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Research report

Cognitive deficits in the rat chronic mild stress model for depression: Relation to anhedonic-like responses

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ABSTRACT

The chronic mild stress (CMS) protocol is widely used to evoke depressive-like behaviours in laboratory rats. The aim of the present study was to examine the effects of chronic stress on cognitive performance.

About 70% of rats exposed to 7 weeks of chronic mild stress showed a gradual reduction in consumption of a sucrose solution, indicating an anhedonic-like state. The remaining rats did not reduce their sucrose intake, but appeared resilient to the stress-induced effects on sucrose intake. Cognitive profiling of the CMS rats revealed that chronic stress had a negative effect on performance in the spontaneous alternation test, possibly reflecting a deficit in working memory. This effect was independent of whether the stressed rats were anhedonic-like or stress-resilient as measured by their sucrose intake. CMS did not influence performance in passive avoidance and auditory cued fear conditioning, however, in rats displaying an anhedonic-like profile, CMS increased freezing behaviour in contextual fear conditioning.

1. Introduction

Stress is known to be one of the causal factors for development of major depression [27]. Based on this observation, the chronic mild stress (CMS) animal model has been developed to mimic the development and progress of clinical depression [49]. In the CMS model, one of the main symptoms of major depression, namely anhedonia, is mimicked [49]. In the CMS procedure, rats or mice are chronically exposed to a variety of mild stressors. During 1–3 weeks of CMS exposure, the animals display a reduction in the consumption of, or preference for, sucrose solution [50]. Decreased sucrose consumption or preference is believed to reflect a decrease in sensitivity to reward [48]. This has been confirmed by a comparable decrease in the rewarding properties of food pellets [35], amphetamine [35], and morphine [4] in chronically stressed rats, as assessed by place preference conditioning. CMS increases the threshold for intracranial ventral tegmental self-stimulation, also indicating decreased sensitivity to rewarding stimuli [32].

In addition to decreasing responsiveness to rewarding stimuli, CMS exposure results in behavioural changes related to major depression, including decreased sexual [22], aggressive [13] and investigative behaviours [47]. Moreover, disruption of normal sleep patterns in animals exposed to CMS includes decreases in active waking and deep sleep, a reduced latency to enter the first REM period [8], and more fragmented sleep patterns [21]. In addition, dysregulation of hypothalamic–pituitary–adrenal (HPA) axis [29,43], and immunological dysfunctions [14,15] have been reported in CMS animals. All of the clinically active classes of antidepressants [47] and electroconvulsive seizure [33] mediate recovery from stress-induced anhedonia.

Previous studies from our laboratories have shown that rats subjected to CMS segregate into two sub-groups: a group of rats that develop anhedonia-like symptoms and a group of rats that appear to be resilient to the influence of chronic stress on hedonic status as assessed by sucrose intake profiles [4]. This segregation was confirmed by place preference conditioning test and on molecular levels by global gene [4] and protein [5] expression analysis.

Increasing focus has been directed towards cognitive disturbances in major depression: there is strong evidence that impaired cognition is a core element of this disorder [10] and

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that antidepressant treatment may ameliorate cognitive impairments in parallel to mood improvement of depressive patients [1,45]. Additionally, studies have shown that untreated major depression is associated with volume loss in the hippocampus [41], a brain region known to be involved in cognitive function. In animals, exposure to stress has also been shown to cause structural [12] and cytogenic changes in the hippocampal region [11,26].

Cognitive impairment in CMS-exposed rats have been shown with several behavioural paradigms. For example, impairment of spatial learning and memory have been demonstrated with the use of the Morris water maze test in mice exposed to CMS [42], deficits in recognition memory have been demonstrated in both rats [34] and mice [16], and CMS has been demonstrated to suppress fear extinction [18].

In the present study, we conducted several behavioural tests to further evaluate the cognitive and emotional profiles of rats exposed to chronic mild stress. The spontaneous alternation behaviour (SAB) task, believed to address working memory function [23,30] was conducted to test this type of memory performance. The step-down passive avoidance (SDPA) and passive avoidance (PA) tasks are both operant conditioning tasks believed to address implicit memory function [6]. Auditory cued fear conditioning was tested with the contextual fear conditioning (CFC) apparatus and performance in this test is also believed to reflect implicit memory function [38]. Finally, the contextual part of the CFC test conducted in the present study is considered to address explicit memory function [38]. In addition to evaluating the cognitive and emotional profiles, the separation of CMS rats into anhedonic-like and resilient rats enabled us to investigate if any cognitive deficits were specific for the anhedonic-like state.

2. Materials and methods

2.1. Subjects

A total of 122 male Wistar rats (Taconic M&B, Ry, Denmark) were used in this study. The animals were singly housed, except when grouping was applied as a stress parameter. Food and water was available ad libitum except when food or/and water deprivation was applied as a stress parameter. The standard 12-h light/dark cycle, with lights on from 6 a.m. to 6 p.m., was only changed in course of stress regime. All testing procedures were in accordance with 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1985) and the 'Danish Animal Experimentation Act'.

