Bromodeoxyuridine and methylazoxymethanol exposure during brain development affects behavior in rats: consideration for a role of nerve growth factor and brain derived neurotrophic factor

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Abstract

Rats prenatally exposed to the neurotoxins methylazoxymethanol (MAM) or 5-Bromo-2'-deoxyuridine (BrdU) are used as animal models of brain maldevelopment. We administered in rats MAM (20 mg/kg), or BrdU (100 mg/kg) or both at gestational day 11. Locomotion was not affected by any prenatal treatment whereas learning was delayed in the Morris maze in MAM animals. BrdU induced decreased NGF and BDNF levels in the hippocampus. In the parietal cortex prenatal BrdU administration induced NGF potentation associated with decreased BDNF. Animals treated with both MAM and BrdU showed also an increased immunopositivity for choline acetyltransferase (ChAT) and low affinity neurotrophins’ receptor (p75) in the septum and Meynert’s nuclei. These findings suggest that embryonic exposure to MAM and/or BrdU may be useful for studying mechanisms associated with neurodegenerative diseases affecting brain morphology and behavior. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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A critical aspect of the mammalian brain development is characterized by neuronal growth, differentiation, migration and proper matching of pre-synaptic axon to specific post-synaptic target neurons. However, the understanding of the mechanisms of these processes is still largely unknown, although it has been shown that trophic factors such as NGF and BDNF play a crucial role in regulating brain development and behavior [1,13]. Animal models of disease, particularly those resembling defects in cortical development, are widely utilized as novel approach to investigate how such defects translate into neurological disorders and behavioral impairments including neuropsychiatric-like diseases. Prenatal administration of 5-Bromo-2'-deoxyuridine (BrdU), a halogenated pyrimidine analog, or methylazoxymethanol (MAM), a compound which has been successfully used to inhibit cortical proliferation, have been extensively adopted as teratogens [3,15]. Embryonic BrdU competes with thymidine for sites on replicating DNA strand inducing brain malformations and several behavioral changes [11]. MAM is a short-acting alkylating agent that methylates nucleic acids, leading to the death of cells that are actively replicating DNA and rats prenatally exposed to MAM display severe impairments in cognition, locomotion and mood which were associated with changes in brain neurotrophins and neuropeptides distribution [6,7,16,17].

Aim of the present study was to compare MAM and BrdU effects on the behavioral and molecular mechanisms associated with changes in brain neurotrophins levels and cognition. We administered in pregnant rats or MAM, or BrdU, or both MAM and BrdU or saline solution as controls. We analyzed also ChAT immunopositivity and p75 neurotrophins’ receptor in selected brain regions [9,12]. According to previous studies [11,17], pregnant rats received, at gestational day 11 (GD11), an intraperitoneal injection of MAM 20 mg/kg or an injection of BrdU (100 mg/kg) or both. Dams of the saline group received saline solution on GD11. At birth all litters were reduced to four males and four females and fostered to the biological dams following behavioral procedures previously described [18]. Post weaning prenatally treated male adult rats (age 6 months) were used for the behavioral and biochemical studies.