Prenatal Kynurenine Treatment in Mice: Effects on Placental and Fetal Brain Kynurenines

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Studies in animals and humans suggest a pathophysiologically significant association between elevated brain kynurenic acid (KYNA) levels and cognitive dysfunction in schizophrenia (SZ) (Schwarcz et al., 2012). The increase in KYNA in the disease may be secondary to a genetic disruption of kynurenine 3-monooxygenase (KMO), a pivotal kynurenine pathway (KP) enzyme with links to SZ endophenotypes (Wonodi et al., 2011). Prenatal exposure to kynurenine (the direct bioprecursor of KYNA) induces cognitive impairments reminiscent of SZ in adult rats (Pocivavsek et al., 2014), suggesting a developmental dimension to the link between KYNA and SZ. To begin exploring the possible role of KMO in this scenario, we now exposed pregnant wild-type (WT= $Kmo^{+/+}$), heterozygous (HET = $Kmo^{+/-}$) (Giorgini et al., 2013) C57BL/6 mice to kynurenine (10 mg/day, given with chow) during the last week of gestation, i.e. from embryonic days (ED) 10/11 to ED17/18. The dams were euthanized on ED17/18, and the levels of KYNA and 3-hydroxykynurenine (3-HK), the product of KMO, were determined in placenta and fetal brain of HET and KMO knockout (KO = $Kmo^{-/-}$) mice (from HET parents). Compared to WT animals (from WT parents), basal levels of KYNA in both placenta and fetal brain tended to be higher in the KO mice. In contrast, basal 3-HK levels in placenta and fetal brain were lower in both groups of mutant animals, reaching a significant reduction in the fetal KO brain ($p<0.05$ vs. WT). Preliminary data indicated that prenatal treatment with kynurenine caused a significantly larger increase in KYNA levels in the placenta and in the fetal brain of KO as compared to WT mice; a trend toward higher KYNA levels compared to WT mice was also observed in both tissues of HET animals. On the other hand, 3-HK levels in fetal brain of kynurenine-treated HET and KO mice tended to be lower than in the corresponding tissue of the WT animals. Jointly, these results revealed that the ratio between KYNA and 3-HK, which are believed to have opposing functions in the brain, is greatly skewed towards KYNA in the fetal brain when KMO is compromised or eliminated. As qualitatively similar phenomena were observed in the placentas of the mutant mice, it remains unclear if the effects seen in the fetal brain of the mutants are tissue-autonomous or secondary to placental biochemistry. The present data therefore raise the possibility that KP activity in the placenta exerts an important influence on fetal brain development (Hsiao and Patterson, 2012) and may thus contribute to the development of adult mental disorders including SZ.

Schwarcz et al. (2012). *Nat. Rev. Neurosci.* 13:465-77.
Wonodi et al. (2011). *Arch. Gen. Psychiat.* 68:665-74.
Pocivavsek et al. (2014). *Psychopharmacology*. 231:2799-809.
Giorgini et al. (2013). *J. Biol. Chem.* 288:36554-66.
Hsiao and Patterson (2012). *Dev. Neurobiol*. 72:1317-26.