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Enhanced circadian photoresponsiveness after prolonged dark adaptation in seven species of diurnal and nocturnal rodents

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Abstract

Previous studies in mice and Syrian hamsters have described an enhancement of circadian photoresponsiveness after exposure to darkness for several weeks. The present study investigated the generality of the phenomenon in 3 diurnal and 4 nocturnal rodent species. In four of the species tested, phase delays of the running-wheel activity rhythm evoked by 1-h light pulses were several-fold larger after 3 to 4 weeks of exposure to darkness than after a single day. This drastic change in photoresponsiveness has important implications for the understanding of the process of photic entrainment. Differences between species that showed a significant effect of dark adaptation and species that showed no effect were not accounted for by temporal niche (diurnal versus nocturnal) or photic sensitivity (albino versus pigmented). Further research is needed to elucidate the mechanisms responsible for inter-species differences in the occurrence of enhanced photoresponsiveness after dark adaptation and to identify the neural substrates of this phenomenon in species that exhibit it.

Keywords

Circadian rhythm; Photic entrainment; Dark adaptation; Locomotor activity; *Arvicanthis niloticus*; *Meriones unguiculatus*; *Mus musculus*; *Mesocricetus auratus*; *Octodon degus*; *Phodopus sungorus*; *Rattus norvegicus*

1. Introduction

Regular, daily oscillations in the level of behavioral and autonomic variables are a ubiquitous feature of mammalian physiology, as well as of the physiology of most eukaryotes. Many of these regular oscillations in mammals are generated by a circadian pacemaker located in the suprachiasmatic nuclei of the hypothalamus [8,31].

Although circadian rhythms can be generated by the circadian pacemaker in the absence of environmental time cues, synchronization to the external world requires sensitivity to such cues. Resetting of the pacemaker by light makes possible the entrainment of the pacemaker by the environmental light-dark cycle, so that activities and functions appropriate for the day time are performed during daylight hours whereas activities and functions appropriate for the night time are performed during the hours of darkness.

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In order for entrainment to occur, the period of a rhythm must be altered to match the period of the light-dark cycle. According to the non-parametric theory of entrainment [24], the matching of the two periods is attained by daily phase shifts that equal the difference between the period of the light-dark cycle and the period of the pacemaker. Appropriate resetting of the circadian pacemaker is possible because its sensitivity to light is not uniform throughout the day; rather, it varies according to a phase-response curve (PRC) that is usually characterized by a phase-delay region during early subjective night, a phase-advance region during late subjective night, and a “dead zone” during most of subjective day [1,15].

In studies of photoresponsiveness of the circadian system, very little attention has been paid to the previous history of photic stimulation of the animals. In many studies, animals were kept in darkness for the duration of the study and were repeatedly exposed to light pulses at intervals of 10 to 46 days without intermediary re-entrainment to a light-dark cycle [6,18-21,25,26,33,34,40,41], so that the actual state of dark adaptation of the animals at the time of each pulse could not be ascertained. In other studies, light-pulse tests were consistently preceded by a standardizing light-dark cycle but the interval in darkness prior to the pulse ranged from 5 to 21 days across studies [4,5,9,10,22,30,39,42,43]. Only three studies in Syrian hamsters [7,35,36] and two studies in mice [27,28] have systematically investigated the effect of duration of dark exposure on circadian photic responsiveness. These studies showed that the magnitude of phase shifts evoked by light pulses is greater the longer the animals are maintained in darkness, up to several weeks [7,27,28,35,36], which implies that most previous studies of phase-response functions had an inherent design flaw.

The finding that the magnitude of phase shifts depends on the duration of previous exposure to darkness has important implications not only for laboratory studies of photic phase-response functions but also for studies of animal behavior in the wild. For instance, animals that are in darkness but have recently been exposed to a natural light-dark cycle are likely to have their circadian pacemakers closely in phase with the zeitgeber and, therefore, not to require large shifts in order to re-establish entrainment. On the other hand, animals that have been in darkness for several weeks (in a burrow or underground tunnel, for example) are likely to have drifted from the appropriate phase angle of entrainment and, consequently, will require greater phase shifts in order to re-establish entrainment. Thus, greater responsiveness to light in dark-adapted animals may be an adaptive feature of the circadian system.

