

# Behavioral and hypothalamic-pituitary-adrenal responses to anterodorsal thalamic nuclei lesions and variable chronic stress in maternally separated rats

Sandra M. Molina\*, Marta M. Suárez, María A. Rivarola

Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Córdoba, Argentina

Received 23 March 2006; received in revised form 4 May 2006; accepted 5 May 2006

## Abstract

In maternally separated rats, variable chronic stress decreased the emotional reactivity and provoked a state of hypoactivity of the hypothalamic-pituitary-adrenal system at 3 months old but increased its activity after the open field test. The anterodorsal thalamic nuclei control of the endocrine response under stress conditions was not manifested however it seems activate grooming behavior.

The development of behavioral and endocrine response to stress is influenced by early postnatal environment. On the other hand, the anterodorsal thalamic nuclei exert an inhibitory influence on the hypothalamic-pituitary-adrenal system under basal and stressful conditions. The aim of this work is to determine the magnitude of behavioral and hypothalamic-pituitary-adrenal responses to variable chronic stress in adult female rats with anterodorsal thalamic nuclei lesions, previously isolated for 4.5 h daily during the first 3 weeks of life. The groups were: non-maternally separated sham and lesioned, maternally separated sham and lesioned with variable chronic stress with and without open field test.

At 3 months old, under variable chronic stress, maternal separation provoked an increase in ambulation in sham and lesioned animals ( $P < 0.01$ ) but this parameter was not modified by lesion in either non-maternally separated or maternally separated groups. Neither the lesion nor the maternal separation changed the defecation and rearing parameter. Grooming behavior was lower in maternally separated lesioned rats ( $P < 0.05$ ). Under variable chronic stress maternal separation decreased adrenocorticotrophin hormone in comparison with non-maternally separated ( $P < 0.001$ ) and the lesion did not alter this response. Regarding corticosterone concentrations, maternal separation did not affect this hormone under variable chronic stress conditions and after the open field test there was an increase of this in both non-maternally separated and maternally separated sham and lesioned ( $P < 0.001$ ).

© 2006 ISDN. Published by Elsevier Ltd. All rights reserved.

**Keywords:** Stress; Maternally separation; Emotionality; Anterodorsal thalamic nuclei

## 1. Introduction

Animals separated from the dam during the neonatal period may exhibit profound and long-lasting alterations of endocrine

and behavioral responses to stressors (Francis et al., 1996; Grino et al., 1995; King, 1996; Levine, 1994; Meaney et al., 1996).

Studies pioneered by Levine (Levine et al., 1956) have demonstrated that brief periods of maternal separation (handling) permanently reduce corticosterone responses to subsequent stressors in infant animals. Increasing the duration and/or amplitude of the separation resulted in hypothalamic-pituitary-adrenal (HPA) hyperactivity (Laad et al., 1996; Meaney et al., 1994; Pinhoker et al., 1993; Plotsky and Meaney, 1993; Vázquez et al., 1996). The long-term consequences of a neonatal maternal separation paradigm have been the most thoroughly investigated to date. There is evidence that duration, frequency and age at separation are critical parameters (Ellenbroek and Cools, 1995; Levine et al., 1992; Rosenfeld et al., 1992; Van Oers et al., 1997). Depending

**Abbreviations:** ADTN, anterodorsal thalamic nuclei; ACTH, adrenocorticotrophin; CORT, corticosterone; CRH, corticotrophin releasing hormone; E, epinephrine; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal system; MR, mineralocorticoid receptor; MS, maternally separated; mRNA, messenger ribonucleic acid; NE, nor epinephrine; NMS, non-maternally separated; PVN, paraventricular nucleus; VCS, variable chronic stress

\* Corresponding author at: Cátedra de Fisiología Animal, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, Vélez Sársfield 299, 5000 Córdoba, Argentina. Tel.: +54 351 4332100; fax: +54 351 4332090.

*E-mail addresses:* msuarez@efn.uncor.edu (S.M. Molina), martasuarez1@hotmail.com (M.M. Suárez).

on the particular manipulation, neonatal maternal separation results in either no change or elevation of basal HPA axis activity, stress hyper-responsiveness, pituitary CRH receptor down-regulation, region-specific alterations in central glucocorticoid (GR) and mineralocorticoid (MR) receptor expression and binding, no change or increased CRH mRNA in the paraventricular nucleus (PVN), and enhanced anxiety (Heim et al., 1997).

These and other findings have established the importance of early experiences for the acquisition of emotional and endocrine coping strategies in later life (Huether, 1998; Rosenblum et al., 1994). Thus, although development of the central nervous system follows a basic blueprint specified by the genes, the final structure is shaped by interaction with the environment. In the long term, the result of this process may be either adaptive or maladaptive to the individual, for instance increasing the risk for developing psychopathology (Plotsky et al., 1998).

