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KYNURENINES IN THE MAMMALIAN BRAIN: WHEN PHYSIOLOGY MEETS PATHOLOGY

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Abstract

The essential amino acid tryptophan is not only a precursor of serotonin but is also degraded to several other neuroactive compounds, including kynurenic acid, 3-hydroxykynurenine and quinolinic acid. The synthesis of these metabolites is regulated by an enzymatic cascade, known as the kynurenine pathway, that is tightly controlled by the immune system. Dysregulations of the pathway, causing hyper- or hypofunction of active metabolites, are associated with neurodegenerative and other neurological disorders, as well as psychiatric diseases such as depression and schizophrenia. With recently developed pharmacological agents, it is now possible to restore metabolic equilibrium and envisage novel therapeutic interventions.

The discovery of kynurenic acid (KYNA) more than 150 years ago [1] and the subsequent elucidation of its biosynthesis and chemical structure initiated a series of discoveries that turned out to have significant implications for the neurosciences. KYNA was the first of the "kynurenines", a group of metabolically related compounds derived from the essential amino acid tryptophan. Biochemical studies during the first part of the 20th century elaborated the enzymatic steps linking the individual members of the kynurenine pathway (Fig. 1), which was found to account for >90% of peripheral tryptophan metabolism in mammals [2]. The importance of the pathway was long thought to stem mainly from the fact that it is a source of the coenzyme NAD^+, which plays a critical role in many fundamental biological processes, including redox reactions required for mitochondrial function.

Numerous studies since the 1970s have demonstrated that kynurenines can influence brain function. The past years have witnessed a surge in new information regarding the roles of kynurenine pathway metabolites not only in brain physiology but also as potential causative factors in several devastating brain diseases. Here we first describe the properties of neuroactive kynurenines, their metabolism in the brain, and the communication between the peripheral and the central kynurenine pathways. Using selected examples and focusing largely on *in vivo* evidence, we then explain how fluctuations in kynurenine pathway metabolites can lead to the deterioration of physiological processes and the emergence of pathological states. Finally, we briefly review recent advances in drug discovery, which

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suggest exciting clinical applications of agents that are designed specifically to restore equilibrium in the cerebral kynurenine pathway.

Neuroactive kynurenines

Kynurenic acid

KYNA is a competitive, broad spectrum antagonist of glutamate receptors, inhibiting all three ionotropic excitatory amino acid receptors — NMDA, kainate and AMPA receptors — to approximately the same degree at high micromolar concentrations [3]. KYNA has a greater affinity for the obligatory glycine co-agonist site of the NMDA receptor, so that this "glycine$_B$" receptor constitutes a preferred molecular target [4]. Because of the competitive nature of KYNA's action at this site, selective glycine$_B$ receptor antagonists can substitute for KYNA [5]; and agonists can counter the actions of KYNA [6–7].

During the past few years, additional targets of KYNA have been identified. Only one of them, the α7 nicotinic acetylcholine receptor (α7nAChR), has so far been verified as a *bona fide* KYNA receptor in the brain [8–10], whereas the role of others, such as the former orphan G-protein coupled receptor GPR35 [11] and the aryl hydrocarbon receptor [12], remains to be elaborated. Notably, the inhibitory action of KYNA at the α7nAChR is non-competitive in nature, and KYNA's effector site on the α7nAChR overlaps with the allosteric potentiating site that can be occupied by the cognition-enhancing drug galantamine [13]. Independent of its actions at receptors, KYNA also has antioxidant properties, which are related to the compound's ability to scavenge hydroxyl, superoxide anion and other free radicals [14–15].

Kynurenine, 3-hydroxykynurenine and downstream kynurenine pathway metabolites

Electrophysiological investigations of other kynurenine pathway metabolites, including kynurenine, 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HANA) and anthranilic acid (Fig. 1), have failed to reveal direct effects on neuronal activity [16]. In fact, there are only a few examples, such as the recently described action of kynurenine as an *in vivo* ligand of the human aryl hydrocarbon receptor [17], and the activation of metabotropic glutamate receptors by xanthurenic acid [18] and 3-HANA's oxidation product cinnabarinic acid [19], of direct effects of these compounds on specific receptors within or outside the brain. However, several kynurenine pathway metabolites probably participate in complex pro- and anti-oxidative processes in the brain [20]. 3-HK and 3-HANA, in particular, auto-oxidize readily under physiological conditions, producing H_2O_2 and highly reactive hydroxyl radicals in the process [21]. But these properties are balanced by the related antioxidant capacity of these compounds, as well as xanthurenic acid, to scavenge peroxyl radicals [22].

Quinolinic acid

The demonstration that an intracerebroventricular injection of quinolinic acid (QUIN) causes seizure activity in mice [23] provided the first evidence that kynurenine pathway metabolites can have central effects. QUIN's excitatory properties are due to its direct, selective stimulation of NMDA receptors, as originally demonstrated using selective NMDA receptor antagonists [24]. Although its potency as an excitant is relatively low (ED_{50}: >100 μM), QUIN is remarkable for its preference for NMDA receptors in the forebrain. This regional selectivity is due to the fact that QUIN has a >10-fold lower affinity to the hindbrain-specific NR2C subunit of the NMDA receptor compared to the NR2B subunit, which predominates in the forebrain [25]. Differential subunit specificity notwithstanding, NMDA receptor activation seems to be obligatory for QUIN function as all neurobiological actions of QUIN described to date can be blocked by NMDA receptor antagonists.

QUIN also potently stimulates lipid peroxidation [26], and this effect is strictly dependent on the presence of Fe^{2+} ions [27]. The generation of reactive oxygen species by QUIN is secondary to the formation and autooxidation of Fe^{2+}-QUIN complexes and can be readily prevented by iron chelation [28]. Moreover, endogenous iron also directly controls the binding of QUIN to the NMDA receptor[29].

Metabolism and regulation of brain kynurenines

Formed by a sequence of mostly glial enzymes (Fig. 1), kynurenine pathway metabolites are normally present in the mammalian brain in concentrations in the nanomolar to low micromolar range [30–35]. With only one noteworthy exception — the high levels of KYNA in the human brain, which possibly signify exceptional neuroactive properties [36] — species differences are relatively minor, although brain concentrations differ with age and between brain regions. The brain activities of the two tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are normally quite low [37], and approximately 60% of metabolism along the kynurenine pathway in the brain is initiated by the pivotal metabolite kynurenine [38], which readily enters the brain from the circulation (see below) and is taken up by glial cells [39]. Intracerebral application of kynurenine in rats has revealed that approximately equal amounts of the primary degradation products 3-HK and KYNA are acutely produced from kynurenine under physiological conditions [40]. Notably, the synthesis of 3-HK and further downstream kynurenine pathway metabolites occurs in microglia, whereas KYNA is formed in astrocytes [41]. In other words, the two main arms of the kynurenine pathway are physically segregated in the brain (Fig. 2).

In contrast to several other kynurenine pathway metabolites, and because of their polar nature and the lack of transport processes, KYNA and QUIN do not cross the blood-brain barrier [42] and must be formed locally within the brain. Experimentally, both metabolites can be recovered from the extracellular milieu soon after their synthesis is stimulated by intracerebral infusions of their precursors kynurenine and 3-HANA, respectively [43–44]. QUIN release appears to be controlled only by bioprecursor availability [45], whereas the release of KYNA can be modulated by several factors. For example, KYNA formation and release decrease substantially in the presence of depolarizing stimuli such as high K^+ or veratridine, or under hypoglycemic conditions [46]. The latter phenomenon is linked to cellular energy metabolism and can be effectively reversed by adding lactate and pyruvate [47]. Like other 2-oxo acids, pyruvate also enhances the extracellular concentration of KYNA on its own by acting as a co-substrate in the transamination of kynurenine [48] (Fig. 2). Interestingly, dopamine may play a specific regulatory role as well, as D-amphetamine reduces KYNA levels in the brain but not in the periphery [49]. Several of these effects are lost in the absence of neurons, indicating that KYNA production in, and release from, astrocytes is dependent on neuronal signals [46]. Finally, although specific organic anion transporters for KYNA might exist in the brain [50], neither KYNA nor QUIN are efficiently removed from the brain's extracellular compartment. Brain efflux therefore constitutes the major disposal mechanism for both metabolites [33, 51].

