European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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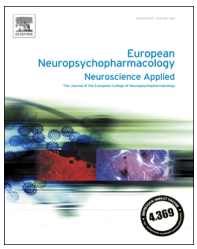

Mouse psychosocial stress reduces motivation and cognitive function in operant reward tests: A model for reward pathology with effects of agomelatine

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Received 4 March 2016; received in revised form 20 May 2016; accepted 18 June 2016

KEYWORDS
Depression;
Decreased motivation;
Animal model;
Operant;
Circadian rhythm;
Agomelatine

Abstract
A major domain of depression is decreased motivation for reward. Translational automated tests can be applied in humans and animals to study operant reward behaviour, aetiopathophysiology underlying deficits therein, and effects of antidepressant treatment. Three inter-related experiments were conducted to investigate depression-relevant effects of chronic psychosocial stress on operant behaviour in mice. (A) Non-manipulated mice were trained on a complex reversal learning (CRL) test with sucrose reinforcement; relative to vehicle (VEH), acute antidepressant agomelatine (AGO, 25 mg/kg *p.o.*) increased reversals. (B) Mice underwent chronic social defeat (CSD) or control handling (CON) on days 1–15, and were administered AGO or VEH on days 10–22. In a progressive ratio schedule motivation test for sucrose on day 15, CSD mice made fewer responses; AGO tended to reverse this effect. In a CRL test on day 22, CSD mice completed fewer reversals; AGO tended to increase reversals in CSD mice associated with an adaptive increase in perseveration. (C) Mice with continuous operant access to water and saccharin solution in the home cage were exposed to CSD or CON; CSD mice made fewer responses for saccharin and water and drank less saccharin in the active period, and drank more water in the inactive period. In a separate CSD cohort, repeated AGO was without effect on

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http://dx.doi.org/10.1016/j.euroneuro.2016.06.009

Please cite this article as: Bergamini, G., et al., Mouse psychosocial stress reduces motivation and cognitive function in operant reward tests: A model for reward.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.06.009

these home cage operant and consummatory changes. Overall, this study demonstrates that psychosocial stress in mice leads to depression-relevant decreases in motivation and cognition in operant reward tests; partial reversal of these deficits by AGO provides evidence for predictive validity.

1. Introduction

Depression is a major and heterogeneous neuropsychiatric disorder. Core psychopathological symptoms are depressed mood, diminished interest in activities, and increased fatigue, together with a number of common symptoms including weight loss or gain, psychomotor agitation or retardation, insomnia or hypersomnia, and reduced concentration and attention (DSM-5, 2013; ICD-10, 1994). The recent Research Domain Criteria (RDoC) project (Cuthbert, 2015; Cuthbert and Insel, 2013) proposes a classification system that takes diagnostic systems into account but also identifies the importance of understanding individual psychopathologies, which have been organised into domains: for example, the Positive valence systems domain, which includes approach motivation, responsiveness to reward and reward learning; and the Arousal/modulatory systems domain which includes arousal, biological rhythms and sleep-wake (Cuthbert and Insel, 2013). Integrating RDoC with depression symptomatology, the Positive valence systems domain is clearly relevant to diminished interest and the Arousal/modulatory systems domain is clearly relevant to insomnia or hypersomnia. Depression is not well-understood in terms of aetio-pathophysiology, and patients with different symptom combinations are also likely to differ at the pathophysiological level. The RDoC approach is conducive with translational research aimed at increasing understanding of disorder pathophysiology. This includes evidence obtained from animal models that combine manipulations with aetiological validity with behavioural readout tests with face validity for specific psychopathologies (Pryce and Seifritz, 2011).

Chronic psychosocial stressors are major aetiological risk factors for depression (Kendler et al., 2003; Kessler, 1997). In mice, one form of environmental manipulation proposed to model aspects of human psychosocial stress is chronic social defeat (CSD). It comprises 10–15 days of continuous intruder status in the home cages of different dominant mice but protected by a divider, with brief daily experience of actual physical attack and defeat (Golden et al., 2011; Kudryavtseva et al., 1991). We and others could demonstrate that CSD leads to increased sensitivity to and impaired coping with aversive stimuli (e.g. Azzinnari et al., 2014). Furthermore, CSD has been reported to result in decreased preference for gustatory reward, namely sweet-tasting sucrose solution, over water in the two-bottle test of consummatory behaviour (Krishnan et al., 2007). Somewhat in contrast, in human depression, patients do not exhibit reduced subjective pleasure when given a rewarding stimulus (Dichter et al., 2010). However, when required to exhibit high effort to obtain reward, depressed patients are less motivated to do so (Sherdell et al., 2012). This evidence that, in depression, positive-valence processing is reduced at the motivational level rather than the consummatory level, highlights the need for animal models of stress-induced impairment of reward motivation and anticipation. These processes can be best-studied using behaviour-outcome (operant) tests.

In order to investigate reward motivation *per se*, a single operant stimulus can be used with reinforcement earned according to a specific schedule. In animal studies, the reinforcer typically takes the form of palatable food. The progressive ratio schedule (PRS) test requires the subject to make an increasing number of responses to obtain successive rewards and is therefore sensitive to assessing the motivation for effortful responding for reward. By conducting the PRS test with the animal subject close to hunger satiety, the anticipated palatability of the sucrose-pellet reward becomes more important relative to its calorific value, thereby increasing the test's sensitivity for assessing reward motivation. For example, in adult rats it has been demonstrated that early life stress leads to decreased responding for reward in a PRS test (Leventopoulos et al., 2009). Using tests comprising two operant stimuli that need to be discriminated between in order to obtain reinforcement, then a number of further depression-relevant reward processes can be investigated. When depressed patients are assessed in discrimination tests that require low effort to obtain reward, typically either symbolic (emoticon e.g. smiling face) or monetary, they do not differ from healthy subjects in terms of accuracy of responding (Taylor Tavares et al., 2008). However, their responding is characterised by high sensitivity to error feedback: when depressed patients make an error and therefore fail to receive reinforcement on a trial, they are more likely to make an incorrect decision on the subsequent trial (Elliott et al., 1996,1997). The probabilistic reversal learning (PRL) test assesses reward-directed decision making under conditions of accurate and misleading reinforcement/feedback (Chamberlain et al., 2006; Cools et al., 2002; Evers et al., 2005; Jocham et al., 2009). The test comprises reversal learning, which requires responding to regular shifts in the contingencies – reward, non-reward – between the two operant stimuli and reinforcement and, superimposed on this, at a certain probability correct responses are not rewarded whereas incorrect responses are rewarded. The proportion of non-rewarded correct responses on which the subject shifts (to the incorrect stimulus) on the next trial, gives a measure of negative feedback sensitivity (NFS). High NFS is indicative of under-estimation of reward probability and is increased in depressed patients (Taylor Tavares et al., 2008). Recently, rodent automated operant PRL tests have been developed,

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