



# Selective pharmacological blockade of the 5-HT<sub>7</sub> receptor attenuates light and 8-OH-DPAT induced phase shifts of mouse circadian wheel running activity

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Recent reports have illustrated a reciprocal relationship between circadian rhythm disruption and mood disorders. The 5-HT<sub>7</sub> receptor may provide a crucial link between the two sides of this equation since the receptor plays a critical role in sleep, depression, and circadian rhythm regulation. To further define the role of the 5-HT<sub>7</sub> receptor as a potential pharmacotherapy to correct circadian rhythm disruptions, the current study utilized the selective 5-HT<sub>7</sub> antagonist JNJ-18038683 (10 mg/kg) in three different circadian paradigms. While JNJ-18038683 was ineffective at phase shifting the onset of wheel running activity in mice when administered at different circadian time (CT) points across the circadian cycle, pretreatment with JNJ-18038683 blocked non-photic phase advance (CT6) induced by the 5-HT<sub>1A/7</sub> receptor agonist 8-OH-DPAT (3 mg/kg). Since light induced phase shifts in mammals are partially mediated via the modulation of the serotonergic system, we determined if JNJ-18038683 altered phase shifts induced by a light pulse at times known to phase delay (CT15) or advance (CT22) wheel running activity in free running mice. Light exposure resulted in a robust shift in the onset of activity in vehicle treated animals at both times tested. Administration of JNJ-18038683 significantly attenuated the light induced phase delay and completely blocked the phase advance. The current study demonstrates that pharmacological blockade of the 5-HT<sub>7</sub> receptor by JNJ-18038683 blunts both non-photic and photic phase shifts of circadian wheel running activity in mice. These findings highlight the importance of the 5-HT<sub>7</sub> receptor in modulating circadian rhythms. Due to the opposite modulating effects of light resetting between diurnal and nocturnal species, pharmacotherapy targeting the 5-HT<sub>7</sub> receptor in conjunction with bright light therapy may prove therapeutically beneficial by correcting the desynchronization of internal rhythms observed in depressed individuals.

**Keywords:** circadian rhythms, 5-HT<sub>7</sub> receptor, phase shift, photic, non-photic, depression, mood, serotonin

## INTRODUCTION

Circadian rhythms are governed by a variety of environmental inputs including light, food, social interaction, and pharmacological agents (Lall et al., 2012; Bloch et al., 2013; Patton and Mistlberger, 2013; Pendergast and Yamazaki, 2014). Of these, light is the most powerful of the synchronizing agents (Klein et al., 1991) and exerts its influence on circadian rhythms by first exciting a subset of retinal ganglion cells that subsequently activate neurons within the master circadian clock located in the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (RHT; Moore and Lenn, 1972; Gooley et al., 2001; Hattar et al., 2002; Panda et al., 2002; Ruby et al., 2002). In addition to photic input, serotonergic pathways can also exert non-photic influence over the synchronization of circadian rhythms either by direct projections from raphe nucleus onto the SCN or indirect via the intergeniculate leaflet onto the SCN (Moga

and Moore, 1997; Pickard and Rea, 1997; Ciarleglio et al., 2011). Working in accordance with each other, the photic and non-photic pathways help ensure proper synchronization of circadian rhythms by responding to a variety of changes in the environment. Recent studies have demonstrated that the misalignment or the inability to adjust to such derivations in the environment give rise to mood disorders in humans (Sprouse, 2004; Grandin et al., 2006; Murray and Harvey, 2010; Salvatore et al., 2010).

Utilizing a “clock in a dish” model, a role for the 5-HT<sub>7</sub> receptor in the modulation of the non-photic regulation of circadian rhythms was noted for the first time when the receptor was initially cloned (Lovenberg et al., 1993). This method demonstrated that the phase advance in neuronal activity of the SCN following administration of the 5-HT<sub>1A/7</sub> receptor agonist 8-OH-DPAT was attenuated by the 5-HT<sub>7/2</sub> receptor antagonist ritanserin, but

not by pindolol, a 5-HT<sub>1A/1B</sub> receptor antagonist (Lovenberg et al., 1993). This finding was later confirmed with the more selective 5-HT<sub>7</sub> receptor antagonist SB-269970 (Sprouse et al., 2004). *In vivo* studies later reported the translational aspects of this cell model by demonstrating that phase advances in wheel running activity induced by 8-OH-DPAT were blocked following the administration of the 5-HT<sub>7</sub> receptor antagonist DR-4004 in hamsters and absent in the 5-HT<sub>7</sub> receptor knockout (KO) mouse (Ying and Rusak, 1997; Ehlen et al., 2001; Horikawa and Shibata, 2004; Gardani and Biello, 2008; Horikawa et al., 2013). In addition to its effects on the non-photically regulated circadian rhythms, there is evidence that the 5-HT<sub>7</sub> receptor may also influence photic regulation of circadian rhythms either by altering the sensitivity to light or modulating the release of serotonin (Ying and Rusak, 1997; Smith et al., 2001).

In addition to regulating circadian rhythms, the 5-HT<sub>7</sub> receptor has been studied extensively for its role in depression. Initial investigation noted that 5-HT<sub>7</sub> receptor KO mice exhibited an antidepressant-like phenotype in models of depression such as the tail suspension and forced swim tests (Guscott et al., 2005; Hedlund et al., 2005). Comparable antidepressant-like effects were found in these behavioral tests with the selective 5-HT<sub>7</sub> receptor antagonist SB-269970 (Wesołowska et al., 2006; Sarkisyan et al., 2010). While many studies have utilized SB-269970 as a tool compound to investigate a role for the 5-HT<sub>7</sub> receptor in various physiologic systems and pathological states, its utility is hampered due to a short half-life and poor drug-like properties (Hagan et al., 2000). Our in-house efforts yielded JNJ-18038683, a selective 5-HT<sub>7</sub> receptor antagonist that exhibits better pharmacokinetic properties than SB-269970. Pre-clinical and clinical evaluation of the compound demonstrated that JNJ-18038683 was efficacious in the mouse tail suspension test and also enhanced serotonin transmission, antidepressant-like properties, and REM sleep suppression induced by the selective serotonin reuptake inhibitor (SSRI) citalopram in rats (Bonaventure et al., 2012). The effects of JNJ-18038683 on REM sleep translated from rodents to humans whereas the antidepressant efficacy needed to be further assessed (Bonaventure et al., 2012). Interestingly, systemic administration of the selective 5-HT<sub>7</sub> receptor agonist LP-211 significantly increased the time spent awake while the direct infusion of this compound into dorsal raphe nucleus, locus coeruleus, basal forebrain, or laterodorsal tegmental nucleus resulted in decreased duration of REM sleep (Monti et al., 2008, 2014; Monti and Jantos, 2014). Similar REM sleep suppressive effects were observed when another selective 5-HT<sub>7</sub> receptor agonist LP-44 was injected directly into the dorsal raphe nucleus (Monti et al., 2008).

