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Kynurenine 3-monooxygenase: an influential mediator of neuropathology

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Mounting evidence demonstrates that kynurenine metabolism may play an important pathogenic role in the development of multiple neurological and neuropsychiatric disorders. The kynurenine pathway consists of two functionally distinct branches that generate both neuroactive and oxidatively reactive metabolites. In the brain, the rate-limiting enzyme for one of these branches, kynurenine 3-monooxygenase (KMO), is predominantly expressed in microglia and has emerged as a pivotal point of metabolic regulation. KMO substrate and expression levels are upregulated by pro-inflammatory cytokines and altered by functional genetic mutations. Increased KMO metabolism results in the formation of metabolites that activate glutamate receptors and elevate oxidative stress, while recent evidence has revealed neurodevelopmental consequences of reduced KMO activity. Together, the evidence suggests that KMO is positioned at a critical metabolic junction to influence the development or trajectory of a myriad of neurological diseases. Understanding the mechanism(s) by which alterations in KMO activity are able to impair neuronal function, and viability will enhance our knowledge of related disease pathology and provide insight into novel therapeutic opportunities. This review will discuss the influence of KMO on brain kynurenine metabolism and the current understanding of molecular mechanisms by which altered KMO activity may contribute to neurodevelopment, neurodegenerative, and neuropsychiatric diseases.

Keywords: neuroinflammation, kynurenine 3-monooxygenase, kynurenine pathway, microglia, neurodevelopmental disorders, neurodegenerative diseases, neuropsychiatric disorders

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Introduction

During healthy conditions, most dietary tryptophan is metabolized in the liver to generate nicotinic acid and subsequent energy-producing co-factors through the kynurenine metabolic pathway (1). Kynurenine metabolites were first identified in urinary excretions, and the observation of a correlation between the disruption of dietary tryptophan metabolism and neuropsychiatric diseases sparked an interest in the potential pathogenic role of kynurenines (2, 3). Identification of receptor targets within the brain provided a putative mechanistic role for kynurenine metabolites in disorders of the central nervous system. The kynurenine pathway (**Figure 1**) diverges along two main metabolic branches that produce metabolites, kynurenic acid (KA), and quinolinic acid (QA), that both bind to the *N*-methyl-D-aspartate receptor (NMDAR) (4). KA or QA modulation of NMDAR

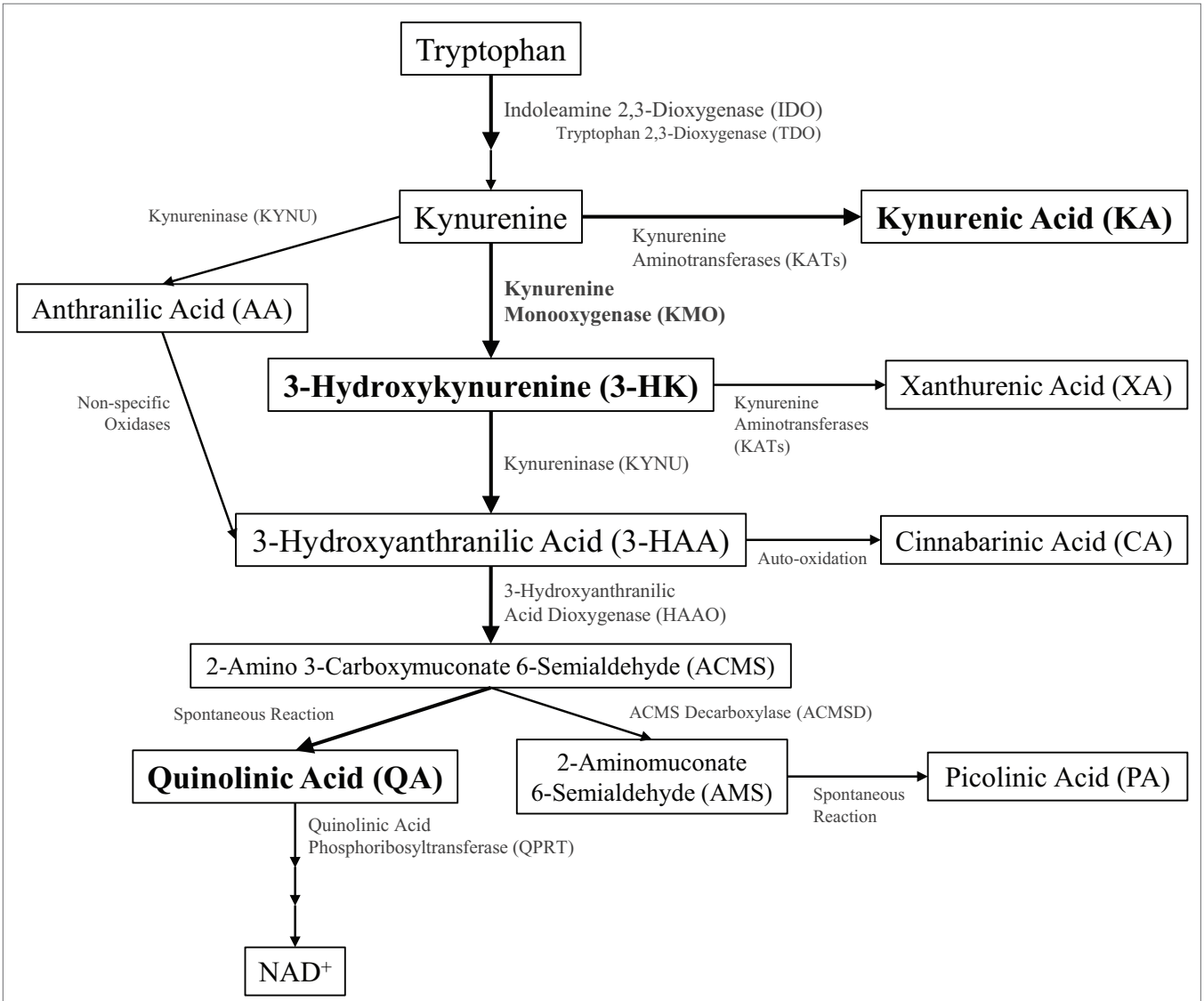

FIGURE 1 | Schematic of kynurenine pathway metabolism. Kynurenine metabolites (inside boxes) and the enzymes that metabolize them (along arrows) are illustrated.

activity and glutamatergic signaling is hypothesized to contribute to the pathogenesis of multiple neurological disorders (5). Under basal conditions, kynurenine metabolism favors the formation of KA within the brain; however, disruptions in homeostasis can shift the balance toward increased production of QA. The rate-limiting step for the production of QA involves oxidation of kynurenine by kynurenine 3-monooxygenase (KMO). As KMO is positioned at a pivotal junction in regulating the production of these two metabolites, changes in KMO expression or activity may contribute to the development of neurodegenerative, neuropsychiatric, and neurodevelopmental diseases. The purpose of this review is to (1) provide evidence of the critical role that KMO plays in maintaining the physiological balance between QA and KA production, (2) present examples of how this balance can be disrupted and associated with neurological diseases, and (3) demonstrate how this evidence supports KMO as a potential therapeutic target for neurological disorders.

