 2018;29:338-348. Modern Greek.*

65. Huang X, Ding W, Wu F, Zhou S, Deng S, Ning Y. *Increased plasma kynurenic acid levels are associated with impaired attention/vigilance and social cognition in patients with schizophrenia. Neuropsychiatr Dis Treat 2020;16:263-271.*

66. Albuquerque EX, Schwarcz R. *Kynurenic acid as an antagonist of α7 nicotinic acetylcholine receptors in the brain: facts and challenges. Biochem Pharmacol 2013;85:1027-1032.*

67. Rossi F, Miggiano R, Ferraris DM, Rizzi M. *The synthesis of kynurenic acid in mammals: an updated kynurenine aminotransferase structural katalogue. Front Mol Biosci 2019;6:7.*

68. Kim H, Chen L, Lim G, Sung B, Wang S, McCabe MF, et al. *Brain indoleamine 2,3-dioxygenase contributes to the comorbidity of pain and depression. J Clin Invest 2012;122: 2940-2954.*

69. Huang L, Ou R, Rabelo de Souza G, Cunha TM, Lemos H, Mohamed E, et al. *Virus infections incite pain hypersensitivity by inducing indoleamine 2,3 dioxygenase. PLoS Pathog 2016;12:e1005615.*

70. Laumet G, Zhou W, Dantzer R, Edralin JD, Huo X, Budac DP, et al. *Upregulation of neuronal kynurenine 3-monooxygenase mediates depression-like behavior in a mouse model of neuropathic pain. Brain Behav Immun 2017;66: 94-102.*

71. Benatti C, Blom JM, Rigillo G, Alboni S, Zizzi F, Torta R, et al. *Disease-induced neuroinflammation and depression. CNS Neurol Disord Drug Targets 2016;15:414-433.*

72. Sakurai M, Yamamoto Y, Kanayama N, Hasegawa M, Mouri A, Takemura M, et al. *Serum metabolic profiles of the tryptophan-kynurenine pathway in the high risk subjects of major depressive disorder. Sci Rep 2020;10:1961.*

73. Fujigaki H, Mouri A, Yamamoto Y, Nabeshima T, Saito K. *Linking phencyclidine intoxication to the tryptophan-kynurenine pathway: therapeutic implications for schizophrenia. Neurochem Int 2019;125:1-6.*

74. Kehr J, Yoshitake T, Ichinose F, Yoshitake S, Kiss B, Gyertyán I, et al. *Effects of cariprazine on extracellular levels of glutamate, GABA, dopamine, noradrenaline and serotonin in the medial prefrontal cortex in the rat phencyclidine model of schizophrenia studied by microdialysis and simultaneous recordings of locomotor activity. Psychopharmacology (Berl) 2018;235:1593-1607.*

75. Flores-Barrera E, Thomases DR, Cass DK, Bhandari A, Schwarcz R, Bruno JP, et al. *Preferential disruption of prefrontal GABAergic function by nanomolar concentrations of the α7nACh negative modulator kynurenic acid. J Neurosci 2017;37:7921-7929.*

76. Kozak R, Campbell BM, Strick CA, Horner W, Hoffmann WE, Kiss T, et al. *Reduction of brain kynurenic acid improves cognitive function. J Neurosci 2014;34:10592-10602.*

77. Buckley PF. *Neuroinflammation and schizophrenia. Curr Psychiatry Rep 2019;21:72.*

78. Laskaris LE, Di Biase MA, Everall I, Chana G, Christopoulos A, Skafidas E, et al. *Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol 2016;173: 666-680.*

79. Gos T, Myint AM, Schiltz K, Meyer-Lotz G, Dobrowolny H,

Busse S, *et al. Reduced microglial immunoreactivity for endogenous NMDA receptor agonist quinolinic acid in the hippocampus of schizophrenia patients. Brain Behav Immun* 2014;41:59-64.

