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The Kynurenine Pathway: A Finger in Every Pie

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Abstract

The kynurenine pathway (KP) plays a critical role in generating cellular energy in the form of nicotinamide adenine dinucleotide (NAD+). Because energy requirements are substantially increased during an immune response, the KP is a key regulator of the immune system. Perhaps more importantly in the context of psychiatry, many kynurenines are neuroactive, modulating neuroplasticity and/or exerting neurotoxic effects in part through their effects on NMDA receptor signaling and glutamatergic neurotransmission. As such, it is not surprising that the kynurenines have been implicated in psychiatric illness in the context of inflammation. However, because of their neuromodulatory properties, the kynurenines are not just additional members of a list of inflammatory mediators linked with psychiatric illness, but in preclinical studies have been shown to be necessary components of the behavioral analogues of depression and schizophrenia-like cognitive deficits. Further, as the title suggests, the KP is regulated by, and in turn regulates multiple other physiological systems that are commonly disrupted in psychiatric disorders, including endocrine, metabolic, and hormonal systems. This review provides a broad overview of the mechanistic pathways through which the kynurenines interact with these systems, thus impacting emotion, cognition, pain, metabolic function, and aging, and in so doing potentially increasing the risk of developing psychiatric disorders. Novel therapeutic approaches targeting the KP are discussed. Moreover, electroconvulsive therapy, ketamine, physical exercise, and certain non-steroidal anti-inflammatories have been shown to alter kynurenine metabolism, raising the possibility that kynurenine metabolites may have utility as treatment response or therapeutic monitoring biomarkers.

1. OVERVIEW

The kynurenine pathway (KP) is best known for its link with inflammatory disease. However, many of its metabolites, collectively termed “kynurenines”, are physiologically active and not only play a key immunoregulatory role, but affect diverse physiological systems. Unlike other reviews which have generally focused on one particular sphere of influence or disorder, this review provides an overview of the impact of the kynurenines on

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several physiological pathways and symptom domains. In so doing, it highlights the importance of the KP to the field of psychiatry, not only in terms of enhancing our mechanistic understanding of pathophysiology, but with respect to current and future therapeutic interventions. While the focus on psychiatric illness is intended to be wide-ranging, by necessity, the depression and schizophrenia literature is emphasized since minimal research has been performed on other psychiatric disorders.

2. BASIC Biochemistry and neurophysiology

Tryptophan (TRP) is converted into several bioactive molecules, the best known of which is serotonin. However, only a small percentage of TRP is metabolized into serotonin. More than 95% of TRP is converted into kynurenine (KYN) and its breakdown products, culminating in the generation of nicotinamide adenine dinucleotide (NAD+), an important cellular energy source[1] (figure 1). The kynurenines are produced in many different tissues, notably in the liver by the enzyme, tryptophan dioxygenase (*TDO*)[2], and cells of the immune system and brain, where indoleamine 2,3-dioxygenase (*IDO*) catalyzes the conversion of TRP to KYN.

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+[3]. The remaining balance of KYN is converted into kynurenic acid (KynA) by the kynurenine aminotransferase (*KAT*) enzymes. This review will focus primarily on two metabolites that have received the most attention in the literature, KynA and QA.

KynA, which is generally considered to be neuroprotective[4], competitively inhibits ionotropic glutamate receptors at high concentrations but preferentially attenuates activity at the glycine co-agonist site of the NMDA receptor[5]. The administration of even low concentrations of KynA (nanomolar range) into the brain is capable of decreasing glutamate levels by 30–40%[6]. KynA is also generally believed to act as a negative allosteric modulator at the α7-nicotinic receptor[7]. More recently, KynA has also been shown to act as an agonist at an orphan G-protein-coupled receptor (GPR35)[8], modulating cAMP production and inhibiting the N-type Ca^{2+} channels of sympathetic neurons and astrocytes[9], ultimately leading to a suppression of several inflammatory pathways[10]. KynA also regulates the immune response through its agonistic effects on the aryl hydrocarbon receptor (AhR), a transcription factor involved in the metabolism of xenobiotics[11]. AhR signaling appears to play an important role in terminating cytokine release in several cell types including macrophages[11].

QA is an NMDA receptor agonist that can additionally inhibit reuptake of glutamate by astrocytes, leading to excitotoxicity[12]. QA exerts neurotoxic effects via at least nine different mechanisms (reviewed in detail elsewhere[13]) 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. QA also potentiates the inflammatory response by inducing the production of proinflammatory mediators in astrocytes[14]. Theoretically, QA may also activate microglia through their NMDA receptors,

a pathway that has been previously shown to trigger neuronal cell death[15] – although see reference[16].

TRP, KYN, and 3HK can be transported across the blood brain barrier. In fact, 60%−80% of KYN in the brain is thought to be of exogenous origin under physiological conditions, being actively transported into the brain by the large neutral amino acid transporter[17, 18]. These figures may approach 100% following systemic immune activation, although if inflammation is limited to the brain, KYN can be produced centrally from TRP[18]. In contrast, the classical view is that KynA and QA poorly cross the blood brain barrier[17], and thus brain KynA and QA are thought to be derived from brain KYN. Nevertheless, the issue of whether molecules pass through the blood brain barrier is complex, and the traditional view that peripheral QA and KynA do not enter the brain may be too simplistic. For instance, in gerbils, a significant correlation between serum and QA was measured in several brain regions ($r \geq 0.53$) and ~50%−70% of subcutaneously-infused radiolabeled QA was eventually detected in the brain and CSF, respectively[19]. Potentially as a result of inflammatory episodes[20], blood brain barrier integrity is putatively decreased in several psychiatric disorders[21]. Thus, the penetrance of circulating QA (and potentially other metabolites) into the CNS may depend on the degree of underlying inflammation. In this regard, the significant correlations between circulating and CSF levels of QA in HIV patients[22] and Hepatitis C patients treated with interferon α[23] ($r=0.65$ and $r=0.72$, respectively), is potentially noteworthy.

3. INFLAMMATION

Proinflammatory cytokines shunt the metabolism of TRP towards KYN by upregulating *IDO* expression. *IDO* is activated primarily via the interferon gamma receptor (IFN-γR)[24], but also through IFN-γR-independent pathways, notably the toll-like receptor 4 (TLR4)[25] and the synergistic activation of TLR4, the interleukin 1 beta receptor (IL-1R)[26, 27], and the tumor necrosis factor alpha receptor (TNFR)[27, 28]. CNS concentrations of KYN also appear to increase via an *IDO*-independent mechanism, i.e. an increase in the transport of KYN into the brain during systemic inflammation[18]. From an evolutionary perspective, activated immune cells need large amounts of energy to fight off an infection and hence QA is needed to produce adequate amounts of NAD^+[29]. Thus, one would expect increased metabolism down the QA branch of the KP under inflammatory conditions, and this is indeed borne out in the preclinical literature. *KMO* but not *KAT-II* expression is increased in rat brain after systemic LPS administration[25, 30], and in human hippocampal progenitor cells, IL-1β was shown to increase *KMO* transcripts[26].

