

Entrainment and Phase Shifting of Circadian Rhythms in Mice by Forced Treadmill Running

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MARCHANT, E. G. AND R. E. MISTLBERGER. *Entrainment and phase shifting of circadian rhythms in mice by forced treadmill running*. *PHYSIOL BEHAV* 60(2) 657–663, 1996.—Daily schedules of spontaneous, drug-, or novelty-induced running can entrain circadian rhythms in rodents. Forced running, by contrast, has been reported to have weak or no effects, although a thorough comparative study in a single species is lacking. To fill this gap, drinking or activity rhythms were monitored in C57 mice subjected to daily, 3-h bouts of forced treadmill running or to 3-h daily access to home cage running wheels. Entrainment to treadmill running was observed in 17/27 mice, and to restricted wheel access in 11/20 mice. Entrainment was affected by availability of a home cage wheel (e.g., 14/16 mice with no wheel entrained to treadmill running). Phase angle of entrainment was related to prior circadian period (τ), and τ following entrainment exhibited aftereffects. No mice entrained to a 3-h daily schedule of water access, suggesting that entrainment to scheduled running was not related to water or associated food intake. Phase shifts in response to single 3-h bouts of treadmill running or wheel access were small and not reliably induced. The entrainment paradigm is thus recommended for further study of behavioral effects on the mouse circadian system; forced running, in particular, offers several methodological advantages. The results do not support prior suggestions that forced and voluntary activity differ in value as nonphotic zeitgebers.

Wheel running C57 mice Nonphotic zeitgebers Water restriction Exercise

THE circadian system in rodents consists of at least one master circadian pacemaker, located in the hypothalamic suprachiasmatic nuclei (SCN) [9], that is entrained by certain periodic environmental stimuli (zeitgebers), such as light–dark (LD), and that in turn drives circadian rhythms in behavior and physiology. This system has traditionally been conceptualized as hierarchical, to the extent that coupling forces were thought to be exerted from zeitgeber to pacemaker, and from pacemaker to behavior, and not in the opposite direction. However, considerable evidence has accumulated demonstrating that spontaneous wheel-running activity, a pacemaker-driven process, can alter pacemaker period (τ) in rats [26], mice [5], and possibly hamsters [11]; but see [19]. In addition, induction of activity or arousal, by a variety of different methods, at certain phases of the circadian cycle can phase shift free-running rhythms in hamsters [13,14,20,21,23] and mice [10]; repeated induction of activity at the same time each day can entrain free-running rhythms in mice [4], hamsters [14,20,22], and rats [11], and can alter the phase angle of entrainment to LD cycles in hamsters [12,16]. Absence of wheel running in response to these stimuli is usually associated with no effect on circadian phase or τ [with exceptions, cf. [6,13,17]]. The motion of the pacemaker thus appears to be subject to both acute

and tonic (feedback) modulation by one or more physiological correlates of locomotor activity.

Some progress has already been made toward identifying at least one of several possible proximate neural pathways by which behavior can modulate the SCN circadian pacemaker in hamsters [2,7]. Additional proximate and distal components of this nonphotic entrainment system remain to be elucidated in this and other species. However, progress may be impeded by the fact that experimental interventions, such as pharmacological antagonists and neural ablations, may attenuate spontaneous or induced levels of wheel-running activity, thus confounding the interpretation of any observed deficit in nonphotic entrainment or shifting [cf., (3,8,18,25)]. One means of circumventing this problem may be to use forced running in a treadmill device. In principle, treadmill running should provide the best experimental control of running intensity and duration, and may overcome deficits in the ability or motivation to run by presenting a simpler locomotor task coupled with a strong incentive. However, entrainment by forced treadmill running has so far been demonstrated in only one study in rats, and, by comparison with some other methods for inducing activity in other species, its effects were characterized as weak (11). Moreover, there have been un-

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published reports that forced running is ineffective in mice (Edgar, personal communication) and hamsters [de Vries and Meijer, cited in (15)], two species that can be readily entrained by unforced scheduled wheel running. These reports of weak or no entrainment by forced running but strong entrainment by voluntary running have contributed to suggestions that the motivation to run may play an important role in determining the potency of behavioral activity as a zeitgeber (6,12,17). In light of this theoretical issue, and the potential advantages of forced treadmill running as a behavioral tool for studying nonphotic entrainment, we compared the ability of forced and voluntary activity to entrain or acutely phase shift the circadian system of mice. We found that when scheduled on a 3-h daily basis, both methods produced equally robust entrainment, but when applied as single 3-h "pulses" at one of two circadian phases, phase shifts were modest and not consistently obtained.

