DISSOCIATION BETWEEN ANHEDONIA, ANXIETY AND BRAIN BDNF LEVELS IN A MOUSE MODEL OF SOCIAL STRESS

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BACKGROUND

Stress represents a main risk factor for the onset and progression of mood disorders such as anxiety and depression. Stress responses can be modulated by a variety of factors, including the social environment. Thus chronic social stress (CSS) has long been used as an animal model to investigate the mechanisms underlying mood disorders. Stress-dependent neurobiological changes include the activation of the hypothalamic-pituitary-adrenal axis (HPA) as well as variations in the expression of neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF) [1]. Under chronic stress conditions, a chronic elevation of glucocorticoids levels (the main hormones of stress), as a consequence of the disruption of the social hierarchy (CSS), can affect brain plasticity inducing a remodelling of selected limbic brain areas. In addition, reduced BDNF levels may lead to increased vulnerability to mood disorders [3]. From a behavioural point of view CSS in mice is able to induce anhedonia (the reduced capacity to perceive a reward), an endophenotype of major depression.

AIM

Main aim of the study is to investigate whether anhedonia represents a reliable index of a depressive-like state in mice undergoing CSS. If so, we expect this reduced capacity to perceive a reward to be associated to other behaviours indicative of a depressive-like state such as increased emotionality, social anxiety and behavioural despair in addition to increased levels of corticosterone and reduced levels of BDNF in the brain.

METHODS

Experimental subjects (C57 male mice)

- SS (Social Stress): 16 mice were divided into 4 cages (4 mice/cage) and social hierarchy was disrupted twice a week for three weeks. Each time a component of a cage was replaced with a mouse housed in one of the remaining three cages;
- SG (Social Group): 8 mice were divided into 2 cages (4 mice/cage) with a stable social hierarchy;
- IC (Isolated Controls): 8 mice were individually housed.

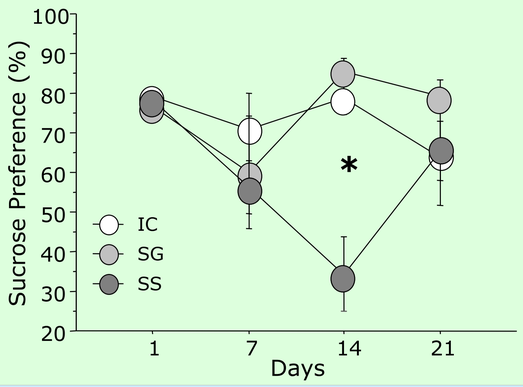
Behavioural tests following 3 weeks of CSS

- Anhedonia was assessed by testing the preference for a 4% sucrose solution before the beginning of the stress procedure (baseline, day 1) and during the CSS (once a week);
- Open field (OF) to assess spontaneous behaviour
- Elevated plus-maze (EPM) to assess emotionality
- Forced swim test (FST) to assess behavioural despair
- Social interaction test (SIT) to assess social anxiety (social challenge).

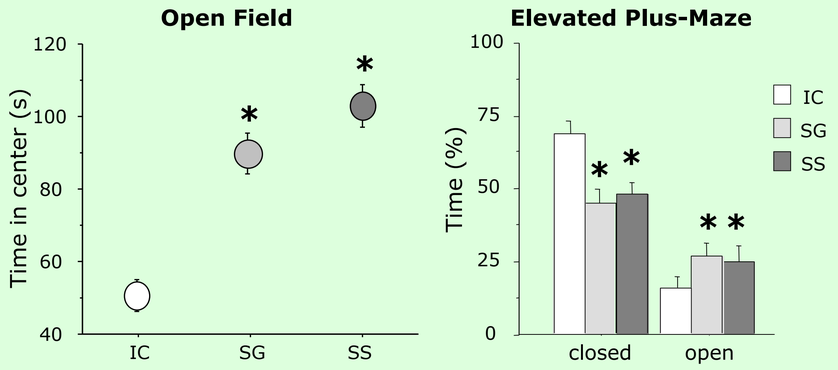
Hormonal and BDNF assessment

- Corticosterone (CORT) levels were measured, at the end of the stress period (three weeks), before (basal) and immediately after (30 minutes) the social challenge (SIT). Blood sampling were collected by tail nick, a non-invasive method;
- BDNF was measured in the frontal cortex, midbrain, hippocampus and hypothalamus following sacrifice and subsequent brain dissection.