Peripheral influences on the brain kynurenine pathway

Brain kynurenines are not autonomous but are linked to, and influenced by, the peripheral kynurenine pathway (Fig. 3). In peripheral organs, kynurenine pathway enzymes are regulated by steroids, growth factors and, most notoriously, several signaling molecules of the immune system [52–55]. It is uncertain to what extent these control mechanisms — including the best-known effect, the stimulation of IDO by interferon γ and other cytokines — operate in the brain under physiological conditions [34, 56]. As tryptophan, kynurenine and 3-HK readily cross the blood-brain barrier [42], it is clear, however, that fluctuations in the blood levels of these metabolites directly affect metabolism in the kynurenine pathway,

including the synthesis of KYNA and QUIN, in the brain. Of note, because of the rather low activity of brain IDO and TDO under physiological conditions (see above), the effects of systemic tryptophan on the brain kynurenine pathway are in part driven by its peripheral conversion to kynurenine and 3-HK, and the subsequent entry of these metabolites into the brain (Fig. 3).

Kynurenine pathway metabolites in normal brain function

In early studies, the effects of KYNA and QUIN, the only neuroactive kynurenine pathway metabolites known at the time, were almost always tested at very high, non-physiological concentrations, i.e. the two compounds essentially functioned as pharmacological probes to examine the downstream effects of glutamate receptor manipulations. These experiments revealed, not unexpectedly, a multitude of chemical and functional consequences, but they were not overly informative with regard to a role of endogenous kynurenines in the mammalian brain. Owing to a lack of appropriate experimental approaches, these studies also failed to identify possible effects of a selective reduction in brain KYNA or QUIN levels.

The development of increasingly specific and potent pharmacological agents targeting individual enzymes in the kynurenine pathway (see below and Table 1) has gradually begun to transform our understanding of the functional roles of kynurenines in the brain. Most of these “kynurenergic” tools are still not ideal, and many of these compounds must be applied intracerebrally because they do not penetrate the blood-brain barrier after systemic administration. Nevertheless, the emerging new tools allow investigations of endogenous kynurenine pathway metabolites *in situ*, i.e. in an environment that maintains the natural anatomical arrangements between glial cells, which synthesize and release kynurenines, and adjacent neurons, which seem to play only a minor role in the production of kynurenine pathway metabolites [57–58].

Studies in which KYNA is administered in concentrations in the endogenous range, studies using selective inhibitors of KYNA’s main biosynthetic enzyme kynurenine aminotransferase II (KAT II), as well as studies using KAT II knockout mice [59], have revealed a broad neuromodulatory role of KYNA on brain chemistry. Thus, within various regions of the rodent forebrain, even modest increases in KYNA cause prompt reductions in extracellular glutamate and dopamine levels [60–61], whereas KYNA synthesis inhibition raises the levels of these neurotransmitters [10, 62], as well as acetylcholine levels[63]. Pharmacological experiments using selective receptor agonists and antagonists (such as galantamine and methyllicaconitine, respectively) indicate that α7nAChRs, rather than NMDA receptors, are the primary target of endogenous KYNA in the normal brain *in vivo* and mediate these bi-directional effects of KYNA on neurotransmitter levels [10, 60–61]. This suggests, conversely, that α7nAChRs and their many physiological functions [64] are controlled by endogenous KYNA.

Fluctuations in brain KYNA levels have distinct behavioral consequences, especially related to cognition. Administered to normal rats and following conversion to nanomolar or low micromolar concentrations of KYNA in the brain, systemic administration of kynurenine causes impairments in visuospatial working memory, contextual learning, sensory gating, and prepulse inhibition of the acoustic startle reflex — all behaviors linked to cholinergic, glutamatergic and dopaminergic neurotransmission [65–68]. Notably, the effect of KYNA on dopaminergic neurotransmission has also been convincingly demonstrated electrophysiologically. Thus, systemic administration of kynurenine, or relatively moderate elevation of brain KYNA levels by pharmacological means, reliably affects the firing of dopaminergic neurons in the midbrain, influencing downstream projection areas such as the

striatum, the nucleus accumbens and the prefrontal cortex [69–70]. Conversely, specific reductions in brain KYNA, caused by genetic elimination of KAT II or acute administration of a KAT II inhibitor, improve contextual memory and spatial discrimination [71] and enhance spatial memory [72] (see below).

Additional mutant mice and enzyme inhibitors (Table 1) have recently become available for studying the complex interplay of peripheral and central kynurenines. These experimental tools are beginning to be used to systematically examine the physiological roles of kynurenine pathway metabolites in the brain [57, 73–75].

Kynurenines in neurological diseases

Kynurenines did not attract significant attention from neurobiologists until the pathological effects of QUIN in the brain were recognized three decades ago. In addition to its usefulness as a readily available, inexpensive excitotoxin, QUIN became recognized for its ability to model neuropathological, neurochemical and clinical features of human diseases such as Huntington's disease and temporal lobe epilepsy [76], raising the specter that an abundance of endogenous QUIN might play a causative role in the pathophysiology of these and other neurological diseases. The discovery of KYNA's neuroprotective and anticonvulsant effects [77] then led to the idea that a reduction in endogenous KYNA or, more generally, any process resulting in an abnormal increase in the QUIN:KYNA ratio in the brain might trigger neuronal lesions in various conditions linked to excitotoxic phenomena [78–80]. However, skepticism concerning a possible pathogenic role of endogenous kynurenine pathway metabolites abounded, especially because endogenous concentrations of QUIN and KYNA in the brain are orders of magnitude lower than those needed to model neurological diseases acutely in rodents or primates *in vivo*.

Huntington's disease

Evidence for a pathophysiologically significant role of abnormal metabolism in the kynurenine pathway is most compelling in the case of Huntington's disease, the first and prototypical disease linked to an excitotoxic mechanism. Studies in post-mortem brains revealed that QUIN levels are substantially elevated in the initial stages of the disease, and especially in those brain regions (neostriatum, cortex) that suffer the most damage [81]. This increase, which coincides with early activation of microglia [82], generates QUIN concentrations that are clearly capable of producing excitotoxic neuronal damage [83–84]. Notably, the elevation in brain QUIN levels in Huntington's disease is accompanied by a quantitatively similar increase in cerebral 3-HK levels [81, 85]. The concentrations of 3-HK reached in the disease are neurotoxic to striatal neurons but, interestingly, not to cerebellar neurons [86]. Of possible pathogenic significance, the neurotoxic properties of these two microglia-derived kynurenine pathway metabolites are synergistic [87–88]. Reductions in brain KYNA levels in Huntington's disease [89] could be physiologically relevant as well, as a deficiency in KYNA enhances vulnerability to QUIN neurotoxicity [90]. Similar changes in the cerebral kynurenine pathway — most reliably the increase in 3-HK levels —, are also seen in mouse models of Huntington's disease [91–92].

The most persuasive arguments favoring a causative link between abnormal kynurenine pathway function and Huntington's disease pathology comes from work in lower model organisms. Thus, a genome-wide loss-of-function screen in yeast showed that the deletion of kynurenine 3-monooxygenase (KMO) potently suppresses the toxicity of a mutant huntingtin fragment, and that elimination of KAT exacerbates toxicity [93]. Interestingly, deletions in the genes encoding 3-hydroxyanthranilic acid dioxygenase (3HAO) and nicotinate phosphoribosyltransferase suppress and enhance, respectively, mutant huntingtin toxicity. Surprisingly, the majority of functionally unrelated genetic suppressors of mutant

huntingtin toxicity in yeast decrease the levels of 3-HK and QUIN, indicating that the kynurenine pathway plays a critical downstream role in the toxic effects of mutant huntingtin [94]. As yeast do not have glutamate receptors, abnormal mitochondrial function and reactive oxygen species, rather than excitotoxicity, link kynurenine pathway manipulations to cell death in this model of Huntington's disease. These factors may therefore also contribute to some aspects of neurodegeneration in the human disease [93]. In a transgenic Drosophila melanogaster model of Huntington's disease, genetic or pharmacological KMO inhibition increased levels of KYNA relative to 3-HK (flies do not produce QUIN) and ameliorated neurodegeneration. Underscoring the roles of 3-HK and KYNA in neuropathology, the neuroprotective effect of KMO inhibition is reduced by feeding the flies 3-HK, whereas feeding KYNA attenuates neurodegeneration. These interventions have no obvious effects in wild-type control flies, indicating that vulnerable organisms are excessively sensitive to manipulations of the kynurenine pathway [95].