Kynurenine Metabolism in the Brain

Tryptophan is metabolized to kynurenine by one of three rate-limiting enzymes; tryptophan 2,3-dioxygenase (TDO), indoleamine-2,3-dioxygenase (IDO1), or indoleamine-2,3-dioxygenase-like protein (IDO2). TDO expression increases in response to substrate levels or corticosteroid stress hormones, while inflammatory stimuli increase IDO1 expression (6, 7). Fluctuations in kynurenine metabolism have the capacity to indicate changes in homeostasis in the body. Under normal physiological conditions, local production of kynurenine within the brain accounts for approximately one-third of the kynurenine

present, while the rest is transported in from the periphery (8). During disease conditions, however, an even larger proportion of brain kynurenine originates from peripheral sources, and the subsequent synthesis of neuroactive kynurenine metabolites also increase and have the capacity to influence neurotransmitter systems within the brain (9).

Kynurenine

Until recently, kynurenine, itself, was considered a biologically inert metabolite. Kynurenine levels and the kynurenine to tryptophan ratio were largely evaluated for their utility as biomarkers for disease. Early hypotheses suggested that increased tryptophan metabolism along the kynurenine pathway could reduce the bioavailability of tryptophan for the synthesis of serotonin resulting in depression-associated behaviors (10). Recent clinical and preclinical data, within the context of inflammation, indicate that the brain is able to compensate for reduced peripheral tryptophan levels leaving central serotonin levels unaffected (11, 12). However, identification of kynurenine as an endothelium-derived vasodilator revealed a more relevant physiological role for this metabolite (13). The subsequent discovery of kynurenine as an endogenous ligand of the aryl hydrocarbon receptor has prompted intense interest into this potential receptor-mediated mechanism by which kynurenine could contribute directly to disease (14). Further, kynurenine is readily transported across the blood–brain barrier, and is the substrate for the synthesis of many metabolites that exert known neurotoxic, neuroactive, and oxidative actions, which have been implicated in a wide range of neuropathologies.

Kynurenic Acid

Under physiological conditions, most kynurenine in the brain is metabolized to KA (**Figure 1**), an NMDAR antagonist, and α_7-nicotinic acetylcholine receptor (α_7nAChR)-negative allosteric modulator (4, 15). Peripheral KA does not cross the blood–brain barrier in appreciable amounts and therefore is not thought to contribute to central actions of KA. Kynurenine aminotransferase (KAT) catalyzes this reaction and is not responsive to inflammatory stimuli as other kynurenine pathway enzymes are. There are three functional KAT isoforms, I and II the most relevant in mammals, and are predominantly expressed in astrocytes, giving rise to cell-type specific compartmentalization kynurenine metabolism (16, 17). Early studies of KA demonstrated that it can be neuroprotective against neuronal damage caused by neurotoxic QA, an effect that is most likely mediated through inhibitory activity at NMDARs (18). More recent studies have demonstrated that elevated KA can lead to disruptions in working memory, sensorimotor gating, and attentional processing tasks (19–21). These results suggest that sustaining physiological levels of KA are likely important in maintaining a basal neuroprotective environment within the brain, but pathophysiological elevation of KA can also be detrimental to normal neuronal functioning.

3-Hydroxykynurenine

During inflammatory conditions and when IDO1 is upregulated, kynurenine metabolism shifts from the predominant production of KA toward the generation of increased amounts of QA. In the first metabolic reaction of this branch, KMO metabolizes kynurenine to 3-hydroxykynurenine (3-HK, **Figure 1**). While KAT enzymes are expressed in astrocytes, KMO is predominantly expressed in microglia, the resident immune cells in the brain (22). In response to inflammatory stimuli or tissue damage, KMO expression and 3-HK production also increase, effectively shuttling kynurenine metabolism toward the production of QA (23). Peripherally generated 3-HK is able to cross the blood–brain barrier by virtue of it hydrophobic nature, increasing its bioavailability in the brain. 3-HK was originally thought to be a cytotoxic metabolite through the generation of reactive oxygen species (24–26). However, more recent studies have demonstrated that 3-HK has the ability to be both antioxidant as well as pro-oxidant depending on the circumstances (27). In the brain, 3-HK may function primarily as a modulator of redox state as opposed to being a neurotoxic metabolite, but the direct neuropathological role of 3-HK remains under investigation.

3-Hydroxyanthranilic Acid

Kynureninase (KYNU) metabolizes 3-HK to 3-hydroxyanthranilic acid (3-HAA, **Figure 1**), another metabolite that is increased during inflammatory conditions (23). 3-HAA has been shown to play a role in T-cell immunity by reducing dendritic cell activation of T-cells and by mediating activated T-cell death (28, 29). Additionally, 3-HAA can induce apoptosis in monocyte-derived cells; however, 3-HAA is also anti-inflammatory and neuroprotective in neuronal and glial cultures (30–32).

Quinolinic Acid

3-Hydroxyanthranilic acid dioxygenase (HAAO) metabolizes 3-HAA into 2-amino 3-carboxymuconate 6-semialdehyde (ACMS, **Figure 1**), which undergoes a non-enzymatic conversion to QA (**Figure 1**), an endogenous NMDAR agonist (33). During inflammatory conditions, QA accumulates and is a major endpoint of kynurenine metabolism. With the capacity to stimulate excitatory glutamatergic signaling, extra-physiological concentrations of QA can result in neurotoxicity or neuronal death, tissue lesions, and seizures (33–35). Additionally, QA neurotoxicity is also attributed to the generation of reactive oxygen species and lipid peroxidation (36–38). Due to its potent neurotoxic properties, any elevation or accumulation of QA can have detrimental effects on not only the local cellular environment but also can impact behavior as well.

Other Kynurenine Metabolites

Anthranilic Acid

Kynurenine can also be metabolized to anthranilic acid (AA, **Figure 1**) by KYNU. However, the affinity of kynurenine for this enzyme is very low, so metabolism only occurs to appreciable amounts when kynurenine concentrations are elevated (39). AA can also be metabolized by non-specific oxidases to generate 3-HAA, a reaction which does appear to contribute significantly to the production of 3-HAA (40). AA does not increase during inflammatory conditions and no receptor activity for AA has been identified presently (23).

