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Invited review

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

Francesca M. Notarangelo, Ana Pocivavsek*

Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

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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 α7 nicotinic acetylcholine (α7nACh) 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 α7nACh 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.

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Contents

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.

* Corresponding author. Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228, USA.
E-mail address: apocivavsek@mprc.umaryland.edu (A. Pocivavsek).

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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.

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 (α7nACh) 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 α7nACh 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