Other neurological diseases

Cerebral kynurenine pathway changes also occur in other neurodegenerative diseases but have not been studied comprehensively. Thus, in the basal ganglia of patients with Parkinson's disease, the concentration of 3-HK is increased, whereas kynurenine and KYNA levels are slightly reduced [96]. In Alzheimer's disease, QUIN immunoreactivity is strongest in glial cells in close proximity to amyloid plaques and also labels neurofibrillary tangles, suggesting that QUIN-induced excitotoxicity or oxidative stress might participate in the pathogenic process [97]. Immunocytochemical studies of IDO and 3-HK provide further evidence that the kynurenine pathway is upregulated in the disease [98]. Also indicative of a role of the kynurenine pathway in Alzheimer's disease, QUIN induces tau phosphorylation in cultured primary human neurons [99].

As predicted from studies in rodent models [23, 100–102], human seizure disorders are also associated with abnormal cerebral kynurenine pathway activity. Of special interest, this impairment can be documented non-invasively by positron emission tomography using ^{11}C-α-methyl-L-tryptophan as a tracer. This *in vivo* imaging methodology, which has so far been used mainly in glioma and epilepsy research, allows the simultaneous assessment of serotonin and kynurenine synthesis in the human brain with high specificity and good sensitivity. The technology has revealed enhanced tryptophan retention and subsequent activation of kynurenine pathway metabolism in gliotic tissue, and can be used to identify epileptogenic lesions interictally and to guide tissue resection during surgery in patients with epilepsy [103]. Once kynurenine pathway metabolites downstream from kynurenine can be reliably identified through further methodological improvements, such imaging techniques — applied longitudinally and in combination with assessments of kynurenine pathway metabolites in blood and cerebrospinal fluid (CSF) — could revolutionize our understanding of kynurenine pathway neurobiology in health and disease.

Studies in animal models have shown that connections between abnormal kynurenine pathway metabolism and neuropathology also exist in animals experiencing acute metabolic or physical insults, such as hypoglycemia [104], cerebral ischemia [105], perinatal hypoxia [106] or traumatic spinal cord injury [107], even though these non-specific events clearly induce and probably involve a multitude of additional pathogenic mechanisms.

Because of the complex interactions between peripheral and central kynurenine pathways, studies describing kynurenine pathway abnormalities in blood, cultured cells and CSF in various human neurological disorders (see [108–110] for reviews) are not unequivocally instructive about the contribution of these abnormalities to the disease. Nevertheless, such studies, including the numerous demonstrations of peripheral IDO activation in neurological disorders, are often useful as predictors and indicators of abnormal kynurenine pathway

function within the brain (see below). They can also help to assess the involvement of kynurenine pathway abnormalities in models of neurological diseases, especially those induced by known pathogens, for example malaria or trypanosome parasites [111–113].

The role of inflammatory mechanisms

Together with other, disease-specific etiological factors, chronic neuroinflammation plays an increasingly appreciated role in the pathogenesis of a large number of neurological diseases [114–115]. Underlying events include brain infiltration of circulating immune cells, activation of resident microglia and other non-neuronal cells, and brain influx of blood-derived, pro-inflammatory cytokines and other immune activators. Alone or jointly, these mechanisms are responsible for the enhanced synthesis of kynurenine from tryptophan within the brain [34, 56] and the subsequent activation of the cerebral kynurenine pathway. In fact, both systemic and central immune stimulation, including cytokine-induced IDO activation, may contribute to cerebral kynurenine pathway activation in neurological disorders (Fig. 3). Not unexpectedly, therefore, the brain kynurenine pathway is often turned on in diseases of viral origin. Common to all these diseases, increases in 3-HK and QUIN levels in the brain outweigh the elevation in KYNA by substantial margins — most dramatically in the case of HIV-1-infected individuals [116–117]. This robust increase in neurotoxic metabolites suggests that blood-derived or locally produced kynurenine is preferentially degraded within activated microglial cells and macrophages [118], but is less available for sequestration to KYNA in astrocytes (Fig. 3).

Kynurenines in psychiatric disorders

Major depressive disorders

Speculation about a role of kynurenines in major depressive disorders dates back several decades to the time when the connection between depression, tryptophan and serotonin was first recognized [119]. However, the exceptional success of serotonin re-uptake inhibitors as antidepressants, paired with the lack of consistent indications of kynurenine pathway changes in depression, essentially stifled efforts to explore a possible involvement of kynurenine pathway metabolites in pathophysiology. However, studies performed during the past 10 years have led to a significant paradigm shift in this regard, and kynurenine pathway dysfunction is now increasingly recognized as a major player in the development and symptomatology of depressive disorders. Similar in principle to the above-mentioned neuro-immune hypothesis of neurological disorders, the pathophysiological concept is based on the realization that the kynurenine:tryptophan ratio in blood is significantly enhanced in patients with depression and correlates with anxiety and cognitive deficits, but not with neurovegetative or somatic symptoms [120–121]. Several lines of evidence indicate that immune system activation of IDO plays a central role here. First, a number of pro-inflammatory cytokines that are known to stimulate IDO, such as interferon α, induce depressive symptoms in patients suffering from cancer or chronic hepatitis C [121–122]. Second, following bacterial infection in mice, chronic up-regulation of IDO by interferon γ or tumor necrosis factor α (TNFα) induces long-lasting depressive-like behaviors, and these effects are largely attenuated when the increase in IDO activity is diminished [123]. Finally, vulnerability to cytokine-induced depression is associated with a polymorphism in *IDO* [124], providing a possible explanation for clinical heterogeneity in the occurrence of depressive symptoms following stimulation of the immune system. Interestingly, bacterial infection also stimulates IDO activity in the placenta [125] and may thus contribute to post partum-depression [126].

How systemic IDO activation — i.e. an excess of circulating kynurenine levels — might lead to depressive behaviors is unclear. Immunohistochemical studies show some microglial

activation (and QUIN immunoreactivity) as well as a reduction in astrocyte numbers in animal models of depression and in post-mortem brains of patients with major depression [127–130]. Like in neurological diseases, but to a lesser extent, enhanced kynurenine influx from the periphery may therefore enhance ratio between the neurotoxic metabolites, i.e. 3-HK and QUIN, and the neuroprotective KYNA. This could increase neuronal vulnerability and adversely affect, for example, the viability of newly generated hippocampal neurons, which are arguably necessary to avert or attenuate depression [131–132]. However, in humans, QUIN and KYNA levels are equally enhanced in the CSF after immune stimulation with interferon α [122], suggesting a more complicated scenario. Moreover, any changes in the cerebral kynurenine pathway in depression may be brain region-specific, as 3-HK levels are reduced in the cortex but enhanced in the striatum and amygdala in an established mouse model of the disease [133]. Definitive resolution of the respective roles of the two kynurenine pathway branches in depression must therefore await improved imaging of brain kynurenine pathway metabolism (see above) and targeted pharmacological interventions in humans and appropriate animal models.

Schizophrenia

Assessment of kynurenine pathway involvement in schizophrenia initially followed a similar trajectory as that for major depression, with early studies failing to establish pathophysiologically significant links [134]. The realization that the psychotomimetic drug ketamine, which produces schizophrenia-like symptoms in normal individuals and exacerbates psychotic features in patients with schizophrenia [135–136], functions as a NMDA receptor antagonist [137], led to the idea that excessive KYNA (by reducing NMDA receptor activity) or an increased ratio of KYNA on one hand, and 3-HK and its downstream metabolites on the other, might play a role in schizophrenia pathology [138]. Brain levels of KYNA are indeed elevated in postmortem brains of patients with schizophrenia, and this increase, which is also seen in the CSF, is unrelated to chronic medication with antipsychotic drugs [139–142]. Brain levels of 3-HK levels, on the other hand, are unchanged [140]. Measurements of the expression and activity of kynurenine pathway enzymes in brain areas known to be involved in schizophrenia pathology (i.e. frontal and anterior cingulate cortices) suggest a scenario in which a reduction in KMO [142–143], combined with an increase in TDO [144–145], increases kynurenine levels [140] and thereby shifts kynurenine pathway metabolism towards enhanced KYNA formation (see Fig. 1). Kynurenine levels are indeed increased in the prefrontal cortex and CSF in patients with schizophrenia [140, 146], possibly as a consequence of peripheral neuroinflammation, which exists in schizophrenia as well (Fig. 3) [147–148]. As explained earlier, a preferential elevation in KYNA levels, leading to tissue concentrations in the high nanomolar range, would then result in increased inhibition of α7nAChRs, subsequently causing an imbalance in glutamate, dopamine and acetylcholine systems, all of which have been linked to schizophrenia pathology [91–95, 149].

