



# 75th Anniversary Celebration Collection Special Section

ASSOCIATE EDITOR: GUNNAR SCHULTE

## Neuroactive Kynurenines as Pharmacological Targets: New Experimental Tools and Exciting Therapeutic Opportunities

 Ana Pocivavsek, Robert Schwarcz, and  Sophie Erhardt

*Department of Pharmacology, Physiology, and Neuroscience, University of South Carolina School of Medicine, Columbia, South Carolina (A.P.); Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland (R.S.); and Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden (S.E.)*

Abstract .....	979
Significance Statement .....	979
I. Introduction .....	979
II. Kynurenine Pathway Enzymes and Their Neuroactive Products .....	980
A. The Formation of Kynurenine from Tryptophan .....	981
1. Tryptophan 2,3-Dioxygenase .....	981
2. Indoleamine 2,3-Dioxygenase 1 .....	981
3. Indoleamine 2,3-Dioxygenase 2 .....	982
4. Kynurenine Formamidase .....	982
a. Kynurenine: the pivotal kynurenine pathway metabolite .....	982
B. Degradation of Kynurenine: An Array of Enzymes and Neuroactive Metabolites .....	983
1. Kynurenine Aminotransferases .....	984
a. Kynurenic acid .....	984
b. Xanthurenic acid .....	986
2. Kynurenine 3-Monooxygenase .....	986
a. 3-Hydroxykynurenine .....	987
3. Kynureninase .....	987
a. Anthranilic acid .....	987
b. 3-Hydroxyanthranilic acid .....	988
4. 3-Hydroxyanthranilic Acid Oxygenase .....	988
a. Quinolinic acid .....	988
5. Biosynthesis of Other Neuroactive Kynurenine Pathway Metabolites .....	989
a. Picolinic acid .....	989
b. Cinnabarinic acid .....	989
III. Kynurenine Pathway in Brain Diseases/Disorders .....	989
A. Pathology-Related Variables .....	989
1. Age .....	989
2. Blood-Brain Barrier Function .....	990
3. Inflammation .....	990

**Address correspondence to:** Dr. Sophie Erhardt, Department of Physiology and Pharmacology, Karolinska Institutet, Solnavägen 9, Biomedicum, 171 65 Stockholm, Sweden. E-mail: sophie.erhardt@ki.se

This work was supported by National Institutes of Health National Institute on Aging [Grant R21 AG080335] (to A.P.) and National Institute of Mental Health [Grant P50 MH103222] (to R.S.) and the Swedish Medical Research Council [Grant 2021-02251\_VR] (to S.E.).

R.S. serves on the scientific advisory board of Kynexis BV. The remaining authors declare no other conflicts of interest.

dx.doi.org/10.1124/pharmrev.124.000239.

B. Neurologic Disorders .....	991
1. Huntington's Disease .....	991
2. Parkinson's Disease .....	991
3. Alzheimer's Disease .....	991
4. Traumatic Brain Injury .....	991
5. Epilepsy .....	992
C. Psychiatric Disorders .....	992
1. Schizophrenia and Bipolar Disorder .....	992
2. Major Depressive Disorders .....	994
IV. Translationally Relevant Pharmacological Manipulation of Brain Kynurenine Pathway	
Metabolism .....	995
A. Tryptophan 2,3-Dioxygenase 2 and Indoleamine 2,3-Dioxygenase 1 .....	995
B. Kynurenine Aminotransferases .....	995
C. Kynurenine 3-Monooxygenase .....	997
D. Kynureninase .....	997
E. 3-Hydroxyanthranilic Acid Dioxygenase .....	998
V. Major Open Questions and Opportunities .....	998
Acknowledgments .....	1000
References .....	1000

**Abstract**—Both preclinical and clinical studies implicate functional impairments of several neuroactive metabolites of the kynurenine pathway (KP), the major degradative cascade of the essential amino acid tryptophan in mammals, in the pathophysiology of neurologic and psychiatric diseases. A number of KP enzymes, such as tryptophan 2,3-dioxygenase (TDO2), indoleamine 2,3-dioxygenases (IDO1 and IDO2), kynurenine aminotransferases (KATs), kynurenine 3-monooxygenase (KMO), 3-hydroxyanthranilic acid oxygenase (3-HAO), and quinolinic acid phosphoribosyltransferase (QPRT), control brain KP metabolism in health and disease and are therefore increasingly considered to be promising targets for the treatment of disorders of the nervous system. Understanding the distribution, cellular expression, and regulation of KP enzymes and KP

metabolites in the brain is therefore critical for the conceptualization and implementation of successful therapeutic strategies.

**Significance Statement**—Studies have implicated the kynurenine pathway of tryptophan in the pathophysiology of neurologic and psychiatric diseases. Key enzymes of the kynurenine pathway regulate brain metabolism in both health and disease, making them promising targets for treating these disorders. Therefore, understanding the distribution, cellular expression, and regulation of these enzymes and metabolites in the brain is critical for developing effective therapeutic strategies. This review endeavors to describe these processes in detail.

## I. Introduction

For innumerable reasons, scientists with a wide range of expertise and interests have been fascinated with the amino acid tryptophan for more than a century. Tryptophan was first identified and described by Frederick Hopkins, who isolated the compound from casein, a major constituent of dairy products, using the enzyme trypsin (hence the name) (Hopkins and Cole, 1901). During the following decades, analysis of biological fluids and tissues of a wide variety of organisms led to the realization that tryptophan itself, as well as many of its

biologically active precursors and degradation products, plays unique roles in the fate and function of all living beings.

As other amino acids, tryptophan is a building block of proteins. In contrast to most other amino acids, however, it has a relatively complex chemical structure and, of special importance in the biological realm, is mainly synthesized by plants, fungi, and micro-organisms (Crawford, 1989; Radwanski and Last, 1995). The dependence on nutritional supply therefore makes tryptophan an “essential” amino acid in mammals and most other eukaryotes.

**ABBREVIATIONS:** 1-MT, 1-methyltryptophan; 3-HANA, 3-hydroxyanthranilic acid; 3-HAO, 3-hydroxyanthranilic acid dioxygenase; 3-HK, 3-hydroxykynurenine;  $\alpha$ 7nAChR,  $\alpha$ 7 nicotinic acetylcholine receptor; ACMSD, 2-amino-3-carboxymuconate-semialdehyde decarboxylase; AD, Alzheimer disease; AhR, aryl hydrocarbon receptor; BD, bipolar disorder; CHDI, Cure Huntington's Disease Initiative; CNS, central nervous system; CSF, cerebrospinal fluid; GRK3, GPCR kinases 3; HD, Huntington disease; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; Kmo<sup>-/-</sup>, Kmo knockout; KP, kynurenine pathway; KYNA, kynurenic acid; LPS, lipopolysaccharide; LTP, long-term potentiation; MDD, major depressive disorder; NMDAR, N-methyl-D-aspartate receptor; OAT, organic anion transporter; PD, Parkinson's disease; PIC, picolinic acid; PLP, pyridoxal phosphate; QUIN, quinolinic acid; SNP, single-nucleotide polymorphism; SNX7, sorting nexin 7; TBI, traumatic brain injury; TDO, tryptophan 2,3-dioxygenase; TNF, tumor necrosis factor; XANA, xanthurenic acid.

The biochemical and functional features of the large number and complex bioactive properties of chemicals in the “tryptophan network” have been the subject of ever-increasing scrutiny and analysis, revealing novel insights into the ubiquitous roles of these compounds in physiological and pathological phenomena in every cell and multicellular organism studied (Palego et al., 2016; Comai et al., 2020). Besides being used in protein synthesis, tryptophan is metabolized into serotonin (5-hydroxytryptamine), melatonin, and neuroactive compounds in the kynurenine pathway (KP) (Fig. 1). However, until the late 1960s there was very little evidence indicating that tryptophan or chemically and metabolically related compounds have biologically significant effects in the nervous system. This changed dramatically with the recognition that the tryptophan metabolite serotonin is a neurotransmitter and is *causally* linked to the pathophysiology of depression and other major brain diseases in humans (Carlsson et al., 1969; Lapin et al., 1972) and that pharmacological modulation of serotonin function in the brain provides remarkable therapeutic benefits (Oxenkrug, 2013). This led to a surge of interest in brain tryptophan metabolism in both experimental animals and humans and, in particular, to an increased awareness that this aspect of tryptophan research has

been ignored for too long, holds promise for fundamentally new neurobiological concepts, and may have novel therapeutic implications. In this context, the KP, the major route of tryptophan metabolism, has garnered attention for its potential role in neuroinflammation and cognitive impairment. Metabolites produced along this pathway can exert neurotoxic or neuroprotective effects, influencing brain function and disease progression. Dysregulation of the KP has been implicated in various neurologic and psychiatric disorders, highlighting the need for further research to explore its therapeutic potential and address gaps in our understanding of brain inflammation and cognitive health. Although relevant extracerebral phenomena, including the role of peripheral tryptophan metabolism, will be briefly described and discussed, the present review will highlight these translationally exciting discoveries from a neuroscience perspective, with special emphasis on the latest pharmacological approaches for possible clinical applications in humans.

## II. Kynurenine Pathway Enzymes and Their Neuroactive Products

In mammals, only a small proportion of tryptophan is converted to serotonin and other biologically active downstream molecules, such as melatonin (which

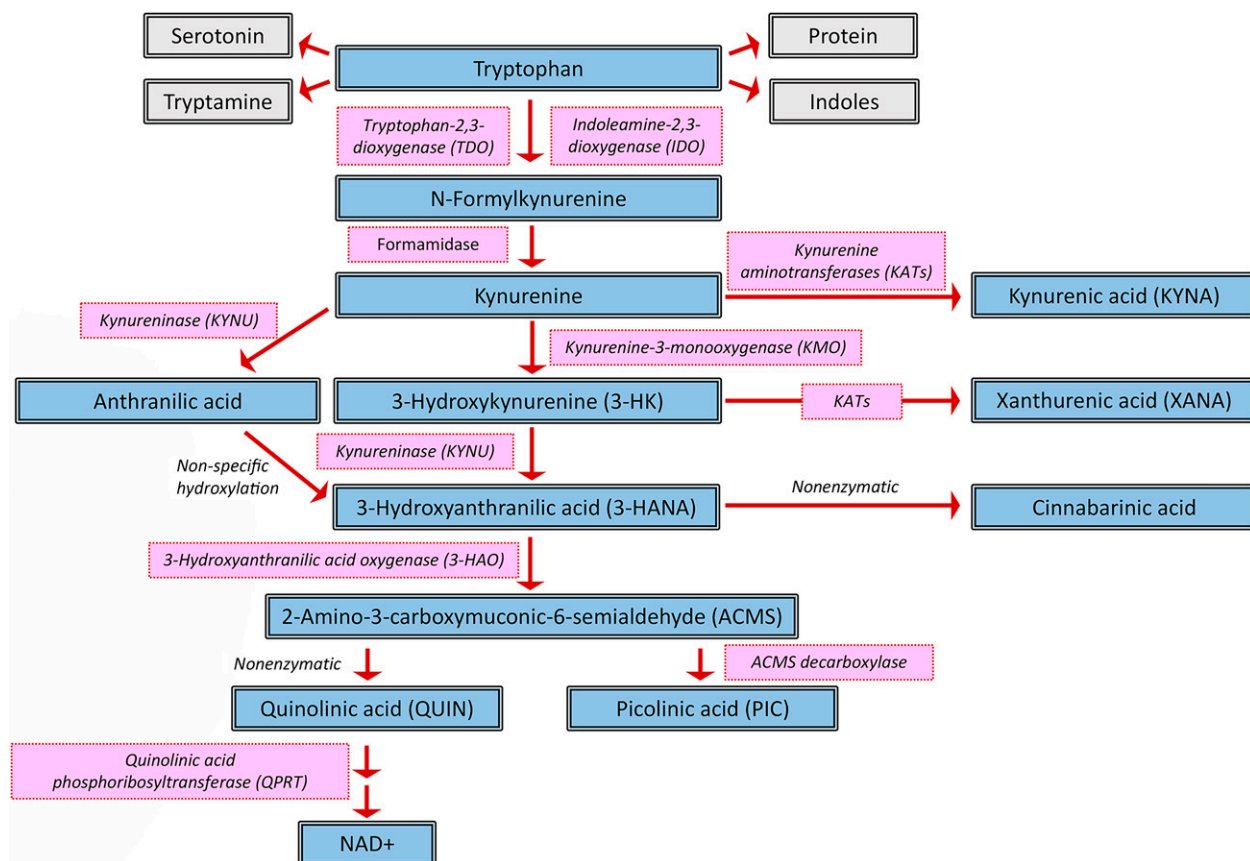


Fig. 1. Tryptophan degradation via the kynurenine pathway in mammalian cells.

regulates sleep and the circadian rhythm; Pereira et al., 2020) and indoles, which affect a large number of physiological processes (Roager and Licht, 2018). The large majority (~95%) of the amino acid is degraded via the KP, named after the pivotal metabolite kynurenine, resulting in a considerable number of neuroactive products that play distinct roles in brain function and dysfunction (Fig. 1). The mechanisms of KP regulation outside and within the brain are highly complex and still require substantive elaboration. However, understanding the basic principles that control this metabolic cascade is critical for the conceptualization of pharmacological interventions to prevent or normalize abnormal KP functions. In the following, we will therefore review the current status of knowledge regarding the neurobiologically and clinically relevant features of the KP. In light of the rapidly expanding information regarding KP biology and its intricacies, and to maintain focus, several related but less directly germane concepts will be referenced appropriately but will not be covered in depth.

#### A. The Formation of Kynurenine from Tryptophan

In mammals as in other biological systems, tryptophan degradation through the KP is initiated by three heme-containing enzymes, i.e., tryptophan 2,3-dioxygenase (TDO2; originally called “tryptophan pyrrolase”) and indoleamine 2,3-dioxygenases (IDO1 and IDO2), all of which convert tryptophan irreversibly to N-formyl-L-kynurenine (Fig. 1). As briefly summarized below, the three dioxygenases differ substantively in tissue distribution and expression and are differentially involved in physiological and pathological phenomena. Notably, however, the three enzymes show only subtle differences in the affinity of the substrate tryptophan (Rafice et al., 2009; Dolšák et al., 2021).

**1. Tryptophan 2,3-Dioxygenase.** TDO2 was long considered to be the sole enzyme that catalyzes the first step of the KP (see Raven, 2017 for a brief history). Its activity is by far highest in the liver, but both the protein and its mRNA are also present in extrahepatic tissues. Although information is quite sparse, this includes the brain, where TDO2 mRNA has been demonstrated (Kindler et al., 2020) and where both mature and immature TDO2-positive neurons have been described (Ohira et al., 2010; Wu et al., 2013). Of note, the enzyme recognizes both L- and D-tryptophan as a substrate (Yamamoto and Hayaishi, 1967), and its activity, unlike that of IDO1 (see below), is induced by tryptophan (Knox, 1966) and by glucocorticoids (Knox, 1966). Although TDO2 activity is generally not stimulated by cytokines and other immune regulatory factors (Yoshida and Hayaishi, 1978; Yoshida et al., 1979), evidence has emerged showing that certain cytokines can induce both IDO and, in some cases, TDO activity (Walker et al., 2013; Urata et al., 2014; Sellgren et al., 2016).

Taken together, these properties indicate that TDO2 plays an important and singular role in the control of tryptophan homeostasis both under physiological conditions and in situations that are associated with increased glucocorticoid formation (such as stress), i.e., TDO2 is normally the key regulator of tryptophan levels in the blood and in peripheral organs. Importantly, as tryptophan easily crosses the blood-brain barrier, changes in TDO2 activity and in circulating tryptophan levels readily affect KP metabolism in the brain (Gál et al., 1978; Larkin et al., 2016).

**2. Indoleamine 2,3-Dioxygenase 1.** Unlike TDO2, IDO—first identified in the 1960s and termed IDO1 after the discovery of a second IDO enzyme (i.e., IDO2; see below)—is ubiquitously distributed in extrahepatic organs of mammals (Yamamoto and Hayaishi, 1967; Yoshida et al., 1980). The enzyme is especially highly expressed in the respiratory system, as well as in the placenta, bone marrow, and lymphoid tissues (Théate et al., 2015). Of significant functional relevance, pioneering studies, also conducted by Yoshida and Hayaishi, (1978), demonstrated that viral and bacterial infections stimulate IDO1 activity in vivo (Yoshida and Hayaishi, 1978; Yoshida et al., 1979) and that the underlying enzyme induction is the result of inflammatory cytokines, such as interferon (IFN)- $\gamma$  (Yoshida et al., 1981). Of note in this context, tumor necrosis factor (TNF)- $\alpha$  can synergistically increase the transcriptional activation of the IDO1 gene in the presence of IFN- $\gamma$  (Babcock and Carlin, 2000; Currier et al., 2000). Together with a large number of supportive and clinically relevant findings (Prendergast et al., 2011; Passarelli et al., 2022), as well as the discovery that IDO1 plays a vital role in preserving maternal T-cell tolerance (Munn et al., 1998), it soon became widely accepted that the induction of IDO1 is closely—and probably causally—related to pathological conditions and host defense mechanisms in a large number of neuroinflammatory conditions. Thus, IDO1 provides protection against pathogens by inhibiting potentially harmful inflammatory processes in the body and, more specifically, is critically involved in immune tolerance (Romani et al., 2008). Moreover, like IDO2 (see below), IDO1 plays an important role as a modulator of B-cell function, though, in contrast to IDO2, it inhibits—whereas IDO2 stimulates—inflammatory B-cell responses (Merlo et al., 2022).

In biochemical terms, IDO1 differs substantively from TDO2. Thus, though IDO1 also recognizes D-tryptophan as a substrate (Capece et al., 2010), the enzyme has lower substrate specificity than TDO2 and is able to process, for example, various indoles (Yeung et al., 2015). Notably, and of likely functional significance, its activity in the periphery is not influenced by (changes in) circulating tryptophan levels.

IDO1 expression and enzyme activity in the brain have been repeatedly documented using histological,

biochemical, and genetic methods (Browne et al., 2012; Larkin et al., 2016). IDO1 is primarily expressed in vascular endothelial cells in vivo (Hansen et al., 2000) but is also found in cultured neurons, astrocytes, and microglial cells (Guillemin et al., 2005b). All of these studies indicate low functional efficacy of brain IDO1 under regular physiological conditions. In line with the realization that the enzyme may be critically involved in inflammatory processes, however, major enzyme induction/up-regulation is seen in brain tumor cells (Herrera-Rios et al., 2020; Ladomersky et al., 2020; Platten et al., 2021), in IFN- $\gamma$ -stimulated cultured glioma cells (Takikawa et al., 1991; Adams et al., 2014), and in macrophages and activated microglial cells of mice with experimental autoimmune encephalomyelitis (Kwidzinski et al., 2005). Interestingly, though the biological implications are still unknown, IDO1 in human macrophages and tumor cells often lacks the heme binding domain, which plays a major role in enzyme activity (Thomas et al., 2001; Lewis-Ballester et al., 2017; Nelp et al., 2018; Behmoaras, 2021).

**3. Indoleamine 2,3-Dioxygenase 2.** More recently, a new IDO isoform—named IDO2—was identified (Metz et al., 2007), and its functional characteristics and biological roles are increasingly understood (Li et al., 2021; Guo et al., 2023). IDO2 likely arose via gene duplication of IDO (Ball et al., 2007) and has distinctive kinetic characteristics and substrate specificity (Austin et al., 2010). Although the enzyme is widely expressed in mammalian organs, including liver and kidney, its low activity seems to argue against a significant role in oxidative tryptophan degradation under normal conditions (Jusof et al., 2017). Distinct cellular localizations of IDO2 have been documented immunohistochemically (Guo et al., 2023). Studied mostly in the cerebral cortex and cerebellum of mice, brain IDO2 has so far been shown to be mainly expressed in neuronal cells (Fukunaga et al., 2012).

Although the physiological relevance of IDO2 is still being elaborated in detail, the enzyme appears to play a distinct role in immunological phenomena. Thus, increased IDO2 expression can lead to the exacerbation of inflammatory responses, and the enzyme is therefore considered to be a proinflammatory mediator of autoimmunity (Merlo and Mandik-Nayak, 2016). Of interest in this context, IFN- $\gamma$  significantly potentiates IDO2 expression in cultured human glioma cells (Adams et al., 2014). Notably, IDO2 protein is strongly upregulated when IDO1 is eliminated as shown in mice devoid of IDO1 (IDO1<sup>-/-</sup> mice; Fukunaga et al., 2012).

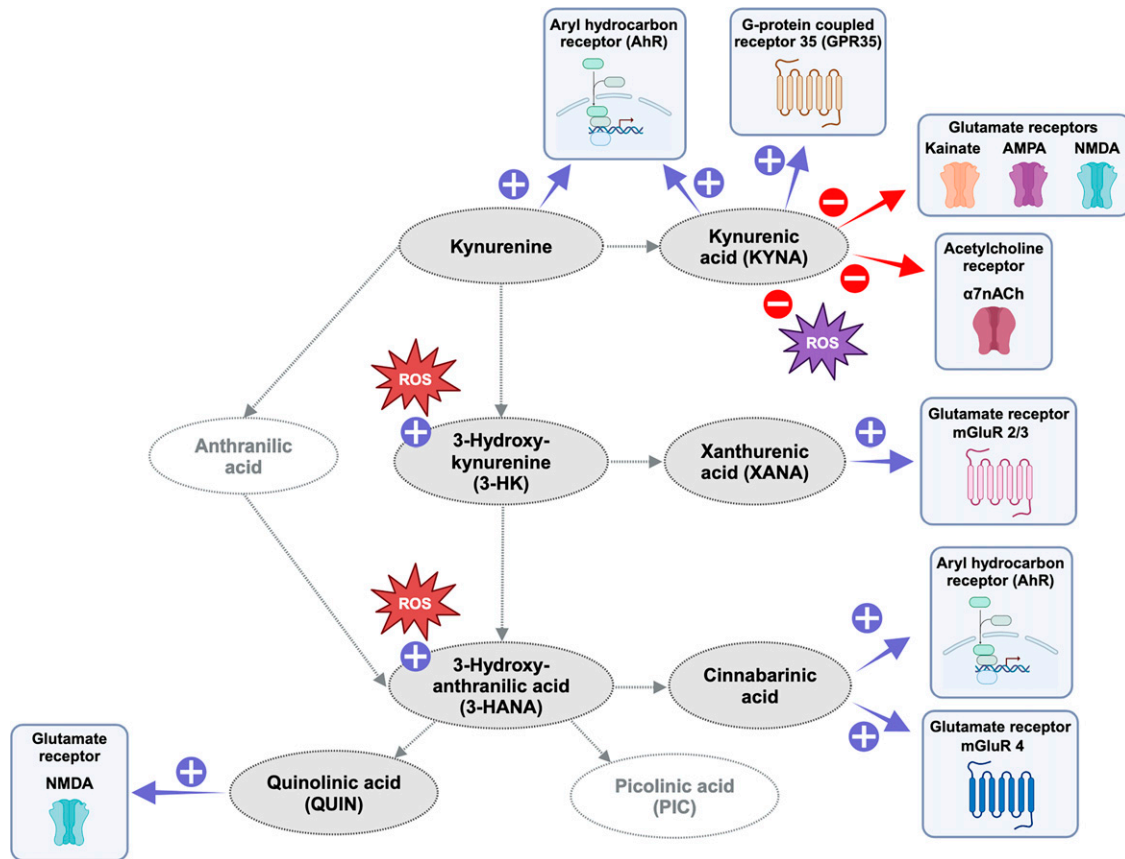
**4. Kynurenine Formamidase.** N-formyl-L-kynurenine (formylkynurenine), the product of TDO2, IDO1, and IDO2 under both physiological and pathological conditions, serves as a substrate of kynurenine formamidase, which is singularly responsible for the next step in the KP, i.e., the synthesis of the pivotal pathway metabolite kynurenine. In spite of its proposed key role in

tryptophan degradation, the enzyme has received relatively little attention compared with both upstream and downstream KP mechanisms, and the conversion of formylkynurenine to kynurenine may even involve alternative mechanisms (Dobrovolsky et al., 2005). In contrast to other enzymes involved in KP metabolism and function, kynurenine formamidase has been more frequently examined in microbiota than in animals (Shinohara and Ishiguro, 1970; Arndt et al., 1973; Brown et al., 1986; Han et al., 2012), and the cellular localization and functionally relevant regulation of the enzyme in the mammalian brain remains essentially unknown (Cumming et al., 1979). The few studies in this respect have focused mostly on the possible role of the enzyme in cancer biology and immunotherapy (Badawy, 2022).

*a. Kynurenine: the pivotal kynurenine pathway metabolite.* Kynurenine, whether synthesized endogenously as summarized above, provided from dietary consumption, or originating from the microbiome community in the digestive tract, is present in low micromolar concentrations in the mammalian blood (Mrštná et al., 2023). In addition to being the major determinant of the formation—and therefore function and dysfunction—of all KP metabolites downstream (see below), kynurenine, within the physiological pH range, is readily oxidized to nonenzymatically produce biologically active molecules (Ramírez Ortega et al., 2021). Importantly, kynurenine activates the aryl hydrocarbon receptor (AhR) at physiological concentrations (see Fig. 2) (Mezrich et al., 2010; Opitz et al., 2011) and thus directly affects, and likely controls, a large number of AhR-dependent processes in health and disease (Rothhammer and Quintana, 2019; Opitz et al., 2023). Notably, and in line with the ability of upstream enzymes to recognize D-tryptophan as a substrate (see above), D-kynurenine is present in mammalian cells and shares several biological qualities of its more prominent enantiomer (Kotake and Ito, 1937; Mason and Berg, 1952).

Competing with tryptophan and several other amino acids, circulating kynurenine [both L- and the D-enantiomers (Fukui et al., 1991; Wang et al., 2012)] readily crosses the blood-brain barrier via the large amino acid transporter (Segawa et al., 1999). Because of the comparatively low activity of brain TDO2, IDO1, and IDO2, approximately 60% of brain kynurenine is normally derived from the circulation. However, local neosynthesis of the compound increases dramatically when brain IDO1 is stimulated by an activated immune system (Saito et al., 1992; Thomas et al., 2014), with major impact on brain diseases (Skorobogatov et al., 2021; see below).

Endogenous kynurenine levels in the mammalian brain are in the submicromolar range (see Table 1) (Beal et al., 1992; Heyes et al., 1998; Schwarcz et al., 2001; Linderholm et al., 2012; Notarangelo et al.,



**Fig. 2.** Key biological actions of neuroactive kynurenine pathway metabolites in the mammalian brain. Purple and red signs indicate agonist and antagonist properties, respectively. ROS, reactive oxygen species.

2012; Drewes et al., 2015; Clark et al., 2016; Fuertig et al., 2016; Sorgdrager et al., 2019; Rentschler et al., 2024). Although not tested sufficiently in many mammalian species but of interest for both physiological considerations and because of potential clinical implications (see below), the concentration of kynurenine in the cerebrospinal fluid (CSF) is at least 10-fold lower than in the brain, with CSF typically being withdrawn from the lumbar region at the L4 to L5 level in human studies. This suggests that kynurenine is readily taken up by and accumulates in—but may not be

released from—brain cells. Kynurenine readily enters neurons and glial cells via  $\text{Na}^+$ -dependent and  $\text{Na}^+$ -independent mechanisms, respectively (Speciale et al., 1989), but uptake into other brain cells has not been studied rigorously so far. Verification will provide significant functional insights since enzymatic or oxidative degradation of kynurenine to biologically active molecules may take place within most, if not all, brain cells.

*B. Degradation of Kynurenine: An Array of Enzymes and Neuroactive Metabolites*

As the pivotal metabolite of the KP, kynurenine serves as a substrate of several enzymes, which are segregated into three distinct branches and produce neuroactive metabolites either directly or through further degradation downstream. The dynamics and roles of some of these metabolites have attracted significant attention of neuroscientists since the 1980s, whereas others are still just beginning to be understood. Focusing on KP function and dysfunction in the brain, the present status of knowledge regarding the biological activity and role of these catabolic branches (Fig. 2) is summarized in the following sections.

TABLE 1

Central levels of key kynurenine pathway metabolites in adult mammals. Ranges of the concentrations of kynurenine, KYNA, 3-HK and QUIN in postmortem brain tissue, in the cerebrospinal fluid, and in the extracellular milieu (collected by in vivo microdialysis). References are provided in the text.