METHOD

A total of 114 male C57BL/6j mice (2–4 months; Charles River, Montreal) were individually housed in plastic cages (47 × 26 × 20 cm) equipped with wire floors, 17 cm running wheels, and contact drinkometers monitored continuously using Activity Counting System interface and software (Simon Fraser University). The mice were first habituated to their home recording cages in a 14:10 LD cycle before blinding by enucleation.

Experiment 1

This experiment examined the effects of daily schedules of forced treadmill running or voluntary home cage wheel running on circadian activity or drinking rhythms. Each mouse ($N = 74$) was assigned to one of the following groups.

Group 1a. This group had forced treadmill running (3 h/day, 6 days/week, 48 days; $N = 11$), with free access to the home cage wheel. The mice were removed from their home cages each day and transported to an automated treadmill in a separate test room. Each mouse was run in a separate lane (45 × 12 × 9 cm) at 16 m/min, with one 10-min rest provided each hour. Running speed was gradually increased to the target level within the first 5–10 min of each session. The mice were thus required to run about 2.8 km in 3 h. Each lane was equipped with a compressed air source triggered if the mouse rode the treadmill to the back of the lane. The mice proved to be avid treadmill runners and were able to run at 16 m/min within the first 3-h session without injury. When mice appeared entrained to treadmill running, access to the home wheel was blocked for 6 days/week.

Group 1b. This group had forced treadmill running (3 h/day, 42 days, $N = 16$), with no access to a home cage wheel. This procedure controlled for possible interactions between home cage wheel running and scheduled treadmill running. Entrainment was assessed by monitoring drinking activity alone.

Group 2a. This group had restricted access to the home cage wheel (3 h/day, 6 days/week, 48 days, $N = 12$). The home cage wheel was manually unlocked at a fixed time each day. The mice were not otherwise induced to run. Drinking activity was not recorded in this group; thus, the home cage wheel was left unlocked for 45 consecutive hours (two circadian cycles) once each week as a "probe" test to assess circadian phase.

Group 2b. This group had restricted access to the home cage wheel (3 h/day, 42 days, $N = 8$), with no weekly probe tests, and thus no access to the home wheel outside of the 3-h daily session. Circadian phase was assessed by drinking activity alone. This condition replicates Edgar and Dement (5).

Group 3. This group had restricted access to water (3 h/day, 53 days, $N = 5$). Forced and voluntary running bouts were as-

sociated with increased drinking during or after the daily session. A water restriction condition was thus included to assess whether a scheduled bout of drinking (and associated food intake) can alone serve to entrain free-running rhythms in the mouse. Circadian phase was assessed by home cage wheel-running activity.

Group 4. This group was undisturbed controls ($N = 22$, 60–80 days). These animals were not directly disturbed, but were exposed to noise in the recording room associated with removal of other animals for treadmill running.

Experiment 2

This experiment examined whether single 3-h bouts of running scheduled at either circadian time (CT) 6 or CT21 could phase shift free-running rhythms in blind mice ($N = 39$). Circadian time was calculated with respect to the onset of the daily "active" period (measured here using drinking activity), which is designated CT12 by convention; CT6 thus represents 6 circadian hours ($6 \times \tau/24$) before activity onset. Running was induced by treadmill (16 m/min) or by unlocking the home cage wheel. Mice in a treadmill "control" group were transferred to the treadmills for 3 h, but were not run. None of these groups had free access to home cage wheels. Individual mice were used for up to three tests in different conditions or circadian test times.

Data Analysis

Data were periodically transferred to a Macintosh computer for display and analysis using Circadia (Behavioral Cybernetics, MA). Data were visually inspected in the form of actograms and average waveforms. Mice were scored as entrained if drinking or home cage wheel-running rhythms assumed a stable phase relation to the imposed activity schedule during at least the last 7 days of the activity schedule, and free-ran from that phase when the schedule was terminated. The time required to achieve a stably entrained state was calculated by fitting a regression line to the beginning of the daily activity period (defined by either drinking activity or wheel running) during the last 7–10 days of the activity schedule and identifying the first day when activity onset occurred within 30 min of this line. Free-running τ before and after exposure to daily running schedules was quantified by regression lines fit to activity onset. The slope of the lines was calculated by computer. Phase shifts in response to single bouts of scheduled running were quantified by comparing regression lines fit to 7–10-day blocks immediately preceding or following the sessions. Lines were fit by both authors, independently, with at least one blind to the conditions. Averages of the two estimates were used. Significance of differences between the three conditions and two circadian times was assessed by ANOVA and Tukey HSD tests. All means are reported + SEM.