3.1. Relevance to Psychiatry

3.1.1. Mood Disorders—There is increasingly persuasive evidence that inflammation plays a pathophysiological role in some cases of depression, with reports of: (a) depression-associated elevations of circulating pro-inflammatory cytokines[31], (b) differential expression of inflammation-related genes in monocytes or peripheral blood mononuclear cells (PBMCs) of subjects with mood disorders[32, 33], (c) depressive episodes occurring in ~30% of patients receiving immune-stimulating treatments[34], (d) the development of depressive

symptoms in some healthy participants given low-dose endotoxin[35], (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)[36], (f) an epidemiological association between depression and diseases with an autoimmune or inflammatory component[37, 38], (g) higher numbers and/or activation of microglial cells measured *in vivo* with positron emission tomography[39], and (h) an increased number and/or activation of microglia/macrophages in depressed suicides at *postmortem*[40].

The effect of inflammatory mediators on neural function – particularly dopaminergic signaling – has been well characterized[41]. What then does the KP contribute to our understanding of the pathophysiology of mood disorders? The short answer is that the kynurenines exert pathological and behavioral effects that extend beyond those of inflammatory mediators. Firstly, preclinical work has shown that the pro-depressive effects of lipopolysaccharide (LPS) can be blocked by the genetic deletion or pharmacological inhibition of *IDO* without affecting cytokine levels, indicating that *IDO* activity within the brain is necessary for the manifestation of depression-like behavior in mice[42]. Similarly, *KMO* knockout mice are protected from the pro-depressive effects of LPS, demonstrating that – at least in mice - neurotoxic kynurenine metabolites are key mediators of inflammation-induced depression-like behaviors[43].

Clearly, similar kinds of experimental manipulations are not possible to perform in humans. Nevertheless, ~30% of patients receiving immune-activating treatments (e.g. IFNα) for hepatitis C or cancer develop depressive episodes that co-occur with KP activation[44]. IFNα treatment-induced depression also coincides with increase in the ratio of KYN to KynA, indicating a role for activation of the QA pathway in the genesis of depression[45]. More recently, depressive symptoms at 6–9 months post initiation of IFNα-treatment were found to be associated with higher plasma concentrations of QA at these timepoints[46].

There is also a growing literature showing cross-sectional reductions in peripheral concentrations of KynA or the ratio of KynA to QA in patients with MDD versus comparison controls[47–57]. Moreover, my colleagues and I have demonstrated that the balance between the KynA and QA pathway metabolism is associated with brain structure and function, particularly the hippocampus. This relative anatomical specificity is consistent with the high density of NMDA receptors in the hippocampus, and preclinical data demonstrating a stronger shift towards the neurotoxic KP in the hippocampus relative to other brain regions[58]. Specifically, we found that lower “neuroprotective indices”, i.e. the ratios of KynA/3HK and KynA/QA, were associated with reduced hippocampal volumes in individuals with MDD[48, 59], concussed athletes with symptoms of depression[60], and individuals with bipolar disorder (BD)[61]. Moreover, a follow-up study showed an inverse relationship between KynA/3HK and left hippocampal activity during the recall of autobiographical memories in depressed participants, indicating a link between kynurenine metabolism and hippocampal function[62].

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 nM) of QA[13, 63]. Interestingly, this is a similar threshold above which QA has been shown to become neurotoxic *in vitro*[13]. Conceivably, when QA is produced at a faster rate than its conversion to NAD+, QA accumulates at toxic concentrations and it is thus possible that increasing the expression or activity of QPRT may have therapeutic benefits in the context of inflammatory illness[64]. Other factors may also be at play. Mitochondrial dysfunction has been implicated in several psychiatric disorders[65, 66] (see section 6) and when cellular bioenergetics are compromised, *KMO* activity is likely increased to compensate for this deficit by producing more NAD+ from QA[67]. This process may become counter-productive during an inflammatory response. Activated immune cells have been reported to shift their metabolism away from NAD-dependent oxidative-phosphorylation to glycolysis and lactic acid production in order to rapidly generate energy, including in hypoxic tissue microenvironments associated with infections[68, 69]. Theoretically, this metabolic shift may also result in an accumulation of QA.

How do KynA and QA impinge on neural function and behavior? As discussed above, KynA is an NMDA receptor antagonist while QA is an NMDA receptor agonist. While QA has a similar potency to glutamate at the NMDA receptor, it remains in the synaptic cleft for a longer period of time due to less-efficient reuptake, and therefore its excitotoxic effects are stronger[70]. Thus, high enough concentrations of QA could contribute to excitotoxicity although QA (and KynA) are perhaps more likely to alter neuroplasticity through the NMDA receptor[71–73] (figure 2). Consequently, the possibility has been raised that the competing actions of KynA and QA at the NMDA receptor may unify the inflammation and glutamate models of depression[74]. This hypothesis receives support from preclinical studies. Notably, Dantzer and colleagues demonstrated that LPS increases QA in the brain but that the pro-depressive effects of LPS could be blocked by low-dose ketamine without altering sickness behavior, inflammatory processes, or *IDO* activity[75]. Rather, the anti-depressant effects of ketamine were shown to be mediated by ketamine's antagonistic effects at the NMDA receptor and the promotion of AMPA receptor-mediated glutamatergic neurotransmission. This result suggests that inflammation-induced activation of the NMDA receptor by QA is a key mechanistic pathway through which inflammation exerts its depressogenic effects[75].

3.1.2. Suicide—Suicidal behavior cuts across diagnostic boundaries and has been strongly linked with inflammation[40, 76]. As in the case of depression, activation of the KP has been reported in suicide attempters[77, 78] but arguably the most salient finding is the relative increase in QA in suicide attempters versus controls. Increased concentrations of QA and decreased concentrations of KynA were found in both the CSF and plasma of suicide attempters[79] and these abnormalities were sustained for two years after the suicide attempt[51]. Consistent with these data, increased numbers of microglia immunoreactive for QA were reported within sub-regions of the anterior cingulate cortex in depressed suicides at postmortem[80]. Brundin and colleagues[81] additionally showed that suicide attempters had reduced levels of the neuroprotective metabolite, picolinic acid (PIC)[82], and a decreased PIC/QA ratio in both the CSF and plasma. 2-amino-3-carboxymuconic-6-semialdehyde

(ACMS) is spontaneously degraded to form QA but can also be converted to PIC by the amino-β-carboxymuconate-semialdehyde-decarboxylase (ACMSD) enzyme (figure 1). Thus, the aforementioned decrease in PIC raises the possibility of a deficiency in ACMSD activity in the context of suicidal behavior[81]. More generally, the collective data suggest that aberrant QA-mediated glutamate signaling driven by altered enzymatic activity at several different points in the KP may contribute to suicidality.

3.1.3. Psychosis and Schizophrenia—The classic dopamine model viewed psychosis and schizophrenia as disorders of excess striatal dopaminergic neurotransmission resulting from increased dopamine synthesis and presynaptic dopamine release[83]. This model was modified over time to take the psychotomimetic effects of non-competitive NMDA receptor antagonists like phencyclidine into account. That is, the upstream cause of the striatal hyperdopaminergia was postulated to be NMDA receptor hypofunction on GABAergic interneurons that in turn disinhibited excitatory projections onto midbrain dopamine neurons[84]. Since KynA is the only known endogenous NMDA receptor antagonist, psychosis and schizophrenia were postulated to be caused by the effect of elevated KynA on glutamatergic and ultimately, dopaminergic neurotransmission[85–87] (figure 3). Consistent with this model, experimentally increasing central levels of KynA has been demonstrated to increase the burst-firing of midbrain dopaminergic neurons in animal models[88], perhaps explaining why increased KynA has been reported in the *postmortem* brain[89], and the CSF[90, 91] of patients with schizophrenia. Similar results have been reported in BD – but the elevation in KynA was reported to be limited to patients with a history of psychosis[86, 87].

