



ELSEVIER

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: [www.elsevier.com/locate/jtherbio](http://www.elsevier.com/locate/jtherbio)

## Early maternal separation promotes alterations in the thermoregulatory profile of adult Wistar rats



C. Melo<sup>a,1</sup>, R.C.L. Vizin<sup>a,1</sup>, N.U. Silva<sup>b</sup>, D.T. Ishikawa<sup>a</sup>, M.B. Echeverry<sup>a,c</sup>, D.C. Carrettiero<sup>a,b</sup>, M.C. Almeida<sup>a,b,\*</sup>

<sup>a</sup> Graduate Program in Neuroscience and Cognition, Universidade Federal do ABC, São Bernardo do Campo, SP, Brazil

<sup>b</sup> Center for Natural and Human Sciences (CCNH), Universidade Federal do ABC, São Bernardo do Campo, SP, Brazil

<sup>c</sup> Center for Mathematics, Computation and Cognition (CMCC), UFABC, São Bernardo do Campo, SP, Brazil

### ARTICLE INFO

#### Keywords:

Depression  
Anxiety  
Stress  
Hyperthermia  
Temperature  
Thermal homeostasis

### ABSTRACT

Stressful lifelong events may influence psychiatric diseases, like depression and anxiety. Interestingly, depressed patients have dysfunction of thermoregulatory cooling mechanisms. Thus, understanding the mechanisms related to the thermoregulatory changes in stress-related pathologies is important to better understand the symptoms and treatments for those diseases. However, the influence of early-life stress on the thermoregulatory profile of adults is unknown. In this study, we aimed to evaluate the thermoregulatory profile of adult male Wistar rats submitted to early-life stress by maternal separation (MS). On postnatal days 2–14, rats were submitted daily to MS for 3 h per day. At 3–4 months of age, anxiety-like behavior was evaluated using the open field test and elevated plus maze, depression-like behavior was evaluated using the forced swim test and thermoregulatory profile were also evaluated. In the behavioral tests, MS animals exhibited anxiety- and depression-like behaviors, and had higher core body temperatures during dark period of the circadian cycle, when compared to controls. In addition, MS animals presented higher hyperthermic and vasoconstriction responses than control animals when exposed to the warmth environment, and engaged in cold-seeking behavior whenever possible to select their preferred ambient temperature. The results suggest that, besides emotional alterations, MS induces a change in the thermoregulatory profile of rats that persists into adulthood.

### 1. Introduction

In endotherms, the ability to regulate the core body temperature (T<sub>c</sub>) at relatively constant levels, even in the presence of abrupt changes in ambient temperature, is crucial to maintaining adequate body homeostasis. Thermoregulatory mechanisms involve autonomic (i.e. heat production/conservation and heat loss mechanisms) and behavioral thermoeffectors (Almeida et al., 2015).

It is accepted that a subset of serotonergic neurons, with projections to forebrain circuits associated with depression, is dysregulated in patients with mood disorders. Based on studies in rodents, this population of serotonergic neurons is located in the interfascicular region of the dorsal raphe nucleus (Owens and Nemeroff, 1994; Mann et al., 2000). Interestingly, it is well established that sympathetic premotor neurons in the medullary raphe nucleus innervate brown adipose tissue and cutaneous vessels (Nagashima et al., 2000; Dimicco and Zaretsky,

2007). This anatomical evidence raises the hypothesis that thermal signaling would alter the activity of brainstem serotonergic neurons associated with both thermoregulatory and mood regulation. In fact, thermal signaling can activate a subpopulation of brainstem serotonergic neurons that are expected to control thermoregulatory responses, but are also likely to play a role, probably via widespread connections to limbic forebrain structures, in cognitive function and mood (Lowry et al., 2009). Moreover, several lines of evidence suggest that individuals with affective disorders have an increased T<sub>c</sub>, which may be due in part to dysfunctional thermoregulatory cooling mechanisms (Hayashida et al., 2010; Hale et al., 2013), and are readily reversible following antidepressant therapy (Hale et al., 2013).

