

RELATIONSHIP BETWEEN BEHAVIORS AND CATECHOLAMINE CONTENT IN PREFRONTAL CORTEX AND HIPPOCAMPUS OF CHRONICALLY STRESSED RATS

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Abstract. *Chronic stress induces over-activation and dysfunction of stress-activated systems, resulting in further brain damage and depressive-like behavior. Depression is a potentially life-threatening disorder that affects people and, therefore, it is one of the most important public health problems. This study examined the effects of chronic restraint stress (CRS: 2 hours × 14 days) on the anxiety-like and depression-like behaviors in rats, as well as on the possible changes in the concentrations of dopamine (DA) and noradrenaline (NA) in the prefrontal cortex and hippocampus. We observed a decrease in the number of entries into open arms and time spent in open arms during the elevated plus-maze test (anxiety-like behavior), as well as the increased immobility during the forced swimming test (depression-like behavior). In addition, we found that CRS increases concentration of NA and decreases concentration of DA in the prefrontal cortex and hippocampus. Also, we recorded a significant correlation between the animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by CRS. The results presented here suggest that there is a relationship between the animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by CRS, which may be important in the research of numerous psychiatric diseases caused by chronic stress.*

Key words: *Chronic restraint stress, anxiety-like behavior, depression-like behavior, dopamine, noradrenaline*

DOI: 10.21175/RadProc.2017-52

1. INTRODUCTION

Chronic stress can provoke anxiety and depressive-like behaviors in rats. The prefrontal cortex connects with regions of the brain that govern emotional behavior and stress responses, such as the amygdala, hypothalamus, and midbrain periaqueductal gray [1]. In addition, the hippocampus is a region that plays a crucial role in learning and memory and is an area also particularly susceptible to chronic stress [2], [3]. The monoaminergic-sympathetic nervous systems play important roles in maintaining homeostasis by inducing various physiological and behavioral changes [4]. It is known that dopamine (DA) and noradrenaline (NA) are key to brain functions.

In this study, we applied the chronic restraint stress (CRS) because Levinstein and Samuels [5] found that CRS is an effective model for obtaining the depressive-like symptoms in rodents. In addition, previous reports showed that CRS can exacerbate neurodegeneration, cognitive deficits and depressive-like behaviors in rats [6]-[8]. However, very little is known about the degree of correlation between animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by CRS (2 hours × 14 days). This study tested the hypothesis

that CRS (2 hours × 14 days) induces depression-like and anxiety-like behaviors and changes in the catecholamine level in the prefrontal cortex and hippocampus. Also, the aim of this study was to determine the degree of correlation between animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by the chronic restraint stress.

Because of the significant role of catecholamines in the regulation of numerous brain functions, detecting the degree of correlation between animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by the chronic restraint stress is important for indicating the possible causative relationship between the stress-activated catecholaminergic systems and behaviors in chronically stressed rats.

2. MATERIALS AND METHODS

2.1. Animals and stress model

In this study Wistar male rats (11-week-old, 300-340 g) were used. Animals were under standard laboratory conditions with water and food *ad libitum*

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and kept three to four per cage. The care was taken to minimize the pain and discomfort of the animals according to the recommendations of the Ethical Committee of the Vinča Institute of Nuclear Sciences, Belgrade, Serbia, which follows the guidelines of the registered “Serbian Society for the Use of Animals in Research and Education”. Animals were divided into two groups: CONTROL group (n=20) was not exposed to any treatment and CRS group (n=20) consisted of animals exposed to the treatment of chronic restraint stress. Restraint stress was performed by placing each animal in a 25 x 7 cm plastic bottle as described previously by Gamaro et al. [9]. Animals in these groups were exposed to 2h of restraint stress every day at random times, during the light period of the light/dark cycle to avoid habituation during the experimental procedure of 14 days [10]. We measured the animals at the beginning and at the end of the experiment. Depression and anxiety-like behaviors were assessed by elevated plus-maze test (EPM) and forced swimming test (FST). Ten animals from each group were tested on the EPM and FST. Animals that were used to test the behavior were not used for further analysis. To reduce the variance in the physiological parameters due to daily rhythms, remaining animals (n=10 from each group) were sacrificed at the same time point in the circadian cycle, between 9:00 and 11:00 am, i.e., one day after the last treatments. Animals were sacrificed under no-stress conditions by rapid decapitation. The prefrontal cortex and hippocampus were isolated. The tissues were immediately frozen and stored in liquid nitrogen until analyzed.