Xanthurenic Acid

The transamination of 3-HK results in xanthurenic acid (XA, **Figure 1**), and this enzymatic reaction is conducted by the same aminotransferase (KAT) that metabolizes kynurenine to KA (41). Within the brain, XA appears to be functionally relevant as it is stored and transported within neuronal vesicles and then released in an activity-dependent manner (41). Further, evidence demonstrates that XA can modulate hippocampal transmission through inhibition of the vesicular glutamate transporter (VGLUT) and was recently identified as an endogenous agonist of metabotropic glutamate receptors (42, 43).

Cinnabarinic Acid

Cinnabarinic acid (CA, **Figure 1**) is produced by the autooxidation of two 3-HAA molecules in a process that also generates superoxide and hydrogen peroxide (44). Synthesis of CA occurs during conditions of elevated reactive oxygen species or in response to inflammatory stimuli (45, 46). CA is a partial agonist at type 4 metabotropic glutamate receptors (mGluR4), activation of which can protect neurons from excitotoxic death (46).

Picolinic Acid

Rather than be converted to QA, ACMS can be metabolized by ACMS decarboxylase (ACMSD) into 2-aminomuconate 6-semialdehyde (AMS, **Figure 1**) that can be non-enzymatically converted to picolinic acid (PA, **Figure 1**) (47). ACMSD expression is low and therefore PA formation does not represent the main route of metabolism of ACMS (47). PA can attenuate QA-induced neurotoxicity through a mechanism independent of influencing neuronal excitation (48).

Influence of Glia on Central Kynurenine Metabolism

Though peripherally produced tryptophan and kynurenine contribute most of the substrate for metabolism in the kynurenine pathway in the brain, KA and QA do not appreciably cross the blood–brain barrier and must be produced locally. Since the enzymes that subsequently direct the metabolism of kynurenine are preferentially expressed in separate cell types, production of these neuroactive metabolites is essentially compartmentalized within the brain and sensitive to inflammatory signals that activate microglia (**Figure 2**).

While most cells in the brain have the capacity to metabolize tryptophan to kynurenine, metabolism of kynurenine to KA occurs mainly in astrocytes, and the production of QA occurs mainly in activated microglia (22, 49). Under basal conditions in the brain, kynurenine is predominantly metabolized to KA in astrocytes, cells that primarily function to maintain homeostasis within the brain (16). However, during neuroinflammatory conditions, kynurenine metabolism shifts to generating neurotoxic QA and microglia become the primary cellular mediators (23). Neuroinflammation includes the propagation of inflammatory signals and the activation of the resident immune cells in the brain, microglia. Shifting the metabolism of kynurenine from astrocytes toward activated microglia during neuroinflammation corresponds with the alteration in production of KA to QA (i.e., increasing the QA to KA ratio). While astrocytes have the capability to clear extracellular QA and metabolize it to nicotinic acid, they are not able to produce it (22). Further, during neuroinflammatory conditions, the capacity of astrocytes to clear QA may be impaired (50). In disease states, microglia can remain active and neuroinflammation can persist, possibly resulting in production and accumulation of neurotoxic kynurenine metabolites. Compartmentalization provides a mechanism to effectively and physically separate the two distinct branches of kynurenine metabolism.

KMO is Positioned at an Influential Regulatory Point in the Kynurenine Pathway

Multiple kynurenine metabolites have the capacity to directly or indirectly influence neuronal processes, both in a beneficial or detrimental manner. However, those with potentially the greatest impact are KA and QA as they can influence excitatory glutamatergic signaling by binding the NMDAR. Many neurological disorders are hypothesized to involve disrupted glutamate signaling, and therefore, modulation of KA or QA production could provide a more relevant therapeutic target (5). During neuroinflammatory conditions, KMO is the principle regulator of the metabolic fate of kynurenine to either KA or QA, and as such, it could be a prominent mediator of neuropathology development (**Figure 2**).

KMO Regulates Quinolinic Acid Production

Kynurenine 3-monooxygenase metabolism of kynurenine increases in response to elevated substrate levels and upregulation in KMO expression, both associated with neuroinflammation, typically characterized by microglia activation, and the propagation of central inflammatory signals. Metabolism continues along the KMO-dependent branch of the pathway producing 3-HK, 3-HAA, and QA, contributing neurotoxic metabolites to this environment of neuroinflammation (23, 51). Though the acute process is typically adaptive, prolonged neuroinflammation or the presence of secondary factors that can exacerbate the neuroinflammatory response (i.e., gene polymorphisms, comorbidity, etc.) often results in maladaptive consequences on normal neuronal functioning (52, 53). Numerous neurological disorders are characterized by chronic inflammation, and their pathology is often associated with microglia activation (54). Consequently, continued neuroimmune stimulation can also result in the production of neurotoxic kynurenine metabolites, 3-HK and QA, that generate reactive oxygen species and increase the potential for glutamate excitotoxicity. *In vivo* administration of 3-HK induces tissue damage that is only attenuated when co-treated with *N*-acetyl-L-cysteine, an antioxidant, not MK-801, an NMDAR antagonist (55). *In vitro* studies have further demonstrated that 3-HK can cause neuronal cell death that is susceptible to glutathione, catalase, and desferrioxamine, antioxidants that demonstrate 3-HK confers its cellular toxicity via the generation of oxidative stress (24–26). However, contradictory studies also demonstrate that 3-HK can reduce markers of oxidative stress, specifically in C6 glioma cells, and protects B-phycoerythrin