Given the association of the 5-HT<sub>7</sub> receptor with mood and circadian rhythms, pharmacological manipulation of this receptor may provide a critical insight into the therapeutic link between depression and circadian disruption. Therefore, the current study was designed to examine a role for the 5-HT<sub>7</sub> receptor in circadian rhythm regulation by administering the selective 5-HT<sub>7</sub> receptor antagonist JNJ-18038683 in both photic and non-photically regulated circadian paradigms. To determine if JNJ-18038683 exerts direct phase resetting properties, a phase response curve was generated by administering the compound to mice at select times

throughout the circadian cycle. Second, mice were administered JNJ-18038683 to determine if the compound alters the non-photically regulated phase shift of wheel running activity induced by 8-OH-DPAT. Finally, JNJ-18038683 was administered prior to a light pulse that occurred at times known to delay (circadian time (CT) 15) or advance (CT 22) the onset of wheel running activity (Daan and Pittendrigh, 1976; Takahashi et al., 1984) in mice to determine the effects of acute pharmacological blockade of the 5-HT<sub>7</sub> receptor on photically induced phase shifts. Results of these studies demonstrate that the 5-HT<sub>7</sub> receptor influences both photic and non-photically regulated aspects of circadian regulation and therefore may provide a therapeutic avenue to alleviate circadian disruptions associated with depression.

## METHODS

### ANIMALS

Studies conducted for the current investigation were performed in accordance with the policies and regulations of the respective IACUC committees at Northwestern University and Janssen Research and Development, L.L.C. For the experiments outlined for the following studies, male C57Bl/6 J mice (average weight ~30 grams) were purchased from Jackson Labs (Sacramento, CA) and allowed to acclimate for at least 2 weeks before being moved to environmental chambers that allowed for the ability to control lighting schedules and modified cages that contained a running wheel. Mice were allowed access to food and water *ad libitum* and maintained under a 12 h light/12 h dark schedule.

### DRUGS

JNJ-18038683 (1-Benzyl-3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-dipropylazepine) was synthesized by medicinal chemistry group at Janssen Research and Development, L.L.C. as the citrate salt form. For formulations, 20% (w/v) hydroxypropyl- $\beta$ -cyclodextrin was used to solubilize the compound and a correction factor of 1.5690 was applied to compensate for the salt form of JNJ-18038683. 8-OH-DPAT (( $\pm$ )-8-Hydroxy-2-dipropylaminotetralin hydrobromide) (Tocris Biosciences) was formulated in saline. A correction factor of 1.32 was applied to compensate for the hydrobromide salt form of 8-OH-DPAT. Both compounds were injected in a volume of 10 mL/kg body mass. With each compound, the pH of the solution was adjusted to neutral before injection.

### EXPERIMENTAL DESIGN

A phase response curve for JNJ-18038683 (10 mg/kg, *i.p.*) was generated by administering the compound at various times across the circadian cycle (CT2, 6, 10, 14, 18, or 22) to separate groups of mice for each time point. For these studies, a single animal was used in more than one injection condition and at least 2 weeks were given between conditions to prevent carry-over, or interference effects from the previous trial.

To determine if JNJ-18038683 alters the phase advance of wheel running activity induced by the 5-HT<sub>1A/7</sub> receptor agonist, 8-OH-DPAT, mice were first randomized into four separate groups. Animals then received an injection of JNJ-18038683 (3 mg/kg, *i.p.*) or vehicle. Thirty minutes later, mice were further

designated to receive 8-OH-DPAT (3 mg/kg, i.p.) or corresponding vehicle at CT6 which had been previously reported to result in a phase advance of the onset of locomotor rhythm by 8-OH-DPAT (Horikawa and Shibata, 2004).

To investigate the role of the 5-HT7 receptor on photic induced phase shifts, JNJ-18038683 (10 mg/kg, s.c.) or vehicle was administered 30 min prior to an acute light pulse (200 lux, 30 min) that occurred at times that are known to produce a photic phase delay (CT 15) or advance (CT 22) of the onset of wheel running activity. As a control for the light pulse, mice were placed in the chamber but not exposed to light. For each treatment, separate groups of mice were used.

### WHEEL RUNNING ACTIVITY RECORDING AND ANALYSIS

Wheel running activity was recorded by a magnetic switch located on the wheel that transferred each revolution as an event to an IBM compatible computer in 5 min bins using ClockLab software. Following at least a one-week acclimation period to adjust to the running wheels and novel cage, mice were released into constant darkness to assess free-running conditions and the onset of activity was monitored. On designated experimental days, the onset of activity (designated by convention as CT 12) was calculated based on the free running phase advance of activity of the previous 7 days. All timing for injections and light exposure was predicated by the calculation of CT 12 for each animal. Wheel running activity was monitored for at least 1 week following treatment or corresponding control conditions for changes to the onset of activity. A phase shift was calculated using ClockLab software and defined as the difference in the onset of activity after treatment vs. onset of activity prior to treatment. Data are expressed as mean  $\pm$  S.E.M. To determine if JNJ-18038683 resulted in a significant phase shift at various time points along the phase response curve, an unpaired *t*-test (Vehicle vs. JNJ-18038683 treated animals) was executed. A one factor, four-level ANOVA followed by *post hoc* analysis was performed for each of the remaining two studies to determine if the phase shift was significant with the four treatment groups ( $p < 0.05$ ). For visualization, a phase advance is denoted as a positive value on the bar graph while a phase delay is graphed as a negative value.

## RESULTS

### PHASE RESPONSE CURVE WITH JNJ-18038683

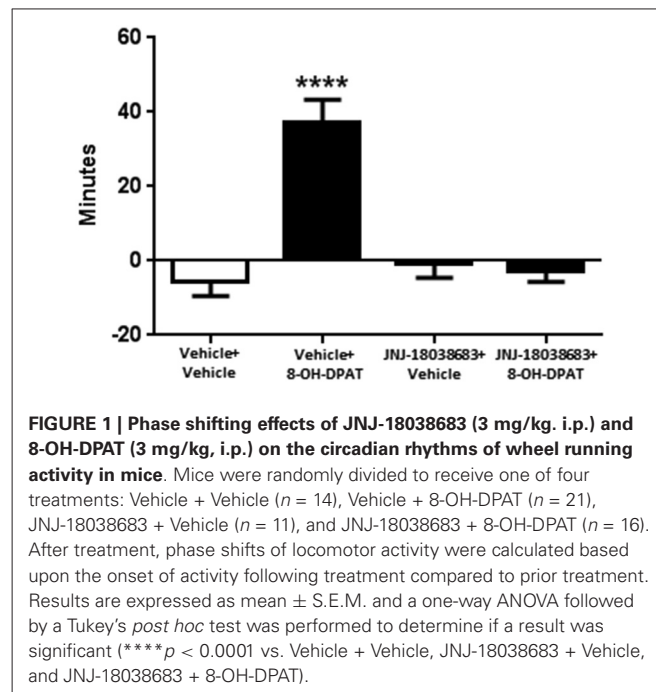
To determine the effects of the pharmacological blockade of the 5-HT7 receptor by JNJ-18038683 (10 mg/kg, i.p.), the compound was administered at various circadian times throughout the subjective circadian cycle (CT 2, 6, 10, 14, 18, 22) and the resulting phase shift was calculated post administration and compared to vehicle. At all times tested, JNJ-18038683 failed to elicit a phase shift as determined by unpaired *t*-test (Table 1). In a separate study, negative results were also obtained following the administration of a higher dose of JNJ-18038683 (20 mg/kg, i.p.) (data not shown).