	Kynurenine	KYNA	3-HK	QUIN
Brain content (pmol/mg protein)				
Human	15–30	0.8–4.0	3–6	1–2
Nonhuman primate	10–40	0.1–0.7	0.4–0.8	1–3
Rat	5–30	0.02–0.3	0.1–0.3	0.1–0.3
Mouse	3–4	0.01–0.05	0.1–0.2	0.4–1
Cerebrospinal fluid (nM)				
Human	25–55	1–3	4–5	10–40
Nonhuman primate	15–400	1–6	1–10	10–200
Extracellular levels (nM)				
Rat	70–90	0.5–3	<2	6–8
Mouse		0.5–2		

**1. Kynurenine Aminotransferases.** Kynurenine aminotransferases (KATs) are responsible for the irreversible conversion of kynurenine to kynurenic acid (KYNA) and of 3-hydroxykynurenine (3-HK) to xanthurenic acid (XANA). Four KAT enzymes, termed KAT I–IV, have been identified, and their presence is well documented in several mammalian organs, including liver, muscle, and brain. The  $K_m$  values of these enzymes for kynurenine are remarkably similar [875  $\mu\text{M}$  for KAT I (= glutamine transaminase K), 660  $\mu\text{M}$  for KAT II (= 2-aminoadipate aminotransferase), 1.5 mM for KAT III (= cysteine conjugate  $\beta$ -lyase 2), and 724  $\mu\text{M}$  for KAT IV (= mitochondrial aspartate aminotransferase)]. The specific contributions of the KAT enzymes to brain-derived KYNA and XANA synthesis have not been fully elucidated; however, it is believed that under normal physiological conditions KAT II accounts for the greatest fraction (60%) of total KAT activity in the rat and human brain (Schmidt et al., 1993; Guidetti et al., 1997; Han et al., 2008; Sathyaasikumar et al., 2017). Although all these enzymes metabolize kynurenine, they differ with regard to their alternate substrates. The classic substrate for KAT II is the lysine metabolite  $\alpha$ -aminoadipate, which is found at low micromolar concentrations in the brain of rodents and humans (Guidetti and Schwarcz, 2003). In contrast, the other KATs use amino acids with higher brain concentrations, such as glutamine and aspartate, as substrates. This, as well as the fact that KAT I and KAT III are optimally active at alkaline pH ( $\sim 9.0$ – $9.5$ ), argues for a preferential role of KAT II in KYNA and XANA neosynthesis under physiological conditions. Experimental evidence for this supposition is provided by using mice with a genetic elimination of the KAT II gene (Kat II<sup>-/-</sup> mice) (Yu et al., 2004), which present with a number of biological changes that are expected in animals with reduced brain KYNA levels and function (see below) (Potter et al., 2010). Of interest, and requiring further clarification in this context, the relative contribution of KAT II to KYNA neosynthesis in the mouse brain changes greatly with age and accounts for only 12% of the process in adulthood (Guidetti et al., 2007a).

**a. Kynurenic acid.** The generation of KYNA has been described in various mammalian cells, including endothelial cells, epithelial cells, fibroblasts, pancreatic islet cells, hepatic cells, skeletal muscle cells, and (mainly) glial cells in the brain. Following its local formation, KYNA is promptly released into the extracellular milieu. Formation of the metabolite in liver and skeletal muscle are major determinants of KYNA found in blood (Cervenka et al., 2017). KYNA is excreted by the kidney (Musajo et al., 1951), effected primarily by the organic anion transporters (OATs) OAT1 and OAT3, which have also been described to be present in the brain (Uwai et al., 2012).

Interest in a role of *endogenous* KYNA in brain physiology originated with the seminal finding of

Perkins and Stone (1982), who described its ability, at mid- to high micromolar concentrations, to inhibit the function of various recently identified ionotropic glutamate receptors in the hippocampus of marmosets. The discovery that KYNA has antiexcitotoxic, i.e., neuroprotective, as well as anticonvulsant, properties (Foster et al., 1984b) then suggested that this compound, which at the time was not known to be present in the brain, deserved further investigation because of its possible link to the pathology of major neurologic disorders. The presence of KYNA in the mammalian brain was indeed soon documented, interestingly revealing substantially higher (low micromolar) levels of the compound in human than in rodent tissue (see Table 1) (Moroni et al., 1988; Turski and Schwarcz, 1988). Additional electrophysiological studies then showed that concentrations of KYNA in the high nanomolar and low micromolar range, i.e., with substantially higher efficacy than reported in the original study of Perkins and Stone (1982), competitively inhibits the strychnine-insensitive glycineB site of the N-methyl-D-aspartate receptor (NMDAR) (Birch et al., 1988; Kessler et al., 1989; Parsons et al., 1997) and *noncompetitively* interferes with the function of the  $\alpha 7$  nicotinic acetylcholine receptor ( $\alpha 7$ nAChR) (Hilmas et al., 2001; Alkondon et al., 2004; Stone, 2007) (see Fig. 2). Later, KYNA was found to also serve as an agonist of GPR35, a G-protein-coupled receptor (Wang et al., 2006), and of the AhR (DiNatale et al., 2010).

Behavioral studies in experimental animals (so far mainly rodents) have provided convincing evidence that endogenous KYNA, acting through one or more of these receptors, alone or in combination with its antioxidant properties (discussed below), plays a significant role in neurophysiology and that impaired KYNA function is likely to be *causally* involved in—and in several cases responsible for—pathological events related to psychiatric and neurologic diseases. Thus, in the behavioral realm, increased brain KYNA have been demonstrated, for example, to dampen prepulse inhibition (Erhardt et al., 2004; Linderholm et al., 2010) and impair spatial learning and memory processes (Chess et al., 2007; Pocivavsek et al., 2012, 2014; Buck et al., 2020) as well as attentional-set shifting (Alexander et al., 2012, 2013) and delayed nonmatch to position behavioral performance (Phenis et al., 2014). Moreover, prolonged increases in brain KYNA levels are associated with exaggerated amphetamine-induced locomotor activity (Olsson et al., 2012; Liu et al., 2014; Erhardt et al., 2017a; Tufvesson-Alm et al., 2020; Zheng et al., 2023), and—of special translational significance—elevated KYNA levels disrupt fear memory consolidation and extinction, leading to disrupted fear responses (Chess et al., 2009; Akagbosu et al., 2012; Klausning et al., 2020; 2024). Also with significant ramifications in this context, elevated KYNA levels

reduce sleep duration and impact arousal phenotypes (Pocivavsek et al., 2017; Rentschler et al., 2021, 2024).

In light of the increasing appreciation that extracellular KYNA is well positioned to impact neurotransmission and that the neurobehavioral effects of KYNA in experimental animals may be of significant relevance for the treatment of a range of major neurologic and psychiatric disorders (see below), the features and dynamics of brain KYNA have received considerable attention; and astrocytes, which contain the vast majority of KAT II in the rat brain (Guidetti et al., 2007b), have received special attention in this context. Since the mammalian brain does not appear to contain processes that degrade KYNA, for example to quinaldic acid, a proposed breakdown product found in rat and human urine (Kaiharu et al., 1956; Turski and Schwarcz, 1988), brain KYNA levels are mostly controlled by the bioavailability of kynurenine and fluctuations in energy metabolism within astrocytes (Gramsbergen et al., 1997; Hodgkins and Schwarcz, 1998). Newly produced KYNA is then rapidly, and  $\text{Ca}^{2+}$ -independently, released into the extracellular milieu (Turski et al., 1989; Kiss et al., 2003). In vivo microdialysis studies in rodents and nonhuman primates indicate that the physiological concentrations in the extracellular compartment are in the low- to midnanomolar range, with little intraspecies variability across brain regions (Swartz et al., 1990; Fukui et al., 1991; Wu et al., 1992, 2010; Beggiato et al., 2013). Since cellular reuptake by OATs or other mechanisms is very modest in the brain (Turski and Schwarcz, 1988; Uwai et al., 2012), extracellular KYNA concentrations in the brain are normally kept in balance by a probenecid-sensitive transport mechanism (Moroni et al., 1988).

Again mainly based on studies in rodents, endogenous, i.e., nanomolar, concentrations of KYNA affect both the  $\alpha 7\text{nAChR}$  and the glycineB site of the NMDAR in the brain—the latter potentially when glycine or D-serine levels are low. These effects, which do not appear to be brain region-specific and include concentration- and time-dependent regulation of several classic neurotransmitters, account for the now widely accepted role of KYNA as an endogenous neuromodulator (see Pocivavsek et al., 2016 for review). Examples include significant, up to 50%, reductions in extracellular glutamate in response to biochemically or pharmacologically induced increases in brain KYNA (Carpenedo et al., 2001; Rassoulpour et al., 2005; Wu et al., 2010; Pocivavsek et al., 2011, 2016). Conversely, extracellular glutamate levels increase quickly when KYNA levels are diminished by pharmacological or genetic interference with, or elimination of, KAT II activity (Konradsson-Geuken et al., 2010; Potter et al., 2010; Wu et al., 2010; Pocivavsek et al., 2011). Similarly, experimentally induced elevations in brain KYNA promptly lower the extracellular levels of GABA and dopamine, whereas

KYNA reduction raises extracellular GABA and dopamine, respectively (Rassoulpour et al., 2005; Wu et al., 2007; Beggiato et al., 2013, 2014). Reductions and elevations of KYNA cause the same effects, i.e., up- and down-regulation, respectively, of extracellular acetylcholine levels in the rat prefrontal cortex (Zmarowski et al., 2009).

Functional assessments are in line with these biochemical effects. This includes several of the behavioral phenomena associated with KYNA, which are well known to involve glutamatergic (dys)function (see above). Moreover, pharmacologically or genetically elevated levels of brain KYNA increase firing rate and burst activity in the ventral tegmental area and substantia nigra dopamine neurons (Erhardt et al., 2001a; Erhardt and Engberg, 2002; Schwieler and Erhardt, 2003; Nilsson et al., 2006; Olsson et al., 2010; Linderholm et al., 2012; Tufvesson-Alm et al., 2018), and a reduction in endogenous KYNA dampens dopaminergic neuronal activity (Schwieler et al., 2006; Linderholm et al., 2016).

The respective roles of  $\alpha 7\text{nAChRs}$  and NMDARs as functionally significant targets of endogenous KYNA in the brain are still not entirely clear. Thus, KYNA-induced reductions in extracellular glutamate, GABA, and dopamine in vivo can be readily prevented by systemic administration of a low dose of galantamine, which potently and specifically prevents KYNA's inhibition of the allosteric potentiating site of the  $\alpha 7\text{nAChR}$  (Lopes et al., 2007; Wu et al., 2007; Konradsson-Geuken et al., 2010; Wu et al., 2010; Beggiato et al., 2013, 2014). Choline, another  $\alpha 7\text{nAChR}$  agonist (Hone and McIntosh, 2023), attenuates the actions of KYNA on extracellular dopamine levels (Rassoulpour et al., 2005), and the effects of KYNA on extracellular glutamate and dopamine levels can be duplicated by—but are not additive with—the selective  $\alpha 7\text{nAChR}$  antagonist methyllycaconitine (Carpenedo et al., 2001; Rassoulpour et al., 2005). Other studies, however, suggest that inhibition of NMDARs, rather than blockade of  $\alpha 7\text{nAChRs}$ , plays a central role in the various neurophysiological effects of KYNA, including regulation of dopaminergic activity (Schwieler et al., 2004, 2006; Linderholm et al., 2007, 2010; Stone, 2020).

Compared with the extensive literature discussing the respective roles of  $\alpha 7\text{nAChRs}$  and NMDARs in the neurobiological effects of KYNA, studies of the possible participation of other KYNA targets, specifically GPR35 and the AhR, as well as a role of specific KYNA-related redox phenomena (see below), are still in their infancy. Of note in this context, however, activation at GPR35 impacts cyclic adenosine monophosphate production and influx of  $\text{Ca}^{2+}$  into astrocytes and modulates glutamate neurotransmission (Moroni et al., 2012; Berlinguer-Palmini et al., 2013), and KYNA signaling through AhRs, as well as the metabolite's



antioxidant properties, may serve a neuroprotective role (García-Lara et al., 2015; Kubicova et al., 2019).

*b. Xanthurenic acid.* The transamination of 3-HK, the product of kynurenine 3-monooxygenase (KMO) (see below), to XANA is catalyzed by KAT II, i.e., the same enzyme that is responsible for the conversion of kynurenine to KYNA (Gobaille et al., 2008; Sathyasaikumar et al., 2017; Maitre et al., 2024). XANA is suggested to be functionally significant within the brain as it is stored and transported in neuronal vesicles and subsequently released in an activity-dependent manner (Gobaille et al., 2008). Subsequently, XANA can regulate excitatory neurotransmission by inhibiting the vesicular glutamate transporter and by acting as an agonist at group II mGlu receptors (see Fig. 2) (Copeland et al., 2013; Fazio et al., 2017).

Interestingly, like KYNA, XANA affects dopaminergic neurotransmission (Taleb et al., 2021). Thus, acute local infusion of XANA dose-dependently stimulates dopamine release in the rat prefrontal cortex. Notably, this effect can also be triggered by peripheral XANA administration, which significantly boosts brain XANA levels and results in a dose-dependent increase in dopamine release in the cortex and striatum. Moreover, similar to the effects of increased brain KYNA levels on the activity of dopamine neurons in the ventral tegmental area (see above), daily administration of XANA reduces the number of spontaneously active dopamine neurons (Taleb et al., 2021).

**2. Kynurenine 3-Monooxygenase.** KMO is an aromatic hydroxylase that catalyzes the hydroxylation of L-kynurenine to 3-HK. A member of the NAD(P)H-dependent flavin monooxygenase family (Okamoto et al., 1967), KMO, which is produced by a single gene and uses flavine adenine dinucleotide as a cofactor, is not only directly responsible for the neosynthesis of 3-HK but also plays a central role in the formation and function of 3-hydroxyanthranilic acid (3-HANA), quinolinic acid (QUIN), and other KP metabolites downstream (see below). Notably, because of its unique position in the KP, illustrated in Fig. 1, KMO is also a key regulator of the formation of XANA in a sidearm of the pathway (see above).

KMO plays a central role in KP metabolism in mammals but is also present in bacteria and fungi. The enzyme, originally named kynurenine hydroxylase, was partially purified for the first time from rat liver mitochondria (Saito et al., 1957), but isolation of the mammalian KMO protein remained challenging, and the crystal structure of human KMO was not described until 2018 (Gao et al., 2018).

In the mammalian brain, KMO is found mainly in microglial cells (Alberati-Giani et al., 1996; Guillemin et al., 2001; Giorgini et al., 2008), though neurons, too, contain a substantive proportion of functional KMO in the adult mouse brain (Sathyasaikumar et al.,

2022). The enzyme is essentially absent from astrocytes, however (Heyes et al., 1997; Guillemin et al., 1999; Sathyasaikumar et al., 2022). In light of the lower  $K_m$  value for kynurenine compared with KATs (see above), KMO is more readily saturated by its substrate, causing KP metabolism to shift toward enhanced KYNA formation with increasing kynurenine levels (Bender and McCreanor, 1982). Moreover, and of substantive significance regarding the role of KP function and dysfunction in the brain, KMO activity is consistently activated under neuroinflammatory conditions (Parrott et al., 2016; Garrison et al., 2018).

Impaired function of KMO is increasingly linked to the pathophysiology of a number of neuropsychiatric disorders (see below). Although *Kmo* knockout (*Kmo*<sup>-/-</sup>) mice, generated by the targeted experimental deletion of the *Kmo* gene, also show changes in the brain expression of other genes that are critically involved in nervous system development and neurotransmission (Erhardt et al., 2017a), these mutant animals have so far been used only to study the biological role of the KP. *Kmo*<sup>-/-</sup> mice show significant changes in KP metabolite levels that affect both brain biochemistry and function. Thus, elimination of KMO results in a significant reduction in cortical and hippocampal 3-HK levels and an increase in cortical KYNA (Giorgini et al., 2013; Tashiro et al., 2017; Erhardt et al., 2017a; Mori et al., 2021; Kubota et al., 2022). This shift in KP metabolism toward elevated KYNA is associated with several cognitive and behavioral impairments, though it also increases neuroprotective properties in the mutant animals (Nahomi et al., 2020; Bondulich et al., 2021). Thus, *Kmo*<sup>-/-</sup> mice show significant deficits in hippocampus-dependent contextual memory when tested in a passive avoidance paradigm (Erhardt et al., 2017a). Similarly, *Kmo*<sup>-/-</sup> mice perform poorly in a spatial working memory test in a T-maze, indicating dysfunctional long-term potentiation (LTP) in the hippocampus (Imbeault et al., 2021). These mutant mice are also impaired in social interactions and display an array of depressive-like phenotypes, showing anxiety-like behaviors in an open field arena, in the elevated plus maze paradigm, and in a light-dark box (Tashiro et al., 2017; Erhardt et al., 2017a; Mori et al., 2021). On the other hand, no deficits in spontaneous alternation in a Y-maze paradigm (Tashiro et al., 2017) or novel object recognition memory (Mori et al., 2021) were found to be associated with KMO deficiency. These discrepancies suggest that although *Kmo*<sup>-/-</sup> mice display certain memory impairments, their cognitive deficits are not seen across all types of memory tasks. Interestingly, behavioral anomalies in *Kmo*<sup>-/-</sup> mice are often exacerbated following challenges with psychoactive drugs. For example, the mutant animals exhibit impairments in prepulse inhibition after being treated with phencyclidine (Kubota et al., 2022), and D-amphetamine potentiates their locomotor activity (Erhardt et al.,

2017a; Kubota et al., 2022). Together with additional supportive evidence (Erhardt et al., 2004; Stone and Darlington, 2013; Parrott and O'Connor, 2015), these findings indicate that KMO plays a critical role in controlling and modulating a number of translationally relevant behavioral phenomena.

*Kmo*<sup>-/-</sup> mice also undergo distinctive changes when exposed to inflammatory challenges, such as lipopolysaccharide (LPS) treatment (Garrison et al., 2018). LPS, a potent inducer of inflammation, has been studied as an activator of the KP (Walker et al., 2013; Larsson et al., 2016; Parrott et al., 2016; Oliveros et al., 2017; Garrison et al., 2018; Clark et al., 2019; Peyton et al., 2019; Imbeault et al., 2020; Tufvesson-Alm et al., 2020; Millischer et al., 2021; Notarangelo and Schwarcz, 2021; Balter et al., 2023; Zheng et al., 2023). Compared with normal mice, LPS administration to KMO-deficient animals causes marked increases in the levels of kynurenine and KYNA and simultaneous reductions in 3-HK and the downstream metabolite QUIN (see below) in the brain (Parrott et al., 2016; Garrison et al., 2018). Interestingly, these effects are associated with an attenuated inflammatory response, evidenced by reduced expression of cytokines such as TNF- $\alpha$  and interleukin (IL)-6 as well as other inflammatory markers (Garrison et al., 2018). This suggests that the changes in KP metabolism in *Kmo*<sup>-/-</sup> mice provide resilience to neuroinflammation.

Related, *Kmo*<sup>-/-</sup> mice are protected from several LPS-induced depressive-like behaviors. For example, LPS-treated mutant animals do not show increased immobility in the tail suspension test or a reduction in spontaneous alternations in the Y-maze (Parrott et al., 2016). This resistance to inflammation-induced behavioral changes aligns with the biochemical data mentioned above and confirms that KMO plays a functionally significant—and translationally relevant—role in the detrimental behavioral effects of systemic inflammation. Of note, *Kmo*<sup>-/-</sup> mice have also been used to evaluate the role of circulating KP metabolites on the nutritional status of niacin after ethanol consumption (Mizutani et al., 2023, 2024).

Given that stress and inflammation heighten KP metabolism both prenatally (Notarangelo and Schwarcz, 2014; Baratta et al., 2020) and in the early postnatal period (Asp et al., 2010; Liu et al., 2014), a dietary strategy was developed to boost kynurenine metabolism during this critical phase (Notarangelo and Pocivavsek, 2017). Kynurenine treatment of dams heterozygous for the *Kmo* gene potentiates the elevation of KYNA levels, and lowers 3-HK and QUIN levels, in the embryonic brain of offspring heterozygous for the *Kmo* gene compared with wild-type control offspring (Beggiato et al., 2018). These findings place special attention on the maternal *Kmo* genotype on modulating fetal brain levels of KP metabolites, which may subsequently have long-lasting impacts

on behavioral outcomes and pathophysiological significance toward the study of neurodevelopmental disorders. Interestingly, *Kmo*<sup>-/-</sup> mice have also been used to evaluate nutritional status after ethanol exposure, drawing attention to the role of circulating KP metabolites in this regard (Mizutani et al., 2023, 2024).

*a. 3-Hydroxykynurenine.* 3-HK is the first metabolite of the “KMO branch” of the KP. In mammals, plasma and CSF 3-HK concentrations are in the low nanomolar range. Under physiological conditions, 3-HK levels in the mammalian brain are low, with a similar regional distribution as kynurenine (see Table 1) (Notarangelo et al., 2012; Pocivavsek et al., 2012; Giorgini et al., 2013; Clark et al., 2019; Schwiler et al., 2020).

As a toxic metabolite that can induce oxidative damage and cell death, elevated levels of 3-HK are associated with pathological conditions (Guidetti et al., 2006; Sathyasaikumar et al., 2010). Locally, 3-HK levels can be enhanced with the application of kynurenine (Guidetti et al., 1995; Beggiato et al., 2018), and extracellular 3-HK is detectable after kynurenine stimulation (Notarangelo et al., 2012). Immune cells, including KMO-containing microglia in the brain, are likely primarily responsible for these effects.

Notably, 3-HK is readily oxidized in the presence of trace metals, such as Cu<sup>2+</sup> and Fe<sup>3+</sup>, and by iron chelators, like hemoglobin (Lugo-Huitrón et al., 2011). Thiols, including glutathione, cysteine, and ascorbic acid, effectively inhibit the oxidative process. By donating electrons, 3-HK can therefore participate in physiologically relevant redox reactions in the brain, modulating antioxidative processes and inducing oxidative damage at higher concentrations.

*3. Kynureninase.* Kynureninase catalyzes the conversion of kynurenine to anthranilic acid and, in the branch initiated by KMO (see above), of 3-HK to 3-HANA (Fig. 1). This enzyme therefore plays a critical role in the KP, influencing the production of several key metabolites with significant biological activities. Within the brain, kynureninase is preferentially expressed in microglial cells (Guillemin et al., 2001, 2003a). In cultured human glioma cells, IFN- $\gamma$  stimulation significantly potentiates the expression of kynureninase (Adams et al., 2014), and a similar increase in kynureninase mRNA expression is observed in IFN- $\gamma$ -stimulated microglial cells (O'Farrell et al., 2017).

*a. Anthranilic acid.* Although elevated brain levels of anthranilic acid, which are normally in the low-to-midmicromolar range (Baran and Schwarcz, 1990), have been linked to inflammatory responses, depression, and oxidative stress, which are contributing factors to various chronic diseases, including neurodegenerative disorders and cancer (Pawlowski et al., 2021; Milusheva et al., 2023), this metabolite has not received sufficient attention so far. However, its role in the brain has

recently been proposed to involve the stimulation of a G-protein-coupled receptor (GPR109A) and, as a consequence, may participate in the preservation of myelin integrity (Oxenkrug and Forester, 2024). Notably, ANA—through mechanisms that have not been elucidated so far—can serve as an efficient bioprecursor of 3-HANA in the brain (Baran and Schwarcz, 1990). By modulating the levels or activity of processes that determine the formation and/or the degradation of anthranilic acid in the brain, it may therefore be possible to influence the production of up- and downstream KP metabolites, thereby preventing adverse effects and promoting beneficial outcomes.

*b. 3-Hydroxyanthranilic acid.* 3-HANA easily auto-oxidizes and thereby generates highly reactive products, including hydrogen peroxide and hydroxyl radicals (Liochev and Fridovich, 2001). Thus, 3-HANA is implicated in various physiological and pathological processes, which are exacerbated by superoxide dismutase but, on the other hand, eliminated by catalase (Iwahashi et al., 1988; Goldstein et al., 2000). However, 3-HANA also possesses antioxidant properties and can scavenge free radicals and therefore protect cells from oxidative stress (Iwahashi et al., 1988; Christen et al., 1990). This dual role of 3-HANA, as both a protector against and a contributor to oxidative stress and neurotoxicity, further emphasizes the complex regulatory mechanisms that are associated with KP metabolism.

*4. 3-Hydroxyanthranilic Acid Oxygenase.* The  $\text{Fe}^{2+}$ -dependent enzyme 3-hydroxyanthranilic acid oxygenase (3-HAO) catalyzes the oxidative ring cleavage of 3-HANA to produce QUIN. Triggered by the emerging interest in the role of QUIN in brain function and dysfunction (see below), anti-3-HAO antibodies were generated in the 1980s and used for the immunocytochemical localization of the enzyme in the rat brain. Based on double-labeling with glial fibrillary acidic protein, astrocytes were reported as the major source of the enzyme in these early studies, both in the normal brain (Okuno et al., 1987; Köhler et al., 1988) and following nerve cell loss, e.g., in a model of chronic epilepsy (Du et al., 1993). Although still failing to demonstrate the presence of 3-HAO in neurons, subsequent work shifted attention away from astrocytes and toward a substantive role of microglia and macrophages (Heyes et al., 1997). Supported by in vivo experiments in which the neosynthesis of QUIN from 3-HANA was shown microscopically by staining with anti-QUIN antibodies (Lehrmann et al., 2001), microglial cells are now widely believed to be the major source of QUIN formation in the brain under physiological conditions and especially in response to immune stimulation (Sahm et al., 2013).

*a. Quinolinic acid.* The initial clues pointing toward the involvement of kynurenines in brain function emerged when seizures were observed in mice injected with QUIN directly into the brain (Lapin,

1978). A few years later, Stone and Perkins discovered that QUIN excites neurons in the central nervous system (CNS) by acting as an agonist at NMDARs with approximately 4 times lower potency than the synthetic ligand NMDA (see Fig. 2) (Stone and Perkins, 1981). Together with the subsequent demonstration that intracerebral injections of QUIN cause selective “axon-sparing” (excitotoxic) neurodegeneration in the rat brain, leading to translationally informative neurochemical, physiological, and behavioral changes (Schwarcz et al., 1983), and the identification of QUIN as a normal brain constituent (Wolfensberger et al., 1983), QUIN became the first KP metabolite to attract significant attention from neuroscientists. Endogenous QUIN is found in the brain in nanomolar concentrations (see Table 1) (Schwarcz et al., 1988; Heyes et al., 1992b; Sinz et al., 1998; Medana et al., 2003; Notarangelo et al., 2012; Drewes et al., 2015; Jacobs et al., 2019; Sorgdrager et al., 2019; Orhan et al., 2024).

The neurotoxic effects of QUIN appear to preferentially affect neurons that are richly endowed with NMDA receptors, such as GABAergic cells in the striatum and pyramidal cells in the hippocampus (Nakanishi, 1992). Calcium influx through NR2A and NR2B subunits appears to be particularly critical in this respect (de Carvalho et al., 1996). Notably, QUIN also produces reactive oxygen species, reduces the levels of natural antioxidants (Guillemin, 2012), and induces phosphorylation of structural proteins, leading to cytoskeletal damage (Rahman et al., 2009; Pierozan et al., 2010).

Brain QUIN levels increase significantly following stimulation of the immune system due to inflammatory effects on macrophages, microglia, and dendritic cells (Heyes et al., 1992b; Atlas et al., 2007). Notably, this results both in the harmful buildup of QUIN within cells (Chen and Guillemin, 2009; Chung et al., 2009) and in the extracellular compartment since newly produced QUIN is readily released and no reuptake process exists (Foster et al., 1984a; Speciale and Schwarcz, 1993).

As QUIN does not penetrate the blood-brain barrier under normal physiological conditions (Fukui et al., 1991), the comparatively higher concentrations of the metabolite in blood and peripheral tissues do not affect QUIN levels in the healthy brain. Intracellular QUIN is controlled by 3-HAO (see above) and its catabolic enzyme quinolinate phosphoribosyltransferase (QPRT), which converts the metabolite to nicotinic acid mononucleotide (NAMN). In turn, NAMN is further degraded to a series of metabolites, eventually producing nicotinamide adenine dinucleotide ( $\text{NAD}^+$ ) (Moroni, 1999), a pivotal cofactor in a multitude of biologically relevant redox-dependent and other processes (Ying, 2007).

Because it is saturated by relatively low QUIN concentrations ( $K_m$ , 1 to 2  $\mu\text{M}$ ) (Foster et al., 1985),

QPRT, which is also preferentially present in non-neuronal cells in the mammalian brain (Köhler et al., 1987), has received significant attention by neurobiologists for its regulation of brain QUIN levels and function in health and disease (Feldblum et al., 1988; Braidy et al., 2011a; Terakata et al., 2012).