Because the effects of dark adaptation on circadian photoresponsiveness have been studied in only two rodent species (mice and Syrian hamsters), both of them nocturnal, the present study was designed to verify the generality of the phenomenon in four nocturnal and three diurnal species.

2. Materials and methods

2.1. Animals

Seven rodent species were used in the study. The three diurnal species were the Nile grass rat (*Arvicanthis niloticus*), the degu (*Octodon degus*), and the Mongolian gerbil (*Meriones unguiculatus*). Whereas Nile grass rats are consistently diurnal, only approximately 50% of degus and Mongolian gerbils are diurnal [32]. Only degus and gerbils deemed to be diurnal were used in this study. The four nocturnal species were the Wistar rat (*Rattus norvegicus*), the domestic mouse (*Mus musculus*), the Siberian hamster (*Phodopus sungorus*), and the Syrian hamster (*Mesocricetus auratus*). Two strains of mice were used: CD-1 (albino) and C57BL/6 (pigmented). Rats, mice, gerbils, and Syrian hamsters were purchased from Charles River Laboratories (Wilmington, MA). Siberian hamsters were purchased from Sun Pet Ltd. (Atlanta, GA) and degus from Sandy's Lakeside (Gaffney, SC). Nile grass rats were obtained from our own colony [29]. All animals were 2 to 5 months old during the study. Baseline data (but no

phase-shift data) from some of the animals have been previously analyzed and published in a separate article [32].

2.2. Equipment

All animals were housed individually in polypropylene cages ($24 \times 36 \times 19$ cm) lined with wood shavings and fed Purina rodent chow (Lab Diet 5001) and water ad libitum. A metallic running wheel (12 cm diameter for species under 80 g and 18 cm diameter for larger species) was attached to each animal cage. Magnetic switches attached to the running wheels were connected to data acquisition boards (Digital Input Card AR-B2001, Acrosser Technology, Taiwan). The data acquisition boards were connected to computers that recorded the number of wheel revolutions in 6-min bins (i.e., 0.1 h intervals).

The animal cages were maintained in individual light-tight, ventilated chambers at 24 ± 2 °C. Lighting conditions in each chamber were controlled by a programmable electronic timer (ChronTrol XT, ChronTrol Corp., San Diego, California) that activated white fluorescent bulbs (General Electric F4T5CW) generating an illuminance of approximately 360 lux (range: 340 to 390 lux across chambers), as measured 8 cm above the cage floor. When called for by the experimental protocol, pulses of white light were administered in each animal's own isolation chamber (1 h, 360 lux) without physical disturbance of the animals. To further reduce disturbance, cages and water bottles were replaced only at monthly intervals, under dim red light if necessary.

2.3. Procedure

All animals were housed under a light-dark cycle with 12 hours of light per day (LD 12:12) for two or more weeks before being released into constant darkness (DD). The same LD cycle was used for all species for the purpose of uniformity. For species that exhibit strong reproductive seasonality (such as the Siberian hamster), however, LD 12:12 does not provide sufficient daily illumination to prevent reproductive inhibition. This was deemed to be an acceptable cost for the institution of a uniform LD cycle for all species, particularly because exposure to short photoperiods enhances (i.e., does not inhibit) circadian photoresponsiveness in Siberian hamsters [26].

Single light pulses (1 h, 360 lux) were presented at one of six times after the beginning of DD: 1, 7, 14, 21, 30, or 40 days. Day 0 was the first day on which the lights did not come on as usual. For each species, 3 to 7 animals were stimulated at each of the intervals of exposure to DD. Approximately 20% of the animals were stimulated at more than one interval. In these cases, the second pulse was always preceded by at least 2 weeks of LD (to cancel any effect of previous exposure to DD) followed by the appropriate interval of DD.