2.2. Elevated plus maze (EPM)

The EPM consisted of four elevated (50 cm) contralateral arms (50 cm long and 10 cm wide) with two opposing arms containing 40 cm high opaque walls. On the day of EPM testing, the rats were transported into the testing room one cage at a time and testing alternated between the pairs of control and chronic stressed rats. Each rat was placed in a closed arm, facing the center platform and cages-mates started in the same closed arm, which was counterbalanced across trials. Each rat was given 5 min to explore the EPM and then returned to its home cage. The EPM was cleaned thoroughly using Naturally Living Pet Odor Eliminator between each rat. EPM performance was recorded using an overhead video camera for later quantification. Video recordings of EPM testing were analyzed by subjective method by two researchers. Open and closed arm entries were defined as the front two paws entering the arm, and open arm time began the moment the front two paws entered the open arm and ended upon exit. Rats that displayed thigmotaxis, and an aversion to the open arms were considered highly anxious [11]. An added measure of anxiety was calculated for the EPM using the following equation, which unifies all EPM parameters into one unified ratio; the anxiety index values range from 0 to 1, with a higher value indicating increased anxiety [12]- [14].

Anxiety index

$$= 1 - \left[\frac{(\text{open arm time}/5 \text{ min}) + (\text{open arm entry}/\text{total entry})}{2} \right]$$

2.3. Forced swim test (FST)

The Porsolt forced swim tank consisted of a clear, cylindrical Plexiglas tank measuring 45 cm high and 20 cm in diameter with a water (28 °C) depth of 30 cm. These testing parameters are consistent with other protocols using FST as a measure of depressive-like behavior [15], [16]. The forced swim test was comprised of a two day protocol [15]. On the first day, a rat was placed into the swim tank for 15 min. Afterwards, the rat was removed and placed under a heat lamp for one hour before being returned to its home cage and transported back to the housing colony. The FST tanks were rinsed after every animal and refilled with fresh tap water (28 °C). On the second day, each rat was placed back into the swim tank for 5 min and behavior was videotaped. As was done during the previous day, each rat was warmed under a heat lamp for one hour before being returned to its home cage and transported back to the animal colony. Video recordings of FST testing were analyzed by subjective method by two researchers. FST behavior was scored using a time sampling technique [17], where every five seconds, behavior was characterized as either swimming, climbing or being immobile. Swimming was defined as a paw movement underwater, climbing was defined as the paws breaching the surface of the water and immobility was defined by a lack of movement. Rats spending more time immobile in the FST have been characterized as reflecting increased depressive-like behavior [16], although some have interpreted it as altered coping responses [18]. For the purpose of this paper, we will use the “depressive-like” description.

2.4. Catecholamine measurement

Prefrontal cortex and hippocampus tissues were homogenized in 0.01 N HCl in the presence of EDTA and sodium metabisulfite. Catecholamine concentration in the prefrontal cortex and hippocampus fractions was determined using 3-CAT Research ELISA kits (Labor Diagnostica Nord, Nordhorn, Germany) according to the manufacturer’s protocol. Absorbance was determined at 450 nm using a microplate reader (Stat Fax 2100). Concentrations were normalized to 1 g of tissues in homogenate. Values were expressed as ng of catecholamine per g of tissues.

2.5. Data analysis

The data are presented as means ± S.E.M. Differences of animal behavior, concentration of DA and NA in prefrontal cortex and hippocampus were analyzed by t-test. Statistical significance was accepted at p<0.05. Correlations of the neurotransmitter levels and animal behavior were analyzed by the Pearson test, using the Sigma Plot v10.0 (with SigmaStat integration).

3. RESULTS

3.1. Changes in animal behavior

The animals exposed to CRS showed significant decrease of total arm entries, percentage of entries into open arms and time spent in open arms compared to control rats. Based on these results, we calculated the

anxiety index (AI). We found that CRS significantly increased AI by 28% ($p < 0.05$, t-test, Figure 1a), compared with the control animals. In addition, CRS significantly increased immobility by 20% ($p < 0.05$, t-test, Figure 1b), compared with the control animals.

Figure 1.