**5. Biosynthesis of Other Neuroactive Kynurenine Pathway Metabolites.** In another side-arm of the KP (Fig. 1), 3-HANA is metabolized by 2-amino-3-carboxymuconate-semialdehyde decarboxylase (ACMSD) to 2-aminomuconic-6-semialdehyde, which is then non-enzymatically converted to picolinic acid (PIC). ACMSD is present in the mammalian brain, albeit at very low levels compared with peripheral organs (Pucci et al., 2007), and has been tentatively linked to brain pathology (Thirtamara-Rajamani et al., 2017). However, its localization in the mammalian brain has not been studied so far.

Although enzymatic formation has also been suggested to be responsible for the neosynthesis of cinnabarinic acid (Rao and Vaidyanahan, 1966), this metabolite is widely believed to be generated nonenzymatically by auto-oxidation of 3-HANA (Christen et al., 1992).

**a. Picolinic acid.** PIC has long been known as an effective but nonselective chelating agent of several biologically active metal ions, including zinc, iron, and copper (Suzuki et al., 1957; Aggett et al., 1989). Its related ability to potently control and regulate the physiological properties of these metals has led to the suggestion that PIC has substantive biological effects, including cellular growth control and antitumor activity (Ruffmann et al., 1987) as well as antifungal and antiviral properties (Fernandez-Pol et al., 1993; Abe et al., 2004). PIC has therefore been used as a tool to introduce bioactive metals *in vivo* and is used, for example, as a nutritional supplement to provide glycemic and lipidemic benefits (Broadhurst and Domenico, 2006).

PIC is present in mammalian blood, peripheral organs, and CSF (Brundin et al., 2016; Jacobs et al., 2019; Louvrou et al., 2024). Interestingly, in spite of the low levels of its biosynthetic enzyme (see above), the concentration of the metabolite in the brain is in line with other KP metabolites (approximately 1  $\mu$ M) (Porter and O'Connor, 2021), though no functionally relevant receptor of PIC has been identified, and the neurophysiological function of endogenous PIC has not been clarified so far. Of note and possible biological significance, high concentrations of PIC can block QUIN-induced neurotoxicity without affecting neuronal excitation (Beninger et al., 1994). PIC-mediated neuroprotection may therefore not involve direct interference with glutamate receptor function but may be related to the ability of the metabolite to chelate endogenous zinc and/or to attenuate calcium-dependent glutamate release (Vrooman et al., 1993; Jhamandas et al., 1998).

**b. Cinnabarinic acid.** Cinnabarinic acid has recently received attention for its ability to function as a mGluR4 receptor and AhR agonist (see Fig. 2) (Fazio et al., 2012). Although it is present in the brain only in trace amounts (around 1 nM) (Ulivieri et al., 2020) and the localization and biochemical disposition of cinnabarinic acid in the normal and abnormal brain remain to be elucidated, its ability to affect the thresholds of inflammatory and neuropathic pain at low concentrations suggests a role of the metabolite as an endogenous regulator of pain transmission (Notartomaso et al., 2022).

### III. Kynurenine Pathway in Brain Diseases/ Disorders

As alluded to earlier, KP metabolites have garnered significant attention for their possible role(s) in the etiology of a number of brain diseases, and new insights could pave the way for novel therapeutic approaches targeting KP metabolism in the human brain (Pocivavsek and Erhardt, 2024). In light of the ever-expanding list of respective pathological events, the following summary places special emphasis on major psychiatric and neurologic disorders. Introductory comments will briefly summarize the current status of knowledge regarding the role of age, blood-brain barrier function, and inflammation in this context.

#### A. Pathology-Related Variables

**1. Age.** Studied most thoroughly in rodents, the continuous presence of most KP enzymes and metabolites has been demonstrated in the mammalian brain from the prenatal period into old age, with metabolite levels frequently shown to increase with advancing age (Gramsbergen et al., 1997; Kepplinger et al., 2005; Braidy et al., 2011b; Wennström et al., 2014; Sorgdrager et al., 2019; Solvang et al., 2022).

KP metabolism in the prenatal period and during adolescence has received most attention in this regard, but relatively little is still known about the synthesis and transfer of circulating kynurenines in the developing brain, their passage from mother to fetus, or the placenta's role in this process. Tryptophan is supplied to the fetus via the placenta (Nicholls et al., 2001), which then provides serotonin and other neuroactive metabolites to the fetal brain (Bonnin et al., 2011) (see Badawy, 2015 and Silvano et al., 2021 for comprehensive reviews of the dynamics of tryptophan metabolite *in utero*). Of note, there is a striking difference between concentrations of kynurenine and its metabolites in the prenatal and postnatal brain. For example, high fetal brain KYNA levels, which have been reported in nonhuman primates (Beal et al., 1992), sheep (Walker et al., 1999), rats (Ceresoli-Borroni and Schwarcz, 2000; Cannazza et al., 2001; Pocivavsek et al., 2014; Pershing et al., 2015), and mice (Notarangelo and Schwarcz, 2014; Beggiato et al., 2018), may provide

neuroprotection during gestation and parturition (Beal et al., 1992; Walker et al., 1999; Ceresoli-Borroni and Schwarcz, 2000) by blunting excessive NMDAR signaling (Bagasrawala et al., 2016). Notably, the levels of other KP metabolites, including kynurenine and 3-HK, are also far higher in the fetal brain than in the postnatal brain (Ceresoli-Borroni and Schwarcz, 2000). After birth, the brain levels of all KP metabolites measured so far decrease rapidly and then stabilize into adulthood (Beal et al., 1992; Walker et al., 1999; Ceresoli-Borroni and Schwarcz, 2000; Notarangelo and Pocivavsek, 2017). This phenomenon is hypothesized to disinhibit NMDAR function and, together with effects on other mechanisms involved, enable brain development during the postnatal period (Balázs et al., 1988; Simon et al., 1992; Komuro and Rakic, 1993).

The production of KP metabolites is regulated differently during the neurodevelopmental period than in the adult brain. This has been most carefully studied with regard to the features of KYNA formation. In vitro studies show that although adult brain KYNA production is highly dependent on the availability of glucose and cellular energy metabolism, the developing brain is less susceptible to glucose deprivation (Gramsbergen et al., 1997). This is likely related to the fact that the developing brain is less dependent on glucose as the main energy source (Nehlig, 1997). Notably, pyruvate affects KYNA formation in the absence of glucose normally during early brain development, indicating that cosubstrate regulation of KYNA neosynthesis is fully functional in the immature brain (Schwarcz et al., 1998).

In alignment with emerging epidemiological findings linking insults during pregnancy to health risks, including neurodevelopmental and psychiatric disorders in offspring (Pearce, 2001; Susser and Bresnahan, 2002; Brown and Derkits, 2010; Pires et al., 2020), preclinical models of prenatal insults (stress, maternal immune activation, obstetric complications) have demonstrated increased KP metabolism in maternal and fetal compartments (Zavitsanou et al., 2014; Notarangelo and Schwarcz, 2016; Notarangelo and Pocivavsek, 2017; Keaton et al., 2019; Baratta et al., 2020). Lasting effects of elevated KP metabolism during neurodevelopment are of clinical significance as an excess of KYNA is found in CSF and post mortem brain tissue from patients with neurodevelopmental and psychiatric disorders, suggesting that KYNA dysregulation causatively impacts these illnesses (see below).

**2. Blood-Brain Barrier Function.** For decades, characterization of the mammalian KP focused exclusively on extracerebral observations, leading to a reasonably comprehensive understanding of the complex biochemical processes that are responsible for the vast majority of tryptophan degradation. Once the

neuroactive properties and presence of KP metabolites in the brain became evident, the relationship between peripheral and central KP metabolism needed to be carefully investigated. Under normal physiological conditions, most acidic metabolites, including KYNA and QUIN, do not cross the blood-brain barrier to a significant extent, whereas others, including kynurenine, readily enter the brain from the circulation and then affect local KP metabolism and function (Gál and Sherman, 1978; Fukui et al., 1991). However, brain access of KP metabolites changes both qualitatively and quantitatively under pathological conditions that are associated with an impaired brain vasculature. The implications of an abnormal blood-brain barrier for both the function and dysfunction of KP metabolites in the brain are not likely to be consistent between brain disorders and require additional detailed scrutiny. These considerations are particularly relevant for studies in humans where changes in blood or CSF levels of KP metabolites are frequently—and at times probably inappropriately—used as indicators of altered KP metabolism and function in the brain (Skorobogatov et al., 2021).

**3. Inflammation.** As mentioned earlier, KP metabolism is stimulated by inflammatory cytokines and chemokines, specifically through the up-regulation of IDO in the initial step of the enzymatic cascade. Inflammatory processes therefore affect both peripheral and central KP dynamics and often result in an imbalance in the formation and levels of neuroactive KP metabolites in the brain. This effect has been shown consistently in both experimental animals and humans (Heyes et al., 1992a; Atlas et al., 2007, 2013; Holtze et al., 2012; Wickström et al., 2021). Although these neurochemical changes may play a substantive role in excitotoxic and other neuropathological events seen after infection, they also often appear to be *causally* associated with short- and long-term cognitive abnormalities in a variety of brain disorders (Schwarcz et al., 2012; Erhardt et al., 2017b; Stone et al., 2024). Notably, immune system-related changes in cerebral KP metabolism are not only seen, as expected, as a consequence of an infection with HIV or in individuals with tick-borne encephalitis and herpes encephalitis (Atlas et al., 2007, 2013; Holtze et al., 2012; Wickström et al., 2021) but also, for example, in patients with cerebral malaria (Medana et al., 2002, 2003; Miu et al., 2009; Holmberg et al., 2017; Hunt et al., 2017). Interestingly, circulating cytokines and chemokines are now increasingly measured in a large number of human brain diseases as part of routine clinical assessments or in the context of treatment trials. In most cases, these studies are not designed to test specific pathophysiological mechanisms linking inflammatory processes with KP abnormalities. More often, they are an attempt to stratify complex (mainly psychiatric) diseases with the hope to generate novel,

testable hypotheses regarding pathogenicity and treatment.

## B. Neurologic Disorders

Dysfunction of KP metabolism has been investigated in a number of neurodegenerative disorders, including Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer's disease (AD).

**1. Huntington's Disease.** HD is a neurodegenerative disorder characterized by progressive loss of motor function and cognitive decline. Although the genetic basis of HD, i.e., the expansion of CAG repeats in the huntingtin gene that leads to the production of mutant huntingtin protein, has been known since the 1990s (Mangiarini et al., 1996), the molecular mechanisms underlying neurodegeneration remain unclear. KP dysregulation may be a significant contributor to the neurodegenerative process in HD since changes in KP metabolism have been observed in the brain of HD patients. Normalization of the KP in individuals with HD may provide special therapeutic benefits in early stages of the disease, where 3-HK and QUIN levels are elevated—and may be causally involved in neurodegeneration—in neostriatum and cortex (Guidetti et al., 2004). Conceptually aligned with a role of the KP in neuropathology of the disease, KYNA levels are reduced in the striatum (Jauch et al., 1995) and in the CSF of HD patients (Heyes et al., 1992b). Notably, brain levels of 3-HK and QUIN are also increased and related to the onset of HD phenotypes in the R6/2 mouse model of HD (Guidetti et al., 2006). Increased KMO activity may be causally related to the elevation in brain 3-HK in R6/2 mice (Sathyasaikumar et al., 2010), but other KP abnormalities may play a role as well. Thus, IDO1 transcription is increased in the YAC128 HD mouse model (Mazarei et al., 2010) and could contribute to the enhanced kynurenine/tryptophan ratio seen in the blood of HD patients (Stoy et al., 2005; Forrest et al., 2010). Elevated levels of kynurenine stimulate the production of 3-HK/QUIN but at the same time, and for unknown reasons, reduce the formation of KYNA. The resulting imbalance of neurotoxic and neuroprotective KP metabolites may then play a causative role in the pathogenesis of HD.

Individuals with HD present with increased inflammatory cytokines, including TNF- $\alpha$  and interleukins, both in the periphery and in the brain (Björkqvist et al., 2008; Silvestroni et al., 2009), and elevations in immune signaling molecules occur prior to the onset of illness and correlate with disease severity and enhanced KP metabolism (Forrest et al., 2010). Immune activation therefore likely contributes to the activation of the KP during HD progression.

Attempts to target KMO pharmacologically or genetically in efforts to restore the balance of cerebral KP metabolism in R6/2 mice have yielded convincing results regarding biochemical consequences. Thus, chronic

administration of the systemically active KMO inhibitor JM6 (Zwilling et al., 2011) as well as crossing with *Kmo* knockout mice (Bondulich et al., 2021) reduced 3-HK levels and increased KYNA in the striatum and cortex, and decreased peripheral inflammation, in R6/2 mice. JM6 treatment also had neuroprotective effects, though neither approach was associated with significant changes in behavioral impairments in the HD model mice.

**2. Parkinson's Disease.** PD is a neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra pars compacta and symptomatology related mostly to motor impairments. Classic biomarkers of PD include  $\alpha$ -synuclein and dopamine metabolites in the CSF (Havelund et al., 2017). KP metabolite levels are altered in the brain of individuals with PD, however. Thus, post mortem analysis of PD brains shows elevated kynurenine/tryptophan ratios and 3-HK levels in the putamen, frontal cortex, and hippocampus (Ogawa et al., 1992; Widner et al., 2002). Related to KP abnormalities, the pathophysiology of PD may therefore involve excessive activation of NMDA receptors, production of reactive oxygen species and lipid peroxidation, and elevation of nitric oxide synthase levels.

**3. Alzheimer's Disease.** AD is the most common neurodegenerative disease, affecting nearly 60 million people across the world. Its pathology is related to a combination of genetic and environmental factors, and perturbations of the KP have been implicated in disease progression. In line with higher levels of brain IDO1 (Bonda et al., 2010), the kynurenine/tryptophan ratio is elevated in the CSF of AD patients (Gulaj et al., 2010). At the site of amyloid plaques, accumulated microglia, astrocytes, and neurons present with increased immunostaining for IDO1 and QUIN (Guillemin et al., 2005a; Bonda et al., 2010; Minhas et al., 2024). Similarly, IDO and QUIN are present in neurofibrillary tangles, and QUIN has been found in intracellular granular deposits within cortical neurons (Guillemin et al., 2005a).

Mechanistic studies demonstrate that amyloid peptide A $\beta$ 1-42 induces IDO1 expression and enhances QUIN production (Guillemin et al., 2003b). A $\beta$ 1-42 peptide drastically elevates a proinflammatory cytokine response, thereby inducing IDO1, TDO2, and KMO activity (Lue et al., 2001; Yamada et al., 2009). Taken together, a misbalance in the KP in AD patients points toward increased formation of excitotoxic metabolites that may contribute to AD pathology.

**4. Traumatic Brain Injury.** Traumatic brain injury (TBI) is a major public health concern that can result from events such as a fall, vehicle accidents, sports injuries, or violent assaults. TBI ranges in severity from mild concussions to severe brain damage, leading to a spectrum of neurologic and cognitive impairments. The pathophysiology of TBI is complex and

involves primary injury from the initial impact and secondary injury processes that include inflammation, oxidative stress, and excitotoxicity. These injuries collectively contribute to neuronal damage and neurologic dysfunction. The KP has been implicated in the secondary injury mechanisms of TBI, though only a limited number of studies have directly investigated the relationship of TBI to KP metabolism (Meier and Savitz, 2022). Generally, research indicates increased initiation of the KP, noted as increased expression of IDO and increased kynurenine in the brain, and enhanced metabolism toward QUIN production. Significant elevations in QUIN (5- to 50-fold) as well as increases in kynurenine and KYNA have been reported in the CSF of individuals after severe TBI (Sinz et al., 1998; Yan et al., 2015). Along with enhanced IDO1 and kynureninase activity, these studies point to a preferred production of QUIN and related increased neurotoxicity (Yan et al., 2015). In preclinical studies, juvenile rabbits receiving controlled cortical impact showed upregulated IDO expression and protein levels, along with enhanced kynurenine concentrations, at the site of injury within hours. These effects lasted up to 3 weeks postinjury and also increased expression of the proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 (Zhang et al., 2018). In rodent studies, increased expression of QUIN occurs within 24 hours at the focal site of cortical injury, subsequently spreading to adjacent sites (Chung et al., 2009). Rats exposed to blast-related TBI show increased KMO and kynureninase expression. Of note in this context, the KMO inhibitor Ro 61-8048 improves the survival of hippocampal neurons in vitro and has beneficial behavioral effects in vivo (Zakhary et al., 2020; Zhang et al., 2022). Although the kynureninase inhibitor benserazide is protective in vitro, it is unable to mitigate the impacts of TBI in vivo (Zhang et al., 2022). In mice, KMO inhibition protects against retinal ganglion cell dysfunction and structural abnormalities, which are observed over a month after high-pressure blast injury (Harper et al., 2019).

**5. Epilepsy.** Epilepsy is a neurologic disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. Seizures can manifest in various forms, ranging from brief lapses of attention and muscle jerks to severe and prolonged convulsions. The underlying causes of epilepsy are diverse, including genetic predispositions, brain injuries, infections, and developmental disorders. Understanding the role of the KP and its metabolites in epilepsy has piqued research interests for decades, particularly with regard to understanding the balance between neuroprotection and neurotoxicity. Elevated levels of QUIN have been associated with increased neuronal excitability and seizure activity, and an increase in KYNA is postulated to occur as a counteractive response that maintains neuronal stability. Direct infusion of QUIN into

the brain induces convulsion in animals (Lapin, 1978), whereas KYNA reduces spontaneous seizure activity (Foster et al., 1984b). The impact of manipulating KP metabolites to regulate seizure activity has been studied in several validated models (Vécsei et al., 1992). Yet although animal studies clearly support a misbalance in the KP when neuronal excitability is induced, findings from clinical studies in individuals with epilepsy are more variable. The first study to evaluate CSF from epileptic patients found decreased kynurenine (Young et al., 1983). CSF levels of KYNA were also lower in individuals with infantile spasms (Yamamoto et al., 1994) or with West syndrome, a rare condition that causes seizures in infants (Yamamoto et al., 1995). However, no changes in KYNA have been found in the CSF of individuals who experience complex partial seizures (Heyes et al., 1994). Recent metabolomic analysis of CSF from individuals who were hospitalized for status epilepticus, a life-threatening prolonged epileptic seizure, revealed an increase in kynurenine and QUIN (Dey et al., 2021; Hanin et al., 2024).

### C. Psychiatric Disorders

During the past 20+ years, the KP has received increasing attention for its potential participation in the pathophysiology of various psychiatric disorders, and several individual KP metabolites have emerged as key players in this context.

Because of its ability to serve as an endogenous antagonist of both NMDARs and  $\alpha$ 7nAChRs, i.e., two receptors with key—and reasonably well understood—roles in brain function and dysfunction, KYNA has become a molecule of particular interest in the study of clinical conditions believed to involve glutamatergic and/or nicotineric neurotransmission.

The excitotoxin QUIN, in contrast, is associated with neuroinflammatory and neurodegenerative processes that are prominent in major depressive disorder (MDD) and suicidality. PIC, although less studied, may modulate immune responses and neurochemical balance, influencing psychiatric symptoms and disease progression.

The following summary addresses ideas and hypotheses regarding the possible roles of these KP metabolites in the context of selected psychiatric disorders.

**1. Schizophrenia and Bipolar Disorder.** Induction of the KP in the brain is consistently found in psychotic disorders. Originally reported more than two decades ago (Erhardt et al., 2001a; Schwarcz et al., 2001), elevated levels of KYNA have been repeatedly observed in the CSF and in post mortem brain tissue of individuals with schizophrenia or bipolar disorder (BD). Notably, increased CSF KYNA levels are seen in both drug-treated and drug-naive patients with schizophrenia (Nilsson et al., 2005; Linderholm et al., 2012; Kegel et al., 2014; Plitman et al., 2017; Wang and Miller, 2018; Cao et al., 2021; Almulla et al., 2022; Inam et al., 2023; Rømer et al., 2023), and

KYNA increases in post mortem brain have been confirmed several times in the disease (Sathyaikumar et al., 2011; Wonodi et al., 2011; Antenucci et al., 2024). Although the levels of kynurenine, the precursor of KYNA, are elevated in both the CSF and cortical brain regions of people with schizophrenia (Miller et al., 2006; Linderholm et al., 2012), the neurotoxic branch of the KP appears to be unaffected as QUIN is found at normal levels in the CSF (Schwarcz et al., 1988; Kegel et al., 2014), and 3-HK levels remain unchanged in the post mortem brain (Schwarcz et al., 2001; Sathyaikumar et al., 2011). Emerging evidence suggests that alterations in the KP, particularly involving KYNA, may also play a role in the pathophysiology of BD, a psychiatric condition characterized by dramatic mood swings, including episodes of mania and depression. Thus, increased levels of both kynurenine and KYNA are found post mortem in the anterior cingulate cortex of BD patients with a history of psychosis (Miller et al., 2006), and patients with BD exhibit elevated levels of KYNA in the CSF (Olsson et al., 2010; Wang and Miller, 2018; Trepci et al., 2021). This elevation is particularly pronounced in BD patients with a history of psychosis (Olsson et al., 2012; Lavebratt et al., 2014; Sellgren et al., 2016). The increased CSF KYNA levels in BD patients have been linked to cognitive impairments, particularly in tasks requiring executive function, such as set shifting (Sellgren et al., 2016). A small study investigating CSF KYNA in twin pairs discordant for BD or schizophrenia showed that KYNA associates with psychotic symptoms and cluster A personality traits, which include paranoid, schizoid, and schizotypal traits (Kegel et al., 2017). In contrast, no changes in CSF QUIN levels have been observed in patients with BD (Trepci et al., 2021). Further indication of a pathophysiological role of KYNA in psychosis comes from research showing that patients infected with HIV type 1 who exhibit psychotic symptoms have higher concentrations of CSF KYNA compared with HIV type 1 patients without such symptoms (Atlas et al., 2007).

Genetic studies have begun to shed light on the potential mechanisms underlying KYNA elevation in psychotic disorder. A genome-wide association study identified a significant association between CSF KYNA levels and the single-nucleotide polymorphism (SNP) rs10158645 within the 1p21.3 locus. This SNP is associated with decreased expression of sorting nexin 7 (SNX7), which has been linked to increased KYNA concentration through a caspase-8-driven activation of the proinflammatory cytokine IL-1 $\beta$  (Sellgren et al., 2016). Indeed, increased CSF levels of IL-1 $\beta$  are seen in BD patients with a history of psychosis as well as in first-episode psychosis patients (Söderlund et al., 2009, 2011). Consistent with these data, post mortem studies show increased mRNA levels of IL-1 $\beta$ , IL-6,

IL-8, and TNF- $\alpha$  in the brains of individuals with both schizophrenia and BD (Fillman et al., 2013; Trépanier et al., 2016). Additional genetic evidence includes the discovery that a genetic variation in the GPCR kinases 3 (GRK3) gene correlates with levels of CSF KYNA and psychotic symptoms in individuals with BD (Sellgren et al., 2021). GRK3, also known as  $\beta$ -adrenergic receptor kinase 2 (ADRBK2), is a member of the GRK family involved in the desensitization of various receptors in the brain, including those for neurotransmitters, like dopamine and serotonin. Decreased GRK3 RNA expression and protein levels have also been observed in post mortem brain tissue (Bychkov et al., 2011) obtained from schizophrenia patients, and polymorphisms in the GRK3 promoter may increase the risk of BD (Barrett et al., 2003; Zhou et al., 2008; McCarthy et al., 2010).

Since the formation of KYNA indirectly relies on the activity of KMO (see above), polymorphisms in the *Kmo* gene might contribute to the elevated central levels of KYNA observed in patients with schizophrenia. Supportive evidence for this pathophysiological hypothesis has been provided by a number of independent investigators over the past two decades. Thus, the *Kmo* gene, located on chromosome 1q42, has been linked to schizophrenia and schizoaffective disorder in families heavily affected by these conditions. Initial studies found associations between schizophrenia and specific SNPs in the *Kmo* gene [rs2275163 in a Japanese cohort (Aoyama et al., 2006) and rs2065799 in a Norwegian cohort (Holtze et al., 2012)], and post mortem studies showed reduced *Kmo* gene expression and KMO enzyme activity in the prefrontal cortex and frontal eye field of schizophrenia patients (Sathyaikumar et al., 2011; Wonodi et al., 2011). Wonodi et al. (2011) explored the association between *Kmo* SNPs and schizophrenia-related oculomotor endophenotypes in a clinical sample and showed that the *Kmo* rs2275163 variant had modest effects on predictive pursuit and visuospatial working memory endophenotypes. This was confirmed in a separate follow-up study (Wonodi et al., 2014).

Interestingly, the nonsynonymous *Kmo* SNP rs1053230 affects CSF KYNA concentrations (Holtze et al., 2012), the C allele of this SNP is linked to reduced *Kmo* expression in lymphoblastoid cell lines (Lavebratt et al., 2014), and hippocampal biopsies obtained from epilepsy patients with at least one C allele showed lower *Kmo* expression than those without the C allele (Lavebratt et al., 2014). Notably, that study also revealed that the C allele is more prevalent among Swedish BD type 1 patients with psychotic features and is associated with higher CSF KYNA levels in these patients. Using the SMRI On-Line Database ([www.stanleygenomics.org](http://www.stanleygenomics.org)), reduced KMO mRNA levels



were found in the prefrontal cortex of patients with schizophrenia or BD with lifetime psychotic features.

KYNA is the only known endogenous NMDAR antagonist present in the brain, leading to the hypothesis that increased production of KYNA might be causally related to schizophrenia and other psychotic disorders. Supporting this hypothesis, experimentally induced increases in brain KYNA levels result in a schizophrenia-like phenotype in animal models (discussed above). In experimental studies, KYNA is also shown to interact in various ways with dopaminergic neurotransmission (Erhardt et al., 2001b, 2009; Erhardt and Engberg, 2002; Wu et al., 2007), and CSF studies show a strong correlation between KYNA and the levels of the dopamine metabolite homovanillic acid (Nilsson et al., 2006, 2007). Possibly related, CSF KYNA is not only associated with a polymorphism in the gene encoding for SNX7 in patients with BD (see above) but also with the CSF concentrations of homovanillic acid (Sellgren et al., 2016). Decreased SNX7 expression was linked to activation of IL-1 $\beta$ , which can, in turn, increase CSF KYNA levels and enhance dopaminergic activity. This signaling pathway may therefore be one of several avenues resulting in the Marx increased synthesis of KYNA and associated impairments in psychotic disorders.

Post mortem studies have also demonstrated an increase in kynurenine levels and TDO2 expression in the prefrontal cortex and anterior cingulate cortex of individuals affected by schizophrenia (Schwarcz et al., 2001; Miller et al., 2004, 2006). More recently, Kindler et al. (2020) found that KYNA levels, the kynurenine/tryptophan ratio, and mRNAs for the enzymes TDO and KATLII were increased in the prefrontal cortex in a “high cytokine schizophrenia subgroup” identified by elevated proinflammatory cytokine mRNAs. Furthermore, peripheral changes in KP metabolites were linked to cognitive deficits and structural human brain volumetric abnormalities. These results further support the hypothesis that central neuroinflammation may be critically involved in the activation of the KP in psychosis, at least in a subgroup of patients (Antenucci et al., 2024).

Peripheral measures of KP metabolites and metabolism in schizophrenia and BD are less consistent. Although an early publication reported increased plasma levels of KYNA in individuals with schizophrenia (Ravikumar et al., 2000), this finding was not confirmed in a number of follow-up studies of patients with either schizophrenia or BD (Myint et al., 2007, 2011; Plitman et al., 2017; Morrens et al., 2020; Cao et al., 2021; Sapienza et al., 2023, 2024). A recent meta-analysis based on 30 studies concluded that peripheral levels of tryptophan are lower, and levels of KYNA are not altered, in schizophrenia. In 14 studies of patients with BD, tryptophan and KYNA were significantly lower in patients compared with healthy controls (Marx et al., 2021). Notably, two recent

studies examined KYNA concentrations in the CSF and plasma of the same individuals—both healthy and diseased—without finding any correlations between the two compartments (Trepici et al., 2021; Orhan et al., 2024). While central levels of KYNA may shed light on underlying pathophysiological mechanisms, peripheral levels may therefore, at best, serve as biomarkers that provide insights into disease progression or treatment response. Notably, however, plasma KP metabolites have been evaluated as potential biomarkers of brain microstructure and function (Poletti et al., 2019; Comai et al., 2022; Hare et al., 2023).

Additional studies of translational interest regarding a role of the KP in schizophrenia and BD have been conducted and have revealed, for example, that cultured dermal fibroblasts derived from patients demonstrate a markedly higher ability to release KYNA compared with cells obtained from healthy controls (Johansson et al., 2013). Another interesting study reported that although there were no baseline differences between controls and people with schizophrenia, the latter exhibited higher distress intolerance levels, and patients who struggled with stressful tasks showed a greater increase in salivary KYNA levels. Moreover, the rise in KYNA correlated with more severe psychiatric symptoms in these individuals (Chiappelli et al., 2014). These and conceptually similar studies can be expected to provide critical new information with regard to the role of KP (dys)function in various aspects of the complex pathophysiology of the disease.