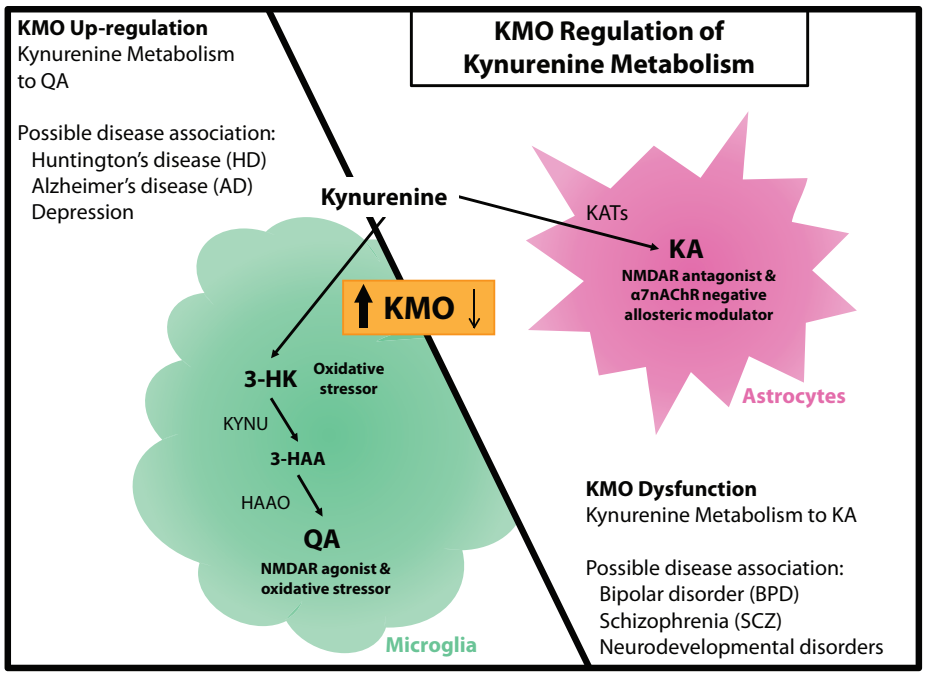

FIGURE 2 | KMO regulation of kynurenine metabolism. (Left panel) KMO upregulation during neuroinflammation results in a shift in kynurenine metabolism that increases production of QA in microglia. This change in metabolism is associated with elevated oxidative stress and glutamate excitotoxicity that could contribute to Huntington's disease (HD), Alzheimer's disease (AD), and even depression. (Right panel) KMO dysfunction as a consequence of genetic mutation favors the production of KA in astrocytes, which is accompanied by disruptions in cognitive performance and psychosis. KA elevations and KMO polymorphisms have been associated with bipolar disorder (BPD), schizophrenia (SCZ), and some neurodevelopmental disorders. KMO has the potential to regulate the production of both QA and KA thereby contributing to the development of multiple neurological disorders.

from peroxyl radical-mediated oxidative damage (56, 57). Despite this evidence, the potential for 3-HK to contribute to oxidative stress and neuronal damage, particularly contributing to disease progression, still remains, as elevated 3-HK levels have been described in neurodegenerative and neuropsychiatric disorders (58).

Quinolinic acid can also induce oxidative damage, specifically lipid peroxidation, which is attenuated by pretreatment with KA or MK-801 (36, 59). Lipid peroxidation produced by QA can also be attenuated by antioxidants, demonstrating that both free radical formation and NMDAR activation contribute to QA-induced oxidative damage (60, 61). As microglia remain activated and continue metabolizing kynurenine, QA production similarly increases and is released into the synapse (62). The breakdown of QA by quinolinic acid phosphoribosyl transferase (QPRT) occurs much slower than the production, therefore QA can rapidly accumulate (63, 64). Elevated QA activates NMDARs, stimulates glutamate release, and prevents glutamate re-uptake by astrocytes (65). As extracellular glutamate concentrations rise from continued release and re-uptake inhibition, the neurons in the synapse can undergo cytotoxic cell death (66). Direct administration of QA is a potent inducer of seizures, a behavioral phenotype of neuronal over-excitation (67). As KA can experimentally attenuate QA excitotoxicity and oxidative damage, the existence of this endogenous antagonism suggests that maintenance of metabolic homeostasis within the brain is important, and, as might be predicted, disruption of metabolic balance could contribute to the underlying pathology of many brain-based diseases. In disorders associated with inflammation and microglia activation, increased KMO-dependent kynurenine metabolism would result in 3-HK and QA accumulation, while a disruption of KMO activity would favor a metabolic shift toward the production of KA. The accumulation in neurotoxic metabolites could in turn contribute oxidative stress and neuronal excitotoxicity. KMO therefore represents a viable therapeutic target for a number of diseases associated with neuroinflammation and neurodegeneration.

KMO Regulates Kynurenic Acid Production

Under physiological circumstances in the brain, a majority of kynurenine is metabolized by KATs to KA, predominantly in astrocytes (49). As KA is an inhibitor of the NMDAR, it was initially thought to be neuroprotective by attenuating over-excitation of glutamatergic neurons (4). Multiple studies demonstrated that as the endogenous antagonist to QA, KA could counteract the damaging and neurotoxic effects of elevations in QA *in vivo* specifically through the NMDAR (4, 18, 68, 69). KA also interacts with the mesocorticolimbic dopamine (DA) area through its antagonism of the NDMAR and therefore has the potential to impact disorders associated with this system (70–72). The inhibitory actions of KA on cholinergic transmission through the α_7nAChR also indirectly influence the regulation of multiple neurotransmitter systems including both GABA and DA signaling

in the striatum (73, 74). Despite the seemingly positive impact KA has on neuronal systems, the beneficial effects of elevated KA only extend so far, as pathophysiological levels have been found to be detrimental. Endogenous central KA can be increased by peripheral administration of kynurenine to rodents and has resulted in disruptions in cognitive performance. Specifically, elevations in KA impair sensorimotor gating, attentional processing of environmental stimuli, spatial working memory, and contextual learning memory (19–21, 75). These behavioral tasks have relevance in neuropsychiatric diseases, such as schizophrenia (SCZ) and bipolar disorder (BPD), characterized by cognitive disruptions and psychosis (76). Though KA can be increased experimentally by administration of kynurenine, recently characterized KMO polymorphisms in the human populations provide a clinical context for elevations in KA contributing to pathophysiology. These genetic alterations in KMO are associated with decreased gene expression and increased KA concentrations in patients suffering from SCZ and BPD (77–80). Together, these data support the notion that deviation of kynurenine metabolic balance too far in either direction may contribute to impaired brain function.

Neurological Disorders and Disrupted Kynurenine Metabolism

Consequences of a persistent imbalance in kynurenine metabolism can be demonstrated experimentally; however, the relevance of kynurenine metabolites to disease pathogenesis has been suggested in several neurological disease contexts, based on patient post-mortem tissue, plasma, and cerebrospinal fluid (CSF) sampling studies. Determination of kynurenine metabolite concentrations in patients diagnosed with neurological disorders allows for more direct correlations between metabolite measures, pathology development, and symptoms. Moreover, preclinical modeling allows for further exploration into the potential mechanism(s) that might connect kynurenine metabolism and disease pathogenesis. Kynurenine metabolic balance in relevant neurodegenerative, neuropsychiatric, and neurodevelopmental disorders is reviewed below (for summary see **Table 1**).

