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Kynurenines and Glutamate: Multiple Links and Therapeutic Implications

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Abstract

Glutamate is firmly established as the major excitatory neurotransmitter in the mammalian brain and is actively involved in most aspects of neurophysiology. Moreover, glutamatergic impairments are associated with a wide variety of dysfunctional states, and both hypo- and hyperfunction of glutamate have been plausibly linked to the pathophysiology of neurological and psychiatric diseases. Metabolites of the kynurenine pathway (KP), the major catabolic route of the essential amino acid tryptophan, influence glutamatergic activity in several distinct ways. This includes direct effects of these “kynurenines” on ionotropic and metabotropic glutamate receptors or vesicular glutamate transport, and indirect effects, which are initiated by actions at various other recognition sites. In addition, some KP metabolites affect glutamatergic functions by generating or scavenging highly reactive free radicals. This review summarizes these phenomena and discusses implications for brain physiology and pathology.

1. INTRODUCTION

The neuroexcitatory properties of glutamate, which is present in the mammalian brain in millimolar concentrations, were first described in the 1950s and immediately suggested a possible role for this amino acid as a chemical messenger (Curtis & Johnston, 1974). Annotation of glutamate as a *bona fide* neurotransmitter was delayed, however, as there were insufficient indications that the compound fulfilled the defining criteria for transmitter substances. Specifically, evidence was lacking concerning the localization of glutamate in axon terminals, its Ca^{2+} -dependent release into the extracellular compartment, the existence of specific glutamate receptors on the postsynaptic neuron, and enzymatic or reuptake mechanisms which could rapidly and selectively terminate the physiological actions of glutamate in the central nervous system (CNS). By the early 1980s, however, investigators had provided ample support for the classification of glutamate as the major excitatory neurotransmitter in the mammalian brain, and newly developed methods such as receptor binding and autoradiography or tract tracing (using ^3H -aspartate as a tool) had begun to delineate the anatomical features of short and long glutamatergic connections in brain and

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CONFLICT OF INTEREST

The author is cofounder of KyNexis LLC, a company that is developing drugs designed to manipulate kynurenine pathway metabolism.

spinal cord (Foster, Mena, Fagg, & Cotman, 1981; Rustioni & Cuénod, 1982; Wiklund, Toggenburger, & Cuénod, 1984; Young & Fagg, 1990). These new insights galvanized efforts to elucidate the nature and intricacies of glutamatergic neurotransmission in depth. In relatively rapid succession, investigators described glutamate-containing vesicles in nerve terminals (Fykse, Christensen, & Fonnum, 1989), discovered the existence of G-protein-coupled “metabotropic” glutamate receptors, which do not use ion transport for signal transduction (Nicoletti et al., 1986; Schoepp & Conn, 1993; Sugiyama, Ito, & Hirono, 1987), elucidated the genes that code for glutamate-related proteins (Keinanen et al., 1990; Monyer et al., 1992), and provided strong evidence for an active role of astrocytes in glutamate-mediated synaptic processes (Derouiche & Frotscher, 1991; Parpura et al., 1994).

Establishment of these fundamental features of glutamatergic transmission was accompanied by the development of an array of new tools, used to address specific biological questions. These methodological advances included highly sensitive analytical techniques (Hu, Mitchell, Albahadily, Michaelis, & Wilson, 1994), genetic approaches (Schwarcz, Hall, & Patrick, 2010), and an array of pharmacological agents (Watkins, 2000). Together with additional and increasingly sophisticated methods (Okubo & Iino, 2011; Setiadi, Heinzelmann, & Kuyucak, 2015), these tools have been used in innumerable in vitro and in vivo studies and revealed that glutamate participates directly or indirectly in essentially all physiological brain functions throughout the entire life span.