The exact circadian times (CT) at which the light pulses were presented were adjusted to each species according to published phase-response curves. By convention, the time of activity onset is designated as CT 0 for diurnal species and as CT 12 for nocturnal species. In order to achieve the largest expected phase delay of the activity rhythm, pulses were presented at CT 14 for Nile grass rats [30], laboratory rats [41], and Syrian hamsters [33], at CT 15 for degus [16] and Siberian hamsters [26], and at CT 16 for mice [18]. Because no phase-response curve has been published for Mongolian gerbils, CT 15 was chosen as a tentative optimal circadian time for this species. Previous studies in mice and Syrian hamsters have indicated that the effects of dark adaptation are comparable in the phase-delay and phase-advance regions of the PRC [7, 27,28].

2.4. Data analysis

Running wheel data were plotted as actograms, and circadian times were determined from the actograms using the daily onset of activity as CT 0 (for diurnal species) or CT 12 (for nocturnal species). Phase shifts were determined by drawing separate eye-fit lines through the onsets for 5 or 6 days before and 6 or 7 days after the pulse (discarding days with transients, if present) and calculating the time between the two lines on the first cycle following the pulse. For pulses presented on the first day in DD, the pre-pulse circadian phase was computed using a single onset (the onset on day 0). In most cases, the onset time on day 0 was similar to the onset times under the previous LD cycle. Several mice, however, exhibited earlier onsets (by 1 or 2 h) on day 0 because of photic masking under the previous LD cycle.

The duration of the active phase of the circadian cycle (α) was calculated as the time difference between the offset and onset of activity in the actograms. Determinations of free-running period were accomplished by the chi-square periodogram procedure [38] using data from day 8 to day 17 in DD (10 days). Additional statistical analysis involved comparison of group means by analysis of variance (ANOVA), post hoc pairwise comparisons by Tukey's HSD test, and computation of linear regressions by the principle of least squares [13].

3. Results

Actograms of activity patterns of representative mice and Mongolian gerbils are shown in Fig. 1. Mice exhibited robust rhythms of running-wheel activity with regular onsets in DD. Light pulses presented to CD-1 mice at CT 16 evoked small phase delays on the 7th day in DD (A) and much greater phase delays on the 40th day in DD (B). Gerbils exhibited weak activity rhythms, and the daily onsets in DD were too variable to allow reliable determination of circadian phase (C). The remaining species exhibited activity rhythms of variable robustness, but phase shifts could be reliably determined in all of them, as exemplified in Fig. 2.

Figure 3 shows the mean phase delays evoked by the light pulses presented at the 6 time points for all species except Mongolian gerbils (for which it was not possible to compute phase shifts). A significant effect of the duration of exposure to constant darkness on the magnitude of phase shifts was found for CD-1 mice ($F_{5, 17} = 5.261$, $p = 0.004$), Syrian hamsters ($F_{5, 17} = 7.468$, $p = 0.001$), Wistar rats ($F_{5, 16} = 16.796$, $p < 0.001$), and degus ($F_{5, 21} = 6.354$, $p = 0.001$), but not for C57BL/6 mice ($F_{5, 22} = 1.481$, $p = 0.236$), Siberian hamsters ($F_{5, 22} = 1.742$, $p = 0.166$), or Nile grass rats ($F_{5, 28} = 0.773$, $p = 0.579$). In the four species in which dark adaptation had a significant effect, the functions became asymptotic by 3 to 4 weeks after transfer to constant darkness. The greatest effect of dark adaptation was observed in Wistar rats (0.1-h shift on day 1 and 3.4-h shift on day 40). The smallest significant effect was observed in degus (0.4-h shift on day 1 and 1.6-h shift on day 40).

Analysis of the duration of the active phase of the circadian cycle (α) in animals that were maintained in DD for 40 days prior to receiving the light pulse revealed a gradual decompression of α in some, but not all, species. Figure 4 shows the mean results for Nile grass rats, Syrian hamsters, and Siberian hamsters. Whereas a significant decompression was observed in Syrian hamsters ($F_{3, 9} = 12.632$, $p = 0.002$), α remained relatively constant in Nile grass rats ($F_{3, 6} = 0.099$, $p = 0.957$) and in Siberian hamsters ($F_{3, 12} = 1.583$, $p = 0.244$).