RESULTS

Experiment 1

Forced treadmill running entrained free-running rhythms in 3/11 mice that had continuous access to a running wheel in their home cages (group 1a; e.g., Fig. 1A). The latency to entrainment within this group of three mice was estimated at 2–10 days. In the entrained state, the onset of home cage activity (CT12) preceded the daily treadmill session by 7–8.5 h (the difference between scheduled activity and CT12 in the entrained state will be referred to as the phase angle of entrainment). Among the eight mice that did not entrain, most showed modulations of free-running rhythms. These included a 6-h phase advance in one mouse when the treadmill session

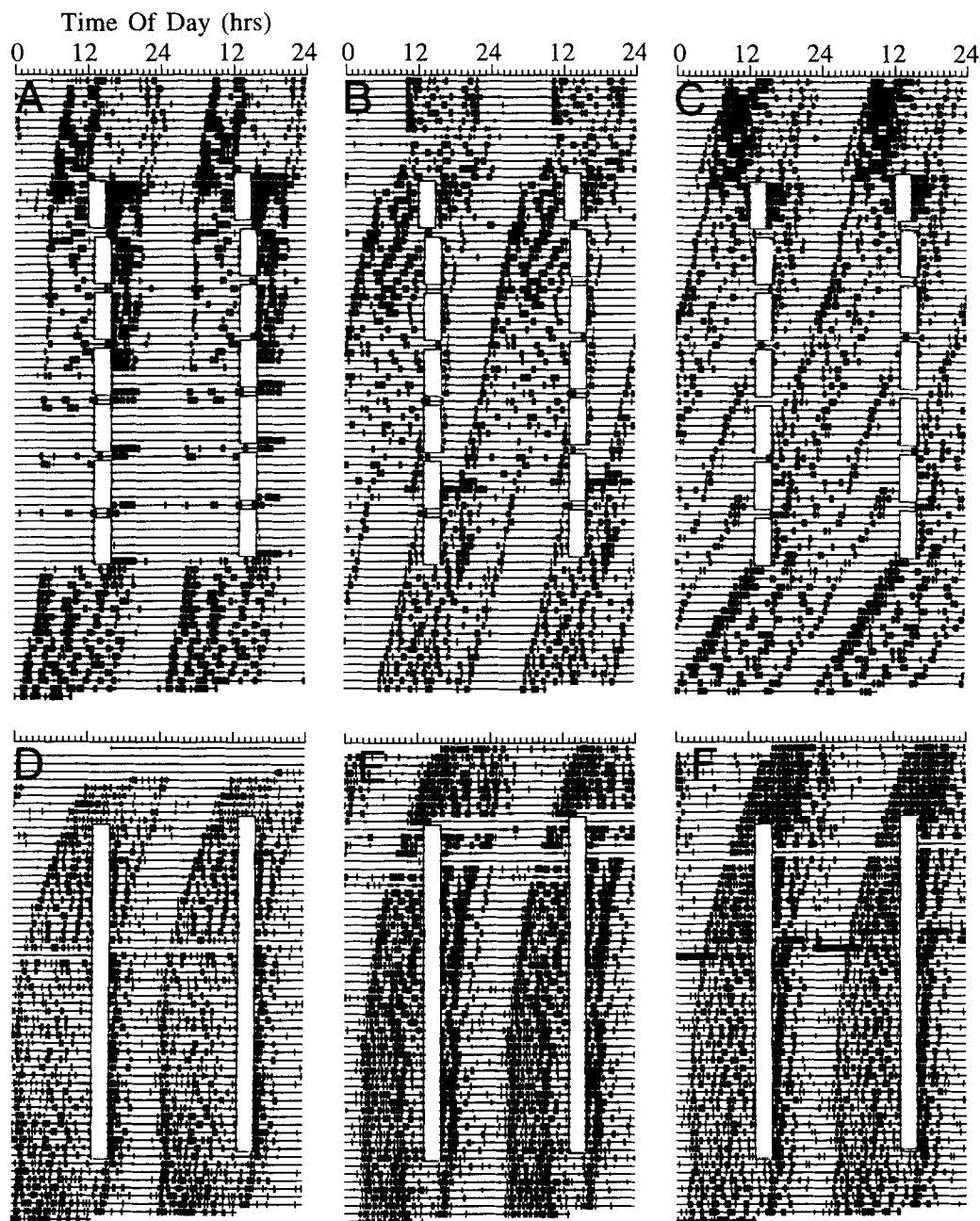


FIG. 1. Double-plotted activity or drinking charts from mice subjected to forced treadmill running. Each line represents 48 consecutive hours, plotted in 10 min bins from left to right. Consecutive days are also aligned vertically. Vertical deflections on each line represent bins in which wheel running (charts A–C) or drinking (D–F) were detected. Hours when mice were removed from their cages for treadmill running are bracketed and whited out on the second of each double plot. (A). Mouse that entrained to forced treadmill running. During the last 3 weeks of treadmill running, the home cage running wheel was blocked for 6 days/week to ensure that entrainment was not due to wheel running after treadmill sessions. (B) Mouse that exhibited a large phase advance when treadmill running occurred at about CT6. (C) Mouse that exhibited τ changes and apparent splitting. (D–F) Three mice from group 1b (no home cage wheel) that entrained to treadmill running.

overlapped with CT5–8 (Fig. 1B), a 3-h phase delay in another mouse after the first treadmill session (CT19–22), and τ changes in most of the other mice (e.g., Fig. 1C). The mouse illustrated in Fig. 1C showed a pattern reminiscent of “splitting,” with a component of activity appearing to uncouple

from the beginning of the subjective night and recoupling with the end of the subjective night.

When the mice were returned to their home cages after treadmill sessions, they usually showed prominent bouts of home cage wheel running (e.g., Fig. 1A). Conceivably, entrainment may

