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Effects of social defeat on sleep and behaviour: Importance of the confrontational behaviour

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HIGHLIGHTS

- Social defeat procedures failed to affect sleep or behaviour in rats.
- Behaviours during the social confrontation, fighter or submissive, revealed effects.
- Fighter rats showed more SWS fragmentation pre and post stress.
- Fighter rats showed a longer latency to leave the start box to explore an open field.
- Fighter rats failed to show startle response decrement.

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ABSTRACT

We studied the short- and long-term effects of a double social defeat (SD) on sleep parameters, EEG power, behaviour in the open field emergence test, corticosterone responsiveness, and acoustic startle responses. Pre-stress levels of corticosterone were assessed before all rats were surgically implanted with telemetric transmitters for sleep recording, and allowed 3 weeks of recovery. Rats in the SD group (n = 10) were exposed to 1 hour SD on two consecutive days, while control rats (n = 10) were left undisturbed. Telemetric sleep recordings were performed before SD (day −1), day 1 post SD, and once weekly for 3 weeks thereafter. The open field emergence test was performed on day 9 and weekly for 2 weeks thereafter. Blood samples for measures of corticosterone responsiveness were drawn after the last emergence test (day 23). Acoustic startle responses were tested on day 24 post SD. Overall, SD rats as a group were not affected by the social conflict. Effects of SD seemed, however, to vary according to the behaviours that the intruder displayed during the social confrontation with the resident. Compared to those SD rats showing quick submission (SDS, n = 5), SD rats fighting the resident during one or both SD confrontations before defeat (SDF, n = 5) showed more fragmented slow wave sleep, both in SWS1 and SWS2. They also showed longer latency to leave the start box and spent less time in the open field arena compared to SDS rats. In the startle test, SDF rats failed to show response decrement at the lowest sound level. Our results indicate that how animals behave during a social confrontation is more important than exposure to the SD procedure itself, and that rapid submission during a social confrontation might be more adaptive than fighting back.

1. Introduction

Psychosocial stress in rats has several behavioural and physiological effects which are often interpreted as parallel to those seen in humans. One commonly used method is the resident–intruder procedure, whereby an intruder rat is exposed to a resident rat in its own home cage [1–3]. This normally leads to aggressive behaviour by the resident, resulting in the defeat of the intruder (social defeat — SD). The period of the psychosocial stress may be prolonged by keeping the intruder animal in the resident's home cage, but protected from injury by wire mesh netting. The effects of psychosocial stress seem to vary according to the behaviour which the intruder displays during the confrontation [4–8].

The number and durations of the SD procedures to which the intruder animals are exposed vary. A single or double exposure to social stress in rodents induces both short-lasting and long-lasting changes on physiological, neuroendocrine and behavioural measures [9–12]. Acute effects observed during the social interaction and during

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the hours that follow immediately include increased slow wave activity (SWA) during sleep, increased plasma corticosterone, noradrenaline and adrenaline concentrations, increased core body temperature and increased heart rate [13–17]. However, all the above mentioned effects seem to disappear within hours. Other effects may last for days or weeks, for example reduced locomotor activity and increased anxiety-like behaviour in the open field and elevated plus maze tests, reduced social interaction, elevated acoustic startle response, reduced sucrose preference, reduced food intake, suppressed body weight gain, and decreased circadian variation in core body temperature [3,18–20].

While some immediate effects of SD dissipate over time, others develop. We have previously reported that rats had increased sleep fragmentation and increased amount of slow wave sleep (SWS) 2 four days after a double social defeat, but not on the day after the second defeat [19]. In an earlier experiment, a single SD induced a progressive increase in immobility in repeated sudden silence tests, reaching a maximum after 3 weeks [2]. In general, our knowledge of the long-term consequences of a stressful social event may be limited because only a few studies employ a sufficient time-span [10]. One reason for studying long-term effects lies in the use of SD in rodents as an animal model of depression and anxiety [2,21–23], and the diagnostic criteria and symptomatology of these. Diagnostic criteria for affective disorders include symptom persistence over time, such as several weeks [24]. Furthermore, symptoms may take time to manifest themselves following a precipitating event, e.g. delayed onset of posttraumatic stress disorder (PTSD).

Disturbed sleep is both a clinical predictor and a symptom of human affective disorders such as depression and anxiety disorders (e.g. generalized anxiety disorder and posttraumatic stress disorder) [25–29]. The alterations of sleep parameters include increased latency to sleep, sleep fragmentation (stage shifts and arousals), amount of rapid eye movement (REM) sleep, and reduced REM sleep latency, total sleep time and amount of deep SWS. Changes in sleep electroencephalographic (EEG) activity, EEG power, include reduced power in the delta range (0.2–4 Hz) and increased high frequency power (>20 Hz) [28,30–32]. In chronic insomniacs, perceived stress and stress-related avoidance behaviour have been associated with decreased delta power and increased high frequency power (>16 Hz) [33]. Chronic hyperarousal is a state associated with both major depression and anxiety disorders [24], as well as with functional somatic disorders [34].

