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Kynurenine pathway dysfunction in the pathophysiology and treatment of depression: evidences from animal and human studies

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Abstract

Treatment-resistant depression affects up to 20% of individuals suffering from major depressive disorder (MDD). The medications currently available to treat depression, including serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), fail to produce adequate remission of depressive symptoms for a large number of patients. The monoamine hypothesis upon which these medications are predicated should be expanded and revised as research elucidates alternative mechanisms of depression and effective methods to treat the underlying pathologic consequences. Research into the role of tryptophan degradation and the kynurenine pathway in the setting of inflammation has brought new insight into potential etiologies of MDD. Further investigation into the connection between inflammatory mediators, tryptophan degradation, and MDD can provide many targets for novel antidepressant therapies. Thus, this review will highlight the role of the kynurenine pathway in the pathophysiology of depression, as well as a novel therapeutic target to classic and new modulators to treat depression based on findings from preclinical and clinical studies.

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Contributors

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Keywords

Kynurenine pathway; Indoleamine 2,3–dioxygenase; Tryptophan; Inflammation; Depression

1. INTRODUCTION

Mental illness is a pervasive category of disorders that account for a larger proportion of disability in developed countries than any other illness, including cancer and heart disease (Reeves et al., 2011). Depressive disorders are also a global issue and the leading cause of burden and disability worldwide, according to the 2010 Global Burden of Disease of the World Health Organization (Ferrari et al., 2013). Major Depressive Disorder (MDD) is a significant public health issue within the United States that affects roughly 3% of adults, or approximately 9 million people (Reeves et al., 2011). The economic burden of MDD in the United States was estimated to be $210 billion in 2010, an increase in over 20% since 2005 (Greenberg et al., 2015). The burden this places on the patients, health care system, and economy as a whole indicates the importance of efficacious treatment of mental illnesses and continued research into the biological etiologies of these complex conditions.

The underlying cause of depression has been difficult to elucidate due to the heterogeneous nature of the disease and is based on cluster of symptoms derived from different etiologies. The monoamine deficiency hypothesis has historically been used to explain how depressive symptoms arise from insufficient levels of monoamine neurotransmitters (Delgado, 2006; Schildkraut, 1965). The serotonergic hypothesis was later developed by Van Praag and Korf (1971), followed by the dopaminergic hypothesis of Willner et al. (1990). However, as evidenced by the latent response to antidepressant medications, specifically reuptake inhibitors, and the prevalence of treatment-resistant depression, it is necessary to continue researching alternative treatment methodologies (Trivedi et al., 2008).

Early generations of antidepressants were the monoamine oxidase inhibitors (MOAIs) and the tricyclic antidepressants (TCAs). The mechanism of action of MOAIs is irreversible inhibition of monoamine oxidase, the enzyme responsible for degradation of serotonin, norepinephrine, and dopamine, thereby increasing synaptic concentrations of these neurotransmitters. TCAs act by decreasing reuptake of serotonin and norepinephrine in the presynaptic neurons, effectively increasing their synaptic concentration (DeBattista, 2012). While MAOIs and TCAs do effectively decrease symptoms of depression in a subset of individuals, they are limited by their considerable side effects and are no longer prescribed as first line treatments for depression (Elhwuegi, 2004).

Current first line antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The selectivity of these drugs has resulted in a treatment option that is better tolerated with fewer side effects, as compared to the MOAIs and TCAs (DeBattista, 2012). However, despite improvements in receptor targeting, SSRIs are no more efficacious than the older TCAs at relieving symptoms of depression (Millan, 2006). Improvements in the side effect profile may increase compliance with treatment programs, but increased efficacy is the ultimate goal for successful pharmacologic management of depression.

Adjuvant therapy with atypical antipsychotics, such as quetiapine, aripiprazole, and olazapine, has been shown to augment the therapeutic effects of SSRIs and has been approved for use in treatment-resistant depression (Bobo and Shelton, 2010; Connolly and Thase, 2011). The detrimental health effects of prolonged atypical antipsychotic use are considered a significant hindrance to the long-term use of this combination, despite the potential benefits. Side effects included significant weight gain, dyslipidemia, and altered glucose metabolism (Davey et al., 2012).

Another important consideration regarding currently available antidepressant treatments is the slow onset of action before clinical improvement is attained. Often, SSRIs and SNRIs require weeks to months of treatment before patients report a diminishment of symptoms (O'Leary et al., 2014). There is also a higher risk of suicide and other deliberate acts of self-harm during the first month of treatment with antidepressants. It has been suggested this is due to an improvement in physical energy that precedes improvements in depressive mood and negative thoughts (Conwell and Heisel, 2012). Identifying faster acting antidepressants is clearly crucial to increasing compliance and decreasing the harmful effects of delayed treatment.

Similarly, related to insufficient therapeutic response of the currently available antidepressants, at least 20% of depressed patients are treatment-resistant—defined as nonresponse to two different pharmacologic classes taken at optimal dose and for sufficient period of time (Berlim and Turecki, 2007). Additionally, approximately 50% of those who are diagnosed with MDD will experience a recurrent or chronic course of the illness (Crown, 2002). Major depression is a complex disorder in which gene-environment interactions affects many areas of the body; it stands to reason that manipulating one molecule or neurotransmitter may not effectively cure the disease (Myint, 2012a). The insufficient therapeutic effect of the currently available antidepressants has moved the field to focus on alternative mechanisms beyond the monoamine hypothesis. Indeed, over the past two decades there has been a shift from the monoamine hypothesis to pathways involving neuroplasticity impairment. Since patients with autoimmune and inflammatory disorders such as diabetes and fibromyalgia often present with depressive symptoms, it has been proposed that depression may be linked to inflammation (McInnis et al., 2014). Indeed, patients with depression had an increase in serum levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (O'Brien et al., 2007). Such pro-inflammatory state has been documented in depressed adolescents as well compared to healthy non-depressed adolescents, suggesting that it may play a role early in the course of illness, suggesting that increased inflammation in MDD is not due to chronicity effects (Gabbay et al 2009). The kynurenine pathway (KP) has been hypothesized to play a key role in processes linking peripheral inflammation and CNS alterations by i) reducing tryptophan availability, and ii) production of oxygen radicals and highly potent neurotoxins (Hochstrasser et al., 2011). Thus, tryptophan degradation and its role in the availability of serotonin have brought attention to the kynurenine pathway as a potential target for future research into alternative treatments for depression.

About 99% of tryptophan (TRP) is metabolized by tryptophan 2,3-dioxygenase (TDO) into kynurenine (KYN) in the liver. However, during active inflammation, indoleamine 2,3 –

dioxygenase (IDO) is activated in extrahepatic tissues to convert TRP to KYN (Leklem, 1971). Kynurenine by itself in not neuroactive but instead is compartmentally hydroxylated by kynurenine-3-monooxygenase (KMO) into 3-hydroxykynurenine (OHK). Further cleavage of OHK by kynureninase yields 3-hydroxyanthranilic acid (3-HAA). After production of 3-HAA, there are two possible degradation arms: one proceeds with complete oxidation of 3-HAA to form adenosine triphosphate (ATP) and a small quantity of picolinic acid (PIC), while the other pathway produces quinolinic acid (QUIN) which is eventually degraded into nicotinamide adenine dinucleotide (NAD) (Leklem, 1971). Conversely, an alternative pathway is the conversion of KYN to kynurenic acid (KYNA)—a glutamate and 17-nicotinic acetylcholine receptor antagonist—by kynurenine aminotransferases (KATs) (Lopresti et al., 2014). Figure 1 portrays the tryptophan degradation pathway.