**2. Major Depressive Disorders.** MDD is a debilitating psychiatric condition characterized by persistent feelings of sadness, loss of interest, and various cognitive and physical symptoms. Since several kynurenines have been implicated in neuroinflammation, oxidative stress, and glutamate neurotransmission, all of which are processes believed to contribute to the development and persistence of depressive symptoms, the KP has been suggested to be actively involved in MDD. Kynurenines have been repeatedly measured in the CSF and brain of MDD patients (Coppen et al., 1972; Ashcroft et al., 1973; Bech et al., 1978; Curzon et al., 1980; Banki et al., 1981; Kaddurah-Daouk et al., 2012; Clark et al., 2016; Paul et al., 2022; Brown et al., 2024), but the results are inconsistent, and a recent systematic review found no significant differences in tryptophan, kynurenine, QUIN, or KYNA levels between MDD patients and healthy controls (Inam et al., 2023).

Recent evidence also suggests a role of KP metabolites in the neurobiology of suicidal behavior. Thus, QUIN, but not KYNA, levels are elevated in the CSF of individuals who attempted suicide, suggesting an overactivation of NMDARs (Erhardt et al., 2013). Interestingly, higher QUIN levels were significantly associated with the degree of suicidal intent and correlated with increased levels of the proinflammatory cytokine IL-6, in line with studies showing that inflammation triggers

QUIN generation (Heyes et al., 1992b; Achim et al., 1993). This provides a neurobiological rationale for the observed efficacy of the NMDAR antagonist ketamine in alleviating symptoms of suicidality (Price et al., 2009; DiazGranados et al., 2010; Zarate et al., 2012). In a separate longitudinal study, QUIN and KYNA levels in the CSF were determined along with depressive and suicidal symptoms over time in psychiatric patients (Bay-Richter et al., 2015). Although QUIN levels were highest at the time of the suicide attempt and decreased during the first year, they remained significantly elevated for up to 2 years. The study also showed that CSF KYNA levels were decreased in these patients compared with healthy individuals and were negatively associated with suicidal ideation and depressive symptoms. Low CSF KYNA had been previously reported in schizophrenia patients with a history of suicidality (Carlborg et al., 2013).

Based on measurements in CSF and blood in conjunction with a suicide attempt across two independent cohorts, there is also evidence that reduced levels of PIC may play a role in suicidality. Importantly, these changes were not related to medication (Brundin et al., 2016). Possibly related (see above), a pilot genotyping study indicated that a single SNP of the ACMSD gene, rs2121337, was associated with increased QUIN in CSF and was more prevalent in suicide attempters than in healthy controls (Brundin et al., 2016). This suggests that reduced ACMSD activity leads to excess QUIN production observed in patients exhibiting suicidal behavior, contributing to increased neuroinflammation and NMDAR activation in vulnerable individuals. Notably, CSF PIC levels were also found to be reduced in a 2-year follow-up study after an initial suicide attempt, suggesting that decreased ACMSD activity may be a trait-marker rather than a state-marker of susceptibility to suicidal behavior (Brundin et al., 2016). A diminished PIC/QUIN ratio in the CSF of individuals who attempted suicide was replicated in a separate cohort (Schwieler et al., 2020), and lower CSF PIC concentrations are also seen in BD patients with a history of suicidal behavior (Trepici et al., 2021). Low CSF PIC may therefore be a bona fide marker of vulnerability for suicidality. Together with evidence mentioned earlier, these data highlight the critical involvement of KP metabolism in the pathophysiology of suicidal behavior, suggesting potential targets for therapeutic intervention.

#### IV. Translationally Relevant Pharmacological Manipulation of Brain Kynurenine Pathway Metabolism

##### 1. Tryptophan 2,3-Dioxygenase 2 and Indoleamine 2,3-Dioxygenase 1

TDO2 and IDO1 have been extensively studied regarding their involvement in several pathological conditions, including malignancies (D'Amato et al., 2015;

Théate et al., 2015), CNS disorders (Miller et al., 2004, 2006; Smith et al., 2012), infections (Boasso and Shearer, 2007; Zelante et al., 2009; Pallotta et al., 2022), and autoimmune diseases (Lee et al., 2014; Pallotta et al., 2014; Mancuso et al., 2015). Notably, TDO2 is not as effective as IDO1 in this regard (Ball et al., 2007). Dysregulation of IDO2 expression has been observed in various types of cancer, including non-small cell carcinoma, pancreatic malignancies, and cervical cancer.

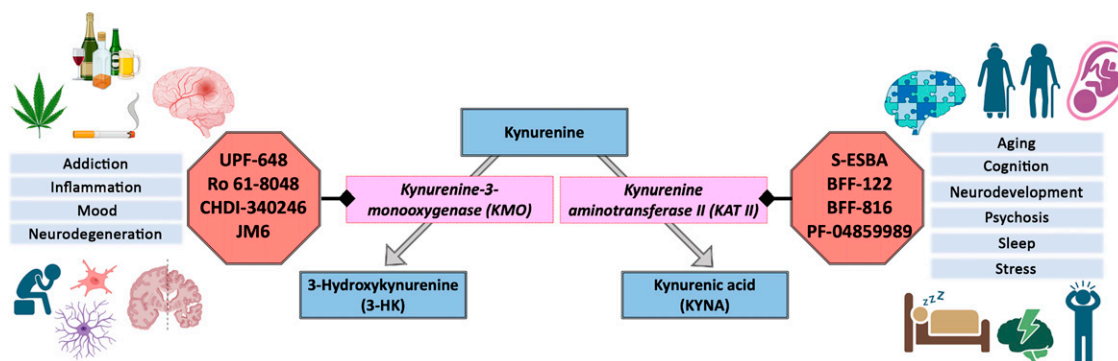
1-Methyltryptophan (1-MT) has been employed in preclinical studies as a selective IDO inhibitor capable of crossing the blood-brain barrier, thus directly impacting brain function. Its major purpose is to mitigate immunosuppressive and neuroinflammatory effects driven by KP activation (Kiank et al., 2010; O'Farrell et al., 2017; Marim et al., 2021). In models of depression, 1-MT administration has been associated with an increase in serotonin availability and a decrease in depressive-like behaviors (Liu et al., 2015). In the context of neurodegenerative diseases, inhibition of IDO1 by 1-MT reduces neuroinflammation and oxidative stress, thereby protecting neuronal integrity and function (Sodhi et al., 2021). IDO1 is therefore a promising therapeutic target for enhancing the effectiveness of immunotherapy in brain disorders (Zhai et al., 2015; Platten et al., 2021).

##### 2. Kynurenine Aminotransferases

A causal link between an experimental reduction in brain KYNA synthesis and behavioral enhancement was first demonstrated using KAT II knockout mice (Yu et al., 2004). These genetically modified animals show improved performance in several behavioral paradigms, including object recognition, passive avoidance, and spatial discrimination. Compared with wild-type control animals, LTP, too, is significantly enhanced in hippocampal slices from KAT II-deficient mice (Potter et al., 2010).

More generally, pharmacological inhibition of KAT enzymes may therefore improve cognitive and behavioral function. Since the transamination of kynurenine to KYNA by KAT I is curbed by the high endogenous levels of the competitive substrate glutamine, KAT II has been considered a more effective target for efforts to reduce brain KYNA levels by pharmacological means. Notably, the crystal structure of KAT II has been resolved, revealing that the protein exists as a functional dimer and contains two active sites with coordinated pyridoxal phosphate (PLP) cofactors (Rossi et al., 2008).

Several potent KAT II inhibitors, including S-ESBA (Pellicciari et al., 2006), BFF-122 (Amori et al., 2009), BFF-816 (Wu et al., 2014), and PF-04859989 (Kozak et al., 2014), have been identified (see Fig. 3). In contrast to the competitive enzyme inhibitors S-ESBA and BFF-816, PF-04859989 and BFF-122 are irreversible inhibitors of KAT II, binding to the PLP cofactor



**Fig. 3.** Pharmacological targeting of two key kynurenine pathway enzymes in the brain and biological implications.

site (Rossi et al., 2010; Dounay et al., 2012). Notably, since PLP participates actively as a cofactor in numerous enzymatic reactions, irreversible binding of a KAT II inhibitor to the PLP site may be associated with unwanted side effects. In fact, PLP was recently shown to play a central role in maintaining homeostatic host-microbiota crosstalk through tryptophan metabolism (Cellini et al., 2020).

S-ESBA was the first selective inhibitor of KAT II synthesized (Pellicciari et al., 2006) and has been an effective tool in preclinical studies. When administered locally in the brain, S-ESBA quickly reduces extracellular KYNA levels (Pellicciari et al., 2006; Amori et al., 2009; Wu et al., 2010; Pocivavsek et al., 2011), and learning and memory are improved in rats that are treated daily with S-ESBA (Pocivavsek et al., 2011). Subsequently, two brain-penetrable KAT II inhibitors became available and have been successfully employed in animal studies. The brain-penetrable compounds PF-04859989 ( $IC_{50}$ , 263 nM; Dounay et al., 2012), administered subcutaneously, and BFF-816 ( $IC_{50}$ , 14  $\mu$ M; Wu et al., 2014), administered by oral gavage, rapidly reduce KYNA in the brain. Even with 5 consecutive days of administration, no tolerance is found with BFF-816 application (Wu et al., 2014). Both compounds have shown promising procognitive impacts in behavioral studies (Kozak et al., 2014; Pocivavsek et al., 2019). Notably, PF-04859989 attenuates stimulant-induced deficits in auditory gating, working memory, and spatial memory, along with improving sustained attention in rodents (Kozak et al., 2014). PF-04859989 also effectively modulates cognitive processes associated with fear discrimination after stress exposure in rats (Klausing et al., 2020). In nonhuman primates, PF-04859989 antagonizes ketamine-induced working memory impairments (Kozak et al., 2014). In mice with a targeted deletion of KMO and basal elevation of KYNA (*Kmo*<sup>-/-</sup> mice; see above), PF-04859989 facilitates LTP, confirming that a pharmacological reduction of KYNA improves learning and memory (Imbeault et al., 2021).

Acutely reducing KYNA with PF-0459989 attenuates sleep disruptions in rodents and improves overall sleep quality (Milosavljevic et al., 2023; Rentschler et al., 2024), suggesting that KAT II inhibition could serve as an efficacious strategy to combat homeostatic sleep impairments. PF-04859989 also effectively dampens basal midbrain dopaminergic firing (Linderholm et al., 2016). KAT II inhibition by BFF-816, too, improves performance in spatial and reference memory (Wu et al., 2014) and stress-induced fear discrimination (Klausing et al., 2024) in rats and attenuates contextual memory deficits in adult offspring exposed to elevated kynurenine during neurodevelopment, an etiologically relevant model for the study of schizophrenia endophenotypes (Pocivavsek et al., 2019).

These preclinical studies indicate that KAT II inhibitors hold promise for enhancing cognitive function in healthy individuals and for overcoming cognitive impairments associated with psychiatric illnesses and neurodegenerative disorders in humans. In fact, any pharmacological or other intervention that decreases KYNA levels, or interferes with its function in the brain, may improve cognitive function. Antioxidants provide interesting options in this context (Lugo-Huitrón et al., 2011; Blanco Ayala et al., 2015, 2021; Blanco-Ayala et al., 2020), and this approach is currently being employed in a clinical trial evaluating N-acetylcysteine as a KAT II inhibitor (clinicaltrials.gov NCT04013555). The development of KAT II inhibitors for use in humans continues, and the first human phase I trial with a selective drug (KYN-5356) is currently in progress (clinicaltrials.gov NCT06225115). Successful completion of clinical trials with KAT II inhibitors would provide critical insights into the mechanistic roles of the KP in disease progression and advance understanding of novel therapeutic strategies for the treatment of neurocognitive and psychiatric disorders.

In addition to KAT II, KAT III appears to play a critical role in the production of KYNA under conditions of immune activation. Thus, an upregulation of KAT III expression is observed in the mouse brain

following repeated LPS injections, increasing brain KYNA levels in both wild-type and KAT II knockout mice. Increased KAT III expression is also seen in post mortem brain tissue from COVID-19-infected patients, and immune activation induces KAT III and increases KYNA production in vitro in human fibroblasts, epidermal cells, and monocytes (Erhardt et al., 2023). These findings identify KAT III as an exciting, novel pharmacological target for treating cognitive impairments associated with psychiatric and infectious diseases.

### 3. Kynurenine 3-Monooxygenase

As inhibition of KMO induces a decrease of 3-HK and QUIN and shifts KP metabolism toward increased production of KYNA, KMO is an attractive therapeutic target for treating various neurodegenerative disorders. Yet, KMO inhibitors are still in preclinical development.

Inhibitors of KMO include halogenated derivatives of L-kynurenine (UPF-648, Ro 61-8048, JM-6), chlorine derivatives [Cure Huntington's Disease Initiative (CHDI)-340246], and chlorinated benzisoxazole (GSK-180) (see Fig. 3). UPF-648 [(1S,2S)-2-(3,4-dichlorobenzoyl)-cyclopropane-1-carboxylic acid] is a potent and selective inhibitor ( $IC_{50}$ , 40 nM) but has poor brain penetrability, thereby limiting its therapeutic potential for CNS diseases (Amaral et al., 2013). Preclinical in vitro and in vivo studies with UPF648 demonstrate inhibition of QUIN neosynthesis and increased KYNA formation (Pellicciari et al., 2003; Amori et al., 2009). Notably, UPF-648 treatment increases KYNA 10-fold in KAT II<sup>-/-</sup> mice, indicating that KAT II is not singularly responsible for KYNA synthesis in the mouse brain. Mice treated with UPF-648 also show reduced QUIN-induced toxicity in the striatum, in line with the hypothesis that an increase in the KYNA:3-HK/QUIN ratio provides neuroprotection (Sapko et al., 2006).

The crystal structure of yeast KMO was successfully determined both in its free form and when co-crystallized with UPF-648 (Amaral et al., 2013). Although the sequences of yeast and human KMO are not 100% homologous, the residues in the ligand binding domain are conserved between species. Discovering the chemical similarities between UPF-648 and L-kynurenine has supported critical molecular modeling of L-kynurenine in the active site, thereby advancing drug discovery efforts.

3,4-Dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl] benzenesulfonamide (Ro-61-8048) is another well known, high-affinity KMO inhibitor ( $IC_{50}$ , 37 nM) (Röver et al., 1997). Treatment with Ro-61-8048 for an extended period reduces the onset of levodopa-induced dyskinesia in a nonhuman primate model of Parkinson's disease (Grégoire et al., 2008) and prevents postischemic neuronal death (Carpenedo et al., 2002). Interestingly, Ro-61-8048 treatment also reduces the rewarding aspects of tetrahydrocannabinol in rodents

by modulating KYNA levels and dopamine release (Justinova et al., 2013).

Since Ro-61-8048 is metabolically unstable, the slow-release prodrug form, JM6, was developed. Prolonged treatment of mice with JM6 inhibits KMO in the periphery, increases brain KYNA levels, and effectively normalizes spatial memory deficits, anxiety phenotypes, and synapse loss in a transgenic mouse model of AD (Zwilling et al., 2011). Moreover, JM6 extends their lifespan and attenuates neuronal damage in the R6/2 mouse model of HD (Zwilling et al., 2011). Subsequent investigation questioned the pharmacokinetic properties of the prodrug, however (Beconi et al., 2012).

Another KMO inhibitor, GSK180 ( $IC_{50}$ , 6 nM), is suitable for intravenous administration and prevents multiple organ dysfunction in a rodent model of acute pancreatitis (Mole et al., 2016). Although the drug is potent and specific, it shows low cell penetration, making it an unattractive candidate for the treatment of CNS disorders. Because of its interest in their therapeutic use for the treatment of HD, the CHDI has patented several KMO inhibitors with the goal of identifying compounds that are capable of crossing the blood-brain barrier. One of the first of these compounds, CHDI-340246 ( $IC_{50}$ , 0.5 nM), showed only limited ability to enter the rat brain following systemic administration in vivo (Toledo-Sherman et al., 2015). As CHDI-340246 does not inhibit other KP enzymes, preclinical testing has continued, and the drug indeed increases brain KYNA levels in rodent HD models (Dominguez and Munoz-Sanjuan, 2014; Beaumont et al., 2016).

More recently, diclofenac, a potent nonsteroidal anti-inflammatory therapeutic, was discovered to inhibit KMO and holds promise for being repurposed for targeting KP metabolism (Hutchinson et al., 2017; Phillips et al., 2017; Shave et al., 2018). Indeed, experimental studies show that diclofenac increases KYNA levels in the rat brain (Schwieler et al., 2005).

Continuing to investigate KMO inhibitors is crucial for advancing therapeutic options for neurodegenerative and neuroinflammatory disorders. Although additional advancements are needed to improve brain permeability, ongoing clinical trials with the first KMO inhibitor, KNS366 (Kynos Therapeutics), show promising preliminary results ([www.isrctn.com](http://www.isrctn.com); ISRCTN10496020). Ongoing and future research is expected to provide valuable data on the efficacy and safety of this unique pharmacological approach.

### 4. Kynureninase

Although pharmacological and genetic manipulations of kynureninase are largely speculative at this stage, they represent exciting opportunities for treating a range of brain disorders, including neurodegenerative disease, psychiatric disorders, and conditions

with neuroinflammation. However, no efficient kynureninase inhibitors have been developed so far.

### 5. 3-Hydroxyanthranilic Acid Dioxygenase

In light of the central role of 3-HAO in the production of QUIN, targeting this enzyme presents a promising therapeutic strategy. By reducing QUIN levels in the brain, inhibitors of 3-HAO may mitigate excitotoxic damage and provide neuroprotection. Of relevance in this context, mice with a targeted elimination of 3-HAO are protected from the negative effects of an immune challenge with LPS on depressive-like behavioral phenotypes, suggesting that reduced kynurenine metabolism toward QUIN is neuroprotective (Parrott et al., 2016). Research into specific inhibitors of 3-HAO is ongoing and shows promising results in reducing QUIN production in the brain (Vallerini et al., 2013), although no clinically approved drugs are currently available.

## V. Major Open Questions and Opportunities

A rapidly expanding body of evidence implicates important roles of KP metabolites in normal brain function and in psychiatric, neurocognitive, and neurodegenerative disorders. Recent advancements in genetic and pharmacological approaches in preclinical models have supported clinical studies in patients, suggesting that normalizing the levels of KP metabolites may be an effective therapeutic approach to achieving brain health. In most neurodegenerative diseases, there is a shift in the KP toward increased production of QUIN and 3-HK and away from KYNA. This imbalance can be corrected with interventions designed to reverse this metabolic shift. Targeting KMO shows potential as a therapeutic target as inhibition of this enzyme increases KYNA levels, whereas decreasing its product 3-HK and the downstream metabolite QUIN. On the opposite spectrum of metabolic shift are neuropsychiatric disorders wherein accumulation of KYNA levels in the brain may influence behavioral endophenotypes related to arousal and cognition in illnesses such as schizophrenia and BD. Targeting KAT enzymes to decrease KYNA formation and function appears to be an attractive therapeutic intervention in this case. Although achieving a balance in KP metabolism in the brain presents itself as an ideal circumstance, several questions remain to be addressed. Some of them are listed below in bullet form.

- *Further clarification of the relationship between peripheral and central KP metabolism.* Studies in animals have repeatedly challenged the notion that measurements of KP metabolite levels in the periphery predict the features of central KP metabolism under either physiological or pathological conditions (Agudelo et al., 2014; Larsson et al., 2016; Baratta et al., 2018; Wright et al., 2021). This has been verified in humans (Sellgren et al.,

2019; Skorobogatov et al., 2021; Orhan et al., 2024). Improved study designs and, in particular, the development of noninvasive methods to monitor KP metabolites in the brain in vivo will have a major impact in the field.

- *Role of bacterial KP metabolites in host KP physiology and pathology.* Research into the role of bacterial metabolites in the KP of the host is a burgeoning field with significant implications for understanding gut-brain interactions. Bacteria in the gut microbiome produce KP metabolites that can influence the host's physiology and pathology by modulating the local and systemic levels of kynurenine and its derivatives (Gheorghe et al., 2019; Schwarcz et al., 2024). Further research in this area could lead to novel probiotic and antibiotic therapies aimed at manipulating gut microbiota to beneficially alter host KP metabolism (Rudzki et al., 2021).
- *Effects of acute and chronic stress on KP physiology and pathology.* Stress is a well known modulator of the immune system and has profound effects on KP metabolism. Acute stress can induce a rapid upregulation of KP metabolites, potentially leading to transient changes in neurotransmitter levels and neuroinflammation. Chronic stress, on the other hand, may cause sustained alterations in KP enzyme activity, contributing to the pathogenesis of chronic inflammatory and neurodegenerative diseases (Agudelo et al., 2014; Porter and O'Connor, 2021; Ye et al., 2024). Further research is warranted to delineate the mechanisms by which different types of stress affect KP physiology and to develop interventions that can mitigate these effects. Understanding stress-induced changes in the KP could lead to targeted treatments for stress-related disorders (Klausing et al., 2020, 2024).
- *Positive and negative effects of chronic interventions with pharmacological agents targeting individual KP enzymes.* Long-term interventions with drugs targeting specific KP enzymes present both opportunities and challenges. Although such interventions hold promise for treating diseases linked to KP dysregulation, they also pose a risk of off-target effects and metabolic imbalances. Chronic inhibition or activation of KP enzymes may lead to unintended consequences, such as accumulation of toxic intermediates or the depletion of essential metabolites. Notably, these interferences may also affect the degradative cascade downstream of QUIN, causing impairments in the formation and function of the essential coenzyme NAD<sup>+</sup>. Comprehensive studies are required to evaluate the long-term safety and efficacy of these pharmacological agents, understanding both their therapeutic potential and adverse effects. This research will be crucial to developing safe, effective

treatments for chronic conditions involving KP dysregulation.

- *Clinically relevant strategies to affect specific processes in the fetal brain pharmacologically with selective “KP drugs.”* The development of selective KP drugs that can safely target the fetal brain is an exciting area of research with the potential to prevent or mitigate neurodevelopmental disorders. These strategies must be meticulously designed to avoid disrupting critical developmental processes while effectively modulating KP metabolites. Prenatal exposure to altered KP metabolism can have lasting impacts on brain development and function (Pocivavsek et al., 2012, 2014; Alexander et al., 2013; Forrest et al., 2013a,b; Pershing et al., 2015; Notarangelo and Pocivavsek, 2017; Beggiato et al., 2018; Rentschler et al., 2021; Wright et al., 2021), highlighting the need for precise, controlled interventions. Research in this area could lead to breakthroughs in preventing conditions like schizophrenia by pharmacologically modulating the KP during critical periods of brain development.
- *Changes in the role(s) of KP metabolism and function in the aging brain.* The role of KP metabolism in the aging brain is an important area of study (Gramsbergen et al., 1992; Comai et al., 2005), particularly given the pathway’s involvement in neurodegenerative disease. As the brain ages, changes in KP enzyme activity and metabolite levels can contribute to cognitive decline, exacerbate sleep impairments, and increase susceptibility to neurological conditions. Research should focus on how these age-related changes in KP function affect brain health and on developing interventions that can preserve cognitive function in the elderly. Understanding the mechanisms behind age-related KP alterations could lead to targeted therapies that address the metabolic changes contributing to neurodegeneration.
- *Selective manipulation of brain KP (dys)function(s) with new genetic tools.* The advent of advanced genetic tools presents new opportunities for selectively manipulating KP function in the brain. These tools can be used to precisely edit genes encoding KP enzymes, allowing the investigation of causal relationships between specific KP dysfunctions and brain disorders. By selectively knocking out or overexpressing KP genes in animal models, we will gain deeper insights into the pathway’s role in brain function and disease. These genetic interventions could pave the way for novel treatments that specifically target KP dysregulation without affecting other metabolic pathways.
- *Causal role of brain KP in the effects of psychedelics.* Psychedelic compounds have been shown to have profound effects on brain function, and recent research suggests that the KP may play a role in mediating these effects. Understanding the interaction between psychedelics and KP metabolism could reveal new mechanisms of action for these substances and identify potential therapeutic applications for mental health disorders (Campanale et al., 2024). Studies should focus on how psychedelics influence KP enzyme activity and metabolite levels and whether these changes contribute to the therapeutic and psychotropic effects of these drugs. Further research could lead to new insights into the neurobiological basis of psychedelic therapeutic advancements occurring in psychiatry.
- *KP and drugs of abuse.* Increasing evidence points to a functionally significant role of KP metabolism in the context of drugs of abuse, for example tetrahydrocannabinol and other Cannabis derivatives (Panlilio et al., 2016; Secci et al., 2019). These phenomena, which may have common features among a variety of addictive substances (Davidson et al., 2023), may be of special pathophysiological relevance at early stages of brain development (i.e. prenatally and during adolescence) (Beggiato et al., 2020, 2022).
- *Changing contributions of various brain cells to KP function and dysfunction during the lifespan.* Different brain cell types, including neurons, astrocytes, and microglia, contribute to KP metabolism, and their roles may change over the lifespan. Understanding how these contributions shift with age and in response to disease is crucial for developing targeted therapies. Research should investigate how the activity of KP enzymes in different cell types affects overall brain metabolism and how these changes contribute to neurodegeneration and other age-related conditions. Advancements in this area could inform the development of cell-specific interventions to modulate KP function and maintain brain health throughout the lifespan.
- *Genetic links between KP and psychiatric conditions.* There is growing evidence of genetic links between KP metabolism and psychiatric conditions, such as depression, schizophrenia, and drug addiction. Identifying genetic variants that influence KP enzyme activity and metabolite levels could provide new biomarkers for these conditions and reveal potential targets for pharmacological intervention. Elucidating the genetic basis of KP dysregulation in psychiatric disorders and exploring how these genetic factors interact with environmental influences such as stress and substance abuse presents promising avenues towards personalized treatment strategies based on an individual’s genetic profile and KP metabolic state.

## Acknowledgments

Figures 2 and 3 were created with BioRender.com.

## Data Availability

This review article contains no datasets generated or analyzed during the present study.

## Authorship Contributions

Wrote or contributed to the writing of the manuscript: Pocivavsek, Schwarcz, Erhardt.

