

THE EFFECT OF CHRONIC SOCIAL INSTABILITY STRESS ON BEHAVIOUR, CYTOKINE AND GR RECEPTOR EXPRESSION AND MONOAMINERGIC BRAIN ACTIVITY IN FEMALE MICE



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1. INTRODUCTION AND AIMS

Studies show that women are at greater risk of developing stress-related disorders such as depression or anxiety. It is also known that sex differences exist both in the type of stressors that can elicit a stress response and in the stress response itself. These differences have been reported in the HPA axis and monoaminergic activity, as well as in cytokine expression. These changes can also underlie anxiety/depressive like behaviour. But while there is abundant literature on the effects of social stress in male rodents, there is a serious lack of information regarding females.

The aim of this work is therefore to analyse the effect of chronic social instability stress on female mice by measuring hormones, cerebral cytokines, central monoaminergic activity and behaviour.

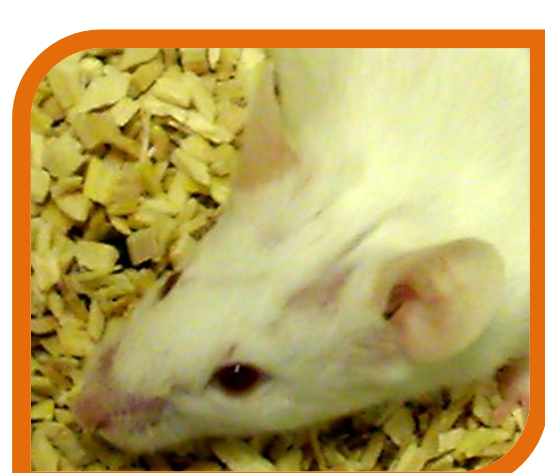
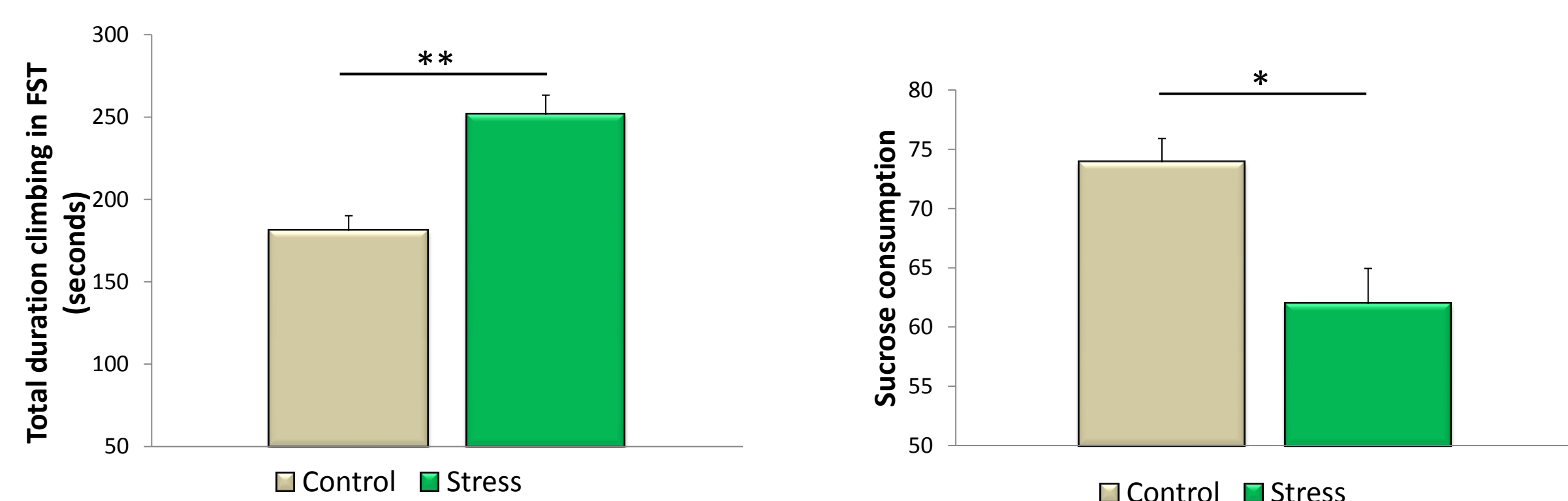
2. MATERIALS AND METHOD

Female CD1 Swiss mice were exposed to chronic social instability stress. This consists of a 4-week period with alternating phases of isolation and crowding (4 mice with no prior contact between them per cage). Control mice remained in groups of three with the same cage mates. In the fifth week, mice were submitted to the sucrose preference test (SPT) and the forced swimming test (FST). Finally, the hippocampus and striatum were removed after sacrifice to measure central monoaminergic activity by high-performance liquid chromatography (HPLC). Also, mRNA expressions of cytokines and glucocorticoid and mineralocorticoid receptors were measured by real time RT-PCR. Furthermore, since previous findings indicate that barbering behaviour may be a consequence of a stress-associated unstable social structure, we measured whisker length after sacrifice, dividing results into three categories: short, medium and long whiskers. Blood was collected on experimental days 0 and 24 by submandibular puncture, and on day 33 by cardiac puncture. Plasma corticosterone levels were measured with enzyme-linked immunosorbent assay (ELISA) kits.

