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Elevated kynurenine pathway metabolism during neurodevelopment: Implications for brain and behavior

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Abstract

The kynurenine pathway (KP) of tryptophan degradation contains several neuroactive metabolites that may influence brain function in health and disease. Mounting focus has been dedicated to investigating the role of these metabolites during neurodevelopment and elucidating their involvement in the pathophysiology of psychiatric disorders with a developmental component, such as schizophrenia. In this review, we describe the changes in KP metabolism in the brain from gestation until adulthood and illustrate how environmental and genetic factors affect the KP during development. With a particular focus on kynurenic acid, the antagonist of $\alpha 7$ nicotinic acetylcholine ($\alpha 7$ nACh) and N-methyl-D-aspartate (NMDA) receptors, both implicated in modulating brain development, we review animal models designed to ascertain the role of perinatal KP elevation on long-lasting biochemical, neuropathological, and behavioral deficits later in life. We present new data demonstrating that combining perinatal choline-supplementation, to potentially increase activation of $\alpha 7$ nACh receptors during development, with embryonic kynurenine manipulation is effective in attenuating cognitive impairments in adult rat offspring. With these findings in mind, we conclude the review by discussing the advancement of therapeutic interventions that would target not only symptoms, but potentially the root cause of central nervous system diseases that manifest from a perinatal KP insult.

Keywords

Kynurenic acid; Schizophrenia; Cognition; Alpha 7 nicotinic receptor; Choline

1. Introduction

The kynurenine pathway (KP) is responsible for over 95% of all tryptophan degradation in the mammalian body and several metabolites of the pathway, collectively termed “kynurenines”, have been implicated in an array of physiological and pathological processes (see Pocivavsek et al., 2015; Schwarcz et al., 2012). In particular, kynurenines have important and unique effects in the central nervous system (CNS) and increasing evidence suggests that they play an important role in brain development.

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Conflicts of interest

The authors declare no conflict of interest.

As shown schematically in Fig. 1A, L-kynurenine (kynurenine) is metabolized from tryptophan by the enzymes indoleamine 2,3-dioxygenase (IDO) 1 and 2, and tryptophan 2,3-dioxygenase (TDO) that produce N-formylkynurenine, a labile intermediate that then rapidly converts to kynurenine. The namesake of the pathway, kynurenine, which also enters the brain from the circulation, is then readily taken up by astrocytes and microglia. In astrocytes, kynurenine aminotransferase (KAT) II predominantly catalyzes the irreversible transamination of kynurenine to kynurenic acid (KYNA) (Guidetti et al., 2007). KYNA, whose mammalian brain concentrations in adulthood are in the nanomolar to low micromolar range, exerts neuroactive properties as an antagonist of the $\alpha 7$ nicotinic acetylcholine ($\alpha 7$ nACh) receptors (Hilmas et al., 2001) and N-methyl-D-aspartate (NMDA) receptors (Perkins and Stone, 1982). KYNA also acts as a ligand of G protein-coupled receptor (GPR) 35 and the aryl hydrocarbon receptor (AhR), two signaling receptors that are functional in both the brain and peripheral organs (Divorty et al., 2015; Julliard et al., 2014; Mackenzie and Milligan, 2015; Moroni et al., 2012; Noakes, 2015). The second branch of the KP is predominantly metabolized in microglial cells (Guillemin et al., 2001, 2003; Heyes et al., 1996; Saito and Heyes, 1996), where the enzyme kynurenine 3-monooxygenase (KMO) metabolizes kynurenine to 3-hydroxykynurenine (3-HK), and the downstream catabolite 3-hydroxyanthranilic acid is formed by the enzyme kynureninase. 3-Hydroxyanthranilic acid is the substrate for 3-hydroxyanthranilic acid 3,4-dioxygenase, present relatively abundantly in the brain, and is converted to quinolinic acid (QUIN). QUIN, present in the brain in nanomolar concentrations, is a selective agonist of the NMDA receptor (Stone, 1993) that can generate free radicals and contribute to neurotoxicity. These metabolites and the functional outcomes of a malfunctional KP have been extensively studied over the last three decades, with a particular focus on modulation of CNS physiology and function (see Pocivavsek et al., 2015; Schwarcz et al., 2012; Stone and Darlington, 2013).

2. Perinatal kynurenine pathway metabolism

Several years ago it was observed that levels of KP metabolites in the brain are higher during fetal development, decrease in the immediate postnatal period and remain lower in adulthood (Fig. 1B) (Beal et al., 1992; Ceresoli-Borroni and Schwarcz, 2000; Walker et al., 1999). Preclinical studies have reported high levels of KYNA in the fetal brain of monkeys (Beal et al., 1992), sheep (Walker et al., 1999), rats (Cannazza et al., 2001; Ceresoli-Borroni and Schwarcz, 2000; Pershing et al., 2015; Pocivavsek et al., 2014a) and mice (Beggiato et al., 2015; Notarangelo and Schwarcz, 2014). These results led to the speculation that high brain KYNA content may have a specific role during neurodevelopment. Some hypotheses implicate a neuroprotective role of large amounts of KYNA during gestation or parturition (Beal et al., 1992; Ceresoli-Borroni and Schwarcz, 2000; Walker et al., 1999), while others suggest that a rapid decrease postnatally is necessary to disinhibit NMDA receptor function and allow these receptors to guide normal brain development (Balazs et al., 1988; Komuro and Rakic, 1992; Simon et al., 1992).