The KYN pathway also plays a role in the metabolism of glucose. The ATP and HAA formed from this pathway activate glycolysis (Quagliariello and Papa, 1964), through which glycogen is stored in the cells to be utilized in case of stress or glucose need. QUIN has also been shown to inhibit gluconeogenesis (Lardy, 1971). It appears that under normal physiological conditions in the brain, the KYN pathway serves mainly for glycogen storage and the production of small amounts of NAD required for ATP synthesis in the central nervous system (Myint, 2012a, b).

TRP depletion is therefore the result of enhanced tryptophan catabolism by TDO in the liver (Takikawa, 2005) and IDO in the lungs, placenta, blood, and brain (Heyes et al., 1993; Mellor and Munn, 1999). Furthermore, serotonin is degraded by IDO into formyl-5-hydroxykynuramine, in addition to the degradation by monoamine oxidase (Pertz and Back, 1988). The enhanced degradation of tryptophan towards kynurenine and away from production of serotonin has been termed the “kynurenine shunt” (Lapin and Oxenkrug, 1969; Mangoni 1974).

The tryptophan degradation pathway and the kynurenine shunt have been connected to a number of psychiatric conditions, suggesting that this biochemical process may have far reaching implications. Patients with BD have shown decreased neuroprotective kynurenine metabolites in their hippocampus and amygdala when compared to control patients (Savitz et al., 2015a). Schizophrenic patients were also identified as having an imbalance between the neuroprotective and neurotoxic metabolites of tryptophan degradation (Kegel et al., 2014). MDD is often associated with a systemic pro-inflammatory state that can be tied to increasing levels of IDO activity in the peripheral tissue and the brain (Heyes et al., 1993). This review will present current research that identifies the kynurenine pathway as a prevalent component of the pathophysiology of depression from studies with animal models and human. In addition, this review will highlight studies that focus on treatment targets associated with the kynurenine pathway and antidepressant responses.

2. SEARCH STRATEGY

For this narrative review, the PubMed/MEDLINE database was searched with the following Boolean terms: “kynurenine”[Mesh] OR “kynureninase”[Supplementary Concept] OR “kynurenine pathway” OR “indolamine-2,3-dioxygenase” OR “tryptophan 2,3-dioxygenase”

OR “kynurenic acid” OR “quinolinic acid” OR “anthranilic acid” OR “3 – Hydroxykynurenine” AND “Depression”[Mesh] OR “Depressive Disorder”[Mesh] OR “Depressive Disorder, Major”[Mesh] OR “Depression”; through March 3rd, 2015.

Observational and experimental studies in human and animal models investigating the role of components of the kynurenine pathway in the pathophysiology of MDD were included. Review articles, case reports, as well as studies that included participants with bipolar depression were excluded. The overall methodological quality of retrieved references was considered for final inclusion. No language restrictions were applied. The citation tracking of included reports was searched in Google Scholar for potentially eligible articles for this review.

3. RESULTS AND DISCUSSION

3.1 Kynurenine pathway in the pathophysiology of depression and its comorbidities

3.1.1 Evidence from human studies: central effects—Recent studies have shown that the kynurenine pathway (KP) plays an important role in depression (Figure 2) (Myint et al., 2007, 2012a, b). Positive correlations were drawn between KYN, QUIN, KYNA and specific pro-inflammatory immunological variables in the cerebrospinal fluid (CSF), and depressive symptoms in patients with hepatitis on IFN-α treatment (Raison et al., 2009). The pro-inflammatory status of patients with major depression has been associated with increases in pro-inflammatory cytokines interleukin-2 (IL-2), IL-6, TNF-α and IFN-γ in addition to decreases in anti-inflammatory cytokines IL-4 and IL-10 (Myint, 2012a). A proton MR spectroscopy study revealed a positive correlation relating KYN, 3-HAA and tCho (cell membrane turnover biomarker) in the right caudate and left putamen with melancholia in adolescent MDD (Gabbay et al., 2010b).

The KYN pathway is seem to be involved with other psychiatric diseases, such as schizophrenia and bipolar disorder. However, the neurobiological effects found in KYN pathway it seems to be different in these diseases and MDD. A recent study measuring the levels of QUIN and KYNA in patients with schizophrenia found depressed QUIN/KYNA ratios in the CSF of schizophrenic patients as compared to controls (Kegel et al., 2014). In fact, elevated KYNA is one of the most consistently found deviations in patients with schizophrenia and BD with psychotic features (Schwarcz et al., 2001; Miller et al., 2006, Linderholm et al., 2012). On the other hand, Savitz et al. (2015a) found a reduction in the neuroprotective KYNA/QUIN ratio, but no difference in the individual KYN metabolites in BD patients, compared to health controls. Reduced KYNA/QUIN ratio in BD patients was linked to amygdala and hippocampus volume reduction (Savitz et al., 2015a). Furthermore, IDO downregulation and 5-HT upregulation has been associated with the antidepressant properties of valproate, an agent used as an antiepileptic and mood stabilizer (Qiu et al., 2014). This pathologic shift towards KYNA and away from QUIN production runs contrary to the major depression model in which KYNA is neuroprotective and QUIN is neurotoxic. Interestingly, interleukin-1 receptor antagonist, QUIN, and KYN were significantly elevated in MDD patients, compared with healthy controls, whereas KYNA, tryptophan, and KYN were positively correlated with hippocampal and amygdala volume in MDD patients (Savitz et al., 2015c), suggesting that an immune-related imbalance in the relative metabolism of

KYNA and QUIN predisposes to depression-associated dendritic atrophy and anhedonia (Savitz et al., 2015c).

The final products of the tryptophan degradation pathway have also been shown to directly alter activity of certain receptors in the brain. QUIN is an *N*-methyl-D-aspartate receptor (NMDA-R) agonist (Schwarcz et al., 1983). Accumulation of QUIN in the brain results in excitotoxicity due to stimulation of NMDA receptors (Okuda et al., 1998). This neurodegenerative effect is counteracted by KYNA, which is an NMDA-R antagonist (Perkins and Stone, 1982). KYNA can thereby act to protect neurons against the excitotoxicity of QUIN (Kim and Choi, 1987). An imbalance between the neuroprotective effects of KYNA and the neurotoxic effects of QUIN was demonstrated in major depression as well as INFα-treatment depression (Myint et al., 2012a,b). When the catabolism of tryptophan is enhanced by increased IDO activity, the production of KYNA is outpaced by the production of OHK by KMO. Activated monocytes in the body can then continue the degradation pathway to produce excess QUIN (Chiarugi et al., 2001). Erhardt et al. (2013) demonstrated that elevated CSF levels of QUIN and IL-6, but not KYNA, were positivity correlated with suicide attempts in patients with MDD. On the other hand, Sublette et al. (2012) showed higher levels of KYN in MDD with history of suicide attempt as compared to MDD without history of suicide attempt; however, in attempters, there was elevated KYN levels and a positive correlation with cytokines activation (Sublette et al., 2011), showing an association between inflammation and KYN pathway stimulation. Also, Bay-Richter et al. (2015) revealed that levels of QUIN increased and KYNA decreased over time in suicidal patients versus healthy controls; high levels of IL-6 were also related to more severe suicidal symptoms. A recent study in adolescents documented similar findings of increased KYN/TRP in suicidal depressed adolescents (Gabbay et al., 2015). Increased levels of pro-inflammatory cytokines, such as IL-6, may be involve with microglia and astrocytes cells activation. Astrocytes and microglia have been identified as the primary site for tryptophan catabolism in the brain (Grant et al., 2000). While the astrocytes are shown to produce mainly KYNA, microglia and macrophages produce mainly QUIN that is then degraded to NAD by neighboring microglia (Guillemin et al., 2001). In studies of major depression, loss of astrocytes has been observed (Rajkowska et al., 1999). This loss might be partly due to the increased toxic KYN metabolites resulting from the pro-inflammatory state induced by the imbalance between the neurotoxic KYN metabolites and the neuroprotective KYNA (Myint, 2012a, b). This pathway, in the absence of inflammation or immune challenge, produces the small amount of NAD required by the central nervous system (Leklem, 1971). Complete depletion of NAD is fatal to the cells, especially if they are under stress, since ATP formation in these cells is dependent on NAD (Myint, 2012a, b).

