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Antidepressants Reverse Short-Photoperiod-Induced, Forced Swim Test Depression-Like Behavior in the Diurnal Fat Sand Rat: Further Support for the Utilization of Diurnal Rodents for Modeling Affective Disorders

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Key Words
Depression · Nontraditional models · Circadian rhythms · *Psammomys obesus* · Photoperiod

Abstract
Recent findings demonstrate strong links between abnormalities in circadian rhythms and sleep and the etiology, pathophysiology and treatment of major affective disorders. Further exploration of these interactions requires the development, identification and utilization of good and predictive animal models. The biology and behavior related to circadian rhythms are significantly different in diurnal and nocturnal rodents. Accordingly, it is possible that exploring the interactions between these mechanisms and affective change in diurnal animals may be advantageous. Recent studies demonstrate that diurnal fat sand rats and Nile grass rats show depression-like behavior when maintained under short-photoperiod (SP) conditions compared with animals maintained under neutral photoperiod (NP) conditions. Moreover, these behaviors were ameliorated after treatment with bright light. The present study further explores the possible utility of sand rats as animal models by testing the effects of antidepressants on the SP-induced depression-like behaviors of sand rats. Sand rats maintained in SP or NP conditions for 3 weeks were treated subchronically (5 injections) with the clinically effective antidepressant bupropion, and their behavior was tested in a number of depression-related tests. Results show that antidepressant treatment reverses the effects of SP conditions in the forced swim test, but that neither SP conditions nor antidepressants influenced sweet solution preference. These results partly support the validity of the sand rat model, but suggest that not all tests that were validated in nocturnal laboratory rodents can be applied to other rodent species and that additional tests should be applied to further explore the validity of the model.

Introduction

The biological underpinning of affective disorders including depression spectrum disorders and bipolar disorder is not clear, but accumulating evidence implicates

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that circadian rhythms, sleep and photoperiods are important factors that are involved in their etiology and treatment [1, 2]. A critical tool to further investigate the link between circadian rhythms, sleep, photoperiods and affect is the development and utilization of appropriate animal models, an area that is repeatedly cited as deficient in the study of psychiatric disorders [3, 4]. Previous studies that tested the effects of altering circadian factors such as photoperiod length in animals have contradictory and complex results. For example, long daylight conditions were reported as anxiolytic in hamsters [5] but appeared to induce an anxiety-like response in voles [6]. These contradictions may be explained by the utilization of different species or varying experimental protocols, but one possible important factor is that these studies use nocturnal rodents to model pathologies in the diurnal human. The circadian physiology, as well as its behavioral consequences in nocturnal and diurnal animals, is significantly different. For example, diurnal mammals are active at times of the day when levels of melatonin are low and when the suprachiasmatic nucleus (the internal clock) is most active, and this is the opposite in nocturnal mammals. In nocturnal rodents, a light pulse at nighttime rapidly reduces activity levels, whereas light triggers activity in diurnal mammals [7, 8]. Melatonin secretion is correlated with increased activity in nocturnal animals and with sleep in diurnal animals [9], and brain regions adjacent to the suprachiasmatic nucleus show significantly different rhythms in diurnal and nocturnal rodents [10, 11]. These signals possibly transit different patterns to downstream targets [10, 12], including targets that were strongly implicated in affective disorders such as the serotoninergic and dopaminergic systems [13, 14]. Considering these differences between diurnal and nocturnal animals, and the need to improve the homology between animals and humans when modeling human behavioral disorders, it is reasonable to consider that the use of diurnal animals as a model species to study interactions between circadian-related systems and mood in humans would be appropriate [15–17]. This possibility is clearly in line with the suggestion that better and more predictive models can be achieved by identifying the best model animal, the species or strain of animal that has the highest homology with the disease-related biology [18–20].

A number of recent studies demonstrated that some diurnal rodents may serve as suitable species to model aspects of human affective disorders [15–17, 21]. These studies demonstrate (1) that fat sand rats *(Psammomys obesus)* or Nile grass rats *(Arvicanthis niloticus)* maintained under a short-photoperiod (SP) schedule develop depression-like behaviors such as increased immobility in the forced swim test (FST), reduced sweet solution preference and reduced aggression in the resident-intruder test [15, 21], (2) that similar behavioral changes in sand rats are induced after chronic melatonin treatment in a regimen that mimics a short day [16], and (3) that the depression-like behavior of sand rats maintained under SP schedule can be attenuated by bright light treatment [17].

To explore the use of the sand rat as a model animal further, the current study examined the effects of the clinically effective antidepressant bupropion on the depression-like behavior induced by SP in this species. Bupropion was selected on the basis of its reported efficacy in the treatment of seasonal affective disorder [22, 23]. We hypothesized that SP conditions in diurnal sand rats will result in depression-like behaviors, and that these behaviors will be ameliorated by antidepressant treatment.

