

# A Nonphotic Stimulus Inverts the Diurnal–Nocturnal Phase Preference in *Octodon degus*

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Mechanisms differentiating diurnal from nocturnal species are thought to be innate components of the circadian timekeeping system and may be located downstream from the circadian pacemaker within the suprachiasmatic nucleus (SCN) of the hypothalamus. In the present study, we found that the dominant phase of behavioral activity and body temperature (Tb) is susceptible to modification by a specific modality of behavioral activity (wheel-running activity) in *Octodon degus*, a mammal that exhibits multiple chronotypes. Seven *Octodon degus* exhibited diurnal Tb and locomotor activity (LMA) circadian rhythms while entrained to a 24 h light/dark cycle (LD 12:12). When the diurnal animals were provided unrestricted access to a running wheel, the overt daily rhythms in these animals inverted to nocturnal. This nocturnal pattern was sustained in constant darkness and returned to diurnal after removal of the

running wheel. Six additional animals exhibited nocturnal chronotypes in LD 12:12 regardless of access to running wheels. Wheel-running activity inverted the phase preference in the diurnal animals without changing the 24 hr mean LMA or Tb levels. Because wheel running did not increase the amplitude of the pre-existing diurnal pattern, simple masking effects on LMA and Tb cannot explain the rhythm inversion. The diurnal–nocturnal inversion occurred without reversing crepuscular-timed episodes of activity, suggesting that diurnal or nocturnal phase preference is controlled separately from the intrinsic timing mechanisms within the SCN and can be dependent on behavioral or environmental factors.

**Key words:** *Octodon degus*; circadian rhythms; wheel running; diurnal–nocturnal; nonphotic; body temperature; locomotor activity

The innate properties of the circadian pacemaker in the suprachiasmatic nuclei (SCN) are necessary and sufficient for the generation of mammalian circadian rhythms (Moore and Eichler, 1972; Stephan and Zucker, 1972; Ralph et al., 1990), but the mechanisms that determine the distinct temporal niches in diurnal, nocturnal, and crepuscular species are not known. Similar neuronal and metabolic activity patterns within the SCN of nocturnal and diurnal species (Inouye and Kawamura, 1979; Schwartz et al., 1983; Sato and Kawamura, 1984) and similar photic phase response characteristics in many diurnal and nocturnal mammals (Johnson, 1990) suggest that the manifest temporal niche may be determined primarily by factors that are downstream from the intrinsic pacemaker mechanism.

In some species, such as the *Octodon degus*, intraspecific variation in chronotype is reported. This hystricomorph rodent has been characterized as diurnal with major episodes of activity at dawn and dusk (Fulk, 1976; Labyak et al., 1997), but diurnal, nocturnal, and crepuscular chronotypes have been observed in the laboratory (Labyak et al., 1997). The factors accounting for differences in chronotype are not known, but expression of specific modalities of activity behavior may be important. For example, unrestricted wheel-running activity differentially elevates

nocturnal activity and body temperature levels in *degus* when they are entrained to a light/dark cycle (Kas and Edgar, 1998), raising the possibility that wheel-running activity influences the overall timing of behavioral activity and other biological rhythms in this species.

Activity-dependent modifications in the expression of circadian rhythms are currently thought to result from nonphotic zeitgeber effects on the phase control system within the SCN, from passive effects that mask the expression of the endogenous circadian rhythm independently from the pacemaker itself, or from some combination thereof. For example, vigorous activity systematically phase shifts circadian rhythms in nocturnal rodents [hamsters (Reebs and Mrosovsky, 1989); rats (Mistlberger, 1991)] and in humans (Van Reeth et al., 1994; Klerman et al., 1998) and can entrain circadian rhythms in nocturnal mice (Edgar and Dement, 1991). Wheel running can also influence entrainment by attenuating photic phase shifts in nocturnal species (Ralph and Mrosovsky, 1992), an effect thought to be mediated via serotonergic projections from the raphe nuclei to the SCN (Morin and Blanchard, 1991; Rea et al., 1994; Bradbury et al., 1997). Finally, wheel running can exert potent exogenous effects on physiological variables that mask their underlying endogenous circadian oscillation. In mice, wheel running potentially increases the duration of wakefulness episodes during the usual nocturnal activity phase but does not otherwise change the fundamental nocturnal timing of the circadian system (Welsh et al., 1988; Edgar et al., 1991a).

