Utilization of Diurnal Rodents in the Research of Depression

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ABSTRACT
Most neuropsychiatric research, including that related to the circadian system, is performed using nocturnal animals, mainly laboratory mice and rats. Mood disorders are known to be associated with circadian rhythm abnormalities, but the mechanisms by which circadian rhythm disruptions interact with depression remain unclear. As the circadian system of diurnal and nocturnal mammals differs, we previously suggested that the utilization of diurnal animal models may be advantageous for understanding these relations. During the last 10 years, we and others established the validity of several diurnal rodent species as a model for the interactions between circadian rhythms and depression. Diurnal rodents respond to photoperiod manipulation in a similar way to humans, the behavioral outcome is directly related to the circadian system, and treatment that is effective in patients is also effective in the model. Moreover, less effective treatments in patients are also less effective in the model. We, therefore, suggest that using diurnal animal models to study circadian rhythms-related affective disorders, such as depression, will provide new insights that will hopefully lead to the development of more effective treatments. Drug Dev Res 77: 347–356, 2016.

Key words: diurnal animal models; affective disorders; sand rats; depression; seasonal affective disorder; circadian rhythms

INTRODUCTION
Considering that humans are diurnal, and that the circadian systems of nocturnal and diurnal mammals differ significantly [Smale et al., 2003; Challet, 2007; Cuesta et al., 2009; Shuboni et al., 2012; Bilu and Kronfeld-Schor, 2013], it is surprising that most neuropsychiatric research, including that related to the circadian system, is performed using mainly nocturnal animals—laboratory mice and rats. We have previously hypothesized that using diurnal rodent models may be advantageous compared with nocturnal rodents in research that aims to understand the underlying mechanisms of the interactions between circadian rhythms and depression. Here, we review studies supporting this hypothesis.

MOOD DISORDERS AND THE CIRCADIAN SYSTEM
It is widely accepted that mood disorders are associated with circadian rhythm abnormalities. Nearly all patients suffering from affective disorders including major depressive disorder, bipolar disorder and seasonal affective disorder (SAD) show significant disruptions
in circadian rhythms including rhythms of activity, sleep, body temperature, blood pressure, hormone secretion, immunity, and monoamines [Born et al., 1997; Bunney and Bunney, 2000; McClung, 2007; Belmaker and Agam, 2008; Kronfeld-Schor and Einat, 2012; McClung, 2013]. Several clinical studies show direct correlations between the severity of rhythm disruptions and the severity of depressive symptoms, and stabilization and restoration of rhythms with antidepressant treatment [Wirz-Justice, 2006; McClung, 2007; Bunney and Bunney, 2015]. Additionally, human genetic association studies implicate clock genes in mood disorders [Benedetti et al., 2003; Johansson et al., 2003; Partonen et al., 2007] and a disruption of the circadian pattern of gene expression in several brain areas is demonstrated in major depressive disorder [Li et al., 2013]. Animal studies also demonstrate affective-like behavioral changes related to targeted mutations in clock genes [Bunney and Bunney, 2000; Roybal et al., 2007; Le-Niculescu et al., 2008]. In spite of all these findings, the mechanisms by which circadian rhythm disruptions interact with depression remain unclear [McClung, 2013]. Here, we suggest that understanding the differences between the circadian system of nocturnal and diurnal mammals, and the utilization of diurnal animal models, may be crucial for our understanding of the biology of affective disorders and for the development of new and more effective treatments.

**DIURNAL AND NOCTURNAL MAMMALS CIRCADIAN SYSTEM**

The earliest mammals were nocturnal insectivores [Crompton, 1980; Gerkema et al., 2013]. Although most current mammals are still nocturnal, independent evolutionary transitions to a diurnal activity pattern have occurred within both closely and distantly related taxa [Kondo et al., 2006]. In spite of the extraordinary advancement in our understanding of the circadian clock mechanism, it is still unclear how the temporal signals from the central circadian clock, which in mammals resides in the suprachiasmatic nucleus (SCN), translate into activity patterns, and how they differ in diurnal and nocturnal mammals. Nevertheless, it is clear that some fundamental differences exist between nocturnal and diurnal mammals (Fig. 1).