An index of gain in photoresponsiveness was computed as the slope of linear regression of the magnitude of phase shift on the duration of exposure to darkness (in units of hours per day) for each species. A coefficient of correlation was then computed for the gain index and the decompression of α (quantified as α_2/α_1 , the quotient of α computed at 35 days after exposure to DD divided by α computed at 5 days after exposure to DD). As shown in Fig. 5A, the gain index was not significantly correlated with the decompression of α .

A coefficient of correlation was also computed for the gain index and the absolute difference between the free-running period of the species and 24.0 h ($|\tau - 24|$). As shown in Fig. 5B, the gain index was not significantly correlated with $|\tau - 24|$. The free-running periods of the various species are listed in Table 1.

4. Discussion

Of seven species investigated in this study, four exhibited significantly enhanced circadian photoresponsiveness after prolonged dark adaptation. One of the species in which enhanced photoresponsiveness could not be demonstrated was the Mongolian gerbil, whose activity rhythm was too imprecise to allow evaluation of phase shifts. In mice, one strain (CD-1) exhibited enhanced photoresponsiveness, whereas another (C57BL/6) did not. Thus, 4 of 7 groups properly tested exhibited enhanced photoresponsiveness after prolonged dark adaptation, which indicates that the phenomenon is not universal but is certainly not limited to the two species previously investigated (mice [27,28] and Syrian hamsters [7,35,36]).

Among the diurnal species, enhanced photoresponsiveness was observed in degus but not in Nile grass rats. Among the nocturnal species, enhanced photoresponsiveness was observed in CD-1 mice, Wistar rats, and Syrian hamsters but not in C57BL/6 mice and Siberian hamsters. Thus, it does not seem that the phenomenon of enhanced photoresponsiveness is segregated according to temporal niche. Enhanced photoresponsiveness was particularly evident in albino animals (CD-1 mice and Wistar rats), but it was also observed in pigmented animals (degus and Syrian hamsters). Hence, the increased photosensitivity associated with albinism is not a requirement for enhanced circadian photoresponsiveness.

Alteration in the phase relationship between two putative oscillators that control the evening and morning bouts of activity has been invoked to explain changes in the activity/rest ratio and concomitant increase in circadian photoresponsiveness [17]. Consistently with this explanation, the magnitude of light-induced phase shift was shown to correlate with the duration of the active phase of the circadian cycle (α) in Syrian hamsters bearing the *tau* mutation [35]. In the present study, Syrian hamsters did exhibit both an increase in the magnitude of phase shifts and a decompression of α after prolonged exposure to darkness, but no significant correlation was found across species (Fig. 5A). Thus, although there may be a causative association between decompression of α and enhanced photoresponsiveness in Syrian hamsters, such association is not generalizable to other rodent species.

Inter-species differences in the enhancement of photoresponsiveness by dark adaptation might also be explained by inter-species differences in the magnitude of phase shifts required for entrainment. That is, species with free-running periods (τ) farther away from 24.0 h require greater phase shifts to attain entrainment [24], and they might benefit more from enhanced photoresponsiveness than do species with free-running periods close to 24.0 h. Thus, species with large values of $|\tau - 24|$ should exhibit greater gains in photoresponsiveness after prolonged exposure to constant darkness. The current results do not support this hypothesis, however. The index of gain in photoresponsiveness was not significantly correlated with $|\tau - 24|$ (Fig. 5B).

The effect of dark adaptation in the circadian system (enhanced phase-shifting response) resembles that observed in the visual system (enhanced visual sensitivity), except that full dark adaptation in the visual system is achieved in less than one hour [3], whereas full adaptation in the circadian system of rodents takes up to 3 or 4 weeks [7,27,28, and Fig. 3 in this study]. A few other non-visual effects of dark adaptation have also been described in the literature. Two recent studies on humans have provided suggestive evidence that prolonged exposure to darkness or dim light may enhance the suppression of melatonin secretion by nocturnal photic stimulation [14,37].