Whether these active and/or passive components of activity behavior account for variation in chronotype or otherwise alter the manifest phase preference in *Octodon degus* is unknown. To address this question, we investigated the timing and overt expression of behavioral activity and body temperature (Tb) circa-

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dian rhythms in *degus* housed with and without running wheels. We found that wheel-running activity inverted circadian rhythms in diurnal animals without altering entrainment of the underlying circadian pacemaker.

## MATERIALS AND METHODS

**Animals.** Thirteen adult (age 10–15 months) male *Octodon degus* were used in this study. The animals were individually housed in Nalgene cages (46 cm long  $\times$  24 cm wide  $\times$  20 cm deep) and maintained in a 24 hr light/dark cycle (LD 12:12; 4 W fluorescent bulbs; lights-on intensity, 30–35 lux). Food and water were available *ad libitum*. Ambient temperature was  $23 \pm 1^\circ\text{C}$ .

**Animal surgery.** Animals were sedated with diazepam (1.6 mg/kg, i.m.), anesthetized (2% isoflurane in medical grade oxygen), and surgically prepared with a miniature biotelemetry transmitter (Barrows, Palo Alto, CA) placed in the abdomen. This transmitter allowed continuous Tb and locomotor activity (LMA) recordings throughout the study. Prophylactic antibiotics were administered preoperatively (chloramphenicol; 30 mg/kg, s.c.) and postoperatively (gentamycin; 40 mg/ml, s.c.). Postoperative pain was managed with buprenorphine (0.03 mg/kg, s.c.). At least 3 weeks of recovery from surgery were permitted before initiation of data collection.

**Protocol.** Animals were individually isolated from environmental cues in a ventilated, light-proof, and sound-attenuating stainless steel recording chamber. Body temperature and LMA were monitored continuously while animals were subjected to four different experimental conditions implemented in succession. First, animals were monitored for at least 15 consecutive days while entrained to LD 12:12 without access to a running wheel. Second, a beveled running wheel (20 cm in diameter and 7 cm wide) was placed in each cage, and data were collected for at least 15 additional days in LD 12:12. Third, the lighting schedule was switched from LD 12:12 to constant darkness (DD; by disconnecting the power source to the lights at the beginning of the subjective night), and free-running circadian rhythms were monitored from animals with running wheels for at least 15 d. Fourth, running wheels were removed from the cages in DD, and data were collected for at least 15 d. In some animals, the order of these protocols was altered to confirm the lack of running-activity order effects on manifest circadian rhythms.

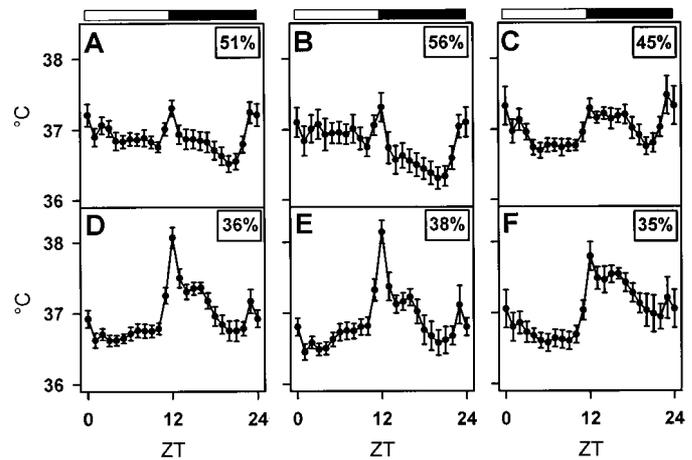
**Data collection and analysis.** Body temperature and LMA biotelemetry signals were detected by a telemetry receiver (Data Sciences, St. Paul, MN) beneath the cage. A microcomputer-based data collection system (Edgar et al., 1991b) sampled LMA as discrete events every 10 sec and Tb ( $^\circ\text{C}$ ) each minute. Mean waveforms for LMA and Tb were computed in hourly bins for each animal as described previously (Edgar et al., 1991a). Mean waveforms were based on 15 consecutive days of data per animal. For each animal, the amount of LMA during the light phase [the sum of LMA counts from zeitgeber time 0 (ZT0) to ZT12] was expressed as a percentage of its total daily amount of LMA (the sum of LMA counts from ZT0 to ZT24). Day–night differences and changes in total daily behavioral activity levels between conditions (with and without running wheels in LD 12:12) were assessed using a Student's *t* test (SigmaStat 1.0; Jandel Scientific, San Rafael, CA).