### NON-PHOTIC REGULATION OF CIRCADIEN RHYTHMS BY THE 5-HT7 RECEPTOR

We then tested whether the 5-HT7 receptor antagonist JNJ-18038683 would attenuate the phase advance of wheel running

**Table 1 | Phase response curve following the administration of the 5-HT7 receptor antagonist JNJ-18038683 (10 mg/kg, i.p.) at various circadian times.**

CT	Phase shift (min.)	
	Vehicle	JNJ-18038683
2	0.0 $\pm$ 0.0	0.25 $\pm$ 0.25
6	0.0 $\pm$ 0.0	-0.15 $\pm$ 0.10
10	-0.20 $\pm$ 0.10	-0.29 $\pm$ 0.20
14	0.0 $\pm$ 0.0	-0.08 $\pm$ 0.08
18	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
22	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0

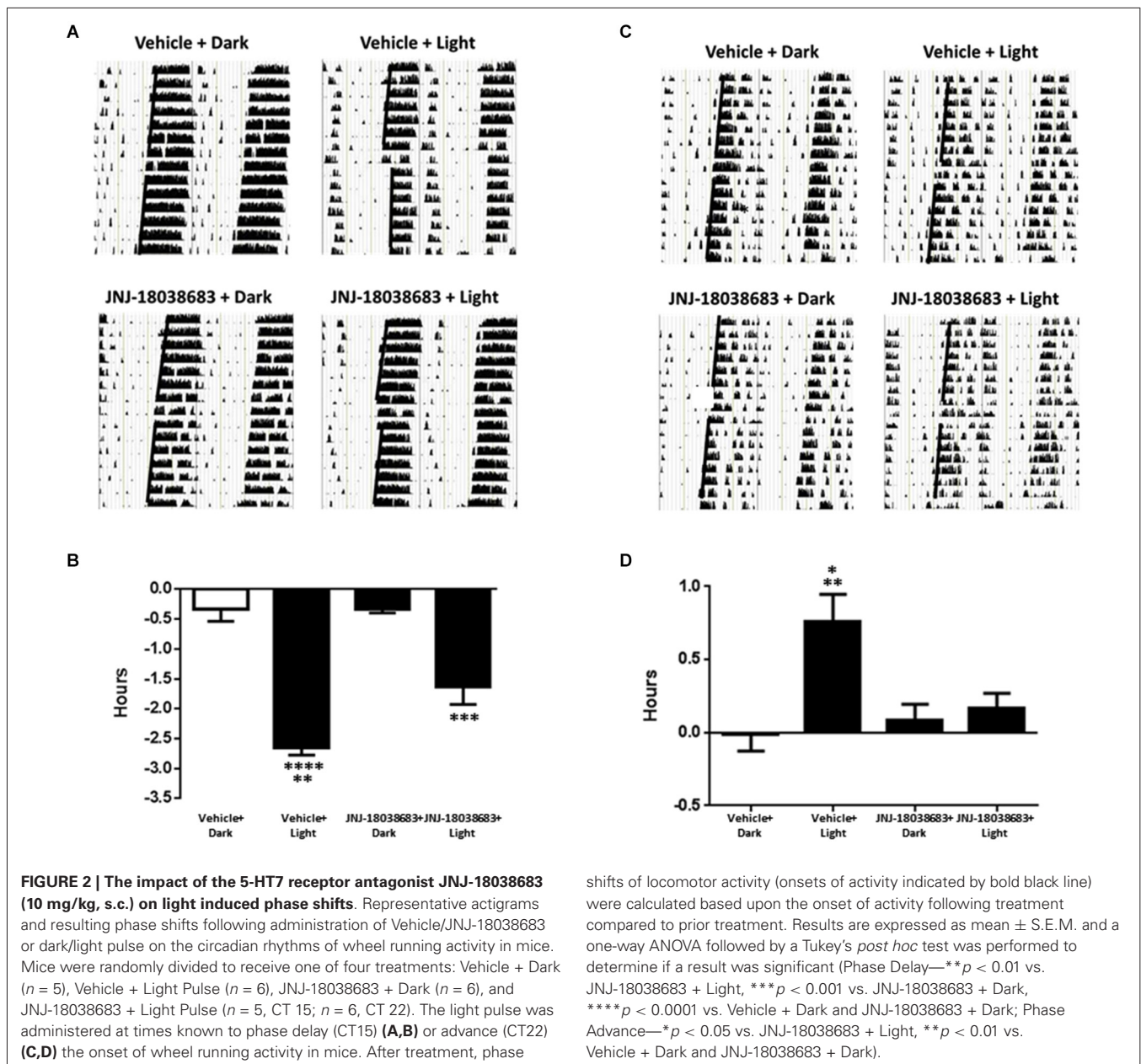


**FIGURE 1 | Phase shifting effects of JNJ-18038683 (3 mg/kg, i.p.) and 8-OH-DPAT (3 mg/kg, i.p.) on the circadian rhythms of wheel running activity in mice.** Mice were randomly divided to receive one of four treatments: Vehicle + Vehicle ( $n = 14$ ), Vehicle + 8-OH-DPAT ( $n = 21$ ), JNJ-18038683 + Vehicle ( $n = 11$ ), and JNJ-18038683 + 8-OH-DPAT ( $n = 16$ ). After treatment, phase shifts of locomotor activity were calculated based upon the onset of activity following treatment compared to prior treatment. Results are expressed as mean  $\pm$  S.E.M. and a one-way ANOVA followed by a Tukey's *post hoc* test was performed to determine if a result was significant (\*\*\*\* $p < 0.0001$  vs. Vehicle + Vehicle, JNJ-18038683 + Vehicle, and JNJ-18038683 + 8-OH-DPAT).

locomotor activity elicited by the 5-HT1A/7 receptor agonist 8-OH-DPAT. Administration of the vehicle for JNJ-18038683 followed by 8-OH-DPAT resulted in a robust phase advance of the onset of locomotor activity during constant dark conditions (37.0  $\pm$  6.3 min,  $F_{(3,58)} = 18.49$   $p < 0.0001$ , one-way ANOVA, Tukey's *post hoc* analysis) when compared to the other three treatment groups (Vehicle + Vehicle: -5.4  $\pm$  4.1 min, JNJ-18038683 + Vehicle -0.9  $\pm$  3.6 min, JNJ-18038683 + 8-OH-DPAT: -2.7  $\pm$  3.0 min) (Figure 1). Comparable to what had been measured during the generation of the phase response curve, the administration of JNJ-18038683 in conjunction with the vehicle for 8-OH-DPAT did not produce any phase shift at CT 6. The administration of the 5-HT7 receptor antagonist JNJ-18038683 completely blocked the phase advance produced by 8-OH-DPAT (Figure 1).