Considerable evidence suggests that the central oscillator of the SCN is coupled with the light:dark (LD) cycle in diurnal and nocturnal mammals in a very similar way [Smale et al., 2003; Cohen and Kronfeld-Schor, 2006; Hagenauer and Lee, 2008; Barak and Kronfeld-Schor, 2013]. This is also the case for rhythms of production of the molecular and neural outputs of the SCN [Gaillard et al., 2008; LeGates et al., 2014]. Hence, it is reasonable to assume that the differences between nocturnal and diurnal mammals emerge from multiple processes operating primarily, perhaps even exclusively, downstream of the SCN, translating the information emanating from the SCN in an opposite way [Smale et al., 2003; Gaillard et al., 2008; Cohen et al., 2010a; Gall et al., 2016]. For example, direct SCN axonal outputs are relatively restricted and similar in nocturnal and diurnal species [reviewed by Gaillard et al., 2008]. The major target of the SCN is the subparaventricular zone (SPVZ) [Rose et al., 1999; Deurveilher and Sembra, 2005; Schwartz et al., 2011], and excitotoxic lesions of ventral and dorsal portions of this area reduce or eliminate circadian rhythms of sleep, locomotor activity, and body temperature in nocturnal lab rats [Lu et al., 2001]. In diurnal Nile grass rats (*Arvicanthis niloticus*), c-Fos rises in the ventral portion of the SPVZ (vSPVZ) 4–5 hours after the end of the active period while in laboratory rats it is highest in the beginning of the light phase when activity declines [Schwartz et al., 2004]. vSPVZ lesions in diurnal Nile grass rats increase the ratio of nighttime to daytime activity [Martinez et al., 2009]. Taken together, these data have led to the suggestion that the vSPVZ is one of the areas translating the information emanating from the SCN in an opposite way, plays an important role in the regulation of circadian rhythms, and may contribute to diurnality in Nile grass rats [Novak et al., 1999; Schwartz et al., 2004; Gaillard et al., 2008; Gall et al., 2016].

Another output of the circadian clock is the hormone melatonin, which is secreted by the pineal gland, and is elevated at night in both nocturnal and diurnal species. Melatonin release time is dictated by the SCN, which stimulates melatonin secretion at night [Moore-Ede Sulzman and Fuller, 1982]. Hence, in both nocturnal and diurnal species melatonin signals night. Moreover, the secretion of melatonin is acutely suppressed by light in both nocturnal and diurnal species, so the duration of melatonin secretion bears information regarding changes in day lengths across the seasons in a similar way in nocturnal and diurnal animals. This information allows animals to anticipate and prepare for seasonal changes in the environment. [e.g., Bartness et al., 1993; Foster and Kreitzman, 2009; Follett, 2015].

Since melatonin is secreted during the night in both diurnal and nocturnal mammals, diurnal species are active when melatonin levels are low, while nocturnal mammals are active when melatonin levels are high. Hence, although melatonin confers the same
information in diurnal and nocturnal mammals (i.e., night phase), they should respond to the same information in ways that promote the opposite patterns of behavior and physiology that they display.

Several types of evidence support this notion. For example, melatonin treatment lowers body temperature in diurnal mammals and elevates it in nocturnal ones (Humans [Cagnacci et al., 1992], rats [Roseboom et al., 1996], golden spiny mice (Acomys russatus) [Zisapel et al., 1998] Degu (Octodon degus) [Vivanco et al., 2007]. Melatonin promotes sleep in diurnal mammals [Dollins et al., 1994; Arendt, 2000; Zhdanova et al., 2002], while in nocturnal mammals it increases activity levels, sleep latency, waking, and sleep fragmentation [Mendelson et al., 1980; Hastings et al., 1992; Huber et al., 1998; Mendelson, 2002]. Melatonin also increases anxiety-like behavior in diurnal rodents and decreases it in nocturnal rodents [Bilu and Kronfeld-Schor, 2013]. Moreover, intake of tryptophan (the precursor of the synthesis of melatonin and serotonin) causes a short term increase in activity in the nocturnal rat, while decreasing it in the diurnal dove [Aparicio et al., 2006]. In a recent study we found a daily rhythm in anxiety-like behavior in three

