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## DUAL INFLUENCES OF EARLY-LIFE MATERNAL DEPRIVATION ON HISTONE DEACETYLASE ACTIVITY AND RECOGNITION MEMORY IN RATS

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**Abstract**—Exposure to stress early in life may negatively impact nervous system functioning, including increasing the proneness to learning and memory impairments later in life. Maternal deprivation, a model of early-life stress, hinders memory in adult rats and lessens brain-derived neurotrophic factor (BDNF) levels in the hippocampus in a very heterogeneous way among individuals. The main goal of the present study was to investigate the possible epigenetic modulation underlying recognition memory impairment and reduced BDNF levels in the hippocampus of adult maternally deprived rats. We also evaluated the potential ameliorating properties of the histone deacetylase (HDAC) inhibitor, sodium butyrate, on memory deficits and BDNF changes related to maternal deprivation. Maternally deprived animals were categorized as ‘inferior learners’ and ‘superior learners’ according to their performance in object recognition memory task in comparison to controls. Results indicated that HDAC activity was higher in individuals submitted to maternal deprivation with the worst cognitive performance (inferior learners). Acute administration of sodium butyrate increased histone H3 acetylation and BDNF levels, and restored recognition memory in maternally deprived animals with the worst cognitive performance. Moreover, we also showed that there is a positive correlation between BDNF levels and memory performance. Taken together, the results indicated that HDAC inhibitors could be considered as a possible therapeutic agent to improve cognitive performance in inferior learners. Further studies need to be conducted for a better comprehension of the mechanisms related to persistent alterations observed in adult life induced by early stressful circumstances and those leading to resilience. © 2017 Published by Elsevier Ltd on behalf of IBRO.

**Key words:** post-natal stress, object recognition, sodium butyrate, histone acetylation, BDNF.

### INTRODUCTION

It is well established that exposure to stress during central nervous system (CNS) development can trigger multiple effects on cognitive function and behavior in adulthood in accordance to: (1) the individual’s genetic background; (2) conditions under which the individual was exposed to stress during the development; and (3) conditions under which the individual is exposed to stress in adulthood – a concept known as three-hit paradigm. Depending on the context, adversity can trigger both a deleterious effect on cognition (increased vulnerability) or an increase in the individual’s ability to adapt to stress in adulthood (increased resilience) and consequently have a better performance in certain cognitive challenges (Pryce et al., 2003; Hulshof et al., 2011; Daskalakis et al., 2013; Suri et al., 2013).

In the last decades, it has been consistently shown that exposure to stress during CNS development, using maternal deprivation paradigms, may induce increased anxiety and stress hormone levels; changes in neurogenesis and apoptosis rates; decrease in neurotrophic factors and enzymes responsible for transducing signals important for learning and cognition in adults (Kaffman and Meaney, 2007). In fact, previous studies conducted by our laboratory have repeatedly demonstrated that exposure to stress during CNS development, using a maternal deprivation paradigm, induces memory impairments in adult life that are accompanied by higher levels of the pro-inflammatory cytokine TNF- $\alpha$  and decreased levels of the neurotrophic factor brain-derived neurotrophic factor (BDNF) in brain areas involved in learning and memory formation (de Lima et al., 2011; Pinheiro et al., 2012, 2015; Garcia et al., 2013). Studies reveal that epigenetic regulation of gene transcription could be involved in the modulation of BDNF expression and memory consolidation in different behavioral paradigms (Lubin et al., 2008; Cowansage et al., 2010; Suri et al., 2013).

It has been suggested that the epigenetic modulation of the expression of BDNF may be linked to cognitive deficits observed in adults who were exposed to stress during CNS development (Lubin et al., 2008; Jarome and Lubin, 2013; Suri et al., 2013). Epigenetic refers to modifications of gene expression without altering the

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**Abbreviations:** ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; HDAC, histone deacetylase; LTM, long-term memory; NOR I, Novel object recognition task I.

genetic code itself. Epigenetic mechanisms, including chromatin remodeling and DNA methylation, have profound regulatory roles in mammalian gene expression in response to environmental stimuli. Chromatin is formed by the genomic DNA chain coiled around octamers formed by proteins called histones (classified as H2A/H2B/H3/H4), which are subject to several types of post-translational modifications that alter gene expression. Among such modifications is the acetylation of lysine residues of histone H3 (favoring gene transcription) and the methylation of lysine residues of histone H3 (which weakens gene transcription). Enzymes that promote acetylation of histones are known as histone acetyltransferases (HATs) while deacetylation is carried out by histone deacetylases (HDACs) (Bonasio et al., 2010). Both groups of enzymes have been studied as possible targets for drug development for the treatment of cognitive impairment accompanying neuropsychiatric disorders (Fischer et al., 2010; Peter and Akbarian, 2011).

