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Effects of chronic mild stress on sexual behavior, locomotor activity and consumption of sucrose and saccharine solutions

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Abstract

Many symptoms of human depressive disorders are also observed in animals after exposure to unpredictable stressors. The chronic mild stress (CMS) paradigm was developed in order to better model the human situation by using chronic mild stressors over a longer period. It is claimed that the model induces anhedonia in the animals, a core symptom of depression in humans. Despite the fact that the CMS model has a high degree of face validity, there are a number of laboratories in which the establishment of the model is less reliably observed. We have examined behavior (sexual activity and open field activity) together with hedonic measures (sucrose and saccharine intake) after exposure to CMS. CMS decreased male sexual activity (e.g. reduced capability to ejaculate) and increased activity in an open field test. The hedonic measures showed diverging results after CMS in our laboratory. Sucrose consumption was reduced, while saccharine consumption did not show a comparable change. It is concluded that CMS induces comparable alterations to some depression-like symptoms in humans. Saccharine consumption is not a reliable indicator of the hedonic responsiveness to CMS.

Keywords: Animal model of depression; Chronic mild stress; Sucrose intake; Saccharine intake; Sexual activity; Open field behavior

1. Introduction

A direct or indirect involvement of stress has been suggested in the development of human depression (e.g. [2,5]). In animals, unpredictable stressors have been shown to induce changes in a wide range of behavioral parameters, including changes in locomotor and explorative behavior, impairment of feeding, drinking and sexual behavior [38]. Such behavioral changes are often seen in human psychiatric disorders. A regime of uncontrollable stress has been used extensively to model the deficits in motivation and reward. In DSM-IV (American Psychiatric Association 1994), anhedonia (loss of interest or pleasure in events that usually would be enjoyed) is defined as a core symptom of depression. Studying the behavioral and rewarding alterations, and the underlying physiological mechanisms in animal models of depression may be useful in obtaining more insight into human depression [3,8].

CMS involves exposure to unpredictable mild stressors over several weeks, designed to mimic the daily hassles that reportedly provoke the onset of depression in humans [2,19]. In the CMS model, the major symptom of human depression, anhedonia, is claimed to be reflected in the animals' decreased consumption of palatable solutions [40]. The intake or preference for sucrose solutions is the hedonic

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measure that has been most widely adopted. However, despite a high degree of face validity of the CMS model, its establishment is not reliably observed [4,21,27,39].

We have earlier reported that a chronic mild stress procedure in rats induced a decrease in sucrose intake per unit body weight, while sucrose intake in a non-stressed control group did not change [14]. The largest effect was obtained after 2 weeks of the stress protocol, and was attenuated thereafter. Also, CMS produced changes in both the structure and the continuity of sleep consistent with sleep abnormalities reported in depressed patients [14].

The main purpose of the present study was to explore whether CMS protocol could lead to other relevant behavioral changes. A decreased sexual drive is often seen in depressed patients. Also, a decrease or increases in spontaneous motor activity (e.g. psychomotor retardation or agitation) are common symptoms of depression in humans. Therefore, we expected that sexual behavior would be diminished and spontaneous activity would be altered in an animal model of depression. D' Aquila et al. [6] found a decreased sucrose intake together with a decreased sexual behavior in CMS rats. However, their animals were not screened for eventual non-copulators. The rats were interacting for the first time and only the mounting behavior was analyzed. In the present study, each rat underwent mating tests to screen for any non-copulators, and copulatory behavior was analyzed in greater detail for 30 min. One of the most frequently used and accepted variable for measure emotionality in rodents is to measure their locomotion in a novel field [13,28]. We used an open-field test to measure the locomotor activity to estimate if the CMS procedure affected the emotionality.

Another objective of the present study was to replicate in our laboratory the decreased sucrose consumption [14] and to test consumption of a different palatable solution. Sucrose and saccharine intake are both commonly accepted measures of anhedonia, and many investigators have reported that consumption is inhibited by CMS [23,25,26,40]. To our knowledge, this is the first study testing both sweet solutions in the same animals.

2. Materials and methods

2.1. Ethical evaluation

The experiment described in this article has been approved by the Norwegian Animal Research Authority and registered by the Authority.

2.2. Animal handling

Sprague–Dawley (Mol:SPD) rats (Møllegaard, Copenhagen, Denmark), 42 male and 24 females, were used in this experiment. On arrival, there were five animals in each transport cage. To minimize stress, they were allowed to remain in the transport cage for 5 days before the males were separated and housed individually in conventional Macrolon type III cages. Females remained housed together in conventional Macrolon type IV cages in a separate room. The home cages were placed in a rack allowing visual, olfactory and auditory contact between animals.

The rats had free access to food (Rodent low protein diet, B and K Universal AS, Norway) and water, except when the CMS procedure required deprivation. Total food intake was not measured. The ambient temperature was 22±1 °C with 52±2% humidity. Male and female rats were kept on a reversed, controlled 12-h light/12-h dark schedule with gradually increasing lighting from 1800 h and lights fully on at 1900 for 10 days before the start of the experiment. Five to seven days have been seen to be a sufficient time period for the synchronization of spontaneous locomotor activity with a new circadian rhythm in male SPD rats [17].

2.3. Grouping

Male rats were divided into two main groups. The experimental group was exposed to chronic mild stress, whereas the control group was given ordinary daily care and housed separately in a different room. A subgroup of each main group was tested for sexual behavior. Thus, there were four groups in total: two control groups, tested/not tested for sexual activity and two CMS groups, tested/not tested for sexual activity. Before the start of the experiment, the groups and subgroups had similar levels of both sucrose intake and sexual behavior. All rats were tested for the open field activity.

2.4. Stress procedure

The CMS procedure (Fig. 1, bottom) was adapted from the procedure described by Willner and collaborators [40] with the addition of some stressors from Moreau and collaborators, e.g. empty bottle of water, restricted food [24], see Gronli et al. [14]. Each week consisted of one period (2 h) of paired caging, one period (3 h) of tilted cage (45°), one period of food deprivation (18 h) immediately followed by 1 h of restricted access to food (5 micropellets), two periods of water deprivation (18 h) immediately followed by 1 h exposure to an empty bottle, one 21 h period with wet cage (200 ml water in 100 g sawdust bedding) and one period with 36 h of continuous light. Thus, stressors were presented both during the rats' active (dark) period and during the inactive (light) period. Control animals were left undisturbed in their room and home cages.

2.5. Sexual behavior

The female rats used in the mating test were of the same strain as the males. They were ovariectomized at least 2 weeks before the test and brought into oestrus by subcuta-