Fig. 1. A schematic comparison between nocturnal and diurnal rodents’ circadian system. Black line represents levels of each parameter. Bars represent light (yellow/gray) and dark (black) hours. Syringe – time of melatonin injection (modified from Bilu and Kronfeld-Schor, 2013), light bulb – time of light pulse, crossed light bulb – time of dark pulse (modified from Cohen et al., 2010a, 2010b Kronfeld-Schor and Barak, 2012). Detailed explanation and citations in the text. [Color figure can be viewed at wileyonlinelibrary.com]
nocturnal rodent species; common spiny mouse (Acomys cahirinus), Tristram’s jird (Meriones tristrami) and laboratory rat, which showed significantly lower levels of anxiety during the dark phase. The three diurnal species used in the study; golden spiny mouse (A. russatus), fat sand rat (Psammomys obesus) and degu (O. degus) showed either an inverse pattern to that of the nocturnal species, or no rhythm at all [Bilu and Kronfeld-Schor, 2013]. Studying the role of melatonin in these rhythms, we found a significant response to daytime melatonin administration in the three nocturnal species studied, which showed significantly lower levels of anxiety during the night and after daytime melatonin administration. One diurnal species (Degu) which showed an inverse pattern to that of the nocturnal species in anxiety-like behaviour rhythm, also had an inverse response to daytime melatonin injection (which increased anxiety-like behaviour), while the two species which showed no rhythm in anxiety-like behaviour (golden spiny mice and fat sand rats) did not respond to melatonin administration [Bilu and Kronfeld-Schor, 2013]. These results further support the hypothesis that although melatonin confers the same information in diurnal and nocturnal mammals (i.e., night phase), they respond to the same information in ways that promote the opposite patterns of behavior and physiology that they display.

Daily rhythms are heavily influenced by light in two major ways. One is through photic entrainment of the SCN and the other is through direct masking, in which light and dark can directly increase or decrease activity [Aschoff, 1960; Aschoff and Vongoetz, 1988; Redlin et al., 2005]. Whereas entraining effects of photic stimuli are similar in nocturnal and diurnal species [Lee and Labyak, 1997; Kas and Edgar, 2000; Cohen and Kronfeld-Schor, 2006; Challet, 2007; Cohen et al., 2009], masking is very different. Specifically, darkness increases activity in nocturnal mammals and is expected to suppresses it in diurnal ones, while light suppresses activity in nocturnal mammals and is expected to increase activity levels in diurnal ones [Aschoff, 1960; Mrosovsky and Hattar, 2003; Redlin and Mrosovsky, 2004; Mrosovsky et al., 2005; Hagenauer and Lee, 2008]. Studying diurnal species, we and others found that in contrast to nocturnal species, they show high diversity in their masking response to light and darkness: some respond as expected from nocturnal species, some as expected from diurnal species, some do not respond at all and some change their response depending on the environmental conditions [Aschoff and Vongoetz, 1988; Redlin and Mrosovsky, 2004; Cohen et al., 2010b; Barak and Kronfeld-Schor, 2013; Langel et al., 2014].

From all of the above, it is clear that the circadian system of nocturnal and diurnal mammals greatly differs. Based on these differences, we suggested that using diurnal model animal may be advantageous for understanding the involvement of circadian rhythms in affective disorders.