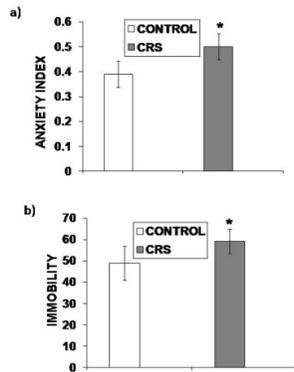


Figure 1. Effects of chronic restraint stress (CRS) on the anxiety index (AI) [a] and immobility [b]. The values are means \pm S.E.M. of 10 rats. Statistical significance: * $p < 0.05$ animals exposed to chronic restraint stress vs. control animals (t-test).

3.2. Changes of the DA and NA concentrations in the prefrontal cortex and hippocampus

We found that in the prefrontal cortex CRS significantly decreased the concentration of DA by 47% ($p < 0.01$, t-test, Figure 2a) and increased NA concentration by 49% ($p < 0.05$, t-test, Figure 2b), compared with control animals. Similar changes are found in the hippocampus. CRS decreased hippocampal concentration of DA by 22% ($p < 0.05$, t-test, Figure 2c) and increased NA concentration by 104% ($p < 0.01$, t-test, Figure 2d), compared with the control animals.

The significant negative correlation was found between DA concentration in the prefrontal cortex and AI (Pearson $R = -0.728$; $p < 0.05$, Figure 3a), as well as between the levels of DA in the prefrontal cortex and immobility (Pearson $R = -0.634$; $p < 0.05$, Figure 3b) of the animals exposed to CRS. Also, the significant negative correlation was found between DA concentration in hippocampus and AI (Pearson $R = -0.670$; $p < 0.05$, Figure 4a), as well as between the levels of DA in the hippocampus and immobility (Pearson $R = -0.738$; $p < 0.05$, Figure 4b) of the animals exposed to CRS. However, the significant positive correlation was found between NA concentration in the prefrontal cortex and AI (Pearson $R = 0.695$; $p < 0.05$, Figure 3c), as well as between the levels of NA in the prefrontal cortex and immobility (Pearson $R = 0.627$; $p < 0.05$, Figure 3d) of the animals exposed to CRS.

Figure 2.

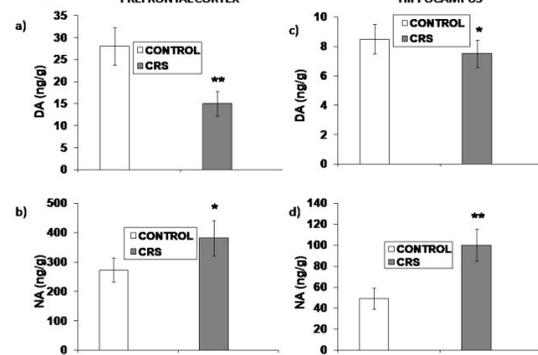


Figure 2. Effects of chronic restraint stress (CRS) on the concentration of dopamine (DA) [a and c] and noradrenaline (NA) [b and d] in the prefrontal cortex and hippocampus. The values are means \pm S.E.M. of 10 rats. Statistical significance: * $p < 0.05$, ** $p < 0.01$ animals exposed to chronic restraint stress vs. control animals (t-test).

Figure 3.

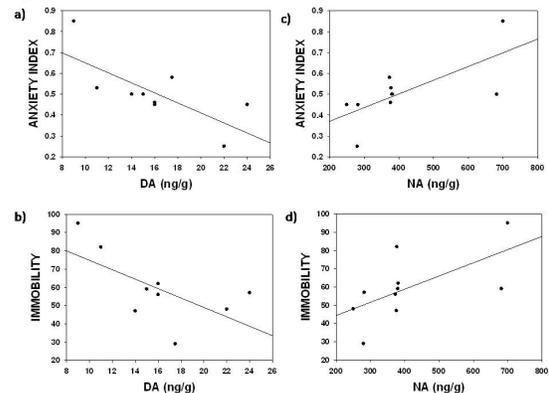


Figure 3. The correlations between DA levels in prefrontal cortex and the anxiety index (AI) as well as the correlations between NA levels in prefrontal cortex and immobility. a) The correlation in the levels of DA in prefrontal cortex and AI of animals exposed to CRS (Pearson); b) The correlation in the levels of DA in prefrontal cortex and immobility of animals exposed to CRS (Pearson); c) The correlation in the levels of NA in prefrontal cortex and AI of animals exposed to CRS (Pearson) and d) The correlation in the levels of NA in prefrontal cortex and immobility of animals exposed to CRS (Pearson).