The effects of wheel-running activity on the manifest phase of Tb in LD 12:12 and DD were examined using digital raster plots. The vertical tick marks in the raster plots were plotted in a density proportional to body temperature values exceeding a 72 hr running mean (72 hr mean calculations moved stepwise in daily increments).

## RESULTS

### Wheel-running effects in LD 12:12

In LD 12:12, the group mean body temperature for the 13 animals studied exhibited crepuscular circadian waveforms (Fig. 1A). Consistent with previous observations in this species (Labyak et al., 1997), however, there were distinct individual day–night differences in average Tb and LMA rhythms. On the basis of the 24 hr distribution of LMA, the animals could be objectively classified into two groups: animals with a diurnal phase preference [ $>50\%$  of the total LMA during the subjective day ( $n = 7$ )] and animals with a nocturnal phase preference [ $<50\%$  of the total LMA during the subjective day ( $n = 6$ )]. The mean circadian waveforms for the Tb of animals with either a diurnal ( $56 \pm 2\%$



**Figure 1.** Mean Tb waveforms of animals without (*A–C*) or with (*D–F*) running wheels. On the basis of the individual day–night differences in LMA, the population of animals (*A*) was classified into two groups exhibiting either  $>50\%$  (*B*) or  $<50\%$  (*C*) of total LMA during the light phase [average percentages ( $\pm$  SEM of 1–4%) are indicated in the upper right corner of each graph]. Light/dark horizontal bars indicate the light/dark cycle.

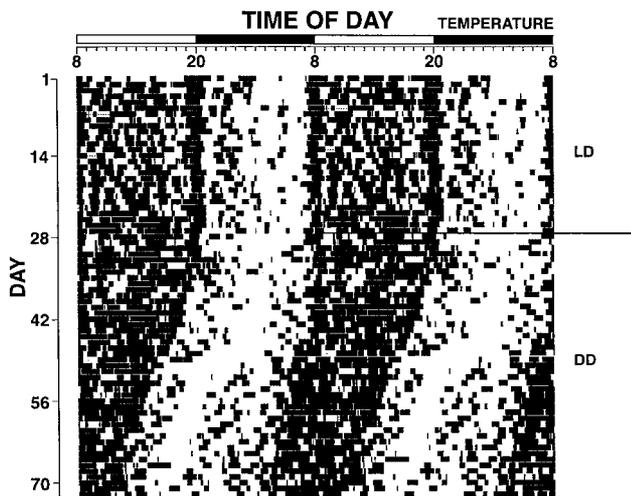
of the total LMA during the subjective day) or nocturnal ( $45 \pm 1\%$  of the total LMA during the subjective day) phase preference are shown in Figure 1, *B* and *C*, respectively.