**DIURNAL RODENTS AS MODEL ANIMALS IN RESEARCH RELATED TO THE INTERACTIONS BETWEEN CIRCADIAN RHYTHMS AND DEPRESSION**

In the last decade, work in our laboratory and work by other researchers explored the possibility of utilizing diurnal rodents as model animals for research of the interactions between circadian rhythms and depression. The first step to evaluate this approach was to explore the validity of a diurnal rodent model in the context of SAD. Modeling SAD was selected because (1) of all affective disorders, SAD is clearly the one that is most directly influenced by photoperiod changes, and therefore has the clearest relationship with circadian rhythms, and (2) there are no specific rodent models that can be used for research on SAD or the effects of bright light exposure—the most frequently used treatment of SAD [Workman and Nelson, 2011]. We developed a series of experiments that included photoperiod length manipulations that are relevant to the disorder. Specifically, maintaining animals under short photoperiod conditions (SP; 5 hours light/14 hours dark) or neutral photoperiod conditions (NP; 12 hours light/12 hours dark) for 3 weeks, a time frame that allows for physiological adaptation [Kronfeld-Schor et al., 2000] and for synchronization of circadian rhythms [Barak and Kronfeld-Schor, 2013]. We hypothesized that diurnal rodents maintained under SP will develop a behavioral phenotype that resembles depression, while nocturnal rodents will not. Indeed, our as well as other labs’ studies on several species of diurnal rodents, clearly show that acclimatization of diurnal rodent species to SP conditions results in the appearance of a depression- and anxiety-like phenotype. These species include the fat sand rat (P. obesus) [Einat et al., 2006; Ashkenazy et al., 2009a], Nile grass rat (A. niloticus) [Ashkenazy-Frolinger et al., 2009; Leach et al., 2013], degu (O. degus) [Ashkenazy-Frolinger et al., 2015] golden spiny mouse (A. russatus) [Ben-Hamo et al., 2016], and the Mongolian gerbil (Meriones unguiculatus) [Juárez-Tapia et al., 2015] (Table 1). This phenotype includes reduced activity in the forced swim test, reduced preference for sweet solution, reduced aggression and social interactions, as well as...
<table>
<thead>
<tr>
<th>Species</th>
<th>Test &amp; measures</th>
<th>NP</th>
<th>SP</th>
<th>Statistics</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sand rats</td>
<td>Open field, spontaneous activity, distance (cm)</td>
<td>55.7 ± 4.3</td>
<td>56.1 ± 4.7</td>
<td>( t(14) = 0.05, ) N.S.</td>
<td>[Ashkenazy et al., 2009a; Einat et al., 2006]</td>
</tr>
<tr>
<td></td>
<td>FST, time to sink 1 &amp; 2 (sec)</td>
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<td></td>
<td>Sink 1 - 64.5 ± 7.2</td>
<td>64.5 ± 7.2</td>
<td>63.9 ± 7.2</td>
<td></td>
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<tr>
<td></td>
<td>Sink 2 - 75.6 ± 6.9</td>
<td>75.6 ± 6.9</td>
<td>74.9 ± 6.9</td>
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<tr>
<td></td>
<td>EPM, open/closed time ratio</td>
<td>0.9 ± 0.1</td>
<td>0.45 ± 0.1</td>
<td>( t(16) = 2.36, ) ( p = 0.03 )</td>
<td></td>
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<tr>
<td></td>
<td>Resident-intruder aggression, # of attacks</td>
<td>19.0 ± 2.4</td>
<td>2.4 ± 2.7</td>
<td>( t(16) = 4.17, ) ( p &lt; 0.001 )</td>
<td></td>
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<tr>
<td>Nile grass rats</td>
<td>Spontaneous activity, counts</td>
<td>430 ± 155</td>
<td>687 ± 137</td>
<td>( t(16) = 1.24, ) N.S.</td>
<td>[Ashkenazy-Frolinger et al., 2009]</td>
</tr>
<tr>
<td></td>
<td>FST, immobility time (sec)</td>
<td>48.4 ± 4.8</td>
<td>85.3 ± 9.5</td>
<td>( t(16) = 3.21, ) ( p = 0.003 )</td>
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<td></td>
<td>Sweet solution preference, saccharin/total liquid</td>
<td>Day 1 - 0.45 ± 0.09</td>
<td>Day 1 - 0.24 ± 0.08</td>
<td>ANOVA, photoperiod effect: ( F(1,15) = 3.3, ) ( p = 0.045 )</td>
<td></td>
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<tr>
<td>Grass Golden</td>
<td>FST, immobility time (sec)</td>
<td>Data not available</td>
<td>Data not available</td>
<td>( t\text{-test}, ) ( p &lt; 0.05 )</td>
<td>[Leach et al., 2013]</td>
</tr>
<tr>
<td>spiny mice</td>
<td>Open field, spontaneous activity, distance (cm)</td>
<td>11333 ± 863</td>
<td>12650 ± 1853</td>
<td>( t(12) = 0.70, ) ( p = 0.5 )</td>
<td>[Ben-Hamo et al., 2016]</td>
</tr>
<tr>
<td></td>
<td>EPM, open/closed time ratio</td>
<td>0.23 ± 0.05</td>
<td>0.1 ± 0.03</td>
<td>( t(26) = 2.4, ) ( p = 0.024 )</td>
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<tr>
<td></td>
<td>Sweet solution preference, saccharin/total liquid</td>
<td>0.6 ± 0.03</td>
<td>0.47 ± 0.05</td>
<td>ANOVA, Photoperiod effect: ( F(1,66) = 5.11, ) ( p = 0.03 )</td>
<td></td>
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<tr>
<td></td>
<td>FST, time to sink 1 &amp; 2 (sec)</td>
<td>191 ± 28</td>
<td>73 ± 13</td>
<td>ANOVA, Photoperiod effect: ( F(1,25) = 11.6, ) ( p = 0.002 )</td>
<td></td>
</tr>
<tr>
<td>Mongolian gerbil</td>
<td>EPM, open/closed time ratio</td>
<td>Data not available</td>
<td>Data not available</td>
<td>( p &lt; 0.05 )</td>
<td>[Juárez-Tapia et al., 2015]</td>
</tr>
<tr>
<td></td>
<td>FST, immobility time (sec)</td>
<td>Data not available</td>
<td>Data not available</td>
<td>( p &lt; 0.05 )</td>
<td></td>
</tr>
<tr>
<td>Degu</td>
<td>Sweet solution preference, saccharin/total liquid</td>
<td>Data not available</td>
<td>Data not available</td>
<td>( t(12) = 2.29, ) ( p = 0.04 )</td>
<td>[Ashkenazy-Frolinger et al., 2015]</td>
</tr>
<tr>
<td></td>
<td>FST, time in center of arena (cm)</td>
<td>137.3 ± 21.6</td>
<td>75.0 ± 9.6</td>
<td>( t(12) = 2.35, ) ( p = 0.037 )</td>
<td></td>
</tr>
</tbody>
</table>