3. RESULTS

3.1. Effects of chronic social instability stress on behaviour

Stressed mice spent more time engaged in climbing behaviour in the FST, and also consumed less sucrose than the control group in the SPT.

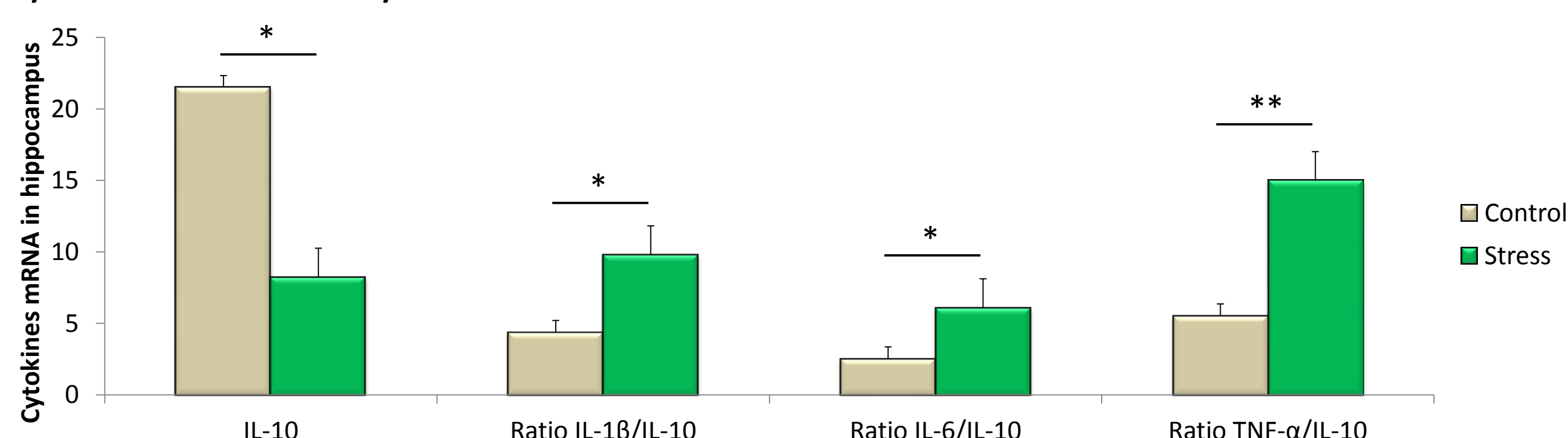


The stressed group had shorter whiskers than the control group.