Others evidences have also shown that autonomic nervous system impairment caused by unpredictable early- or adult-life stressors may induce physiological changes that considerably reflect a disturbance of T<sub>c</sub> regulation. In “fight or flight” situations in animals, the

\* Correspondence to: Universidade Federal do ABC (UFABC), Natural and Humanities Sciences Center (CCNH), Rua Arcturus, 03, Jardim Antares, São Bernardo do Campo, SP 09606-070, Brazil.

E-mail address: [camila.almeida@ufabc.edu.br](mailto:camila.almeida@ufabc.edu.br) (M.C. Almeida).

<sup>1</sup> Authors equally contributed to the manuscript.

<https://doi.org/10.1016/j.jtherbio.2018.09.013>

Received 10 July 2018; Received in revised form 18 September 2018; Accepted 19 September 2018

Available online 20 September 2018

0306-4565/ © 2018 Elsevier Ltd. All rights reserved.

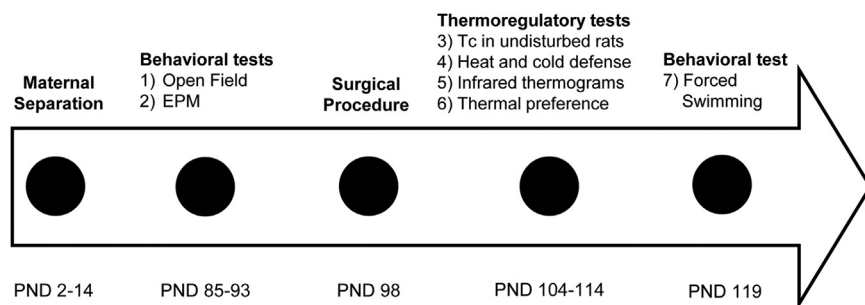


Fig. 1. Time course of experimental procedures performed, where PND means postnatal day. Behavioral tests include: open field, elevated plus maze (EPM) and forced swimming. Thermoregulatory tests include: body temperature measurements in undisturbed rats, cold and heat stress response and thermal place preference tests.

hypothalamic-pituitary-adrenal axis is activated for the secretion of glucocorticoids, referred to as the psychological stress response, and psychocortical stress-induced hyperthermia is a well-described event (Nakamura, 2015). In fact, hypothalamic-pituitary-adrenal axis activity has been associated with anxiety and depression, and it is especially vulnerable to the effects of the chronic mild-stress exposure, as well as alterations in 5-HT function within the dorsal raphe nucleus, hippocampus and prefrontal cortex (Benute et al., 2009; Van den Hove et al., 2014).

The maternal separation model (MS) for rodents induces a greater susceptibility of the hypothalamic-pituitary-adrenal axis to acute stress in adults, which is linked to a number of epigenetic factors and neuronal changes (Nishi et al., 2014; Shu et al., 2015). Thus, the MS model is well established for early stress, with several studies showing a correlation between episodes of major depression after the occurrence of stressful events (Kendler et al., 1999; Anisman and Matheson, 2005; Gronli et al., 2005), with stressful life events suggested to be the cause that stimulates the emergence of depressive symptoms (Anisman and Matheson, 2005; Gronli et al., 2005; Sousa et al., 2014). Besides depressive-like behavior, MS can be accompanied by anxiety-like behavior and cognitive deficits in some cases (Huot et al., 2002).

Since early stress promotes mood dysfunction in adult life and alteration in the thermoregulatory profile has been related to mood disorders, we hypothesize that mood dysfunction induced by early-life stress could be accompanied by abnormalities in the thermoregulatory system in the adult-life characterized by an increase in body temperature and altered thermoeffector recruitment. Thus, using MS as a model for the induction of stressful events that lead to anxiety- and/or depression-like behaviors in adults, this study aimed to evaluate the thermoregulatory profile of adult Wistar rats submitted to early MS.