### PHOTIC REGULATION OF CIRCADIEN RHYTHMS BY THE 5-HT7 RECEPTOR

To determine the effects of pharmacological blockade of the 5-HT7 receptor on photic control of circadian rhythms,



JNJ-18038683 was administered prior to a light pulse and the potential alterations in the onset of mouse wheel running activity was analyzed. In vehicle treated animals, light exposure resulted in a significant phase shift in the onset of activity at both times tested (CT 15:  $-2.65 \pm 0.12$  h;  $F_{(3,18)} = 42.37$ ; CT22:  $0.76 \pm 0.19$  h;  $F_{(3,19)} = 6.757$  one way ANOVA, Tukey's *post hoc* analysis) (Figures 2A–D). Administration of JNJ-18038683 attenuated the light-induced phase delay ( $-1.64 \pm 0.29$  h) (Figures 2C,D) while the resulting phase advance following light exposure at CT 22 was completely blocked by the compound (Figures 2A,B).

## DISCUSSION

The present investigation examined the impact of the 5-HT7 receptor antagonist JNJ-18038683 on non-photic and photic

regulation of the circadian rhythm of wheel running activity in mice. Results reported from these studies demonstrate that the compound did not exert direct non-photic or photic phase resetting properties by itself. However, JNJ-18038683 was able to block the non-photic phase advance of wheel running activity induced by the 5-HT<sub>1A/7</sub> receptor agonist 8-OH-DPAT. In addition, JNJ-18038683 completely blocked the phase advance and significantly attenuated the phase delay of wheel running activity induced by a light pulse.

## PHASE RESPONSE CURVE OF JNJ-18038683

To determine if JNJ-18038683 exerts direct non-photic or photic phase resetting effects in free running mice, the compound was administered at specified times across the circadian cycle. At all

times tested, JNJ-18038683 failed to elicit a phase shift when compared to vehicle treated mice. The lack of effect with JNJ-18038683 on phase shifts in mice was similar to what has been reported for the 5-HT<sub>2/7</sub> receptor antagonist, ritanserin and a more selective 5-HT<sub>7</sub> receptor antagonist SB-269970 in hamsters and rats (Antle et al., 1998; Duncan et al., 2004; Westrich et al., 2013). While antagonists for the 5-HT<sub>7</sub> receptor do not modulate non-photic regulation of circadian rhythms, agonists for this receptor (8-OH-DPAT and LP-211) are capable of shifting the onset of wheel running activity in constant conditions (Horikawa and Shibata, 2004; Adriani et al., 2012). In addition, fluoxetine that inhibits the reuptake of serotonin and therefore, universally activates the serotonergic system has been shown to induce non-photic phase shifts (Cuesta et al., 2008, 2009). Therefore, global activation of the serotonergic system or direct pharmacological activation of the 5-HT<sub>7</sub> receptor may be needed to induce photic or non-photic phase shifts.

#### **NON-PHOTIC REGULATION OF CIRCADIAN RHYTHMS BY THE 5-HT<sub>7</sub> RECEPTOR**

The second study was designed to determine if the acute pharmacological blockade of the 5-HT<sub>7</sub> receptor with the selective antagonist JNJ-18038683 impacted the phase advance of wheel running activity induced by 8-OH-DPAT in mice. The timing of 8-OH-DPAT administration was based on previous studies that demonstrated a robust phase advance when the compound was injected at CT 6 (Horikawa and Shibata, 2004). When JNJ-18038683 was administered before 8-OH-DPAT in the current study, the phase advance induced by the agonist was completely blocked demonstrating the impact of the 5-HT<sub>7</sub> receptor on non-photic phase resetting of circadian rhythms. Since 8-OH-DPAT is an agonist for both the 5-HT<sub>1</sub> and 5-HT<sub>7</sub> receptors, future studies will utilize selective agonists for the 5-HT<sub>7</sub> receptor (i.e., LP-44 or LP-211) to further elucidate the role of the 5-HT<sub>7</sub> receptor on non-photic regulation of circadian rhythms.

Earlier *in vivo* and *in vitro* studies from other labs have provided some insight into a mechanism by which the 5-HT<sub>7</sub> receptor regulates non-photic control of circadian rhythms. During mid-subjective day, micro-injection of 8-OH-DPAT or 5-Carboxamidotryptamine (5-CT) into the dorsal raphe nucleus activates 5-HT<sub>7</sub> receptors and subsequently phase advances the circadian rhythms of wheel running activity in hamsters (Mintz et al., 1997; Duncan et al., 2004; Duncan and Davis, 2005). These phase shifts were blocked by the administration of the selective 5-HT<sub>7</sub> receptor antagonist SB-269970 (Duncan et al., 2004). Further investigation delineated this model to show that the activation of the 5-HT<sub>7</sub> receptor inhibits glutamate release within the dorsal raphe nucleus resulting in the inhibition of the release of GABA from interneurons which subsequently relieves the inhibition on serotonergic neurons located within the dorsal or medial raphe nucleus (Glass et al., 2003; Harsing et al., 2004; Duncan and Congleton, 2010). The subsequent release of serotonin onto the SCN results in non-photic phase modulation (Duncan and Congleton, 2010). Therefore, administration of JNJ-18038683 may be acting on 5-HT<sub>7</sub> receptors within the dorsal raphe nucleus to inhibit glutamate release and thus blocking

the non-photic phase shifts induced by 8-OH-DPAT. However, further studies are needed to define specific pathways in which the 5-HT<sub>7</sub> receptor modulates non-photic circadian re-setting since the receptor is localized not only within the dorsal/median raphe nucleus to modulate GABA release, but also within the primary circadian oscillator of the SCN and other brain regions known to influence circadian rhythms such as the thalamus that could potentially impact NPY release which has been shown to alter non-photic phase shifts (Mrosovsky, 1996; Belenky and Pickard, 2001; Neumaier et al., 2001; Bonaventure et al., 2002; Gamble et al., 2006; Matthys et al., 2011; Hughes and Piggins, 2012).