My own professional journey turned out to be closely linked to these major developments. After receiving my PhD degree in 1974, I had the good fortune of joining the laboratory of Joseph (Joe) Coyle, who had recently opened his laboratory at Johns Hopkins University after completing his training with Julius Axelrod at the NIMH. Aware of intriguing studies showing the survival of dopaminergic afferents in the otherwise neuron-depleted neostriatum of Huntington’s disease victims (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Bird, Mackay, Rayner, & Iversen, 1973; McGeer, McGeer, & Fibiger, 1973), Joe suggested that I try to duplicate this unusual neurochemical signature by an intrastriatal injection of kainic acid in rats. This idea was triggered by groundbreaking studies of John Olney, who had reported “axon-sparing” neurodegenerative properties of glutamate a few years earlier (Olney & Sharpe, 1969) and had more recently introduced the term “excitotoxicity” after noticing remarkable quantitative parallels between the neuroexcitatory and neurotoxic properties of a number of glutamate analogs (Olney, Ho, & Rhee, 1971). Joe argued that a focal injection of kainate, the most potent excitotoxin described by Olney (Olney, Rhee, & Ho, 1974), may be an optimal tool for testing his hypothesis that an excitotoxic mechanism underlies the devastating neuronal loss seen in Huntington’s disease patients and, possibly, in other neurodegenerative diseases. Experimental verification followed (Coyle & Schwarcz, 1976) and immediately raised the possibility that glutamate may be *causally* involved in the pathophysiology of several major neurological disorders.

This exciting conceptual breakthrough not only catapulted Joe to almost instant stardom among neuroscientists but also suggested an entirely new therapeutic approach to avert neurodegeneration, namely blockade of glutamate-induced overexcitation of vulnerable neurons. Naturally, interesting discussions ensued at the time among the relatively small

group of glutamate aficionados, who needed to reconcile the neurodestructive property of glutamate with its emerging status as a major—though still putative— neurotransmitter. This “glutamate enigma” attracted a cadre of talented new investigators, who would soon play major roles in establishing the intricacies of glutamatergic neurotransmission and elaborate its dysfunction in a wide variety of pathological conditions.

2. NEUROBIOLOGY OF KYNURENINES: THE EARLY YEARS

Although glutamate is a *bona fide* excitotoxin, its ability to cause neuronal damage and necrosis is limited by rapid uptake into astrocytes and presynaptic nerve terminals (Danbolt, 2001). Under physiological conditions, these transporters, as well as catabolic enzymes (Bixel, Shimomura, Hutson, & Hamprecht, 2001), prevent neurotoxic effects in vivo even when glutamate is applied at high concentrations and for an extended period of time (Mangano & Schwarcz, 1983). However, glutamate-induced excitotoxicity occurs readily when glutamate transport is compromised (Rothstein et al., 1996), and this mechanism is believed to contribute to neuropathology in numerous CNS disorders. Glutamate’s role in various neurological and psychiatric diseases is still being studied in laboratories around the world and has been described and discussed in many authoritative reviews (see, for example, Blasco, Mavel, Corcia, & Gordon, 2014; Parsons & Raymond, 2014; Plitman et al., 2014).

In my search for more potent *endogenous* excitotoxins, I became intrigued by a brief report describing the excitatory actions of quinolinic acid (QUIN) on rat cortical neurons (Stone & Perkins, 1981). Though quite obscure to neurobiologists, QUIN had previously been shown to possess convulsive properties (Lapin, 1978) and had long been known as an intermediate metabolite of the so-called kynurenine pathway (KP), which converts the essential amino acid tryptophan to NAD^+ , a cofactor of many critical enzymatic reactions (Opitz & Heiland, 2015; Fig. 1). Notably, pharmacological experiments revealed that QUIN caused neuronal excitation by selectively activating *N*-methyl-D-aspartate (NMDA) receptors, a recently identified major subtype of ionotropic glutamate receptors (McLennan, 1981; Stone & Perkins, 1981; Watkins & Evans, 1981). As Joe and I had demonstrated the potent excitotoxic properties of NMDA a few years earlier (Schwarcz, Scholz, & Coyle, 1978), I hypothesized that QUIN, too, may cause discrete neuronal lesions upon intracerebral application in rodents. This was rapidly verified (Schwarcz, Whetsell, & Mangano, 1983). However, though QUIN excitotoxicity was effectively blocked by the coadministration of selective NMDA receptor antagonists (Whetsell & Schwarcz, 1983), we and others soon noticed distinct neurotoxic characteristics, which differentiated QUIN not only from NMDA itself but also from kainic acid and another potent excitotoxin, ibotenic acid, which had become a popular lesioning tool because of its ability to reliably produce well-circumscribed, axon-sparing neuronal loss upon intracerebral injection (Köhler & Schwarcz, 1983; Schwarcz et al., 1979). Thus, QUIN is ineffective as a neurotoxin in the early postnatal period (Steiner, McBean, Köhler, Roberts, & Schwarcz, 1984), affects neuronal populations differentially within a given brain region (Beal et al., 1986; Schwarcz et al., 1983), is far less potent in the cerebellum (Köhler, 1983), and, interestingly, is dependent on the integrity of afferent glutamatergic fibers (Schwarcz, Foster, French, Whetsell, & Köhler, 1984). Some of these features parallel QUIN’s electrophysiological properties (Perkins &

Stone, 1983), providing further indirect support for an intimate mechanistic link between physiology and pathology.

