Prenatal exposure to methylazoxymethanol acetate in the rat alters neurotrophin levels and behavior: considerations for neurodevelopmental diseases

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Abstract

We did a single injection of methylazoxymethanol acetate (MAM) in pregnant rats on gestational day (GD) 11 or 12 to investigate the long-lasting effects of early entorhinal cortex (EC) and hippocampus maldevelopment on behavior, brain nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) levels, and the neurotrophin receptor p75 and choline acetyltransferase (ChAT) immunoreactivity. Adult animals treated with MAM had compromised EC development and showed changes in locomotion and displacement activities. In addition, rats treated on GD 12 had increased concentration of NGF and BDNF in the EC and hippocampus if compared to control rats. Prenatal MAM administration did not affect significantly p75 and ChAT distribution in the EC and septum. Results are discussed in reference to the neurodevelopmental hypothesis of psychiatric disorders. © 2000 Elsevier Science Inc. All rights reserved.

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Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are expressed in a variety of brain regions both during prenatal development and adult life [11]. High concentrations of NGF and BDNF are present in the developing central nervous system (CNS) [52] where they are known to play a crucial role in growth, plasticity, and function of brain neurons and in a variety of CNS disorders, including those associated with deficits in cognitive functions [31]. NGF is also a neurotrophin influencing the development and functioning of the forebrain cholinergic neurons [30,38,46,61] and participates in the neuroregulation and fine-tuning of behavior [2]. Moreover, it has also been shown that cholinergic pathways are implicated in the pathogenesis of neuropsychiatric diseases [10,60]. Both NGF and BDNF have been found in the cortical association areas as the entorhinal cortex (EC) and their expression undergoes significant changes following chemical or surgical insults [22,44]. The EC and the hippocampus are associational areas [40] where neurotrophins are expressed playing a key role in the regulation of the behavior, and entorhinal–hippocampal projections may be among the first cortical connections to be established in the human brain. Human studies on EC and hippocampus also revealed that changes in these brain areas are associated with a wide number of neuropsychiatric disorders [57] and recent studies have suggested that neurotrophic factors may also be implicated in neurodevelopmental disorders [14,53].

Thus, the aim of the present investigation was to characterize in an animal model of maldevelopment of both EC and hippocampus the long-lasting changes on behavior and neurochemical markers such as NGF, and BDNF implicated in cholinergic and non-cholinergic brain neurotransmission. This animal model [29,58,59] consists in disrupting the EC/hippocampal axis during the earliest stages of cortical proliferation in rats by administering a single injection of methylazoxymethanol acetate [MAM, [18,27]] in pregnant rats at gestational day (GD) 11 or 12...