## References

- Abe S, Hu W, Ishibashi H, Hasumi K, and Yamaguchi H (2004) Augmented inhibition of *Candida albicans* growth by murine neutrophils in the presence of a tryptophan metabolite, picolinic acid. *J Infect Chemother* **10**:181–184.
- Achim CL, Heyes MP, and Wiley CA (1993) Quantitation of human immunodeficiency virus, immune activation factors, and quinolinic acid in AIDS brains. *J Clin Invest* **91**:2769–2775.
- Adams S, Teo C, McDonald KL, Zinger A, Bustamante S, Lim CK, Sundaram G, Braidy N, Brew BJ, and Guillemin GJ (2014) Involvement of the kynurenine pathway in human glioma pathophysiology. *PLoS One* **9**:e112945.
- Aggett PJ, Fenwick PK, and Kirk H (1989) An in vitro study of the effect of picolinic acid on metal translocation across lipid bilayers. *J Nutr* **119**:1432–1437.
- Agudelo LZ, Femenia T, Orhan F, Porsmyr-Palmertz M, Gojny M, Martinez-Redondo V, Correia JC, Izadi M, Bhat M, Schuppe-Koistinen I, et al. (2014) Skeletal muscle PGC-1 $\alpha$  modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell* **159**:33–45.
- Akagbosu CO, Evans GC, Gulick D, Suckow RF, and Bucci DJ (2012) Exposure to kynurenic acid during adolescence produces memory deficits in adulthood. *Schizophr Bull* **38**:769–778.
- Alberati-Giani D, Ricciardi-Castagnoli P, Köhler C, and Cesura AM (1996) Regulation of the kynurenine metabolic pathway by interferon- $\gamma$  in murine cloned macrophages and microglial cells. *J Neurochem* **66**:996–1004.
- Alexander KS, Pocivavsek A, Wu H-Q, Pershing ML, Schwarcz R, and Bruno JP (2013) Early developmental elevations of brain kynurenic acid impair cognitive flexibility in adults: reversal with galantamine. *Neuroscience* **238**:19–28.
- Alexander KS, Wu H-Q, Schwarcz R, and Bruno JP (2012) Acute elevations of brain kynurenic acid impair cognitive flexibility: normalization by the alpha7 positive modulator galantamine. *Psychopharmacology (Berl)* **220**:627–637.
- Alkondon M, Pereira EFR, Yu P, Arruda EZ, Almeida LEF, Guidetti P, Fawcett WP, Sapko MT, Randall WR, Schwarcz R, et al. (2004) Targeted deletion of the kynurenine aminotransferase ii gene reveals a critical role of endogenous kynurenic acid in the regulation of synaptic transmission via alpha7 nicotinic receptors in the hippocampus. *J Neurosci* **24**:4635–4648.
- Almulla AF, Vasupanrajit A, Tunvirachaisakul C, Al-Hakeim HK, Solmi M, Verkerk R, and Maes M (2022) The tryptophan catabolite or kynurenine pathway in schizophrenia: meta-analysis reveals dissociations between central, serum, and plasma compartments. *Mol Psychiatry* **27**:3679–3691.
- Amaral M, Levy C, Heyes DJ, Lafite P, Outeiro TF, Giorgini F, Leys D, and Scrutton NS (2013) Structural basis of kynurenine 3-monooxygenase inhibition. *Nature* **496**:382–385.
- Amori L, Guidetti P, Pellicciari R, Kajiji Y, and Schwarcz R (2009) On the relationship between the two branches of the kynurenine pathway in the rat brain in vivo. *J Neurochem* **109**:316–325.
- Antenucci N, D'Errico G, Fazio F, Nicoletti F, Bruno V, and Battaglia G (2024) Changes in kynurenine metabolites in the gray and white matter of the dorsolateral prefrontal cortex of individuals affected by schizophrenia. *Schizophrenia (Heidelb)* **10**:27.
- Aoyama N, Takahashi N, Saito S, Maeno N, Ishihara R, Ji X, Miura H, Ikeda M, Suzuki T, Kitajima T, et al. (2006) Association study between kynurenine 3-monooxygenase gene and schizophrenia in the Japanese population. *Genes Brain Behav* **5**:364–368.
- Arndt R, Junge W, Michelssen K, and Krisch K (1973) Isolation and molecular properties of formamidase from rat liver cytoplasm. *Hoppe Seylers Z Physiol Chem* **354**:1583–1590.
- Ashcroft GW, Blackburn IM, Eccleston D, Glen AI, Hartley W, Kinloch NE, Lonergan M, Murray LG, and Pullar IA (1973) Changes on recovery in the concentrations of tryptophan and the biogenic amine metabolites in the cerebrospinal fluid of patients with affective illness. *Psychol Med* **3**:319–325.
- Asp L, Holtze M, Powell SB, Karlsson H, and Erhardt S (2010) Neonatal infection with neurotropic influenza A virus induces the kynurenine pathway in early life and disrupts sensorimotor gating in adult Tap1 $^{-/-}$  mice. *Int J Neuropsychopharmacol* **13**:475–485.
- Atlas A, Franzen-Röhl E, Söderlund J, Jönsson EG, Samuelsson M, Schwieler L, Sköldenberg B, and Engberg G (2013) Sustained elevation of kynurenic acid in the cerebrospinal fluid of patients with herpes simplex virus type 1 encephalitis. *Int J Tryptophan Res* **6**:89–96.
- Atlas A, Gisslén M, Nordin C, Lindström L, and Schwieler L (2007) Acute psychotic symptoms in HIV-1 infected patients are associated with increased levels of kynurenic acid in cerebrospinal fluid. *Brain Behav Immun* **21**:86–91.
- Austin CJD, Mailu BM, Maghazal GJ, Sanchez-Perez A, Rahlfs S, Zocher K, Yuasa HJ, Arthur JW, Becker K, Stocker R, et al. (2010) Biochemical characteristics and inhibitor selectivity of mouse indoleamine 2,3-dioxygenase-2. *Amino Acids* **39**:565–578.
- Babcock TA and Carlin JM (2000) Transcriptional activation of indoleamine dioxygenase by interleukin 1 and tumor necrosis factor alpha in interferon-treated epithelial cells. *Cytokine* **12**:588–594.
- Badawy AA (2015) Tryptophan metabolism, disposition and utilization in pregnancy. *Biosci Rep* **35**:e00261.
- Badawy AA-B (2022) Tryptophan metabolism and disposition in cancer biology and immunotherapy. *Biosci Rep* **42**:e00261.
- Bagasrawala I, Zecevic N, and Radonjić NV (2016) N-Methyl D-Aspartate Receptor Antagonist Kynurenic Acid Affects Human Cortical Development. *Front Neurosci* **10**:435.
- Balázs R, Hack N, and Jørgensen OS (1988) Stimulation of the N-methyl-D-aspartate receptor has a trophic effect on differentiating cerebellar granule cells. *Neurosci Lett* **87**:80–86.
- Ball HJ, Sanchez-Perez A, Weiser S, Austin CJD, Astelbauer F, Miu J, McQuillan JA, Stocker R, Jermin LS, and Hunt NH (2007) Characterization of an indoleamine 2,3-dioxygenase-like protein found in humans and mice. *Gene* **396**:203–213.
- Balter LJ, Li X, Schwieler L, Erhardt S, Axelsson J, Olsson MJ, Lasselin J, and Lekander M (2023) Lipopolysaccharide-induced changes in the kynurenine pathway and symptoms of sickness behavior in humans. *Psychoneuroendocrinology* **153**:106110.
- Banki CM, Vojnik M, and Molnar G (1981) Cerebrospinal fluid amine metabolites, tryptophan and clinical parameters in depression. Part 1. Background variables. *J Affect Disord* **3**:81–89.
- Baran H and Schwarcz R (1990) Presence of 3-hydroxyanthranilic acid in rat tissues and evidence for its production from anthranilic acid in the brain. *J Neurochem* **55**:738–744.
- Baratta AM, Buck SA, Buchla AD, Fabian CB, Chen S, Mong JA, and Pocivavsek A (2018) Sex Differences in Hippocampal Memory and Kynurenic Acid Formation Following Acute Sleep Deprivation in Rats. *Sci Rep* **8**:6963.
- Baratta AM, Kanyuch NR, Cole CA, Valafar H, Deslauriers J, and Pocivavsek A (2020) Acute sleep deprivation during pregnancy in rats: Rapid elevation of placental and fetal inflammation and kynurenic acid. *Neurobiol Stress* **12**:100204.
- Barrett TB, Hauger RL, Kennedy JL, Sadovnick AD, Remick RA, Keck PE, McElroy SL, Alexander M, Shaw SH, and Kelseo JR (2003) Evidence that a single nucleotide polymorphism in the promoter of the G protein receptor kinase 3 gene is associated with bipolar disorder. *Mol Psychiatry* **8**:546–557.
- Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Träskman-Bendz L, Guillemin GJ, Erhardt S, and Brundin L (2015) A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. *Brain Behav Immun* **43**:110–117.
- Beal MF, Swartz KJ, and Isacson O (1992) Developmental changes in brain kynurenic acid concentrations. *Brain Res Dev Brain Res* **68**:136–139.
- Beaumont V, Mrzljak L, Dijkman U, Prejse R, Heims M, Rassoulpour A, Tombaugh G, Gelman S, Bradaia A, Steidl E, et al. (2016) The novel KMO inhibitor CHDI-340246 leads to a restoration of electrophysiological alterations in mouse models of Huntington's disease. *Exp Neurol* **282**:99–118.
- Bech P, Kirkegaard C, Bock E, Johannessen M, and Rafaelsen OJ (1978) Hormones, electrolytes, and cerebrospinal fluid proteins in manic-melancholic patients. *Neuropsychobiology* **4**:99–112.
- Beconi MG, Yates D, Lyons K, Matthews K, Clifton S, Mead T, Prime M, Winkler D, O'Connell C, Walter D, et al. (2012) Metabolism and pharmacokinetics of JM6 in mice: JM6 is not a prodrug for Ro-61-8048. *Drug Metab Dispos* **40**:2297–2306.
- Beggiato S, Antonelli T, Tomasini MC, Tanganelli S, Fuxe K, Schwarcz R, and Ferraro L (2013) Kynurenic acid, by targeting alpha7 nicotinic acetylcholine receptors, modulates extracellular GABA levels in the rat striatum in vivo. *Eur J Neurosci* **37**:1470–1477.
- Beggiato S, Ieraci A, Tomasini MC, Schwarcz R, and Ferraro L (2020) Prenatal THC exposure raises kynurenic acid levels in the prefrontal cortex of adult rats. *Prog Neuropsychopharmacol Biol Psychiatry* **100**:109883.
- Beggiato S, Ieraci A, Zuccarini M, Di Iorio P, Schwarcz R, and Ferraro L (2022) Alterations in rat prefrontal cortex kynurenic acid levels are involved in the enduring cognitive dysfunctions induced by tetrahydrocannabinol exposure during the adolescence. *Front Psychiatry* **13**:966406.
- Beggiato S, Notarangelo FM, Sathyasaikumar KV, Giorgini F, and Schwarcz R (2018) Maternal genotype determines kynurenic acid levels in the fetal brain: Implications for the pathophysiology of schizophrenia. *J Psychopharmacol* **32**:1223–1232.
- Beggiato S, Tanganelli S, Fuxe K, Antonelli T, Schwarcz R, and Ferraro L (2014) Endogenous kynurenic acid regulates extracellular GABA levels in the rat prefrontal cortex. *Neuropharmacology* **82**:11–18.
- Behmoaras J (2021) The versatile biochemistry of iron in macrophage effector functions. *FEBS J* **288**:6972–6989.
- Bender DA and McCreanor GM (1982) The preferred route of kynurenine metabolism in the rat. *Biochim Biophys Acta* **717**:56–60.
- Beninger RJ, Colton AM, Ingles JL, Jhamandas K, and Boegman RJ (1994) Picolinic acid blocks the neurotoxic but not the neuroexcitant properties of quinolinic acid in the rat brain: evidence from turning behaviour and tyrosine hydroxylase immunohistochemistry. *Neuroscience* **61**:603–612.
- Berlinguer-Palmini R, Masi A, Narducci R, Cavone L, Maratea D, Cozzi A, Sili M, Moroni F, and Mannaioni G (2013) GPR35 activation reduces Ca $^{2+}$  transients and contributes to the kynurenic acid-dependent reduction of synaptic activity at CA3-CA1 synapses. *PLoS One* **8**:e82180.
- Birch PJ, Grossman CJ, and Hayes AG (1988) Kynurenic acid antagonises responses to NMDA via an action at the strychnine-insensitive glycine receptor. *Eur J Pharmacol* **154**:85–87.
- Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, Raibon E, Lee RV, Benn CL, Soulet D, et al. (2008) A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *J Exp Med* **205**:1869–1877.

- Blanco Ayala T, Lugo Huitrón R, Carmona Aparicio L, Ramírez Ortega D, González Esquivel D, Pedraza Chaverri J, Pérez de la Cruz G, Ríos C, Schwarcz R, and Pérez de la Cruz V (2015) Alternative kynurenine acid synthesis routes studied in the rat cerebellum. *Front Cell Neurosci* **9**:178.
- Blanco Ayala TB, Ramírez Ortega DR, Ovalle Rodríguez PO, Pineda B, Pérez de la Cruz G P D L, González Esquivel DG, Schwarcz R, Sathyaasikumar KV, Jiménez Anguiano AJ, and Pérez de la Cruz V P D L (2021) Subchronic N-acetylcysteine Treatment Decreases Brain Kynurenine Acid Levels and Improves Cognitive Performance in Mice. *Antioxidants (Basel)* **10**:147.
- Blanco-Ayala T, Sathyaasikumar KV, Uys JD, Pérez-de-la-Cruz V, Pidugu LS, and Schwarcz R (2020) N-Acetylcysteine Inhibits Kynurenine Aminotransferase II. *Neuroscience* **444**:160–169.
- Boasso A and Shearer GM (2007) How does indoleamine 2,3-dioxygenase contribute to HIV-mediated immune dysregulation. *Curr Drug Metab* **8**:217–223.
- Bonda DJ, Mailankot M, Stone JG, Garrett MR, Stanisewska M, Castellani RJ, Siedlak SL, Zhu X, Lee H-G, Perry G, et al. (2010) Indoleamine 2,3-dioxygenase and 3-hydroxykynurenine modifications are found in the neuropathology of Alzheimer's disease. *Redox Rep* **15**:161–168.
- Bondulich MK, Fan Y, Song Y, Giorgini F, and Bates GP (2021) Ablation of kynurenine 3-monooxygenase rescues plasma inflammatory cytokine levels in the R6/2 mouse model of Huntington's disease. *Sci Rep* **11**:5484.
- Bonnin A, Goeden N, Chen K, Wilson ML, King J, Shih JC, Blakely RD, Deneris ES, and Levitt P (2011) A transient placental source of serotonin for the fetal forebrain. *Nature* **472**:347–350.
- Briday N, Guillemin GJ, and Grant R (2011a) Effects of Kynurenine Pathway Inhibition on NAD Metabolism and Cell Viability in Human Primary Astrocytes and Neurons. *Int J Tryptophan Res* **4**:29–37.
- Briday N, Guillemin GJ, Mansour H, Chan-Ling T, and Grant R (2011b) Changes in kynurenine pathway metabolism in the brain, liver and kidney of aged female Wistar rats. *FEBS J* **278**:4425–4434.
- Broadhurst CL and Domenico P (2006) Clinical studies on chromium picolinate supplementation in diabetes mellitus—a review. *Diabetes Technol Ther* **8**:677–687.
- Brown SJ, Christofides K, Weissleder C, Huang X-F, Shannon Weickert C, Lim CK, and Newell KA (2024) Sex- and suicide-specific alterations in the kynurenine pathway in the anterior cingulate cortex in major depression. *Neuropsychopharmacology* **49**:584–592.
- Brown AS and Derkits EJ (2010) Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry* **167**:261–280.
- Brown D, Hitchcock MJ, and Katz E (1986) Purification and characterization of kynurenine formamidase activities from *Streptomyces parvulus*. *Can J Microbiol* **32**:465–472.
- Browne CA, O'Brien FE, Connor TJ, Dinan TG, and Cryan JF (2012) Differential lipopolysaccharide-induced immune alterations in the hippocampus of two mouse strains: effects of stress. *Neuroscience* **225**:237–248.
- Brundin L, Sellgren CM, Lim CK, Grit J, Pålsson E, Landén M, Samuelsson M, Lundgren K, Brundin P, Fuchs D, et al. (2016) An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. *Transl Psychiatry* **6**:e865.
- Buck SA, Baratta AM, and Pocivavsek A (2020) Exposure to elevated embryonic kynurenine in rats: Sex-dependent learning and memory impairments in adult offspring. *Neurobiol Learn Mem* **174**:107282.
- Bychkov ER, Ahmed MR, Gurevich VV, Benovic JL, and Gurevich EV (2011) Reduced expression of G protein-coupled receptor kinases in schizophrenia but not in schizoaffective disorder. *Neurobiol Dis* **44**:248–258.
- Campanale A, Inserra A, and Comai S (2024) Therapeutic modulation of the kynurenine pathway in severe mental illness and comorbidities: A potential role for serotonergic psychedelics. *Prog Neuropsychopharmacol Biol Psychiatry* **134**:111058.
- Cannazza G, Chiarugi A, Parenti C, Zanoli P, and Baraldi M (2001) Changes in kynurenine, anthranilic, and quinolinic acid concentrations in rat brain tissue during development. *Neurochem Res* **26**:511–514.
- Cao B, Chen Y, Ren Z, Pan Z, McIntyre RS, and Wang D (2021) Dysregulation of kynurenine pathway and potential dynamic changes of kynurenine in schizophrenia: A systematic review and meta-analysis. *Neurosci Biobehav Rev* **123**:203–214.
- Capece L, Arrar M, Roitberg AE, Yeh S-R, Marti MA, and Estrin DA (2010) Substrate stereo-specificity in tryptophan dioxygenase and indoleamine 2,3-dioxygenase. *Proteins* **78**:2961–2972.
- Carlborg A, Jokinen J, Jönsson EG, Erhardt S, and Nordström P (2013) CSF kynurenine acid and suicide risk in schizophrenia spectrum psychosis. *Psychiatry Res* **205**:165–167.
- Carlsson A, Jonason J, and Lindqvist M (1969) On the mechanism of 5-hydroxytryptamine release by thymoleptics. *J Pharm Pharmacol* **21**:769–773.
- Carpeneo R, Meli E, Peruginelli F, Pellegrini-Giampietro DE, and Moroni F (2002) Kynurenine 3-mono-oxygenase inhibitors attenuate post-ischemic neuronal death in organotypic hippocampal slice cultures. *J Neurochem* **82**:1465–1471.
- Carpeneo R, Pittaluga A, Cozzi A, Attucci S, Galli A, Raiteri M, and Moroni F (2001) Presynaptic kynurenate-sensitive receptors inhibit glutamate release. *Eur J Neurosci* **13**:2141–2147.
- Cellini B, Zelante T, Dindo M, Bellet MM, Renga G, Romani L, and Costantini C (2020) Pyridoxal 5'-Phosphate-Dependent Enzymes at the Crossroads of Host-Microbe Tryptophan Metabolism. *Int J Mol Sci* **21**:5823.
- Ceresoli-Borroni G and Schwarcz R (2000) Perinatal kynurenine pathway metabolism in the normal and asphyctic rat brain. *Amino Acids* **19**:311–323.
- Cervenka I, Agudelo LZ, and Ruas JL (2017) Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science* **357**:eaaf9794.
- Chen Y and Guillemin GJ (2009) Kynurenine pathway metabolites in humans: disease and healthy States. *Int J Tryptophan Res* **2**:1–19.
- Chess AC, Landers AM, and Bucci DJ (2009) L-kynurenine treatment alters contextual fear conditioning and context discrimination but not cue-specific fear conditioning. *Behav Brain Res* **201**:325–331.
- Chess AC, Simoni MK, Alling TE, and Bucci DJ (2007) Elevations of endogenous kynurenine acid produce spatial working memory deficits. *Schizophr Bull* **33**:797–804.
- Chiappelli J, Pociavsek A, Nugent KL, Notarangelo FM, Kochunov P, Rowland LM, Schwarcz R, and Hong LE (2014) Stress-induced increase in kynurenine acid as a potential biomarker for patients with schizophrenia and distress intolerance. *JAMA Psychiatry* **71**:761–768.
- Christen S, Peterhans E, and Stocker R (1990) Antioxidant activities of some tryptophan metabolites: possible implication for inflammatory diseases. *Proc Natl Acad Sci U S A* **87**:2506–2510.
- Christen S, Southwell-Keely PT, and Stocker R (1992) Oxidation of 3-hydroxyanthranilic acid to the phenoxazinone cinnabarinic acid by peroxyl radicals and by compound I of peroxidases or catalase. *Biochemistry* **31**:8090–8097.
- Chung RS, Leung YK, Butler CW, Chen Y, Eaton ED, Pankhurst MW, West AK, and Guillemin GJ (2009) Metallothionein treatment attenuates microglial activation and expression of neurotoxic quinolinic acid following traumatic brain injury. *Neurotox Res* **15**:381–389.
- Clark SM, Notarangelo FM, Li X, Chen S, Schwarcz R, and Tonelli LH (2019) Maternal immune activation in rats blunts brain cytokine and kynurenine pathway responses to a second immune challenge in early adulthood. *Prog Neuropsychopharmacol Biol Psychiatry* **89**:286–294.
- Clark SM, Pociavsek A, Nicholson JD, Notarangelo FM, Langenberg P, McMahon RP, Kleinman JE, Hyde TM, Stiller J, Postolache TT, et al. (2016) Reduced kynurenine pathway metabolism and cytokine expression in the prefrontal cortex of depressed individuals. *J Psychiatry Neurosci* **41**:386–394.
- Comai S, Bertazzo A, Brughera M, and Crotti S (2021) Tryptophan in health and disease. *Adv Clin Chem* **95**:165–218.
- Comai S, Costa CVL, Ragazzi E, Bertazzo A, and Allegri G (2005) The effect of age on the enzyme activities of tryptophan metabolism along the kynurenine pathway in rats. *Clin Chim Acta* **360**:67–80.
- Comai S, Melloni E, Lorenzi C, Bollettini I, Vai B, Zanardi R, Colombo C, Valtorta F, Benedetti F, and Poletti S (2022) Selective association of cytokine levels and kynurenine/tryptophan ratio with alterations in white matter microstructure in bipolar but not in unipolar depression. *Eur Neuropsychopharmacol* **55**:96–109.
- Copeland CS, Neale SA, and Salt TE (2013) Actions of Xanthurenic acid, a putative endogenous Group II metabotropic glutamate receptor agonist, on sensory transmission in the thalamus. *Neuropharmacology* **66**:133–142.
- Coppen A, Brooksbank BW, and Peet M (1972) Tryptophan concentration in the cerebrospinal fluid of depressive patients. *Lancet* **1**:1393.
- Crawford IP (1989) Evolution of a biosynthetic pathway: the tryptophan paradigm. *Annu Rev Microbiol* **43**:567–600.
- Cumming RB, Walton MF, Fuscoe JC, Taylor BA, Womack JE, and Gaertner FH (1979) Genetics of formamidase-5 (brain formamidase) in the mouse: localization of the structural gene on chromosome 14. *Biochem Genet* **17**:415–431.
- Currier AR, Ziegler MH, Riley MM, Babcock TA, Telbis VP, and Carlin JM (2000) Tumor necrosis factor-alpha and lipopolysaccharide enhance interferon-induced antichlamydial indoleamine dioxygenase activity independently. *J Interferon Cytokine Res* **20**:369–376.
- Curzon G, Kantamaneni BD, Van Boxel P, Gillman PK, Bartlett JR, and Bridges PK (1980) Substances related to 5-hydroxytryptamine in plasma and in lumbar and ventricular fluids of psychiatric patients. *Acta Psychiatr Scand Suppl* **280**:3–20.
- D'Amato NC, Rogers TJ, Gordon MA, Greene LI, Cochran DR, Spoelstra NS, Nemkov TG, D'Alessandro A, Hansen KC, and Richer JK (2015) A TDO2-AhR signaling axis facilitates anoikis resistance and metastasis in triple-negative breast cancer. *Cancer Res* **75**:4651–4664.
- Davidson M, Rashidi N, Hossain MK, Raza A, Nurgali K, and Apostolopoulos V (2023) Tryptophan and Substance Abuse: Mechanisms and Impact. *Int J Mol Sci* **24**:2737.
- de Carvalho LP, Bochet P, and Rossier J (1996) The endogenous agonist quinolinic acid and the non endogenous homoquinolinic acid discriminate between NMDAR2 receptor subunits. *Neurochem Int* **28**:445–452.
- Dey S, Banerjee Dixit A, Tripathi M, Doddamani RS, Sharma MC, Lalwani S, Chandra PS, and Banerjee J (2021) Altered hippocampal kynurenine pathway metabolism contributes to hyperexcitability in human mesial temporal lobe epilepsy-hippocampal sclerosis. *Br J Pharmacol* **178**:3959–3976.
- DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Vieira R, and Zarate Jr CA (2010) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* **71**:1605–1611.
- DiNatale BC, Murray IA, Schroeder JC, Flaveny CA, Lahoti TS, Laurenzana EM, Omiecinski CJ, and Perdev GH (2010) Kynurenine acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. *Toxicol Sci* **115**:89–97.
- Dobrovolsky VN, Bowyer JF, Pabarcus MK, Heflich RH, Williams LD, Doerge DR, Arvidsson B, Bergquist J, and Casida JE (2005) Effect of arylformamidase (kynurenine formamidase) gene inactivation in mice on enzymatic activity, kynurenine pathway metabolites and phenotype. *Biochim Biophys Acta* **1724**:163–172.
- Dolšák A, Gobec S, and Sova M (2021) Indoleamine and tryptophan 2,3-dioxygenases as important future therapeutic targets. *Pharmacol Ther* **221**:107746.
- Dominguez C and Munoz-Sanjuan I (2014) Foundation-directed therapeutic development in Huntington's disease. *J Med Chem* **57**:5479–5488.
- Dounay AB, Anderson M, Bechle BM, Campbell BM, Claffey MM, Evdokimov A, Ervard E, Fonseca KR, Gan X, Ghosh S, et al. (2012) Discovery of Brain-Penetrant, Irreversible Kynurenine Aminotransferase II Inhibitors for Schizophrenia. *ACS Med Chem Lett* **3**:187–192.
- Drewes JL, Meulendyke KA, Liao Z, Witwer KW, Gama L, Ubaida-Mohien C, Li M, Notarangelo FM, Tarwater PM, Schwarcz R, et al. (2015) Quinolinic acid/