The realization that QUIN-induced striatal lesions duplicate the histopathological features of Huntington's disease better than other known excitotoxins (Beal et al., 1986) and that hippocampal pyramidal cells are more vulnerable to QUIN than granule cells (Schwarcz et al., 1983), as also observed in temporal lobe epilepsy (Margerison & Corsellis, 1966), soon suggested a possible etiological connection between endogenous QUIN and various brain disorders. Formed locally by 3-hydroxyanthranilic acid 3,4-dioxygenase (Foster, White, & Schwarcz, 1986), QUIN is present in the mammalian brain in mid- to high nanomolar concentrations (Schwarcz et al., 1983; Wolfensberger et al., 1983), and prolonged exposure to nanomolar QUIN causes excitotoxic damage in relevant in vitro preparations (Kerr, Armati, Guillemin, & Brew, 1998; Whetsell & Schwarcz, 1989). Elevations in cerebral QUIN levels, which are seen in the early stages of Huntington's disease (Guidetti, Luthi-Carter, Augood, & Schwarcz, 2004) and in various infectious diseases affecting the brain (Achim, Heyes, & Wiley, 1993; Heyes, Saito, Crowley, et al., 1992), may therefore cause progressive nerve cell loss in humans.

An active involvement of the KP in brain dysfunction became even more plausible when it was realized that kynurenic acid (KYNA), a metabolite produced in a dead-end side arm of the pathway, has neuroprotective properties (Foster, Vezzani, French, & Schwarcz, 1984). Discovered in the Stone laboratory (Perkins & Stone, 1982), KYNA competitively inhibits the function of all known ionotropic glutamate receptors at high (millimolar) concentrations but attenuates activity at the glycine coagonist (glycine_B) site of the NMDA receptor preferentially, and also competitively, with an IC₅₀ value of ~10 μ M (Birch, Grossman, & Hayes, 1988; Kessler, Terramani, Lynch, & Baudry, 1989). More recent studies revealed that KYNA is, in fact, quite promiscuous with regard to its effector sites, also inhibiting the α 7 nicotinic acetylcholine receptor noncompetitively as a negative allosteric modulator (Hilmas et al., 2001; Lopes et al., 2007) and activating the G-protein-coupled receptor GPR35 (Wang et al., 2006) as well as the aryl hydrocarbon receptor (DiNatale et al., 2010) in the nanomolar to micromolar range. Like QUIN, KYNA is present in the mammalian brain at concentrations in the nanomolar range (human>nonhuman primate>rodents; Moroni, Russi, Lombardi, Beni, & Carlà, 1988; Turski et al., 1988). Of the four kynurenine aminotransferases (KATs) that convert the pivotal KP metabolite kynurenine irreversibly to KYNA (Guidetti, Amori, Sapko, Okuno, & Schwarcz, 2007; Han, Cai, Tagle, & Li, 2010), KAT II is most important for producing rapidly mobilizable KYNA in the brain (see Pocivavsek, Notarangelo, Wu, Bruno, & Schwarcz, 2015, for review).

In spite of their ability to excite and inhibit, respectively, glutamate receptors, neither QUIN nor KYNA, are classic neurotransmitters. Immunocytochemical analyses (Chen et al., 2010; Du et al., 1992; Guidetti, Hoffman, Melendez-Ferro, Albuquerque, & Schwarcz, 2007; Lehrmann, Molinari, Speciale, & Schwarcz, 2001), studies in cell preparations and tissue slices in vitro (Guillemin et al., 2001; Heyes, Chen, Major, & Saito, 1997; Heyes, Saito, & Markey, 1992; Speciale & Schwarcz, 1993; Turski, Gramsbergen, Traitler, & Schwarcz, 1989), and experiments using lesioned animals in vivo (Ceresoli, Fuller, & Schwarcz, 1996) revealed that both metabolites are formed in, and subsequently released from, nonneuronal