80. Condray R, Dougherty GG Jr, Keshavan MS, Reddy RD, Haas GL, Montrose DM, *et al. 3-Hydroxykynurenine and clinical symptoms in first-episode neuroleptic-naive patients with schizophrenia. Int J Neuropsychopharmacol* 2011;14:756-767.

81. Johansson AS, Owe-Larsson B, Asp L, Kocki T, Adler M, Hetta J, *et al. Activation of kynurenine pathway in ex vivo fibroblasts from patients with bipolar disorder or schizophrenia: cytokine challenge increases production of 3-hydroxykynurenine. J Psychiatr Res* 2013;47:1815-1823.

82. Chiappelli J, Rowland LM, Notarangelo FM, Wijtenburg SA, Thomas MAR, Pocivavsek A, *et al. Salivary kynurenic acid response to psychological stress: inverse relationship to cortical glutamate in schizophrenia. Neuropsychopharmacology* 2018;43:1706-1711.

83. Bortz DM, Wu HQ, Schwarcz R, Bruno JP. *Oral administration of a specific kynurenic acid synthesis (KAT II) inhibitor attenuates evoked glutamate release in rat prefrontal cortex. Neuropharmacology* 2017;121:69-78.

84. Dounay AB, Anderson M, Bechle BM, Evrard E, Gan X, Kim JY, *et al. PF-04859989 as a template for structure-based drug design: identification of new pyrazole series of irreversible KAT II inhibitors with improved lipophilic efficiency. Bioorg Med Chem Lett* 2013;23:1961-1966.

85. Mándi Y, Vécsei L. *The kynurenine system and immunoregulation. J Neural Transm (Vienna)* 2012;119:197-209.

86. Worton SA, Greenwood SL, Wareing M, Heazell AE, Myers J. *The kynurenine pathway; a new target for treating maternal features of preeclampsia? Placenta* 2019;84:44-49.

87. Badawy AA. *Tryptophan metabolism, disposition and utilization in pregnancy. Biosci Rep* 2015;35:e00261.

88. Badawy AA, Namboodiri AM, Moffett JR. *The end of the road for the tryptophan depletion concept in pregnancy and infection. Clin Sci (Lond)* 2016;130:1327-1333.

89. Weyh C, Krüger K, Strasser B. *Physical activity and diet shape the immune system during aging. Nutrients* 2020;12:622.

90. Duan KM, Ma JH, Wang SY, Huang Z, Zhou Y, Yu H. *The role of tryptophan metabolism in postpartum depression. Metab Brain Dis* 2018;33:647-660.

91. Baïlara KM, Henry C, Lestage J, Launay JM, Parrot F, Swendsen J, *et al. Decreased brain tryptophan availability as a partial determinant of post-partum blues. Psychoneuroendocrinology* 2006;31:407-413.

92. Quan C, Wang S, Duan K, Ma J, Yu H, Yang M, *et al. The role of kynurenine pathway and kynurenic aminotransferase alleles in postpartum depression following cesarean section in Chinese women. Brain Behav* 2020;10:e01566.

93. Comai S, Bertazzo A, Brughera M, Crotti S. *Tryptophan in health and disease. Adv Clin Chem* 2020;95:165-218.

94. Agus A, Planchais J, Sokol H. *Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe* 2018;23:716-724.

95. Laurans L, Venteclef N, Haddad Y, Chajadine M, Alzaid F, Metghalchi S, *et al. Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health. Nat Med* 2018;24:1113-1120.

96. Evrensel A, Ceylan ME. *Fecal microbiota transplantation and its usage in neuropsychiatric disorders. Clin Psychopharmacol Neurosci* 2016;14:231-237.

97. Favennec M, Hennart B, Caiazzo R, Leloire A, Yengo L, Verbanck M, *et al. The kynurenine pathway is activated in human obesity and shifted toward kynurenine monooxygenase activation. Obesity (Silver Spring)* 2015;23:2066-2074.