Huntington's Disease

Huntington's disease (HD) is a severe neurodegenerative disorder that is characterized by motor, cognitive, and neuropsychiatric symptoms. Early experimental models demonstrated that glutamate-mediated excitotoxicity in the basal ganglia could mirror the neuronal degeneration seen in HD patients (129). Therefore, it is possible that elevated levels of QA, which can cause excitotoxicity could contribute to the pathogenesis of HD. Though early attempts to measure QA in post-mortem cortical tissue indicated no difference between HD patients and controls, later studies demonstrated that both KA and 3-HK were elevated suggesting an overall increase in kynurenine metabolism (**Table 1**) (81, 84, 87, 88). More specifically, it was later established that both QA and 3-HK are increased in striatal and cortical regions during the early stages of HD (Grade 0/1), suggesting temporal specificity for the disruption in kynurenine metabolism (**Table 1**) (89). Further, HD patients present with elevated markers of oxidative stress, which can be propagated by 3-HK and QA supporting the hypothesis that these metabolites can contribute to HD pathogenesis (130, 131). The YAC128, R6/2, Hdh^{Q92}/Hdh^{Q111}, and FBV/N mutant HD mouse models all have endogenous disruptions in the kynurenine pathway that result an increase in neurotoxic metabolites that accumulate as the mice age (**Table 1**) (88, 90, 93). These mutant HD mouse models demonstrate that the development of HD-like pathology can parallel changes in kynurenine metabolism. As the enzyme upstream of the synthesis of both 3-HK and QA, KMO is a relevant potential therapeutic target for the modulation of this imbalance in kynurenine metabolites. Interestingly, inhibition of KMO ameliorates HD-associated neurodegeneration both in a *Drosophila melanogaster* HD fly model (Htt93Q) and in the R6/2 mutant HD mouse model (92, 100). Taken together, the data from patient analyses and preclinical studies demonstrate that HD is associated with elevated neurotoxic kynurenine metabolites, 3-HK and QA, and targeting KMO to repair this disease-associated imbalance has therapeutic promise in treating neurodegeneration.

Huntington's disease is also considered to be an inflammatory disease as elevations in plasma inflammatory markers have been described both in patients and in a HD-mutant mouse model (132). This peripheral response most likely is a mirror of the neuroinflammatory response accompanying disease progression (133, 134). Neuroinflammation in HD has mainly been characterized by microglia activation particularly associated with the brain regions of greatest neurodegeneration (135, 136). Indeed, an imaging study demonstrated that in HD pre-symptomatic gene carriers, microglia activation was already elevated and it correlated with regions undergoing neurodegeneration (137). The R6/2 mutant HD mouse model also exhibits neuroinflammation and microglia activation associated with HD-like pathology development (138). Microglia are likely involved in the pathogenesis of HD and produce neurotoxic 3-HK and QA when activated providing a clear link between disrupted kynurenine metabolism and HD-associated pathology development.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and is a serious neurodegenerative disorder defined by a dramatic decline in cognitive function. Though AD pathology is characterized by amyloid-β plaque and hyper-phosphorylated tau neurofibrillary tangle accumulation, the pathogenesis of this disease is still not fully understood (139). Early analysis of post-mortem brain samples from AD patients failed to reveal an increase in kynurenine metabolism (**Table 1**) (86, 87, 95). Even so, more recent assessments of peripheral kynurenine metabolites in AD patients have indicated that serum 3-HK and QA concentrations were elevated while the KA concentration decreased (**Table 1**) (98, 99, 101). Further, one study specifically demonstrated that serum QA concentration was inversely correlated with cognitive performance in AD patients (99). Kynurenine pathway activation and production of neurotoxic metabolites have also been characterized in association with AD pathology. Both IDO1 and QA were increased in AD post-mortem hippocampal tissue specifically associated with the perimeter of amyloid-β plaques (140). As the accumulation of plaques and tangles results in

TABLE 1 | Neurological diseases with disrupted kynurenine metabolism – a focus on KMO regulated metabolites.

Disease	Species	Observation	Reference
Huntington's disease (HD)	Human	↑ KA (post-mortem brain, motor cortex)	(81)
	Human	(n.d.) QA (post-mortem brain, putamen, or frontal cortex)	(82)
	Human	(n.d.) QA (cerebrospinal fluid)	(83)
	Human	↑ 3-HK (post-mortem brain, frontal and temporal cortex)	(84)
	Human	↑ Kynurenine/KA Ratio (post-mortem brain, putamen) ↓ KA (cerebrospinal fluid)	(85)
	Human	↓ KA (post-mortem brain, five cortical regions) ↓ 3-HK (post-mortem brain, inferior temporal gyrus)	(86)
	Human	↓ KA (cerebrospinal fluid) (n.d.) QA (cerebrospinal fluid)	(5)
	Human	↑ 3-HK (post-mortem brain, frontal and temporal cortex, putamen)	(87)
	Human	↑ KA (post-mortem brain, cerebral cortex) ↑ 3-HK (post-mortem brain, cerebral cortex, and striatum)	(88)
	FBV/N mice	↑ KA (brain, cortex, and striatum) ↑ 3-HK (brain, cortex, and striatum)	(88)
	Human	↑ 3-HK (Grade 0/1 post-mortem brain, striatum, and frontal cortex) ↑ QA (Grade 0/1 post-mortem brain, striatum, and frontal cortex) (n.d.) 3-HK (Grade 2–4 post-mortem brain, striatum, or frontal cortex) (n.d.) QA (Grade 2–4 post-mortem brain, striatum, or frontal cortex) (n.d.) KA (Grade 0–4 post-mortem brain, striatum, or frontal cortex)	(89)
	R6/2 mice	↑ 3-HK with age (brain, cortex, striatum, and cerebellum) (n.d.) QA with age (brain, cortex, striatum and cerebellum) (n.d.) KA (brain, cortex, striatum, and cerebellum)	(90)
	Hdh^{Q92} and Hdh^{Q111} mice	↑ 3-HK (15–17 mo. brain, cortex, striatum, and cerebellum) ↑ QA (15–17 mo. brain, cortex, and striatum) (n.d.) KA (brain, cortex, striatum, or cerebellum)	(90)
	YAC128 mice	↑ 3-HK with age (brain, cortex, striatum, and cerebellum) ↑ QA with age (brain, cortex, and striatum) (n.d.) KA (brain, cortex, striatum, or cerebellum)	(90)
	R6/2 mice	↑ KMO activity with age (brain, cortex)	(91)
	Htt93Q flies	↑ 3-HK/KA ratio (fly heads)	(92)
	YAC128 mice	↓ 3-HK (3 mo. brain, striatum) ↓ QA (3 mo. brain, cerebellum) ↑ 3-HK (12 mo. brain, striatum) ↑ QA (12 mo. brain, cerebellum)	(93)
Alzheimer's disease (AD)	Human	(n.d.) QA (post-mortem brain, frontal, temporal, or parietal cortex)	(94)
	Human	(n.d.) QA (post-mortem brain, six cortical regions, hippocampus, or caudate) (n.d.) QA (cerebrospinal fluid)	(95)
	Human	(n.d.) KA (post-mortem brain, four cortical regions, or caudate) (n.d.) 3-HK (post-mortem brain, inferior and middle temporal gyrus, or caudate)	(86)
	Human	↓ KA (cerebrospinal fluid) (n.d.) QA (cerebrospinal fluid)	(5)
	Human	(n.d.) 3-HK (post-mortem brain, temporal cortex)	(87)
	Human	↓ 3-HK (cerebrospinal fluid)	(96)
	Human	↑ KA (post-mortem brain, putamen and caudate nucleus) (n.d.) KA (post-mortem brain, frontal cortex, hippocampus, or cerebellum) (n.d.) 3-HK (post-mortem brain, frontal cortex, hippocampus, cerebellum, putamen, or caudate nucleus)	(97)
	Human	↓ KA (serum and red blood cells)	(98)
	Human	↓ KA (serum) ↑ QA (serum)	(99)
	APPtg mice	↑ KA (6 mo. brain, cortex) (n.d.) 3-HK (6 mo. brain, cortex) (n.d.) QA (6 mo. brain, cortex)	(100)
	Human	↑ 3-HK (serum) (n.d.) KA (serum) (n.d.) QA (serum)	(101)
Depression	Human	(n.d.) KA (urinary excretions following tryptophan loading) (n.d.) 3-HK (urinary excretions following tryptophan loading)	(102)
	Human	↓ KA (serum)	(103)
	Human	↑ QA (cerebrospinal fluid) ↑ QA (cerebrospinal fluid, suicide attempters) (n.d.) KA (cerebrospinal fluid, suicide attempters)	(104)