Today, still very little is known about local synthesis and/or entry of circulating kynurenines in the immature brain, the transfer of these metabolites from the mother to the fetus and the role of the placenta during gestation. Tryptophan is an essential amino acid that has to be

provided from the mother to the fetus via transplacental transfer (Nicholls et al., 2001b). Recent studies have demonstrated that the placenta serves as a major source of neuroactive metabolites to the fetal brain, including serotonin, which is also a metabolite of tryptophan (Bonnin et al., 2011). In line with these findings, it is possible that fetal brain kynurenine originates from tryptophan degradation in the placenta, which expresses both tryptophan-degrading enzymes IDO and TDO (Manuelpillai et al., 2005; Suzuki et al., 2001). Alternatively, kynurenine could be transferred to the fetus from the maternal circulation via transplacental transfer (Goeden et al., 2015). The placenta also expresses other KP enzymes, including kynureninase, KAT, KMO, 3-hydroxyanthranilic acid 3,4-dioxygenase and quinolinic acid phosphoribosyltransferase (see Fig. 1A) (Ligam et al., 2005; Manuelpillai et al., 2005). In line with the expression of the KP enzymes, the metabolites of the pathway, including KYNA, 3-HK and QUIN, have been detected in the placenta (Beggiato et al., 2014a, 2015; Manuelpillai et al., 2005; Notarangelo and Schwarcz, 2014; Notarangelo et al., 2015). Regardless of the origin of kynurenine in the fetus, the higher levels of the KP namesake in the fetal brain could in part also be responsible for higher levels of its metabolites KYNA and 3-HK (Beggiato et al., 2015; Ceresoli-Borroni and Schwarcz, 2000). However, it is important to consider whether and to what extent the acidic compounds QUIN and KYNA, which do not actively cross the blood–brain barrier in adulthood (Fukui et al., 1991), can access the fetal or neonatal brain directly from the circulation. With regard to the postnatal period, it is known that immediately after birth, cerebral KP metabolite levels rapidly decline (Beal et al., 1992; Ceresoli-Borroni and Schwarcz, 2000; Walker et al., 1999) and change gradually until adulthood. This striking difference between prenatal and postnatal concentrations of kynurenine and its metabolites, as shown in Fig. 1B, is particularly intriguing and requires further investigation.

During development, the production of cerebral KP metabolites is also regulated differently than in the adult brain. Cerebral KYNA production has been examined by *in vitro* studies using rodent brain slices at different postnatal days (Gramsbergen et al., 1997). While in the adult brain KYNA production is influenced by the cellular energy metabolism and decreases after glucose deprivation, in the developing brain KYNA production is less susceptible to glucose deprivation, as shown at both postnatal day (PND) 1 and 14. This difference between the developing and the mature adult brain is likely due to the lesser dependence on glucose as the main energy source in the developing brain (Nehlig, 1997). In contrast, co-substrate regulation is fully functional in the immature brain, as the addition of pyruvate is able to double KYNA formation in the absence of glucose at PND 7 (Schwarcz et al., 1998). Taken together, there are striking differences between the regulation of KP metabolism in the developing brain versus the mature brain.

3. Role of KP receptor targets in the developing nervous system

The cortex is richly endowed from an early age in two key receptor targets of KP metabolites, the $\alpha 7$ nACh and NMDA receptors (Ben-Ari et al., 1997; Dwyer et al., 2009). In that regard, a range of studies suggest that dysfunctional neurotransmission at these receptors from early neurodevelopment may be causally related to CNS abnormalities in a variety of disorders, including schizophrenia (SZ), autism-spectrum disorder (ASD), and

attention deficit hyperactivity disorder (ADHD) (Chang et al., 2014; Deutsch et al., 2011; Martin and Freedman, 2007; Timofeeva and Levin, 2011; Young et al., 2007).