Studies in animals and humans indicate that elevated KYNA levels may be especially relevant for the cognitive deficits seen in schizophrenia. Thus, in rats, acute KYNA elevation in the prefrontal cortex causes the characteristic impairment in cognitive flexibility seen in schizophrenia [150–151]. Moreover, experimentally induced increases in KYNA synthesis in the developing brain, perhaps mimicking prodromal events in schizophrenia, produce long-lasting deficits in spatial and contextual learning and memory, as well as impaired cognitive flexibility, in the adult animal [152–155]. Finally, in schizophrenia patients, a single nucleotide polymorphism (SNP) in the KMO gene is associated with smooth pursuit eye movement and visuospatial working memory [143, 156]. The study of kynurenine pathway metabolism in schizophrenia, and possibly also in other psychiatric diseases (such as bipolar disorder, drug abuse and autism spectrum disorders; [157–159]), may therefore be particularly

rewarding using an approach focused on distinct sub-domains of psychopathology (endophenotypes).

Targeting the kynurenine pathway

An increasingly diverse armamentarium of pharmacological agents has been developed for the study of the kynurenine pathway in health and disease (Table 1). Alone or in combination with exogenously supplied kynurenines, specific enzyme inhibitors can now be used to examine physiological events in the brain and to normalize cerebral kynurenine pathway function when needed. Two classes of inhibitors, targeting KAT II and KMO, respectively, have so far contributed most to our understanding of kynurenine pathway neurobiology.

KAT II inhibitors

The first-generation specific KAT II inhibitor, (*S*)-4-(ethylsulfonyl)benzoylalanine (ESBA), was introduced in 2006 [160] and turned out to be an excellent tool for examining the disposition and function of endogenous KYNA in the rat brain. Irrespective of brain region and dosage, intracerebral application of ESBA or other KAT II inhibitors causes no more than a 30–40% reduction in extracellular KYNA, indicating that KAT II controls only a fraction of KYNA in the extracellular milieu *in vivo*. This relatively small decrease is sufficient, however, to significantly increase the extracellular concentrations of glutamate, dopamine and acetylcholine, i.e. the same neurotransmitters that are reduced when KYNA levels are even moderately elevated (see above). This suggests that the KAT II-dependent pool of KYNA, which can be readily mobilized, provides tonic inhibition of its central receptor target(s). Notably, preliminary data demonstrate that the pro-cognitive effects of genetic elimination of KAT II [71] or acute application of ESBA [72] (Fig. 4) mentioned above can be duplicated by administration of second-generation, brain-penetrable KAT II inhibitors [161–162], and that this intervention also attenuates ketamine-induced working memory deficits in monkeys [163–164]. These results bode well for the use of KAT II inhibitors in humans, especially in diseases like schizophrenia, where cognitive deficits might be related to high brain KYNA levels (Fig. 5).

KMO inhibitors

First-generation KMO inhibitors demonstrated anticonvulsant and neuroprotective efficacy in various model systems *in vivo* [90, 95, 165–167]. Ro 61-8048, the most widely used KMO inhibitor, was introduced in 1997 [168]. This compound has pronounced neuroprotective and anti-dyskinetic effects when used systemically in animal models of focal or global ischemia [169] and L-dopa-induced dyskinesia [170], respectively. Ro 61-8048 also has substantial anti-inflammatory effects in an animal model of sleeping sickness [113] and delays death in a mouse model of cerebral malaria [171]. Like all KMO inhibitors tested so far, Ro 61-8048 raises brain KYNA levels following systemic application, and this increase is probably responsible for the remarkable central effects of the compound. In normal animals, the increase in brain KYNA is not accompanied by a reduction in the levels of brain 3-HK and QUIN, suggesting that the enzyme inhibitor does not cross the blood-brain barrier. This was verified in the course of a recent study demonstrating neuroprotection with JM6, a pro-drug of Ro 61-8048, in mouse models of Huntington's disease and Alzheimer's disease (Fig. 4). Thus, the beneficial effects of JM6 treatment were achieved exclusively through peripheral KMO inhibition, leading to moderate, persistent elevations of brain KYNA levels [172]. Interestingly, application of a KMO inhibitor in conditions of strong immune stimulation, perhaps involving KMO blockade in activated endothelial cells and pericytes of the blood-brain barrier, causes a reduction in brain 3-HK and QUIN levels within the brain

parenchyma [173–174]. This may provide additional benefit to patients with neurodegenerative diseases (Fig. 5).

Other kynurenine pathway inhibitors

Inhibitors of IDO and TDO, prominent as potential cancer therapies [175–176], have so far not been used to study the cerebral kynurenine pathway directly, although these enzyme inhibitors might offer innovative, novel treatment options for brain tumors and for neurological and psychiatric diseases that are caused or exacerbated by immune system dysfunction. Of other agents targeting individual kynurenine pathway enzymes specifically, kynureninase inhibitors [177–178] and the 3HAO inhibitor 4-Cl-3-hydroxyanthranilic acid [179] have been sparingly but successfully used in neurobiological research. Most interestingly, 4-Cl-3-hydroxyanthranilic acid, an effective blocker of microglial QUIN neosynthesis *in vivo* [180], preserves white matter and effects functional recovery in a model of spinal cord injury, without, however, enhancing KYNA levels [181].

Challenges for future research

It is clear that the kynurenine pathway, a highly conserved metabolic machinery, has evolved to serve important regulatory functions in the mammalian brain. As we explore the largely unknown role(s) of kynurenines in cell biology, we are likely to uncover the functional significance of distinct intracellular processes they might influence. Specific questions abound. For example, does the strict association of KMO with the outer mitochondrial membrane [182] signify a specific mitochondrial function of 3-HK or downstream metabolites? More generally, is there a physiological role for the pro- and anti-oxidative effects of KYNA, 3-HK and 3-HANA [14–15, 20–22] or for the ability of QUIN [28] or picolinic acid [183] to chelate bioactive metal ions? Are any of these intracellular functions brain-specific, and do they differ between various glial cells or between resting and activated glia? And if so, what are the functional consequences of this diversity?

Another promising line of investigation, which has been only sparingly pursued so far [125, 184–185], will explore the possibility that the role of brain kynurenines changes over the course of the life span. Do kynurenines derived from the mother shape metabolism along the kynurenine pathway, and the function of pathway metabolites, in the fetal brain? Do kynurenines, maybe through their involvement in mitochondrial processes and oxidative stress, contribute to apoptotic cell death in the aged brain? Or, more generally, are the neuromodulatory effects of kynurenines age-specific, perhaps involving qualitatively distinct intra- and intercellular mechanisms during brain development and during ageing?

For several reasons, further elucidation of the mechanisms that control and maintain equilibrium between peripheral and central kynurenine pathways in mammals will probably remain a major research objective. First, normal homeostasis between the two compartments is delicate and complex, and influenced by a considerable number of environmental and physiological factors. These mechanisms are still poorly understood. Second, as briefly reviewed here, changes in the levels of circulating kynurenines under inflammatory conditions can either increase (in neurological disorders) or reduce (in schizophrenia) the ratio between neurotoxic and neuroprotective kynurenine pathway metabolites in the brain. Resolution of this puzzling quandary, which has pathophysiologically relevant implications, will require a thorough assessment of kynurenine pathway function in multiple brain cell types and various disease models. These studies will clarify, in essence, how physiology can be usurped to produce distinct brain pathologies. Finally, new information is needed to confidently predict the desired physiological effects or clinical improvements caused by selective kynurenine pathway enzyme inhibitors (see above). To optimize efficacy and minimize the risk of adverse side effects, especially when used in conjunction with other

drugs, it will be especially important to discriminate between the consequences of peripheral and central enzyme inhibition and to compare acute and chronic effects of novel pharmacological agents. As shown in Fig. 5, illustrating the effects of manipulating the KYNA:3-HK ratio in the brain under physiological and pathological conditions, interventions with specific "kynurenergic" drugs must then be carefully tailored to achieve the intended benefit and avoid harmful outcomes. Successful improvement of brain function or effective treatment of brain disorders by selective targeting of individual kynurenines in the human brain would constitute the ultimate reward of these efforts.