have been mediated by this bout of voluntary running stimulated in response to forced running. To test this, a second group (group 1b) of mice that did not have access to home cage wheels were subjected to scheduled treadmill running. Of these, 14/16 showed stable entrainment (e.g., Fig. 1D–F). The latency to entrainment was estimated at 23 ± 2 days, and the onset of the daily active period (measured by the drinking rhythm) during steady-state entrainment preceded the treadmill session by 11.2 ± 0.6 h. One of the mice that did not clearly entrain within 42 days showed a slowing of τ , suggesting that stable entrainment would likely have been achieved if the schedule had been continued. The other mouse showed modulations of τ indicative of relative coordination. The difference in percentage of animals entraining within groups 1a and 1b was significant ($p < 0.001$).

Scheduled access to the home cage wheel produced results very similar to 3-h forced treadmill running. Among mice whose wheels were unlocked for 45 h “probe” tests each week to assess circadian phase (group 2a), 5/12 entrained to the 3-h daily wheel access (e.g., Fig. 2A). Modulations of τ were common in mice that did not entrain (e.g., Fig. 2B). Among mice that had access to home cage wheels for 3 h/day without weekly probe tests, 6/8 entrained (Figs. 2D–E), and one appeared likely to entrain if the schedule had been continued. The latency to and phase angle of entrainment were very similar in these two groups, and averaged 23.7 ± 0.8 days and 12.0 ± 0.4 h, respectively ($N = 11$, pooled). These values did not differ significantly from those obtained from mice that entrained to forced treadmill running.

Mice that did entrain to restricted home cage wheel access ran when the wheel was unlocked, averaging 2843 ± 530 wheel counts/3 h (range of 1026–8092 counts/3 h across animals), and were on most days active for at least the first hour of wheel access, and usually for the entire 3 h. The amount of running in some of these mice varied widely from day to day. Among mice that did not entrain, some showed little or no running on most days, whereas others ran a great deal (over 5000 counts/3 h) at some circadian phases of wheel access (CT12–23), but not at other phases (usually about CT0–11). In these cases, failure to entrain may have been due to a failure to run sufficiently at the critical phase.