#### **PHOTIC REGULATION OF CIRCADIAN RHYTHMS BY THE 5-HT<sub>7</sub> RECEPTOR**

In addition to the non-photic influence of circadian rhythms, serotonin can also alter photic responsiveness of the SCN possibly by acting via the 5-HT<sub>7</sub> receptor. Early studies associated the 5-HT<sub>7</sub> receptor with changes in the sensitivity of light in SCN neurons. Administration of serotonin, 5-CT, or 8-OH-DPAT reduced the firing of SCN neurons located in the hamster following a light pulse (Ying and Rusak, 1997). This decrease in neuronal firing was subsequently reversed by applying ritanserin or clozapine which are known to antagonize the 5-HT<sub>7</sub> receptor but not the 5-HT<sub>1A/B/D</sub> receptor antagonist, cyanopindolol or the 5-HT<sub>1A</sub> receptor antagonist WAY-100635 (Ying and Rusak, 1997). In subsequent studies, hypothalamic excitatory post synaptic currents evoked by optic nerve stimulation which mimics a light pulse were reduced when the 5-HT<sub>1A/B</sub> agonist TFMPP was added to the bath (Smith et al., 2001). The change in these glutamate dependent currents within the hypothalamus were significantly attenuated with ritanserin, thus further implicating a role for the 5-HT<sub>7</sub> receptor in photic control of circadian rhythms by modulating glutamate transmission (Smith et al., 2001). The additional findings that TFMPP had little effect in this model in 5-HT<sub>1B</sub> receptor KO mice and was minimally attenuated with the 5-HT<sub>1A</sub> receptor antagonist WAY-100635, provide some indirect evidence that the role of the 5-HT<sub>7</sub> receptor in modulating photic control of circadian rhythms may be in coordination with other serotonergic receptors and glutamatergic neurotransmission.

Additional studies have investigated a role for the 5-HT<sub>7</sub> receptor in the photic control of circadian rhythms by generating a phase response curve of light in 5-HT<sub>7</sub> receptor KO and corresponding WT mice (Gardani and Biello, 2008). Overall, the phase shifts induced by the light pulse were comparable in magnitude and direction between WT and 5-HT<sub>7</sub> receptor KO mice except at CT 22 (Gardani and Biello, 2008). At this time point, the light pulse resulted in the requisite phase advance in WT mice but a phase delay in the 5-HT<sub>7</sub> receptor KO mice (Gardani and Biello, 2008). Interestingly, while the current study measured a significant attenuation of the light induced phase delay at CT 15 with the administration of JNJ-18038683, there was no difference in WT or 5-HT<sub>7</sub> receptor KO mouse when the light pulse was administered at CT 14 or 16 which replicated an earlier report (Sprouse et al., 2003). The difference in regards to the light induced phase shift at these earlier time points

between the pharmacological and the genetic deletion of the receptor may be the result of compensatory mechanisms involved in the phase resetting after a light pulse at these earlier time points of the subjective dark phase in the 5-HT7 receptor KO mouse.

Since this is the first report of attenuation of phase shifts following light pulses following the acute pharmacological blockade of the 5-HT7 receptor, additional studies are needed to further investigate the mechanism by which the 5-HT7 receptor is modulating the photic control of circadian rhythms. Results from these studies will provide an explanation as to why pharmacological blockade of the 5-HT7 receptor resulted in diminished photic induced phase shifts as opposed to an enhancement given the finding that activation of the 5-HT7 receptor inhibits the RHT input to the SCN by decreasing glutamate (Ying and Rusak, 1997; Smith et al., 2001). In addition, since antagonists selective for the 5-HT7 receptor lack direct photic-like phase shifting effects by themselves, the actions of these 5-HT7 receptor antagonists are probably due to the coordination with other serotonin receptors including the 5-HT1A and 5-HT1B receptors (Ying and Rusak, 1997; Rea, 1998; Smith et al., 2001).

Similar to our findings that JNJ-18038683 diminished photic induced phase resetting, pharmacological agents that are known to activate the serotonin system such as SSRIs (fluoxetine, citalopram, fluvoxamine, and paroxetine) also reduce the phase shift induced by a light pulse in the hamster (Gannon and Millan, 2007). Interestingly, fluoxetine potentiates the light induced phase shift in the diurnal species *Arvicanthis ansorgei* (Cuesta et al., 2008). These contrasting effects between nocturnal and diurnal species may be explained by the differential regulation of brain concentrations of serotonin corresponding to arousal state and also may be due to the changes in expression of circadian controlled genes following a light pulse in nocturnal and diurnal animals (Faradji et al., 1983; Poncet et al., 1993; Rea et al., 1994; Weber et al., 1998; Cuesta et al., 2008). While the current study did not measure the changes in the expression of such genes in response to pharmacological manipulation of the 5-HT7 receptor, Westrich and colleagues reported that the *in vitro* period as measured by a luciferase reporter linked to the PER2 gene, can be shortened by the 5-HT7 receptor agonist AS-19 and subsequently blocked by the 5-HT7 receptor antagonist SB-269970 (Westrich et al., 2013).

Due to the possible potentiation of the effects of light in diurnal species such as humans, 5-HT7 receptor antagonists may provide an interesting adjunctive therapy for the antidepressant effects associated with bright light therapy. The idea of adjunctive therapy with a 5-HT7 receptor antagonist arose from earlier studies in which JNJ-18038683 or SB-269970 enhanced the antidepressant-like effects of an SSRI in pre-clinical studies (Bonaventure et al., 2007, 2012; Wesolowska et al., 2007). When JNJ-18038683 was administered in combination with citalopram, there was an enhancement of serotonin transmission, antidepressant-like behavior, and REM sleep suppression induced by the SSRI in rodents (Bonaventure et al., 2012). In another study, Westrich et al. demonstrated that the administration of escitalopram or the 5-HT7 receptor antagonist SB-269970

was ineffective at phase shifting wheel running activity in rats, however, the co-administration of escitalopram with SB-269970 resulted in phase delays in rodent wheel running (Westrich et al., 2013). In addition to adjunctive therapy with an SSRI, a 5-HT7 receptor antagonist may also provide useful adjunctive therapy to bright light exposure in humans. While bright light therapy has been used for several decades as a stand-alone antidepressant therapy for seasonal affective disorder (Pail et al., 2011), it has also been used in conjunction with SSRI for major depressive disorder to bolster and hasten the antidepressant properties of SSRIs since the onset of mood improvement may take several weeks and also to increase the responsiveness in those individuals who are resistant to treatment with SSRIs by themselves (Benedetti et al., 2003; Blier, 2003; Martiny, 2004; Martiny et al., 2004; Wirz-Justice et al., 2005). There is clinical evidence that bright light therapy with sertraline can be therapeutically beneficial as an adjunct therapy for depression resulting in significant reductions in the HAM-D scale of depression (Martiny et al., 2005a,b). In addition, combining bright light therapy with citalopram has been shown to accelerate the onset of the anti-depressant properties of the SSRI (Benedetti et al., 2003). Therefore, combining bright light therapy with JNJ-18038683 may enhance the antidepressant effects of the light exposure in humans. Findings from these studies help provide insight into the translational therapeutic benefits of combining a 5-HT7 receptor antagonist with additional antidepressant modalities including bright light therapy that would correct the various circadian disruptions that are commonly associated with depression.