98. Song P, Ramprasath T, Wang H, Zou MH. *Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. Cell Mol Life Sci* 2017;74:2899-2916.

99. Castro-Portuguez R, Sutphin GL. *Kynurenine pathway, NAD$^+$ synthesis, and mitochondrial function: targeting tryptophan metabolism to promote longevity and healthspan. Exp Gerontol* 2020;132:110841.

100. Kim BJ, Lee SH, Koh JM. *Clinical insights into the kynurenine pathway in age-related diseases. Exp Gerontol* 2020;130:110793.

101. Zádori D, Veres G, Szalárdy L, Klivényi P, Vécsei L. *Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines. J Alzheimers Dis* 2018;62:523-547.

102. Lovelace MD, Varney B, Sundaram G, Lennon MJ, Lim CK, Jacobs K, *et al. Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases. Neuropharmacology* 2017;112(Pt B):373-388.

103. Lim CK, Fernández-Gomez FJ, Braidy N, Estrada C, Costa C, Costa S, *et al. Involvement of the kynurenine pathway in the pathogenesis of Parkinson's disease. Prog Neurobiol* 2017;155:76-95.

104. Achtyes E, Keaton SA, Smart L, Burmeister AR, Heilman PL, Krzyzanowski S, *et al. Inflammation and kynurenine pathway dysregulation in post-partum women with severe and suicidal depression. Brain Behav Immun* 2020;83:239-247.

105. Roman M, Irwin MR. *Novel neuroimmunologic therapeutics in depression: a clinical perspective on what we know so far. Brain Behav Immun* 2020;83:7-21.

106. Dounay AB, Tuttle JB, Verhoest PR. *Challenges and opportunities in the discovery of new therapeutics targeting the kynurenine pathway. J Med Chem* 2015;58:8762-8782.

107. Jacobs KR, Castellano-Gonzalez G, Guillemin GJ, Lovejoy DB. *Major developments in the design of inhibitors along the kynurenine pathway. Curr Med Chem* 2017;24:2471-2495.

108. Park LT, Kadriu B, Gould TD, Zanos P, Greenstein D, Evans

JW, et al. A randomized trial of the N-Methyl-d-aspartate re-ceptor glycine site antagonist prodrug 4-chlorokynurenine in treatment-resistant depression. Int J Neuropsychopharmacol 2020;23:417-425.

109. Walker AK, Wing EE, Banks WA, Dantzer R. Leucine com-petes with kynurenine for blood-to-brain transport and pre-vents lipopolysaccharide-induced depression-like behavior in mice. Mol Psychiatry 2019;24:1523-1532.

110. Guloksuz S, Arts B, Walter S, Drukker M, Rodriguez L, Myint AM, et al. The impact of electroconvulsive therapy on the tryptophan-kynurenine metabolic pathway. Brain Behav Immun 2015;48:48-52.

111. Wu Y, Zhong X, Mai N, Wen Y, Shang D, Hu L, et al. Kynurenine pathway changes in late-life depression. J Affect Disord 2018;235:76-81.

112. Zhou Y, Zheng W, Liu W, Wang C, Zhan Y, Li H, et al. Antidepressant effect of repeated ketamine administration on kynurenine pathway metabolites in patients with uni-polar and bipolar depression. Brain Behav Immun 2018;74: 205-212.

113. Agudelo LZ, Femenía T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V, et al. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 2014;159:33-45.

114. Schlittler M, Goiny M, Agudelo LZ, Venckunas T, Brazaitis M, Skurvydas A, et al. Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynur-enic acid in humans. Am J Physiol Cell Physiol 2016;310: C836-C840.

115. Savitz JB, Teague TK, Misaki M, Macaluso M, Wurfel BE, Meyer M, et al. Treatment of bipolar depression with mino-cycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. Transl Psychiatry 2018;8:27.