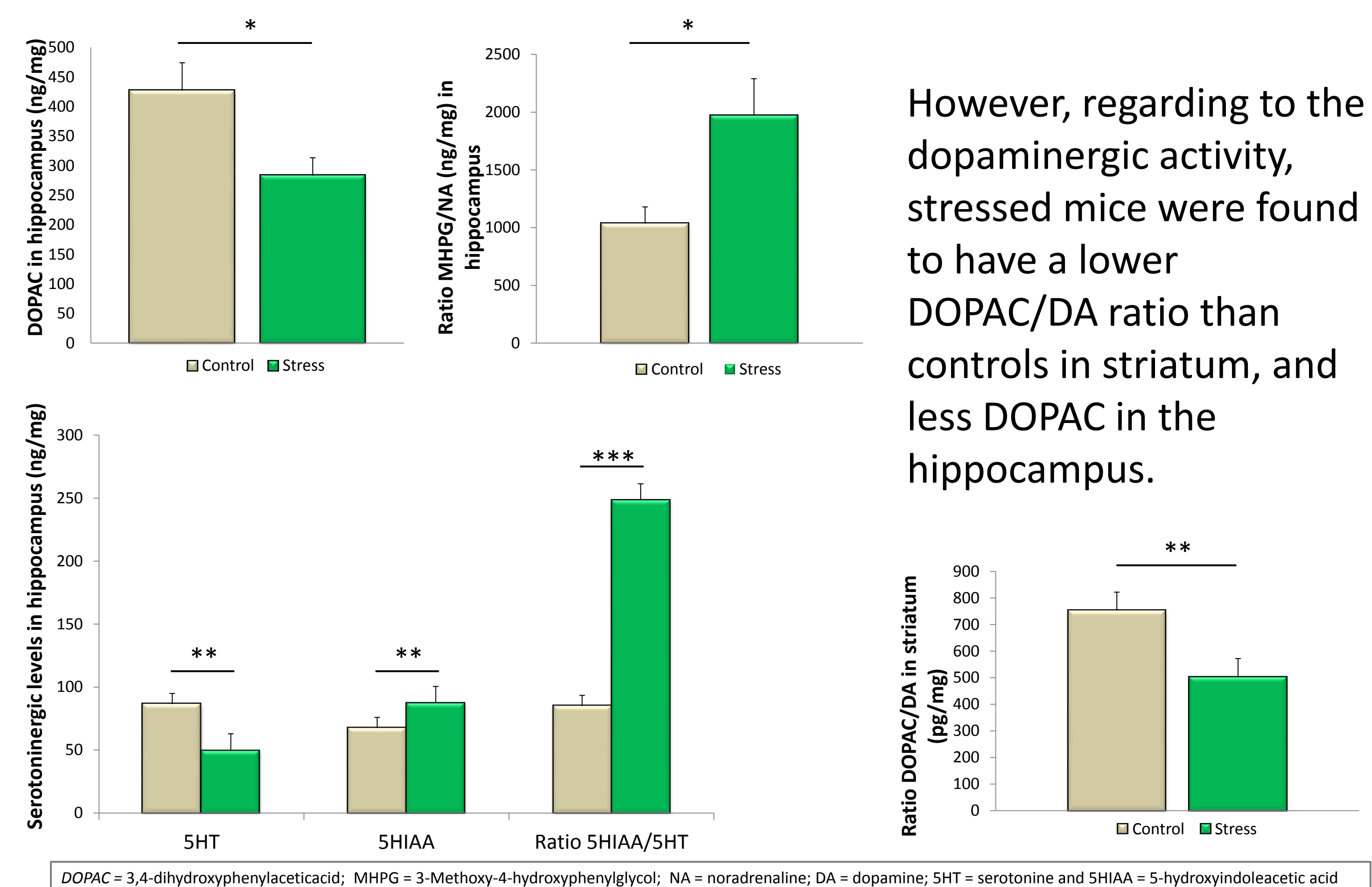
3.2. Effects on pro- and anti-inflammatory cytokines

Cytokine mRNA expressions in the hippocampus showed a lower level of anti-inflammatory cytokine IL-10, and higher ratios of IL-1 β /IL-10, IL-6/IL-10 and TNF α /IL-10 in stressed mice.



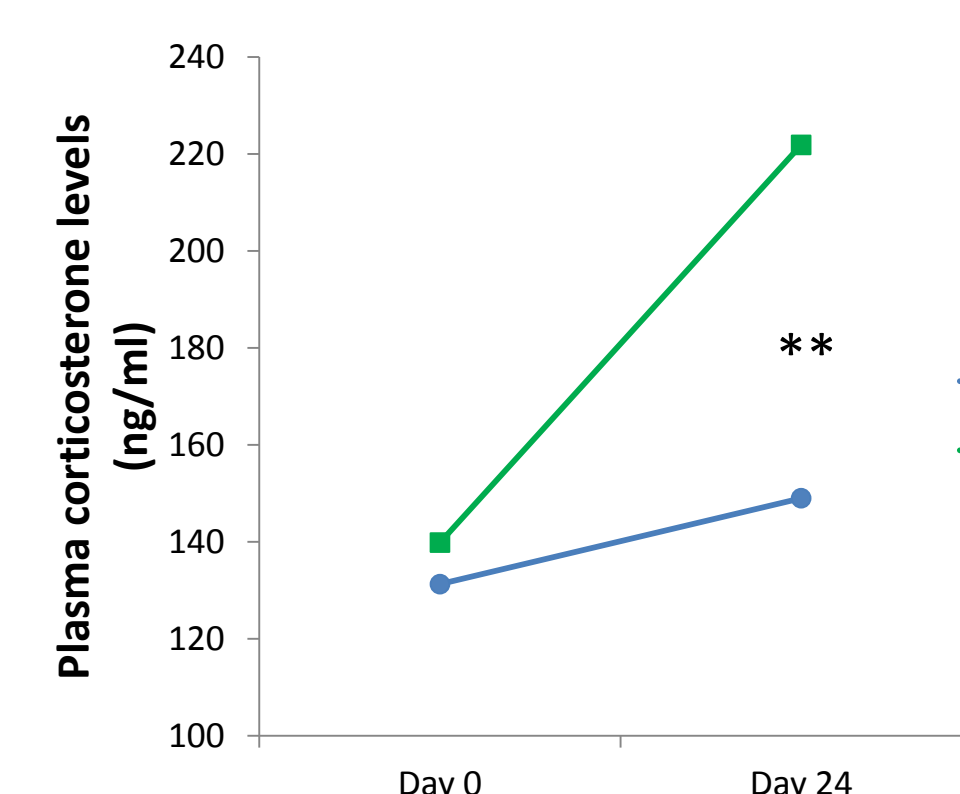
3.3. Effects on central monoaminergic activity