2.2. Sucrose consumption test

Initially, the animals were trained to consume a palatable sucrose solution (1.5%). The training endured for 5 weeks, where the sucrose test was made twice a week during the first 3 weeks and once a week during the last 2 weeks. Animals were food and water deprived 14 h before the test, which consisted of 1-h exposure to a bottle with a 1% sucrose solution. Sucrose consumption was monitored by weighing the bottles at the beginning and end of the test. During the stress period the sucrose consumption test was performed once a week. Independent of the sucrose consumption test, water intake was monitored once a week by weighing the water bottles before and after a 24 h period.

2.3. Weight of the animals

Weight gain was monitored once a week. The weight of animals was 230 ± 10 g at the beginning of adaptation for sucrose consumption, and 330 ± 50 g at the beginning of the stress regime.

2.4. Chronic mild stress protocol

On the basis of sucrose intakes in the three final baseline tests, animals were divided into two matched groups and placed in separate rooms. One group was exposed to chronic mild stressors and the other was left unchallenged. The unchallenged group was food and water deprived 14 h before sucrose consumption test only.

The stress procedure was optimized in our laboratory in Aarhus [26] and is a slight modification of the protocol developed by Papp [18,39]. The stress protocol consisted of seven different stressors: one period of intermittent illumination, stroboscopic light, grouping, food or water deprivation, and two periods of soiled cage and no stress, and three periods of 45° cage tilting. All stressors lasted from 10 to 14 h.

2.5. Study design

The results from the present project were obtained from two separate CMS studies with identical project designs. All behavioural tests were conducted after 6–8 weeks of exposure to CMS. As the exposure of the rats to each test may have significant effects on their behaviour in subsequent tests, we employed the tests thought to evoke less emotionality in the animal first and the most provocative last. No rats were exposed to more than one test in which a foot shock was included.

2.6. Behavioural tests

All the experiments were done during the 12 h-light cycle from 10 a.m. to 4 p.m. Generally, the rats were placed in the experimental room at least 1 h prior to the test. In between subjects the apparatus was thoroughly cleaned with water wetted paper towels and dried with cloth in the SAB test and a 70% ethanol solution for all other tests.

2.7. Spontaneous alternation behaviour

The apparatus consisted of a y-maze with three arms (50 cm long × 18 cm wide), surrounded by black Plexiglass walls (35 cm high). The central platform of triangular shape measures 18 cm × 18 cm × 18 cm and also included a 5 cm area into the arms. Illumination was provided by a small lamp situated above the center of the maze. Light intensities were 1–2 lux in the arms and 5 lux in the center area.

Each rat was placed at the end of one of the arms (facing the end of the arm), and was allowed to explore all the arms freely for 12 min testing period. The series of entries and the total number of entries was recorded by a trained observer. An entry into an arm was defined as the animal placing all four paws in that arm. An alternation was defined as visits into all three arms on consecutive occasions. The number of maximum alternations was the total number of arm entries minus 2. The alternation ratio was calculated as the number of alternations divided by maximum alternations.

2.8. Contextual and auditory cued fear conditioning

The contextual fear conditioning apparatus consisted of two transparent plastic chambers (24 cm × 30 cm × 30 cm) with stainless steel grid floors (19 rods of 4 mm in diameter). Each chamber was located inside an insulated plastic cabinet reducing potential influence from outside light and noise. A house light situated in the plastic cabinet provided the illumination. The experimental procedure was conducted on two consecutive days with one conditioning session carried out on day 1 and two test sessions on day 2.

Conditioning session: rats were gently placed in the test chambers and allowed to explore the chamber for 180 s. This period was followed by presentation of a tone (30 s, 95 dB, 2 kHz) co-terminating with a shock (2 s, 0.7 mA). After a 30 s period rats were removed from the chambers.

Contextual memory session: rats were facing the same context as on day 1, excluding the auditory cue and the foot shock, and allowed to explore the context for 180 s.

Control and auditory cue memory session: a black plastic box was inserted into the test chamber to change the context. Rats were placed into the new context and allowed to explore these surroundings for 180 s. This period was followed by presentation of a tone (180 s, 95 dB, 2 kHz).

In all sessions, movement was monitored by an infrared sensor situated in the ceiling of the test chambers. Freezing was defined as time periods of more than 10 s with no movement. Freezing ratios were calculated by the total amount of time spent freezing divided by the duration of the experiment (180 s).

2.9. Step-down passive avoidance

The step-down apparatus consisted of a transparent plastic cubicle (24 cm × 30 cm × 30 cm) with a stainless steel grid floor (19 rods of 4 mm in diameter). A wooden platform (15 cm × 9 cm × 3 cm) was placed on the grid floor in the back left corner. Rats were transported from their home stable to the experimental laboratory immediately before commencing trials and transported back to home stable immediately after the trial. The experimental procedure consisted of two trials: an acquisition trial and a retention trial with an inter-trial interval of 24 h.

Acquisition trial: the rat was gently placed on the platform, bordered by a transparent Plexiglass cylinder, with the nose facing the left corner of the box. The rat