Animals and Methods

Animals

Adult male fat sand rats (*P. obesus;* approx. 6 months old; Harlan, Jerusalem) were used. The animals were individually housed in standard plastic cages (21 × 31 × 13 cm) positioned in temperature-controlled rooms (25°C). Due to the propensity of sand rats to develop diabetes when fed regular rodent chow, the animals were provided with special low-energy pellets (product 19560; Koplock, Israel) and water ad libitum. All experimental procedures were approved by the Tel-Aviv University institutional animal care and use committee (protocol No. L-09-018 and L-07-077) and followed NIH guidelines for the care and treatment of laboratory animals.

Forty sand rats were divided into 2 photoperiod length groups (n = 20/group), SP (5 h light/19 h dark) and neutral photoperiod (NP; 12 h light/12 h dark). These photoperiod schedules were chosen based on previous results which demonstrated that this SP regimen results in the development of depression- and anxiety-like behaviors compared with the NP regimen [15, 16]. As in our previous studies [15, 16, 21], the animals were maintained in the different photoperiod conditions for 3 weeks, a time period that was found to be sufficient in a variety of rodents for physiological acclimation [24] and synchronization of circadian rhythms [25]. After 3 weeks of acclimatization to the photoperiod conditions, the groups were subdivided into treatment (bupropion) and control (vehicle) subgroups.

Drugs

Bupropion. The animals were administered intraperitoneal injections of either bupropion hydrochloride (Sigma, St. Louis, Mo., USA) 8 mg/kg diluted in saline, or vehicle solution. The injection volume for all animals was 0.1 ml. The bupropion dose was se-

lected from the range of effective doses of the drug in rodent models [26, 27]. Injections were administered once daily for 5 days, 4 h after the onset of light. The experiment therefore included 4 groups of 10 animals: saline/NP; saline/SP; bupropion/NP, and bupropion/SP. Behavioral tests started after 5 injection days, and treatment continued during the days of behavioral testing.

Behavioral Tests

The same animals were tested for preference of a sweet saccharin solution and for activity in the FST. In order to minimize the effect of one test on the other test, the nonintrusive sweet solution preference test was conducted before the more intrusive FST.

Sweet Solution Preference. Sweet solution preference is a model for assessing unconditioned reward-seeking behavior in rodents. This test had been used as an index of the changes in motivation and reward in animal models of anhedonia in affective disorders [28–30]. Following the acclimatization period and the initial treatment period, the animals were provided with bottles containing 0.1% saccharin solution for 4 days in addition to their regular food and water. This version of the sweet solution preference test includes 2 bottles present, a sweet solution bottle and a regular tap water bottle. The water and saccharin solution bottles were weighed daily, 5 h after the onset of light in each room, and daily sweet solution preference was calculated as the rate of saccharin solution consumption out of total liquid consumption. This test was initially developed using sucrose solution, but because of the sensitivity of sand rats to sugar, a saccharin solution was preferred. Although the use of sucrose is more common, experiments performed with saccharin were demonstrated also to be sensitive to depression-related manipulation and drugs [28].

Forced Swim Test. The FST is commonly used to assess manipulations that induce depression-like behaviors [31, 32] and antidepressant effects in rats and mice [33]. With some methodological alterations, this test was successfully used to evaluate depression-like behavior in sand rats [15–17]. The animals underwent the FST over 2 consecutive days, with the second day serving as the test session. The tests were conducted starting 1 h after the onset of light, and within the light period of the SP group, as detailed elsewhere [15–17]. In contrast with rats and mice, sand rats cannot float well and when they stop actively swimming or struggling they sink into the water. Most animals swim and struggle, then sink, start swimming or struggling again while going above water, sink again and so on. We have previously established that the 'time to sink' is a valid measure in the test, conceptually equivalent to 'floating time' in rats and mice [15–17]. To prevent the drowning of the animals, we have established a rescue criterion, and when an animal sank and stayed completely immersed in water (above the tip of the snout) for 5 s, it was taken out of the water (i.e. 'rescued') by the experimenter and the test was terminated. Most animals reached rescue criteria after a number of 'sink' events, and within a few minutes from the start of the test. The main measures in this version of the FST are 'time to first sink' and 'time to second sink' [15–17].

Statistical Analysis

Data from the sweet solution preference test were analyzed using repeated measures ANOVA with photoperiod (short or neutral) and drug treatment (bupropion or saline) as main factors, and day as a repeated measure factor. The FST data were analyzed using a two-way ANOVA with photoperiod and drug treatment as main factors. When results of ANOVA indicated significant interaction, the ANOVA was followed by post hoc tests. $p < 0.05$ was considered significant.

