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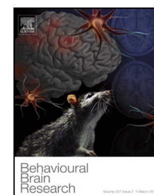

Research report

Long-lasting monoaminergic and behavioral dysfunctions in a mice model of socio-environmental stress during adolescence

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HIGHLIGHTS

- Stress during adolescence compromises the capacity of the HPA axis ability to properly respond to a stressor in adulthood.
- Socio-environmental stress during adolescence causes non-adaptive rearrangement in the CNS.
- Long-lasting changes in neural pathways and behavior in stressed adolescent male mice.

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ABSTRACT

Adolescence is one of the critical periods of development and has great importance to health for an individual as an adult. Stressors or traumatic events during this period are associated with several psychiatric disorders as related to anxiety or depression and cognitive impairments, but whether negative experiences continue to hinder individuals as they age is not as well understood. We determined how stress during adolescence affects behavior and neurochemistry in adulthood. Using an unpredictable paradigm (2 stressors per day for 10 days) in Balb/c mice, behavioral, hormonal, and neurochemical changes were identified 20 days after the cessation of treatment. Adolescent stress increased motor activity, emotional arousal and vigilance, together with a reduction in anxiety, and also affected recognition memory. Furthermore, decreased serotonergic activity on hippocampus, hypothalamus and cortex, decreased noradrenergic activity on hippocampus and hypothalamus, and increased the turnover of dopamine in cortex. These data suggest behavioral phenotypes associated with emotional arousal, but not depression, emerge after cessation of stress and remain in adulthood. Social-environmental stress can induce marked and long-lasting changes in HPA resulting from monoaminergic neurotransmission, mainly 5-HT activity.

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1. Introduction

The experiences in perinatal phase are assimilated by the central nervous system (CNS) and contribute to the formation of innervation patterns. However, it is during adolescence that there is a neuronal reorganization in several regions of the mammalian CNS [3], similar to that seen in humans [23], other primates [33,53] and rodents [58].

It is during this rearrangement of synapses and receptors that changes in the neurotransmitter pathways occurs [6,54] and a decreased synaptic estimated at 40% [49], which can cause important adaptive functional changes as the development of abstract reasoning [5,55] and maturation of motor, cognitive and emotional skills.

Regarding mammalian development strategy, adolescents respond to stress differently than during any other stage of life [24]. In addition, the current literature shows that stress response to adverse social-environmental experiences can be associated with lasting changes in behavioral, neurobiology and neuroendocrinology levels [4,12,31,37,38,52], predisposing animals to the development of psychopathology such as depression and anxiety disorders in adulthood [3,27,36,37,64].

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In fact, recent studies show that rodents subjected to stress-inducing models during adolescence are more anxious and less motivated, symptoms similar to those seen in humans with depression or anxiety disorders [29,48]. In addition, situations of fear and ill-treatment during adolescence in humans increase the risk of aggressive behavior and impairment of social interaction in adulthood [14,40,47], as well in other species [17,41,62,63,66].

Many studies have evaluated the alterations in monoaminergic activity and behavior in adult rodents subjected to stress [9]. Unpredictable stress models are useful tools for the study of these dysregulations that are closely related with affective and emotional disorders. However, in adolescent rodents, long-term effects of unpredictable stress are still poorly characterized.

Thus, the aim of this study was to clarify the regulatory effects of adolescent stress in brain monoamine activity, as well as possible behavioral changes.

2. Methods

2.1. Animals

Forty-four male Balb/c mice (4 weeks; 20 ± 2 g) from the Department of Pathology (School of Veterinary Medicine, University of São Paulo) were used. Animals were housed in groups of five per cage in a controlled environment (22 ± 2 °C temperature and 55–65% humidity) and in artificially lighted rooms on a well-defined 12 h light/dark cycle (lights on at 6:00 am). Food and water were provided *ad libitum* throughout the experiment except during stress sessions and behavioral testing. Mice were acclimated to the new environment for a week before experimental procedures. The experiments were performed in accordance with the guidelines of the Bioethical Committee on Care and Use of Laboratory Animal Resources of the School of Veterinary Medicine, University of São Paulo, Brazil (protocol no 4485180614), which are similar to those of the National Research Council, USA. All animals were weighed every three days and the weight gain was calculated.

