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Voluntary exercise enhances activity rhythms and ameliorates anxiety- and depression-like behaviors in the sand rat model of circadian rhythm-related mood changes

Katy Tal-Krivisky [a], Noga Kronfeld-Schor [a], Haim Einat [b,c,d,*]

[a] Dept. of Zoology, Tel-Aviv University, Tel-Aviv, Israel
[b] School of Behavioral Sciences, Tel Aviv-Yaffo Academic College, Tel-Aviv, Israel
[c] Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beersheba, Israel
[d] College of Pharmacy, University of Minnesota, USA

HIGHLIGHTS

- Diurnal fat sand rats are an advantageous model for circadian effects on mood.
- In short photoperiods (SP), sand rats develop depression- and anxiety-like behaviors.
- Voluntary exercise in sand rats strengthens circadian activity rhythms.
- Voluntary exercise in sand rats ameliorates SP-induced pathological behavior.

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ABSTRACT

Physical exercise is a non-pharmacological treatment for affective disorders. The mechanisms of its effects are unknown although some suggest a relationship to synchronization of circadian rhythms. One way to explore mechanisms is to utilize animal models. We previously demonstrated that the diurnal fat sand rat is an advantageous model for studying the interactions between photoperiods and mood. The current study was designed to evaluate the effects of voluntary exercise on activity rhythms and anxiety and depression-like behaviors in sand rats as a step towards better understanding of the underlying mechanisms.

Male sand rats were housed in short photoperiod (SP; 5 h light/19 h dark) or neutral light (NP; 12 h light/12 h dark) regimens for 3 weeks and divided into subgroups with or without running wheels. Activity was monitored for 3 additional weeks and then animals were tested in the elevated plus-maze, the forced swim test and the social interaction test.

Activity rhythms were enhanced by the running wheels. As hypothesized, voluntary exercise had significant effects on SP animals' anxiety- and depression-like behaviors but not on NP animals.

Results are discussed in the context of interactions between physical exercise, circadian rhythms and mood. We suggest that the sand rat model can be used to explore the underlying mechanism of the effects of physical exercise for mood disorders.

1. Introduction

Abnormalities of the internal clock are hypothesized to be a critical component of affective disorder pathophysiology [1–3]. Mood disorders such as major depressive disorder (MDD), bipolar disorder (BPD) and seasonal affective disorder (SAD) are strongly associated with disruption in biological rhythms including the sleep/wake cycle, social rhythms, appetite, hormone levels and body temperature [2,4,5].

In mammals, the primary endogenous clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and its neurons have an internal rhythm of about 24 h which can be synchronized by external time givers (zeitgebers) in an adaptive process called entrainment. The entrainment process leads to synchronization of the internal clock to a 24 hour rhythm. The most important zeitgeber of the SCN is light, but other cues such as social interactions and physical activity are also

* Corresponding author at: Professor and Director of Psychobiology Laboratory, School of Behavioral Sciences, Tel Aviv-Yaffo Academic College, 2 Rabenu Yeruham St., Tel-Aviv 6818211, Israel.
E-mail address: haimh@mta.ac.il (H. Einat).

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able to entrain the clock [6]. Other than the central clock, peripheral clocks were identified in almost all cells in the body [7,8]. These clocks are mostly dependent on the master clock of the SCN but are also dependent on other cues such as temperature, glucose levels and glucocorticoids. Under certain conditions (e.g., shift work and jet-lag) these oscillators may desynchronize from the SCN control, leading to chronodisruption or internal desynchronization [9,10], which in animal models was shown to lead to depressive-like behavior [11,12] and may lead to depression in humans [12–16]. The complex nature of interactions between internal desynchronization and affective disorders is not fully understood. While dysregulation of clocks may and have an etiological role in certain types of depression, such as bipolar disorder (BPD) or seasonal affective disorder (SAD) it may also be the consequences of affective pathology in other disorders [2].

Antidepressants and mood stabilizers are the leading treatments for affective disorders and were demonstrated to have significant effects on circadian rhythms [17,18]. Other interventions that are used in the context of affective disorders and are clearly related to circadian rhythms include sleep deprivation, light treatment and physical exercise [1,19,20]. Exercise is an emerging non-pharmacological treatment that may benefit individuals afflicted with affective disorders [21,22], but the mechanisms involved in the antidepressant effects of physical exercise are unknown [20,22]. Yet, physical exercise was found to act as a zeitgeber, strengthen the circadian system and accelerate re-entrainment in human and rodent sleep–wake cycles, supporting its application as a treatment for circadian rhythm misalignment resulting from jet-lag or shift-work [20,23–26].