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## REFERENCES

- Adriani, W., Travaglini, D., Lacivita, E., Saso, L., Leopoldo, M., and Laviola, G. (2012). Modulatory effects of two novel agonists for serotonin receptor 7 on emotion, motivation and circadian rhythm profiles in mice. *Neuropharmacology* 62, 833–842. doi: 10.1016/j.neuropharm.2011.09.012
- Antle, M. C., Marchant, E. G., Niel, L., and Mistlberger, R. E. (1998). Serotonin antagonists do not attenuate activity-induced phase shifts of circadian rhythms in the Syrian hamster. *Brain Res.* 813, 139–149. doi: 10.1016/s0006-8993(98)01048-8
- Belenky, M. A., and Pickard, G. E. (2001). Subcellular distribution of 5-HT(1B) and 5-HT(7) receptors in the mouse suprachiasmatic nucleus. *J. Comp. Neurol.* 432, 371–388. doi: 10.1002/cne.1109
- Benedetti, F., Colombo, C., Pontiggia, A., Bernasconi, A., Florita, M., and Smeraldi, E. (2003). Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J. Clin. Psychiatry* 64, 648–653. doi: 10.4088/jcp.v64n0605
- Blier, P. (2003). The pharmacology of putative early-onset antidepressant strategies. *Eur. Neuropsychopharmacol.* 13, 57–66. doi: 10.1016/s0924-977x(02)00173-6
- Bloch, G., Herzog, E. D., Levine, J. D., and Schwartz, W. J. (2013). Socially synchronized circadian oscillators. *Proc. Biol. Sci.* 280:20130035. doi: 10.1098/rspb.2013.0035
- Bonaventure, P., Dugovic, C., Kramer, M., De Boer, P., Singh, J., Wilson, S., et al. (2012). Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor antagonist, on rapid eye movement sleep and in major depressive disorder. *J. Pharmacol. Exp. Ther.* 342, 429–440. doi: 10.1124/jpet.112.193995
- Bonaventure, P., Kelly, L., Aluisio, L., Shelton, J., Lord, B., Galici, R., et al. (2007). Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances

- 5-HT transmission, antidepressant-like behavior and rapid eye movement sleep suppression induced by citalopram in rodents. *J. Pharmacol. Exp. Ther.* 321, 690–698. doi: 10.1124/jpet.107.119404
- Bonaventure, P., Nepomuceno, D., Kwok, A., Chai, W., Langlois, X., Hen, R., et al. (2002). Reconsideration of 5-hydroxytryptamine (5-HT)<sub>7</sub> receptor distribution using [(3)H]5-carboxamidotryptamine and [(3)H]8-hydroxy-2-(di-n-propylamino)tetraline: analysis in brain of 5-HT(1A) knockout and 5-HT(1A/1B) double-knockout mice. *J. Pharmacol. Exp. Ther.* 302, 240–248. doi: 10.1124/jpet.302.1.240
- Ciarleglio, C. M., Resuehr, H. E., and McMahon, D. G. (2011). Interactions of the serotonin and circadian systems: nature and nurture in rhythms and blues. *Neuroscience* 197, 8–16. doi: 10.1016/j.neuroscience.2011.09.036
- Cuesta, M., Clesse, D., Pévet, P., and Challet, E. (2009). New light on the serotonergic paradox in the rat circadian system. *J. Neurochem.* 110, 231–243. doi: 10.1111/j.1471-4159.2009.06128.x
- Cuesta, M., Mendoza, J., Clesse, D., Pévet, P., and Challet, E. (2008). Serotonergic activation potentiates light resetting of the main circadian clock and alters clock gene expression in a diurnal rodent. *Exp. Neurol.* 210, 501–513. doi: 10.1016/j.expneurol.2007.11.026
- Daan, S., and Pittendrigh, C. S. (1976). A functional analysis of circadian pacemakers in nocturnal rodents. *J. Comp. Physiol.* 106, 253–266. doi: 10.1007/bf01417857
- Duncan, M. J., and Congleton, M. R. (2010). Neural mechanisms mediating circadian phase resetting by activation of 5-HT<sub>7</sub> receptors in the dorsal raphe: roles of GABAergic and glutamatergic neurotransmission. *Brain Res.* 1366, 110–119. doi: 10.1016/j.brainres.2010.09.103
- Duncan, M. J., and Davis, V. A. (2005). Cyclic AMP mediates circadian phase shifts induced by microinjection of serotonergic drugs in the hamster dorsal raphe nucleus. *Brain Res.* 1058, 10–16. doi: 10.1016/j.brainres.2005.07.016
- Duncan, M. J., Grear, K. E., and Hoskins, M. A. (2004). Aging and SB-269970-A, a selective 5-HT<sub>7</sub> receptor antagonist, attenuate circadian phase advances induced by microinjections of serotonergic drugs in the hamster dorsal raphe nucleus. *Brain Res.* 1008, 40–48. doi: 10.1016/j.brainres.2004.02.025
- Ehlen, J. C., Grossman, G. H., and Glass, J. D. (2001). In vivo resetting of the hamster circadian clock by 5-HT<sub>7</sub> receptors in the suprachiasmatic nucleus. *J. Neurosci.* 21, 5351–5357.
- Faradji, H., Cespuoglio, R., and Jouvét, M. (1983). Voltammetric measurements of 5-hydroxyindole compounds in the suprachiasmatic nuclei: circadian fluctuations. *Brain Res.* 279, 111–119. doi: 10.1016/0006-8993(83)90168-3
- Gamble, K. L., Paul, K. N., Karom, M. C., Tosini, G., and Albers, H. E. (2006). Paradoxical effects of NPY in the suprachiasmatic nucleus. *Eur. J. Neurosci.* 23, 2488–2494. doi: 10.1111/j.1460-9568.2006.04784.x
- Gannon, R. L., and Millan, M. J. (2007). Evaluation of serotonin, noradrenaline and dopamine reuptake inhibitors on light-induced phase advances in hamster circadian activity rhythms. *Psychopharmacology (Berl)* 195, 325–332. doi: 10.1007/s00213-007-0903-z
- Gardani, M., and Biello, S. M. (2008). The effects of photic and nonphotic stimuli in the 5-HT<sub>7</sub> receptor knockout mouse. *Neuroscience* 152, 245–253. doi: 10.1016/j.neuroscience.2007.10.028
- Glass, J. D., Grossman, G. H., Farnbauch, L., and Dinardo, L. (2003). Midbrain raphe modulation of nonphotic circadian clock resetting and 5-HT release in the mammalian suprachiasmatic nucleus. *J. Neurosci.* 23, 7451–7460.
- Gooley, J. J., Lu, J., Chou, T. C., Scammell, T. E., and Saper, C. B. (2001). Melanopsin in cells of origin of the retinohypothalamic tract. *Nat. Neurosci.* 4:1165. doi: 10.1038/nn768
- Grandin, L. D., Alloy, L. B., and Abramson, L. Y. (2006). The social zeitgeber theory, circadian rhythms and mood disorders: review and evaluation. *Clin. Psychol. Rev.* 26, 679–694. doi: 10.1016/j.cpr.2006.07.001
- Guscott, M., Bristow, L. J., Hadingham, K., Rosahl, T. W., Beer, M. S., Stanton, J. A., et al. (2005). Genetic knockout and pharmacological blockade studies of the 5-HT<sub>7</sub> receptor suggest therapeutic potential in depression. *Neuropharmacology* 48, 492–502. doi: 10.1016/j.neuropharm.2004.11.015
- Hagan, J. J., Price, G. W., Jeffrey, P., Deeks, N. J., Stean, T., Piper, D., et al. (2000). Characterization of SB-269970-A, a selective 5-HT<sub>7</sub> receptor antagonist. *Br. J. Pharmacol.* 130, 539–548. doi: 10.1038/sj.bjp.0703357
- Harsing, L. G. Jr., Prauda, I., Barkoczy, J., Matyus, P., and Juranyi, Z. (2004). A 5-HT<sub>7</sub> heteroreceptor-mediated inhibition of [3H]serotonin release in raphe nuclei slices of the rat: evidence for a serotonergic-glutamatergic interaction. *Neurochem. Res.* 29, 1487–1497. doi: 10.1023/b:nere.0000029560.14262.39
- Hattar, S., Liao, H. W., Takao, M., Berson, D. M., and Yau, K. W. (2002). Melanopsin-containing retinal ganglion cells: architecture, projections and intrinsic photosensitivity. *Science* 295, 1065–1070. doi: 10.1126/science.1069609
- Hedlund, P. B., Huitron-Resendiz, S., Henriksen, S. J., and Sutcliffe, J. G. (2005). 5-HT<sub>7</sub> receptor inhibition and inactivation induce antidepressant-like behavior and sleep pattern. *Biol. Psychiatry* 58, 831–837. doi: 10.1016/j.biopsych.2005.05.012
- Horikawa, K., Fuji, K., Fukazawa, Y., and Shibata, S. (2013). Two distinct serotonin receptors co-mediate non-photic signals to the circadian clock. *J. Pharmacol. Sci.* 123, 402–406. doi: 10.1254/jphs.13170sc
- Horikawa, K., and Shibata, S. (2004). Phase-resetting response to (+)8-OH-DPAT, a serotonin 1A/7 receptor agonist, in the mouse in vivo. *Neurosci. Lett.* 368, 130–134. doi: 10.1016/j.neulet.2004.06.072
- Hughes, A. T., and Piggins, H. D. (2012). Feedback actions of locomotor activity to the circadian clock. *Prog. Brain Res.* 199, 305–336. doi: 10.1016/b978-0-444-59427-3.00018-6
- Klein, D. C., Moore, R. Y., and Reppert, S. M. (1991). *Suprachiasmatic Nucleus. The Mind's Clock*. New York: Oxford University Press.
- Lall, G. S., Atkinson, L. A., Corlett, S. A., Broadbridge, P. J., and Bonsall, D. R. (2012). Circadian entrainment and its role in depression: a mechanistic review. *J. Neural Transm.* 119, 1085–1096. doi: 10.1007/s00702-012-0858-z
- Lovenberg, T. W., Baron, B. M., De Lecea, L., Miller, J. D., Prosser, R. A., Rea, M. A., et al. (1993). A novel adenylyl cyclase-activating serotonin receptor (5-HT<sub>7</sub>) implicated in the regulation of mammalian circadian rhythms. *Neuron* 11, 449–458. doi: 10.1016/0896-6273(93)90149-1
- Martiny, K. (2004). Adjunctive bright light in non-seasonal major depression. *Acta Psychiatr. Scand. Suppl.* 110, 7–28. doi: 10.1111/j.1600-0447.2004.00460\_2.x
- Martiny, K., Lunde, M., Simonsen, C., Clemmensen, L., Poulsen, D. L., Solstad, K., et al. (2004). Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy. A placebo-controlled study. *Acta Psychiatr. Scand.* 109, 230–234. doi: 10.1046/j.1600-0447.2003.00256.x
- Martiny, K., Lunde, M., Undén, M., Dam, H., and Bech, P. (2005a). Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr. Scand.* 112, 117–125. doi: 10.1111/j.1600-0447.2005.00574.x
- Martiny, K., Lunde, M., Undén, M., Dam, H., and Bech, P. (2005b). Adjunctive bright light in non-seasonal major depression: results from patient-reported symptom and well-being scales. *Acta Psychiatr. Scand.* 111, 453–459. doi: 10.1111/j.1600-0447.2005.00532.x
- Matthys, A., Haegeman, G., Van Craenenbroeck, K., and Vanhoenacker, P. (2011). Role of the 5-HT<sub>7</sub> receptor in the central nervous system: from current status to future perspectives. *Mol. Neurobiol.* 43, 228–253. doi: 10.1007/s12035-011-8175-3
- Mintz, E. M., Gillespie, C. F., Marvel, C. L., Huhman, K. L., and Albers, H. E. (1997). Serotonergic regulation of circadian rhythms in Syrian hamsters. *Neuroscience* 79, 563–569. doi: 10.1016/s0306-4522(96)00696-3
- Moga, M. M., and Moore, R. Y. (1997). Organization of neural inputs to the suprachiasmatic nucleus in the rat. *J. Comp. Neurol.* 389, 508–534. doi: 10.1002/(sici)1096-9861(19971222)389:3<508::aid-cne11>3.0.co;2-h
- Monti, J. M., and Jantos, H. (2014). The role of serotonin 5-HT<sub>7</sub> receptor in regulating sleep and wakefulness. *Rev. Neurosci.* 25, 429–437. doi: 10.1515/revneuro-2014-0016
- Monti, J. M., Leopoldo, M., and Jantos, H. (2008). The serotonin 5-HT<sub>7</sub> receptor agonist LP-44 microinjected into the dorsal raphe nucleus suppresses REM sleep in the rat. *Behav. Brain Res.* 191, 184–189. doi: 10.1016/j.bbr.2008.03.025
- Monti, J. M., Leopoldo, M., and Jantos, H. (2014). Systemic administration and local microinjection into the central nervous system of the 5-HT<sub>7</sub> receptor agonist LP-211 modify the sleep-wake cycle in the rat. *Behav. Brain Res.* 259, 321–329. doi: 10.1016/j.bbr.2013.11.030
- Moore, R. Y., and Lenn, N. J. (1972). A retinohypothalamic projection in the rat. *J. Comp. Neurol.* 146, 1–14. doi: 10.1002/cne.901460102
- Mrosovsky, N. (1996). Locomotor activity and non-photic influences on circadian clocks. *Biol. Rev. Camb. Philos. Soc.* 71, 343–372. doi: 10.1111/j.1469-185x.1996.tb01278.x
- Murray, G., and Harvey, A. (2010). Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord.* 12, 459–472. doi: 10.1111/j.1399-5618.2010.00843.x