Glutamate receptors play an essential role in brain development and particularly the NMDA receptors, which can be both activated or inhibited by the KP metabolites, QUIN and KYNA, respectively. NMDA receptors have been implicated in modulating neuronal migration, synapse formation (Dikranian et al., 2001; Udin and Grant, 1999), neurite outgrowth and the formation of spines (Ultanir et al., 2007), and other factors that contribute to neuronal plasticity that rapidly occurs during neurodevelopment (Drian et al., 2001; du Bois and Huang, 2007; Fagiolini et al., 2003; Iwasato et al., 2000). The significance of NMDA receptor malfunction developmentally has been studied using agents to directly block the receptors (Dikranian et al., 2001; Harris et al., 2003; Ikonomidou et al., 1999; Vincent et al., 2004). Structural and behavioral abnormalities that occur as a result of blocking these receptors are relevant for the study of various neuropsychiatric disorders (Abekawa et al., 2007; du Bois and Huang, 2007; Lindahl et al., 2008; Rinaldi et al., 2007; Stefani and Moghaddam, 2005).

Cholinergic neurotransmission through the $\alpha 7$ nACh receptors has also been implicated in regulating neuronal growth and differentiation developmentally (Zheng et al., 1994). Several studies have shown highly regulated expression of $\alpha 7$ nACh receptors in the developing brain during periods critical to establishing synaptic plasticity. The embryonic brains of the chick and rodent highly express $\alpha 7$ nACh mRNA and protein (Broide et al., 1995; Couturier et al., 1990; Wang and Schmidt, 1976) and a striking reduction of the receptor is evidenced in many regions of the brain during postnatal development (Broide et al., 1995; Fiedler et al., 1990; Fuchs, 1989). While acetylcholine (ACh) is the primary activator of $\alpha 7$ nACh receptors in adulthood, recent investigations suggest that prenatally choline, a precursor of ACh synthesis, acts as a selective agonist of $\alpha 7$ nACh receptors (Alkondon et al., 1999; Descarries et al., 2005; Meyer et al., 1998; Papke et al., 1996). High levels of the receptor agonist choline prenatally may play an important role in regulating $\alpha 7$ nACh receptor activity during development (reviewed in Freedman and Ross, 2015), and the endogenous antagonist KYNA may help to regulate the activation of these receptors, maintaining an important balance prenatally.

Although qualitative differences have been reported during postnatal development (Alkondon et al., 2011), we can speculate that KYNA may be able to antagonize both the NMDA and $\alpha 7$ nACh receptors during prenatal and early postnatal development. In adulthood, KYNA can bind both the glycine co-agonist site on the NMDA receptors (Stone and Darlington, 2002) and the allosteric potentiating site of the $\alpha 7$ nACh receptors (Lopes et al., 2007). While some *ex vivo* studies dispute the actions of KYNA on $\alpha 7$ nACh receptors (Arnaiz-Cot et al., 2008; Dobelis et al., 2012; Mok et al., 2009), several *in vivo* and electrophysiological studies suggest that $\alpha 7$ nACh receptors are the preferential target of endogenous KYNA in the brain (Alkondon et al., 2004; Hilmas et al., 2001; Konradsson-Geuken et al., 2010; Rassoulpour et al., 2005; Wu et al., 2007). These nicotinic receptors are likely the first site of action for KYNA antagonism, and inhibition of $\alpha 7$ nACh receptors subsequently leads to a cascade of neuromodulatory events *in vivo*. In the brain, $\alpha 7$ nACh receptors are abundantly located at the presynaptic terminals (Vizi and Lendvai, 1999), and

in vivo bi-directional changes in KYNA regulate the release of neurotransmitters, including glutamate (Carpenedo et al., 2001; Konradsson-Geuken et al., 2010; Pocivavsek et al., 2011; Wu et al., 2010), gamma-aminobutyric acid (GABA) (Beggiato et al., 2013, 2014b), dopamine (Amori et al., 2009b; Pocivavsek et al., 2015; Rassoulpour et al., 2005; Wu et al., 2007) and ACh (Zmarowski et al., 2009). In this regard, excessive blockage of $\alpha 7$ nACh receptors by increased levels of KYNA may be causally related to cognitive deficits attributed to a loss of function of these neurotransmitters systems (Bruno et al., 2006; Cao et al., 2005; Fallon et al., 2007; Gioanni et al., 1999; Lopez et al., 2001; Rousseau et al., 2005) that are tightly regulated by $\alpha 7$ nACh receptors found on cortical interneurons, projecting neurons, and various cortical afferents (Cao et al., 2005; Dickinson et al., 2008; Krenz et al., 2001; Schroder et al., 1989; Wang et al., 2006a). While this reviews our current understanding of the role of $\alpha 7$ nACh receptors in modulating neurotransmitter systems in adulthood, future studies will need to investigate the effect of KYNA on these and potentially other neurotransmitters during brain development.