NP – Neutral photoperiods (12 hours light/12 hours dark); SP – Short photoperiods (5 hours light/19 hours dark). All tests were conducted during the light phase.
increased anxiety-like behavior in tests such as the elevated plus-maze and the open field (Table 1). Further support for the advantage of using diurnal model animals for the study of depression comes from some work in diurnal rhesus macaque, which reported that exposure to a similar photoperiod manipulation results in SAD symptoms [Qin et al., 2015]. Moreover, as we hypothesized, acclimatization of several nocturnal mice strains to SP conditions did not have any consistent effects and no clear behavioral phenotype (Table 2) [Flaisher-Grinberg et al., 2011], as was the case when they were maintained under a reversed photoperiod with 19 hours light/5 hours dark (Table 2) [Flaisher-Grinberg et al., 2011], demonstrating again that nocturnal rodents are not just a mirror image of diurnal rodents.

After demonstrating that diurnal rodents respond to SP in a way that is homologous to human SAD, work was planned in order to verify that these changes are indeed related to circadian mechanisms. To this end we tested the effects of melatonin administration in a schedule that mimics SP on the behavior of the fat sand rat [Ashkenazy et al., 2009a]. Melatonin at a dose of 100 µg was administered for 3 weeks, 5 hours, and 8.5 hours after light onset. The study was designed as a 2 × 2 experiment with photoperiod length (SP or NP as above) and melatonin administration as main factors. As expected, the sand rats that received melatonin in a way that mimics SP developed a depression- and anxiety-like behavioral phenotype as under SP conditions (Table 3) [Ashkenazy et al., 2009a]. These results strongly support our notion that in diurnal animals, the depression- and anxiety-like phenotype that develops during short photoperiod conditions is directly related to mechanisms of circadian rhythms.

To further examine the relationship between the behavioral changes and depression, the next step was to evaluate predictive validity of the model. Predictive (treatment) validity was first evaluated with bupropion, an antidepressant considered to be effective in the treatment of SAD in humans [Westrin and Einat, 2012; LeGates et al., 2014]. Whereas the efficacy of bright light treatment was repeatedly subjected to numerous studies [Prasko, 2008; Kronfeld-Schor and Einat, 2012; Le-Gates et al., 2014].