The reported increase in KynA in schizophrenia and psychosis may originate from inflammation-driven increases in KYN[92]. As in the case of mood disorders, there is evidence that inflammation may play a mechanistic role in schizophrenia[93] and PET studies have reported increased microglial activation in patients with schizophrenia[94]. The problem with this model is that inflammation should theoretically cause an increase in the production of QA and NAD+ at the expense of KynA as is seen in depression. In fact, my colleagues and I did indeed find a decrease in serum KynA in patients with schizoaffective disorder, psychotic BD, and MDD relative to healthy controls[50]. Further, it was the patients with affective psychosis who showed the largest decrease in KynA. Similarly, Myint et al. had previously reported a reduction in KynA together with an increase in 3HK in the plasma of the patients with schizophrenia compared with healthy controls, and this decrease in the KynA/3HK ratio significantly increased relative to baseline after 6 weeks of treatment[95]. Further research is needed to test whether schizophrenia and psychosis-associated reductions in KynA are limited to the periphery, and if so, why peripheral and central KynA concentrations appear to be in opposite directions to each other (as opposed to simply uncorrelated).

Conceivably, some as yet uncharacterized brain-specific immune process is elevating central but not peripheral concentrations of KynA. Another possibility is that psychosis-related increases in KynA could theoretically be related factors other than inflammation. Cortisol is known to activate *TDO*[96] and adrenergic activity may increase *IDO* activity through IFNγ[97]. Hong and colleagues showed that salivary KynA concentrations increased immediately after

a stress-inducing cognitive task in schizophrenia although there was no difference in KynA concentrations between participants with schizophrenia and healthy controls over time[97]. However, stress has also been reported to increase the productions of neurotoxic kynurenines: self-reported stressful life events were positively correlated with 3HK, but not KynA concentrations in elderly subjects at risk of dementia[98]. Genetic variants may also influence KP metabolism. For instance, a functional SNP in the KMO gene that decreases *KMO* activity was associated with elevated KynA concentrations in the CSF that were specific to BD patients with psychosis[87]. Conceivably, biotypes of psychotic disorders that differ in genetics, the degree of underlying inflammation or other etiological factors such as stress-induced HPA axis dysfunction may also differ in KynA. Differential changes in KynA in the acute versus the recovery phase of illness may also affect findings[50]. Larger sample sizes are required to disentangle these putative effects.

3.1.4. Cognition—As in the case of schizophrenia, there are two competing narratives as to the role of the KP in cognition. On the one hand, neurotoxic metabolites such as QA have been shown to damage the brain and lead to cognitive deficits. For instance, Heisler and O'Connor demonstrated that mice deficient in *IDO* or *KMO* were protected from endotoxin-induced deficits in novel object recognition, a task dependent on normal functioning of the hippocampus[99]. This result is potentially consistent with our report of an association between lower serum KynA to 3HK concentrations and greater hippocampal activity (indicating more effortful recall) during an autobiographical memory task in MDD subjects[62]. The link between "cold" cognitive deficits and KP metabolism has not been widely studied in patients with mood disorders although there is some equivocal evidence to suggest that lower neuroprotective ratios (e.g. KynA/3HK) are associated with greater cognitive impairment in BD[100].

On the other hand, elevated KynA has been postulated to underlie the cognitive deficits associated with schizophrenia. In preclinical studies, elevation of brain KynA through the genetic or pharmacological knockdown of *KMO*, has been shown to induce cognitive abnormalities that bear some resemblance to those observed in schizophrenia, including prepulse inhibition of the acoustic startle reflex[101], learning and memory[102], and cognitive flexibility[103]. Conversely, reducing brain KynA through pharmacological inhibition or genetic knockdown of *KAT-II*, improves cognitive function[73, 102]. Consistent with these preclinical data, subjects with schizophrenia (and to a lesser extent healthy controls) who were homozygous for a single nucleotide polymorphism (SNP) in the *KMO* gene that reduces *KMO* activity, had lower scores than their counterparts on a range of neuropsychological tests[104].

3.1.5. Pain—While pro-inflammatory cytokines may alone be pain-inducing, preclinical work has demonstrated that *IDO* activation also contributes to inflammation-related pain and associated depression-like behavior. With respect to behavior, the hippocampus appears to play a central role: Kim et al. demonstrated that the induction of chronic pain in rats with Freund's adjuvant induced depressive-like behavior together with *IDO* upregulation in the hippocampus via IL-6 signaling[105]. Both the nociceptive and depression-like behavior was attenuated in *IDO* gene knockouts or by pharmacological inhibition of *IDO*[105]. Consistent

with these data, virus-induced *IDO* expression in the lungs and lymphoid tissue was reported to induce pain hypersensitivity. This effect was absent in *IDO* knockouts but could be recapitulated by intravenously-administered KYN[106].

Because glutamate signaling through the NMDA receptor can produce hypersensitivity of the spinal sensory neurons thereby increasing pain sensation, the NMDA receptor is a key therapeutic target in pain disorders[107]. An example is ketamine which exerts analgesic effects by blocking NMDA receptors at sub-anesthetic doses[107]. Thus, it is not surprising that neurotoxic KP metabolites have been implicated in pain-related behavior. In a preclinical study, spared nerve injury was shown to increase *KMO* expression and QA concentration (but decrease KynA) in the contralateral hippocampus via an IL-1-dependent mechanism[108]. Pharmacological inhibition of *KMO* eliminated the depression-like behavior but not the mechanical allodynia likely because inhibition of NMDA receptors in the spinal cord is required for analgesia[108].

The increase in metabolism down the neurotoxic branch of the KP in both mood disorders and pain conditions has led to the hypothesis that the activation of NMDA receptors by QA may be a common pathophysiological mechanism that explains their high level of comorbidity[109]. Chronic pain is a significant risk factor for depression: 30–60% of individuals with clinical pain have comorbid depression[110]. Conversely, idiopathic pain is common in MDD. For instance, 75% of subjects in the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study reported pain[111].

4. Infectious Disease, Immune Tolerance and Immunosuppression

Activation of the KP is an important negative feedback loop that short-circuits the inflammatory response[112, 113]. This process initially was hypothesized to be predominantly mediated through T-cells which are sensitive to reductions in TRP, an important energy source for the T-cells. However, the reduction in TRP is now generally viewed through the lens of increased substrate utilization to provide the required energy (via the conversion of QA to NAD+) for the immune response[114]. Rather, increases in KYN, 3HK, and 3-HAA suppress and induce the apoptosis of Th1 and natural killer cells (NKC) as well as down-regulate the expression of CD8+ receptors, impairing their cytotoxic activity[112] (figure 4). In addition, TGFβ production and consequently regulatory T-cell (Treg) numbers are increased, leading to a tolerogenic environment[112].