2.2. Model of unpredictable stress in adolescence

Mice were randomly split into two groups: control animals (C) and stress-exposed animals (S). The stressed group were submitted to an unpredictable stress model and subjected to a random application time and pattern of stressful situations for 10 days with adaptations of protocol of Cox et al. [18], as described in Table 1. The control group remained in its home-cage (5 animals per cage) throughout the experimental protocol and left undisturbed. All stressors of unpredictable stress are described in Supplementary material (Table S1).

2.3. Behavioral assessment

Behavioral tests were performed for evaluated changes in activity, anxiety, depression, learning and memory. All behavioral experiments were always performed during the evening (2:00 to 4:00 PM), in order to minimize possible interference from changes in the circadian rhythm. Before each session, the apparatus was cleaned with a 5% solution of alcohol in water. This procedure has been used in order to eliminate olfactory cues of the previous animal, and thus avoid potential interference with the behavior of animals evaluated. Twelve animals of each group were subjected to the open field test (OF), light-dark test and tail suspension test (TST), with a 24 h interval between each test. The other twenty-two animals were subjected to the novel object recognition test.

2.3.1. Open field test (OF)

Individual mice were placed in a circular arena (50 × 50 cm) and allowed to explore for 5 min while being recorded overhead [25]. Total distance traveled (cm), frequency and time (s) in center and peripheral zone were analyzed with the use of Ethovision® XT-7 (Noldus Information Technology®, Leesburg, VA, USA). One day following the last day of stress protocol, all animals of both groups were submitted in open field testto evaluate the short-term effects in general locomotor activity. Twenty days later, the animals were in adulthood, new tests were carried to evaluate the long-term effects of stress in OFT.

2.3.2. Light-dark box test

A box (45 cm × 20 cm) was used with an open white chamber connected by a square door (5 cm × 5 cm) to another covered black chamber [19]. The black chamber occupied one-third of the box. Each mouse was placed in the center of the white chamber and recorded for 5 min Video recordings were later analyzed with Ethovision® and the time latency for the first entry in dark chamber, the time spent in each chamber, as well as number of transitions between them, was noted. To control for odor cues, the box was thoroughly cleaned with 5% ethanol, dried, and ventilated for a few minutes between mice.

2.3.3. Tail suspension test (TST)

This test was performed essentially as described [57]. Briefly, immobility was measured during 6 min of session while the mice were suspended by the midpoint of the tail, 40 cm above the surface. Time spent immobile, frequency of immobility and latency to the first immobility on this test were used to measure behavioral despair. The test was assessed by a blinded observer.

2.3.4. Novel object recognition test

This task is based on the innate tendency of rodents to differentially explore novel objects over familiar ones. This test was performed for three days, On the first day, mice were placed into an OF apparatus just for habituation. On second day, 24 h later, in the training trial, the animals were presented with a pair of identical objects until they had explored the objects for 20 s in a 5-min period. Finally, on the third day in the testing trial, one of the familiar objects was changed for another object and the animals were left in the OF for 5 min. Exploration of the objects is considered as any investigative behavior (head orientation or sniffing). The exploration time for the familiar object (FO) or the novel object (NO) during the test phase was recorded and the time spent with the novel object was calculated in percentage. To control for odor cues, the OF arena and the objects were thoroughly cleaned with 5% ethanol, dried, and ventilated for a few minutes between mice. The test was assessed by a blinded observer.

2.4. Adrenal weight

Right adrenals of animals were collected after euthanasia. The relative adrenal weight (organ weight/body weight) was calculated.

2.5. Corticosterone (CORT)

After sixty-five days of life mice were rapidly decapitated. Trunk blood was collected between 8:00 and 10:00 a.m. to avoid possible effects of circadian variations on serum corticosterone levels. Samples were stored at −80 °C until biochemical testing. Corticosterone serum levels were determined by the enzyme-linked-immunosorbent assay (ELISA) method using a commercial CORT enzyme immunoassay kit (ARBOR ASSAYS®). All samples were analyzed in duplicate and were run in just one assay. The

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