A previous study on mice provided experimental support for the hypothesis that enhanced circadian photoresponsiveness results from the lack of exposure to light per se and not from collateral effects of exposure to constant darkness (such as absence of entrainment) [28]. The neural bases of enhanced circadian responsiveness remain unknown, however. The mammalian circadian system uses all three of the known retinal photopigments (rhodopsin, cone opsin, and melanopsin) [12,23], and any or all of them may be involved in the process of circadian dark adaptation. A recent study on Wistar rats documented a progressive increase in melanopsin expression in retinal ganglion cells during 5 days of exposure to constant darkness [11], which places melanopsin as a possible candidate for the substrate of dark adaptation in the circadian system.

The meager knowledge of neural substrates notwithstanding, the effect of dark adaptation on circadian photoresponsiveness can be substantial, as evinced by the results of this study. For instance, on the day after release into constant darkness, phase delays of only a few minutes are evoked in CD-1 mice and Wistar rats; three weeks later, phase delays of 2 to 3 hours can be evoked (Fig. 3). This has important implications for the non-parametric theory of entrainment [24]. Because full dark adaptation of the circadian system requires 3 to 4 weeks in darkness, animals maintained under full light-dark cycles in the laboratory or in nature are not dark adapted. They are photically stimulated each day and, consequently, have a reduced responsiveness to light. For CD-1 mice, for example, one would expect a maximal phase delay of 0.4 h in response to a 1-h light pulse presented on the first circadian cycle following the termination of an LD 12:12 cycle (day 0). Considering that the free-running period of mice is 23.6 h on average, a maximal daily phase delay of 0.4 h would prevent entrainment to LD 12:12 for all mice with circadian periods shorter than average. Yet, all mice can entrain to LD 12:12, and many can entrain to LD cycles with periods up to 28 h [2]. A normal LD cycle contains more than just 1 h of light per day, but how the additional light contained in an LD cycle produces the full shift required for entrainment in non-dark-adapted mice (and other species) remains to be elucidated. It likely involves the integration of discrete light-induced shifts as well as a continuous effect of photic stimulation on the pacemaker.

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Fig. 1.

Actograms of running-wheel activity of two representative mice (left) and a representative gerbil (right). In each actogram, time of day is indicated on the horizontal axis and number of days on the vertical axis. The dark and light rectangles above the actograms indicate the duration of the dark and light phases of the prevailing light-dark cycle. **A** (mouse): a 1-h light pulse presented at CT 16 on the 7th day in darkness (open circle) evoked a small phase delay of the activity rhythm. **B** (mouse): a 1-h light pulse presented at CT 16 on the 40th day in darkness (open circle) evoked a large phase delay of the activity rhythm. **C** (gerbil): although a rhythmic pattern of activity was evident both under a light-dark cycle (LD) and in constant darkness (DD), the daily onsets of activity in DD were rather variable and did not allow reliable determination of circadian phase.

Fig. 2.

Actograms of running-wheel activity of representative individuals from four species: Nile grass rat (A), degu (B), Siberian hamster (C), and Wistar rat (D). In each actogram, time of day is indicated on the horizontal axis and number of days on the vertical axis. The animals were in darkness and received a single 1-h light pulse (360 lux) at the time indicated by the open circle.

Fig. 3.

Magnitude of phase delays evoked by 1-h light pulses (360 lux) presented at different times after transfer to constant darkness. Each bar corresponds to the mean ($\pm$ SE) phase delay exhibited by 3 to 7 individuals. The ordinates are scaled differently for different species.

Fig. 4.

Mean ($\pm$ SE) duration of the active phase of the circadian cycle (α) as a function of time spent in DD for Nile grass rats, Syrian hamsters, and Siberian hamsters.

Fig. 5. Gain in circadian photoresponsiveness as a function of the decomposition of α (A) and as a function of the absolute difference between the free-running period of the species and 24.0 h (B).

Table 1

Free-running periods (h) computed from day 8 to day 17 in DD in animals previously maintained under LD 12:12 for two or more weeks

<i>Species</i>	<i>Mean</i>	<i>SE</i>
C57BL/6 mouse	23.67	0.05
CD-1 mouse	23.58	0.06
Siberian hamster	23.81	0.04
Syrian hamster	24.09	0.02
Wistar rat	24.22	0.03
Nile grass rat	23.94	0.04
Degu	23.71	0.08
Mongolian gerbil	24.24	0.05