During unrestricted access to a running wheel, all animals showed nocturnal phase preference while entrained to a light/dark cycle. Voluntary wheel-running activity resulted in a significant decrease of LMA during the subjective day in all animals (Fig. 1*D–F*). In animals with a diurnal phase preference (Fig. 1*B*), wheel-running activity inverted the phase preference from day to night (from  $56 \pm 2$  to  $38 \pm 3\%$  of total LMA during the subjective day;  $p = 0.0002$ ) and significantly increased the mean absolute Tb at night (Fig. 1*E*;  $p = 0.03$ ). Wheel-running activity inverted the diurnal–nocturnal phase preference in these animals without changing the overall behavioral activity levels [ $1792 \pm 179$  counts/24 hr (without running wheel) vs  $1790 \pm 258$  counts/24 hr (with running wheel);  $p > 0.9$ ] or the 24 hr mean Tb levels [ $36.8 \pm 0.1^\circ\text{C}$  (without running wheel) vs  $36.9 \pm 0.1^\circ\text{C}$  (with running wheel)]. In animals that expressed  $<50\%$  of the total LMA during the subjective day (Fig. 1*C*), nocturnal phase preference was sustained during unrestricted access to a running wheel (Fig. 1*F*). Also in these animals, wheel-running activity did not affect the total daily levels of behavioral activity [ $1837 \pm 221$  counts/24 hr (without running wheel) vs  $2136 \pm 377$  counts/24 hr (with running wheel);  $p > 0.5$ ]. Furthermore, the amount of LMA during the subjective day decreased significantly from  $45 \pm 1$  to  $35 \pm 4\%$  ( $p = 0.01$ ).

### Entrained versus free-running

To test whether the wheel-running-related inversion of phase preference depended on influences of the light/dark cycle, we also studied Tb and LMA circadian rhythms in DD. Animals that exhibited diurnal preference without running wheels (in LD 12:12) showed no changes in phase preference when lighting was switched to DD. The mean and above mean Tb levels were observed during the subjective day in both LD 12:12 and DD (Fig. 2).

In LD 12:12, animals with running wheels in the cage showed nocturnal phase preference for both Tb and LMA circadian



**Figure 2.** A double raster plot of Tb data obtained from a representative animal exhibiting a diurnal phase preference when housed without a running wheel in its cage. In LD 12:12 (LD; days 1–27), an entrained, diurnal rhythm of Tb was observed. In DD (days 28–73), the animal exhibited a circadian rhythm that free-ran (period length = 23.80 hr) from the phase of previous entrainment to the light/dark cycle. Vertical tick marks in the plot indicate when the Tb was equal to or above the mean Tb (see Materials and Methods). Light/dark horizontal bars on the TIME OF DAY-axis indicate the light/dark cycle. Lights were on from 08:00 to 20:00 (8 P.M.).

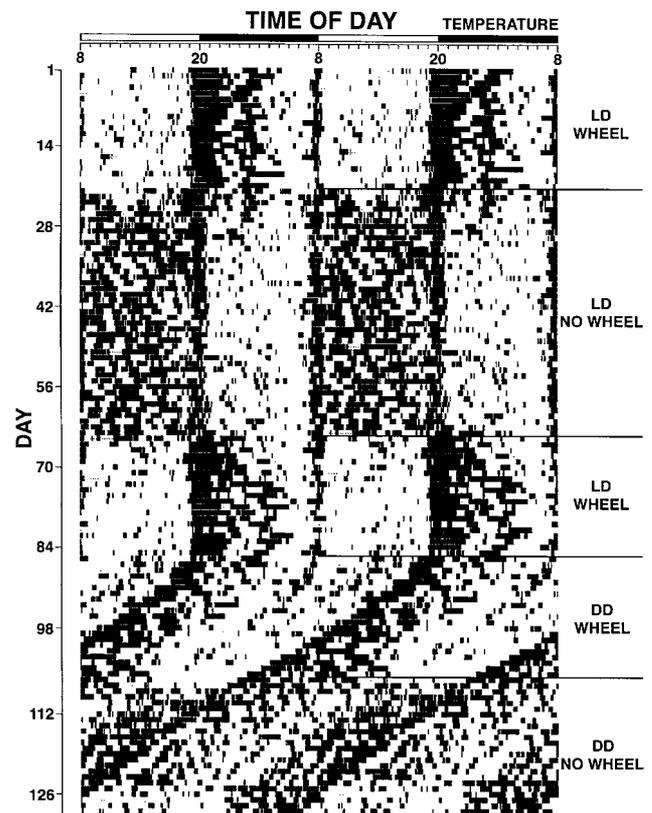
rhythms. Mean and above mean Tb levels were observed at night (Figs. 3, 4, days 1–22). Removal of the running wheel (in LD 12:12) inverted the phase preference from day to night within two circadian cycles (Fig. 3, day 23); however, no reversal of the crepuscular-timed episodes of activity [seen at circadian time 12 (CT12) and CT23] was observed. Reintroduction of a running wheel (Fig. 3, day 65) switched the temporal domain of activity back to nighttime (CT12–CT24), demonstrating that wheel-running-dependent inversion of phase preference is a reversible phenomenon. After release into DD the animals maintained the phase preference that was previously nocturnal (in LD 12:12) (Figs. 3, day 86, 4, day 23), demonstrating that this preference was not attributable to darkness but to the circadian phase of subjective night. Removal of the running wheel in constant darkness (Figs. 3, day 107, 4, day 72) inverted the phase preference, suggesting that the inversion of the temporal domain of activity behavior was caused by wheel-running activity.