### TABLE 2. Behavioral Effects of Short or Long Photoperiods in Mice

<table>
<thead>
<tr>
<th>Behavioral test</th>
<th>Tested in light phase</th>
<th>Tested in dark phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous locomotor activity</td>
<td>SP: 3498 ± 463; NP: 3169 ± 477; LP: 4584 ± 342</td>
<td>SP: 4463 ± 601; NP: 4599 ± 603; LP: 4962 ± 544</td>
</tr>
<tr>
<td>(counts in 60 min session)</td>
<td>LP increased spontaneous activity, SP had no effect: LP ≠ NP (p = 0.025), SP Vs. NP (p = 0.59)</td>
<td>No effect: LP Vs. NP (p = 0.67), SP Vs. NP (p = 0.87)</td>
</tr>
<tr>
<td>Sweet solution preference</td>
<td>SP: 0.77 ± 0.02; NP: 0.68 ± 0.02; LP: 0.59 ± 0.04</td>
<td>SP: 0.497 ± 0.05; NP: 0.533 ± 0.03; LP: 0.463 ± 0.05</td>
</tr>
<tr>
<td>(preference – mean across 2 days)</td>
<td>LP decreased and SP increased sweet solution preference; LP ≠ NP (p = 0.02), SP ≠ NP (p = 0.03)</td>
<td>No effect: LP Vs. NP (p = 0.25), SP Vs. NP (p = 0.54)</td>
</tr>
<tr>
<td>Elevated plus-maze</td>
<td>SP: 0.13 ± 0.02; NP: 0.07 ± 0.02; LP: 0.18 ± 0.03</td>
<td>SP: 0.23 ± 0.05; NP: 0.33 ± 0.04; LP: 0.34 ± 0.04</td>
</tr>
<tr>
<td>(open/closed time ratio)</td>
<td>LP (significantly) and SP (trend) increased open/closed time ratio: LP ≠ NP (p = 0.002), SP ≠ NP (p = 0.08)</td>
<td>No effects: LP Vs. NP (p = 0.81), SP Vs. NP (p = 0.12)</td>
</tr>
<tr>
<td>Resident-intruder test</td>
<td>SP: 0.42 ± 0.09; NP: 0.38 ± 0.09; LP: 0.43 ± 0.1</td>
<td>SP: 0.38 ± 0.1; NP: 0.47 ± 0.1; LP: 0.48 ± 0.1</td>
</tr>
<tr>
<td>(aggression time ratio)</td>
<td>No effects: LP Vs. NP (p = 0.71), SP Vs. NP (p = 0.77)</td>
<td>No effect: LP Vs. NP (p = 0.97), SP Vs. NP (p = 0.53)</td>
</tr>
<tr>
<td>Forced swim test</td>
<td>SP: 196 ± 11; NP: 217 ± 12; LP: 209 ± 12</td>
<td>SP: 34 ± 11; NP: 31 ± 11; LP: 30 ± 6</td>
</tr>
<tr>
<td>(immobility time in 5 min session - sec)</td>
<td>No effects: LP Vs. NP (p = 0.64), SP Vs. NP (p = 0.2)</td>
<td>No effect: LP Vs. NP (p = 0.98), SP Vs. NP (p = 0.83)</td>
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</tbody>
</table>

NP – Neutral photoperiods (12 hours light/12 hours dark); SP – Short photoperiods (5 hours light/19 hours dark); LP – Long photoperiods (19 hours light/5 hours dark). For details, see [Flaisher-Grinberg et al., 2011].
established in SAD patients [Rosenthal et al., 1984] and to some extent in major depression patients [Kripke et al., 1992; Kripke, 1998; Lieverse et al., 2011], there was no model that responds to light treatment, and this lack of a suitable animal model hinders the research on the specific mechanisms of the therapeutic effect of bright light exposure. To explore the possibility that the diurnal rodent model are responsive to bright light exposure, two complementary experiments were conducted, evaluating the effects of either morning or evening bright light administration on the depression- and anxiety-like behaviors induced by SP conditions in fat sand rats. Because in SAD patients morning bright light is considered more effective than evening bright light [Avery et al., 1991; Lewy et al., 1998], we expected to find the same in the sand rats. The results support our hypothesis and show that 3 weeks of morning bright light treatment ameliorated the behavioral effects of SP (Table 4) [Ashkenazy et al., 2009b; Krivisky et al., 2012] and that morning exposure to bright light has a significantly stronger effect than