One affective disorder that is strongly related to biological rhythms is seasonal affective disorder (SAD), a disorder in which patients experience depressive episodes starting in the fall or winter when days get shorter and lasting until spring, when they experience remission [27]. To the best of our knowledge, physical exercise is yet to be thoroughly investigated as a possible beneficial intervention for SAD, but at least in one study, aerobic exercise was associated with significant reductions in depression severity, which was comparable to the effects of bright light treatment [28].

One way to explore treatment effects and mechanisms of therapeutic action is to utilize appropriate animal models [29]. In that context, we previously demonstrated that the fat sand rat, a diurnal rodent, is an advantageous model animal for seasonal affective disorder despite the fact that when in laboratory conditions these animals do not maintain a classical diurnal activity pattern [30]. When maintained in short photoperiod conditions (19 h dark/5 h light, SPs), sand rats develop an anxiety- and depression-like phenotype that is relieved after treatment with bright light or with antidepressant drugs [31–35]. The current study was therefore designed to evaluate the effects of voluntary exercise (wheel running) on activity rhythms and anxiety- and depression-like behaviors in sand rats acclimated to short photoperiod as a step towards later exploration of possible mechanisms.

2. Materials and methods

2.1. Animals

Sixty four male fat sand rats (*Psammomys obesus*; ~6 months old; Harlan, Jerusalem) were used for the experiment. Animals were individually housed in standard plastic cages (42 cm × 26 cm × 15 cm) positioned in temperature-controlled rooms (25 °C). Animals were provided with ad-lib tap water and special low-energy pellets (product 19560, Koplock, Israel). The special food is needed because sand rats develop diabetes when fed with regular rodent chow [36].

All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) and the Israeli Ministry of Health guide for the care and use of laboratory animals and were approved by the Tel-Aviv University IACUC (protocol # L-12-050).

2.2. Photoperiod conditions

Sand rats were acclimated to short photoperiod (SP; 5 h light/19 h dark, N = 30) with lights on at 08:00 and off at 13:00 or to neutral photoperiod (NP; 12 h light/12 h dark) with lights on at 08:00 and off at 20:00. Light intensity was 800 lx. The photoperiod regimen was chosen based on previous results demonstrating that this SP regimen results in the development of depression- and anxiety-like behaviors compared with the neutral photoperiod regimen (12L/12D) [31–33] and based on the activity pattern of sand rats in nature, where they are active for about 5 h around midday during winter [37,38]. Animals were maintained in these photoperiod conditions for 3 weeks before the start of any manipulation or testing. This time period was found to be sufficient for physiological acclimation [39] and synchronization of circadian rhythms [40].

It is important to note that the study was run as two separate experiments: the first evaluated the effects of running wheels in animals acclimated to neutral photoperiods and the second evaluated the effects of running wheels in sand rats acclimated to short photoperiods. The separation into two experiments was done because of technical limitations.

2.3. Treatment

After 3 weeks of acclimatization, each photoperiod condition group of sand rats was further divided into two groups (N = 16/subgroup): One subgroup was transferred to new cages containing running wheels while the other group was transferred to new cages without running wheels. General activity was recorded for 3 weeks using infrared detectors (general activity detector: Intrusion detector model MH10; Crow group, Kiriat-Teufa, Israel) and wheel running activity was recorded using inductive sensors (SI18-C, Aeco sensors, Italy) connected to a computer. Data were collected at 6-min intervals via designated software (ICPC, Netanya, Israel). Three weeks later, the animals underwent a series of behavioral experiments to evaluate their anxiety- and depression-like behaviors as described below.

2.4. Behavioral tests

Following 3 weeks of in-cage recording of animals' activity and wheel running, sand rats were subjected to 3 standard behavioral tests for anxiety- and depression-like behaviors. The tests were performed in succession, one per day and included the elevated plus maze (EPM), forced swim test (FST) and social interaction (SI) test.

2.4.1. Elevated plus-maze

The EPM is frequently used to evaluate anxiety-like behavior in rodents including mice [64], voles [65], hamsters [62], rats [63] and sand rats [31,32,33,35]. The test presents the rodent with a conflict between the tendency to remain in a safe enclosed area and the need to explore new environments that could hold an adaptive value [66]. For the present study, a black aluminum EPM was used. The maze consisted of two open arms (50 cm long and 10 cm wide) and two closed arms (same dimensions with 15 cm high walls). The plus maze was elevated 50 cm above the floor and light levels at the open arms were 200 lx. The test started at least an hour after light onset in the rooms (09:00) and animals were tested only during the next 3.5 h, well within the light hours in the colony rooms of the SP group. Sand rats were individually placed in the center of the maze, and their behavior was digitally recorded for a 5 min session. Recordings were used for later manual scoring of behaviors. At the end of the session animals were returned to their cages and the maze was wiped clean with 70% ethanol before the start of the next session. Scoring of the EPM included the time and the number of entries into each arm and was done by an investigator blind to treatment.