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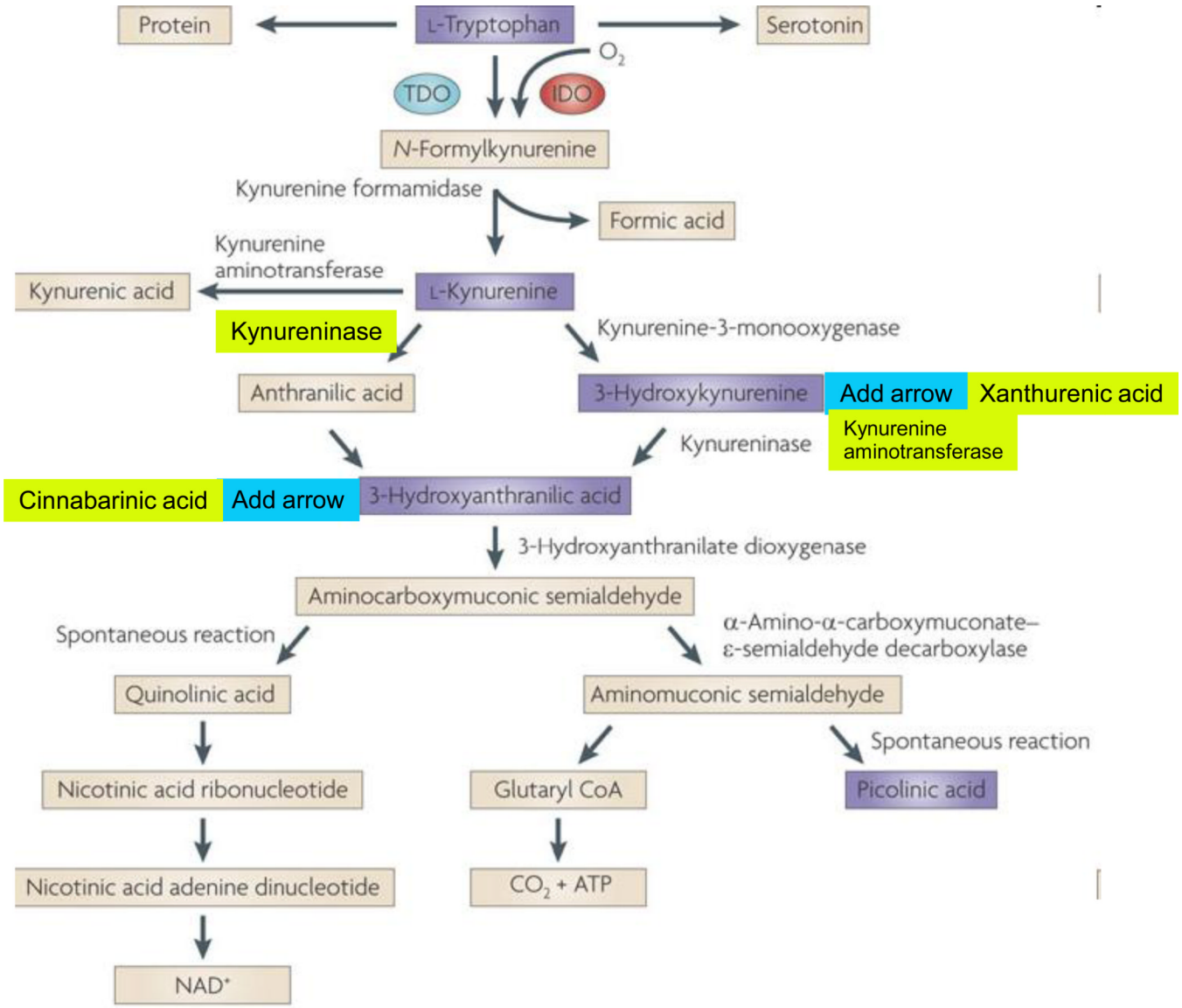


Figure 1. The kynurenine pathway of tryptophan degradation in mammals

The kynurenine pathway is initiated by the transformation of tryptophan to N-formylkynurenine by indoleamine 2,3-dioxygenases (IDO) 1 [186] and 2 [187], and tryptophan 2,3-dioxygenase (TDO) [188]. N-formylkynurenine is degraded by formamidase to yield the pivotal metabolite kynurenine. Compared to peripheral organs, the activities of these enzymes in the brain are normally low. Kynurenine undergoes irreversible transamination to form kynurenic acid (KYNA). Four kynurenine aminotransferases (KATs) have so far been shown to catalyze this reaction [189]. In the mammalian brain, KAT II is thought to be the main biosynthetic enzyme of KYNA as it does not recognize competing abundant amino acids as substrates [190]. No degradative enzyme of KYNA has yet been described in the mammalian brain.

A second branch of the kynurenine pathway, competing with KYNA synthesis by KATs, is initiated by kynurenine 3-monooxygenase (KMO) and kynureninase, which catalyze the degradation of kynurenine to 3-hydroxykynurenine (3-HK) and anthranilic acid, respectively [177]. The *in vivo* disposition of kynurenine in the brain depends on the cellular

localization, intracellular compartmentalization and kinetic characteristics of these two degradative enzymes, as well as KATs [41, 57]. Like kynurenine, 3-HK serves as a substrate of competing enzymes: kynureninase and KAT II. Mammalian kynureninase preferentially recognizes 3-HK over kynurenine, catalyzing the formation of 3-HANA [191]. Compared to peripheral organs and for unknown reasons, anthranilic acid is a far better precursor of 3-HANA than 3-HK within the brain [30]. KAT II, and possibly other KATs, convert 3-HK to xanthurenic acid, which, like KYNA, appears to constitute a dead-end product of the kynurenine pathway.

In addition to being oxidized non-enzymatically to cinnabarinic acid, 3-HANA is the substrate of 3-hydroxyanthranilic acid 3,4-dioxygenase (3HAO), which is present in relative abundance in the brain [192], forming α-amino-α-carboxymuconic-ω-semialdehyde. The kynurenine pathway branches then branches into two arms. Under physiological conditions, α-amino-α-carboxymuconic-ω-semialdehyde spontaneously rearranges to form QUIN with a half-life of approximately 20 minutes. QUIN synthesis may therefore be regulated both at the level of 3HAO (for example by Fe^{2+} [193]) and by changes in the intracellular milieu (pH, temperature) to influence the second, non-enzymatic step. Notably, the brain seems to contain very little α-amino-α-carboxymuconic-ω-semialdehyde carboxylase, an enzyme which deflects the metabolic cascade towards the production of picolinic and glutaric acids [194]. The cerebral activity of QUIN's degradative enzyme, quinolinate phosphoribosyltransferase, is very low [195], making this enzyme one of the gatekeepers for the synthesis of NAD^+ [196–197].