Recent studies have also identified alternative targets of KYNA that may contribute to cellular signaling mechanisms, such as GPR 35 (Wang et al., 2006b). By binding GPR 35, KYNA affects cyclic adenosine monophosphate (cAMP) production and subsequent Ca^{2+} flux in astrocytes. These signaling properties of KYNA at GPR 35 may contribute to its regulatory role of neurotransmission (Berlinguer-Palmini et al., 2013) and the action of KYNA neuro-developmentally on this target should be explored. Other targets include AhR, which is activated by both KYNA and kynurenine (DiNatale et al., 2010; Opitz et al., 2011). AhR is widely distributed and expressed through various regions of the brain in adulthood (Petersen et al., 2000), and it is present on neurons, endothelial cells, and astrocytes (Filbrandt et al., 2004). During fetal development, AhR can regulate a variety of biological processes, including cell division and differentiation (Puga et al., 2009), but its expression is limited to the placenta and epithelial cells of the fetus, as it is absent in the fetal brain according to one report (Jiang et al., 2010). A recent publication reported an increase in KYNA in AhR-null mice and higher expression of the synthesizing enzyme KAT II. These animals were protected against neurological damage by an excitotoxic lesion with QUIN suggesting that high levels of KYNA in AhR-null mice induce a neuroprotective effect against neurotoxic insults (Garcia-Lara et al., 2015). To fully understand the impact of KP malfunction on neurodevelopment, more extensive follow-up studies should be designed to investigate prenatal and early post-natal targets of KYNA and other kynurenines.

4. Environmental insults and genetic manipulations: effects on perinatal KP metabolism

KP metabolite concentrations in the developing brain fluctuate in response to environmental stimuli, such as maternal infection, maternal stress or an insult such as hypoxia (see below). Maternal exposure to infection or stressful conditions adversely affects brain development and increases the risk for the offspring to develop psychiatric symptoms (Brown and Patterson, 2011; Fineberg and Ellman, 2013). In line with this notion, in rodents, both immune activation and stress during pregnancy cause rapid elevations of KP metabolites in the fetal brain (Notarangelo and Schwarcz, 2014; Notarangelo et al., 2015); however, the

impact of these insults on long-lasting changes of KP in the offspring are still under investigation.

Perinatal hypoxia causes rapid alterations in brain structure and function affecting neurodevelopment and this deficiency in oxygen during the perinatal period has been linked to the development of psychiatric disorders later in life (Nyakas et al., 1996; Rosso et al., 2000). During pregnancy, hypoxia in the fetus may be caused by placental insufficiency reducing the capacity of the placenta to transfer amino acids to the fetus, including the transport of tryptophan and kynurenine (Nicholls et al., 2001b). Surprisingly, while kynurenine levels are reduced in the plasma, placental insufficiency causes an elevation of both KYNA and QUIN in the fetal brain twenty-four hours after the insult (Nicholls et al., 2001b). However, after several days, KYNA content is reduced in certain regions of the fetal brain, while QUIN is still elevated (Nicholls et al., 2001a; Walker et al., 1999), and this increase can in turn have functional significance and potential long-term effects in the offspring. It has been reported that QUIN administration during the gestational period causes neuronal cell body injury and symptoms of edema in the brain of young offspring (Beskid, 1994). However, the developing brain (PND 7) is more resistant to QUIN-induced neurotoxic damage, compared to adult brain (Foster et al., 1983).

In addition to modeling hypoxia, several studies have investigated the effect of reduced oxygen, asphyxia, on KP after birth. Asphyxia at the time of birth induces opposite effects on the neonatal brain content of KYNA and 3-HK during the first twenty-four hours after the insult, with a profound increase in KYNA and a reduction in 3-HK levels (Baran et al., 2001; Ceresoli-Borroni and Schwarcz, 2001). Lack of oxygen leads to a decreased KMO activity (Dang et al., 2000) and this enzymatic change likely underlies the rapid reduction in 3-HK and parallel increase in KYNA levels seen in the neonatal brain of asphyctic pups (Ceresoli-Borroni and Schwarcz, 2001). The rapid elevation of brain KYNA levels immediately after an episode of birth asphyxia is likely a protective response against neuronal injury (Baran et al., 2001; Ceresoli-Borroni and Schwarcz, 2001). In that regard, direct administration of KYNA offers a partial neuroprotection after hypoxic-ischemia in PND 7 neonatal rats (Andine et al., 1988).

KP metabolite levels in the developing brain are also affected by genetic manipulations of the metabolic enzymes. Specifically, mice with a targeted deletion of the *Kmo* or *Kat II* gene (Giorgini et al., 2013; Yu et al., 2004) constitute valuable tools to understand the regulation and function of the KP in the brain. Examination of the placenta and fetal brain from wild-type and *Kmo* knock-out animals during pregnancy (embryonic day [ED] 17–18) demonstrates an increase in basal KYNA levels (Beggiato et al., 2014a), as previously reported in the brain of adult mice (Giorgini et al., 2013). Conversely, 3-HK levels are eliminated in the *Kmo* knock-out placental tissues and fetal brains. Interestingly, prenatal treatment of the pregnant dam with kynurenine in the last week of gestation causes a larger increase in KYNA levels in both the placenta and fetal brain of *Kmo* knock-out compared to wild-type animals (Beggiato et al., 2014a), suggesting that kynurenine is preferentially metabolized to KYNA in the fetal brain when KMO is reduced.