Microglia is known to produce inflammatory mediators, so it is possible that these pro-inflammatory cytokines may induce the KP in the brain (Myint et al., 2012a, b). Elevated levels of microglial density have been found in the postmortem examination of suicidal patients with major depression and schizophrenia (Steiner et al., 2008). In addition, the activation of the KP in microglia leads to formation of potentially neurotoxic KYN metabolites, such as QUIN (Mayhew et al., 2015). In a postmortem study, an association was found between severe depression and increased density of QUIN immunopositive microglia in the anterior cingulate cortex (Stone et al., 2000). A similar study identified significantly

increased QUIN immunoreactivity in the prefrontal cortex of patients with MDD and bipolar depression (Steiner et al., 2011). However, in the hippocampus from patients suffering uni- and bipolar depression a reduction in QUIN-immunoreactive microglia was observed (Busse et al., 2014). This indicates that microglia might exert a toxic or neuroprotective role, depending on brain area.

3.1.2 Evidence from human studies: peripheral effects—It is well known that the central nervous system (CNS) is in constant communication with the peripheral body systems. Many studies have used peripheral markers to better understand diffuse nature of mood disorder pathologies, such as depression. The IDO enzyme is activated in extrahepatic tissue, such as the lungs, kidneys, spleen, blood, and brain, during situations of inflammation, infection or oxidative stress (Heyes et al., 1993; Mellor and Munn, 1999). In addition, IDO activity is increased by the pro-inflammatory molecule interferon-γ (IFN-γ) (Carlin et al., 1987). IDO is most likely involved in the pathophysiology of depression (Kim et al., 2012) and may even be the link between inflammation and depression (Quak et al., 2014). IDO is activated by pro-inflammatory cytokines, including IL-6 and IL-1β, and IDO activity is associated with a decrease in serotonin content and an increase in KYN content, which in turn actives QUIN and glutamate receptor (Kim et al., 2012; Heyes and Lackner, 1990). Findings from Raison et al. (2009) suggest that peripheral activation of IDO leads to parallel activation of the KP in the brain. In a population-based Young Finns Studies demonstrated a positive correlation between peripheral activation of IDO and depressive symptoms at baseline and follow-up (Elovainio et al., 2012), and with depressive symptoms and carotid atherosclerosis in women (Elovainio et al., 2011). Recently, higher levels of serum IDO and inflammatory mediators (TNF-α, IFN-γ and C-reactive protein) and lower levels of 5-HT were found at baseline in MDD women compared to health controls (Zoga et al., 2014). On the other hand, undergoing effective treatment decreased IDO and TNF-α and these effects were positively linked to patient improvement (Zoga et al., 2014). Myint et al. (2013) found an association between serum IFN-γ gene CA repeat polymorphisms, higher KYN concentrations, and an increase in serum TRP breakdown in patients with depression. In addition, a study showed that 53.7% of patients in treatment with IFN-α develop depressive symptoms associated with TRP depletion and a high neurotoxic challenge (KYN to kynurenic acid quotient) (Baranyi et al., 2013). In patients with malignant melanoma on IFN-α therapy, an increase in plasma KYN and neopterin concentrations, as well as in the KYN/TRP ratio was observed (Capuron et al., 2003). Moreover, MDD patients not receiving antidepressants showed lower TRP concentrations, which were associated with depressive symptoms (Capuron et al., 2003).

In melancholic MDD adolescents KYN/TRP ratios in blood were elevated and TRP concentrations were reduced compared to non-melancholic MDD adolescents (Gabbay et al., 2010a). A study performed in adolescents with anhedonia and MDD found a significant correlation between IDO activity in blood and anhedonia. The correlation was even more significant when medicated patients were excluded, potentially due to the anti-inflammatory effects of antidepressants (Gabbay et al., 2012). These findings displayed an important role of KYN pathway in anhedonia in adolescents suffering MDD.

Somatization in depression was associated with higher serum levels of IDO activity (Anderson et al., 2012), KAT activity, and with enhanced neurotoxic potential (Maes et al., 2011). On the other hand, Hughes et al. (2012) found no differences in IDO expression, plasma KYN levels and metabolites levels in MDD patients, when compared to controls. A reduction in circulating TRP concentrations was noted (Hughes et al., 2012). Increases in IL-6, decreases in KYNA, or increases in the KYN/KYNA ratio showed a significant association with the development of depressive symptoms in patients with cytokine therapy induced depression (Wichers et al., 2005). Interestingly, IDO activation via IL-6 is a pathway involved with regulation of TRP availability (Anderson et al., 2013). The KYN/KYNA ratio is used to estimate how much of the KYN is degraded into KYNA. The amount of KYNA was found to be significantly lower in depressed patients than healthy controls, indicating an imbalance in the kynurenine pathway. This imbalance persisted, even after treatment with SSRIs for six weeks (Myint et al., 2012b). Several studies have indicated that the presence of depression with other comorbid conditions, such cancer, HIV and pain, may be related, at least in part, to dysregulation in the KYN pathway. In cancer patients, KYN levels pre- and post-treatment were measured; KYN levels predicted the trajectory of depression and were an important factor associated with depression and fatigue (Pertl et al., 2013). The severity of depressive symptoms in HIV-infected patients was associated with lower plasma levels of TRP and a higher plasma KYN/TRP ratio (Martinez et al., 2014).