- tryptophan ratios predict neurological disease in SIV-infected macaques and remain elevated in the brain under cART. *J Neurovirol* **21**:449–463.
- Du F, Williamson J, Bertram E, Lothman E, Okuno E, and Schwarcz R (1993) Kynurenine pathway enzymes in a rat model of chronic epilepsy: immunohistochemical study of activated glial cells. *Neuroscience* **55**:975–989.
- Erhardt S, Blennow K, Nordin C, Skogh E, Lindström LH, and Engberg G (2001a) Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia. *Neurosci Lett* **313**:96–98.
- Erhardt S and Engberg G (2002) Increased phasic activity of dopaminergic neurones in the rat ventral tegmental area following pharmacologically elevated levels of endogenous kynurenic acid. *Acta Physiol Scand* **175**:45–53.
- Erhardt S, Gravenfors Y, and Schwieler L (2023) Identification of Kat III as a Novel Pharmacological Target for the Treatment of Cognitive Impairment. *Neuropsychopharmacology* **48**:355–495.
- Erhardt S, Lim CK, Linderholm KR, Janelidze S, Lindqvist D, Samuelsson M, Lundberg K, Postolache TT, Träskman-Bendz L, Guillemin GJ, et al. (2013) Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology* **38**:743–752.
- Erhardt S, Oberg H, Mathé JM, and Engberg G (2001b) Pharmacological elevation of endogenous kynurenic acid levels activates nigral dopamine neurons. *Amino Acids* **20**:353–362.
- Erhardt S, Olsson SK, and Engberg G (2009) Pharmacological manipulation of kynurenic acid: potential in the treatment of psychiatric disorders. *CNS Drugs* **23**:91–101.
- Erhardt S, Pocivavsek A, Repici M, Liu X-C, Imbeault S, Maddison DC, Thomas MAR, Smalley JL, Larsson MK, Muchowski PJ, et al. (2017a) Adaptive and Behavioral Changes in Kynurenine 3-Monooxygenase Knockout Mice: Relevance to Psychotic Disorders. *Biol Psychiatry* **82**:756–765.
- Erhardt S, Schwieler L, Emanuelsson C, and Geyer M (2004) Endogenous kynurenic acid disrupts prepulse inhibition. *Biol Psychiatry* **56**:255–260.
- Erhardt S, Schwieler L, Imbeault S, and Engberg G (2017b) The kynurenine pathway in schizophrenia and bipolar disorder. *Neuropharmacology* **112**:297–306.
- Fazio F, Lionetto L, Curto M, Iacovelli L, Copeland CS, Neale SA, Bruno V, Battaglia G, Salt TE, and Nicoletti F (2017) Cinnabarinic acid and xanthurenic acid: Two kynurenine metabolites that interact with metabotropic glutamate receptors. *Neuropharmacology* **112**:365–372.
- Fazio F, Lionetto L, Molinaro G, Bertrand HO, Acher F, Ngomba RT, Notartomaso S, Curini M, Rosati O, Scarselli P, et al. (2012) Cinnabarinic acid, an endogenous metabolite of the kynurenine pathway, activates type 4 metabotropic glutamate receptors. *Mol Pharmacol* **81**:643–656.
- Feldblum S, Rougier A, Loiseau H, Loiseau P, Cohadon F, Morselli PL, and Lloyd KG (1988) Quinolinic-phosphoribosyl transferase activity is decreased in epileptic human brain tissue. *Epilepsia* **29**:523–529.
- Fernandez-Pol JA, Klos DJ, and Hamilton PD (1993) Cytotoxic activity of fusaric acid on human adenocarcinoma cells in tissue culture. *Anticancer Res* **13**:57–64.
- Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, and Weickert CS (2013) Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry* **18**:206–214.
- Forrest CM, Khalil OS, Pizar M, Darlington LG, and Stone TW (2013a) Prenatal inhibition of the tryptophan-kynurenine pathway alters synaptic plasticity and protein expression in the rat hippocampus. *Brain Res* **1504**:1–15.
- Forrest CM, Khalil OS, Pizar M, McNair K, Kornisiuk E, Snitcosky M, Gonzalez N, Jerusalinsky D, Darlington LG, and Stone TW (2013b) Changes in synaptic transmission and protein expression in the brains of adult offspring after prenatal inhibition of the kynurenine pathway. *Neuroscience* **254**:241–259.
- Forrest CM, Mackay GM, Stoy N, Spiden SL, Taylor R, Stone TW, and Darlington LG (2010) Blood levels of kynurenines, interleukin-23 and soluble human leucocyte antigen-G at different stages of Huntington's disease. *J Neurochem* **112**:112–122.
- Foster AC, Miller LP, Oldendorf WH, and Schwarcz R (1984a) Studies on the disposition of quinolinic acid after intracerebral or systemic administration in the rat. *Exp Neurol* **84**:428–440.
- Foster AC, Vezzani A, French ED, and Schwarcz R (1984b) Kynurenic acid blocks neurotoxicity and seizures induced in rats by the related brain metabolite quinolinic acid. *Neurosci Lett* **48**:273–278.
- Foster AC, Whetsell WO, Bird ED, and Schwarcz R (1985) Quinolinic acid phosphoribosyltransferase in human and rat brain: activity in Huntington's disease and in quinolinic-acid lesioned rat striatum. *Brain Res* **336**:207–214.
- Fuertig R, Ceci A, Camus SM, Bezdard E, Luippold AH, and Hengerer B (2016) LC-MS/MS-based quantification of kynurenine metabolites, tryptophan, monoamines and neopterin in plasma, cerebrospinal fluid and brain. *Bioanalysis* **8**:1903–1917.
- Fukui S, Schwarcz R, Rapoport SI, Takada Y, and Smith QR (1991) Blood-brain barrier transport of kynurenines: implications for brain synthesis and metabolism. *J Neurochem* **56**:2007–2017.
- Fukunaga M, Yamamoto Y, Kawaso M, Arioka Y, Murakami Y, Hoshi M, and Saito K (2012) Studies on tissue and cellular distribution of indoleamine 2,3-dioxygenase 2: the absence of IDO1 upregulates IDO2 expression in the epididymis. *J Histochem Cytochem* **60**:854–860.
- Gál EM and Sherman AD (1978) Synthesis and metabolism of L-kynurenine in rat brain. *J Neurochem* **30**:607–613.
- Gál EM, Young RB, and Sherman AD (1978) Tryptophan loading: consequent effects on the synthesis of kynurenine and 5-hydroxyindoles in rat brain. *J Neurochem* **31**:237–244.
- Gao J, Yao L, Xia T, Liao X, Zhu D, and Xiang Y (2018) Biochemistry and structural studies of kynurenine 3-monooxygenase reveal allosteric inhibition by Ro 61-8048. *FASEB J* **32**:2036–2045.
- García-Lara L, Pérez-Severiano F, González-Esquivel D, Elizondo G, and Segovia J (2015) Absence of aryl hydrocarbon receptors increases endogenous kynurenic acid levels and protects mouse brain against excitotoxic insult and oxidative stress. *J Neurosci Res* **93**:1423–1433.
- Garrison AM, Parrott JM, Tuñón A, Delgado J, Redus L, and O'Connor JC (2018) Kynurenine pathway metabolic balance influences microglia activity: Targeting kynurenine monooxygenase to dampen neuroinflammation. *Psychoneuroendocrinology* **94**:1–10.
- Gheorghe CE, Martin JA, Manriquez FV, Dinan TG, Cryan JF, and Clarke G (2019) Focus on the essentials: tryptophan metabolism and the microbiome-gut-brain axis. *Curr Opin Pharmacol* **48**:137–145.
- Giorgini F, Huang S-Y, Sathyaikumar KV, Notarangelo FM, Thomas MAR, Tararina M, Wu H-Q, Schwarcz R, and Muchowski PJ (2013) Targeted deletion of kynurenine 3-monooxygenase in mice: a new tool for studying kynurenine pathway metabolism in periphery and brain. *J Biol Chem* **288**:36554–36566.
- Giorgini F, Möller T, Kwan W, Zwilling D, Wacker JL, Hong S, Tsai L-CL, Cheah CS, Schwarcz R, Guidetti P, et al. (2008) Histone deacetylase inhibition modulates kynurenine pathway activation in yeast, microglia, and mice expressing a mutant huntingtin fragment. *J Biol Chem* **283**:7390–7400.
- Gobaille S, Kemmel V, Brumar D, Dugave C, Aunis D, and Maitre M (2008) Xanthurenic acid distribution, transport, accumulation and release in the rat brain. *J Neurochem* **105**:982–993.
- Goldstein LE, Leopold MC, Huang X, Atwood CS, Saunders AJ, Hartshorn M, Lim JT, Faget KY, Muffat JA, Scarpa RC, et al. (2000) 3-Hydroxykynurenine and 3-hydroxyanthranilic acid generate hydrogen peroxide and promote alpha-crystallin cross-linking by metal ion reduction. *Biochemistry* **39**:7266–7275.
- Gramsbergen JB, Hodgkins PS, Rassoulpour A, Turski WA, Guidetti P, and Schwarcz R (1997) Brain-specific modulation of kynurenic acid synthesis in the rat. *J Neurochem* **69**:290–298.
- Gramsbergen JB, Schmidt W, Turski WA, and Schwarcz R (1992) Age-related changes in kynurenic acid production in rat brain. *Brain Res* **588**:1–5.
- Grégoire L, Rassoulpour A, Guidetti P, Samadi P, Bédard PJ, Izzo E, Schwarcz R, and Di Paolo T (2008) Prolonged kynurenine 3-hydroxylase inhibition reduces development of levodopa-induced dyskinesias in parkinsonian monkeys. *Behav Brain Res* **186**:161–167.
- Guidetti P, Amori L, Sapko MT, Okuno E, and Schwarcz R (2007a) Mitochondrial aspartate aminotransferase: a third kynurenate-producing enzyme in the mammalian brain. *J Neurochem* **102**:103–111.
- Guidetti P, Bates GP, Graham RK, Hayden MR, Leavitt BR, MacDonald ME, Slow EJ, Wheeler VC, Woodman B, and Schwarcz R (2006) Elevated brain 3-hydroxykynurenine and quinolinic levels in Huntington disease mice. *Neurobiol Dis* **23**:190–197.
- Guidetti P, Eastman CL, and Schwarcz R (1995) Metabolism of [5-3H]kynurenine in the rat brain in vivo: evidence for the existence of a functional kynurenine pathway. *J Neurochem* **65**:2621–2632.
- Guidetti P, Hoffman GE, Melendez-Ferro M, Albuquerque EX, and Schwarcz R (2007b) Astrocytic localization of kynurenine aminotransferase II in the rat brain visualized by immunocytochemistry. *Glia* **55**:78–92.
- Guidetti P, Luthi-Carter RE, Augood SJ, and Schwarcz R (2004) Neostriatal and cortical quinolinic levels are increased in early grade Huntington's disease. *Neurobiol Dis* **17**:455–461.
- Guidetti P, Okuno E, and Schwarcz R (1997) Characterization of rat brain kynurenine aminotransferases I and II. *J Neurosci Res* **50**:457–465.
- Guidetti P and Schwarcz R (2003) Determination of alpha-amino adipic acid in brain, peripheral tissues, and body fluids using GC/MS with negative chemical ionization. *Brain Res Mol Brain Res* **118**:132–139.
- Guillemin GJ (2012) Quinolinic acid, the inescapable neurotoxin. *FEBS J* **279**:1356–1365.
- Guillemin GJ, Brew BJ, Noonan CE, Takikawa O, and Cullen KM (2005a) Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. *Neuropathol Appl Neurobiol* **31**:395–404.
- Guillemin GJ, Kerr SJ, Smythe GA, Armati PJ, and Brew BJ (1999) Kynurenine pathway metabolism in human astrocytes. *Adv Exp Med Biol* **467**:125–131.
- Guillemin GJ, Kerr SJ, Smythe GA, Smith DG, Kapoor V, Armati PJ, Croitoru J, and Brew BJ (2001) Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. *J Neurochem* **78**:842–853.
- Guillemin GJ, Smith DG, Smythe GA, Armati PJ, and Brew BJ (2003a) Expression of the kynurenine pathway enzymes in human microglia and macrophages. *Adv Exp Med Biol* **527**:105–112.
- Guillemin GJ, Smythe G, Takikawa O, and Brew BJ (2005b) Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia* **49**:15–23.
- Guillemin GJ, Smythe GA, Veas LA, Takikawa O, and Brew BJ (2003b) A beta 1-42 induces production of quinolinic acid by human macrophages and microglia. *Neuroreport* **14**:2311–2315.
- Gulaj E, Pawlak K, Bien B, and Pawlak D (2010) Kynurenine and its metabolites in Alzheimer's disease patients. *Adv Med Sci* **55**:204–211.
- Guo L, Appelbaum B, Mooij-Kalverda K, Houtkooper RH, van Weeghel M, Vaz FM, Dijkhuis A, Dekker T, Smids BS, Duitman JW, et al.; Amsterdam UMC COVID-19 Biobank study Group (2023) Prolonged indoleamine 2,3-dioxygenase-2 activity and associated cellular stress in post-acute sequelae of SARS-CoV-2 infection. *EBioMedicine* **94**:104729.
- Han Q, Cai T, Tagle DA, Robinson H, and Li J (2008) Substrate specificity and structure of human amino acid aminotransferase/kynurenine aminotransferase II. *BioSci Rep* **28**:205–215.
- Han Q, Robinson H, and Li J (2012) Biochemical identification and crystal structure of kynurenine formamidase from *Drosophila melanogaster*. *Biochem J* **446**:253–260.
- Hanin A, Chollet C, Demeret S, Di Meglio L, Castelli F, and Navarro V (2024) Metabolic changes in adults with status epilepticus: A human case-control study. *Epilepsia* **65**:929–943.
- Hansen AM, Driussi C, Turner V, Takikawa O, and Hunt NH (2000) Tissue distribution of indoleamine 2,3-dioxygenase in normal and malaria-infected tissue. *Redox Rep* **5**:112–115.

- Hare SM, Adhikari BM, Mo C, Chen S, Wijtenburg SA, Seneviratne C, Kane-Gerard S, Sathyaikumar KV, Notarangelo FM, Schwarcz R, et al. (2023) Tryptophan challenge in individuals with schizophrenia and healthy controls: acute effects on circulating kynurenine and kynurenine acid, cognition and cerebral blood flow. *Neuropsychopharmacology* **48**:1594–1601.
- Harper MM, Woll AW, Evans LP, Delcau M, Akurathi A, Hedberg-Buenz A, Soukup DA, Boehme N, Hefti MM, Dutca LM, et al. (2019) Blast Preconditioning Protects Retinal Ganglion Cells and Reveals Targets for Prevention of Neurodegeneration Following Blast-Mediated Traumatic Brain Injury. *Invest Ophthalmol Vis Sci* **60**:4159–4170.
- Havelund JF, Heegaard NHH, Færgeman NJK, and Gramsbergen JB (2017) Biomarker Research in Parkinson's Disease Using Metabolite Profiling. *Metabolites* **7**:42.
- Herrera-Rios D, Mughal SS, Teuber-Hanselmann S, Pierscianek D, Sucker A, Jansen P, Schimming T, Klode J, Reifensberger J, Felsberg J, et al. (2020) Macrophages/Microglia Represent the Major Source of Indolamine 2,3-Dioxygenase Expression in Melanoma Metastases of the Brain. *Front Immunol* **11**:120.
- Heyes MP, Jordan EK, Lee K, Saito K, Frank JA, Snoy PJ, Markey SP, and Gravell M (1992a) Relationship of neurologic status in macaques infected with the simian immunodeficiency virus to cerebrospinal fluid quinolinic acid and kynurenine acid. *Brain Res* **570**:237–250.
- Heyes MP, Saito K, Chen CY, Proescholdt MG, Nowak TS, Li J, Beagles KE, Proescholdt MA, Zito MA, Kawai K, et al. (1997) Species heterogeneity between gerbils and rats: quinolinic acid production by microglia and astrocytes and accumulations in response to ischemic brain injury and systemic immune activation. *J Neurochem* **69**:1519–1529.
- Heyes MP, Saito K, Crowley JS, Davis LE, Demitrack MA, Der M, Dilling LA, Elia J, Kruesi MJ, Lackner A, et al. (1992b) Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. *Brain* **115**:249–1273.
- Heyes MP, Saito K, Devinsky O, and Nadi NS (1994) Kynurenine pathway metabolites in cerebrospinal fluid and serum in complex partial seizures. *Epilepsia* **35**:251–257.
- Heyes MP, Saito K, Lackner A, Wiley CA, Achim CL, and Markey SP (1998) Sources of the neurotoxin quinolinic acid in the brain of HIV-1-infected patients and retrovirus-infected macaques. *FASEB J* **12**:881–896.
- Hilmas C, Pereira EF, Alkondon M, Rassoulpour A, Schwarcz R, and Albuquerque EX (2001) The brain metabolite kynurenine acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. *J Neurosci* **21**:7463–7473.
- Hodgkins PS and Schwarcz R (1998) Interference with cellular energy metabolism reduces kynurenine acid formation in rat brain slices: reversal by lactate and pyruvate. *Eur J Neurosci* **10**:1986–1994.
- Holmberg D, Franzén-Röhl E, Idro R, Opoka RO, Bangirana P, Sellgren CM, Wickström R, Färnert A, Schwieler L, Engberg G, et al. (2017) Cerebrospinal fluid kynurenine and kynurenine acid concentrations are associated with coma duration and long-term neurocognitive impairment in Ugandan children with cerebral malaria. *Malar J* **16**:303.
- Holtze M, Saetre P, Engberg G, Schwieler L, Werge T, Andreassen OA, Hall H, Terenius L, Agartz I, Jönsson EG, et al. (2012) Kynurenine 3-monooxygenase polymorphisms: relevance for kynurenine acid synthesis in patients with schizophrenia and healthy controls. *J Psychiatry Neurosci* **37**:53–57.
- Hone AJ and McIntosh JM (2023) Nicotinic acetylcholine receptors: Therapeutic targets for novel ligands to treat pain and inflammation. *Pharmacol Res* **190**:106715.
- Hopkins FG and Cole SW (1901) A contribution to the chemistry of proteids: Part I. A preliminary study of a hitherto undescribed product of tryptic digestion. *J Physiol* **27**:418–428.
- Hunt NH, Too LK, Khaw LT, Guo J, Hee L, Mitchell AJ, Grau GE, and Ball HJ (2017) The kynurenine pathway and parasitic infections that affect CNS function. *Neuropharmacology* **112**:389–398.
- Hutchinson JP, Rowland P, Taylor MRD, Christodoulou EM, Haslam C, Hobbs CI, Holmes DS, Homes P, Liddle J, Mole DJ, et al. (2017) Structural and mechanistic basis of differentiated inhibitors of the acute pancreatitis target kynurenine-3-monooxygenase. *Nat Commun* **8**:15827.
- Imbeault S, Goiny M, Liu X, and Erhardt S (2020) Effects of IDO1 and TDO2 inhibition on cognitive deficits and anxiety following LPS-induced neuroinflammation. *Acta Neuropsychiatr* **32**:43–53.
- Imbeault S, Gubert Olivé M, Jungholm O, Erhardt S, Wigström H, Engberg G, and Jardebrand K (2021) Blockade of KAT II Facilitates LTP in Kynurenine 3-Monooxygenase Depleted Mice. *Int J Tryptophan Res* **14**:11786469211041368.
- Inam ME, Fernandes BS, Salagre E, Grande I, Vieta E, Quevedo J, and Zhao Z (2023) The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a systematic review and meta-analysis of cerebrospinal fluid studies. *Braz J Psychiatry* **45**:343–355.
- Iwahashi H, Ishii T, Sugata R, and Kido R (1988) Superoxide dismutase enhances the formation of hydroxyl radicals in the reaction of 3-hydroxyanthranilic acid with molecular oxygen. *Biochem J* **251**:893–899.
- Jacobs KR, Lim CK, Blennow K, Zetterberg H, Chatterjee P, Martins RN, Brew BJ, Guillemin GJ, and Lovejoy DB (2019) Correlation between plasma and CSF concentrations of kynurenine pathway metabolites in Alzheimer's disease and relationship to amyloid-beta and tau. *Neurobiol Aging* **80**:11–20.
- Jauch D, Urbanska EM, Guidetti P, Bird ED, Vonsattel JP, Whetsell WO, and Schwarcz R (1995) Dysfunction of brain kynurenine acid metabolism in Huntington's disease: focus on kynurenine aminotransferases. *J Neurol Sci* **130**:39–47.
- Jhamandas KH, Boegman RJ, Beninger RJ, and Flesher S (1998) Role of zinc in blockade of excitotoxic action of quinolinic acid by picolinic acid. *Amino Acids* **14**:257–261.
- Johansson A-S, Owe-Larsson B, Asp L, Kocki T, Adler M, Hetta J, Gardner R, Lundkvist GBS, Urbanska EM, and Karlsson H (2013) Activation of kynurenine pathway in ex vivo fibroblasts from patients with bipolar disorder or schizophrenia: cytokine challenge increases production of 3-hydroxykynurenine. *J Psychiatr Res* **47**:1815–1823.
- Jusof FF, Bakmiwewa SM, Weiser S, Too LK, Metz R, Prendergast GC, Fraser ST, Hunt NH, and Ball HJ (2017) Investigation of the Tissue Distribution and Physiological Roles of Indoleamine 2,3-Dioxygenase-2. *Int J Tryptophan Res* **10**:1178646917735098.
- Justinova Z, Mascia P, Wu H-Q, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, et al. (2013) Reducing cannabinoid abuse and preventing relapse by enhancing endogenous brain levels of kynurenine acid. *Nat Neurosci* **16**:1652–1661.
- Kaddurah-Daouk R, Yuan P, Boyle SH, Matson W, Wang Z, Zeng ZB, Zhu H, Dougherty GG, Yao JK, Chen G, et al. (2012) Cerebrospinal fluid metabolome in mood disorders—remission state has a unique metabolic profile. *Sci Rep* **2**:667.
- Kaiharu M, Price JM, and Takahashi H (1956) The conversion of kynurenine acid to quinolonic acid by humans and rats. *J Biol Chem* **223**:705–708.
- Keaton SA, Heilman P, Bryleva EY, Madaj Z, Krzyzanowski S, Grit J, Miller ES, Jälmy M, Kalapotharakos G, Racicot K, et al. (2019) Altered Tryptophan Catabolism in Placentas From Women With Pre-eclampsia. *Int J Tryptophan Res* **12**:1178646919840321.
- Kegel ME, Bhat M, Skogh E, Samuelsson M, Lundberg K, Dahl M-L, Sellgren C, Schwieler L, Engberg G, Schuppe-Koistinen I, et al. (2014) Imbalanced kynurenine pathway in schizophrenia. *Int J Tryptophan Res* **7**:15–22.
- Kegel ME, Johansson V, Wetterberg L, Bhat M, Schwieler L, Cannon TD, Schuppe-Koistinen I, Engberg G, Landén M, Hultman CM, et al. (2017) Kynurenine acid and psychotic symptoms and personality traits in twins with psychiatric morbidity. *Psychiatry Res* **247**:105–112.
- Kepplinger B, Baran H, Kainz A, Ferraz-Leite H, Newcombe J, and Kalina P (2005) Age-related increase of kynurenine acid in human cerebrospinal fluid - IgG and beta2-microglobulin changes. *Neurosignals* **14**:126–135.
- Kessler M, Terramani T, Lynch G, and Baudry M (1989) A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists. *J Neurochem* **52**:1319–1328.
- Kiank C, Zeden J-P, Drude S, Domanska G, Fusch G, Otten W, and Schuett C (2010) Psychological stress-induced, IDO1-dependent tryptophan catabolism: implications on immunosuppression in mice and humans. *PLoS One* **5**:e11825.
- Kindler J, Lim CK, Weickert CS, Boerrigter D, Galletly C, Liu D, Jacobs KR, Balzan R, Bruggemann J, O'Donnell M, et al. (2020) Dysregulation of kynurenine metabolism is related to proinflammatory cytokines, attention, and prefrontal cortex volume in schizophrenia. *Mol Psychiatry* **25**:2860–2872.
- Kiss C, Ceresoli-Borroni G, Guidetti P, Zielke CL, Zielke HR, and Schwarcz R (2003) Kynurenate production by cultured human astrocytes. *J Neural Transm (Vienna)* **110**:1–14.
- Klausing AD, Fukuwatari T, Bucci DJ, and Schwarcz R (2020) Stress-induced impairment in fear discrimination is causally related to increased kynurenine acid formation in the prefrontal cortex. *Psychopharmacology (Berl)* **237**:1931–1941.
- Klausing AD, Fukuwatari T, DeAngeli N, Bucci DJ, and Schwarcz R (2024) Adrenalectomy exacerbates stress-induced impairment in fear discrimination: A causal role for kynurenine acid? *Biochem Pharmacol* **116**:350.
- Knox WE (1966) The regulation of tryptophan pyrrolase activity by tryptophan. *Adv Enzyme Regul* **4**:287–297.
- Köhler C, Eriksson LG, Okuno E, and Schwarcz R (1988) Localization of quinolinic acid metabolizing enzymes in the rat brain. Immunohistochemical studies using antibodies to 3-hydroxyanthranilic acid oxygenase and quinolinic acid phosphoribosyltransferase. *Neuroscience* **27**:49–76.
- Köhler C, Okuno E, Flood PR, and Schwarcz R (1987) Quinolinic acid phosphoribosyltransferase: preferential glial localization in the rat brain visualized by immunocytochemistry. *Proc Natl Acad Sci U S A* **84**:3491–3495.
- Komuro H and Rakic P (1993) Modulation of neuronal migration by NMDA receptors. *Science* **260**:95–97.
- Konradsson-Geuken A, Wu HQ, Gash CR, Alexander KS, Campbell A, Sozeri Y, Pellicciari R, Schwarcz R, and Bruno JP (2010) Cortical kynurenine acid bidirectionally modulates prefrontal glutamate levels as assessed by microdialysis and rapid electrochemistry. *Neuroscience* **169**:1848–1859.
- Kotake Y and Ito N (1937) The intermediate metabolism of tryptophan: XXV. Isolation of d-kynurenine. *J Biochem (Japan)* **25**:71–77.
- Kozak R, Campbell BM, Strick CA, Horner W, Hoffmann WE, Kiss T, Chapin DS, McGinnis D, Abbott AL, Roberts BM, et al. (2014) Reduction of brain kynurenine acid improves cognitive function. *J Neurosci* **34**:10592–10602.
- Kubicova L, Hadacek F, Bachmann G, Weckwerth W, and Chobot V (2019) Coordination Complex Formation and Redox Properties of Kynurenine and Xanthurenic Acid Can Affect Brain Tissue Homeodynamics. *Antioxidants (Basel)* **8**:476.
- Kubota H, Kunisawa K, Nijima M, Hirakawa M, Mori Y, Hasegawa M, Fujigaki S, Fujigaki H, Yamamoto Y, Saito K, et al. (2022) Deficiency of kynurenine 3-monooxygenase exacerbates impairment of prepulse inhibition induced by phencyclidine. *Biochem Biophys Res Commun* **629**:142–151.
- Kwidzinski E, Bunse J, Aktas O, Richter D, Mutlu L, Zipp F, Nitsch R, and Bechmann I (2005) Indolamine 2,3-dioxygenase is expressed in the CNS and down-regulates autoimmune inflammation. *FASEB J* **19**:1347–1349.
- Ladomersky E, Zhai L, Lauing KL, Bell A, Xu J, Kocherginsky M, Zhang B, Wu JD, Podojil JR, Platanias LC, et al. (2020) Advanced Age Increases Immunosuppression in the Brain and Decreases Immunotherapeutic Efficacy in Subjects with Glioblastoma. *Clin Cancer Res* **26**:5232–5245.
- Lapin IP (1978) Stimulant and convulsive effects of kynurenines injected into brain ventricles in mice. *J Neural Transm* **42**:37–43.