## 2. Methods

### 2.1. Ethical approval

All procedures were approved by the local ethics committee from Universidade Federal do ABC (CEUA/UFABC, Protocol no. 034/2014) and efforts were made to minimize the number of animals used and their suffering. All procedures are also in agreement with the Arrive guidelines in animals research in vivo experiments, the U.K. Animals Scientific Procedures Act (1986) and Directive 2010/63/EU.

### 2.2. Animals and maternal separation (MS)

Eight couples of Wistar rats (3 months old; weight: 280–370 g) were obtained from INFAR – UNIFESP (São Paulo, Brazil) and housed in a room with a 12/12 light-dark cycle (lights on at 7 a.m.), a controlled temperature ( $23 \pm 1^\circ\text{C}$ ) and humidity (85%), and free access to food and water. One male and one female rat were kept in a cage for coupling. Females were then separated from males, and pregnant females were inspected daily at 9:30 a.m. for birth verification. The litters were randomly divided into experimental (MS) and control groups, and were kept complete (unless bigger than 10 pups) with both genders

(balanced number of males and females) until the weaning day. The day of delivery was defined as postnatal day 0 (PND 0). The MS group was separated from their mothers daily, from 9 a.m. to 12 p.m., on postnatal days 2–14 (PND 2–14) (El Khoury et al., 2006; Loria et al., 2010). During the separation period, the pups were kept in a cage on a heat pad maintained at  $37^\circ\text{C}$  (Gareau et al., 2006; Clinton et al., 2014). The pups were then returned to their mothers after 3 h. In the control group, the pups were left with their mothers undisturbed. At 21 days of age, the pups were weaned and transferred to a new cage with 3–4 animals per cage. They were left undisturbed until three months of age, except for routine animal care procedures. Only male adult rats (37 animals in total) were used in behavioral and thermoregulatory experiments in this study.

### 2.3. Study design

All experimental procedures were performed between 10 a.m. and 4 p.m. in the same temperature-controlled room with low ambient light and constant background noise. For each litter, animals (both MS or control) were randomly assigned to one of three groups (G1, G2 or G3), where animals in G1 were submitted to tests 3, 4, 5, 6 and 7; G2 were submitted to 1, 2, 3, 4 and 7; and G3 were submitted to tests 1, 2, 6 and 7 (Fig. 1) and posterior blind evaluation. In order to minimize the effects of anesthesia and surgery, all behavioral tests were performed before datalogger implantation, except for the forced swim test. The order of experiments was chosen based on the level of stress caused by each test, such that less stressful experiments were performed first (van Gaalen and Steckler, 2000). At 3 months of age, rats were weighed to evaluate body mass.

### 2.4. Surgical procedures

Surgical procedures were performed in adult rats submitted or not to early MS. Animals were anesthetized with ketamine-xylazine (100 and 10 mg/kg, intraperitoneal, respectively) and prophylactically treated with an analgesic anti-inflammatory (ketoprofen 5 mg/kg, intramuscular), and a single dose of pentabiotic (48.000 IU, intramuscular). Each rat was implanted with a miniature datalogger (SubCue Dataloggers, Calgary, AB, Canada) in the peritoneal cavity via a midline laparotomy. Abdominal muscles and skin were sutured in layers (Vizin et al., 2015). The abdominal temperature was used as an index of Tc, and dataloggers were programmed to record data at 10 min intervals. After the end of the experiments, animals were euthanized with urethane 30% (10 mL/Kg) and dataloggers were removed to upload temperature data.

### 2.5. Behavioral tests

#### 2.5.1. Open field test

The open field consisted of a circular arena, 60 cm in diameter, with surrounding acrylic walls 50 cm high to prevent escape. This test assessed locomotor function and anxiety-like exploratory behavior (Walsh and Cummins, 1976; Cao et al., 2016). Animals were placed

Download English Version:

<https://daneshyari.com/en/article/11029202>

Download Persian Version:

<https://daneshyari.com/article/11029202>

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