Increased MHPG/NA and 5HIAA/5HT ratios in the stressed mice indicate higher noradrenergic and serotonergic activity in the hippocampus. The stressed mice also had lower 5HT and increased 5HIAA levels.



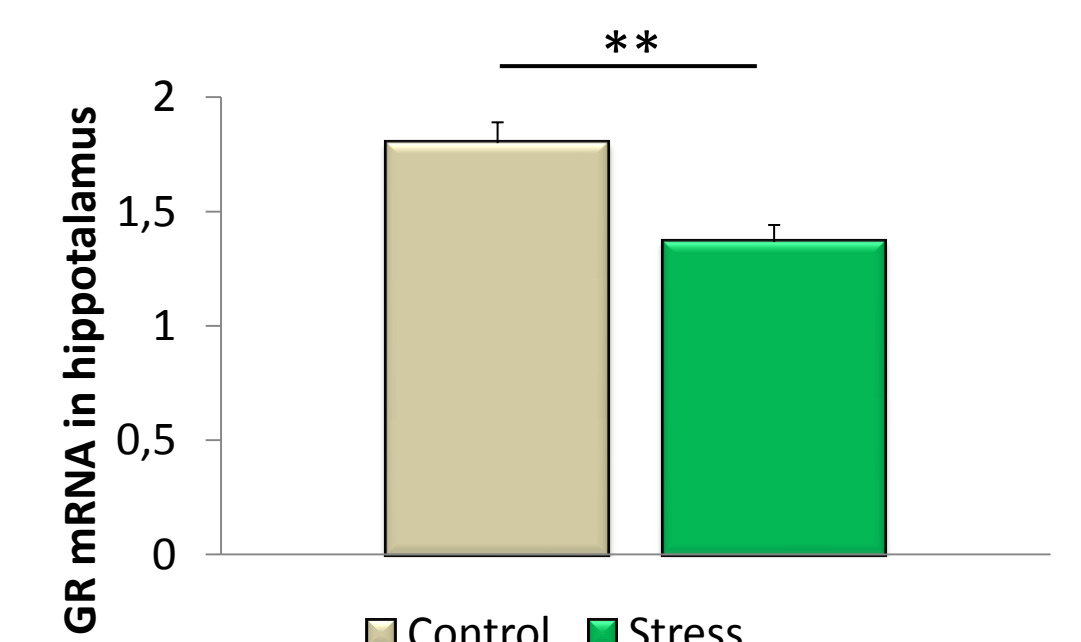
However, regarding to the dopaminergic activity, stressed mice were found to have a lower DOPAC/DA ratio than controls in striatum, and less DOPAC in the hippocampus.

3.4 Effects on corticosterone plasma levels and GR expression



The stressed group had higher plasma corticosterone levels on day 24 of the stress period than controls, whereas no differences were observed between the two groups as regards basal measures.

The stressed group had a lower GR expression in hypothalamus.



Mean values (\pm SEM) * p < 0.05; ** p < 0.01; *** p < 0.001
Chi² analysis distribution (Whiskers' length) *** p < 0.001.

4. CONCLUSIONS

- Chronic social instability stress induced anxiety/depressive-like behaviours in female mice, as reflected in a lower sucrose consumption in the Sucrose Preference Test and more time engaged in climbing behaviour in the Forced Swimming Test. The stressed group had shorter whiskers, which implies social instability-related stress.
- This stress model also affects immune activity and is reflected in increased proinflammatory cytokine/IL-10 ratios.
- Elevated, MHPG/NA and 5HIAA/5HT ratios revealed higher activity in the hippocampus, whereas the DOPAC/DA ratio revealed a lower level of dopaminergic activity in the striatum in stressed mice.
- High corticosterone levels and low GR-mRNA expression reflect changes in the hypothalamic-pituitary-adrenal axis.
- All these changes together may indicate that chronic social instability stress generate changes that may be associated to the pathogenesis of anxiety/depressive-like symptoms.

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