cells. QUIN and KYNA therefore fit the mold of “gliotransmitters,” which are increasingly understood to play major roles in both synaptic transmission and neuronal dysfunction (Araque et al., 2014). Perhaps somewhat unexpected in view of their close metabolic relationship (Fig. 1), QUIN and KYNA are segregated in separate cellular compartments. Specifically, QUIN, derived from kynurenine via three consecutive enzymatic steps [kynurenine-3-monooxygenase (KMO), kynureninase, and 3-hydroxyanthranilic acid dioxygenase], is preferentially synthesized in microglial cells, whereas KYNA, the product of KATs, is mainly formed in astrocytes (Guillemin et al., 2001).

Although their release mechanism(s) have not been elaborated, newly synthesized QUIN and KYNA are both known to promptly enter the extracellular milieu (Speciale & Schwarcz, 1993; Turski et al., 1989) and can then affect their respective pre- and postsynaptic target sites on neurons or elsewhere. Actions are terminated when the compounds are removed from the brain by a probenecid-sensitive transport process (Moroni et al., 1988; Morrison, Morishige, Beagles, & Heyes, 1999) or, possibly, by cellular reuptake (Uwai, Honjo, & Iwamoto, 2012).

3. KYNURENERGIC MODULATION OF GLUTAMATE FUNCTION: SEVERAL DISTINCT MECHANISMS

In addition to influencing excitatory neurotransmission by directly acting on glutamate receptors, QUIN and KYNA also modulate glutamate function indirectly. For example, QUIN-induced stimulation of NMDA receptors in the rat cerebral cortex causes substantive increases in glutamate release (Connick & Stone, 1988). On the other hand, even modest elevations in KYNA rapidly *reduce* the extracellular concentration of glutamate. This effect, first described in the rat striatum by Moroni and coworkers (Carpenedo et al., 2001), has been studied in considerable detail, mainly using in vivo microdialysis in unanesthetized rodents. As summarized elsewhere (Pocivavsek et al., 2015), KYNA concentrations in the midnanomolar range consistently—and reversibly—decrease glutamate levels by 30–40% in every brain region studied so far. Pharmacological studies indicate that this effect, which occurs very rapidly (Konradsson-Geuken et al., 2009) and is also achieved by applying KYNA’s immediate bioprecursor kynurenine (Alexander, Wu, Schwarcz, & Bruno, 2012), is mediated by KYNA’s inhibition of $\alpha 7$ nicotinic receptors, which are prominently situated on glutamatergic nerve terminals in the mammalian brain (Alexander et al., 2012; Grilli et al., 2006; Livingstone, Dickinson, Srinivasan, Kew, & Wonnacott, 2010). Selective inhibition of NMDA receptors, a possible alternative mechanism, is unlikely to contribute because the effect of KYNA on extracellular glutamate is not duplicated by the specific and potent NMDA/glycine_B receptor antagonist 7-chlorokynurenic acid (Beggiato et al., 2014).

Redox phenomena also play a role in the neuroactive properties of kynurenines and appear to participate in their effects on glutamatergic mechanisms in the brain. Thus, QUIN generates reactive oxygen species, and this effect increases the excitotoxic potency of the metabolite (Santamariá et al., 2001). In contrast, KYNA can function as a free radical scavenger and antioxidant (Lugo-Huitrón et al., 2011), and these properties may play a role in its neuroprotective actions (Zádori, Klivényi, Plangar, Toldi, & Vécsei, 2011). Notably,

several other KP metabolites— kynurenine, 3-hydroxykynurenine (3-HK), and 3-hydroxyanthranilic acid (3-HANA) (Fig. 1)—are also involved in intra- and extracellular redox phenomena and/or the generation or elimination of reactive free radicals. These properties account for the ability of these compounds to affect neuronal viability (Giles, Collins, Stone, & Jacob, 2003; Leipnitz et al., 2007; see Reyes-Ocampo et al., 2014, for review).

