Impaired brain development in the rat following prenatal exposure to methylazoxymethanol acetate at gestational day 17 and neurotrophin distribution

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Several neuropsychiatric disorders, including schizophrenia, are the consequence of a disrupted development of the CNS. Accordingly, intrauterine exposure to toxins may increase the risk for psychopathology. We investigated whether prenatal exposure of rats to the neurotoxin methylazoxymethanol acetate led to long-term changes in cerebral neurotrophin levels. We measured the brain levels of nerve growth factor and brain derived neurotrophic factor in young adult and adult rats. Decreased nerve growth factor or brain derived neurotrophic factor were found in the parietal cortex accompanied by altered neurotrophin content in the hippocampus and entorhinal cortex. The present study is the first to show long-lasting effects of a single prenatal exposure to a neurotoxin on adult levels of neurotrophins in brain regions implicated in neuropsychiatric disorders. NeuroReport 15:1791–1795 © 2004 Lippincott Williams & Wilkins.

Key words: BDNF; MAM; NGF; Schizophrenia

INTRODUCTION

Methylazoxymethanol acetate (MAM) exposure during development affects brain cytoarchitecture, behavior and neurotrophins in the rat. MAM alkylates the DNA of proliferating neurons, killing the mitotic cells [1]. If administered at gestational day (GD) 11 or 12, MAM induces disrupted development of the entorhinal-hippocampal axis [2–4], whereas at GD15 and 16 the hypothalamus and selective striatal, cortical, hippocampal and thalamic areas are particularly affected [1] (see Table 1 for further information). Disrupted development in these brain areas is associated with specific behavioral impairments. One potential mechanism through which this neurotoxin may disrupt development may be via changes in nerve growth factor (NGF) or brain derived neurotrophic factor (BDNF) levels. NGF and BDNF are neurotrophins that play key roles in the development, maintenance and function of the peripheral and central nervous system [5], regulating neural processes including synaptic function and plasticity, as well as impacting neuronal survival. Rats exposed to MAM at GD11 and GD12 when tested as adults exhibited high levels of NGF and BDNF in the entorhinal cortex but reduced levels in the hippocampus and parietal cortex (GD15) [3,4,6]; this supports a potential role for NGF and BDNF in the cellular atrophy observed following prenatal exposure to MAM. One time point that is of particular interest is the effect of MAM on GD17 because MAM administration at this time point may lead to disruption of brain circuits of known relevance to schizophrenia [7,8]. Adult rats exposed at GD17 to MAM show small-to-moderate reductions in the thickness of limbic and paralimbic cortices. Furthermore, these rats have significant deficits in cognitive tasks that depend on prefrontal-and hippocampal-striatal circuits and behave as rats with frontal lesions. Thus the aim of the present study was to investigate the changes in NGF and BDNF following exposure in utero to MAM at GD17 in those brain areas sensitive to MAM-induced cellular ablation such as the hippocampus and cortex. We predicted that prenatal MAM administration would induce selective disruption of both NGF and BDNF levels of the rat brain.

MATERIALS AND METHODS

Subjects and treatments: Timed pregnant Fisher 344 rats (Rattus norvegicus) were obtained from Harlan, USA; animals were mated over a period of 4 h, which was defined as day 0 of gestation (GD0). Females with a vaginal plug