On the other hand, *Kat2* knock-out mice have lower KYNA levels compared to wild-type controls in the striatum and hippocampus during early postnatal time-points, PND 14 and 21 (Alkondon et al., 2004; Potter et al., 2010; Sapko et al., 2006). In contrast, the levels of KYNA are essentially normal in the adulthood, demonstrating a less significant role for KAT II in the adult mouse brain (Alkondon et al., 2004; Sapko et al., 2006). No major differences in the levels of the other KP metabolites were observed in these animals (Sapko et al., 2006). At PND 21, the decrease in tissue KYNA levels is paralleled by a reduction in extracellular KYNA content and concomitant elevation of extracellular glutamate in the hippocampus (Potter et al., 2010). The biochemical changes observed in these mice are associated with pro-cognitive effects in the adolescent mice (PND 21). Specifically, *Kat2* knock-out animals display improved performance in hippocampal-dependent behavioral tasks, enhanced long-term potentiation (LTP) and $\alpha 7$ nACh receptor activity (Alkondon et al., 2004; Potter et al., 2010). However, the *Kat2* knock-out animals also display an increased susceptibility to an excitotoxic insult during development when KYNA levels are reduced but not in adulthood. Importantly, this enhanced vulnerability to excitotoxic insult is attenuated by normalizing brain KYNA levels (Sapko et al., 2006). Taken together, these data show that both environmental and genetic factors affect brain KP metabolism and function during development.

5. Pre- and postnatal KP manipulation to study neuropathology and behavior of neurodevelopmental disorders

Despite the breadth of literature on the importance of NMDA and $\alpha 7$ nACh receptors in neurodevelopment, not much is known about the regulation of their function during development. The KP metabolites, including the NMDA agonist QUIN and the neuro-modulator KYNA, may contribute to the regulation of these receptors developmentally and in return influence cortical maturation (see above). In that regard, a number of studies have modeled an increase in KP metabolism during different stages of pre- and postnatal development, as maturation of the brain is a dynamic process that begins embryonically and continues into young adulthood. Several of these approaches have found that neurodevelopment is quite susceptible to alterations in kynurenine metabolism and studies have focused on molecular and behavioral phenotypes in adulthood after manipulations during various developmental periods (see Table 1).

The hypothetical connection between perinatal stimulation of the KP and CNS dysfunction later in life may have relevance to the study of various neurodevelopmental diseases and disorders, including SZ, ASD, and ADHD (Chang et al., 2014; Deutsch et al., 2011; Martin and Freedman, 2007; Timofeeva and Levin, 2011; Young et al., 2007). As stress and infections are known to increase KP metabolism prenatally (Notarangelo and Schwarcz, 2014; Notarangelo et al., 2015) and during early postnatal development (Asp et al., 2010; Liu et al., 2014), several studies have attempted to model this phenotype by directly increasing kynurenine levels in the immature rodent brain (Table 1). The first paradigm that studied chronic elevation of kynurenine metabolism during pre- and postnatal development was continuous feeding of kynurenine-laced chow to pregnant rat dams from ED 15 to weaning (PND 21). Brain KYNA levels were elevated during the entire treatment period and

upon weaning, the offspring were fed normal rodent chow throughout adulthood. Biochemical and behavioral testing in adulthood (PND 56) showed remarkable abnormalities, including increased extracellular KYNA and a parallel reduction of extracellular glutamate in both the prefrontal cortex and hippocampus (Alexander et al., 2013; Pocivavsek et al., 2012). The adult offspring also displayed behavioral impairments in hippocampal learning and memory and prefrontal mediated executive function (Alexander et al., 2013; Pocivavsek et al., 2012) that can potentially be explained by the abnormal biochemical phenotype. As follow-up to these studies, the impact of elevating kynurenine and KYNA was investigated only during the last week of gestation (ED 15–22), when KYNA levels are already exceptionally high in normal developing fetal brain (Beal et al., 1992; Cannazza et al., 2001; Ceresoli-Borroni and Schwarcz, 2000; Walker et al., 1999; see previous section). The prenatal insult was sufficient to cause similar biochemical and behavioral abnormalities in adult offspring (PND 56) (Pershing et al., 2015; Pocivavsek et al., 2014a). In addition, reductions in several markers of prefrontal excitability, including expression of the $\alpha 7$ nAChR, mGluR2, dendritic spine density, and a subsensitive response to mesolimbic stimulation of glutamate release in the prefrontal cortex, were observed (Pershing et al., 2015). This model, termed “EKyn”, highlights the impact of elevated KYNA levels during the last week of gestation in rodent development as a sensitive period that impacts molecular, biochemical, and behavioral phenotypes in adulthood.