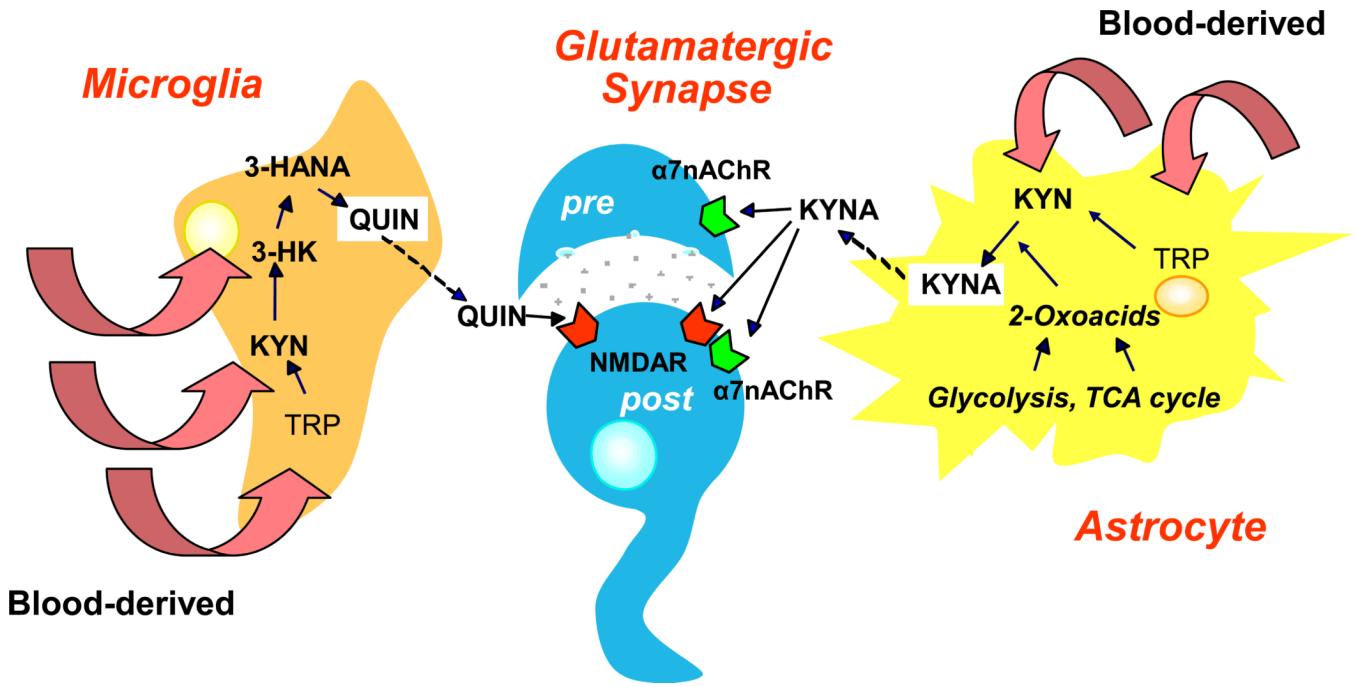
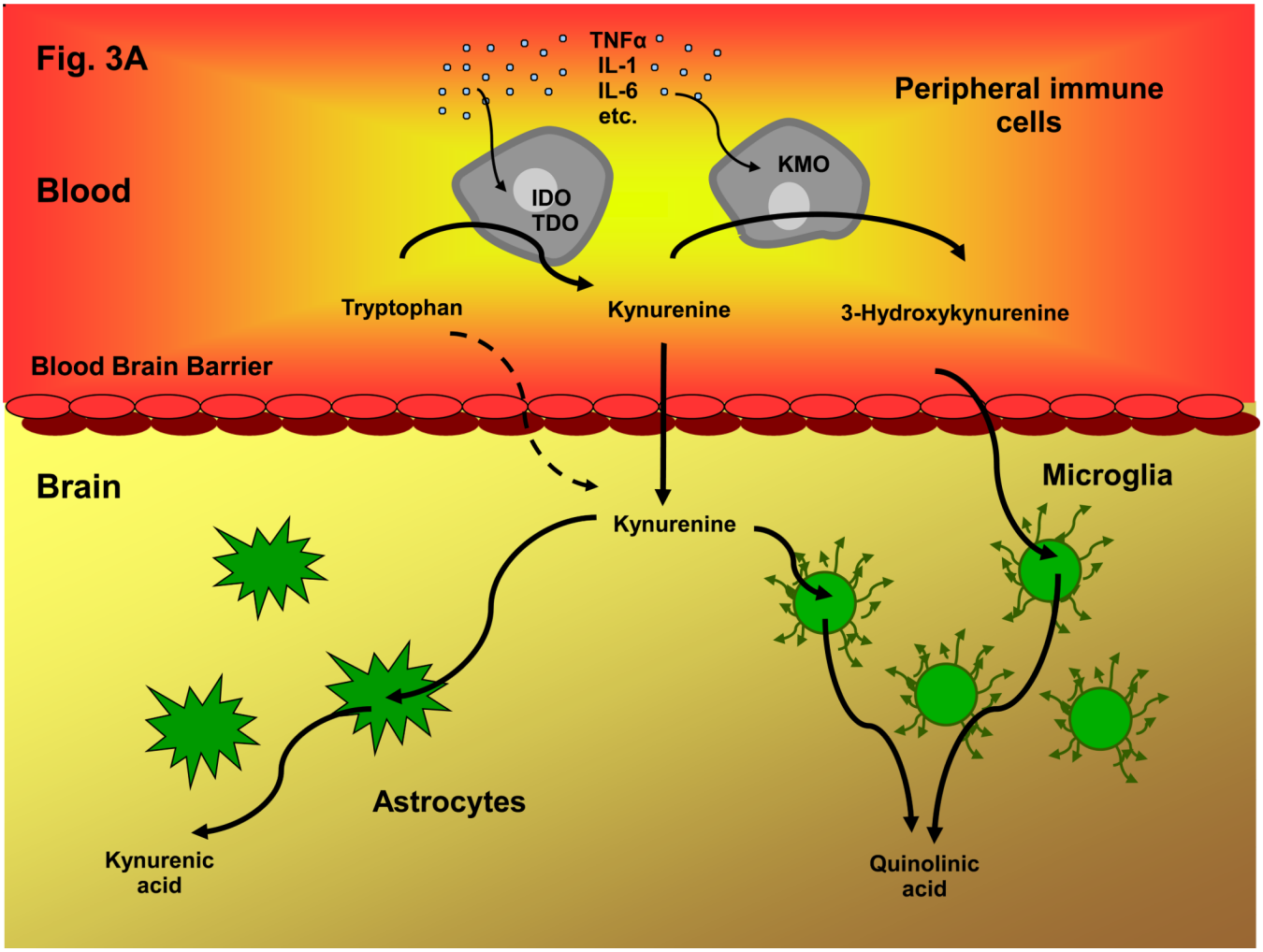


Figure 2. Segregation of the two Kynurenine Pathway Branches in the Brain

Under physiological conditions, kynurenine pathway enzymes in the mammalian brain are preferentially, although not exclusively, localized in non-neuronal cells [57–58]. Metabolism of the pathway is driven by blood-derived tryptophan (TRP), kynurenine (KYN) or 3-hydroxykynurenine (3-HK), or by locally formed metabolites. Of functional significance, the two branches of the pathway are physically segregated in the brain. Astrocytes, which harbor KATs but do not contain KMO and therefore cannot produce 3-HK from KYN [41, 198–199], account for kynurenic acid (KYNA) biosynthesis, which is regulated by intracellular metabolic events [46–48]. 3-HK and its major downstream metabolites are synthesized in microglial and other cells of monocytic origin [118, 200]. Once synthesized within glial cells, quinolinic acid (QUIN) and KYNA are promptly released into the extracellular milieu to affect their pre- and postsynaptic (“pre” and “post”) neuronal targets. 3-HANA: 3-Hydroxyanthranilic acid, α7nAChR: α7 nicotinic acetylcholine receptor, TCA: Tricarboxylic acid.