(Continued)

TABLE 1 | Continued

Disease	Species	Observation	Reference
	Human	↑ QA (cerebrospinal fluid, following suicide attempt) ↓ KA (cerebrospinal fluid, following suicide attempt)	(105)
	Human	(n.d.) KA (serum) (n.d.) QA (serum)	(106)
	Human	(n.d.) KA (serum) (n.d.) 3-HK (serum) (n.d.) QA (serum)	(107)
	Human	↓ KA/QA ratio (serum) (n.d.) KA (serum) (n.d.) 3-HK (serum) (n.d.) QA (serum)	(108)
Inflammation-associated depression	Human	↑ Kynurenine/KA ratio (interferon-α treatment, serum)	(109)
	Human	↓ KA (interferon-α treatment, serum)	(110)
	Human	↑ KA (interferon-α treatment, cerebrospinal fluid) ↑ QA (interferon-α treatment, cerebrospinal fluid) (n.d.) QA (interferon-α treatment, plasma)	(12)
	C57BL/6J mice	↑ 3-HK [lipopolysaccharide (1 mg/kg), brain] ↑ QA [lipopolysaccharide (1 mg/kg), brain] (n.d.) KA [lipopolysaccharide (1 mg/kg), brain]	(23)
Bipolar disorder (BPD)	Human	(n.d.) KA (post-mortem brain, anterior cingulate)	(111)
	Human	↓ KA (serum)	(112)
	Human	↑ KA (cerebrospinal fluid)	(113)
	Human	↑ KA (cerebrospinal fluid, with history of psychotic features)	(114)
	Human	↑ KA (cultured fibroblasts) ↑ 3-HK (cultured fibroblasts)	(115)
	Human	↑ KA [cerebrospinal fluid, with KMO Arg(452) mutant allele] ↓ KMO expression [post-mortem brain, with KMO Arg(452) mutant allele, hippocampus]	(80)
	Human	↓ KA/QA ratio (serum) (n.d.) KA (serum) (n.d.) 3-HK (serum) (n.d.) QA (serum)	(116)
Schizophrenia (SCZ)	Human	(n.d.) QA (cerebrospinal fluid)	(83)
	Human	↑ KA (post-mortem brain, dorsolateral prefrontal cortex) (n.d.) KA (post-mortem brain, frontopolar area, or tertiary visual association cortex) (n.d.) 3-HK (post-mortem brain, dorsolateral prefrontal cortex, frontopolar area, or tertiary visual association cortex)	(117)
	Human	↑ KA (cerebrospinal fluid)	(118)
	Human	(n.d.) 3-HK (serum)	(119, 120)
	Human	↓ KA (serum) ↑ 3-HK (serum)	(121)
	Human	↑ KA (post-mortem brain, frontopolar area) (n.d.) KA (post-mortem brain, dorsolateral prefrontal cortex) ↓ KMO activity (post-mortem brain, dorsolateral prefrontal cortex, and frontopolar area)	(122)
	Human	↑ KA (cerebrospinal fluid, with KMO rs1053230 single nucleotide polymorphism)	(79)
	Human	↑ KA (cerebrospinal fluid)	(123)
	Human	↓ KA (cerebrospinal fluid, following suicide attempt)	(124)
	Human	↑ KA (cultured fibroblasts) ↑ 3-HK (cultured fibroblasts)	(115)
	Human	↑ KA (cerebrospinal fluid) (n.d.) QA (cerebrospinal fluid) ↓ QA/KA ratio (cerebrospinal fluid)	(125)
Neurodevelopmental disorders	Human	↑ KA (Down syndrome, post-mortem brain, frontal cortex) (n.d.) KA (Down syndrome, post-mortem brain, temporal cortex)	(126)
	BTBR T+tf/J mice	KMO single nucleotide polymorphisms (3, autism spectrum disorder behavioral model)	(127)
	Human	(n.d.) KA (ADHD, serum) (n.d.) 3-HK (ADHD, serum)	(128)

Disruptions in kynurenine metabolites are described in Huntington's disease (HD), Alzheimer's disease (AD), depression, bipolar disorder (BPD), schizophrenia (SCZ), and neurodevelopmental disorders. Only three kynurenine metabolites, 3-HK, KA, and QA, were included in this table as they demonstrate potential changes in KMO activity that could result in neuropathological consequences. Only animal studies with endogenous model disease disruptions were incorporated in the table (i.e., genetic mutant model). (n.d.), no difference between disorder/mutant animal samples and healthy control/control animal samples.

microglial activation and neuroinflammation, it is feasible that this stimulates kynurenine metabolism and neurotoxic metabolite production in AD (141). *In vitro*, Aβ-42, the neurotoxic constituent of amyloid-β plaques, can induce IDO1 upregulation and QA production in human macrophages and microglia (142). Elevated neurotoxic kynurenine metabolite production arising from microglia activation may in turn contribute to the pathogenesis of AD. As in HD, increased extracellular glutamate and neuronal excitotoxicity are thought to contribute to the degeneration of neurons as AD pathology accumulates (143, 144). AD patients also have elevated markers of oxidative stress, both of which an elevation in neurotoxic QA and 3-HK can propagate (145). Specifically, QA has been shown to prompt tau phosphorylation *in vitro* indicating that it may have a direct influence on development of AD-associated pathology (146). These data provide evidence that inflammation associated with markers of AD pathology may upregulate kynurenine metabolism and the production of neurotoxic metabolites. Though directly focusing on inflammation therapeutically has had little success in AD patients, targeting the kynurenine pathway, further downstream still remains a viable option. In the APPtg AD mouse model, peripheral inhibition of KMO attenuated spatial memory loss and synapse loss associated with an increase in brain KA (100). These data demonstrate that KMO could provide a treatment focus in AD with the intent of preventing neurotoxic metabolite accumulation.

