This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier’s archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/copyright
A possible relationship between circadian rhythms and major affective disorders has been strongly implicated, including major depressive disorder (MDD), bipolar disorder (BDP) and seasonal affective disorder (SAD) (for a recent review see [1]). The understanding of the underlying biological basis of such relationship demands the utilization of appropriate animal models. Most research is performed with nocturnal rodents while some of the effects of daylight cycles or melatonin levels in nocturnal animals may differ greatly from effects in diurnal species (including humans). Recent studies suggested the diurnal fat Sand rat as an appropriate model animal to study circadian mechanisms involvement in mood and anxiety disorders, especially seasonal affective disorder (SAD). These studies demonstrated that Sand rats chronically exposed to short daylight (SD), or to melatonin regimen mimicking short daylight, show anxiety- and depression-like behaviors. These findings established face and construct validity for the model. The present study evaluated predictive validity by testing the effects of bright light treatment in Sand rats exposed to chronic SD.

Sand rats maintained on SD for 3 weeks were treated with 1 h daily 3000 lx light for 3 weeks, 1 h after “lights on” (during the light phase of the light-dark cycle), and their behavior tested in the sweet solution preference test (SSP), elevated plus-maze (EPM) and forced swim test (FST) and compared with control animals without treatment. Results indicate that bright light treatment reduced anxiety-like behavior in the EPM and depression-like behavior in the FST but not SSP. It is suggested that the results support the possibility that the diurnal Sand rat might be a preferred model animal for the study of SAD.

Most animal research was performed with nocturnal animals while modeling disorders in the diurnal humans. Some of the behavioral effects of altering daylight cycles or of melatonin levels in nocturnal animals may differ greatly from effects in diurnal species. For example, melatonin is secreted during the dark in both diurnal and nocturnal mammals, so nocturnal mammals are active when melatonin levels are high, while diurnal mammals are active when melatonin levels are low [6]. In nocturnal rodents a nighttime light pulse reduces activity levels, whereas light triggers activity in diurnal mammals [7]. It is therefore conceivable that using diurnal model animals may give us a much better understanding of the effects of circadian rhythms on mood in humans, and also possibly better ways to develop improved treatments for affective disorders [8–10].

Recent studies suggested the use of the diurnal fat Sand rat (Psammommys Obesus) as an appropriate model animal to study circadian mechanisms involvement in mood and anxiety disorders, especially SAD [8,9]. The rationale for that proposal was that SAD is clearly linked to patterns of circadian rhythms [11–14] and that the underlying physiology of circadian rhythms is significantly different between diurnal and nocturnal species [15,16]. A diurnal mammal could therefore be a better model species, an animal that is susceptible to the same variables as humans [17] for SAD compared to nocturnal rodents [8–10].
Indeed, studies demonstrated that Sand rats exposed to 3 weeks or more of short daylight (5 h light; 19 h dark), show anxiety- and depression-like behaviors [8, 9]. Moreover, administration of melatonin to Sand rats in a regimen that mimics short daylight resulted in a similar anxiety- and depression-like phenotype [8].

The establishment of a possible animal model for a disease demands support from three axes of validity: (1) face validity—similarities between the behavioral phenotype of the model and the behavior observed in the disorder; (2) construct validity—possible shared underlying mechanisms and (3) predictive validity—that the model will be affected by the treatments that are known to be effective in the disorder [18–21]. Whereas the previous studies suggested face and construct validity for the possibility of using Sand rats as a model animal for SAD, there were no indications yet for predictive validity. The most effective treatment for SAD is bright light therapy [11, 22–26]. The present study was therefore designed to explore the effects of bright light treatment on Sand rats maintained in short daylight conditions.

Considering the relative hardship in obtaining enough Sand rats for studies, especially at a similar age range and sex, and in light of the repeated demonstration that under short daylight, Sand rats develop depression- and anxiety-like behaviors, the present study did not include long daylight control groups.

