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Cocaine exposure modulates dopamine and adenosine signaling in the fetal brain

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Abstract

Exposure to cocaine during the fetal period can produce significant lasting changes in the structure and function of the brain. Cocaine exerts its effects on the developing brain by blocking monoamine transporters and impairing monoamine receptor signaling. Dopamine is a major central target of cocaine. In a mouse model, we show that cocaine exposure from embryonic day 8 (E8) to E14 produces significant reduction in dopamine transporter activity, attenuation of dopamine D1-receptor function and upregulation of dopamine D2-receptor function. Cocaine's effects on the D1-receptor are at the level of protein expression as well as activity. The cocaine exposure also produces significant increases in basal cAMP levels in the striatum and cerebral cortex. The increase in the basal cAMP levels was independent of dopamine receptor activity. In contrast, blocking the adenosine A2a receptor downregulated of the basal cAMP levels in the cocaine-exposed brain to physiological levels, suggesting the involvement of adenosine receptors in mediating cocaine's effects on the embryonic brain. In support of this suggestion, we found that the cocaine exposure downregulated adenosine transporter function. We also found that dopamine D2- and adenosine A2a-receptors antagonize each other's function in the embryonic brain in a manner consistent with their interactions in the mature brain. Thus, our data show that prenatal cocaine exposure produces direct effects on both the dopamine and adenosine systems. Furthermore, the dopamine D2 and adenosine A2a receptor interactions in the embryonic brain discovered in this study unveil a novel substrate for cocaine's effects on the developing brain.

Introduction

Cocaine exposure during the fetal period can lead to lasting impairment of neurological function (Chasnoff et al., 1989a; Chasnoff et al., 1989b; Chiriboga et al., 1993; Chiriboga et al., 2009; Delaney-Black et al., 1996; Eyler et al., 2009; Kosofsky and Wilkins, 1998). Cocaine exerts its effects by blocking the activity of monoamine transporters. Central actions of cocaine are believed to be mainly due to blockade of the dopamine transporter, the resulting decrease in dopamine re-uptake at the synapse and increase in extracellular dopamine levels (Bhide, 2009; Meyer et al., 1993; Ritz et al., 1990; Ritz et al., 1987). Persistent increases in extracellular

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