Of interest in this context, and in line with a rapidly growing literature linking redox processes to glutamatergic dysfunction (Robert, Ogunrinu-Babarinde, Holt, & Sontheimer, 2014), the generation of free radicals by 3-HK exacerbates the excitotoxic effects of QUIN (Chiarugi, Meli, & Moroni, 2001; Guidetti & Schwarcz, 1999). This synergism could be of special relevance for the etiology of Huntington's disease, which presents with elevated levels of both 3-HK and QUIN in vulnerable brain areas (Guidetti et al., 2004), but may also be emblematic of other, as yet unexplored, functional interactions between KP metabolites.

Two other, comparatively obscure, kynurenines may also be intimately involved in glutamatergic neurotransmission (see Fig. 1). Xanthurenic acid, the product of irreversible transamination of 3-HK by KATs, is a potent inhibitor of the vesicular glutamate transporter VGlut2, which controls the recycling of glutamate in nerve terminals (Neale, Copeland, Uebele, Thomson, & Salt, 2013). Like cinnabarinic acid (Fazio et al., 2012), an unstable, proapoptotic KP metabolite that is formed oxidatively from 3-HANA (Hiramatsu et al., 2008), xanthurenic acid also stimulates metabotropic glutamate receptor activity (Fazio et al., 2015) and may therefore be involved in a wide spectrum of glutamatergic processes.

4. TARGETING KYNURENINES TO TARGET GLUTAMATE

The realization that KP metabolites downstream of kynurenine, through diverse mechanisms, are capable of influencing the fate of the major excitatory neurotransmitter in the CNS stimulated efforts to manipulate their brain levels and function by specifically targeting individual pathway enzymes (Fig. 1). One approach, namely genomic elimination of these enzymes, has allowed investigators to examine long-term effects on peripheral and central KP metabolism in knockout mice. These studies have so far essentially confirmed the roles of KAT II (Yu et al., 2004), KMO (Giorgini et al., 2013), and QUIN phosphoribosyltransferase (Fukuoka, Kawashima, Asuma, Shibata, & Fukuwatari, 2012; Tararina et al., 2012) in the regulation of cerebral KP dynamics. That is, the deletions predictably affected the brain levels of the immediate enzymatic products and/or substrates. Perhaps of greatest interest, brain KYNA levels are dramatically increased in the absence of KMO, indicating a functional shift of KP metabolism toward KYNA formation when brain KMO activity is compromised (Giorgini et al., 2013). Evaluation of the mouse mutants is still in its infancy, making it difficult, for example, to predict the effects of additional experimental challenges to these animals on brain QUIN and KYNA levels. In the near future, the generation and use of mice with a deletion of 3-hydroxyanthranilic acid dioxygenase and kynureninase, and of various conditional knockout animals can be expected to reveal additional interesting intricacies of cerebral KP metabolism.

Medicinal chemists and pharmacologists face several formidable challenges when trying to generate compounds that selectively target the brain KP. Whereas some goals and potential obstacles, such as the need to generate brain-penetrant molecules and to elucidate the crystal structure of the targeted proteins, are common to all areas of neuropharmacology, others are not. One special problem is related to the fact that the pivotal KP metabolite kynurenine serves as a common substrate of several enzymes of interest, namely KATs, KMO, and kynureninase (Fig. 1). Competitive inhibitors based on the structure of kynurenine therefore often lack selectivity and attenuate the activity of more than one of these enzymes (Carpenedo et al., 1994; Varasi et al., 1996). Another difficulty for rational drug design stems from the segregation of the targeted enzymes between astrocytes, microglial cells, and, possibly, neurons (Guillemin et al., 2007, 2001). For example, definitive information is lacking with regard to changes in the cellular expression of KP enzymes during glial development, activation, or silencing. Together with the complex and largely unresolved relationship between peripheral and cerebral KP dynamics (Schwarcz, Bruno, Muchowski, & Wu, 2012), these uncertainties complicate the design of compounds which can be used with confidence to selectively influence the formation and function of neuroactive KP metabolites in the brain.

