Long-lasting effects of prenatal MAM treatment on water maze performance in rats: 
Associations with altered brain development and neurotrophin levels

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Abstract

We previously reported that prenatal methylazoxymethanol (MAM) administered on days 11 and 12 of rat pregnancy induces structural changes in the cytoarchitecture of the hippocampal–entorhinal axis. We also showed that young and middle-aged prenatally treated MAM animals displayed changes in brain neurotrophin levels [Neurosci. Lett. 309 (2001) 113; Physiol. Behav. 71 (2000) 57]. To continue this line of investigation, the working hypothesis adopted was that prenatal MAM administration, by interfering with limbic neurogenesis, could impair learning and memory ability of aged animals in the water maze. It was found that injection of MAM during early rat brain development induced deficits in both the acquisition and retention phases of the Morris maze. These behavioral changes were associated with significant changes in brain nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), reduced choline acetyltransferase (ChAT) immunoreactivity in forebrain cholinergic neurons and loss of neuropeptide Y (NPY) immunodistribution in cells of the entorhinal cortex. This finding, as well as confirming previous studies showing that injection of prenatal MAM administration induces significant changes in hippocampal–entorhinal axis neurogenesis and marked behavioral deficits in adult life, provides additional experimental evidence supporting the hypothesis that loss of NGF and/or BDNF-receptive or producing cells can co-occur at the onset of neurodevelopmental disorders. © 2002 Published by Elsevier Science Inc.

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1. Introduction

It is known from developmental mammalian brain studies that neurogenesis is characterized by cell migration and differentiation before a given group of neurons reaches their final structural and topographical localization within the CNS. The time schedule for cell migration and differentiation is known to be regulated by neurotrophins [8,29]. Failure of or impairments in these processes can lead to severe neurological deficits in postnatal life [19]. One specific aspect of this development strategy is that disruption of cell migration from the cortical proliferative zone can produce long-lasting changes in the neuronal structural organization of the entorhinal cortex and hippocampus leading to severe neuropathologies in humans [11,49]. Selective lesions of the entorhinal–hippocampal axis have been carried out in animal models of neurodevelopmental disease by injecting drugs, which interfere with cell division and/or migration during specific time points of brain neurogenesis.

Prenatal methylazoxymethanol acetate (MAM) treatment at different gestational days (GD) has been used to produce animal models for neuropathologies characterized by disorders in neuronal cells and for human brain dysgenesis including epileptogenic cortical malformations [13,23,57]. In particular, to induce maldevelopment of the entorhinal–hippocampal axis, we administered MAM at GD11 or GD12, which kills neuroblasts undergoing mitosis of rat fetal life [26,52]. Indeed, prenatal MAM exposure at GD13 or later elicits marked microencephaly with gross changes in all brain areas and behavior [13]. We demonstrated that prenatal MAM treatment at GD11 and GD12 induced changes in the behavior [25,26,52,53]. Young rats prenatally...