In individuals with Type D personality, which is related to negative affectivity in social situations, increased symptoms of depression and anxiety were noted (Altmaier et al., 2013). In addition, in Type D individuals, lower levels of TRP and KYN were related, but not associated, with depression or anxiety (Altmaier et al., 2013). Positive correlation in TRP catabolism was also found in patients with depression and irritable bowel syndrome (IBS) (Fitzgerald et al., 2008). Individuals with severe IBS exhibited higher levels of KYN/TRP ratio, compared to less severe symptoms and controls, and were more than doubled when linked to depression and anxiety compared to less severe (Fitzgerald et al., 2008). Among patients with coronary artery disease, IDO peripheral activation was correlated with severity of depressive symptoms (Swardfager et al., 2009). Also, a meta-analysis of depressive patients showed significantly decreased TRP levels, which was associated with an increase in KYN/KYNA ratio (Ogawa et al., 2014). Plasma from patients with chronic pain and depression had an elevated KYN/TRP ratio (Kim et al. 2012). A recent study found a reduction of the KYNA/QUIN ratio in serum of depressed and remitted phases of MDD patients, compared to healthy controls (Savitz et al., 2015b). Moreover, a negative correlation between KYNA/QUIN and anhedonia in depressed patients was demonstrated, as well as a negative correlation between lifetime number of depressive episodes and KYNA/QUIN, and a positive correlation between the number of months in remission and KYNA/QUIN (Savitz et al., 2015b).

It has also been proposed that the imbalanced KYN pathway can induce glial-neuronal network impairment that might contribute to the recurrent and chronic nature of MDD (Myint et al., 2012a, b). Patients with MDD show lower tryptophan availability and higher tryptophan breakdown, in addition to lower mean plasma KYNA (Myint et al., 2007). However, a difference in plasma kynurenine or tryptophan concentrations was not found (Myint et al., 2007). The tryptophan-kynurenine pathway provides a link between the

immune activation present in MDD and the neurochemical and cellular abnormalities that have been attributed to mood disorders (Myint, 2012a, b). This evidence suggests that the KYN pathway in periphery could be associated with KYN toxic pathway activation in the CNS, leading to neuroinflammatory processes.

3.1.3 Evidence from preclinical studies: central and peripheral effects—The role of the kynurenine pathway in central and peripheral processes is often studied concurrently with animal models of depression. Henry et al. (2009) found that immune system stimulation with lipopolysaccharide (LPS) has been shown to induce cytokine production in the mouse brain with concurrent production of IDO mRNA in microglia. In an animal model of depression, LPS administration produced depressive-like effects and was associated with a more pronounced induction of peripheral and brain IDO and a higher turnover rate of brain serotonin when compared to young adult mice at 24 hours post-LPS injection (Goubout et al., 2008). Mice injected with LPS also displayed depressive-like behavior in the forced swimming test (FST), paralleled by an increase in the KYN/TRP ratio in the serum and IDO in the brainstem (Dobos et al., 2012). A study using western blot analysis correlated an increase in aromatic L-amino acid decarboxylase and IDO in the hippocampus of stressed rats with progression of depressive behavior (Jia et al., 2013). The effects of the TRP-KYN pathway are different in periphery and brain areas. For example, Laugeray et al. (2010) found that rats subjected to chronic stress had an increase in TRP catabolism along the KP in the periphery, whereas in the amygdala and striatum TRP was preferentially metabolized to QUIN, and in the cingulate cortex QUIN was reduced. In addition, the KYN/TRP ratio in the periphery was linked to the magnitude of depressive and anxiety-like behaviors (Laugeray et al., 2011). The effects of LPS on the KP may vary depending on the strain of rodent. In fact, mRNA expression of IDO enzymes and immune activation was altered in BALB-c mice, but not in the C57BL/6J strain after LPS administration (Browne et al., 2012). On the other hand, intracerebroventricular administration of LPS in C57BL/6J mice induced depressive-like behavior and increased IDO expression, synthesis and secretion of TNF-α and IL-6, and activation of inducible isoform of nitric oxide synthase (iNOS) in the hippocampus (Fu et al., 2010). The effects of LPS was time dependent (Fu et al., 2010), suggesting that differences in C57BL/6J mice exerted by LPS could be influenced by time and route administration.

Depressive-like behavior and increased TRP catabolism in mice was extended after infection with Mycobacterium bovis, Bacillus Calmette-Guérin (BCG) (Kelley et al., 2013). KYN pathway was also strongly associated with depressive-like behavior in rodents treated with HIV transactivator of transcription protein (Lawson et al., 2011). BCG in rodents induced depressive and sickness behavior, however only depressive-like behavior was associated with increased levels of TNF-α and peripheral IDO activation (Moreau et al., 2005, 2008). A study using a mouse model of metabolic syndrome (MetS), which is linked to activation of cytokines in brain tissue, showed that LPS administration in MetS mice significantly increased brain KYN/TRP ratio, IL-1β and TNF-α (Dinel et al., 2014). LPS injection in MetS mice was associated with a decrease in hippocampal brain-derived neurotrophic factor (BDNF) (Dinel et al., 2014), an important protein involved in neuroplasticity and the pathophysiology of depression (Ignácio et al., 2014; Réus et al., 2013). Mice subjected to

UCMS demonstrated a higher peripheral KYN pathway activity (Laugeray et al., 2010). Viral mimetic Poly I:C induced symptoms of depression and anxiety in rats accompanied by increased expression of IL-1β, IL-6, TNF-α and CD11b and by decreased expression of BDNF and it's receptor TrkB in the hippocampus and frontal cortex (Gibney et al., 2013).

In conclusion, multiple animal models of depression, including chronic stress or depressive-like behavior induced by infection or LPS, have been associated with kynurenine pathway activation both centrally and peripherally.

3.2 Kynurenine pathway as a potential strategy for the treatment of depression: evidences from in vitro, in vivo and human studies

The fact that standard antidepressants usually require approximately one month or more to manifest their antidepressant effects suggest that regulation of pathways other than the monoaminergic system, such as neuroplasticity or immune system regulation, could be involved with symptom improvement in depressive patients (Berton and Nestler, 2006). Moreover, the higher risk of suicide and other deliberate acts of self-harm during the first month of treatment is not uncommon. It has been thought to be due to a mismatch in symptom improvement; that is, physical energy improves first, while resolution of depressive mood and negative thoughts is more gradual (Conwell and Heisel, 2012).

Previous studies have shown that monoaminergic-based antidepressants also act on the KYN pathway. Immune system or KYN pathway modulators have been shown to produce antidepressant effects (Figure 2). The antidepressant sertraline produced a reduction in the KYN/MEL (melatonin) ratio and 3-Hydroxykynurenine (3-OHKY)/MEL ratio in MDD patients, compared to pretreatment (Zhu et al., 2013). Interestingly, patients who showed poor response to sertraline treatment did not experience changes in these pathways. Thus, antidepressant effects of sertraline appear to be linked to KYN pathway regulation. Mackay et al. (2009) showed a positive correlation between KYN metabolite concentrations and psychiatric rating scores in depressive patients treated for 18 weeks with fluoxetine, an SSRI. Single Nucleotide Polymorphism (SNP) in enzymes involved with KYN metabolism (TPH-2, KMO and KAT) were shown to be altered in patients with depression and BD compared to control populations (Claes et al., 2011). SNPs in the genes IDO1 and IDO2 exhibited an association with citalopram treatment in depressive patients (Cutler et al., 2012). Thus, the genes involved with KYN pathway may play an important role in both pathogenesis and treatment of mood disorders. However, in patients with IFN-α therapy depression and anxiety the symptoms were not linked to variants in the IDO gene (Galvao de Almeida et al., 2011), though these discrepancies could be related to the cross-sectional study design.