The immediate effects of maternal deprivation include increased CORT basal levels from postnatal day 8 and increased ACTH and CORT responses to mild stress (Levine et al., 1992; Avishai-Eliner et al., 1995). A minimum of 2 h of separation is required to induce minimal significant elevations in basal CORT levels (Avishai-Eliner et al., 1995; Kuhn et al., 1990; Levine et al., 1992; Pinhoker et al., 1993), and at least 8 h of maternal separation are required to see HPA axis hyper-responsiveness to stress (Cirulli et al., 1994; Levine et al., 1992; Stanton et al., 1988). On the other hand, evidence suggests that factors such as the nature, intensity, duration and frequency of stressful situation determine the endocrine and behavioral responses.

Among the long-term consequences of maternal separation, we have demonstrated that daily maternal separation for 4.5 h during the three first weeks of life produces at 3 months old a diminished ACTH response but enhanced CORT plasmatic levels (Suárez et al., 2001).

Unfortunately the long-term consequences recorded of maternal separation on emotional reactivity are not uniform due to the several different maternal separation protocols and behavioral tests applied. The reported consequences of maternal deprivation paradigm indicated that, whereas some authors find no effect of this manipulation on emotionality (Biagini et al., 1998; Crnic, 1981; Von Hoersten et al., 1993; Lehmann et al., 1999, 1998; Ogawa et al., 1994), others report decreased emotionality (Kaneko et al., 1994) and attenuated neuroendocrine response to stress (Suchecki and Tufik, 1997).

The central nervous system plays a crucial role in the elicitation and modulation of compensatory stress response patterns. Although a large number of neurotransmitter, neuropeptides, and neuromodulators are activated in various brain regions during exposure to stress, one can predict that specific neuronal circuits exist to optimize effective, rapid and efficient responses to restore disturbed homeostasis and ensure minimal damage to the organism.

The limbic system plays an important role in the control of emotional behavior and in endocrine function. A stress stimulus in pups causes the generation of a non-specific pattern of arousal in the associative cortex and in the limbic structures,

and these have been shown to alter the basal activity of the HPA system and the balance between noradrenergic and serotonergic functioning (Mathews et al., 1996; Vázquez et al., 2000). Thus, the findings of persistent effects of early life stress on the HPA axis provide a neurobiological substrate for the analysis of the possible modulatory role of the anterodorsal thalamic nuclei (ADTN).

Our previous studies led us to place the anterodorsal thalamic nuclei (ADTN) among the extrahypothalamic limbic centers, which are involved in regulating CORT and adrenal catecholamine secretion or release in rats. Lesions of the ADTN provoked an increase in plasma ACTH, CORT, and NE concentration in non-maternally separated animals and an increase in plasma ACTH, NE and E concentration in maternally separated animals, which indicates an inhibitory influence of ADTN on adrenal function (Suárez et al., 2002, 2004, 2001).

This study focused especially on the effects of maternal infant separation under stress situations on the regulation exerted by ADTN on the HPA axis. We used a chronic variable stress (VCS) model since previously we had observed that habituation occurs with repeated exposure to the same homotypic stressor (Suárez and Perassi, 1995). Besides, it is known that such a procedure alters emotional behavior and this stress paradigm best reproduces that daily stress to which a human being is exposed. With this purpose in mind we analyzed plasma ACTH and CORT, and the open field test under stressful conditions in female rats that were subjected to periodic maternal separation as neonates. Considering previous work (Suárez et al., 2002) we observed an endocrine response after the open field test in MS. In the present study we analyzed whether those responses were maintained under VCS conditions.

## 2. Material and methods

### 2.1. Animals and housing

Female Wistar rats were used since a more accentuated response to ADTN lesion was indicated in this sex group by previous results (Suárez et al., 1987). All animals were subjected to the same conditions. They were housed in a temperature-controlled room ( $22 \pm 2$  °C) under artificial illumination (12:12 h light–dark; lights on at 07:00 h), with water and food available ad lib.

All rats were handled daily by the same investigator from weaning to minimize stress reactions to manipulation. Handling consisted of picking up each rat from its home cage by placing the hand over its back, with the thumb and forefinger pressing its forelegs towards its head. Each rat was then placed briefly in another cage and finally returned to its home cage. On the day of sacrifice, the rat was picked up in the same way but, instead of being placed into a cage, it was immediately decapitated. Rats were decapitated between 09:00 and 12:00 h on diestrus, which was determined by examination of vaginal smears, in order to avoid unwanted variability linked to diurnal fluctuations and estrous cycle changes in circulating hormone levels.

Experiments were performed in accordance with protocols approved by the Animal Care Committee of the University of Córdoba, Argentina.

### 2.2. Maternal separation procedure

On postnatal day 1, litters were culled to eight pups (four females and four males when possible). Pups were separated of their mother daily for 4.5 h during the first 3 weeks of life (Ogawa et al., 1994). Each separation consisted of removing the mother from the home cage. The mother was placed alone in a

Download English Version:

<https://daneshyari.com/en/article/2787242>

Download Persian Version:

<https://daneshyari.com/article/2787242>

[Daneshyari.com](https://daneshyari.com)