



Alteration of neurotrophin and cytokine expression in lymphocytes as novel peripheral markers of spatial memory deficits induced by prenatal stress



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HIGHLIGHTS

- Prenatal stress induced spatial memory impairment in adult female mice.
- Memory alteration was related to GR, BDNF and Th1/Th2 balance changes in the hippocampus.
- These changes were found in peripheral lymphocytes as well.
- Lymphocytes could be peripheral markers of susceptibility to behavioral alteration.

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ABSTRACT

Much evidence has suggested that early life adversity can have a lasting effect on behavior. The aim of this study was to explore the impact of prenatal exposure to stress on cognition in adult life and how it impacts chronic stress situations. In addition, we investigated the participation of glucocorticoids, neurotrophins and cytokines in prenatal stress effects. For this purpose, pregnant mice were placed in a cylindrical restraint tube for 2 h daily during the last week of pregnancy. Control pregnant females were left undisturbed during their entire pregnancy period. Object-in-place task results showed that adult female mice exposed to prenatal stress exhibited an impairment in spatial memory. However, in the alternation test this memory deficit was only found in prenatally stressed mice submitted to chronic stress. This alteration occurred in parallel with a decrease in BDNF, an increase in glucocorticoid receptors and an alteration of Th1/Th2 in the hippocampus. Interestingly, these changes were observed in peripheral lymph nodes as well. However, none of the mentioned changes were observed in adult male mice. These results indicate that lymphoid cells could be good candidates as peripheral markers of susceptibility to behavioral alterations associated with prenatal exposure to stress.

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1. Introduction

Stress and adaptation to stress requires numerous homeostatic adjustments. Allostasis refers to the adaptive processes that maintain

homeostasis through interrelations between the hypothalamus–pituitary–adrenal axis (HPA), sympathetic–parasympathetic efferent pathways and chemical messengers (hormones, neurotransmitters, interleukins, neurotrophins) [1]. These mediators of the stress response promote adaptation in the aftermath of acute stress, but they also contribute to allostatic overload: the wear and tear on the body and brain that results from being “stressed out” [2]. While a response to stress is a necessary survival mechanism, prolonged stress can produce severe consequences that affect behavioral, endocrine and immunological parameters [2]. Among these parameters, the hippocampus, which is a

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limbic area involved in learning and memory, is particularly sensitive to stress [3]. In particular, structural alterations of the hippocampal formation and reduction of neurogenesis in the adult dentate gyrus have been observed in different animal models of chronic stress [4,5].

Exposure to early life adversity may deeply affect brain development leading to long-lasting effects on neuronal structure and behavior playing a key role in the etiology of anxiety and mood disorders. Several evidence reveals that neuronal and synaptic changes induced by prenatal stress (PS) exposure are highly region-specific. On the structural level the most dramatic changes are found in limbic and prefrontal cortical areas, those regions which are involved in cognitive as well as emotional functions. In this context, the hippocampus has been the classically studied brain area to investigate PS-related effects (for a review see [6]).

Moreover, PS can result in stable long-term changes in central and peripheral stress response systems as well as influence the response to stress in adulthood [7,8]. It has also been found that prenatal stress (PS) induces an enhanced fear-like behavioral profile and dysregulation of brain noradrenergic and HPA activity after a stress during adulthood [8,9]. However, there are studies in animals [10–12] that suggest that PS has an adaptive effect that helps offspring respond appropriately to stressors in the environment. Genetic predisposition, including animal strain, polymorphism and gender, are factors that contribute to vulnerability/resilience against PS [13].

In addition, there are other factors, such as neurotrophins and cytokines, that have been shown to be involved in stress-related pathology [14,15], even though the alteration of their levels under PS has not been exhaustively studied.

Neurotrophins are a family of secreted growth factors that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and NT4. They play crucial roles in the formation and plasticity of neuronal networks and have been shown to be involved in the pathophysiology of suicide [16] and depression [17].