Depressed patients stimulated with LPS demonstrated an increase in IFN-γ and IL-10 in blood cultures. However, when the antidepressant imipramine and celecoxib (a cyclooxygenase-2 inhibitor) were added, IL-10 levels were decreased (Krause et al., 2012). Kocki et al. (2012) reported that 24–48 hours of exposure to SSRIs or TCAs stimulated the synthesis of KYNA (neuroprotective) and decreased OHK (neurotoxic) in astroglial cultures.

Studies with rodents have also shown that classical antidepressants act on the KYN pathway and that KYN pathway modulators produce antidepressant effects. Sprague-Dawley rats subjected to unpredictable chronic mild stress (UCMS), an animal model of depression, and QUIN microinjection into the hippocampus exhibited depressive-like behavior, increased levels of glutamate, and altered levels of the glutamate receptors subunit (Chen et al., 2013). On the other hand, Ro61-8048 (a QUIN antagonist) and MK-801 (a glutamate antagonist) reversed depressive-like behavior as well as glutamatergic system alterations (Chen et al., 2013).

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 (Franklin et al., 2012). Treatment with the SSRI antidepressant paroxetine reversed these alterations in KYN pathway, but not the depressive behavior (Franklin et al., 2012). Danzhi Xiaoyao San (DXS), which is used in the prevention and treatment of affective disorders in China, was administrated to rats subjected to animal models of unpredictable chronic mild stress (UCMS). Treatment was effective in reversing anhedonic behavior (Zhu et al., 2015). In the same study, DXS decreased IL-6 and TNF-α in the serum, and downregulated IDO activity and KYN production, and upregulated TRP in the hippocampus (Zhu et al., 2015).

The antidepressant citalopram exerted antidepressive-like effects and increased turnover of 5-HT via IDO inhibition in the hippocampus, amygdala and hypothalamus of stressed rats (Ara and Bano, 2012). Fluoxetine administration reduced depressive-like behaviors in tumor-bearing mice, but did not have an effect on KMO mRNA or IDO expression (Norden et al., 2015). On the other hand, in a BV-2 microglial cell line, fluoxetine alone or in combination with acetylsalicylic acid inhibited microglial activation and attenuated LPS-induced production of IL-1β, expression of IDO, and the depletion of 5-HT (Yang et al., 2014). The anti-inflammatory effects of combined treatment with fluoxetine and acetylsalicylic acid were mediated by NF-κB activation and p38 MAPK and ERK1/2 phosphorylation (Yang et al., 2014). In rats with combined exposure of LPS and chronic mild stress (CMS), treatment with the antidepressants imipramine and pentoxyphylline (an anti-TNF-α) were effective in reversing depressive-like behavior and the elevated KYN/TRP ratio and TNF-α gene expression induced by both LPS and CMS in the hippocampus (Elgarf et al., 2014). Agomelatine, a melatonergic antidepressant, was able to reverse LPS-induced IL-1β and IL-6 production in the brain and periphery. Agomelatine also prevented the LPS-dependent increase in KMO (Molteni et al., 2013). Pre-treatment with etanercept, a TNF-α antagonist, partially diminished BCG-induced IDO activation and depressive-like behavior (O'Connor et al., 2009a). Interestingly, IDO activation is seen to mediate depressive behavior following BCG infection. In fact, both IDO inhibitor treated mice and IDO-deficient mice did not exhibit depressive-like behavior after BCG infection (O'Connor et al., 2009b).

Ketamine, an antagonist of NMDA receptors, has been described as a revolutionary new antidepressant drug (Abdallah et al., 2015), and its antidepressant effects seem to be mediated by the MAPK pathway (Réus et al., 2014). Interestingly, ketamine presents antioxidant (Réus et al., 2015a) and anti-inflammatory properties (Réus et al., 2015b) in rodents subjected to the animal model of maternal care deprivation. Prenatal inhibition of the

KP alters the expression of proteins involved with glutamatergic signally in rat brains both during development (Forrest et al., 2013a) and adult life (Forrest et al., 2013b). In LPS-induced anhedonic behavior, ketamine produced antidepressant effects (Walker et al., 2013). However, while ketamine abrogated the LPS-induced depressive-like behavior mediated by a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) in adult rats, and it did not have effects on IDO activity or pro-inflammatory cytokines (Walker et al., 2013). These animal studies suggest a temporal relationship between stress, kynurenine pathway activation, ketamine administration, and the production of depressive-like symptoms in later in life. More studies are warranted to study the effects of ketamine administration during different stages of brain development.

In restraint stress of Sprague-Dawley rats, allopurinol, a TDO inhibitor, attenuated depressive-like behavior and reduced circulating KYN concentrations (Gibney et al., 2014). TDO activity was inhibited and an increase in 5-HT levels in the hippocampus of rats was observed after treatment with tolmetin and sulindac (non-steroidal anti-inflammatory agents) (Dairam et al., 2006). In fractalkine receptor deficient mice ($CX3CR1^{-/-}$), LPS injection induced an enhancement in mRNA expression of IL-1β, IDO and KMO in microglia in hippocampus and prefrontal cortex at 4 and 24 hours after LPS injection (Corona et al., 2010). In addition, activated microglia in $CX3CR1^{-/-}$ mice was associated with depressive-like behavior (Corona et al., 2010). LPS-induced neuroinflammation and depressive-like behavior in $CX3CR1^{-/-}$ was abrogated by 1-MT, an IDO inhibitor (Corona et al., 2013). Furthermore, 1-MT was able to prevent depressive-like behavior induced by stress (Dobos et al., 2012). Lawson et al. (2013) also demonstrated that genetic deletion or pharmacological inhibition of IDO1 attenuated the anhedonic behavior and duration of immobility time during the tail suspension test, induced by intracerebroventricular infusion of LPS. In LPS-induced depressive behavior, minocycline, which indirectly inhibits IDO and 1-MT, exhibited antidepressant-like action and regulated KYN/TRP ratios in the plasma and brain of LPS treated mice (O'Connor et al., 2009c). Minocycline and 1-MT also normalized the KYN/TRP and 5-HT/TRP ratios and prevented depressive-like behavior induced by an animal model of epilepsy (Xie et al., 2014). 1-MT treatment also reversed anxiety and anhedonic behavior induced by systemic LPS administration in mice, and in contrast administration of l-kynurenine (an enzymatic product of IDO) induced anxiogenic and depressive behavior in mice (Salazar et al., 2012). Therefore, the inhibition of TDO and IDO enzymes, which results in decreased conversion of TRP to KYN, appears to be an important target for antidepressant effects.

4. CONCLUSION

Dysregulation in the kynurenine pathway is evident in depression and has been reported by both animal and human studies. In fact, the kynurenine pathway is associated with not only the diagnosis of MDD but also the severity of depressive symptoms. However, the pathophysiologic mechanisms involved in kynurenine pathway dysfunctions are still not fully understood. Results from human studies are not always reproducible and are sometimes contradictory; the findings are dependent on the stage of depression, age, and brain anatomic area involved. IFN-α therapy may be predictive of the depressive symptoms that are mediated by kynurenine toxic pathway activation. Additionally, the kynurenine

pathway could represent the link between MDD and medical conditions such as cancer, pain, and cardiovascular diseases. Thus, future studies are needed to better characterize the role of KYN and its key regulators in the progression of depression. Some classical antidepressants do mediate the kynurenine pathway, decrease inflammation, and reduce toxic KYN metabolites, but there are no kynurenine pathway-specific medications currently available for MDD. Inhibition of IDO could be a therapeutic target for novel MDD treatment based on its central role in the kynurenine pathway. The ability of kynurenine modulators to improve depressive symptoms indicates a new avenue for therapeutic interventions in the treatment of MDD.