In spite of these impediments, significant advances have been made in KP pharmacology. Substrate analogs were found to be rather effective competitive inhibitors of 3-hydroxyanthranilic acid dioxygenase, though the use of these compounds in experimental studies has been limited because of their chemical instability or inability to cross the blood-brain barrier (Fornstedt-Wallin, Lundström, Fredriksson, Schwarcz, & Luthman, 1999). Potent kynureninase inhibitors have been synthesized as well (Heiss, Anderson, & Phillips, 2003; Walsh, O'Shea, & Botting, 2003) but await careful evaluation for their ability to influence the fate of individual KP metabolites in the mammalian brain. Efforts to generate selective KMO inhibitors have been far more productive thus far, resulting in a series of selective agents, including chemicals unrelated to the kynurenine structure (Amori, Guidetti, Pellicciari, Kajii, & Schwarcz, 2009; Röver, Cesura, Huguenin, Kettler, & Szenté, 1997; Speciale et al., 1996). As expected, and in line with observations in KMO knockout mice (see above), systemic administration of KMO inhibitors raises cerebral KYNA levels in vivo, even though in most cases the effect may be secondary to increased brain entry of circulating kynurenine (Röver et al., 1997; Speciale et al., 1996; Zwilling et al., 2011).

Inhibitors of KAT II allow investigators a direct route to reduce the levels of KYNA in the brain and, in particular, to target the KYNA pool that appears to be most relevant for the rapid mobilization of this neuromodulator (Pocivavsek et al., 2015). The first selective inhibitor, (*S*)-4-(ethylsulfonyl)benzoylalanine, was described in 2006 (Pellicciari et al., 2006) and has been used successfully as an experimental tool in the rodent brain. This compound, which must be applied intracerebrally, as well as newer, systemically active agents (Kozak et al., 2014; Wu et al., 2014), reliably decreases the extracellular concentration of KYNA by 30–40%, irrespective of brain region (Amori, Wu, et al., 2009; Pellicciari et al., 2006; Wu et al., 2010).

In line with the effect seen in the brain of KAT II knockout mice (Wu, Rassoulpour, & Schwarcz, 2007), the acute pharmacological reduction of KYNA formation by KAT II

inhibition is associated with a rapid, approximately twofold *increase* in extracellular glutamate levels (Konradsson-Geuken et al., 2010; Wu et al., 2010). Causality was verified in experiments in which cotreatment with minute (nanomolar) concentrations of KYNA abolished the rise in glutamate produced by the KAT II inhibitor (Pocivavsek et al., 2011). Moreover, the glutamate increase following the attenuation of KYNA synthesis is blocked by low doses of galantamine, a positive allosteric modulator of the $\alpha 7$ nicotinic receptor (Beggiato et al., 2014; Lopes et al., 2007). Therefore, even modest fluctuations in endogenous KYNA *bidirectionally* control the extracellular levels of glutamate, and these neuromodulatory effects of the astrocyte-derived KP metabolite appear to be preferentially mediated by $\alpha 7$ nicotinic receptors that are located presynaptically on glutamatergic axon terminals (Grilli et al., 2006; Livingstone et al., 2010).

5. FUNCTIONAL IMPLICATIONS AND CLINICAL RELEVANCE

Awareness that endogenously formed KP metabolites can affect glutamate receptors and extracellular levels of the neurotransmitter in the brain in many different ways raises questions regarding the *functional* significance of these neurochemical phenomena. As glutamate participates actively in virtually all neurophysiological processes from prenatal development to old age, testable hypotheses abound. Whereas causality can be more readily evaluated using in vitro model systems such as cultured brain cells (eg, Alkondon et al., 2004; Pierozan, Ferreira, De Lima, & Pessoa-Pureur, 2015) or brain tissue slices (eg, Wuarin & Dudek, 1991), biological relevance can only be fully ascertained in vivo. The role of endogenous kynurenines in glutamatergic neurotransmission must therefore be verified in behaving laboratory animals, demonstrating that selective genetic or pharmacological manipulations of KP metabolism *predictably* influence glutamate functions.

Because of the established bidirectional modulation of glutamate by fluctuating KYNA levels (see earlier), experimental up- and downregulation of KYNA, causing reductions and elevations, respectively, in extracellular glutamate, has so far provided the most compelling evidence for functional consequences of changes in cerebral KP metabolism. Thus, an increase in brain KYNA, effected by focal application of nanomolar concentrations of KYNA itself, by kynurenine administration, or by genomic KMO elimination, causes an array of cognitive impairments which are classically linked to glutamatergic dysfunctions (see Pocivavsek et al., 2015, for review). Conversely, reductions in brain KYNA, caused either acutely by pharmacological inhibition of KAT II or chronically in KAT II knockout mice, result in cognitive enhancement in several well-established paradigms (Kozak et al., 2014; Pocivavsek et al., 2011; Potter et al., 2010; Wu et al., 2014). Of note in this context, variations in the KMO gene influence a range of cognitive domains in humans—possibly by modulation of KYNA levels in the brain (Wonodi et al., 2014).