A different approach to elevating fetal brain KYNA levels has been to pharmacologically inhibit KMO, by systemically administering Ro 61–8048 (Rover et al., 1997). This tool has been applied to pregnant dams in late gestation (i.e. on ED 14, ED 16, and ED 18) and results in a striking increase in KYNA in the embryo. The adolescent offspring (PND 21) display increased neuronal excitability, an increase in GluN2A/2B subunits of the NMDA receptor and an elevation in the postsynaptic density marker PSD95 (Forrest et al., 2013a). In adult offspring (PND 60), a number of changes in excitability are found, including decreases in dendritic number and complexity of projections, as well as disruptions in LTP (Forrest et al., 2013b, 2015; Khalil et al., 2014; Pizar et al., 2014). Together, these approaches signify the importance of a balanced and homeostatic KP metabolism during fetal brain development, as increases in KYNA induce long-lasting biochemical, neuropathological, and behavioral abnormalities.

A number of studies have also focused on manipulating KP metabolism in the early postnatal period or in adolescence, both time-points relevant for continued brain development. Sequential systemic injections of kynurenine from PND 7 to 16 in mice (Liu et al., 2014) or PND 7 to 10 in rats (Iaccarino et al., 2013) result in enhanced amphetamine-induced locomotor activity and deficits in social interaction, respectively. Intermittent treatment of adolescent rats with systemic injections of kynurenine results in impaired hippocampal-mediated cognition, assessed by novel object recognition and contextual fear memory, as well as dysfunctional social interaction in adulthood (PND 61) (Akagbosu et al., 2012; Trecartin and Bucci, 2011). Importantly, this intermittent adolescent kynurenine treatment paradigm results in dysfunctional LTP after a burst of high-frequency stimulation (DeAngeli et al., 2014). The plethora of studies manipulating KP metabolism during brain development support the hypothesis that increased amounts of KYNA during critical

neurodevelopmental periods induce long-lasting translationally-relevant changes to the study of various psychiatric diseases and disorders.

6. Implications for interventions in psychiatric disorders

SZ is a psychiatric disorder that has been epidemiologically and neuropathologically characterized as neurodevelopmental, as the clinical presentation of SZ typically occurs in young adulthood after puberty. The long period between the hypothesized neurodevelopmental insult and the manifestation of the disorder later in life is a key characteristic of the disorder (Castle et al., 1998; DeLisi, 2008; Kinney et al., 2010; Meyer and Feldon, 2010). Cognitive abnormalities, as well as deficits related to glutamatergic and nicotinic neurotransmission, are key features of SZ, and the connection between this disorder and KP dysfunction has been extensively investigated. Pathologically, studies using postmortem brain tissue and cerebrospinal fluid of individuals with SZ report a consistent increase in KP metabolism toward KYNA formation (Erhardt et al., 2001; Linderholm et al., 2012; Miller et al., 2006; Nilsson et al., 2005; Sathyaikumar et al., 2011; Schwarcz et al., 2001), while no changes in 3-HK levels have been documented (Sathyaikumar et al., 2011). These changes do not appear to be related to prolonged treatment with antipsychotic drugs (Ceresoli-Borroni et al., 2006; Linderholm et al., 2012; Nilsson et al., 2005; Sathyaikumar et al., 2011). The elevations in both kynurenine and KYNA observed in SZ may result from alterations in the activity of kynurenine degrading enzyme KMO. A reduction in KMO may result in an increase in kynurenine production and enhanced metabolism towards KYNA formation (Sathyaikumar et al., 2011). Both gene expression studies (Miller et al., 2004, 2006; Wonodi et al., 2011) and enzyme activity measurements (Sathyaikumar et al., 2011; Wonodi et al., 2011) have characterized impairments in KP enzymes in various brain regions in individuals with SZ.

The concept that increased KYNA concentrations are causally related to cognitive impairments in patients with SZ supports the notion that targeting KYNA formation may present clinical benefit. The focus of these efforts has primarily been on pharmacological KAT II inhibition and the feasibility of this approach has been investigated preclinically (Amori et al., 2009a; Pellicciari et al., 2006; Pocivavsek et al., 2011; Wu et al., 2010). A rather small decrease in brain KYNA induced by acute KAT II inhibition in the rodent brain is sufficient to induce pro-cognitive effects (Kozak et al., 2014; Pocivavsek et al., 2011; Wu et al., 2014). These pre-clinical studies show promise for the translatability of KAT II inhibition clinically as two orally active compounds, BFF-816 (Pocivavsek et al., 2014b; Wu et al., 2014) and PF-04859989 (Dounay et al., 2012; Kozak et al., 2014), readily overcome contextual memory, working memory, spatial memory, and sustained attention deficits in models relevant to the study of SZ preclinically.