Alzheimer's disease is associated with the development and propagation of neuroinflammation in response to the accumulation of amyloid-β plaques and tau tangles. Post-mortem analyses have revealed that both microglia and astrocytes become upregulated and activated as AD-associated neuropathology develops (141, 147). One imaging study demonstrated that microglia activation is specifically correlated with cognitive status, which could not be predicted by amyloid-β load (148). Transgenic mouse models that develop AD-related neuropathology also exhibit microgliosis and astrocytosis associated with the advancement of pathology (149, 150). These data further demonstrate the significance of microglia to AD pathology and the relevance of neurotoxic kynurenine metabolites to the progression of AD.

Depression

Depression is a highly debilitating neuropsychiatric disorder with a diverse symptom profile, including depressed mood, anxiety, anhedonia, fatigue, and cognitive impairment. Unfortunately, less than half of affected individuals experience satisfactory therapeutic benefit from typical antidepressant treatments (151). Studies describing kynurenine metabolism in patients with depression report increases in CSF QA and decreases in plasma KA and the KA/QA ratio (**Table 1**) (103, 104, 108). Despite these data, other studies report no difference in kynurenine metabolism between patients with depression and controls (**Table 1**) (106, 107). Analysis of kynurenine metabolites in patients with depression who had also attempted suicide revealed an elevation in CSF QA and a decrease in KA (**Table 1**) (104, 105). These results suggest a role for altered kynurenine metabolism in the pathogenesis of depression, and additional studies have demonstrated that inflammation can induce both depression symptoms and metabolic changes. Specifically, interferon-α therapy, used to treat hepatitis C, increases the prevalence of depression symptoms in the patients receiving treatment, and the severity of symptoms are correlated with elevations in CSF QA (12, 109). It was recently proposed that kynurenine pathway enzyme expression could be a valid etiological classification system for patients diagnosed with depression (152). As inflammation-induced alterations in the kynurenine pathway represents a significant gene by environment interaction, such a classification system could potentially provide a more precise way to treat patients, both genetically and pharmacologically.

Inflammation is hypothesized to be a major contributor to the pathogenesis of depression and clinically, administration of endotoxin can directly precipitate depression symptoms (153, 154). Further, patients who suffer from chronic inflammatory diseases are significantly more likely to develop symptoms of depression than healthy adults (155). While direct clinical evidence in patients of depression that inflammation activates microglia and upregulates KMO within the brain is lacking, it is feasible that inflammation induces an imbalance in kynurenine metabolism elevating neurotoxic QA production that results in depression-related symptoms (10, 156). Preclinically, inflammatory stimuli induce depressive-like behaviors that are dependent on increased kynurenine production by IDO1, demonstrating that kynurenine metabolism is necessary for inflammation-related behaviors (11, 157–160). Our lab recently demonstrated that KMO-deficient mice were protected from inflammation-induced deficits in recognition memory, a depressive-like behavior (160). These data provide preliminary evidence that inflammation-induced depressive-like behaviors are specifically dependent on neurotoxic kynurenine metabolism. A recent study demonstrated that lipopolysaccharide (LPS)-induced depressive-like behaviors can be attenuated with administration of the NMDAR antagonist ketamine, and LPS treatment induces accumulation of central 3-HK and QA (23). These results indicate that inflammation-induced depressive-like behavioral changes are in part mediated by NMDAR activation, which could potentially be accomplished by the elevation in QA, an NMDAR agonist. Inflammatory stimuli can undoubtedly alter kynurenine metabolism favoring neurotoxic metabolism through KMO, which appears to contribute to the mechanism by which inflammation results in depression and related behaviors.

Though post-mortem samples from patients with depression have been analyzed for microglia activation, the results from multiple studies are inconsistent (161, 162). They generally favor elevated microglia activation in patients with depression and a significant increase in activation in patients who also committed suicide (163). Preclinically, inflammatory stimuli can induce depressive-like behaviors that are associated with a neuroinflammatory response including microglia activation (164). Minocycline, a microglial activation inhibitor, has been demonstrated to attenuate inflammation-induced depressive-like behaviors (165). Together, these data strongly suggest that microglia could potentially be involved in the pathogenesis of depression behaviors that are associated with inflammation and altered kynurenine metabolism.

Bipolar Disorder

BPD is defined by alternating periods of mania, which often features psychosis, and depression interspersed with symptom-free intervals, known as euthymia (166). Further, cognitive impairments such as those in executive functioning and verbal memory are present in all states of BPD (167). During the euthymic phase of patients with BPD, the concentration of CSF KA was found to be significantly elevated (**Table 1**) (113). Specifically, higher levels of CSF KA were correlated with a history of psychosis or having experienced a recent manic episode in BPD patients (**Table 1**) (114). Acute psychotic symptoms in HIV-1-infected patients were also associated with elevations in CSF KA, further confirming the significance of alterations in KA concentration on the development of psychosis behavior (168). Dysregulation in the DA system is thought to be one of the mechanisms responsible for BPD symptomology, therefore it is possible that KA influences psychosis through its interaction with DA (169, 170). Analysis of the KMO Arg(452) mutant allele in BPD patients, which reduces KMO expression and increases KA production, also revealed an association with psychotic symptoms during manic episodes (**Table 1**) (80). These are further data to support the role of KMO in the production of KA and the influence of KA concentration on psychosis in BPD.

Another mechanism thought to contribute to the pathogenesis of BPD is immune activation, specifically through the production of pro-inflammatory cytokines (171, 172). Recent data points to an explicit role for IL-1β as CSF concentrations were increased in euthymic BPD patients compared to controls and were correlated with a recent history of at least one manic episode (173). Associated with this inflammatory paradigm, a recent study found that the serum KA/QA ratio was decreased in BPD patients contrary to previous studies demonstrating an elevation in KA (**Table 1**) (116). Further, isolation of BPD patient skin fibroblasts demonstrated increased baseline production of both KA and 3-HK, however, pro-inflammatory cytokine stimulation only resulted in elevated 3-HK accumulation (115). In accord with this hypothesis, elevated neuroinflammatory markers and glia cell (microglia and astrocytes) activation have been described in post-mortem BPD patient tissue samples (174, 175). Neuroinflammation in BPD patients would propagate the production of neurotoxic kynurenine metabolites similar to those that have already been described in patients. Though studies may support alternate activation of these two branches of metabolism in BPD, it is clear that there is a disruption that could be therapeutically targeted by focusing on altering kynurenine metabolism at KMO in microglia.