Linkage between cerebral KP metabolism and glutamatergic tone is best documented in pathological situations. This is likely due to the fact that enhanced glutamate function has long been understood to play a defining role in the etiology of a large number of brain diseases at all stages of life, and the related realization that correction of these abnormalities may provide clinical benefits. Decades after the discovery of the neurotoxic and convulsant properties of glutamate and its congeners, which suggested that massive overexcitation

underlies neurodegenerative and seizure disorders (see above), it has become clear that glutamate hypofunction is also pathogenic and therefore undesirable (Coyle, Tsai, & Goff, 2003). Interventions aimed at attaining glutamate homeostasis must therefore be subtle and carefully tailored in order to achieve clinical improvement and avoid the exacerbation of pathological features.

Although frequently based on the measurement of KP metabolites in the blood and therefore providing only circumstantial evidence, kynurenergic abnormalities are increasingly proposed to be critical *causative* factors in the pathogenesis of several brain disorders that are conventionally considered glutamate-related. Examples range from neurological symptoms and diseases, including neuropathic pain, traumatic brain injury, Parkinson's disease, and Alzheimer's disease, to psychiatric conditions, such as major depression, schizophrenia, drug abuse, and posttraumatic stress disorder (Campbell, Charych, Lee, & Möller, 2014; Schwarcz et al., 2012; Vécsei, Szálardy, Fülöp, & Toldi, 2013). A large number of studies in laboratory animals show that these KP abnormalities, which can often be traced to events early in life and/or to infections or other impairments of the immune system (Akagbosu, Evans, Gulick, Suckow, & Bucci, 2012; Liu et al., 2014; Notarangelo et al., 2014; Pershing et al., 2015), may, in fact, *precede* glutamatergic dysfunctions. Pharmacological manipulation of cerebral KP metabolites is therefore increasingly recognized not only as an innovative venue to normalize glutamate function in various CNS diseases but also as a possible means to prevent pathology.

The idea to modulate excessive glutamatergic activity indirectly by reducing endogenous QUIN or increasing endogenous KYNA levels originated soon after these two putative pathogens, as well as their proximal biosynthetic enzymes, were identified in the mammalian brain. The first *bona fide* proof of concept was provided by using the kynurenine analog nicotinylalanine, which selectively boosts cerebral KYNA levels without affecting QUIN and displays neuroprotective and anticonvulsant efficacy in laboratory studies (Moroni, Russi, Gallo-Mezo, Moneti, & Pellicciari, 1991; Russi et al., 1992). The obvious therapeutic implications of this discovery, and especially the observation that nicotinylalanine inhibits both KMO and kynureninase, two enzymes in the QUIN branch of the KP (Fig. 1; Carpenedo et al., 1994), stimulated interest especially in the realm of *neurological* research. As KMO was identified as the more promising target for drug development (Chiarugi et al., 1995), novel KMO inhibitors with higher selectivity and potency were synthesized and shown to have remarkably beneficial effects in animal models of stroke (Cozzi, Carpenedo, & Moroni, 1999), cerebral malaria (Clark et al., 2005), and Huntington's disease (Zwilling et al., 2011), among others (Grégoire et al., 2008; Rojewska, Piotrowska, Makuch, Przewlocka, & Mika, 2016). Notably, centrally active KMO inhibitors may also ameliorate brain disorders which are causally related to impairments in the immune system and an associated stimulation of the QUIN branch of the KP (Achim et al., 1993; Heyes, Saito, et al., 1992; Steiner et al., 2011). While efficacy in humans has yet to be tested, clinical trials are expected in the near future (Dounay, Tuttle, & Verhoest, 2015).

Increases in brain KYNA levels, which are observed in various catastrophic brain disorders including schizophrenia and Alzheimer's disease (Baran, Jellinger, & Deicke, 1999; Schwarcz et al., 2001), have been postulated to play important roles in the occurrence and

progression of cognitive dysfunctions (Erhardt, Olsson, & Engberg, 2009; Schwarcz et al., 2012). This makes KAT II inhibition a potential therapeutic approach, and evidence for this hypothesis has recently been obtained in relevant preclinical studies (Koshy Cherian et al., 2014; Kozak et al., 2014; Pocivavsek et al., 2011; Wu et al., 2014). As in the case of KMO inhibitors, first concept assessments using KAT II inhibitors in humans are currently in the planning stage (Dounay et al., 2015).