### Crepuscular-timed activity

Although wheel-running activity inverted the temporal domain of activity from day to night, the episodes of activity at dawn and dusk remained entrained to LD 12:12. Wheel-running activity did not reverse the crepuscular-timed episodes of activity within a circadian cycle (Fig. 3, days 1–85). In DD, the endogenous period length of the dusk circadian component was initially shorter than the dawn component, causing a small transient change in their phase relationship. A stable phase relationship between the dawn and the dusk circadian component was established  $24 \pm 2$  d after the light source was disconnected. Consistent with observations in LD 12:12, the inversion of phase preference in DD occurred without reversing the crepuscular-timed episodes of behavioral activity within a circadian cycle (Figs. 3, 4).

### DISCUSSION

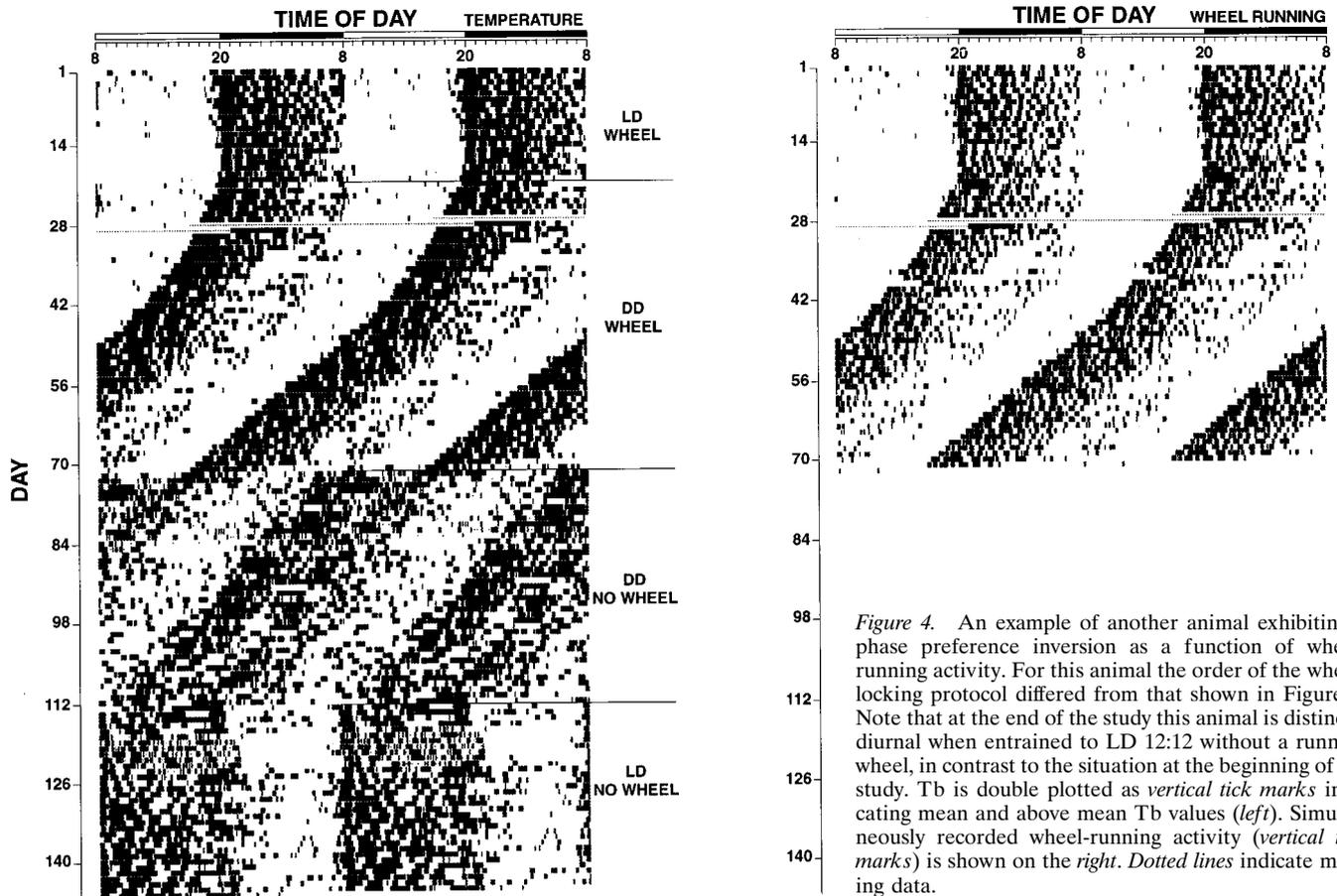
This study showed that unrestricted wheel-running activity can invert the diurnal Tb and LMA rhythms to nocturnal in *Octodon*



**Figure 3.** The inversion of phase preference as a function of wheel-running activity in *Octodon degus*. The timing of mean and above mean Tb is indicated by vertical tick marks (see Materials and Methods). In this representative animal, wheel-running activity inverted the phase preference in both LD 12:12 and in DD.

*degus*. Because the diurnal–nocturnal inversion was observed in both a light/dark cycle and constant darkness, the effect seems to be solely dependent on wheel-running activity. Comparable inversions in behavioral timing have been observed previously as a consequence of seasonal changes in photoperiod in salmon (Eriksson, 1973), “spontaneously” in the cotton rat (Johnston and Zucker, 1983), or as a function of wheel-running activity in voles that are exposed to a light/dark cycle (Gerkema et al., 1990). To