An alternative approach to counteract the effects of increased KYNA in neuropsychiatric disorders, including SZ, is to act on the direct targets of the metabolite in the brain. In this regard, agents that modulate the $\alpha 7$ nACh receptors, such as galantamine (Alexander et al., 2012; Phenis et al., 2014) or $\alpha 7$ nACh partial agonists (Pershing et al., 2014), have successfully overcome behavioral impairments caused by increased KYNA. Taken together, these approaches support the idea that KAT II inhibition or pharmacological modulators of

$\alpha 7$ nACh receptors attenuate the function of KYNA at its predominant biological target in adult brain and may have translatable implications for the treatment of cognitive impairments associated with psychiatric disorders.

As reviewed here, the possible role of KP dysfunction during development and its impact on neuropsychiatric disorders can begin as early as prenatal gestation and early postnatal development. Recent studies suggest that early interventions are able to rescue behavioral impairments in adulthood (Nomura et al., 2015; Schulz et al., 2014; Wu et al., 2015). Therefore, early interventions targeting KP enzymes, in particular inhibition of KAT to decrease KYNA levels during critical developmental periods, may attenuate the root cause of long-lasting phenotypic changes, rather than just symptoms in the adult offspring. Alternatively, perinatal choline supplementation has been used as an approach to stimulate $\alpha 7$ nACh receptors during early development, prior to the availability of endogenous acetylcholine (reviewed in Freedman and Ross, 2015), as choline is a selective agonist for the $\alpha 7$ nACh receptors (Albuquerque et al., 1998; Alkondon et al., 1999; Fayuk and Yakel, 2004). Historically, a number of preclinical studies have focused on supplementing the diet of pregnant and lactating rodent dams with choline. The benefits of choline-supplementation include long-term improvements in sensory inhibition (Stevens et al., 2008, 2014), as well as attenuation of either *in utero* stress exposure (Schulz et al., 2014) or maternal immune activation (Wu et al., 2015) on both anxiety- and cognitive-related behaviors in adulthood. A recent study extended this research by feeding normal and supplemented choline diets, perinatally, to mice carrying the null mutation for the $\alpha 7$ nACh receptor gene (*Chrna7*) and demonstrated that the *Chrna7* null-mutant failed to show behavioral improvements with choline-supplementation, strongly implicating functional $\alpha 7$ nACh receptors as the mechanism (Stevens et al., 2014). However, additional mechanisms working in parallel with $\alpha 7$ nACh receptor stimulation should be considered, including changes in gene expression, particularly DNA methylation, noted after choline supplementation during development (reviewed in Blusztajn and Mellott, 2012).

In an effort to overcome the impact of elevated KYNA during the prenatal period in our EKyn model (described above; Pocivavsek et al., 2014a), we recently treated pregnant and lactating Wistar rats with choline-supplemented diet, from ED 15 to PND 21, in combination with the embryonic kynurenine treatment from ED 15 to ED 22 (Fig. 2A). Upon weaning, all offspring received normal diet and we tested the adult (PND 56–85) male offspring in a contextual memory task, the passive avoidance paradigm. There were no significant differences in the approach latency on day 1 of the task (Fig. 2B), demonstrating an innate preference of all animals to approach the dark side of the paradigm. After entering the dark compartment, the animals received an aversive shock and were tested in the paradigm after twenty-four hours to assess contextual memory. As previously shown (Pocivavsek et al., 2014a), EKyn offspring were significantly impaired, displayed as a short avoidance latency on day 2 of the contextual memory task (Fig. 2C). Importantly, EKyn offspring that received choline-supplemented diet displayed an attenuation of the memory impairment, demonstrating that pre- and postnatal choline-supplementation is protective against the EKyn insult. These are the first data to demonstrate that developmental supplementation with an $\alpha 7$ nACh receptor agonist can overcome the deficits induced by elevated KP metabolism during this critical period. Ongoing studies are designed to

investigate the impact of choline-supplementation on both biochemical and molecular phenotypes during development and in adulthood.

7. Summary

Atypical levels of KP metabolites, in particular KYNA, during development have been linked to several biochemical and behavioral abnormalities. KP impairment *in utero* or during early postnatal development may be causally linked to phenotypic abnormalities, including cognitive deficits, in various psychiatric disorders that stem from an initial developmental insult, as hypothesized to occur in SZ. This review has highlighted some of the models that have been developed to study this hypothesis. Targeted interventions aimed to directly reduce KP metabolites or their sites of action during critical developmental periods may constitute novel therapeutic strategies to treat and, possibly, to prevent the manifestation of neuropsychiatric and other CNS disorders.