As the effects of exposure to stress during CNS development are very heterogeneous among individuals, the aim of the present study was to investigate whether the influences of early maternal separation on memory in adult rats could be associated with HDAC activity and levels of histone H3 acetylation, or with BDNF levels in hippocampus (a key brain region for learning and memory), by dividing animals submitted to maternal deprivation in groups with higher or lower memory performance. We also investigated the use of a HDAC inhibitor (sodium butyrate, NaBu) in ameliorating memory deficits induced by maternal deprivation.

## EXPERIMENTAL PROCEDURES

### Experimental design

The animals were submitted to maternal deprivation from post-natal day 1–14. When they reached adulthood (3 months old), these animals were tested in an object recognition task in order to identify who were the individuals submitted to maternal deprivation with worse and better cognitive performance, categorizing them in two groups in relation to controls: inferior learners (IL) and superior learners (SL). One month later the same animals were submitted to a new acquisition session of the object recognition (in order to induce a new memory consolidation phase). Immediately after training, these animals received an intraperitoneal administration of vehicle (control group) or NaBu, an HDAC inhibitor (Reolon et al., 2011; Silva et al., 2012; Blank et al., 2015). These animals were then divided into two other groups: (1) those who were euthanized 3 h after the training session for biochemical analysis (non-deprived, ND; deprived-superior learners, D-SL; and deprived inferior learners, D-IL) and (2) those who were submitted to the long-term memory (LTM) retention test of object recognition (only ND and D-IL). The purpose of this subdivision was to verify if the effects of NaBu on HDAC activity, histone H3 acetylation, and BDNF levels during memory consolidation phase (subgroup 1) and on memory (subgroup 2) in controls (ND) and maternally deprived animals (D-IL). All the D-SL animals were euth-

anized 3 h after training session for biochemical analysis. Table 1 summarizes the experimental design and the distribution of experimental groups.

### Animals

Pregnant Wistar rats were provided by the Centro de Modelos Biológicos Experimentais (CeMBE/PUCRS), Pontifical Catholic University, Porto Alegre, Brazil. Within 48 h after birth, each litter was standardized to contain eight rat pups of both genders. Pups were kept together with their mothers in plastic cages with sawdust bedding at room temperature of  $21 \pm 1$  °C and a 12/12-h light/dark cycle (lights ON at 7 a.m.). Pups were weaned at the age of 3 weeks. Only the males were raised in groups of three to five in individually ventilated cages with sawdust bedding. After weaning animals were given ad libitum access to standardized rat chow and tap water. All experimental procedures were carried out in conformity with the Guide for the Care and Use of Laboratory Animals and followed the recommendations on animal use of the Brazilian Guidelines for the Care and Use of Animals in Research and Teaching (DBCA, published by CONCEA, MCTI). Experimental protocols were approved by the Ethics Committee for the Use of Animals of Pontifical Catholic University (CEUA 14/00397). All efforts were made to minimize animal suffering and to reduce the number of animals used.

### Maternal deprivation

Maternal deprivation was carried out as previously reported (Levine, 1967; de Lima et al., 2011; Pinheiro et al., 2015, 2013; Garcia et al., 2013).

From postnatal days 1–14, rat pups were divided into two different experimental rearing conditions: (1) non-deprived (ND) or (2) deprived (D). In the deprived (D) group of animals, the dam was removed from the cage, and the litter was weighed and immediately left for a 180-min daily period in which each litter was kept in a plastic cage with bedding material in an adjacent room to their dams on an incubator at the temperature of 35 °C to avoid hypothermia. Right after the maternal deprivation period, pups were put back in their home cages and rolled in the bedding material, and the dam was returned. Animals from the ND group were weighed daily, being away from their dams for a maximum period of 15 min, aiming to control for possible effects induced by manipulation and contact to experimenters. In rats, the mother is normally off the litter for periods of 20–25 min (Jans and Woodside, 1990). Thus, only the group submitted to a 180-min period of separation (deprived), and not the group exposed to a brief manipulation and weighing procedure (non-deprived), can be considered maternally deprived.

### Open-field behavior

When ND and D animals completed 3 months of age, behavioral evaluation in the open-field was carried out, 24 h before object recognition training. Open-field behavior was measured as described in previous

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