Selective inhibition of QUIN's immediate biosynthetic enzyme 3-hydroxyanthranilic acid dioxygenase, the most direct approach to investigate an active role of QUIN in brain pathology, has only been sporadically exploited because of the lack of sufficiently stable test compounds. However, efficacy has been demonstrated in established in vivo seizure models in rats and mice (Luthman, 2000), and protective effects have been shown against both anoxia- and inflammation-induced neuronal damage in organotypic tissue cultures (Luthman, Radesäter, & Oberg, 1998). These results bode well for further hypothesis testing with newly developed inhibitors of this enzyme (Vallerini et al., 2013).

6. CONCLUSION

As reviewed briefly in this report, the multiple effects of various KP metabolites provide the organism with many opportunities to selectively influence and control the actions of glutamate in the CNS. However, though progress has been made, efforts to understand the complex links between KP metabolism and glutamate-related phenomena are still in their infancy.

The challenges for future research are multidimensional. Perhaps most importantly, there is a need to clarify how peripheral KP metabolites influence KP function in the brain and thus secondarily affect glutamatergic neurotransmission. These insights must be based on a comprehensive understanding of the dynamics of circulating kynurenines, including the respective roles of nutrition (Badawy, 2015; Le Floch, Otten, & Merlot, 2011) and the gut microbiome (O'Mahony, Clarke, Borre, Dinan, & Cryan, 2015). Special attention must be paid to the regulation of KP enzymes, including the readily inducible upstream enzymes tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenases 1 and 2 (Ball, Jusof, Bakmiwewa, Hunt, & Yuasa, 2014) in peripheral organs. Among other variables, study designs will have to consider chronological age, qualitative and quantitative differences between species (and strains), as well as distinct responses of individual pathway enzymes under varying physiological and environmental conditions.

Key goals of future research also include the careful characterization of the connection between xanthurenic and cinnabarinic acids, 3-HK, 3-HANA, and QUIN, respectively, and glutamate *within* the brain. These experiments should focus on mechanisms other than the already reasonably well-defined bidirectional relationship of KYNA and glutamate and will likely involve the study of oxidative processes and free radicals, which are known for their cross talk with glutamate function (Reyes-Ocampo et al., 2014; Robert et al., 2014). One of the many interesting questions in this context concerns the effects of impaired QUIN phosphoribosyltransferase activity, which results in chronically elevated brain QUIN levels, on brain glutamate (Fukuoka et al., 2012; Tararina et al., 2012; cf. Fig. 1).

Correct interpretation of clinical observations, including newly discovered biochemical, genetic, and epigenetic links between KP metabolism and “glutamatergic brain diseases,” will be critically dependent on such in-depth understanding of KP physiology. However, as mentioned earlier, KP dynamics—and KP biology in general—undergo substantive qualitative changes under many pathological conditions, often in relation to activation of the immune system. These changes must be carefully documented and discussed before definitive conclusions regarding an etiologically relevant involvement of the KP are drawn and, in particular, before advocating specific KP-based therapeutic interventions.

Finally, in view of the realization that the KP constitutes a promising drug target, there can be little doubt that novel, selective pharmacological agents with improved potency, and pharmacokinetic and pharmacodynamic properties will become available soon. These compounds will be invaluable as experimental tools and potential drug candidates. It will therefore be imperative to compare their acute and chronic effects in model systems to assess possible adaptive changes in KP metabolism, and consequently of glutamate function, in the brain. These studies may not only uncover surprising additional intricacies of an already complex metabolic pathway but may also reveal unsuspected new clinical opportunities.

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ABBREVIATIONS

3-HANA	3-hydroxyanthranilic acid
3-HK	3-hydroxykynurenine
KAT	kynurenine aminotransferase
KMO	kynurenine-3-monooxygenase
KP	kynurenine pathway
KYNA	kynurenic acid
QUIN	quinolinic acid

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Fig. 1.

The kynurenine pathway of tryptophan degradation. Enzymes and neuroactive metabolites with established or putative links to glutamatergic brain functions are denoted in gray (print version) or red (electronic version).