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Abbreviations

KP	Kynurenine pathway
CNS	central nervous system
IDO	indoleamine-2,3-dioxygenase
TDO	tryptophan-2,3-dioxygenase
KAT	kynurenine aminotransferase
KYNA	kynurenic acid
α7nACh	alpha 7 nicotinic acetylcholine
NMDA	N-methyl-D-aspartate
GPR 35	G protein-coupled receptor 35
AhR	aryl hydrocarbon receptor
KMO	kynurenine 3-monooxygenase
3-HK	3-hydroxykynurenine
QUIN	quinolinic acid
PND	postnatal day
ACh	acetylcholine

ED	embryonic day
SZ	schizophrenia
ASD	autism-spectrum disorder
ADHD	attention deficit hyperactivity disorder
LTP	long-term potentiation

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Fig. 1.

(A) Kynurenine pathway (KP) of tryptophan degradation. (B) Compared to the adult rodent brain, KP metabolites (kynurenine, KYNA and 3-HK) are elevated in the fetal rodent brain (ED 22). Data are adapted from Ceresoli-Borroni and Schwarcz, 2000.

Fig. 2.

Perinatal choline supplementation attenuates contextual memory impairments of EKyn offspring in adulthood. (A) Embryonic kynurenine treatment (EKyn): kynurenine-treated dams were fed a diet of normal wet rodent chow laced with 100 mg kynurenine per dam per day from ED 15 to ED 22. Control dams (ECon) were fed normal diet (0.1% choline chloride). Choline-supplemented dams were fed choline-laced diet (0.5% choline chloride) from ED 15 to PND 21 in combination with either ECon or EKyn treatment. Upon weaning, all offspring were fed normal rodent chow until behavioral testing was performed in adult animals between PND 65–85. (B) Adult male animals were tested in the passive avoidance paradigm. No differences in approach latency were observed on the training day. (C) Avoidance latency differed significantly between ECon and EKyn offspring, but did not differ between the ECon + choline and EKyn + choline animals. All data are the mean $\pm$ SEM. Results were analyzed using a one-way repeated measures analysis of variance (ANOVA) with treatment group as a between-subject factor. Post hoc analysis was performed using a Bonferroni t test correction. * $P < 0.05$ versus control (ECon). $N = 11$ –12 per group.

Table 1

Kynurenine pathway manipulation during development: Short and long-term effects.

Manipulation Model	Age of manipulation	KP alteration after manipulation	Age of testing	KP biochemistry at testing	Behavioral impairment	Structural/Functional changes in the brain	References
Embryonic Kynurenine (EKyn): Food laced with kynurenine fed to pregnant rat dams	ED 15 to ED 22	Increased fetal brain KYNA	PND 56	Increased KYNA in adult offspring	Impaired spatial learning, reference memory, and contextual memory Impaired attentional set-shifting	Decreased dendritic spine density, expression of $\alpha 7$ nACh and mGluR2, and evoked glutamate release	Pocivavsek et al., 2014 Pershing et al., 2015
Pharmacological inhibition of KMO by treating pregnant rat dams with Ro-61-8048	ED 14, ED 16, and ED 18	Increased KYNA in the fetal brain	PND 21			Increased neuronal excitability, GluN2A/2B subunits, and PSD95	Forrest et al., 2013a
			PND 60			Decreased GluN2A and sonic hedgehog. Increased doublecortin. Paired-pulse stimulation deficit and impaired LTP	Forrest et al., 2013b
						Decreased dendritic spine number and complexity in hippocampus	Khalil et al., 2014
						Changes in various proteins including DISC1 and unc5H3 in the cerebellum, increased complexity of dendritic trees	Pisar et al., 2014
						Impaired LTP in hippocampus	Forrest et al., 2015

Manipulation Model	Age of manipulation	KP alteration after manipulation	Age of testing	KP biochemistry at testing	Behavioral impairment	Structural/Functional changes in the brain	References
Developmental Kynurenine (DevKyn): Food laced with kynurenine fed to pregnant rat dams	ED15 to PND 21	Increased KYNA and 3-HK at weaning	PND 56	Increased KYNA, but no change in 3-HK, in adult offspring	Impaired spatial learning, reference memory, and contextual memory Impaired attentional set-shifting	Decreased extracellular glutamate in hippocampus Decreased extracellular glutamate in prefrontal cortex	Pocivavsek et al., 2012 Alexander et al., 2013
Peripheral administration of kynurenine to rats	PND 7 to 10	Increased cortical KYNA and QUIN	PND 70		Impaired social behavior		Iaccarino et al., 2013
Peripheral administration of kynurenine to mice	PND 7 to 16	Increased cortical KYNA	PND 90		Impaired amphetamine-induced locomotor activity, pre-pulse inhibition, working memory in a trace-fear conditioning task	Potentiated dopamine release in response to d-amphetamine administration	Liu et al., 2014
Peripheral administration of kynurenines to rats	PND 27 to 35	Increased cortical KYNA	PND 61	No change in cortical KYNA in adult offspring	Impaired social behavior Impaired novel object recognition and contextual fear memory Increased motivational value by sign tracking		Trecartin and Bucci, 2011 Akagbosu et al., 2012 DeAngeli et al., 2014