Immune suppression is not only needed to resolve the inflammatory response but also in pregnancy where the allogenic fetus has to be protected from the mother's immune response. Munn and Mellor initially demonstrated that pregnant mice given an *IDO* inhibitor rejected semiallogenic but not syngenic fetuses, suggesting that the maternal T-cells response against paternal MHC antigens may occur through an *IDO*-dependent mechanism[115]. Nevertheless, the applicability of Munn and Mellor's model to humans remains controversial since blocking *IDO* does not completely inhibit T-cell function *in vitro*[116] and TRP is required by the fetus for normal development[116, 117]. Some researchers have concluded that the putative depletion of TRP is either highly localized or that increased utilization of TRP has a more

modest effect on immunotolerance in the context of pregnancy via the production of immunosuppressive KP metabolites[114, 116].

4.1 Relevance to Psychiatry

If chronic activation of the KP leads to a state of immune tolerance that increases susceptibility to infections and malignancies then one would expect to observe this phenomenon in a subgroup of individuals with psychiatric disorders. At least in the case of mood disorders, impairments of adaptive immunity are well-characterized. These impairments take the form of reduced numbers, gene expression and mitogen-stimulated proliferation of lymphocytes[33], reduced NKC numbers or cytotoxicity[118, 119], and increased numbers of Treg cells[118]. The public health consequences of compromised cellular immunity are significant. Depressed and stressed individuals are more vulnerable to infection[120], show reduced immunogenic responses to vaccines, acutely[121], and may even lose humoral immunity more rapidly in cases where the onset of depression occurs many years after vaccination[122]. In a similar vein, depression also predicts greater mortality in cancer patients[123].

Given its putative role in fetal tolerance, it is plausible that the kynurenines play a role in the development of postpartum depression. Conceivably, increases in KYN, 3HK, and 3-HAA, which suppress Th1 and NKC[112] may protect against fetal rejection at the expense of increasing the risk of depression. In women without depressive symptoms, TRP levels were reported to increase within two days of birth whereas this increase was absent in women with mild increases in depressive symptoms ("postpartum blues")[124]. Partly consistent with this result, an increase in KYN as well as amino acids that compete with TRP for transport across the blood brain barrier was found in the first three days after birth in a general population sample[125]. This finding was postulated to reflect a decrease in the brain availability of TRP, which was in turn hypothesized to result in "postpartum blues"[125]. Bergink and colleagues observed a shift towards the QA pathway in the first two months postpartum but this phenomenon occurred in both women with mood disorders and healthy controls[126]. However, a recent study reported increased serum concentrations of 3HK and 3HK/KYN (putatively reflecting increased *KMO* activity) in women with postpartum depression versus those without postpartum depression after cesarean section[127].

5. METABOLISM AND METABOLIC DISEASE

Immune cells are important regulators of energy metabolism in adipose tissue modulating lipid storage, glucose homeostasis, and the expenditure of energy[128]. Macrophages in particular accumulate and shift to a pro-inflammatory state as fat levels increase, theoretically leading to the preferential production of neurotoxic KP metabolites. Emerging preclinical evidence suggests that the kynurenines could play a mechanistic role in the evolution of metabolic dysfunction. A high-fat diet increased *IDO* expression in the plasma, adipose tissue, and muscle of mice, however, *IDO* knockout animals were protected from the obesogenic, inflammatory, and insulin resistance-inducing effects of the diet[129]. This effect appeared to be dependent on the maintenance of a healthy microbiome through the production of sufficient indole derivatives from TRP[129]. Another mechanistic pathway

conceivably relates to the balance between 3HK/QA and KynA production. An increase in 3HK and its metabolite xanthurenic acid (XA) is thought to interfere with insulin production and activity, and therefore with glucose homeostasis[130]. Ruas and colleagues also point out that the sustained activation of NMDA receptors on pancreatic β-cells may impair the function of these cells, raising the possibility that excess QA is a driver of metabolic disease[128]. KynA in contrast, serves as an endogenous measure of nutrient availability in *Caenorhabditis elegans* with KynA levels increasing during fasting, thus forming a homeostatic feedback loop that allows feeding behavior to be altered[131]. In a recent study, KynA was also reported to increase energy expenditure and promote an anti-inflammatory environment in adipose tissue thereby ameliorating the negative effects of a high-fat diet on weight and adiposity in a mouse-model of obesity[132]. Genetic deletion of GPR35 caused a progressive increase in obesity and loss of glucose tolerance suggesting that the effect of KynA was mediated by activation of GPR35 and downstream crosstalk with a variety of cellular pathways involved in thermogenesis, lipid metabolism and immunoregulation[132].

5.1 Relevance to Psychiatry

MDD is highly correlated with obesity and the two disorders have an overlapping biology[133, 134]. Similarly, there is a bidirectional relationship between metabolic diseases such as type II diabetes (T2D) and depression. Individuals with T2D are more likely to become depressed while a history of depression increases the risk of T2D[135]. One component of the shared biology is chronic low-grade inflammation, with the effect of pro-inflammatory cytokines the major focus of attention. However, given the preclinical studies linking kynurenines with metabolic function and the robust evidence for decreased KynA in depression[47–57], it is conceivable that dysregulation of the KP is part of this shared biology and may be a fruitful avenue for future research. Extant evidence suggests that patients with T2D display the same pattern of reduced KynA versus QA-pathway metabolism as in depression with reports of reduced expression of *KAT1* and *KAT2* in skeletal muscle[136] and increases in QA over the course of a longitudinal study increasing the risk of T2D[137]. Similarly, pro-inflammatory macrophages in the adipose tissue of obese women were shifted towards the neurotoxic branch of the KP and *KMO* expression was positively correlated with hemoglobin A1c levels[138].

6. AGING AND NEURODEGENERATIVE DISEASE

The biological mechanisms underlying aging are not yet well understood. One factor that consistently has been shown to correlate with age is mitochondrial activity. The age-associated reprograming of mitochondrial gene expression is thought to be a leading cause of cellular senescence, which is characterized by a state of permanent cell-cycle arrest and the acquisition of a proinflammatory phenotype named the senescence-associated secretory phenotype (SASP)[139]. Mitochondrial dysfunction is underpinned by many factors but at least two relate to the KP. Neurotoxic KP metabolites may directly compromise mitochondrial function - a mammalian cell-line overexpressing human *KMO* showed increased production of 3HK and reactive oxygen species, leading to impaired mitochondrial capacity[67]. Another pathway may involve an age-associated decrease in PGC-1 activity[140]. PGC-1 is a cofactor for the peroxisome proliferator-activated receptor (PPAR) family of

transcription factors that regulate mitochondrial biogenesis and function. At least in muscle, activation of the PGC-1-PPARα/δ pathway increases circulating concentrations of the neuroprotective metabolite, KYNA[141]. PGC-1 expression is decreased in several neurodegenerative disorders[140] and consistent with this putative decrease in PPAR signaling, there is evidence for increased metabolism down the neurotoxic branch of the KP in Alzheimer's Disease (AD) and Parkinson's Disease (PD)[142, 143]. For instance, plasma concentrations of KynA are decreased in AD[144] and postmortem studies have reported decreases in KynA in the frontal cortex, putamen, and substantia nigra of PD patients[145]. Further, genetic variants of ACMSD, which converts 3HAA (a precursor of QA) to PIC, are replicated risk factors for PD, providing additional evidence that excess QA may cause PD-associated excitotoxicity[146].