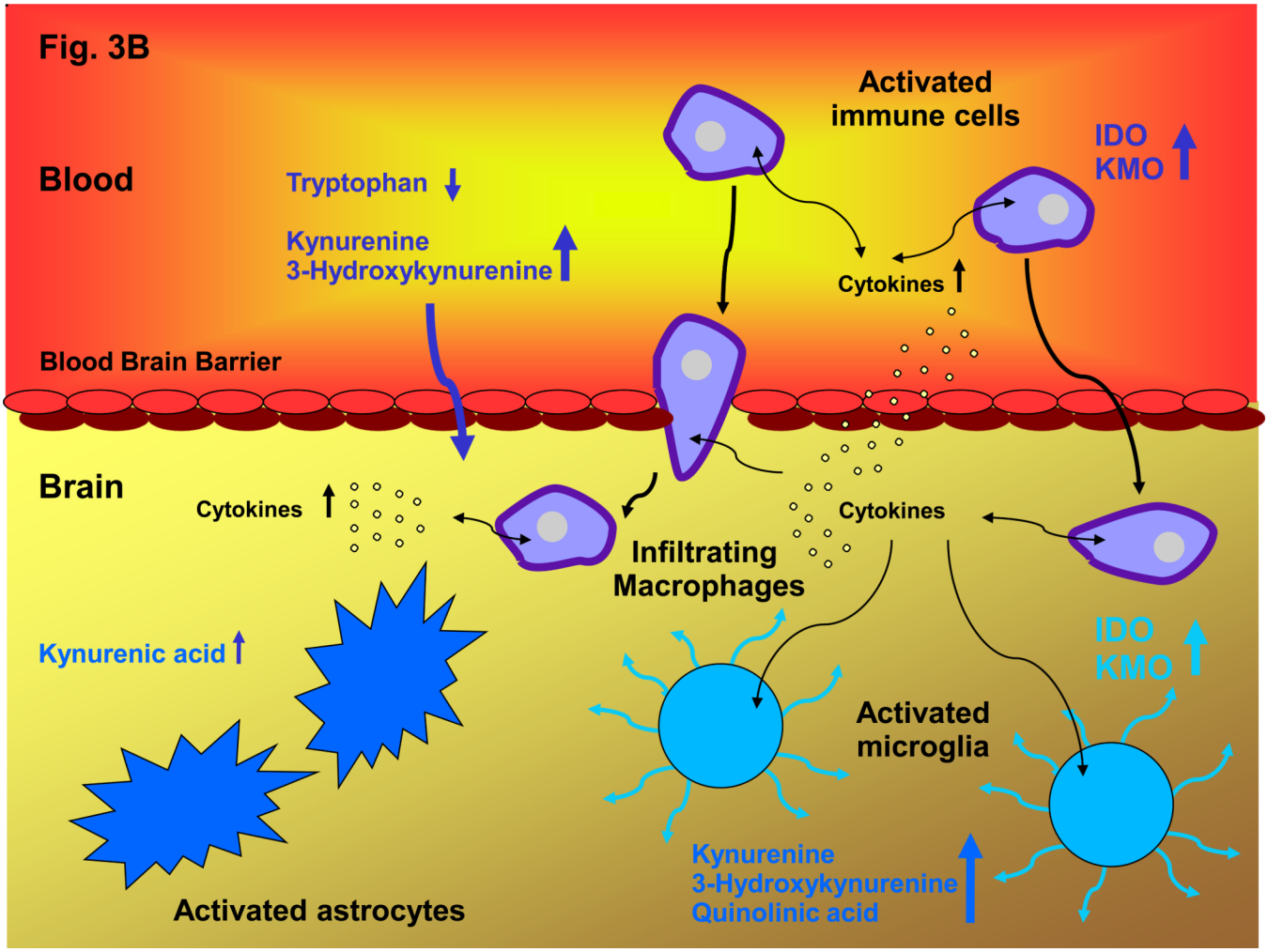
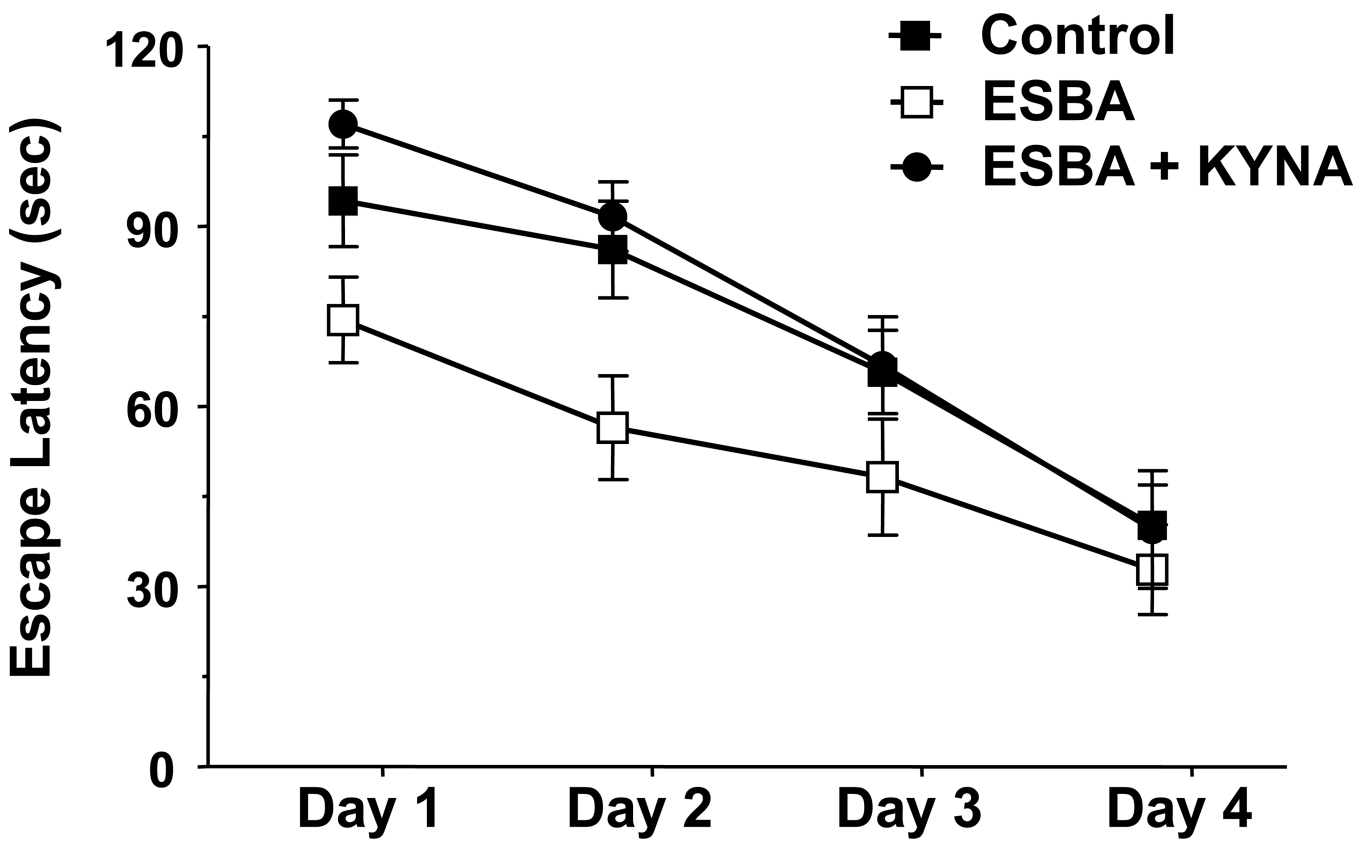


Figure 3. Communication between Peripheral and Central Kynurenine Pathways under Normal and Inflammatory Conditions

A: In the periphery, the degradation of tryptophan and the subsequent formation of circulating kynurenines is normally regulated by steroid hormones, cytokines and growth factors. These factors stimulate IDO [123, 175], and also activate, or lead to the up-regulation of, other kynurenine pathway enzymes including TDO [201] and KMO [118, 132]. Jointly, they control the levels of circulating tryptophan, kynurenine and 3-HK, which all readily cross the blood-brain barrier using the large neutral amino acid transporter [42]. Together with kynurenine pathway metabolism within glial cells, brain uptake of these kynurenines therefore determines kynurenine pathway flux in the brain; **B:** Inflammatory conditions stimulate the kynurenine pathway both in the periphery and in the brain. Activation of kynurenine pathway enzymes, especially IDO and KMO, in peripheral immune cells – such as dendritic cells and macrophages – promotes the production of kynurenine and its downstream metabolites in the blood. Increased influx of the brain-permeable metabolites, in some cases aided by a leaky blood-brain barrier [173], as well as infiltration of macrophages or microbial pathogens [113], then leads to an excess of kynurenines in the brain parenchyma. Furthermore, infiltrating cytokines stimulate the kynurenine pathway in activated microglial cells and blood-borne cells within the brain [202]. Together, these peripheral and central events connect neuroinflammatory mechanisms with abnormal metabolism along the kynurenine pathway, and brain pathology.