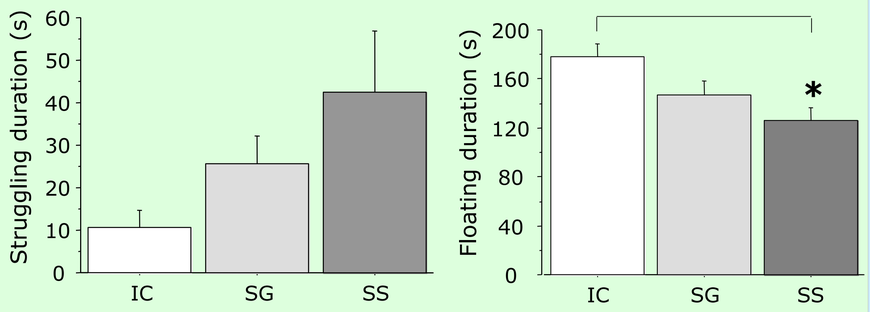
Chronic disruption of the social hierarchy leads to anhedonia



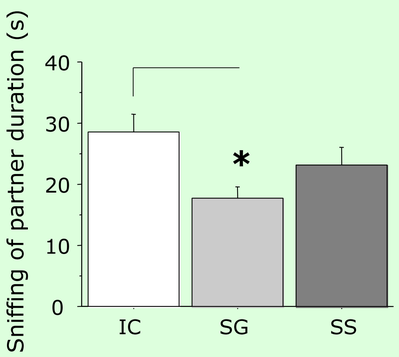
Socially-housed mice (SS and SG) are characterised by reduced emotionality spending significantly more time in the centre of the OF as well as in the open arms of the EPM



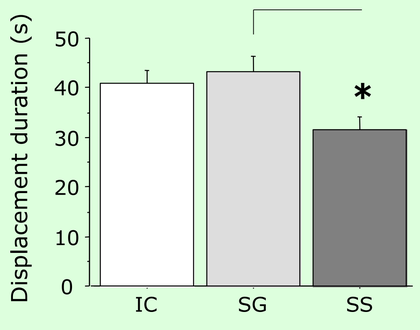
In the Forced Swim Test the SS group shows a reduction in behaviours indicative of a depressive-like state



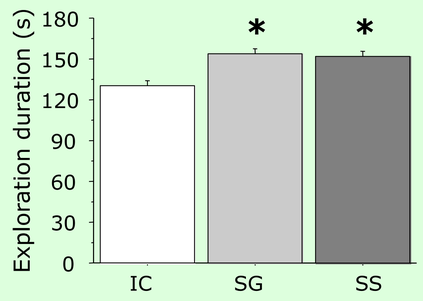
The SS group, which experienced a chronic disruption of the social hierarchy, shows a greater behavioural arousal in a social context



IC and SS interact more with a novel conspecific partner

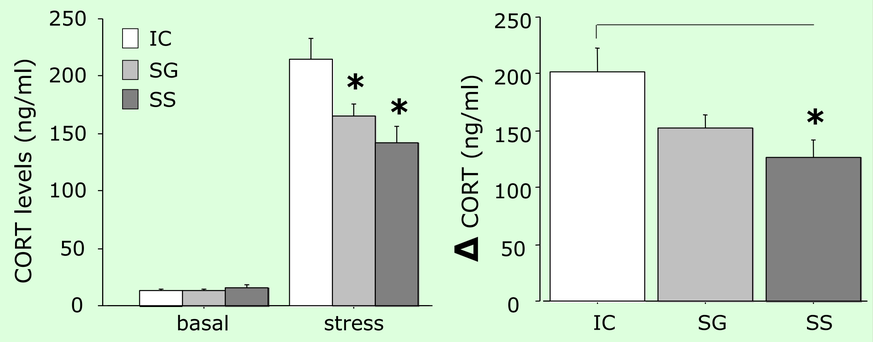


The SS group performs a lower amount of displacement behaviours suggesting a better ability to cope with a social stressful challenge