In addition, the significant positive correlation was found between NA concentration in the hippocampus and AI (Pearson $R = 0.629$; $p < 0.05$, Figure 4c), as well as between the levels of NA in the hippocampus and immobility (Pearson $R = 0.700$; $p < 0.05$, Figure 4d) of the animals exposed to CRS.

Figure 4.

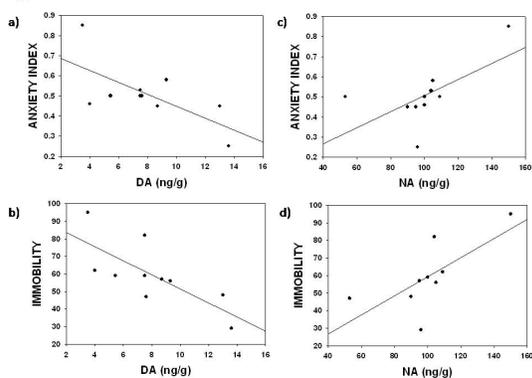


Figure 4. The correlations between DA levels in hippocampus and AI as well as the correlations between NA levels in hippocampus and immobility. a) The correlation in the levels of DA in hippocampus and AI of animals exposed to CRS (Pearson); b) The correlation in the levels of DA in hippocampus and immobility of animals exposed to CRS (Pearson); c) The correlation in the levels of NA in hippocampus and AI of animals exposed to CRS (Pearson) and d) The correlation in the levels of NA in hippocampus and immobility of animals exposed to CRS (Pearson).

4. DISCUSSION

In the present study we found that the animals exposed to CRS showed the decrease of total arm entries, percentage of entries into open arms and time spent in open arms during the EPM, as well as the increased immobility during the FST. In addition, an important observation of this study is that CRS significantly increased the anxiety index. Our data support the hypothesis that CRS influences anxiety and depressive-like behavior in rodents which is in accordance with the recent studies of Chiba et al. [19] and Haenisch et al. [20]. In addition, we observed that CRS significantly decreased the animal weight by 20% compared with the control animals. This result shows that CRS is a strong stressor and it can affect the animal weight. Also, our results show that exposure to CRS leads to the decreased DA and increased NA concentrations in the prefrontal cortex and hippocampus. Significantly decreased concentration of DA and increased concentration of NA were observed in the brain in many pathophysiological conditions. For example, significantly decreased concentration of DA and increased concentration of NA were observed in the prefrontal cortex in aggressive rats [21]. Also, the decreased concentration of DA was observed in many psychiatric and neurological disorders. It is known that several antidepressants increase DA levels in the prefrontal cortex [22]. Also, raising the DA level in patients with Parkinson's disease with l-3,4-dihydroxyphenylalanine improves their working memory deficit [23]. It is known that repeated stressful stimuli strongly affect the activity of the central noradrenergic system [24]. In addition, levels of NA are elevated in depressed patients [25]. An important result in this work is that CRS induce significant increase of hippocampal NA concentration ($p < 0.01$), which confirm that the hippocampus is particularly sensitive to chronic stress [26], [27]. In a study by Leonard [25], significant negative correlations between aggressive responses and the DA synthesis capacity

were observed especially in the midbrain. In our study, we recorded significant negative correlation between the levels of DA in both brain areas and AI, as well as between the levels of DA in both investigated brain regions and immobility. In addition, we recorded significant positive correlation between the levels of NA in both investigated brain regions and AI, as well as between the levels of NA in both brain areas and immobility. Our data support the hypothesis that a close link may exist between the activation of the central catecholaminergic system and anxiety and depressive-like behavior, which is in accordance with studies of Leonard [25]. Our results confirm the hypothesis that the neurobiology of stress and the neurobiology of social behavior are deeply intertwined.

5. CONCLUSION

In conclusion, our results show a relationship between the animal behavior and levels of neurotransmitters in the prefrontal cortex and hippocampus in stress conditions provoked by CRS, which may be important in the research of numerous psychiatric diseases caused by chronic stress.

Acknowledgement: This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Contract No. III 41027.

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