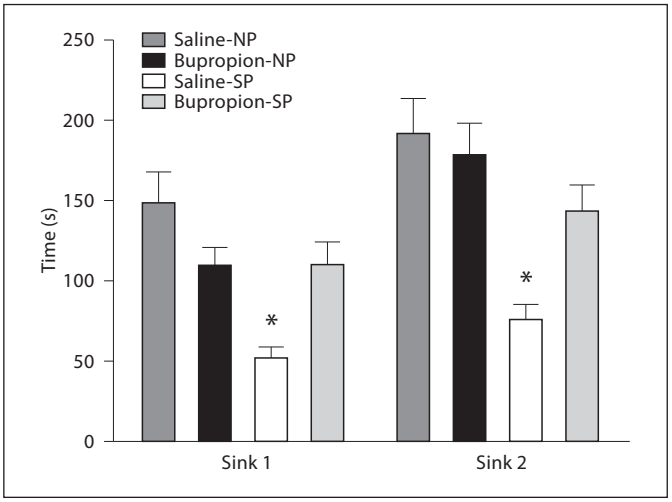

Fig. 1. Time to first and second sink in the FST for sand rats maintained under SP or NP conditions and treated with bupropion or vehicle. n = 10/group. * Statistically significant difference from all other groups.

Results

Bupropion treatment to sand rats maintained under SP conditions delayed the appearance of depression-like behavior in the FST but had no significant effects in the sweet solution test. SP conditions significantly reduced the time to sink in the FST, and this depression-like behavior was attenuated by bupropion treatment. These effects were evident for both sink 1 [photoperiod effect: $F(1, 32) = 9.92$, $p = 0.004$; bupropion effect: $F(1, 32) = 0.4$, $p = 0.51$; photoperiod × bupropion interaction: $F(1, 32) = 10.2$, $p = 0.003$; post hoc: saline-SP group different from all other groups] and for sink 2 [photoperiod effect: $F(1, 32) = 15.32$, $p < 0.001$; bupropion effect: $F(1, 32) = 2.0$, $p = 0.17$; photoperiod × bupropion interaction: $F(1, 32) = 4.69$, $p = 0.04$; post hoc: saline-SP group different from all other groups] (fig. 1). However, manipulation of photoperiod length or administration of bupropion had no effect on the preference of sand rats for sweet solution [ANOVA; photoperiod effect: $F(1, 34) = 0.06$, $p = 0.81$; bupropion effect: $F(1, 34) = 0.42$, $p = 0.52$; photoperiod × bupropion interaction: $F(1, 34) = 2.7$, $p = 0.11$] (table 1).

Table 1. Saccharin test

Experiment and measure	Group	Day 1	Day 2	Day 3	Day 4
Bupropion; saccharin/total liquid preference	saline-NP	0.47 ± 0.07	0.49 ± 0.09	0.41 ± 0.1	0.67 ± 0.08
	bupropion-NP	0.4 ± 0.06	0.31 ± 0.09	0.22 ± 0.07	0.52 ± 0.1
	saline-SP	0.4 ± 0.08	0.38 ± 0.08	0.39 ± 0.1	0.51 ± 0.11
	bupropion-SP	0.42 ± 0.05	0.42 ± 0.08	0.57 ± 0.11	0.53 ± 0.1

Values denote means ± SE.

Discussion

The development of novel, valid and predictive models for the study of affective disorders is a critical task [4, 34]. Mechanisms related to circadian rhythms, sleep and photoperiod are significantly involved in the etiology of affective disorders [1]. Considering this and the physiological differences between diurnal and nocturnal animals, it has recently been proposed that diurnal rodents may be appropriate as a model animal for the study of affective disorders [15–17, 21, 35]. Recent studies suggest that the fat sand rat is a suitable species for the study of the relationship of circadian rhythms and mood disorders, and that the behavioral responses to short light period in this animal may validly model depression-like symptoms in humans [15–17]. The present results partially support the model by demonstrating that the depression-like effects of SP in sand rats tested by the FST are ameliorated by treatment with antidepressant drugs.

In an additional pilot experiment, we tested the effects of imipramine on the behavior of SP sand rats in the FST. Animals were maintained under SP conditions, as described above, injected with 15 mg/kg imipramine or vehicle for 7 days and tested in the FST. The results of this pilot experiment show similar results to the effects of bupropion. Imipramine treatment lengthened the time to sink 1 from 31.8 ± 2.6 s in the vehicle group to 52.4 ± 4.4 s [$t(11) = 3.9$; $p = 0.003$], and the time to sink 2 from 43.7 ± 1.9 s in the vehicle group to 62.9 ± 13.9 s [$t(11) = 4.2$; $p = 0.002$]. These results support the generality and predictive validity of this model, and its use for testing the antidepressant potential of novel compounds.