Consistent with these clinical data, preclinical studies have demonstrated that *KMO* inhibition ameliorates degeneration in models of neurodegenerative diseases such as AD[147], PD[148], and Huntington's disease[149]. Further, knockdown of *kynureninase* (the enzyme that converts 3HK to 3HAA) not only increased the lifespan of *C. elegans,* but also delayed age-dependent paralysis in worms expressing amyloid β[150] (a model of neurodegenerative disease).

6.1 Relevance to Psychiatry

Markers of cellular senescence including increased mitochondrial DNA copy number and SASP gene expression signatures have been reported in a range of psychiatric disorders[151]. Similarly, imaging studies are suggestive of reduced ATP availability in the brain in mood and psychotic disorders during high energy demand, potentially coinciding with a shift in energy production away from oxidative phosphorylation due to mitochondrial dysfunction[65, 66]. Consistent with these data, psychiatric disorders are associated with an increased risk of developing diseases of aging, including neurodegenerative disorders such as AD[152] and PD[153]. The underlying mechanisms linking accelerated cellular aging and neurodegeneration with psychiatric illness are still unclear but conceivably may partly involve dysregulation of the balance between neurotoxic and neuroprotective kynurenine metabolites in the context of mitochondrial dysfunction and inflammation.

7. SEX HORMONES

Males and females differ significantly in immune function. Females for example, respond more strongly to infections and vaccines, and are significantly more likely than males to suffer from inflammatory and autoimmune diseases[154]. These sex differences likely relate to the close interaction between hormones and the immune system. For instance, estrogen, androgen, and progesterone receptors are expressed on most immune cells, and many genes of the innate immune system contain estrogen response elements[155, 156]. Interestingly, estrogen was reported almost 60 years ago to exert an inhibitory effect on the *KAT* enzymes, leading to a decrease in KynA[157]. This finding was recently extended by an *in vitro* study which reported that estradiol disulfate is a strong inhibitor of the *KAT-I* and *KAT-II* enzyme isoforms[158]. However, the effects of estrogen are likely dose and context-dependent since treatment of rhesus monkeys with estradiol also resulted in a significant reduction in the

expression of *KMO* in the raphe[159]. Progesterone is generally considered to have neuroprotective properties although as in the case of estrogen, its effects on the immune system may be complex. *In vitro* treatment of human macrophages with a supra-physiological dose of progesterone was shown to attenuate IFNγ-induced activation of the KP, decrease QA, and increase KynA concentrations[160].

7.1 Relevance to Psychiatry

The lifetime prevalence of MDD in women is twice that of men[161]. This statistic has traditionally been attributed to psychosocial or hormonal factors. However, given evidence of sex differences in immune function[154] and the effects of estrogen on the *KAT* and *KMO* enzymes, the higher rate of depression in women versus men may also be related to alterations in KP metabolism that increase vulnerability to depression in females[162]. Consistent with these *in vitro* and preclinical studies, my colleagues and I reported that in both depressed subjects and healthy controls, women had reduced serum concentrations of KynA relative to males, and further that women taking oral contraceptives (OC) had lower levels of KynA relative to women not taking OC[162]. In contrast to depression, the prevalence of schizophrenia in males is ~2.5 times greater than in females[163]. If, as has been hypothesized, elevated brain KynA is a pathophysiological mechanism underlying schizophrenia, then estrogen-associated decreases in KynA may be protective, conceivably partly explaining why females are at lower risk for schizophrenia-related disorders.

8. THERAPEUTIC IMPLICATIONS

Dysregulation of the KP is a candidate pathogenic mechanism for psychiatric disorders. Preclinical work has demonstrated that KP metabolites play a causal role in the manifestation of the behavioral analogues of depression and schizophrenia-like cognitive deficits. Cross-sectional studies of clinical populations are generally consistent with the animal literature although cannot demonstrate causality. Thus, in theory, modulation of KP metabolism holds therapeutic potential. Enzymes in the KP are druggable. *IDO* inhibitors are in various stages of development for the treatment of cancer[164] and clinical trials are underway with drugs that target various points in the metabolic pathway (see below). Further, because the KP is a nexus for diverse physiological processes – immunological, endocrine, metabolic, hormonal – that are dysregulated across multiple psychiatric disorders, unlike anti-inflammatory medications, modulation of the KP could theoretically benefit multiple biotypes of mood and psychotic disorders.

8.1 Novel Medications

Given evidence for increased production of neurotoxic metabolites at the expense of KynA in mood disorders, inhibiting *KMO* or augmenting activity of the *KAT* enzymes could conceivably have anti-depressant and neuroprotective effects. *KMO* inhibitors have shown some efficacy in preclinical models of neuropathic pain[165], HD, and AD[147]. However, because of the central regulatory role of the KP, an excess reduction in QA together with an abnormal elevation in KynA may be an undesirable outcome of therapeutic approaches involving inhibition of *KMO*. Further, because *KMO* inhibition may drive-up circulating KYN concentrations which can then be converted into QA in the CNS (see below), sufficient

brain penetrance is likely needed for therapeutic efficacy. As a result of these challenges, additional approaches are in development.

First-in-human clinical trials for MDD are currently underway with the KynA analogue, 4-chlorokynurenine or AV-101 (NCT02484456 and NCT03078322). Like KynA, AV-101 is a selective antagonist at the glycine-binding site of the NMDA receptor. Manufactured by VistaGen, AV-101 recently received Fast Track Designation by the FDA for the treatment of MDD[166]. Another potential intervention is predicated on the mechanics of KYN transport across the blood brain barrier. KYN is transported across the blood brain barrier by the large amino acid transporter (LAT1) where, under inflammatory conditions, it is preferentially metabolized into neurotoxic metabolites. Therefore, reducing the access of circulating KYN to the brain will in theory have therapeutic effects. Dantzer and colleagues have recently demonstrated that leucine treatment is a feasible method of competitively blocking the LAT1 to prevent exogenous KYN from entering into the brain[167]. Moreover, they reported that leucine blocked LPS-induced depression-like behavior in mice without affecting levels of inflammation or sickness behavior[167]. A phase 2 clinical trial to test the anti-depressant effects of leucine in individuals with MDD is in progress (NCT03079297).

8.2 Extant Treatments

While compounds targeting the KP hold promise as novel treatments, the literature suggests that several current treatments for depression alter KP metabolism. A recent study showed that prior to treatment with electroconvulsive therapy (ECT), depressed patients had significantly lower levels of serum KynA/QA than controls which increased significantly after three ECT treatments performed over two weeks[56]. Similarly, in another study, increases in KynA and KynA/3HK were observed in depressed patients receiving twice-weekly ECT for an average of three weeks[168].

In mice, Dantzer and colleagues demonstrated that ketamine was able to abrogate LPS-induced depressive behavior likely by blocking QA-mediated activation of NMDA receptors[75]. The link between ketamine and the KP has also been investigated in clinical populations. 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[169]. Partially consistent with this result, a non-significant reduction in KYN and KYN/TRP also was reported in ketamine responders versus non-responders at two hours and 24 hours post initial infusion[53]. 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[170]. Further, the elevation in KynA was greater in treatment responders versus non-responders. Metabolites in the QA pathway were not measured but the increase in the ratio of KynA to KYN suggested that ketamine may shunt metabolism of kynurenine towards KynA[170].