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Highlights

- Dysregulation in the kynurenine pathway is evident in depression.
- Kynurenine pathway is associated the severity of depressive symptoms.
- Kynurenine pathway could represent the link between MDD and medical conditions.
- Kynurenine modulators could be new therapeutic targets to MDD.

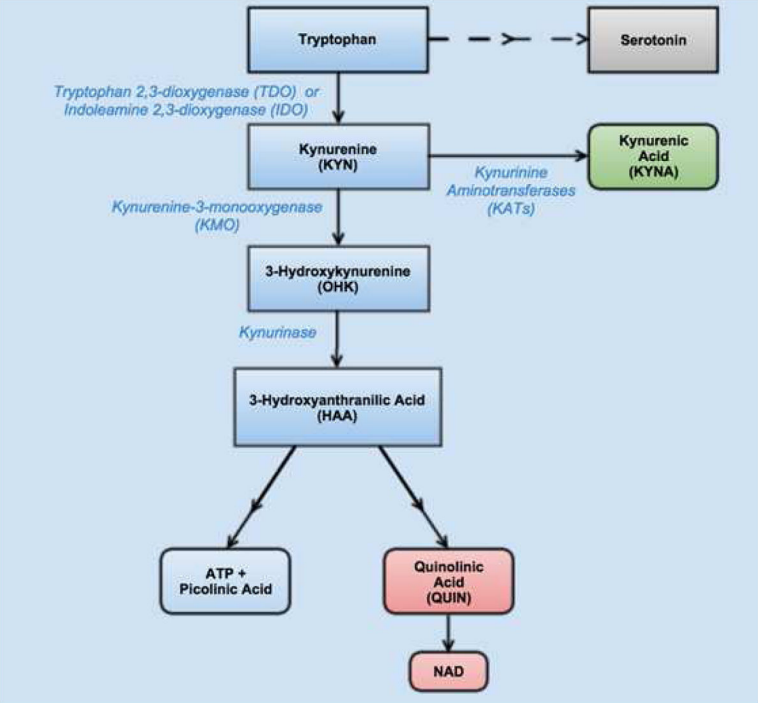

Figure 1.

The tryptophan degradation pathway. Tryptophan is degraded by either tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) into kynurenine (KYN). Kynurenine is further degraded into either 3-Hydroxykynurenine (OHK) by kynurenine-3-monooxygenase (KMO) or into kynurenic acid (KYNA) by kynurinine aminotransferases (KATs). OHK goes on to be degraded by kynurinase to produce 3-hydroxyanthranillic acid (HAA). Finally, HAA can be degraded into either ATP or small amounts of picolinic acid or into quinolinic acid (QUIN) and further into NAD. KYNA has been hypothesized to be neuroprotective while QUIN has been hypothesized to be neurodegradative.

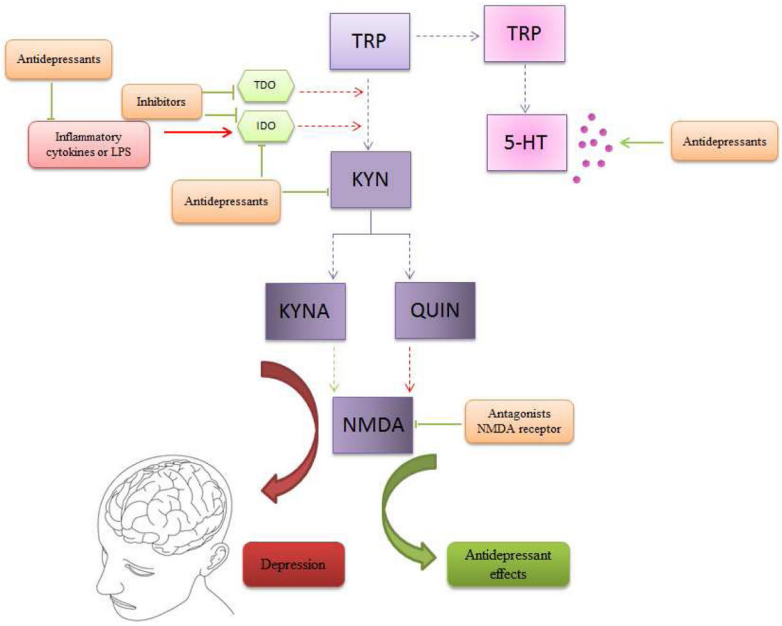

Figure 2.

The role of kynurenine pathway (KP) in the pathophysiology of depression and as a therapeutic target. Proinflammatory cytokines as well LPS may induce indoleamine 2,3-dioxygenase (IDO) activation, which in turn increase KYN levels and its toxic metabolite quinolinic acid (QUIN). In addition, IDO activation is linked to serotonin (5-HT) depletion. Increased inflammation and toxic KP activation, including excitotoxicity by n-methyl-D-aspartate (NMDA) receptor, as well as decreased 5-HT levels are associated with pathophysiology of depression (red arrows). On the other hand, antidepressant drugs acting to decrease pro-inflammatory cytokines, kynurenine (KYN) levels and its metabolites. Antidepressants also increase 5-HT levels. Inhibitors of TDO and IDO enzymes decrease KYN levels and exert antidepressant effects. Antagonists of NMDA receptor, such as ketamine decrease excitotoxicity induced by NMDA receptor activation and exert antidepressant effects (green arrows).

Table 1

Observational and experimental studies with human sample.