<table>
<thead>
<tr>
<th>Test &amp; measure</th>
<th>NP-V</th>
<th>NP-M</th>
<th>SP-V</th>
<th>SP-M</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPM, open/closed time ratio</td>
<td>0.9 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.45 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>ANOVA, photoperiod effect: F(1, 52) = 2.8, n.s.; melatonin effect: F(1, 52) = 4.82, p = 0.035; photoperiod X melatonin interaction: F(2, 51) = 6.94, p = 0.013; post hoc: NP-V different than SP-V and NP-M with a strong tendency for difference from SP-M (p = 0.07)</td>
</tr>
<tr>
<td>FST, Time to sink 1 &amp; 2</td>
<td>Sink 1 – 135 ± 11</td>
<td>Sink 2 – 83 ± 12</td>
<td>Sink 1 – 47 ± 11</td>
<td>Sink 2 – 80 ± 14</td>
<td>Repeated Measures ANOVA, photoperiod effect: F(1,2) = 4.33, p = 0.046; melatonin effect: F(1, 52) = 3.18 (n.s.); photoperiod X melatonin interaction: F(1, 52) = 7.34, p = 0.011; post hoc: NP-V different from all other groups.</td>
</tr>
<tr>
<td>Resident-intruder aggression, # of attacks</td>
<td>12 ± 2.4</td>
<td>6 ± 2.4</td>
<td>2.4 ± 2.7</td>
<td>6.1 ± 2.5</td>
<td>ANOVA, photoperiod effect: F(1, 52) = 10.37, p = 0.003; melatonin effect: F(1, 52) = 3.76, n.s.; photoperiod X melatonin interaction: F(2, 51) = 11.72, p = 0.002; post hoc: NP-V group different from all other groups.</td>
</tr>
</tbody>
</table>

NP-V – Neutral photoperiods (12 hours light/12 hours dark) injected with vehicle; NP-M – Neutral photoperiods injected with melatonin; SP-V – Short photoperiods (5 hours light/19 hours dark) injected with vehicle; SP-M – Short photoperiods injected with melatonin. For details, see [Ashkenazy et al., 2009a].

**TABLE 4. Effects of Treatment on Short Photoperiod-Induced Behavior in Fat Sand Rats**

<table>
<thead>
<tr>
<th>Treatment/test</th>
<th>Forced swim test</th>
<th>Elevated plus-maze</th>
<th>Social interaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning bright light</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>[Ashkenazy et al., 2009a; Krivisky et al., 2012]</td>
</tr>
<tr>
<td>Evening bright light</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>[Krivisky et al., 2012]</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>[Krivisky et al., 2011]</td>
</tr>
<tr>
<td>Exercise</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>[Tal-Krivisky et al., 2015]</td>
</tr>
</tbody>
</table>

+ indicates an antidepressant-like effect, – indicates no effect, +/- indicates a borderline (trend) effect, N/A indicates not available (not tested).
evening exposure to bright light (Table 4) [Krivisky et al., 2012]. Although a direct comparison between the bright light experiments and the bupropion experiment is impossible (different experiments) we suggest that as in humans, bright light exposure is at least as effective as antidepressants in the model.

All the studies described above focused on SAD-related phenomena, but SAD was only a “test-case” for a broader concept. We chose to explore SAD-related pathology and treatment because of the clear connection of SAD to photoperiod, and because there were no rodent models for the disorder [Workman and Nelson, 2011]. We suggest that deciphering the mechanisms underlying SAD and its treatment will improve our understanding of depression in general, and that using diurnal animal models will advance our understanding of other circadian rhythms related diseases as well.

CONCLUSIONS

Wealth of research results now establishes the validity of diurnal rodents as a model for studying the interactions between circadian rhythms and depression. Diurnal rodents respond to photoperiod manipulation in a similar way to humans, the behavioral outcome is directly related to the circadian system, and treatments that are effective in patients are also effective in the model, whereas less effective treatments in patients are also less effective in the model [Ashkenazy et al., 2009a; Krivisky et al., 2012]. We suggest that using diurnal animal models to study circadian rhythms related affective disorders such as depression, will produce new insights which will eventually lead to the development of more effective treatments.

REFERENCES


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