our knowledge, however, diurnal–nocturnal inversions as a function of volitional wheel-running activity have not been observed in constant darkness within a species. Wheel running inverted the Tb and LMA phase preference to nocturnal in 100% of the animals classified diurnal under baseline conditions (without running wheels in LD 12:12;  $n = 7$ ). The other half of the population studied exhibited a nocturnal phase preference under baseline conditions ( $n = 6$ ), and wheel running increased the amplitude of the existing nocturnal Tb and LMA patterns.

The individual differences in the timing and expression of behavioral activity and Tb observed in *degus* without access to a running wheel are comparable with those previously reported for this species (Labyak et al., 1997). On the basis of variables derived from the behavioral activity and Tb rhythms, Labyak et al. (1997) classified *Octodon degus* into three chronotypes: morning, intermediate (crepuscular), and evening types. Morning and evening types also have been observed in humans (Foret et al., 1982). Our data suggest that wheel running may be a factor that contributes to variation in rhythm chronotypes within this species. Furthermore, even though the diurnal or nocturnal modality



**Figure 4.** An example of another animal exhibiting a phase preference inversion as a function of wheel-running activity. For this animal the order of the wheel-locking protocol differed from that shown in Figure 3. Note that at the end of the study this animal is distinctly diurnal when entrained to LD 12:12 without a running wheel, in contrast to the situation at the beginning of the study. Tb is double plotted as vertical tick marks indicating mean and above mean Tb values (left). Simultaneously recorded wheel-running activity (vertical tick marks) is shown on the right. Dotted lines indicate missing data.