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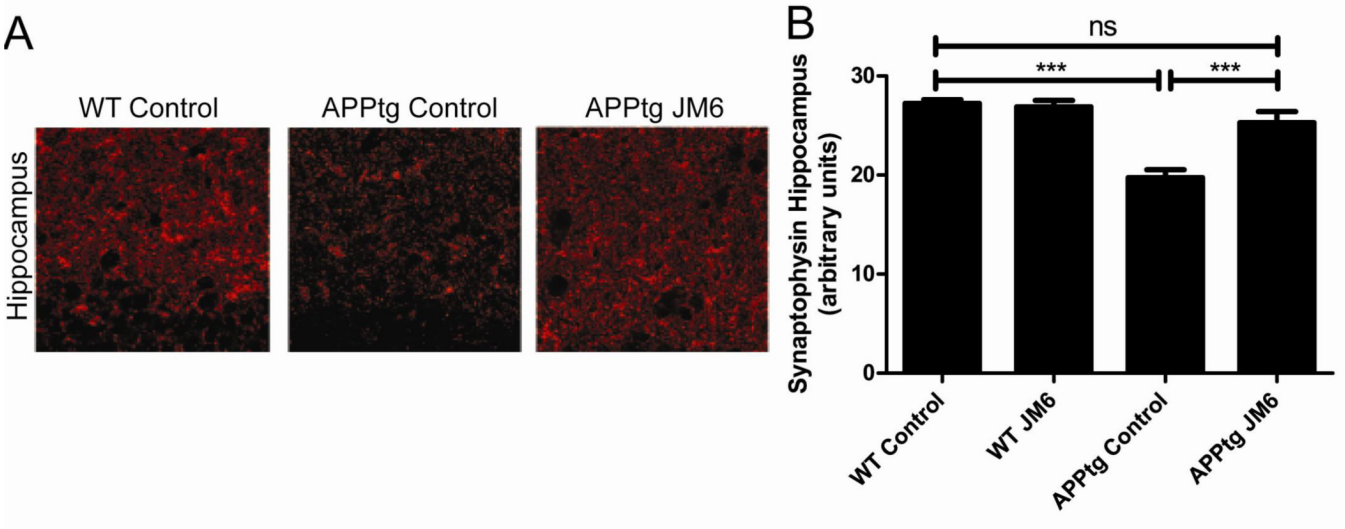

B

Figure 4. Effects of Kynurenine Pathway Manipulation on Cognition and Neurodegeneration

A: Inhibition of endogenous KYNA synthesis with the KAT II inhibitor (*S*)-4-(ethylsulfonyl)benzoylalanine (ESBA), administered intracerebroventricularly 90 min prior to daily training (Days 1–4), facilitates learning in a spatial working memory task (the Morris water maze test) in normal rats. Co-administration of KYNA eliminates this effect (see [72] for details); **B:** JM6, a peripherally acting pro-drug of the KMO inhibitor Ro 61-8048, prevents synaptic loss in a transgenic mouse model of Alzheimer's disease (APPtg mice). JM6 was administered orally for 120 days, and the brain was evaluated in 8-month-old APPtg mice. Left: Representative image (630X) of serial sections of the hippocampus of wild-type or APPtg mice immunostained with an antibody for synaptophysin. Right: Quantification of synaptophysin levels in the hippocampus of APPtg mice treated with JM6. Synaptophysin levels in APPtg mice treated with JM6 are not significantly different from those found in wild-type mice (see [172] for details).

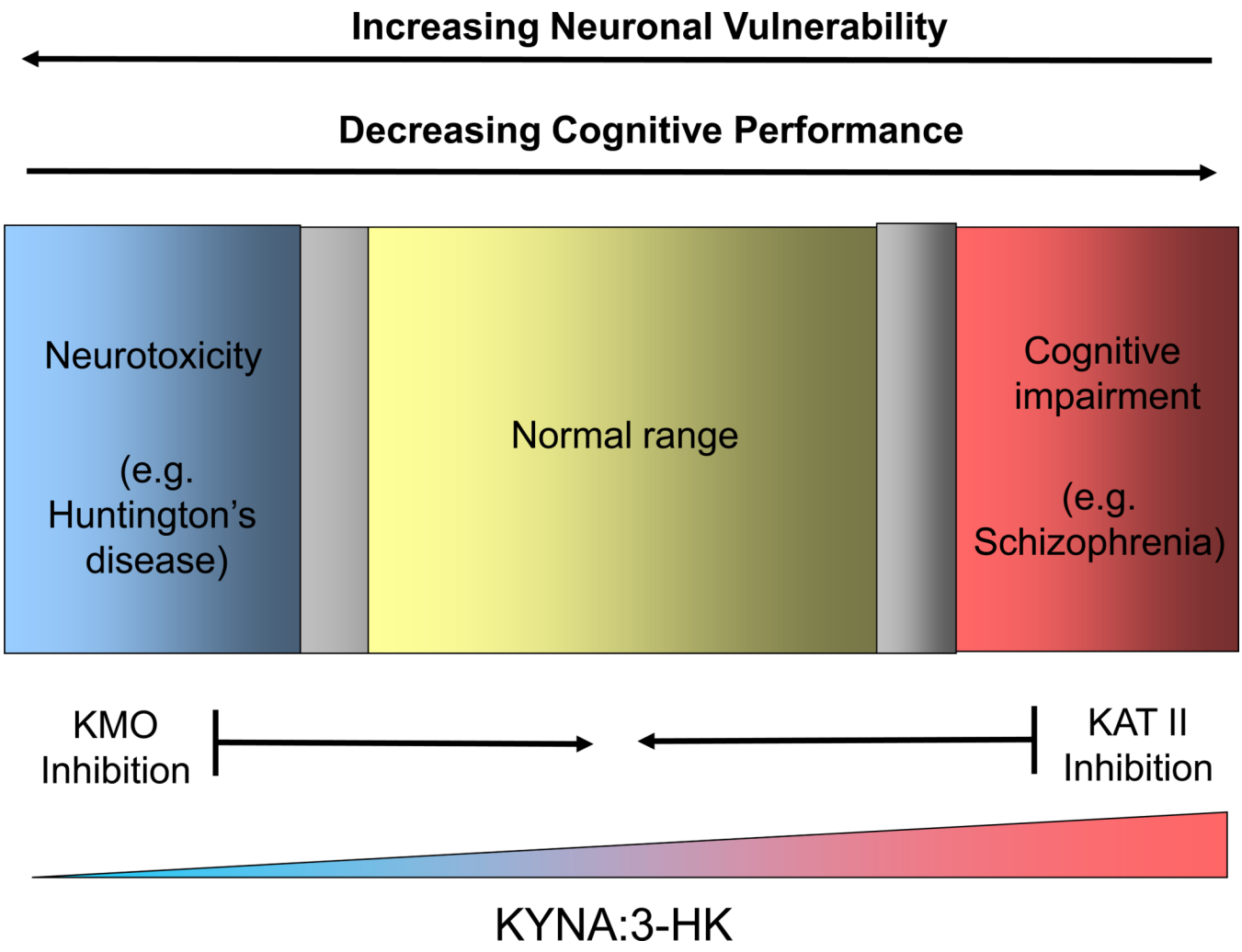

Figure 5. Targeting Brain Kynurenines Pharmacologically: Focus on KAT II and KMO

As KAT II and KMO are directly responsible for the formation of KYNA and 3-HK, respectively, specific inhibitors of these enzymes can be used to manipulate the ratio between these two neuroactive metabolites pharmacologically. Increases in the KYNA:3-HK ratio are desirable in neurodegenerative diseases such as Huntington's disease, which present with an excess of neurotoxic 3-HK (and QUIN) in the brain [81, 85, 92]. Conversely, lowering of the KYNA:3-HK ratio in the brain will improve cognitive capabilities, providing special benefits in diseases such as schizophrenia, which show enhanced brain levels of KYNA [140]. In the normal brain, fluctuations in the KYNA:3-HK ratio will have moderate effects on neuronal viability and cognition, limited to the physiological range. Pharmacological interventions with specific "kynurenergic" agents, such as KAT II or KMO inhibitors, should therefore be tailored to achieve the intended benefits and minimize potentially harmful consequences. The gray areas indicate transition zones between the physiological range and pathologies.

Table 1

Synthetic inhibitors of kynurenine pathway enzymes

Enzyme	Inhibitor	Reference
IDO	1-methyl-tryptophan	203
	4-amino-1,2,5-oxodiazole-3-carboximidamide	176
TDO	(*E*)-6-fluoro-3-[2-(4'-pyridyl)-vinyl]-1*H*-indole	178
	(*E*)-3-[2-(4'-pyridyl)-vinyl]-1*H*-indole	178
KAT II	(*S*)-4-(ethylsulfonyl)benzoylalanine (ESBA)	160
	[(*S*)-(-)-9-(4-aminopiperazine-1-yl)-8-fluoro-3-methyl-6-oxo-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene-5-carboxylic acid] (BFF122)	204
KMO	3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide (Ro 61-8048)	168
	[(1*S*,2*S*)-2-(3,4-dichlorobenzoyl)-cyclopropane-1-carboxylic acid] (UPF648)	204
Kynureninase	o-methoxybenzoylalanine	177
	2-amino-4-[3'-hydroxyphenyl]-4-hydroxybutanoic acid	205
3HAO	4-chloro-3-hydroxyanthranilic acid	179
	4,6-di-bromo-3-hydroxyanthranilic acid	206