AUTHOR, ANO	SAMPLE	DESIGN	ASSESSMENT	MAIN FINDINGS
ALTMAIER, 2013	n=1502 community sample	Cross-sectional Population-based study	Depressive (PHQ-9) and anxious (GAD-7) symptoms	Lower levels of TRP and KYN were associated with type D personality, while no significant associations could be found for depressive and anxious symptoms
BAY-RICHTER, 2015	n=66 (30 patients with suicide attempters and 36 HC)	Cross-sectional study	Cytokines and kynurenine metabolites in CSF; depressive symptoms (MADRS) and symptoms of suicidality over time (SUAS)	QUIN was increased and KA decreased over time in suicidal patients compared to HC Significant association between low KA and severe depressive symptoms, as well as between high OL-6 levels and more severe suicidal symptoms was found
BARANYI, 2013	n=41 patients with chronic HCV	Clinical study Interferon-α treatment	TRP, KYN and QUIN were assessed before, during (at 1, 3, 6 and 9 months) and after the end of IFN-α treatment	53.7% of patients fulfilled the criteria for treatment-related MDD TRP depletion and KYN and QUIN elevated levels in depressive patients
CAPURON, 2003	n=26 patients with malignant melanoma	Randomized clinical trial, double blind Interventions: placebo or paroxetine, beginning 2 weeks before IFN-alpha treatment	TRP, KYN, Neopterin (a marker of immune activation) and depressive symptoms (HDRS) were assessed at baseline and at 2, 4, and 12 weeks of treatment	IFN-α therapy increased plasma KYN, Neopterin concentrations, and KYN/TRP ratio Antidepressant-free patients lower TRP was correlated with depressive symptoms
CLAES, 2011	n=338 (266 MDD, 72 bipolar depression, and 310 population controls)	Case-control study	TPH2, KMO and KAT SNPs and haplotype association analysis	SNP in enzymes involved with KYN metabolism (TPH-2, KMO and KAT) were shown to be altered in patients with MDD and BD compared to population control
CUTLER, 2012	n=1953 participants enrolled in the Sequenced Treatment Alternatives to Relieve Depression study	Clinical study	Genotypes corresponding to 94 SNPs in the genes IDO1 and IDO2 were extracted from a larger genome-wide set	SNP in the genes IDO1 and IDO2 exhibited association to citalopram treatment in depressive patients
ELOVAINIO, 2011	n=986 young with cardiovascular risk	Cohort study	IDO, KYN-TRP ratio and depressive symptoms (BDI)	Positive correlation between IDO activation with depressive symptoms and carotid atherosclerosis in women
ELOVAINIO, 2012	n=986 young with cardiovascular risk	Cohort study	IDO and depressive symptoms (BDI)	Positive correlation between IDO and depressive symptoms at baseline and follow-up
ERHARDT, 2013	n=100 (64 medication-free suicide attempters and 36 HC)	Clinical study	QUIN and KYNA were assessed in CSF; suicidality (SIS) and severity of depressive symptoms (MADRS)	QUIN and IL-6, but not KYNA, was elevated in patients with suicide attempters. QUIN levels correlated with the total scores on Suicide Intent Scale They verified a significant decrease of QUIN in patients who came for follow-up lumbar punctures within 6 months after the suicide attempt
FITZGERALD, 2008	n=74 females (41 IBS subjects and 33 controls)	Case-control study	KYN, TRP and IFN-gamma; IDO (KYN/TRP); Depression and anxiety	Individuals with severe IBS exhibited higher levels of IDO, compared to less severe symptoms and controls, and

AUTHOR, ANO	SAMPLE	DESIGN	ASSESSMENT	MAIN FINDINGS
			(PHQ) and IBS (IBS self-report ordinal scales)	were over twice when linked to depression and anxiety compared to less severe
GABBAY, 2010A	n=72 adolescents	Cross-sectional study	KYN, TRP, KYN/TRP (estimating IDO activity), 3-HAA/KYN (reflecting neurotoxic load), and diagnosis groups by K-SADS	IDO activity were elevated and TRP concentrations were reduced in adolescents with M-MDD compared to non M-MDD and HC
GABBAY, 2010B	n=20 adolescents	Cross-sectional study	KYN, 3-HAA, striatal total choline, and diagnosis groups by K-SADS	In M-MDD patients was found a positive correlation between KYN, 3-HAA, and striatal total choline in the right caudate and the left putamen brain areas
GABBAY, 2012	n=56 adolescents	Cross-sectional study	KYN, TRP, IDO, MDD (K-SADS) and anhedonia (BDI-II - item 4 and 12; CDRS-R - item 2; and K-SADS-PL - page 8)	IDO activity and anhedonia scores were positively correlated in the group psychotropic medication-free adolescents with MDD and in a combined group of MDD subjects and healthy controls
GALVÃO, 2011	n=277 hepatitis C patients	Cross-sectional study	IDO SNPs were genotyped (rs3824259; rs10089084 and rs35099072); Current depression and anxiety disorder (MINI)	Current major depression and/or current anxiety disorder was significantly associated with IFN-α-related depression In patients in IFN-α therapy depression and anxiety symptoms were not linked to variants in the IDO gene
HUGHES, 2012	n=78 (39 patients with MDD and 39 HC)	Case-control study	Plasma IL-6, TNF-a, IL-1 b, IFN-c and CRP; TRP, KYN metabolites using HPLC; Depressive symptoms (HDRS)	IDO expression, plasma KYN levels and metabolites levels were not different between MDD patients, when compared to controls A reduction in circulating TRP concentrations was correlated with HDRS score
MACKAY, 2009	n=63 (28 patients treated with fluoxetine 20 mg/day, 12 patients treated with fluoxetine 20 mg/day together with T3, and 23 patients received counselling with no antidepressant therapy)	Clinical study treatment for 18 weeks	5-HT, 5-HIAA, tryptophan metabolites, BDNF, and IL-2, CRP were measured in peripheral blood, depressive symptoms (BDI, HDRS)	Showed a correlation between KYN metabolites concentration and psychiatric rating scores in depressive patients treated for 18 weeks with fluoxetine, an SSRI
MAES, 2011	n=146 psychiatric inpatients (117 patients and 35 HC)	Clinical study Inpatient treatment Center for Psychiatric and psychosomatic disorders	TRP, KYN, KA, IDO (KYN/TRP ratio), KAT (KYN/KA ratio), somatization symptoms (SSI, SOMS), depression (BDI)	TRP is lower in patients than in HC and lower in somatization than in depression KA is lower in patients than in HC, and lower in somatization than in depression The severity of somatization was correlated with KY/TRP and KY/KA (positive) and TRP (negative) KYN and KA were correlated in controls, somatization + depression, and depression, but not in somatization
MARTINEZ, 2014	n=504 HIV-infected	Cross-sectional study nested a cohort study	TRP, KYN, dietary diversity, and severity of depressive symptom (HSCL-D)	The severity of depressive symptoms in HIV-infected patients was correlated with lower plasma levels of TRP and a higher plasma KYN/TRP ratio

AUTHOR, ANO	SAMPLE	DESIGN	ASSESSMENT	MAIN FINDINGS
MYINT, 2007	n=247 (56 MDD patients hospitalized during 6-week and 189 HC)	Clinical study	QUIN, TRP, 3-HAA, and MDD (SCID)	Higher levels of TRP breakdown and protective KYN pathway metabolites were decreased in patients with depression compared to controls The neuroprotective ratio increased after treatment in those with first episodes
MYINT, 2013	n=218 (125 MDD patients and 93 HC)	Case-control study with clinical sample	CA-repeat polymorphism in intron 1 of the interferon-γ gene, TRP, KYN, 5HIAA, depressive symptoms (HDRS)	IFN-α gene CA repeat polymorphisms was associated higher KYN concentrations, and increase in TRP breakdown in patients with depression compared to HC
PERTL, 2013	n=61 breast cancer patients prior to chemotherapy	Clinical study	IFN-γ, IL-6, TNF-α, CRP, KYN;	KYN levels predicted the trajectory of depression and were an important factor associated with depression and fatigue
RAISON, 2009	n=27 HCV patients (16 in treatment group and 11 awaiting therapy)	Clinical study Therapy with IFN-alpha/ ribavirin for 12 weeks	TRP, KYN, QUIN and KA were measured in cerebrospinal fluid (CSF) and blood; IL-6, sIL6R, sTNFR2, MCP-1, IFN; MDD (SCID) and depressive symptoms (MADRS)	Increased levels of KYN, QUIN and KYNA in CSF were correlated with increase of depressive symptoms after IFN-α treatment
SAVITZ, 2015B	n=128 unmedicated subjects (49 MDD, 21 remitted MDD, and 58 HC)	Cross-sectional study	KYNA, QUIN, 3-hydroxykynurenine, and MDD (SCID)	Showed a reduction in KYNA/ QUIN ratio among MDD and remitted MDD patients, compared to HC An inverse correlation between KYNA/ QUIN and anhedonia in MDD patients was demonstrated, as well as a negative correlation between number of depressive episodes and KYNA/QUIN, and a positive correlation between the number of months in remission and KYNA/QUIN
SAVITZ, 2015C	n=49 unmedicated subjects (29 MDD and 20 HC)	Cross-sectional study	KYNA, QUIN, KYN, TRP, IL-1, and MDD (SCID)	Interleukin-1 receptor antagonist, QUIN, and KYN were significantly elevated in MDD patients, compared to HC KYNA, TRP, and KYN were positively correlated with hippocampal and amygdala volume in MDD patients
SUBLETTE, 2011	n=61 (14 MDD with history of suicide attempt, 16 MDD, and 31 HC)	Cross-sectional study	KYN, TRP, neopterin, MDD (SCID), depressive symptoms (BDI and HDRS)	Plasma kynurenine levels are elevated in MDD patients with history of suicide attempters, compared to MDD patients without history of suicide attempters and HC
SWARDFAGER, 2009	n=95 patients with coronary artery disease from a cardiac rehabilitation facility	Cross-sectional study	IDO (KYN/TRP), MDD (SCID), depressive symptoms (CES-D)	IDO activation was correlated with severity of depressive symptoms among patients with coronary artery disease
WICHERS, 2005	n=16 patients with HCV, free of psychiatric disorders	Clinical study Therapy with IFN-alpha	TRP, KYN, KA, IDO, KYN/KA, and depressive symptoms (MADRS) All assessments were carried out at baseline and 1, 2, 4, 8, 12 and 24 weeks	MADRS score increased during IFN-alpha treatment as did the IDO activity, and the KYN/KA ratio MADRS score was associated over time with the KYN/KA