- Lapin IP, Oxenkrug GF, and Azbekyan SG (1972) Involvement of brain serotonin in the stimulant action of amphetamine and of cholinolytics. *Arch Int Pharmacodyn Ther* **197**:350–361.
- Larkin PB, Sathyasaikum KV, Notarangelo FM, Funakoshi H, Nakamura T, Schwarcz R, and Muchowski PJ (2016) Tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase 1 make separate, tissue-specific contributions to basal and inflammation-induced kynurenine pathway metabolism in mice. *Biochim Biophys Acta* **1860**:2345–2354.
- Larsson MK, Faka A, Imbeault S, Gojny M, Orhan F, Oliveros A, Ståhl S, Liu XC, Choi DS, et al. (2016) Repeated LPS Injection Induces Distinct Changes in the Kynurenine Pathway in Mice. *Neurochem Res* **41**:2243–2255.
- Lavebratt C, Olsson S, Backlund L, Frisén L, Sellgren C, Priebe L, Nikamo P, Träskman-Bendz L, Cichon S, Vawter MP, et al. (2014) The KMO allele encoding Arg452 is associated with psychotic features in bipolar disorder type I, and with increased CSF KYNA level and reduced KMO expression. *Mol Psychiatry* **19**:334–341.
- Lee A, Kanuri N, Zhang Y, Sayuk GS, Li E, and Ciorba MA (2014) IDO1 and IDO2 non-synonymous gene variants: correlation with crohn's disease risk and clinical phenotype. *PLoS One* **9**:e115848.
- Lehrmann E, Molinari A, Speciale C, and Schwarcz R (2001) Immunohistochemical visualization of newly formed quinolate in the normal and excitotoxically lesioned rat striatum. *Exp Brain Res* **141**:389–397.
- Lewis-Ballester A, Pham KN, Batabyal D, Karkashon S, Bonanno JB, Poulos TL, and Yeh S-R (2017) Structural insights into substrate and inhibitor binding sites in human indoleamine 2,3-dioxygenase 1. *Nat Commun* **8**:1693.
- Li P, Xu W, Liu F, Zhu H, Zhang L, Ding Z, Liang H, and Song J (2021) The emerging roles of IDO2 in cancer and its potential as a therapeutic target. *Biomed Pharmacother* **137**:11295.
- Linderholm KR, Alm MT, Larsson MK, Olsson SK, Gojny M, Hajos M, Erhardt S, and Engberg G (2016) Inhibition of kynurenine aminotransferase II reduces activity of midbrain dopamine neurons. *Neuropharmacology* **102**:42–47.
- Linderholm KR, Andersson A, Olsson S, Olsson E, Snodgrass R, Engberg G, and Erhardt S (2007) Activation of rat ventral tegmental area dopamine neurons by endogenous kynurenic acid: a pharmacological analysis. *Neuropharmacology* **53**:918–924.
- Linderholm K, Powell S, Olsson E, Holtze M, Snodgrass R, and Erhardt S (2010) Role of the NMDA-receptor in Prepulse Inhibition in the Rat. *Int J Tryptophan Res* **3**:1–12.
- Linderholm KR, Skogh E, Olsson SK, Dahl M-L, Holtze M, Engberg G, Samuelsson M, and Erhardt S (2012) Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. *Schizophr Bull* **38**:426–432.
- Liochev SI and Fridovich I (2001) The oxidation of 3-hydroxyanthranilic acid by Cu,Zn superoxide dismutase: mechanism and possible consequences. *Arch Biochem Biophys* **388**:281–284.
- Liu X-C, Holtze M, Powell SB, Terrando N, Larsson MK, Persson A, Olsson SK, Orhan F, Kegel M, Asp L, et al. (2014) Behavioral disturbances in adult mice following neonatal virus infection or kynurenine treatment—role of brain kynurenic acid. *Brain Behav Immun* **36**:80–89.
- Liu Y-N, Peng Y-L, Liu L, Wu T-Y, Zhang Y, Lian Y-J, Yang Y-Y, Kelley KW, Jiang C-L, and Wang Y-X (2015) TNF $\alpha$  mediates stress-induced depression by upregulating indoleamine 2,3-dioxygenase in a mouse model of unpredictable chronic mild stress. *Eur Cytokine Netw* **26**:15–25.
- Lopes C, Pereira EFR, Wu H-Q, Purushottamachar P, Njar V, Schwarcz R, and Albuquerque EX (2007) Competitive antagonism between the nicotinic allosteric potentiating ligand galantamine and kynurenic acid at  $\alpha 7^*$  nicotinic receptors. *J Pharmacol Exp Ther* **322**:48–58.
- Louvrou V, Solianik R, Brazaitis N, and Erhardt S (2024) Exploring the effect of prolonged fasting on kynurenine pathway metabolites and stress markers in healthy male individuals. *Eur J Clin Nutr* **78**:677–683.
- Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, Murphy GM, Brachova L, Yan SD, Walker DG, Shen Y, et al. (2001) Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. *Glia* **35**:72–79.
- Lugo-Huitrón R, Blanco-Ayala T, Ugalde-Muniz P, Carrillo-Mora P, Pedraza-Chaverrí J, Silva-Adaya D, Maldonado PD, Torres I, Pinzón E, Ortiz-Islas E, et al. (2011) On the antioxidant properties of kynurenic acid: free radical scavenging activity and inhibition of oxidative stress. *Neurotoxicol Teratol* **33**:538–547.
- Maitre M, Taleb O, Jeltsch-David H, Klein C, and Mensah-Nyagan A-G (2024) Xanthurenic acid: A role in brain intercellular signaling. *J Neurochem*
- Mancuso R, HERNIS A, Agostini S, Rovaris M, Caputo D, Fuchs D, and Clerici M (2015) Indoleamine 2,3 Dioxygenase (IDO) Expression and Activity in Relapsing-Remitting Multiple Sclerosis. *PLoS One* **10**:e0130715.
- Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trotter Y, Lehrach H, Davies SW, et al. (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* **87**:493–506.
- Marim FM, Teixeira DC, Queiroz-Junior CM, Valiate BVS, Alves-Filho JC, Cunha TM, Dantzer R, Teixeira MM, Teixeira AL, and Costa VV (2021) Inhibition of Tryptophan Catabolism Is Associated With Neuroprotection During Zika Virus Infection. *Front Immunol* **12**:702048.
- Marx W, McGuinness AJ, Rocks T, Ruusunen A, Cleminson J, Walker AJ, Gomedda-Costa S, Lane M, Sanches M, Diaz AP, et al. (2021) The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a meta-analysis of 101 studies. *Mol Psychiatry* **26**:4158–4178.
- Mason M and Berg CP (1952) The metabolism of d- and l-tryptophan and d- and l-kynurenine by liver and kidney preparations. *J Biol Chem* **195**:515–524.
- Mazarei G, Neal SJ, Becanovic K, Luthi-Carter R, Simpson EM, and Leavitt BR (2010) Expression analysis of novel striatal-enriched genes in Huntington disease. *Hum Mol Genet* **19**:609–622.
- McCarthy MJ, Barrett TB, Nissen S, Kelseo JR, and Turner EE (2010) Allele specific analysis of the ADRBK2 gene in lymphoblastoid cells from bipolar disorder patients. *J Psychiatr Res* **44**:201–208.
- Medana IM, Day NPJ, Salahifar-Sabet H, Stocker R, Smythe G, Bwanaisa L, Njobvu A, Kayira K, Turner GDH, Taylor TE, et al. (2003) Metabolites of the kynurenine pathway of tryptophan metabolism in the cerebrospinal fluid of Malawian children with malaria. *J Infect Dis* **188**:844–849.
- Medana IM, Hien TT, Day NP, Phu NH, Mai NTH, Chu'ong LV, Chau TTH, Taylor A, Salahifar H, Stocker R, et al. (2002) The clinical significance of cerebrospinal fluid levels of kynurenine pathway metabolites and lactate in severe malaria. *J Infect Dis* **185**:650–656.
- Meier TB and Savitz J (2022) The Kynurenine Pathway in Traumatic Brain Injury: Implications for Psychiatric Outcomes. *Biol Psychiatry* **91**:449–458.
- Merlo LMF and Mandik-Nayak L (2016) IDO2: A Pathogenic Mediator of Inflammatory Autoimmunity. *Clin Med Insights Pathol* **9**:21–28.
- Merlo LMF, Peng W, and Mandik-Nayak L (2022) Impact of IDO1 and IDO2 on the B Cell Immune Response. *Front Immunol* **13**:886225.
- Metz R, Duhadaway JB, Kamasani U, Laury-Kleintop L, Muller AJ, and Prendergast GC (2007) Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan. *Cancer Res* **67**:7082–7087.
- Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, and Bradford CA (2010) An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol* **185**:3190–3198.
- Miller CL, Llenos IC, Dulay JR, Barillo MM, Yolken RH, and Weis S (2004) Expression of the kynurenine pathway enzyme tryptophan 2,3-dioxygenase is increased in the frontal cortex of individuals with schizophrenia. *Neurobiol Dis* **15**:618–629.
- Miller CL, Llenos IC, Dulay JR, and Weis S (2006) Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder. *Brain Res* **1073–1074**:25–37.
- Millischer V, Heinzl M, Faka A, Resl M, Trepci A, Klammer C, Egger M, Dieplinger B, Clodi M, and Schwieler L (2021) Intravenous administration of LPS activates the kynurenine pathway in healthy male human subjects: a prospective placebo-controlled cross-over trial. *J Neuroinflammation* **18**:158.
- Milosavljevic S, Smith AK, Wright CJ, Valafar H, and Pocivavsek A (2023) Kynurenine aminotransferase II inhibition promotes sleep and rescues impairments induced by neurodevelopmental insult. *Transl Psychiatry* **13**:106.
- Milusheva M, Todorova M, Gledacheva V, Stefanova I, Feizi-Dehnyabi M, Pencheva M, Nedialkov P, Tumbarski Y, Yanakieva V, Tsonova S, et al. (2023) Novel Anthranilic Acid Hybrids-An Alternative Weapon against Inflammatory Diseases. *Pharmaceuticals (Basel)* **16**:1660.
- Minhas PS, Jones JR, Latif-Hernandez A, Sugiura Y, Durairaj AS, Wang Q, Mhatre SD, Uenaka T, Craspe J, Conley T, et al. (2024) Restoring hippocampal glucose metabolism rescues cognition across Alzheimer's disease pathologies. *Science* **385**:eabm6131.
- Miu J, Ball HJ, Mellor AL, and Hunt NH (2009) Effect of indoleamine dioxygenase-1 deficiency and kynurenine pathway inhibition on murine cerebral malaria. *Int J Parasitol* **39**:363–370.
- Mizutani A, Goto C, Fujigaki H, Yamamoto Y, Saito K, Hatayama S, and Fukuwatari T (2024) Chronic Ethanol Intake Impairs Niacin Nutritional Status in Mice. *J Nutr Sci Vitaminol (Tokyo)* **70**:1–8.
- Mizutani A, Sato M, Fujigaki H, Yamamoto Y, Saito K, Hatayama S, and Fukuwatari T (2023) Establishment of Model Mice to Evaluate Low Niacin Nutritional Status. *J Nutr Sci Vitaminol (Tokyo)* **69**:305–313.
- Mole DJ, Webster SP, Uings I, Zheng X, Binnie M, Wilson K, Hutchinson JP, Mirguet O, Walker A, Beauflis B, et al. (2016) Kynurenine-3-monooxygenase inhibition prevents multiple organ failure in rodent models of acute pancreatitis. *Nat Med* **22**:202–209.
- Mori Y, Mouri A, Kunisawa K, Hirakawa M, Kubota H, Kosuge A, Nijima M, Hasegawa M, Kurahashi H, Murakami R, et al. (2021) Kynurenine 3-monooxygenase deficiency induces depression-like behavior via enhanced antagonism of  $\alpha 7^*$  nicotinic acetylcholine receptors by kynurenic acid. *Behav Brain Res* **405**:113191.
- Moroni F (1999) Tryptophan metabolism and brain function: focus on kynurenine and other indole metabolites. *Eur J Pharmacol* **375**:87–100.
- Moroni F, Cozzi A, Sili M, and Mannaioni G (2012) Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery. *J Neural Transm (Vienna)* **119**:133–139.
- Moroni F, Russi P, Lombardi G, Beni M, and Carli V (1988) Presence of kynurenic acid in the mammalian brain. *J Neurochem* **51**:177–180.
- Morrens M, De Picker L, Kampen JK, and Coppens V (2020) Blood-based kynurenine pathway alterations in schizophrenia spectrum disorders: A meta-analysis. *Schizophr Res* **223**:43–52.
- Mrstná K, Krémová LK, and Švec F (2023) Advances in kynurenine analysis. *Clin Chim Acta* **547**:117441.
- Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, Brown C, and Mellor AL (1998) Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science* **281**:1191–1193.
- Mussajo L, Chiancone FM, Coppini D, and Ginoulhiac E (1951) [The influence of vitamin B6 on the excretion of kynurenic acid as compared with the excretion of xanthurenic acid]. *Bull Soc Chim Biol (Paris)* **33**:1292–1296.
- Myint AM, Kim Y-K, Verkerk R, Park SH, Scharpé S, Steinbusch HWM, and Leonard BE (2007) Tryptophan breakdown pathway in bipolar mania. *J Affect Disord* **102**:65–72.
- Myint AM, Schwarz MJ, Verkerk R, Mueller HH, Zach J, Scharpé S, Steinbusch HWM, Leonard BE, and Kim YK (2011) Reversal of imbalance between kynurenic acid and 3-hydroxykynurenine by antipsychotics in medication-naive and medication-free schizophrenic patients. *Brain Behav Immun* **25**:1576–1581.
- Nahomi RB, Nam M-H, Rankenberg J, Rakete S, Houck JA, Johnson GC, Stankowska DL, Pantcheva MB, MacLean PS, and Nagaraj RH (2020)

- Kynurenic Acid Protects Against Ischemia/Reperfusion-Induced Retinal Ganglion Cell Death in Mice. *Int J Mol Sci* **21**:1795.
- Nakanishi S (1992) Molecular diversity of glutamate receptors and implications for brain function. *Science* **258**:597–603.
- Nehlig A (1997) Cerebral energy metabolism, glucose transport and blood flow: changes with maturation and adaptation to hypoglycaemia. *Diabetes Metab* **23**:18–29.
- Nelp MT, Kates PA, Hunt JT, Newitt JA, Balog A, Maley D, Zhu X, Abell L, Allentoff A, Borzilleri R, et al. (2018) Immune-modulating enzyme indoleamine 2,3-dioxygenase is effectively inhibited by targeting its apo-form. *Proc Natl Acad Sci U S A* **115**:3249–3254.
- Nicholls T, Nitsos I, Smythe G, and Walker DW (2001) Kynurenine production and catabolism in fetal sheep with embolized or nonembolized placentas. *Am J Obstet Gynecol* **185**:988–995.
- Nilsson LK, Linderholm KR, Engberg G, Paulson L, Blennow K, Lindström LH, Nordin C, Karanti A, Persson P, and Erhardt S (2005) Elevated levels of kynurenic acid in the cerebrospinal fluid of male patients with schizophrenia. *Schizophr Res* **80**:315–322.
- Nilsson LK, Linderholm KR, and Erhardt S (2006) Subchronic treatment with kynurenine and probenecid: effects on prepulse inhibition and firing of midbrain dopamine neurons. *J Neural Transm (Vienna)* **113**:557–571.
- Nilsson LK, Nordin C, Jönsson EG, Engberg G, Linderholm KR, and Erhardt S (2007) Cerebrospinal fluid kynurenic acid in male and female controls - correlation with monoamine metabolites and influences of confounding factors. *J Psychiatr Res* **41**:144–151.
- Notarangelo FM and Pocivavsek A (2017) Elevated kynurenine pathway metabolism during neurodevelopment: Implications for brain and behavior. *Neuropharmacology* **112**:275–285.
- Notarangelo FM and Schwarcz R (2014) Restraint stress during pregnancy raises kynurenic acid levels in placenta and fetal brain. *Soc Neurosci Abstr* **39**:348–316.
- Notarangelo FM and Schwarcz R (2016) Restraint Stress during Pregnancy Rapidly Raises Kynurenic Acid Levels in Mouse Placenta and Fetal Brain. *Dev Neurosci* **38**:458–468.
- Notarangelo FM and Schwarcz R (2021) A single prenatal lipopolysaccharide injection has acute, but not long-lasting, effects on cerebral kynurenine pathway metabolism in mice. *Eur J Neurosci* **54**:5968–5981.
- Notarangelo FM, Wu H-Q, Macherone A, Graham DR, and Schwarcz R (2012) Gas chromatography/tandem mass spectrometry detection of extracellular kynurenine and related metabolites in normal and lesioned rat brain. *Anal Biochem* **421**:573–581.
- Notartomaso S, Boccella S, Antenucci N, Ricciardi F, Fazio F, Liberatore F, Scarselli P, Scioli M, Mascio G, Bruno V, et al. (2022) Analgesic Activity of Cinnabaric Acid in Models of Inflammatory and Neuropathic Pain. *Front Mol Neurosci* **15**:892870.
- O'Farrell K, Fagan E, Connor TJ, and Harkin A (2017) Inhibition of the kynurenine pathway protects against reactive microglial-associated reductions in the complexity of primary cortical neurons. *Eur J Pharmacol* **810**:163–173.
- Ogawa T, Matson WR, Beal MF, Myers RH, Bird ED, Milbury P, and Saso S (1992) Kynurenine pathway abnormalities in Parkinson's disease. *Neurology* **42**:1702–1706.
- Ohira K, Hagihara H, Toyama K, Takao K, Kanai M, Funakoshi H, Nakamura T, and Miyakawa T (2010) Expression of tryptophan 2,3-dioxygenase in mature granule cells of the adult mouse dentate gyrus. *Mol Brain* **3**:26.
- Okamoto H, Yamamoto S, Nozaki M, and Hayaishi O (1967) On the submitochondrial localization of l-kynurenine-3-hydroxylase. *Biochem Biophys Res Commun* **26**:309–314.
- Okuno E, Köhler C, and Schwarcz R (1987) Rat 3-hydroxyanthranilic acid oxygenase: purification from the liver and immunocytochemical localization in the brain. *J Neurochem* **49**:771–780.
- Oliveros A, Wininger K, Sens J, Larsson MK, Liu XC, Choi S, Faka A, Schwieler L, Engberg G, Erhardt S, et al. (2017) LPS-induced cortical kynurenic acid and neurogranin-NFAT signaling is associated with deficits in stimulus processing during Pavlovian conditioning. *J Neuroimmunol* **313**:1–9.
- Olsson SK, Samuelsson M, Saetre P, Lindström L, Jönsson EG, Nordin C, Engberg G, Erhardt S, and Landén M (2010) Elevated levels of kynurenic acid in the cerebrospinal fluid of patients with bipolar disorder. *J Psychiatry Neurosci* **35**:195–199.
- Olsson SK, Sellgren C, Engberg G, Landén M, and Erhardt S (2012) Cerebrospinal fluid kynurenic acid is associated with manic and psychotic features in patients with bipolar I disorder. *Bipolar Disord* **14**:719–726.
- Opitz CA, Holfelder P, Prentzell MT, and Trump S (2023) The complex biology of aryl hydrocarbon receptor activation in cancer and beyond. *Biochem Pharmacol* **216**:115798.
- Opitz CA, Litzenburger UM, Sahn F, Ott M, Tritschler I, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, et al. (2011) An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* **478**:197–203.
- Orhan F, Schwieler L, Engberg G, and Samuelsson M (2024) Kynurenine Metabolites in CSF and Plasma in Healthy Males. *Int J Tryptophan Res* **17**:11786469241245323.
- Oxenkrug G (2013) Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. *Curr Drug Targets* **14**:514–521.
- Oxenkrug G and Forester B (2024) Anthranilic Acid, a GPR109A Agonist, and Schizophrenia. *Int J Tryptophan Res* **17**:11786469241239125.
- Paleo L, Betti L, Rossi A, and Giannaccini G (2016) Tryptophan Biochemistry: Structural, Nutritional, Metabolic, and Medical Aspects in Humans. *J Amino Acids* **2016**:8952520.
- Pallotta MT, Orabona C, Bianchi R, Vacca C, Fallarino F, Belladonna ML, Volpi C, Mondanelli G, Gargaro M, Allegrucci M, et al. (2014) Forced IDO1 expression in dendritic cells restores immunoregulatory signalling in autoimmune diabetes. *J Cell Mol Med* **18**:2082–2091.
- Pallotta MT, Rossini S, Suvieri C, Coletti A, Orabona C, Macchiarulo A, Volpi C, and Grohmann U (2022) Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme. *FEBS J* **289**:6099–6118.
- Panlilio LV, Thorndike EB, Nikas SP, Alapafuja SO, Bandiera T, Cravatt BF, Makriyannis A, Piomelli D, Goldberg SR, and Justinova Z (2016) Effects of fatty acid amide hydrolase (FAAH) inhibitors on working memory in rats. *Psychopharmacology (Berl)* **233**:1879–1888.
- Parrott JM and O'Connor JC (2015) Kynurenine 3-Monooxygenase: An Influential Mediator of Neuropathology. *Front Psychiatry* **6**:116.
- Parrott JM, Redus L, Santana-Coelho D, Morales J, Gao X, and O'Connor JC (2016) Neurotoxic kynurenine metabolism is increased in the dorsal hippocampus and drives distinct depressive behaviors during inflammation. *Transl Psychiatry* **6**:e918.
- Parsons CG, Danyasz W, Quack G, Hartmann S, Lorenz B, Wollenburg C, Baran L, Przegalinski E, Kostowski W, Krzascik P, et al. (1997) Novel systemically active antagonists of the glycine site of the N-methyl-D-aspartate receptor: electrophysiological, biochemical and behavioral characterization. *J Pharmacol Exp Ther* **283**:1264–1275.
- Passarelli A, Pisano C, Cecere SC, Di Napoli M, Rossetti S, Tambaro R, Ventriglia J, Gherardi F, Iannacone E, Venanzio SS, et al. (2022) Targeting immunometabolism mediated by the IDO1 Pathway: A new mechanism of immune resistance in endometrial cancer. *Front Immunol* **13**:953115.
- Paul ER, Schwieler L, Erhardt S, Boda S, Trepci A, Kämpe R, Asratian A, Holm L, Yngve A, Dantzer R, et al. (2022) Peripheral and central kynurenine pathway abnormalities in major depression. *Brain Behav Immun* **101**:136–145.
- Pawlowski T, Pawlak D, Inglot M, Zalewska M, Marciniak D, Bugajska J, Janocha-Litwin J, and Malyszczak K (2021) The role of anthranilic acid in the increase of depressive symptoms and major depressive disorder during treatment for hepatitis C with pegylated interferon-alpha2a and oral ribavirin. *J Psychiatry Neurosci* **46**:E166–E175.
- Pearce BD (2001) Schizophrenia and viral infection during neurodevelopment: a focus on mechanisms. *Mol Psychiatry* **6**:634–646.
- Pellicciari R, Amori L, Costantino G, Giordani A, Macchiarulo A, Mattoli L, Pevarello P, Speciale C, and Varasi M (2003) Modulation of the kynurine pathway of tryptophan metabolism in search for neuroprotective agents. Focus on kynurenine-3-hydroxylase. *Adv Exp Med Biol* **527**:621–628.
- Pellicciari R, Rizzo RC, Costantino G, Marinuzzi M, Amori L, Guidetti P, Wu H-Q, and Schwarcz R (2006) Modulators of the kynurenine pathway of tryptophan metabolism: synthesis and preliminary biological evaluation of (S)-4-(ethylsulfonyl) benzoylalanine, a potent and selective kynurenine aminotransferase II (KAT II) inhibitor. *ChemMedChem* **1**:528–531.
- Pereira N, Naufel MF, Ribeiro EB, Tufik S, and Hachul H (2020) Influence of Dietary Sources of Melatonin on Sleep Quality: A Review. *J Food Sci* **85**:5–13.
- Perkins MN and Stone TW (1982) An iophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. *Brain Res* **247**:184–187.
- Pershing ML, Bortz DM, Pocivavsek A, Fredericks PJ, Jørgensen CV, Vunck SA, Leuner B, Schwarcz R, and Bruno JP (2015) Elevated levels of kynurenic acid during gestation produce neurochemical, morphological, and cognitive deficits in adulthood: implications for schizophrenia. *Neuropharmacology* **90**:33–41.
- Peyton L, Oliveros A, Tufvesson-Alm M, Schwieler L, Starski P, Engberg G, Erhardt S, and Choi D-S (2019) Lipopolysaccharide Increases Cortical Kynurenic Acid and Deficits in Reference Memory in Mice. *Int J Tryptophan Res* **12**:1178646919891169.
- Phenis D, Vunck SA, Schwarcz R, and Bruno JP (2014) Acute elevations of brain kynurenic acid induce working memory deficits: Relative contributions of alpha7 nicotinic and NMDA receptor activity. *Soc Neurosci Abstr* **39**:51–10.
- Phillips RS, Anderson AD, Gentry HG, Güner OF, and Bowen JP (2017) Substrate and inhibitor specificity of kynurenine monooxygenase from *Cytophaga hutchinsonii*. *Bioorg Med Chem Lett* **27**:1705–1708.
- Pieroan P, Zamoner A, Soska AK, Silvestrin RB, Loureiro SO, Heimfarth L, Mello e Souza T, Wajner M, and Pessoa-Pureur R (2010) Acute intrastratial administration of quinolinic acid provokes hyperphosphorylation of cytoskeletal intermediate filament proteins in astrocytes and neurons of rats. *Exp Neurol* **224**:188–196.
- Pires GN, Benedito L, Cortese R, Gozal D, Gulia KK, Kumar VM, Tufik S, and Andersen ML (2020) Effects of sleep modulation during pregnancy in the mother and offspring: Evidences from preclinical research. *J Sleep Res* **30**:e13135.
- Platten M, Friedrich M, Wainwright DA, Panitz V, and Opitz CA (2021) Tryptophan metabolism in brain tumors - IDO and beyond. *Curr Opin Immunol* **70**:57–66.
- Plitman E, Iwata Y, Caravaggio F, Nakajima S, Chung JK, Gerretsen P, Kim J, Takeuchi H, Chakravarty MM, Remington G, et al. (2017) Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull* **43**:764–777.
- Pocivavsek A, Baratta AM, Mong JA, and Viehweg SS (2017) Acute Kynurenine Challenge Disrupts Sleep-Wake Architecture and Impairs Contextual Memory in Adult Rats. *Sleep* **40**:zsx141.
- Pocivavsek A, Elmer GI, and Schwarcz R (2019) Inhibition of kynurenine aminotransferase II attenuates hippocampus-dependent memory deficit in adult rats treated prenatally with kynurenine. *Hippocampus* **29**:73–77.
- Pocivavsek A and Erhardt S (2024) Kynurenic acid: translational perspectives of a therapeutically targetable gliotransmitter. *Neuropsychopharmacology* **49**:307–308.
- Pocivavsek A, Notarangelo FM, Wu HQ, Bruno JP, and Schwarcz R (2016) Astrocytes as pharmacological targets in the treatment of schizophrenia: focus on kynurenic acid, in *Modeling the Psychopathological Dimensions Of Schizophrenia: From Molecules to Behavior* (Pletnikov MV and Waddington J, eds) pp 423–443, Elsevier Academic Press, London, UK.
- Pocivavsek A, Thomas MAR, Elmer GI, Bruno JP, and Schwarcz R (2014) Continuous kynurenine administration during the prenatal period, but not during adolescence, causes learning and memory deficits in adult rats. *Psychopharmacology (Berl)* **231**:2799–2809.