Physical exercise protects against the future onset of depression[171] and can be an efficacious treatment for MDD[172]. In a landmark study, skeletal muscle exercise was shown to protect against stress-induced depression in mice by increasing expression of the *KAT* enzymes in muscle, thereby reducing KYN concentrations in the periphery and by implication, KYN

levels and neurotoxic metabolites in the brain[141]. Further, human volunteers displayed increased *KAT* gene expression in muscle after a three-week endurance exercise program[141]. In a follow-up study, endurance exercise was found to increased plasma concentrations of KynA as well as KynA/QA and well-conditioned subjects appeared to show adaptive increases in *KAT* expression in the muscle tissue[173]. Nevertheless, discrepant effects have been reported in several other studies[174] likely because of the diversity of the trial designs, types of exercise and the length of the regimens employed. At least three ongoing clinical trials of exercise propose alterations in the KP as secondary outcome measures (NCT03539835; NCT02765568, and NCT03324152).

Given a pathoetiological role for inflammatory processes in mood disorders, there is emerging interest in employing anti-inflammatory medications to treat a subgroup of depressed patients with systemic inflammation. Among the medications that have shown therapeutic potential are cyclooxygenase (COX) inhibitors – particularly COX-1 inhibitors[175]. We recently completed the first clinical trial of aspirin for the treatment of bipolar depression. Patients receiving low-dose aspirin, which preferentially inhibits COX-1, were significantly more likely to respond to treatment than placebo-treated subjects, suggesting that aspirin may be an efficacious adjunctive treatment for bipolar depression[176]. Interestingly, the COX-1 inhibitors, indometacin and diclofenac increased brain levels of KynA in the rat[177, 178] and KynA levels in both the plasma and the hippocampus were shown to be significantly increased one hour after a single dose of ibuprofen[179]. Whether the impact of COX inhibition on KynA is independent of its general anti-inflammatory effects remains to be determined but either way these data raise the possibility that changes in KP metabolism may contribute to the putative anti-depressant effects of COX inhibitors.

9. SUMMARY AND FUTURE DIRECTIONS

Given its central role in immune function and energy metabolism, any dysregulation of KP metabolism is likely to “reverberate through the system”, ultimately impacting neural function and leading to neuropsychiatric disorders and associated medical comorbidity. While preclinical studies have demonstrated that the KP plays a causal role in psychiatric illness that is independent of inflammatory processes *per se*, one challenge for the field is to extend this work to humans by developing methods to experimentally manipulate KP activity with the necessary degree of specificity to draw causal conclusions. Beyond the immune system, the KP also interacts with other physiological systems and clarifying how inflammation, stress, pain, metabolic, and hormonal dysfunction overlap or differ from each other in their downstream effects on the KP may help to advance the field. Third, the role of genetic or epigenetic factors in influencing the activity of other key KP enzymes such as ACMSD, QPRT, and the KATs, is ripe for exploration. Finally, in addition to clinical trials of novel therapeutic interventions, an assessment of whether the kynurenines possess clinical utility as biomarkers of response to existing treatments is indicated. Since dysregulation of the KP may weaken the capacity for neuroplasticity, the kynurenines may also hold promise as prognostic biomarkers for mood disorders and schizophrenia.

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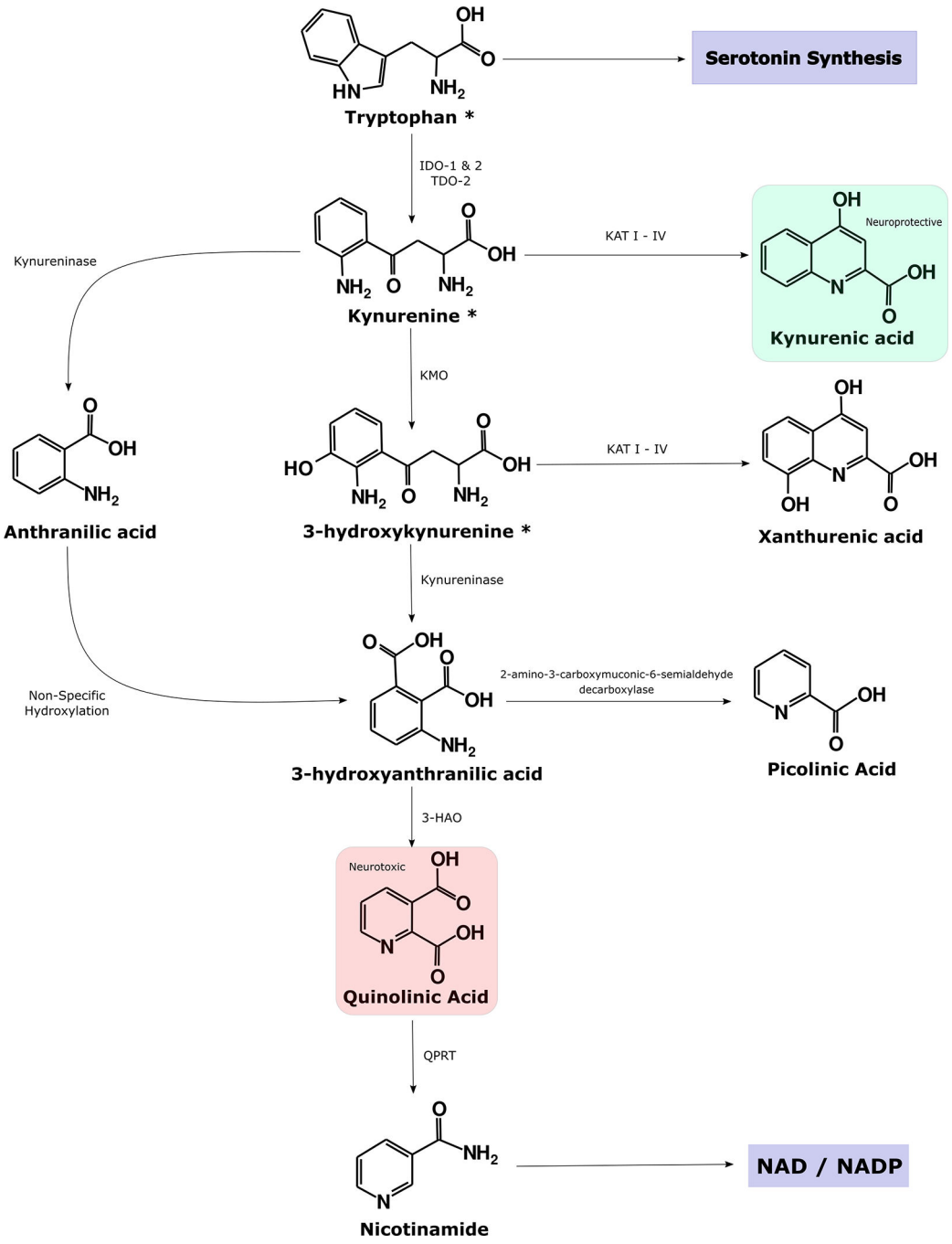

Figure 1: Simplified Illustration of the Kynurenine Pathway.