Our primary aim in this study was to examine the short-term and long-term effects of the SD procedure in rats on physiology and behaviour — sleep parameters, EEG power, startle responses, behaviour in an open field emergence test as well as the corticosterone response to the emergence test. We expected that socially defeated rats compared to controls would show high acoustic startle responses, high corticosterone responsiveness, and that in the emergence test they would show longer latencies to leave the start box and spend less time in the open test arena. Further, that they would show long-term alterations in sleep parameters and EEG power parallel to those seen in human affective disorders.

Effects of SD seem to vary according to the behaviour which the intruder displays during the confrontations. Generally, studies have shown that rats that are passive and show quick submission seem more affected by the defeat than those that fight back or oppose the resident during the social conflict [4–8]. Rats with this passive coping strategy during the confrontation display a higher corticosterone response to defeat, and a higher level of neuronal activation in the amygdala and medial prefrontal cortex [4]. Rats that are passive also show longer-lasting disturbance in diurnal rhythm of heart rate, body temperature and locomotor activity, higher body weight loss and different stress-induced immune changes than those that fight back [5,6].

Our secondary aim was therefore to investigate whether short-term or long-term effects of the resident–intruder procedure would be related to the intruder animals' behaviours during the social confrontations. Here we expected that rats showing rapid submission in the social defeat would exhibit the most pronounced alterations in sleep, EEG power, behaviour and corticosterone response.

All procedures were performed on animals implanted with telemetric devices to allow long-term measurements of EEG and electromyogram (EMG).

2. Methods

2.1. Ethical evaluation

The experiments described in this article have been approved by the Norwegian Animal Research Authority and registered by the authority. The experiment has thus been conducted in accordance with Norwegian laws and regulations controlling experiments in live animals. Norway has signed and ratified The European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific purposes, of March 18, 1986.

2.2. Design

An overview of the experimental design is shown in Fig. 1.

Blood samples for pre-stress levels of corticosterone measures were taken at least one day before implantation of the telemetric transmitter. After surgery, the animals were allowed 3 weeks of recovery. Rats in the SD group were exposed to social defeat on two consecutive days (−1 and 0). Meanwhile, rats in the control group were left undisturbed in their home cages. Telemetric sleep recordings were performed before SD (day −1), day 1 post SD, and once a week for 3 weeks thereafter (on day 7, day 14 and day 21 post SD). The open field emergence test was performed once a week (on day 9, day 16 and day 23 post SD). Blood samples for measures of corticosterone responsiveness were drawn 5 min after the last emergence test (day 23), and acoustic startle responses were tested on day 24 post SD.

2.3. Animals and housing

Experiments were performed with 20 outbred male Wistar rats (Taconic, Denmark). On the day after arrival, they were separated, housed individually and allowed 5 days of acclimatisation, before 5 days of handling (one minute per day). The cages were individually ventilated (IVC) polypropylene Euro-standard Type III H cages (425 × 266 × 185 mm — floor area: 800 cm^2). Within the cages there was an average ambient temperature of 23 °C and an average relative humidity of 52%. The rats were exposed to a 12:12 hour light/dark schedule with lights on at 08:00 h and lights off at 20:00 h. A progressive increase in lighting started at 07:00 h and progressive dimming started at 19:00 h. The rats had free access to food and water. Bedding (Bee Kay Bedding, Scanbur BK) was changed once a week. The rats were randomly assigned to SD and control groups (n = 10) after the postoperative period when they reached their preoperative bodyweight.

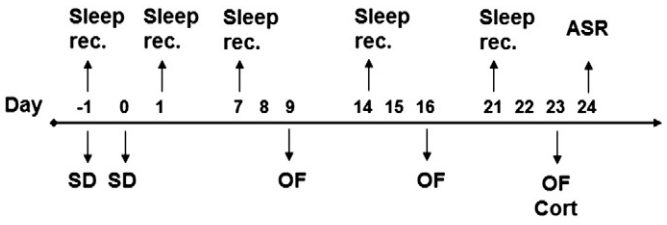

Fig. 1. An overview of the experimental design for the two experimental groups: social defeat (SD) and control (n = 10 each group). Procedures are identical on all days in both groups except on day −1 and day 0 when the stress procedure was conducted. ASR — acoustic startle response; Cort — blood sampling for corticosterone measure; OF — open field emergence test; SD — social defeat; Sleep rec. — Sleep recording.