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Effects of chronic social stress on central dopamine receptors in adult mice, as assessed by means of quantitative autoradiography

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Introduction: An important aetiological factor of depression is chronic stress; subsequent anhedonic behaviour and reductions in motivation for reward are core symptoms. Such behavioural changes are thought to link with reduced brain dopamine (DA) function as DA is important in the regulation of reward-related behavior. A mouse model of chronic social stress-induced reduced reward motivation, an essential research tool in studies on the mechanisms of stress effects and in search for novel therapeutic targets, has been developed (1). The present study aimed at investigating the effects of chronic social stress on the binding activity of dopamine D1 and D2 receptors in brain regions associated with reward processing: medial prefrontal cortex, amygdala, nucleus accumbens (NAcc) and ventral tegmental area (VTA) as well as dorsal striatum. In addition, stress effects on NAcc tissue dopamine turnover were investigated.

Methods: Adult male C57BL/6 mice were exposed to chronic social stress (CSDS) in the form of continuous distal exposure to and brief daily attack by (with minimum physical injury) dominant CD-1 mice for 15 days (1). Control mice (CON) were handled daily. Brains were collected on day 16. In coronal sections, receptor autoradiography was applied to quantify specific binding of D1 and D2 dopamine receptors with the selective radioligands, [3H]SCH23390 and [3H]Raclopride, respectively (2). In a separate cohort, brains were collected on day 16 and dopamine and DOPAC tissue levels in NAcc were measured using HPLC-ED.

Results: In the VTA the mean D1 receptor binding was increased by >130% in CSS when compared to CON mice ($p<0.05$; n=7-8/group). In the other brain regions there was a tendency to an increase in dopamine D1 receptor binding in CSS vs CON mice. D2 receptor binding was not affected by CSS in any of the brain regions analysed. In NAcc, the DOPAC/DA ratio was decreased in CSS mice ($p<0.05$; n=10-11/group), indicating reduced DA turnover.

Conclusion: The present findings indicate that CSS-induced reduced reward motivation co-occurs with increased D1 receptor binding in the VTA and reduced DA turnover in the NAcc. The stress-induced increase in VTA D1 binding status could be a neuroplastic compensation of reduced DA function that emerges in the course of stress exposure. This study adds to evidence that the D1 receptor constitutes a possible therapeutic target for reward psychopathologies in stress-related neuropsychiatric disorders.

Reference:

1. Azzinnari D et al. (2014) *Neuropharmacology* 85: 328-341
2. Leventopoulos M et al. (2009) *Neuropharmacology* 56: 692–701