Schizophrenia

SCZ is a neuropsychiatric disorder defined by positive symptoms (psychosis and paranoia), negative symptoms (social deficits and anhedonia), and cognitive dysfunction. The mechanisms underlying the pathogenesis of SCZ are not well understood. Currently, it is believed that SCZ results from neurocircuit-level disruptions in neurotransmitters including dysfunction in DA and glutamate systems (176). Post-mortem tissue analysis of SCZ patients revealed an increase in KA that was associated with decreased KMO activity rather than alterations in KAT activity (**Table 1**) (117, 122). CSF KA concentration was also elevated in SCZ patients while there was no change in CSF QA concentration (**Table 1**) (118, 123, 125). Interestingly, CSF KA was significantly decreased in SCZ patients who attempted suicide compared to non-attempters (**Table 1**) (124). Studies that were conducted to determine the correlation between KMO gene polymorphisms and SCZ diagnosis did not reveal any significant relationships (77, 177). However, one KMO polymorphism that potentially impacts substrate interaction, rs1053230, correlated with elevated CSF KA concentrations in SCZ patients, further demonstrating the link between KMO and disrupted kynurenine metabolism (**Table 1**) (79). Studies have demonstrated that KA can disrupt cognitive performance through its interaction with the glutamate system and it has the potential to contribute to psychotic symptoms by influencing DA signaling. Preclinically, reducing endogenous levels of KA can prevent amphetamine- and ketamine-induced disruptions in sustained attention, working memory, and spatial memory tasks, paradigms used to experimentally model SCZ deficits (178). Together, these data provide justification for better understanding the impact of disrupted kynurenine metabolism on SCZ pathogenesis and the potential relevance of targeting KMO therapeutically in SCZ.

While the potential for the involvement of inflammation and pro-inflammatory cytokines in the pathogenesis of SCZ exists, the data analyzing the supporting neuropathological evidence are inconsistent. Initial examination of SCZ post-mortem tissue indicated a reduction in density of astrocyte markers (GFAP) when compared to normal controls (179). More recent SCZ post-mortem tissue investigations have revealed upregulation of both microglia and astrocyte markers (180–182). An additional binding analysis revealed that QA-specific microglia were reduced in SCZ, but overall microglia density was unchanged (183). A recent imaging study in SCZ patients found no difference in microglia activation in white or gray matter, contradicting the multiple post-mortem studies (184). Despite these varying results, it is clear that there is potential for a pathological role of neuroinflammation and glia involvement in SCZ (185).

Neurodevelopment

Brain development and maturation is a dynamic process that begins in the embryo and continues well into the young adult years (186). However, neurodevelopment appears to be quite susceptible to disruptions in kynurenine metabolism. Kynurenine supplemented chow fed to gestating mothers prenatally and offspring postnatally elevates KA in adolescences and adults (187, 188). Exogenous kynurenine treatment during these periods also results in disruptions in contextual memory, spatial working memory, and cognitive flexibility in adults (187–190). Specifically, elevating KA with kynurenine during a prenatal period decreases dendritic spine density and markers of excitatory transmission (evoked glutamate release and mGluR2 receptor expression) (190). Kynurenine metabolism during neurodevelopment was also targeted by administering a KMO inhibitor to pregnant dams in late gestation, which results in an

immediate increase in KA in the embryo (191). In adolescence, this treatment results in an increase in neuronal excitability, an increase in GluN2A/2B subunits of the NMDAR and elevated PSD95, a post-synaptic density marker (191). Adults also show changes in excitability, decreases in dendritic complexity and number, disruptions in long-term potentiation, and increased neurogenesis (192–194). These results clearly demonstrate that alterations in kynurenine metabolism occurring during development can significantly impact normal neuronal functioning in adolescence and continue into adulthood. The BTBR T+tf/J spontaneous mutant mouse has been used preclinically to model behaviors of autism spectrum disorder (ASD), one neurodevelopmental disorder (195). The BTBR mouse model is characterized by repetitive behaviors, communication deficits, and social deficits that are also associated with three KMO polymorphisms specific to the BTBR strain (127). This correlation suggests that in the BTBR mouse model, a disruption in KMO function may contribute to the development of ASD-like behavior. Though there are only a couple of studies analyzing kynurenine metabolite disruptions in the context of neurodevelopmental disorders (see **Table 1**), the strong preclinical data supports the importance of KMO and its regulation in proper development.

Immune activation, either in pregnant mothers or in early development, provides a more clinically relevant model for determining the impact of disrupted kynurenine metabolism during neurodevelopment. Preclinical maternal immune activation (MIA) is modeled by administration of Poly I:C, an immune mimetic, to pregnant dams, which results in disruptions in sensorimotor gating and spontaneous locomotor activity in adult offspring (196, 197). There are also significant increases in microglia activation in the offspring of MIA dams (197, 198). When neonatal pups are given an immune stimulus (Poly I:C, influenza, LPS), this also results in disturbances in adulthood including impaired sensorimotor gating and working memory concurrent with elevated microglia activation (199–201). Though these models demonstrate the association of microglia activation with behaviors that result from impaired neurodevelopment, few studies have directly characterized microglia activation in patients with neurodevelopmental disorders. A recent imaging study established that young adults diagnosed with ASD have significantly elevated microglia activation in multiple brain regions (202). These data further support the possibility that microglia contribute to neurodevelopmental disorders, both during development and throughout maturation.

Conclusion/Future Research

Kynurenine metabolites have the capacity to directly or indirectly affect neuronal functioning under both basal and during pathological conditions. Though evidence suggests that multiple neurological disorders are associated with disruptions in central kynurenine metabolism (**Table 1**), it is unclear whether these changes occur during disease progression or contribute directly to disease initiation. Determination of the specific impact that disruptions in kynurenine metabolism have on the pathogenesis of neurological disorders will allow for better understanding of individual diseases and provide an additional therapeutic objective. Preclinical evidence demonstrates that neurotoxic QA and inhibitory KA can both be detrimental physiologically and behaviorally when levels become elevated. Therefore, with the capacity to direct kynurenine metabolism to both QA and KA, KMO provides a potential target for treatment intervention. While the ability to modulate KMO activity would be a powerful tool to determine if targeting it therapeutically is feasible, few techniques currently exist with therapeutic potential. Until recently, KMO pharmacological inhibitors were limited modulating kynurenine metabolism to the periphery as they did not cross the blood–brain barrier (9). However, a newly described competitive inhibitor was demonstrated preclinically to have the ability to inhibit KMO peripherally and partially penetrate the blood–brain barrier (203). Though proposed for therapeutic use in HD patients, the data reviewed here clearly demonstrate that treatment with an effective KMO inhibitor could potentially be beneficial to patients diagnosed with other neurological disorders. Additionally, KMO-deficient mice have biochemically characterized providing a valuable preclinical research tool to further explore the biological and pathophysiological role of KMO (204). Whether disrupted kynurenine metabolism is a biomarker of disease risk or a treatment target for slowing the disease progression, it is clear that the kynurenine pathway is clinically relevant to neurological disorders. Therefore, it is necessary to understand the significance of maintaining the balance between KA and QA production through KMO, both in health and neurological diseases.

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