Adult male (n = 20, 6 months old) Sand rats (Harlan, Jerusalem Israel) were divided into two groups (n = 10/group) and were individually housed in standard plastic cages (21 cm × 31 cm × 13 cm) and in separate temperature-controlled rooms (25°C) under a 5 h light/19 h dark cycle. This lighting regime was set based on previous results [9], and according to activity patterns in nature, where during winter Sand rats are active for about 5 h daily [27, 28]. Animals were provided ad lib with special low-energy pellets (product 19560, Koploch, Israel); Atriplex branches and water, and remained under these conditions for 3 weeks prior to onset of experiments. This time period is sufficient for physiological acclimation [29], and synchronization of circadian rhythms [30]. All experimental procedures were approved by the Tel-Aviv University IACUC (protocol # L07-077) and were conducted in accordance with NIH guidelines for the treatment and care of laboratory animals.

After the 3-week acclimation of the two groups to short daylight, one group (n = 10) was treated with bright light, full spectrum, 10000 lx (Sunbox company, USA, Sunlight Jr 220v). Due to the light location in the room each Sand rat was exposed to 3000 lx. The bright light treatment started 1 h after the onset of the light phase and continued for 1 h daily, for 3 weeks. The length and amplitude of light treatment were found sufficient in treating SAD in humans [1]. Following 3 weeks of treatment all animals underwent behavioral tests as detailed below while continuing the light treatment.

To minimize the effects of behavioral experience on results, experiments were conducted from the least to the most intrusive. The order of experiments for the two groups of Sand rats was, accordingly: (1) Sweet solution preference (SSP); (2) Elevated plus maze (EPM); (3) Forced swim test (FST).

SSP was used to assess reward-seeking (hedonic) responses [31–33]. For 4 days, animals were provided with a bottle containing 1% saccharin solution in addition to their regular food and water. The saccharin solution bottles were weighed daily 5 h after room light onset, and daily consumption (ml) was calculated and normalized for body weight.

The EPM was used to test anxiety-like behavior. It was constructed from black painted aluminum, with two open arms (50 cm × 10 cm) and two enclosed arms (50 cm × 10 cm × 15 cm), elevated 50 cm above the ground and illuminated (200 lx at the maze floor level). Approximately 1 h after light treatment, Sand rats were individually placed at the center of the maze and allowed to explore freely for 5 min. Behavior was videotaped from above the center of the maze and tapes were scored by a blind observer for time spent in each section of the maze and number of entries. Time spent in the arms and number of entries were used to compute time and entries ratio (open/closed) that were used for analysis.

The FST is commonly used to evaluate antidepressant effects in rats and mice [34]. With some modifications it was successfully used in Sand rats [8, 9]. Animals were tested over two consecutive days, similar to the standard procedures for rats [35]. Testing started approximately 1 h after light treatment and conducted within the light phase.

Animals were placed in an opaque plastic cylinder, 30 cm in diameter and 45 cm high filled with water (21–23°C) to a depth of 25 cm, preventing the Sand rats from touching the floor or escaping. Behavior was videotaped from above and tapes were used for scoring. Sand rats are not as good swimmers as rats and mice and, accordingly, the testing procedure was modified to eliminate the possibility of drowning [8, 9]. In brief, when an animal became entirely immersed in water (above the tip of the snout) for 5 s it was rescued by the experimenter and test was terminated. Accordingly, the behavioral measures were the first and second times that an animal was completely immersed in water (sink 1 and sink 2) and the time to reach rescue criteria [8, 9].

Repeated measures ANOVA was used to analyze weight (across weeks), SSP (across days of test) and sinking in the FST. Students’ t-test was used to analyze time ratio and entries ratio in the EPM and time to reach rescue criteria in the FST. Statistical significance was set at p < 0.05 (two tailed).

Light treatment did not affect weight changes across treatments and did not affect SSP (Table 1). However, light treatment had an anxiolytic-like effect in the EPM and animals treated with bright light spent more time in the open arms of the maze compared with untreated subjects [Fig. 1 open/closed time ratio: t(17) = 2.24, p = 0.038]. Moreover, in the FST, bright light treatment significantly delayed the appearance of sinking behavior [Fig. 2; ANOVA across sink 1 and 2; Treatment effect: F(1,17) = 7.49, p = 0.014; Time effect: F(1,17) = 14.03, p = 0.002; Interaction effect: F(1,17) = 0.8, p = 0.38], post hoc comparison for first sink: t(17) = 2.44, p = 0.03; for second sink: t(17) = 2.74, p = 0.015, and had a similar trend to delay reaching rescue criteria (data not shown).