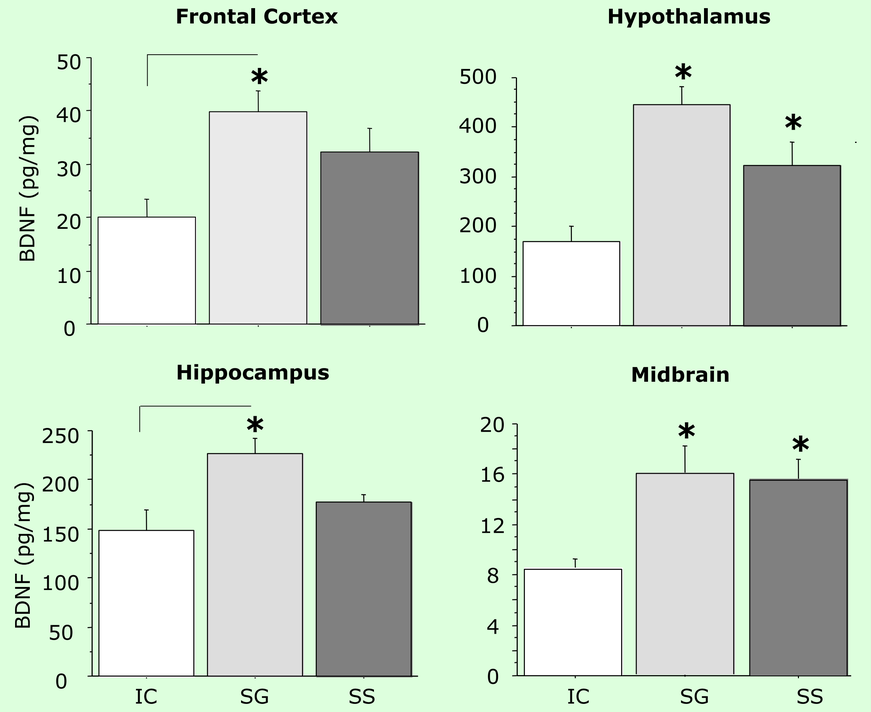


SS and SG mice spent more time exploring the novel environment

Reduced corticosterone levels following a social challenge suggest a differential activation of HPA axis as result of the social experience



Social isolation leads to reduced BDNF levels in different brain regions



CONCLUSIONS

- ✓ The group undergoing a chronic disruption of the social hierarchy (SS), showed the highest levels of anhedonia. However, this feature was totally dissociated from behavioural items indicative of despair.
- ✓ In addition, the SS group was characterized by a general condition of behavioural arousal showing reduced emotionality, in the OF and EPM tests, and spending less time performing displacement behaviours while increasing the time spent investigating the novel environment and the novel conspecific partner in the Social Interaction Test. Thus in this context the SS group did not show "social anhedonia".
- ✓ From a behavioural and neuroendocrine point of view, IC mice appear more vulnerable to stress since they showed higher floating levels as well as higher CORT levels (HPA axis activation) in response to a stressful social challenge although these mice failed to show anhedonia while isolated (21 days).
- ✓ Reduced BDNF levels might indicate a reduced plasticity in both the IC and SS groups in a number of brain regions thus suggesting that isolation and chronic disruption of the social hierarchy represent two different but powerful stressors for mice.
- ✓ In conclusion, there appears to be no direct relationship between anhedonia and other behaviours indicative of a depressive-like state or reduced levels of BDNF. In addition social isolation appears strongly related to increased emotionality, stress reactivity and leads to reduced BDNF levels, an indirect marker of brain plasticity.

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