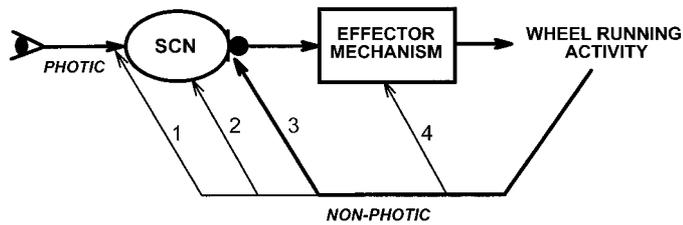
of a species is generally thought to be innate, the present data suggest that environmental and/or behavioral factors can dramatically alter the apparent modality of entrainment. Thus, activity-dependent diurnal–nocturnal inversion raises critically important issues regarding the criteria that define the circadian phenotype of a species.

The diurnal–nocturnal inversion observed in this study cannot be explained by simple masking effects of wheel-running activity on the Tb and LMA rhythms. Masking effects are influences of environmental or behavioral factors on the overt rhythm that are independent from the process of entrainment (Aschoff et al., 1982). For example, in mice, volitional wheel-running activity increases the amplitude of the circadian sleep/wake rhythm by increasing the amounts of wakefulness during the activity phase (Welsh et al., 1988; Edgar et al., 1991a). In the present study, wheel-running activity inverted the diurnal dominant phase of animals housed without running wheels rather than simply increasing the amplitude of the existing overt diurnal pattern. Therefore, classical masking effects of wheel running on Tb and LMA do not account for the inversion of the existing overt diurnal pattern observed in this study.

Wheel-running activity does not appear to invert the overt diurnal patterns to nocturnal by changing the fundamental mechanisms of circadian rhythm entrainment. Comparable with previous findings (Labyak et al., 1997; Kas and Edgar, 1998), our findings show that *degus* exhibited prominent crepuscular episodes of behavioral activity and Tb while entrained to a light/dark cycle. The crepuscular timing of behavioral activity is thought to reflect a circadian rhythm generated by at least two oscillators

that are coupled within the SCN (Pittendrigh and Daan, 1976). When entrained to a light/dark cycle, one oscillator synchronizes to dawn (morning oscillator), and the other synchronizes to dusk (evening oscillator). Wheel running inverted the temporal domain of LMA and Tb without reversing the crepuscular episodes of behavioral activity within a circadian cycle. Furthermore, inversion of the phase preference occurred almost instantaneously (within two circadian cycles) without evidence of phase transients (progressive changes in rhythm phase during the course of a phase shift), after the presentation or removal of the running wheel. Therefore, our data suggest that mechanisms determining the overt diurnal or nocturnal rhythm in this species are separate from phase control mechanisms within the circadian pacemaker.

The inversion of the overt rhythms may also be explained by circadian inhibition of some but not all of the behaviors at particular times of day. For example, in the present study, the circadian pacemaker potentially could inhibit wheel-running activity during the subjective day without inhibiting the expression of LMA during the subjective day in animals housed without running wheels. Circadian inhibition of wheel-running activity during the subjective day is evident in nocturnal mice (Edgar et al., 1997) and hamsters (Vogelbaum and Menaker, 1992). For example, when mice are subjected to a daily schedule of voluntary wheel running (e.g., 2 hr/d, starting at a fixed time every day), the wheel-running levels during the subjective day are suppressed when compared with that during the subjective night. In contrast to these reports, however, circadian inhibition of wheel-running activity during the subjective day is not observed in *Octodon degus* when given daily schedules of volitional wheel running