The present study used two behavioral tests to evaluate the effects of bupropion, the FST and the sweet solution preference test. These tests were designed to evaluate two separate domains of depression; the FST measures depression-like reduction in the attempts to escape an aversive situation [36], whereas the sweet solution test measures anhedonia [30]. Considering the complex nature of affective disorders, it is always recommended to evaluate models in more than one test and to select tests for separate behavioral domains of the disease [3].

The results of the FST clearly replicate our previous findings demonstrating that SP conditions induce depression-like behavior in the test. Additionally, the present results demonstrate that bupropion significantly attenuates the effects of the SP. The pilot data using imipramine show similar effects. These data support the predictive validity of the sand rat model and of the utilization of the modified FST in that context. One limitation to the present FST results is that the present study did not include a test for activity levels, but our previous studies with sand rats demonstrated that photoperiod manipulations did not affect generalized activity levels [15], and that the interpretation of the FST data in the context of depression is therefore feasible. Yet, because of the possible effects of bupropion of increasing activity levels, this issue should be taken into consideration.

Interestingly, in the present study, manipulations of photoperiod or bupropion did not result in changes in sweet solution preference in the sand rats. These results are in some contrast with our previous data showing that SP conditions induce a reduction in sweet solution preference resembling the anhedonia domain of depression [16]. It is, however, possible that whereas this test is easily replicable in rats and mice, its utility in the sand rat is limited. Only one study showed that SP conditions reduce the preference of sweet solution in sand rats [16], while another study as well as the current results show no such effect [17]. It is possible that sand rats do not develop a strong preference for sweet solution because sugars are not part of their natural diet. Sand rats can develop nutritionally induced diabetes when exposed to sugars [37], and it is conceivable that sweet solution does not hold the same rewarding value for them as it does for mice and rats. To further explore the utilization of the sweet solu-

tion preference test in sand rats, we conducted a small concentration/response experiment with saccharin concentrations of 0.01, 0.1 and 1.0 g/l. The results of this small experiment suggest that sand rats do not develop a preference for saccharin solutions as the preference rates across days and concentrations were in the range of 0.40–0.54, indicating a random distribution of drinking patterns between the saccharin solution and water (data not shown). These results as well as the results of one previous study [17] and the results of the present experiment suggest that the sweet solution preference test may not be a good test for sand rats. Clearly, additional tests for other domains of depression-like behavior should be added to the model in the future. We have previously demonstrated that SP conditions also reduce aggression in the resident-intruder test, another depression-like behavior [16]. This test was not used in the current experiment but should also be evaluated for the effects of antidepressant drugs. As for the sweet solution preference test, the current data suggest that the sand rats have no preference for 'sweet'. We are now trying to identify other tastes that these species might have a preference for and that can serve to evaluate hedonic-like behaviors. In nature, the favorite diet of sand rats are the leaves of the *Atriplex* plant, and it is possible that these leaves can be used in the future as a replacement for sweet solution.

The identification of the most appropriate model animal to explore specific questions had repeatedly been mentioned as a critical component in the development of good models for disease [20, 35]. In that context, the use of nontraditional animals had already been demonstrated to be a resource for knowledge that cannot be obtained using standard laboratory species. For example, the studies on monogamous voles had a significant contribution to the understanding of the biology of social behavior and bond formation [38–40], with important implications for human behavior and human pathology [41]. Similarly, we suggest that diurnal rodents may be appropriate species to model the interactions between circadian rhythms, photoperiods, sleep and affective disorders in humans. Additional studies are now being designed and performed to gain further understanding about the underlying biology of the behavioral changes induced by photoperiod manipulations and antidepressant treatment in the sand rat.

It is also suggested that care should be taken to explore the utility of tests that were developed for standard laboratory species as appropriate tools to evaluate the behavior of nontraditional animals. For example, the sweet solution preference test has repeatedly been demonstrated to be an effective tool for testing reward seeking in mice and rats [28, 30, 42], but our results suggest that this test may not be a reliable measure in sand rats. Moreover, other tests should be modified to fit with the innate behaviors of the species, as done with the FST. Attention to test design for different species had been recognized even with laboratory animals and should be emphasized when working with nontraditional rodents.

The current study was therefore able to clearly demonstrate the interaction between SP and antidepressant treatment for only one test, the FST, and this may not be enough to strongly suggest the validity of the model. However, attempts are currently made to examine these interactions in other traditional tests related to affective and anxiety disorders in order to develop an appropriate test battery for these species. Additional attempts are made to start and examine the underlying biology of the effects of photoperiod manipulation on this diurnal rodent, especially in the context of systems previously implicated in depression.

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