- Neumaier, J. F., Sexton, T. J., Yracheta, J., Diaz, A. M., and Brownfield, M. (2001). Localization of 5-HT(7) receptors in rat brain by immunocytochemistry, in situ hybridization and agonist stimulated cFos expression. *J. Chem. Neuroanat.* 21, 63–73. doi: 10.1016/s0891-0618(00)00092-2
- Pail, G., Huf, W., Pjrek, E., Winkler, D., Willeit, M., Praschak-Rieder, N., et al. (2011). Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology* 64, 152–162. doi: 10.1159/000328950
- Panda, S., Sato, T. K., Castrucci, A. M., Rollag, M. D., Degrip, W. J., Hogenesch, J. B., et al. (2002). Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. *Science* 298, 2213–2216. doi: 10.1126/science.1076848
- Patton, D. F., and Mistlberger, R. E. (2013). Circadian adaptations to meal timing: neuroendocrine mechanisms. *Front. Neurosci.* 7:185. doi: 10.3389/fnins.2013.00185
- Pendergast, J. S., and Yamazaki, S. (2014). Effects of light, food and methamphetamine on the circadian activity rhythm in mice. *Physiol. Behav.* 128, 92–98. doi: 10.1016/j.physbeh.2014.01.021
- Pickard, G. E., and Rea, M. A. (1997). Serotonergic innervation of the hypothalamic suprachiasmatic nucleus and photic regulation of circadian rhythms. *Biol. Cell* 89, 513–523. doi: 10.1016/s0248-4900(98)80007-5
- Poncet, L., Denoroy, L., and Jouvet, M. (1993). Daily variations in in vivo tryptophan hydroxylation and in the contents of serotonin and 5-hydroxyindoleacetic acid in discrete brain areas of the rat. *J. Neural Transm. Gen. Sect.* 92, 137–150. doi: 10.1007/bf01244873
- Rea, M. A. (1998). Photic entrainment of circadian rhythms in rodents. *Chronobiol. Int.* 15, 395–423. doi: 10.3109/07420529808998699
- Rea, M. A., Glass, J. D., and Colwell, C. S. (1994). Serotonin modulates photic responses in the hamster suprachiasmatic nuclei. *J. Neurosci.* 14, 3635–3642.
- Ruby, N. F., Brennan, T. J., Xie, X., Cao, V., Franken, P., Heller, H. C., et al. (2002). Role of melanopsin in circadian responses to light. *Science* 298, 2211–2213. doi: 10.1126/science.1076701
- Salvadore, G., Quiroz, J. A., Machado-Vieira, R., Henter, I. D., Manji, H. K., and Zarate, C. A. Jr. (2010). The neurobiology of the switch process in bipolar disorder: a review. *J. Clin. Psychiatry* 71, 1488–1501. doi: 10.4088/JCP.09r05259gre
- Sarkisyan, G., Roberts, A. J., and Hedlund, P. B. (2010). The 5-HT(7) receptor as a mediator and modulator of antidepressant-like behavior. *Behav. Brain Res.* 209, 99–108. doi: 10.1016/j.bbr.2010.01.022
- Smith, B. N., Sollars, P. J., Dudek, F. E., and Pickard, G. E. (2001). Serotonergic modulation of retinal input to the mouse suprachiasmatic nucleus mediated by 5-HT1B and 5-HT7 receptors. *J. Biol. Rhythms* 16, 25–38. doi: 10.1177/074873040101600104
- Sprouse, J. (2004). Pharmacological modulation of circadian rhythms: a new drug target in psychotherapeutics. *Expert Opin. Ther. Targets* 8, 25–38. doi: 10.1517/eott.8.1.25.26408
- Sprouse, J., Reynolds, L., Fujiwara, R., and Siuciak, J. (2003). *Circadian Rhythm Phenotype of 5-HT7 Receptor Knockout Mice: Greater Role for 5-HT1A in Mediating Drug-Induced Phase Shifts*. Program No. 512.8. Washington, DC: Society for Neuroscience.
- Sprouse, J., Reynolds, L., Li, X., Braselton, J., and Schmidt, A. (2004). 8-OH-DPAT as a 5-HT7 agonist: phase shifts of the circadian biological clock through increases in cAMP production. *Neuropharmacology* 46, 52–62. doi: 10.1016/j.neuropharm.2003.08.007
- Takahashi, J. S., DeCoursey, P. J., Bauman, L., and Menaker, M. (1984). Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature* 308, 186–188. doi: 10.1038/308186a0
- Weber, E. T., Gannon, R. L., and Rea, M. A. (1998). Local administration of serotonin agonists blocks light-induced phase advances of the circadian activity rhythm in the hamster. *J. Biol. Rhythms* 13, 209–218. doi: 10.1177/074873098129000057
- Wesołowska, A., Nikiforuk, A., Stachowicz, K., and Tatarczyńska, E. (2006). Effect of the selective 5-HT7 receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology* 51, 578–586. doi: 10.1016/j.neuropharm.2006.04.017
- Wesołowska, A., Tatarczyńska, E., Nikiforuk, A., and Chojnacka-Wójcik, E. (2007). Enhancement of the anti-immobility action of antidepressants by a selective 5-HT7 receptor antagonist in the forced swimming test in mice. *Eur. J. Pharmacol.* 555, 43–47. doi: 10.1016/j.ejphar.2006.10.001
- Westrich, L., Sprouse, J., and Sánchez, C. (2013). The effects of combining serotonin reuptake inhibition and 5-HT7 receptor blockade on circadian rhythm regulation in rodents. *Physiol. Behav.* 110–111, 42–50. doi: 10.1016/j.physbeh.2012.12.009
- Wirz-Justice, A., Benedetti, F., Berger, M., Lam, R. W., Martiny, K., Terman, M., et al. (2005). Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol. Med.* 35, 939–944. doi: 10.1017/s003329170500437x
- Ying, S. W., and Rusak, B. (1997). 5-HT7 receptors mediate serotonergic effects on light-sensitive suprachiasmatic nucleus neurons. *Brain Res.* 755, 246–254. doi: 10.1016/s0006-8993(97)00102-9

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