Tryptophan (TRP) is predominantly converted into kynurenine (KYN) by the *indoleamine 2,3-dioxygenase* (*IDO*) isozymes and *tryptophan dioxygenase* (*TDO*). *IDO-1* is expressed in various immune cells throughout the body, notably dendritic cells, monocytes, and macrophages. Less is known about the more recently discovered *IDO-2* enzyme although it is more selectively expressed in dendritic cells, liver, kidney, and the brain[180] and it does not appear to have a significant effect on peripheral kynurenine concentration[181]. This review focuses on *IDO-1* (hereafter *IDO*). *TDO-2* is an alternative nomenclature for *TDO*. KYN

can be metabolized into kynurenic acid (KYNA), which is usually considered to be neuroprotective, by the *KAT* isozymes. Alternatively, it may be converted into anthranilic acid by *kynureninase* or 3-hydroxykynurenine (3HK) by *kynurenine mono-oxygenase* (*KMO*). Metabolism down the latter pathway increases under inflammatory conditions[25, 30]. 3HK is a free radical generator while quinolinic acid (QA) is a known neurotoxin and gliotoxin. Thus, metabolites in this pathway are usually considered to be neurotoxic. QA is the endogenous source of nicotinamide and nicotinamide adenine dinucleotide (NAD+).

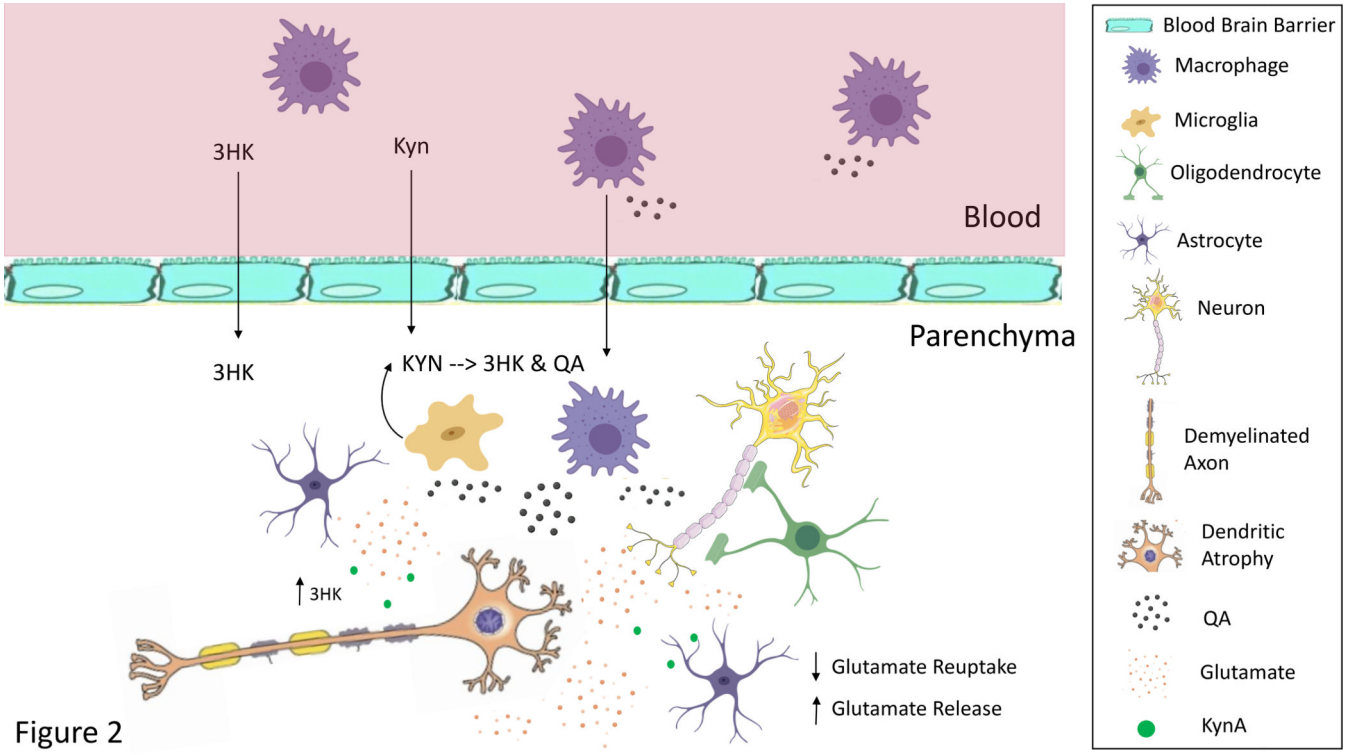

Figure 2: Heuristic Model of the Pathological Effects of Neurotoxic Kynurenines.

Under inflammatory conditions circulating macrophages produce more kynurenine (KYN), 3-hydroxykynurenine (3HK), and quinolinic acid (QA). 3HK can cross the blood brain barrier damaging neuronal cells through the production of free radicals. KYN also crosses the blood brain barrier where it is preferentially metabolized into 3HK and QA by microglia. Further, macrophages can infiltrate the brain parenchyma, where they are estimated to produce 32 times more QA than resident microglia[182]. Thus, although QA is usually found in low nanomolar concentrations in the human brain and CSF, a significant increase in QA levels to micromolar concentrations likely occurs in patients with neuroinflammation[183]. QA may contribute to the excitotoxic processes caused by the deficient glutamate reuptake (and paradoxical release) by dysfunctional astrocytes. Dendritic atrophy and remodeling also likely occurs altering functional connectivity. Further, 3HK and QA may damage oligodendrocytes leading to white matter abnormalities. Oligodendrocytes are highly sensitive to inflammation and reductions in their numbers or density are one of the most prominent findings in mood disorders at postmortem[40]. Note that other inflammatory mediators also play an important role in these neuropathological processes. Only the kynurenines are shown in the figure for clarity.