Sand rats maintained in short daylight conditions develop depression- and anxiety-like behaviors [8, 9]. The present results show that these behaviors can be reversed with bright light treatment [22] and therefore support the use of the diurnal Sand rat as a model animal for SAD.

The present study used two measures for the evaluation of depression-like or antidepressant-like effects, the SSP test and the FST. These measures were previously demonstrated to be sensitive...
to short daylight in the Sand rat with stronger evidence for the effects in the modified FST [8,9]. The present study clearly shows that bright light treatment had an antidepressant-like effect in the FST but did not find a similar effect in the SSP measure. Sweet solution preference representing hedonia/anhedonia had been strongly validated in rats and mice [32,33,36,37] but not for the Sand rat. Specifically, only one study indicated that short daylight reduces SSP in the Sand rat [8] but it is not clear at this time if Sand rats indeed prefer sweet taste. Interestingly, Sand rats quickly develop diabetes when exposed to sucrose [38,39] and it is possible that the sweet stimulus does not have the same rewarding value in Sand rats as compared to rats and mice. Moreover, only one saccharin concentration was used in this study, one that was previously effective [8], but it is possible that a different concentration might be more appropriate to explore antidepressant effects of treatment as even with different strains of mice and rats, sweet solution concentration is critical for distinguishing the effects of treatment (e.g. [33]). Unfortunately, the limited availability of animals did not allow for a concentration response curve experiment.

Yet, the effects of bright light treatment in the FST were clear. This test in the Sand rats is significantly modified compared with the tests in mice or in rats which are different from each other [34]. The reasons for the modifications and the specific method are explained in detail elsewhere [8,9] but the core of the difference is that because Sand rats do not float unlike other mammals, it is suggested that a diurnal animal may be the more appropriate choice for SAD and possibly also as a model for additional affective disorders, especially their domains or endophenotypes that are strongly related with circadian clocks.

The EPM, was used to evaluate anxiety-like behavior [40] as this measure was demonstrated to be sensitive to light and melatonin manipulations in the Sand rat [8]. The results demonstrate that bright-light treatment has an anxiolytic-like effect in this test and the animals that were exposed to treatment show significantly higher open/closed time ratio.

Even though light therapy has been used for decades for treating SAD, and its effectiveness has been widely demonstrated, its therapeutic mechanism is still unknown. The first published paper which used light treatment for SAD was based on the assumption that SAD is a consequence of exposure to short photoperiod, and therefore exposure to artificial light in the morning and in the evening could lengthen the photoperiod [41]. However, later studies suggested that light treatment in the middle of the day was effective [23] and that combined morning and evening exposures had an additional benefit over morning’s only treatment [42]. The effect of light on SAD may be mediated by melatonin. However, the effect of melatonin may be indirect and light may act by phase shifting or synchronizing the internal clock, or short photoperiod deprives susceptible patients of sufficient quanta of light essential for maintaining a euthymic state (reviewed by [43]). Since animal models for SAD are very limited, research aimed at exploring the therapeutic mechanism of light was mainly conducted in humans, and therefore limited in its abilities to explore related brain mechanisms. Here we present an appropriate animal model for SAD, which demonstrates face [8,9] construct [8] and predictive validity (this paper), and therefore may help to explore the underlying pathophysiology and the mode of action of treatment in SAD.

Appropriate animal models are essential to explore the biological basis of disease and to develop new treatments [44,45]. It was repeatedly suggested that the most appropriate models are the ones which are based on the baseline behavior of a unique species or strain rather than on a manipulation that temporarily alters the behavior to the pathological-like phenotype (e.g. [10,17]). In a way, this approach was also the basis for the attempts to screen different mice strains for a variety of phenotypes (e.g. [46–49]) or to develop genetic models demonstrating pathological-like behaviors (e.g. [44,47,50]). Because of the vast differences in the physiological and behavioral responses to daylight between diurnal and nocturnal mammals, it is suggested that a diurnal animal may be the more appropriate choice as a model for human disorders related to circadian rhythms. The present study in combination with previous ones supports the possibility of using the Sand Rat as a new model animal for SAD and possibly also as a model for additional affective and anxiety disorders, especially their domains or endophenotypes that are strongly related with circadian clocks.

Acknowledgement

Study was supported by the National Institute for Psychobiology in Israel, founded by the Charles E. Smith Family (to NKS) and a University of Minnesota Graduate school Grant in Aid of Research (to HE).

References