**Figure 5.** Activity-dependent influences on the mammalian circadian timekeeping system. The SCN generates circadian rhythms, such as wheel-running activity, via effector mechanisms. Wheel-running activity can influence photic transduction at the circadian pacemaker (arrow 1), can directly phase-shift the circadian pacemaker (arrow 2), and can impose exogenous influences on the overt rhythm by action on effector mechanisms (arrow 4). The present study suggests that wheel-running activity can also influence the circadian timekeeping system by inverting the phase preference (arrow 3) independent from the pathways noted above (arrows 1, 2, 4; see Discussion for further explanation).

similar to those used in mice (Edgar et al., 1997; M. J. H. Kas and D. M. Edgar, unpublished observations). On the basis of these observations and the evidence that diurnal wheel-running activity has been observed in *degus* (Labyak and Lee, 1995), it seems unlikely that strict nocturnal circadian control of wheel-running activity in *Octodon degus* accounts for the diurnal–nocturnal inversion observed in this study.

Because the diurnal–nocturnal inversion in *Octodon degus* is independent from interactions with the light/dark cycle, from simple masking effects of wheel running on the LMA and Tb rhythms, from pacemaker phase control, or from circadian inhibition of wheel running during the subjective day, the present study suggests that a nonphotic stimulus can modulate mechanisms that determine the phase preference in this species. On the basis of the present data, we hypothesize that these mechanisms are located peripheral to the intrinsic timing system within the circadian pacemaker (Fig. 5).

The biological advantages of the diurnal–nocturnal inversion of phase preference observed in this species are not known; however, the rapid change in phase preference (within two circadian cycles) suggests that it may serve as an adaptation mechanism to sudden changes in the species's natural environment. A field study reported that *Octodon degus* has both diurnal and nocturnal predators (Fulk, 1976). Although an inversion of the phase preference may increase survival of a species in response to a change in the temporal aspects of predation (e.g., seasonal effects on predator activity), the nature of the ecological changes in predator prevalence is not expected to be as sudden as the observed phase preference inversion. In addition to biotic factors (such as predator risk), abiotic factors (e.g., food intake, ambient temperature) may influence the timing of behavioral activity in a species. For example, wheel-running activity in *degus* could be anticipatory to other motivated behaviors [e.g., food intake (Mistlberger, 1994)] that somehow influence the manifest phase preference without altering the underlying circadian timing of activity at dawn and dusk. Alternatively, behavioral thermoregulation may contribute to activity-dependent phase preference. For example, ambient temperature affects the spatial distribution of *degus* in its natural environment, independent of predator pressure (Lagos et al., 1995). At high ambient temperatures (warm season, mean of  $27.2 \pm 1.5^\circ\text{C}$  with a maximum of  $39.3 \pm 2.9^\circ\text{C}$ ), *degus* selects covered rather than open microhabitats, indicating that this species compensates for external heat exposure by choosing sheltered areas (e.g., under shrubs) (Lagos et al., 1995). A laboratory

study showed that this species selects cooler ambient temperatures when Tb increases, suggesting that behavioral thermoregulation may influence activity levels in this species (Refinetti, 1996). In the present study, wheel-running activity (in LD 12:12) occurred at a time of day that is normally associated with cooler ambient temperatures, namely, the dark phase. This suggests that the animals selected the dark phase to compensate for the heat production during wheel running. However, our data provided evidence that this was not a passive response to changes in ambient temperature. For example, the day–night fluctuations of ambient temperature (in LD 12:12) in the recording environment were minimal ( $\pm 1^\circ\text{C}$ ). In addition, the nocturnal phase preference in animals with running wheels was sustained in the absence of the light/dark cycle, showing that *degus* selected to be active during the subjective night in situations in which the ambient temperature did not change over the circadian day. Thus, *degus* may be preprogrammed to change the timing of behavioral activity to reduce the risk of hyperthermia via a nonphotic feedback pathway that acts downstream from the intrinsic timing mechanism within the circadian pacemaker.

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