Several studies have demonstrated that immune system can signal the central nervous system through the action of cytokines (for a review see [18]). Among others, cytokines can be classified by their action: pro-inflammatory or anti-inflammatory; and by the type of T lymphocyte that produce them: T-helper 1 lymphocytes (Th1) or T-helper 2 lymphocytes (Th2). In general, Th-1 lymphocytes release cytokines enhancing the cell mediated immune response (i.e. IFN- γ , IL-2). Whereas, Th-2 cytokines (i.e. IL-4, IL-10) enhance the humoral response by activating cells to express antibodies. Th-1 cytokines are mainly pro-inflammatory, while Th-2 cytokines are mainly anti-inflammatory. Equilibrium between pro and anti-inflammatory is essential to maintain the homeostasis in the immune system [15]. In addition, shifts in the Th1/Th2 balance have been involved in the pathogenesis of many human illnesses, such as autoimmune diseases, sleep disturbance, major depression and other disorders [15,19]. It has been proposed that immunity might play an important role in maintenance, protection and repair of both a healthy and diseased CNS [20]. Recently, we found a correlation between poor memory performance and a shift to Th2 responses [21].

In this context, the purpose of the present study was to analyze the impact of PS exposure on behavior and cognition in adult life as well as the impact of PS on chronic stress situations. In addition, we investigated if these long-lasting effects induced by prenatal stress exposure were related to alterations in stress reactivity and/or changes in cytokine and/or neurotrophin levels in hippocampus. Furthermore, we analyzed if the molecular changes in hippocampus are also found in lymphocytes in order to propose these cells as peripheral markers of susceptibility to behavioral alterations. Because several studies have reached a consensus that PS has sex-specific adverse effects on behavior [22], we compared the PS effects in males and females in this study.

2. Materials and methods

2.1. Animals

Inbred 60-day-old BALB/c mice were acquired from the Veterinary School of the University of Buenos Aires (Argentina). The mice were housed and maintained on a 12/12 light/dark cycle under a controlled temperature (18–22 °C). Animals were taken care of and sacrificed according to the rules of the “Guide for the Care and Use of Laboratory Animals” (NIH) (revision 2011) and to the EC Directive 86/609/EEC (revision 2010). The experimental protocol was also approved by the Institutional Committee for the Use and Care of Laboratory Animal rules (CICUAL, School of Medicine, University of Buenos Aires, Argentina) under resolution 2962/10 and 2947/13.

2.2. Experimental design

Fig. 1 shows a scheme of the experimental design used in the present work. Pregnant mice were divided in two groups, one left undisturbed and the other submitted to restraint stress. Both 60 day old prenatally unstressed and stressed female and male offspring were randomly assigned to the following groups: acute stress, chronic stress and undisturbed groups. The combination of prenatal and adult treatment resulted in the following six groups: mice that never were exposed to stress (offspring from unstressed females that were left undisturbed, CN), mice from unstressed females that received chronic stress as adults (CN-CS), mice exposed only to prenatal stress (PS), mice that received both prenatal stress and chronic stress as adults (PS-CS), mice from unstressed females that received acute stress as adults (CN-AS), and mice that received both prenatal stress and acute stress as adults (PS-AS). With the exception of animals used for determining plasma corticosterone levels, all animals were used for behavioral testing and several biochemical and molecular determinations. After behavioral testing, mice were left undisturbed in their home cages for 48 h prior to sacrifice.

2.3. Prenatal stress

The PS model was conducted as we previously described [23] according to the protocol reported by Popova et al. [24]. Briefly, 40 pregnant mice were placed in a cylindrical restraint tube (4 cm diameter, 10 cm long) for 2 h daily (from 10 AM to 12) from day 15 of pregnancy until delivery (days 20–21). Non-exposed control pregnant female ($n = 40$) were left undisturbed during their entire pregnancy. Food intake and body weight were not different between the control and stressed pregnant mice. Pregnant females gave birth to about four or five pups per litter. No differences were found between the number and weight of alive pups between the control and stressed pregnant females, as previously reported [23]. In addition, no changes in maternal behavior were observed throughout lactation. Pups from both control and stressed mothers were separated at postnatal day 21 and placed in an identical environment up to an age of 60 days. To exclude possible litter effects, mice from different litters were randomly assigned to each group.

2.4. Stress in adult life

To determine behavioral changes induced by chronic stress exposure, offspring of 60 days of age were restrained by placing each animal in a well-ventilated polypropylene tube (2.8 cm diameter–11.5 cm long) for 2 h starting at 10:00 AM, and then the mice were returned to their cages. This procedure was repeated for 3 weeks and then the mice were left undisturbed for 1 day before behavioral tests or sacrifice.

In order to assess stress reactivity, corticosterone levels were determined in animals submitted or not to acute stress. Offspring of 60 days of age were restrained by placing each animal in a well-ventilated polypropylene tube (2.8 cm diameter–11.5 cm long) for 2 h

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