- Pocivavsek A, Wu H-Q, Elmer GI, Bruno JP, and Schwarcz R (2012) Pre- and postnatal exposure to kynurenine causes cognitive deficits in adulthood. *Eur J Neurosci* **35**:1605–1612.
- Pocivavsek A, Wu H-Q, Potter MC, Elmer GI, Pellicciari R, and Schwarcz R (2011) Fluctuations in endogenous kynurenic acid control hippocampal glutamate and memory. *Neuropsychopharmacology* **36**:2357–2367.
- Poletti S, Melloni E, Aggio V, Colombo C, Valtorta F, Benedetti F, and Comai S (2019) Grey and white matter structure associates with the activation of the tryptophan to kynurenine pathway in bipolar disorder. *J Affect Disord* **259**:404–412.
- Porter GA and O'Connor JC (2021) Chronic Unpredictable Stress Alters Brain Tryptophan Metabolism and Impairs Working Memory in Mice without Causing Depression-Like Behaviour. *Neurol Neurobiol (Tallinn)* **4**:10.31487/j.nnb.2021.03.03.
- Potter MC, Elmer GI, Bergeron R, Albuquerque EX, Guidetti P, Wu H-Q, and Schwarcz R (2010) Reduction of endogenous kynurenic acid formation enhances extracellular glutamate, hippocampal plasticity, and cognitive behavior. *Neuropsychopharmacology* **35**:1734–1742.
- Prendergast GC, Chang MY, Mandik-Nayak L, Metz R, and Muller AJ (2011) Indoleamine 2,3-dioxygenase as a modifier of pathogenic inflammation in cancer and other inflammation-associated diseases. *Curr Med Chem* **18**:2257–2262.
- Price RB, Nock MK, Charney DS, and Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* **66**:522–526.
- Pucci L, Perozzi S, Cimadamore F, Orsomando G, and Raffaelli N (2007) Tissue expression and biochemical characterization of human 2-amino 3-carboxymuconate 6-semialdehyde decarboxylase, a key enzyme in tryptophan catabolism. *FEBS J* **274**:827–840.
- Radwanski ER and Last RL (1995) Tryptophan biosynthesis and metabolism: biochemical and molecular genetics. *Plant Cell* **7**:921–934.
- Rafice SA, Chauhan N, Efimov I, Basran J, and Raven EL (2009) Oxidation of L-tryptophan in biology: a comparison between tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase. *Biochem Soc Trans* **37**:408–412.
- Rahman A, Ting K, Cullen KM, Braidy N, Brew BJ, and Guillemin GJ (2009) The excitotoxin quinolinic acid induces tau phosphorylation in human neurons. *PLoS One* **4**:e6344.
- Ramírez Ortega D, Ugalde Muñoz PE, Blanco Ayala T, Vázquez Cervantes GI, Lugo Huitrón R, Pineda B, González Esquivel DF, Pérez de la Cruz G, Pedraza Chaverrí J, Sánchez Chapul L, et al. (2021) On the Antioxidant Properties of L-Kynurenine: An Efficient ROS Scavenger and Enhancer of Rat Brain Antioxidant Defense. *Antioxidants (Basel)* **11**:31.
- Rao PV and Vaidyanahan CS (1966) Enzymic conversion of 3-hydroxyanthranilic acid into cinnabarinic acid. Partial purification and properties of rat-liver cinnabarinic synthase. *Biochem J* **99**:317–322.
- Rassoulpour A, Wu H-Q, Ferre S, and Schwarcz R (2005) Nanomolar concentrations of kynurenic acid reduce extracellular dopamine levels in the striatum. *J Neurochem* **93**:762–765.
- Raven EL (2017) A short history of heme dioxygenases: rise, fall and rise again. *J Biol Inorg Chem* **22**:175–183.
- Ravikumar A, Deepadevi KV, Arun P, Manojkumar V, and Kurup PA (2000) Tryptophan and tyrosine catabolic pattern in neuropsychiatric disorders. *Neurol India* **48**:231–238.
- Rentschler KM, Baratta AM, Ditty AL, Wagner NTJ, Wright CJ, Milosavljevic S, Mong JA, and Pocivavsek A (2021) Prenatal Kynurenine Elevation Elicits Sex-Dependent Changes in Sleep and Arousal During Adulthood: Implications for Psychotic Disorders. *Schizophr Bull* **47**:1320–1330.
- Rentschler KM, Milosavljevic S, Baratta AM, Wright CJ, Piroli MV, Tentor Z, Valafar H, O'Reilly C, and Pocivavsek A (2024) Reducing brain kynurenic acid synthesis precludes kynurenine-induced sleep disturbances. *J Sleep Res* **33**:e14038.
- Roager HM and Licht TR (2018) Microbial tryptophan catabolites in health and disease. *Nat Commun* **9**:3294.
- Romani L, Fallarino F, De Luca A, Montagnoli C, D'Angelo C, Zelante T, Vacca C, Bistoni F, Fioretti MC, Grohmann U, et al. (2008) Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. *Nature* **451**:211–215.
- Rømer TB, Jeppesen R, Christensen RHB, and Benros ME (2023) Biomarkers in the cerebrospinal fluid of patients with psychotic disorders compared to healthy controls: a systematic review and meta-analysis. *Mol Psychiatry* **28**:2277–2290.
- Rossi F, Garavaglia S, Montalbano V, Walsh MA, and Rizzi M (2008) Crystal structure of human kynurenine aminotransferase II, a drug target for the treatment of schizophrenia. *J Biol Chem* **283**:3559–3566.
- Rossi F, Valentina C, Garavaglia S, Sathyaikumar KV, Schwarcz R, Kojima S-I, Okuwaki K, Ono S-I, Kajii Y, and Rizzi M (2010) Crystal structure-based selective targeting of the pyridoxal 5'-phosphate dependent enzyme kynurenine aminotransferase II for cognitive enhancement. *J Med Chem* **53**:5684–5689.
- Rothhammer V and Quintana FJ (2019) The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol* **19**:184–197.
- Röver S, Cesura AM, Huguenin P, Kettler R, and Szenté A (1997) Synthesis and biochemical evaluation of N-(4-phenylthiazol-2-yl)benzenesulfonamides as high-affinity inhibitors of kynurenine 3-hydroxylase. *J Med Chem* **40**:4378–4385.
- Rudzik L, Stone TW, Maes M, Misiak B, Samochoew J, and Szulc A (2021) Gut microbiota-derived vitamins - underrated powers of a multipotent ally in psychiatric health and disease. *Prog Neuropsychopharmacol Biol Psychiatry* **107**:110240.
- Ruffmann R, Schlick R, Chirigios MA, Budzynsky W, and Varesio L (1987) Antiproliferative activity of picolinic acid due to macrophage activation. *Drugs Exp Clin Res* **13**:607–614.
- Sahm F, Oezen I, Opitz CA, Radlwimmer B, von Deimling A, Ahrendt T, Adams S, Bode HB, Guillemin GJ, Wick W, et al. (2013) The endogenous tryptophan metabolite and NAD<sup>+</sup> precursor quinolinic acid confers resistance of gliomas to oxidative stress. *Cancer Res* **73**:3225–3234.
- Saito Y, Hayaishi O, and Rothberg S (1957) Studies on oxygenases; enzymatic formation of 3-hydroxy-L-kynurenine from L-kynurenine. *J Biol Chem* **229**:921–934.
- Saito K, Markey SP, and Heyes MP (1992) Effects of immune activation on quinolinic acid and neuroactive kynurenines in the mouse. *Neuroscience* **51**:25–39.
- Sapienza J, Agostoni G, Dall'Acqua S, Sut S, Nasini S, Martini F, Marchesi A, Bechi M, Buonocore M, Cocchi F, et al. (2024) The kynurenine pathway in treatment-resistant schizophrenia at the crossroads between pathophysiology and pharmacotherapy. *Schizophr Res* **264**:71–80.
- Sapienza J, Spangaro M, Guillemin GJ, Comai S, and Bosia M (2023) Importance of the dysregulation of the kynurenine pathway on cognition in schizophrenia: a systematic review of clinical studies. *Eur Arch Psychiatry Clin Neurosci* **273**:1317–1328.
- Sapko MT, Guidetti P, Yu P, Tagle DA, Pellicciari R, and Schwarcz R (2006) Endogenous kynurenate controls the vulnerability of striatal neurons to quinolinate: Implications for Huntington's disease. *Exp Neurol* **197**:31–40.
- Sathyaikumar KV, Pérez de la Cruz V, Pineda B, Vázquez Cervantes GI, Ramírez Ortega D, Donley DW, Severson PL, West BL, Giorgini F, Fox JH, et al. (2022) Cellular Localization of Kynurenine 3-Monooxygenase in the Brain: Challenging the Dogma. *Antioxidants (Basel)* **11**:315.
- Sathyaikumar KV, Stachowski EK, Amori L, Guidetti P, Muchowski PJ, and Schwarcz R (2010) Dysfunctional kynurenine pathway metabolism in the R6/2 mouse model of Huntington's disease. *J Neurochem* **113**:1416–1425.
- Sathyaikumar KV, Stachowski EK, Wonodi I, Roberts RC, Rassoulpour A, McMahon RP, and Schwarcz R (2011) Impaired kynurenine pathway metabolism in the prefrontal cortex of individuals with schizophrenia. *Schizophr Bull* **37**:1147–1156.
- Sathyaikumar KV, Tararina M, Wu H-Q, Neale SA, Weisz F, Salt TE, and Schwarcz R (2017) Xanthurenic Acid Formation from 3-Hydroxykynurenine in the Mammalian Brain: Neurochemical Characterization and Physiological Effects. *Neuroscience* **367**:85–97.
- Schmidt W, Guidetti P, Okuno E, and Schwarcz R (1993) Characterization of human brain kynurenine aminotransferases using [3H]kynurenine as a substrate. *Neuroscience* **55**:177–184.
- Schwarcz R, Bruno JP, Muchowski PJ, and Wu H-Q (2012) Kynurenines in the mammalian brain: when physiology meets pathology. *Nat Rev Neurosci* **13**:465–477.
- Schwarcz R, Foo A, Sathyaikumar KV, and Notarangelo FM (2024) The Probiotic *Lactobacillus reuteri* Preferentially Synthesizes Kynurenine Acid from Kynurenine. *Int J Mol Sci* **25**:3679.
- Schwarcz R, Poeggeler B, Rassoulpour A, Ceresoli-Borroni G, and Hodgkins PS (1998) Regulation of kynurenic acid levels in the developing rat brain. *Amino Acids* **14**:243–249.
- Schwarcz R, Rassoulpour A, Wu HQ, Medoff D, Tamminga CA, and Roberts RC (2001) Increased cortical kynurenate content in schizophrenia. *Biol Psychiatry* **50**:521–530.
- Schwarcz R, Tamminga CA, Kurlan R, and Shoulson I (1988) Cerebrospinal fluid levels of quinolinic acid in Huntington's disease and schizophrenia. *Ann Neurol* **24**:580–582.
- Schwarcz R, Whetsell WO, and Mangano RM (1983) Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. *Science* **219**:316–318.
- Schwieler L, Engberg G, and Erhardt S (2004) Clozapine modulates midbrain dopamine neuron firing via interaction with the NMDA receptor complex. *Synapse* **52**:114–122.
- Schwieler L and Erhardt S (2003) Inhibitory action of clozapine on rat ventral tegmental area dopamine neurons following increased levels of endogenous kynurenic acid. *Neuropsychopharmacology* **28**:1770–1777.
- Schwieler L, Erhardt S, Erhardt C, and Engberg G (2005) Prostaglandin-mediated control of rat brain kynurenic acid synthesis—opposite actions by COX-1 and COX-2 isoforms. *J Neural Transm (Vienna)* **112**:863–872.
- Schwieler L, Erhardt S, Nilsson L, Linderholm K, and Engberg G (2006) Effects of COX-1 and COX-2 inhibitors on the firing of rat midbrain dopaminergic neurons—possible involvement of endogenous kynurenic acid. *Synapse* **59**:290–298.
- Schwieler L, Trepci A, Krzyzanowski S, Hermansson S, Granqvist M, Piehl F, Venckunas T, Brazaitis M, Kamandulis S, Lindqvist D, et al. (2020) A novel, robust method for quantification of multiple kynurenine pathway metabolites in the cerebrospinal fluid. *Bioanalysis* **12**:379–392.
- Secci ME, Mascia P, Sagheddu C, Beggiano S, Melis M, Borelli AC, Tomasini MC, Panlilio LV, Schindler CW, Tanda G, et al. (2019) Astrocytic Mechanisms Involving Kynurenic Acid Control Delta(9)-Tetrahydrocannabinol-Induced Increases in Glutamate Release in Brain Reward-Processing Areas. *Mol Neurobiol* **56**:3563–3575.
- Segawa H, Fukasawa Y, Miyamoto K, Takeda E, Endou H, and Kanai Y (1999) Identification and functional characterization of a Na<sup>+</sup>-independent neutral amino acid transporter with broad substrate selectivity. *J Biol Chem* **274**:19745–19751.
- Sellgren CM, Gracias J, Jungholm O, Perlis RH, Engberg G, Schwieler L, Landen M, and Erhardt S (2019) Peripheral and central levels of kynurenic acid in bipolar disorder subjects and healthy controls. *Transl Psychiatry* **9**:37.
- Sellgren CM, Imbeault S, Larsson MK, Oliveros A, Nilsson IAK, Codeluppi S, Orhan F, Bhat M, Tufvesson-Alm M, Gracias J, et al. (2021) GRK3 deficiency elicits brain immune activation and psychosis. *Mol Psychiatry* **26**:6820–6832.
- Sellgren CM, Kegel ME, Bergen SE, Ekman CJ, Olsson S, Larsson M, Vawter MP, Backlund L, Sullivan PF, Sklar P, et al. (2016) A genome-wide association study of kynurenic acid in cerebrospinal fluid: implications for psychosis and cognitive impairment in bipolar disorder. *Mol Psychiatry* **21**:1342–1350.

- Shave S, McGuire K, Pham NT, Mole DJ, Webster SP, and Auer M (2018) Diclofenac Identified as a Kynurenine 3-Monooxygenase Binder and Inhibitor by Molecular Similarity Techniques. *ACS Omega* **3**:2564–2568.
- Shinohara R and Ishiguro I (1970) The purification and properties of formamidase from rat liver. *Biochim Biophys Acta* **198**:324–331.
- Silvano A, Seravalli V, Strambi N, Cecchi M, Tartarotti E, Parenti A, and Di Tommaso M (2021) Tryptophan metabolism and immune regulation in the human placenta. *J Reprod Immunol* **147**:103361.
- Silvestroni A, Faul RLM, Strand AD, and Möller T (2009) Distinct neuroinflammatory profile in post-mortem human Huntington's disease. *Neuroreport* **20**:1098–1103.
- Simon DK, Prusky GT, O'Leary DD, and Constantine-Paton M (1992) N-methyl-D-aspartate receptor antagonists disrupt the formation of a mammalian neural map. *Proc Natl Acad Sci U S A* **89**:10593–10597.
- Sinz EH, Kochanek PM, Heyes MP, Wisniewski SR, Bell MJ, Clark RS, DeKosky ST, Blight AR, and Marion DW (1998) Quinolinic acid is increased in CSF and associated with mortality after traumatic brain injury in humans. *J Cereb Blood Flow Metab* **18**:610–615.
- Skorobogatov K, De Picker L, Verkerk R, Coppens V, Leboyer M, Müller N, and Morrens M (2021) Brain Versus Blood: A Systematic Review on the Concordance Between Peripheral and Central Kynurenine Pathway Measures in Psychiatric Disorders. *Front Immunol* **12**:716980.
- Smith AK, Simon JS, Gustafson EL, Novello S, Cubells JF, Epstein MP, Devlin DJ, Qiu P, Albrecht JK, Brass CA, et al. (2012) Association of a polymorphism in the indoleamine-2,3-dioxygenase gene and interferon-alpha-induced depression in patients with chronic hepatitis C. *Mol Psychiatry* **17**:781–789.
- Söderlund J, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, Landén M, and Engberg G (2011) Elevation of cerebrospinal fluid interleukin-1s in bipolar disorder. *J Psychiatry Neurosci* **36**:114–118.
- Söderlund J, Schröder J, Nordin C, Samuelsson M, Walther-Jallow L, Karlsson H, Erhardt S, and Engberg G (2009) Activation of brain interleukin-1beta in schizophrenia. *Mol Psychiatry* **14**:1069–1071.
- Sodhi RK, Bansal Y, Singh R, Saroj P, Bhandari R, Kumar B, and Kuhad A (2021) IDO-1 inhibition protects against neuroinflammation, oxidative stress and mitochondrial dysfunction in 6-OHDA induced murine model of Parkinson's disease. *Neurotoxicology* **84**:184–197.
- Solvang S-EH, Hodge A, Watne LO, Cabral-Marques O, Nordrehaug JE, Giles GG, Dugué P-A, Nygård O, Ueland PM, McCann A, et al. (2022) Kynurenine Pathway Metabolites in the Blood and Cerebrospinal Fluid Are Associated with Human Aging. *Oxid Med Cell Longev* **2022**:5019752.
- Sorgdrager FJH, Vermeiren Y, Van Faassen M, van der Ley C, Nollen EAA, Kema IP, and De Deyn PP (2019) Age- and disease-specific changes of the kynurenine pathway in Parkinson's and Alzheimer's disease. *J Neurochem* **151**:656–668.
- Speciale C and Schwarcz R (1993) On the production and disposition of quinolinic acid in rat brain and liver slices. *J Neurochem* **60**:212–218.
- Speciale C, Hares K, Schwarcz R, and Brookes N (1989) High-affinity uptake of L-kynurenine by a Na<sup>+</sup>-independent transporter of neutral amino acids in astrocytes. *J Neurosci* **9**:2066–2072.
- Stone TW (2007) Kynurenine acid blocks nicotinic synaptic transmission to hippocampal interneurons in young rats. *Eur J Neurosci* **25**:2656–2665.
- Stone TW (2020) Does kynurenine acid act on nicotinic receptors? An assessment of the evidence. *J Neurochem* **152**:627–649.
- Stone TW and Darlington LG (2013) The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders. *Br J Pharmacol* **169**:1211–1227.
- Stone TW and Perkins MN (1981) Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. *Eur J Pharmacol* **72**:411–412.
- Stone TW, Darlington LG, Badawy AA-B, and Williams RO (2024) The Complex World of Kynurenine Acid: Reflections on Biological Issues and Therapeutic Strategy. *Int J Mol Sci* **25**:9040.
- Stoy N, Mackay GM, Forrest CM, Christofides J, Egerton M, Stone TW, and Darlington LG (2005) Tryptophan metabolism and oxidative stress in patients with Huntington's disease. *J Neurochem* **93**:611–623.
- Susser E and Bresnahan M (2002) Epidemiologic approaches to neurodevelopmental disorders. *Mol Psychiatry* **7** (Suppl 2):S2–3.
- Suzuki K, Yasuda M, and Yamasaki K (1957) Stability Constants of Picolinic and Quinaldic Acid Chelates of Bivalent Metals. *J Phys Chem* **61**:229–231.
- Swartz KJ, During MJ, Freese A, and Beal MF (1990) Cerebral synthesis and release of kynurenine acid: an endogenous antagonist of excitatory amino acid receptors. *J Neurosci* **10**:2965–2973.
- Takikawa O, Habara-Ohkubo A, and Yoshida R (1991) Induction of indoleamine 2,3-dioxygenase in tumor cells transplanted into allogeneic mouse: interferon-gamma is the inducer. *Adv Exp Med Biol* **294**:437–444.
- Taleb O, Maammar M, Klein C, Maitre M, and Mensah-Nyagan AG (2021) A Role for Xanthurenic Acid in the Control of Brain Dopaminergic Activity. *Int J Mol Sci* **22**:6974.
- Tashiro T, Murakami Y, Mouri A, Imamura Y, Nabeshima T, Yamamoto Y, and Saito K (2017) Kynurenine 3-monooxygenase is implicated in antidepressant-responsive depressive-like behaviors and monoaminergic dysfunctions. *Behav Brain Res* **317**:279–285.
- Terakata M, Fukuwatari T, Sano M, Nakao N, Sasaki R, Fukuoka S-I, and Shibata K (2012) Establishment of true niacin deficiency in quinolinic acid phosphoribosyltransferase knockout mice. *J Nutr* **142**:2148–2153.
- Théate I, van Baren N, Pilotte L, Moulin P, Larrieu P, Renaud J-C, Hervé C, Gutierrez-Roelens I, Marbaix E, Sempoux C, et al. (2015) Extensive profiling of the expression of the indoleamine 2,3-dioxygenase 1 protein in normal and tumoral human tissues. *Cancer Immunol Res* **3**:161–172.
- Thirataraj-Rajamani K, Li P, Escobar Galvis ML, Labrie V, Brundin P, and Brundin L (2017) Is the Enzyme ACMSD a Novel Therapeutic Target in Parkinson's Disease? *J Parkinsons Dis* **7**:577–587.
- Thomas S, DuHadaway J, Prendergast GC, and Laury-Kleintop L (2014) Specific in situ detection of murine indoleamine 2, 3-dioxygenase. *J Cell Biochem* **115**:391–396.
- Thomas SR, Salahifar H, Mashima R, Hunt NH, Richardson DR, and Stocker R (2001) Antioxidants inhibit indoleamine 2,3-dioxygenase in IFN-gamma-activated human macrophages: posttranslational regulation by pyrrolidine dithiocarbamate. *J Immunol* **166**:6332–6340.
- Toledo-Sherman LM, Prime ME, Mrzljak L, Beconi MG, Beresford A, Brookfield FA, Brown CJ, Cardaun I, Courtney SM, Dijkman U, et al. (2015) Development of a series of aryl pyrimidine kynurenine monooxygenase inhibitors as potential therapeutic agents for the treatment of Huntington's disease. *J Med Chem* **58**:1159–1183.
- Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, and Bazinet RP (2016) Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Mol Psychiatry* **21**:1009–1026.
- Trepci A, Sellgren CM, Pålsson E, Brundin L, Khanlarkhani N, Schwieler L, Landén M, and Erhardt S (2021) Central levels of tryptophan metabolites in subjects with bipolar disorder. *Eur Neuropsychopharmacol* **43**:52–62.
- Tufvesson-Alm M, Imbeault S, Liu X-C, Zheng Y, Faka A, Choi D-S, Schwieler L, Engberg G, and Erhardt S (2020) Repeated administration of LPS exaggerates amphetamine-induced locomotor response and causes learning deficits in mice. *J Neuroimmunol* **349**:577401.
- Tufvesson-Alm M, Schwieler L, Schwarcz R, Goiny M, Erhardt S, and Engberg G (2018) Importance of kynurenine 3-monooxygenase for spontaneous firing and pharmacological responses of midbrain dopamine neurons: Relevance for schizophrenia. *Neuropharmacology* **138**:130–139.
- Turski WA and Schwarcz R (1988) On the disposition of intrahippocampally injected kynurenine acid in the rat. *Exp Brain Res* **71**:563–567.
- Turski WA, Gramsbergen JB, Traitter H, and Schwarcz R (1989) Rat brain slices produce and liberate kynurenine acid upon exposure to L-kynurenine. *J Neurochem* **52**:1629–1636.
- Ulivieri M, Wieroniska JM, Lionetto L, Martinello K, Cieslik P, Chocyk A, Curto M, Di Menna L, Iacovelli L, Traficante A, et al. (2020) The Trace Kynurenine, Cinnabarinic Acid, Displays Potent Antipsychotic-Like Activity in Mice and Its Levels Are Reduced in the Prefrontal Cortex of Individuals Affected by Schizophrenia. *Schizophr Bull* **46**:1471–1481.
- Urata Y, Koga K, Hirota Y, Akiyama I, Izumi G, Takamura M, Nagai M, Harada M, Hirata T, Yoshino O, et al. (2014) IL-1beta increases expression of tryptophan 2,3-dioxygenase and stimulates tryptophan catabolism in endometrioma stromal cells. *Am J Reprod Immunol* **72**:496–503.
- Uwai Y, Honjo H, and Iwamoto K (2012) Interaction and transport of kynurenine acid via human organic anion transporters hOAT1 and hOAT3. *Pharmacol Res* **65**:254–260.
- Vallerini GP, Amori L, Beato C, Tararina M, Wang X-D, Schwarcz R, and Costantino G (2013) 2-Aminocinnolinic acid 1-oxides are chemically stable inhibitors of quinolinic acid synthesis in the mammalian brain: a step toward new antiexcitotoxic agents. *J Med Chem* **56**:9482–9495.
- Vécsei L, Miller J, MacGarvey U, and Beal MF (1992) Kynurenine and probenecid inhibit pentylentetrazol- and NMDA-induced seizures and increase kynurenine acid concentrations in the brain. *Brain Res Bull* **28**:233–238.
- Vrooman L, Jhamandas K, Boegman RJ, and Beninger RJ (1993) Picolinic acid modulates kainic acid-evoked glutamate release from the striatum in vitro. *Brain Res* **627**:193–198.
- Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, and Dantzer R (2013) NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology* **38**:1609–1616.
- Walker DW, Curtis B, Lacey B, and Nitsos I (1999) Kynurenine acid in brain and cerebrospinal fluid of fetal, newborn, and adult sheep and effects of placental embolization. *Pediatr Res* **45**:820–826.
- Wang AK and Miller BJ (2018) Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. *Schizophr Bull* **44**:75–83.
- Wang J, Simonavicius N, Wu X, Swaminath G, Reagan J, Tian H, and Ling L (2006) Kynurenine acid as a ligand for orphan G protein-coupled receptor GPR35. *J Biol Chem* **281**:22021–22028.
- Wang X-D, Notarangelo FM, Wang J-Z, and Schwarcz R (2012) Kynurenine acid and 3-hydroxykynurenine production from D-kynurenine in mice. *Brain Res* **1455**:1–9.
- Wennström M, Nielsen HM, Orhan F, Londos E, Minthon L, and Erhardt S (2014) Kynurenine Acid levels in cerebrospinal fluid from patients with Alzheimer's disease or dementia with Lewy bodies. *Int J Tryptophan Res* **7**:1–7.
- Wickström R, Fowler Å, Goiny M, Millischer V, Yberg S, and Schwieler L (2021) The Kynurenine Pathway is Differentially Activated in Children with Lyme Disease and Tick-Borne Encephalitis. *Microorganisms* **9**:322.
- Widner B, Leblhuber F, and Fuchs D (2002) Increased neopterin production and tryptophan degradation in advanced Parkinson's disease. *J Neural Transm (Vienna)* **109**:181–189.
- Wolfensberger M, Amsler U, Cuénod M, Foster AC, Whetsell WO, and Schwarcz R (1983) Identification of quinolinic acid in rat and human brain tissue. *Neurosci Lett* **41**:247–252.
- Wonodi I, McMahon RP, Krishna N, Mitchell BD, Liu J, Glassman M, Hong LE, and Gold JM (2014) Influence of kynurenine 3-monooxygenase (KMO) gene polymorphism on cognitive function in schizophrenia. *Schizophr Res* **160**:80–87.
- Wonodi I, Stine OC, Sathyaikumar KV, Roberts RC, Mitchell BD, Hong LE, Kajii Y, Thaker GK, and Schwarcz R (2011) Downregulated kynurenine 3-monooxygenase gene expression and enzyme activity in schizophrenia and genetic association with schizophrenia endophenotypes. *Arch Gen Psychiatry* **68**:665–674.
- Wright CJ, Rentschler KM, Wagner NTJ, Lewis AM, Beggiato S, and Pociavsek A (2021) Time of Day-Dependent Alterations in Hippocampal Kynurenine Acid, Glutamate, and GABA in Adult Rats Exposed to Elevated Kynurenine Acid During Neurodevelopment. *Front Psychiatry* **12**:734984.

- Wu H-Q, Okuyama M, Kajii Y, Pocivavsek A, Bruno JP, and Schwarcz R (2014) Targeting kynurenine aminotransferase II in psychiatric diseases: promising effects of an orally active enzyme inhibitor. *Schizophr Bull* **40** Suppl 2:S152–158.
- Wu H-Q, Pereira EFR, Bruno JP, Pellicciari R, Albuquerque EX, and Schwarcz R (2010) The astrocyte-derived alpha7 nicotinic receptor antagonist kynurenic acid controls extracellular glutamate levels in the prefrontal cortex. *J Mol Neurosci* **40**:204–210.
- Wu H-Q, Rassoulpour A, and Schwarcz R (2007) Kynurenic acid leads, dopamine follows: a new case of volume transmission in the brain? *J Neural Transm (Vienna)* **114**:33–41.
- Wu HQ, Ungerstedt U, and Schwarcz R (1992) Regulation of kynurenic acid synthesis studied by microdialysis in the dorsal hippocampus of unanesthetized rats. *Eur J Pharmacol* **213**:375–380.
- Wu W, Nicolazzo JA, Wen L, Chung R, Stankovic R, Bao SS, Lim CK, Brew BJ, Cullen KM, and Guillemin GJ (2013) Expression of tryptophan 2,3-dioxygenase and production of kynurenic pathway metabolites in triple transgenic mice and human Alzheimer's disease brain. *PLoS One* **8**:e59749.
- Yamada A, Akimoto H, Kagawa S, Guillemin GJ, and Takikawa O (2009) Proinflammatory cytokine interferon-gamma increases induction of indoleamine 2,3-dioxygenase in monocyte cells primed with amyloid beta peptide 1-42: implications for the pathogenesis of Alzheimer's disease. *J Neurochem* **110**:791–800.
- Yamamoto H, Murakami H, Horiguchi K, and Egawa B (1995) Studies on cerebrospinal fluid kynurenic acid concentrations in epileptic children. *Brain Dev* **17**:327–329.
- Yamamoto H, Shindo I, Egawa B, and Horiguchi K (1994) Kynurenic acid is decreased in cerebrospinal fluid of patients with infantile spasms. *Pediatr Neurol* **10**:9–12.
- Yamamoto S and Hayaishi O (1967) Tryptophan pyrrolase of rabbit intestine. D- and L-tryptophan-cleaving enzyme or enzymes. *J Biol Chem* **242**:5260–5266.
- Yan EB, Frugier T, Lim CK, Heng B, Sundaram G, Tan M, Rosenfeld JV, Walker DW, Guillemin GJ, and Morganti-Kossmann MC (2015) Activation of the kynurenic pathway and increased production of the excitotoxin quinolinic acid following traumatic brain injury in humans. *J Neuroinflammation* **12**:110.
- Ye F, Dong M-C, Xu C-X, Jiang N, Chang Q, Liu X-M, and Pan R-L (2024) Effects of different chronic restraint stress periods on anxiety- and depression-like behaviors and tryptophan-kynurenic metabolism along the brain-gut axis in C57BL/6N mice. *Eur J Pharmacol* **965**:176301.
- Yeung AWS, Terentis AC, King NJC, and Thomas SR (2015) Role of indoleamine 2,3-dioxygenase in health and disease. *Clin Sci (Lond)* **129**:601–672.
- Ying W (2007) NAD<sup>+</sup> and NADH in brain functions, brain diseases and brain aging. *Front Biosci* **12**:1863–1888.
- Yoshida R and Hayaishi O (1978) Induction of pulmonary indoleamine 2,3-dioxygenase by intraperitoneal injection of bacterial lipopolysaccharide. *Proc Natl Acad Sci U S A* **75**:3998–4000.
- Yoshida R, Imanishi J, Oku T, Kishida T, and Hayaishi O (1981) Induction of pulmonary indoleamine 2,3-dioxygenase by interferon. *Proc Natl Acad Sci U S A* **78**:129–132.
- Yoshida R, Nukiwa T, Watanabe Y, Fujiwara M, Hirata F, and Hayaishi O (1980) Regulation of indoleamine 2,3-dioxygenase activity in the small intestine and the epididymis of mice. *Arch Biochem Biophys* **203**:343–351.
- Yoshida R, Urade Y, Tokuda M, and Hayaishi O (1979) Induction of indoleamine 2,3-dioxygenase in mouse lung during virus infection. *Proc Natl Acad Sci U S A* **76**:4084–4086.
- Young SN, Joseph MH, and Gauthier S (1983) Studies on kynurenic acid in human cerebrospinal fluid: lowered levels in epilepsy. *J Neural Transm* **58**:193–204.
- Yu P, Di Prospero NA, Sapko MT, Cai T, Chen A, Melendez-Ferro M, Du F, Whetsell WO, Guidetti P, Schwarcz R, et al. (2004) Biochemical and phenotypic abnormalities in kynurenic acid aminotransferase II-deficient mice. *Mol Cell Biol* **24**:6919–6930.
- Zakhary G, Sherchan P, Li Q, Tang J, and Zhang JH (2020) Modification of kynurenic pathway via inhibition of kynurenic hydroxylase attenuates surgical brain injury complications in a male rat model. *J Neurosci Res* **98**:155–167.
- Zarate CA, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, and Luckenbaugh DA (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* **71**:939–946.
- Zavitsanou K, Lim CK, Purves-Tyson T, Karl T, Kassiou M, Banister SD, Guillemin GJ, and Weickert CS (2014) Effect of maternal immune activation on the kynurenic pathway in preadolescent rat offspring and on MK801-induced hyperlocomotion in adulthood: amelioration by COX-2 inhibition. *Brain Behav Immun* **41**:173–181.
- Zelante T, Fallarino F, Bistoni F, Puccetti P, and Romani L (2009) Indoleamine 2,3-dioxygenase in infection: the paradox of an evasive strategy that benefits the host. *Microbes Infect* **11**:133–141.
- Zhai L, Lauing KL, Chang AL, Dey M, Qian J, Cheng Y, Lesniak MS, and Wainwright DA (2015) The role of IDO in brain tumor immunotherapy. *J Neurooncol* **123**:395–403.
- Zhang Y, Wang L, and Ren W (2022) Blast-related traumatic brain injury is mediated by the kynurenic pathway. *Neuroreport* **33**:569–576.
- Zhang Z, Rasmussen L, Saraswati M, Koehler RC, Robertson C, and Kannan S (2018) Traumatic Injury Leads to Inflammation and Altered Tryptophan Metabolism in the Juvenile Rabbit Brain. *J Neurotrauma*. DOI: 10.1089/neu.2017.5450 [published ahead of print].
- Zheng Y-R, Tufvesson-Alm M, Trepci A, Imbeault S, Li X-Q, Schwieler L, Engberg G, and Erhardt S (2023) Dual administration of lipopolysaccharide induces behavioural changes in rats relevant to psychotic disorders. *Acta Neuropsychiatr* **1**–13.
- Zhou X, Barrett TB, and Kelsoe JR (2008) Promoter variant in the GRK3 gene associated with bipolar disorder alters gene expression. *Biol Psychiatry* **64**:104–110.
- Zmarowski A, Wu H-Q, Brooks JM, Potter MC, Pellicciari R, Schwarcz R, and Bruno JP (2009) Astrocyte-derived kynurenic acid modulates basal and evoked cortical acetylcholine release. *Eur J Neurosci* **29**:529–538.
- Zwilling D, Huang S-Y, Sathyaikumar KV, Notarangelo FM, Guidetti P, Wu H-Q, Lee J, Truong J, Andrews-Zwilling Y, Hsieh EW, et al. (2011) Kynurenic acid 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* **145**:863–874.