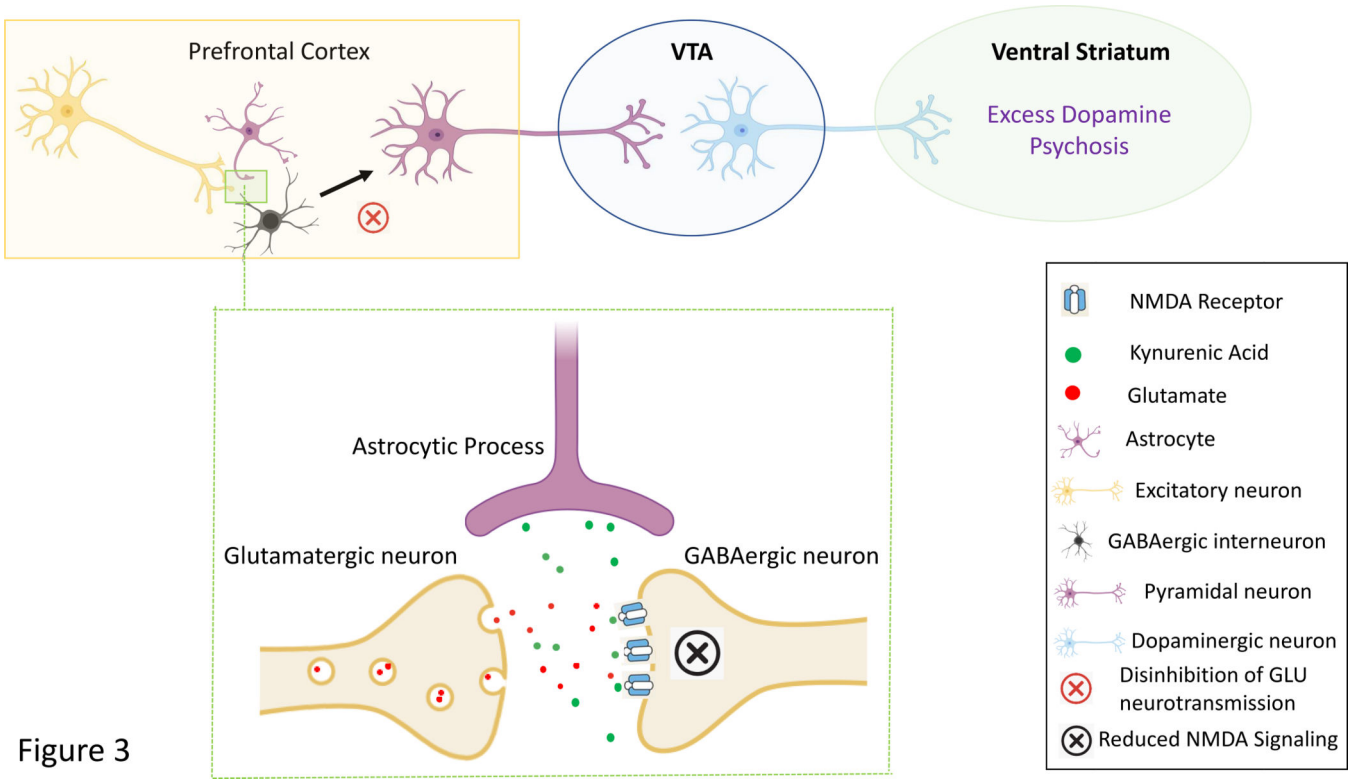

Figure 3

Figure 3: Simplified Model of the Putative Psychosis-Inducing Effects of Kynurenic Acid

Cortical GABAergic interneurons normally exert an inhibitory tone on glutamatergic pyramidal neurons that project to the ventral tegmental area (VTA) and modulate dopaminergic neurotransmission. Excess kynurenic acid production by astrocytes may cause NMDA receptor hypofunction on cortical GABA interneurons leading to reductions in GABAergic neurotransmission and the disinhibition of cortical glutamate projections. Theoretically, this abnormally increased glutamatergic activity causes overactivation of the mesolimbic DA pathway and the excessive release of dopamine in the ventral striatum, ultimately leading to the development of psychosis.

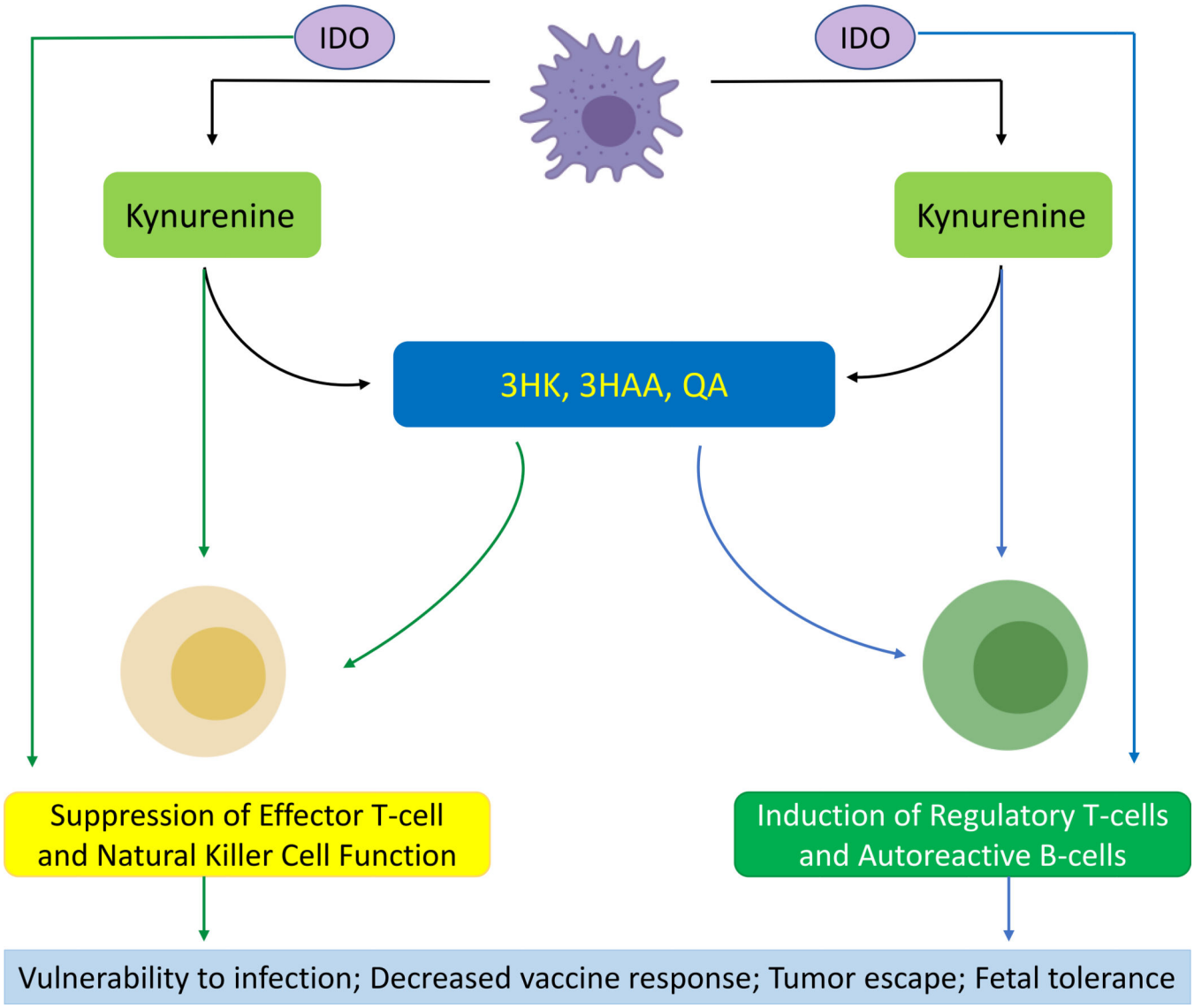

Figure 4: The Immune-Modulatory Effects of Kynurenine Pathway Activation

The kynurenine pathway may explain the counter-intuitive phenomenon of co-occurring inflammation and immunosuppression in depression. Under inflammatory conditions, *IDO* is upregulated, catalyzing the conversion of tryptophan (TRP) to kynurenine (KYN). KYN is preferentially metabolized down the quinolinic acid (QA) pathway into 3-hydroxykynurenine (3HK), 3-hydroxyanthranilic acid (3HAA), and QA. *IDO*, KYN and its metabolites exert a variety of immunosuppressive effects, including downregulation of NKC receptors and induction of NKC death[184]; induction of lymphocyte cell-cycle arrest and apoptosis, and downregulation of the T-cell receptor (TCR)[185] (readers left, green arrows). They also promote a tolerogenic environment by facilitating the differentiation of naïve T-cells into regulatory T-cells (T_{reg})[186] and the development of autoreactive B-cells[187]. This suppression of adaptive immune function has clinical consequences, including increased

vulnerability to infectious disease, deficient vaccine-induced immunogenicity, and tumor escape[120–122] (reader's right, blue arrows).