AUTHOR, ANO	SAMPLE	DESIGN	ASSESSMENT	MAIN FINDINGS
			after treatment was initiated	ratio, but not with the TRP/CAA ratio.
ZHU, 2013	n=75 Outpatients with MDD (35 patients treated with sertraline and 40 placebo)	Randomized clinical trial double-blind 4-week trial	5-MTPOL, MEL, KYN/MEL, and 3-OHKY/MEL ratios post-treatment compared to pretreatment Depressive symptoms (HDRS)	Antidepressant sertraline produced a reduction in the KYN/MEL ratio and 3-Hydroxykynurenine 3-OHKY/MEL ratio in MDD patients, compared to pretreatment
ZOGA, 2014	n=80 females (40 MDD patients and 40 HC)	Case-control study with clinical sample	IDO, TNF-α, IFN-γ, CRP and 5-HT	Higher levels of IDO and inflammatory markers, and lower levels of 5-HT at baseline of patients Undergoing effective treatment decreased IDO and TNF-α and was positively linked to patient improvement

Legend:

3-HAA = 3-hydroxyanthranilic acid; 3-OHKY = 3-Hydroxykynurenine; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HT = 5-hydroxytryptamine serotonin; 5-MTPOL = 5-Methoxytryptophol; BD = Bipolar Disorder; BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies-Depression Scale; CDRS-R = Children's Depression Rating Scale-Revised; CSF = cerebrospinal fluid; HC = Healthy Control; HCV = hepatitis C virus; HDRS = Hamilton Depression Rating Scale; HSCL-D = Hopkins Symptom Checklist for Depression; IBS = irritable bowel syndrome; IDO = Indoleamine 2,3 dioxygenase; IL-6 = Interleukin IFN-α = Interferon alpha; KA = Kynurenic acid; KAT = kynurenine amino transferase; KMO = kynurenine 3 monooxygenase; 6; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version; KYN = L-kynurenine; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = Major Depressive Disorder; M-MDD = MDD with melancholic features; MEL = Melatonin; MCP-1 = Monocyte chemoattractant protein 1; PHQ = 9-item Public Health Questionnaire; QUIN = Metabolized to quinolinic acid; SCID = Structured Clinical Interview for DSM Disorders; sIL6R = Soluble IL-6 receptor; SIS = Suicide Intent Scale; SUAS = Suicide Assessment Scale; SOMS = Somatoform Symptoms; SSI = Somatic Symptom Index; sTNFR2 = Soluble tumor necrosis factor receptor 2; TPH-2 = Tryptophan hydroxylase 2; TRP = Catabolizes L-tryptophan.

Table 2

Evidences of the kynurenine pathway in depression from animal studies.

AUTHOR, YEAR	ANIMAL MODEL	MAIN FINDINGS
GOUBOUT, 2008	LPS	Advance in age was associated with depressive-like behavior, elevated peripheral and brain IDO, and turnover rate of brain 5-HT
MOREAU, 2005; 2008	BCG	Depressive-like behavior was correlated with increased levels of TNF-α and peripheral IDO activation
DOBOS, 2012	LPS	IDO inhibitor prevented depressive-like behavior
LAUGERAY, 2010	Chronic stress	KYN/TRP ratio in the periphery was linked to the magnitude of depressive and anxiety-like behaviors
CHEN, 2013	UCMS and QUIN microinjection	Depressive-like behavior, increased levels of glutamate and altered levels of glutamate receptors subunit. Glutamate and QUIN antagonists reversed behavior and neurochemical alterations
GIBNEY, 2013	poly I:C	Depression and anxiety-like behavior, elevated expression pro-inflammatory cytokines, and decreased expression of BDNF and it receptor TrkB in hippocampus and frontal cortex
FRANKLIN, 2012	TRP diet depletion	Depressive-like behavior was correlated with increased levels of KYN and reduced levels of KYNA. Paroxetine treatment reversed these alterations in KYN pathway, but not in depressive behavior
ARA, 2012	Chronic stress	Citalopram treatment exerted antidepressive-like behavior and increased turnover of 5-HT via IDO inhibition in brain
ELGARF, 2014	LPS and CMS	Imipramine and pentoxyphylline were effective to reverse depressive-like behavior and the elevated levels in the hippocampal KYN/TRP ratio and TNF-α gene expression induced by both LPS and CMS
GIBNEY, 2014	Restraint stress	TDO inhibitor attenuated depressive-like behavior and reduced circulating KYN concentrations
CORONA, 2013	CX3CR1$^{-/-}$ and LPS	IDO inhibitor reversed neuroinflammation and depressive-like behavior
LAWSON, 2013	LPS	Genetic deletion or pharmacological inhibition of IDO1 attenuated anhedonic behavior
O'CONNOR, 2009C	LPS	Minocycline and 1-MT exhibited antidepressant-like behavior and regulated KYN/TRP ratio in the plasma and brain
XIE, 2014	Epilepsy	Minocycline and 1-MT normalized KYN/TRP and 5-HT/TRP ratio and prevented depressive-like behavior

Legend: 5-HT = 5-hydroxytryptamine serotonin; CMS = Chronic mild stress; CX3CR1$^{-/-}$ = fractalkine receptor deficient; IDO = Indoleamine 2,3 dioxygenase; BCG = Bacillus Calmette-Guérin; BDNF = brain-derived neurotrophic factor; KYNA = kynurenic acid; KYN = kynurenine; LPS = lipopolysaccharide; QUIN = Quinolinic acid; TDO = tryptophan 2,3-dioxygenase; TNF-α = tumor necrosis factor alpha; TRP = Catabolizes L-tryptophan; UCMS = unpredictable chronic mild stress.