Mice that entrained to treadmill or home cage wheel access exhibited a group mean free-running τ of 23.53 ± 0.04 h during the week prior to entrainment ($N = 27$, one case missing sufficient preentrainment data), and 23.80 ± 0.03 h during the first 7–10 days following entrainment (paired $t = 6.56$, $p < 0.0009$). Mice that did not entrain to scheduled treadmill or home cage running ($N = 20$) exhibited pre- and postschedule τ s of 23.67 ± 0.05 h and 23.63 ± 0.04 h, respectively (paired $t = 0.687$, $p > 0.5$). Free-running τ of these mice prior to the activity schedules was, as a group, significantly longer (i.e., closer to 24 h) than τ of mice that did entrain ($t = 2.70$, $p = 0.01$). The failure of these mice to entrain is thus not related to unusually short τ , although it is conceivable that observed τ was outside of the range of entrainment in some individual cases.

Among the 28 mice that entrained to scheduled activity, the latency to entrainment ranged from 2–33 days and the phase angle of entrainment ranged from 8–16 h. The phase angle of entrainment was related to τ prior to entrainment, such that shorter τ was associated with a more advanced phase (i.e., a longer interval between CT12 and the beginning of scheduled running) (Pearson $r = 0.407$, $p = 0.04$). The latency to entrainment was not related to τ , but was related to the circadian phase at which the first session of scheduled running began. The phase of the first session ranged from CT13 to CT22 across animals; the later the phase on day 1 of scheduled running, the shorter the latency ($r = -0.673$, $p < 0.0009$). Differences in latency are

thus at least in part due to individual differences in the timing of the first (and thus subsequent) sessions. The group mean phase of the first session did not differ between mice that entrained and those that did not.

During scheduled wheel access and following treadmill running sessions, visual inspection of actograms and average waveforms revealed considerable drinking activity. To test whether drinking mediated entrainment, five mice were subjected to a 3 h/day water access schedule. None of these animals entrained, although modest τ changes were observed in two cases (e.g., Fig. 2C). Free-running τ of these animals was similar to the other groups (23.68 ± 0.03 h).

A total of 22 mice were allowed to free-run without direct physical disturbance. Free-running τ measured for the weeks before and after the activity schedules carried out on neighboring mice was 23.74 ± 0.07 h and 23.62 ± 0.05 h, respectively (paired $t = 1.91$, $p = 0.07$). τ lengthened (i.e., moved toward 24 h) from time 1 to time 2 in only 3/22 cases. No spontaneous phase shifts or rhythm dissociations were apparent (e.g., Fig. 2F).

Experiment 2

The effects of single, 3-h bouts of treadmill running, treadmill transfer without running, and home cage running at two circadian phases are summarized in Fig. 3. From a total of 90 tests only a few very clear phase shifts were obtained (e.g., Fig. 4A, B). Nonetheless, a significant effect of treatment and circadian phase was evident, $F(5, 84) = 5.39$, $p < 0.0009$. The mean shift induced by forced treadmill running at CT6 (21 ± 8 min, i.e., a phase advance) differed significantly from that induced at CT21 (-12 ± 4 min, i.e., a phase delay; $p < 0.001$), although it did not differ from the mean shift induced by transfer to the treadmill without running (6 ± 4 min; $p = 0.2$). The mean shift induced by unlocking the home wheel at CT6 (15 ± 6 min) differed marginally from the shift induced by home wheel access at CT21 (-3 ± 3 min; $p = 0.04$). Due to technical limitations, the amount of wheel running expressed during wheel access was recorded in only 13/26 cases. Nonetheless, a significant relationship was evident between the amount of running and the absolute shift size (i.e., the greater the running response, the larger the phase advance or delay in this subsample) ($r = 0.590$, $p = 0.03$).

DISCUSSION

This study demonstrates that daily schedules of either forced treadmill running or voluntary home cage wheel running can entrain circadian rhythms in blind mice, with the following characteristics under the conditions used: 1) entrainment was generally preceded by an extended period of transients, as the free-running rhythm gradually phase delayed until a stable phase was attained. 2) The stable phase attained was related to τ prior to the activity schedule; shorter τ was associated with a more advanced phase angle of entrainment, suggesting that the pace-maker attains maximal phase delays late in the subjective night or early in the subjective day, about 10–14 h after CT12. 3) Following the schedules, drinking or wheel-running rhythms free-run from the apparent phase of entrainment, with τ exhibiting “aftereffects” (i.e., τ was closer to 24 h after entrainment than before). These characteristics of entrainment, and the percentage of animals entraining, did not differ between the forced and voluntary running groups, suggesting that these two methods of inducing activity, at the parameters utilized, have a similar potency and common mechanism.

Scheduled activity appeared to be a more potent zeitgeber when mice did not have free access to a home cage wheel, because the percentage of animals entraining was significantly

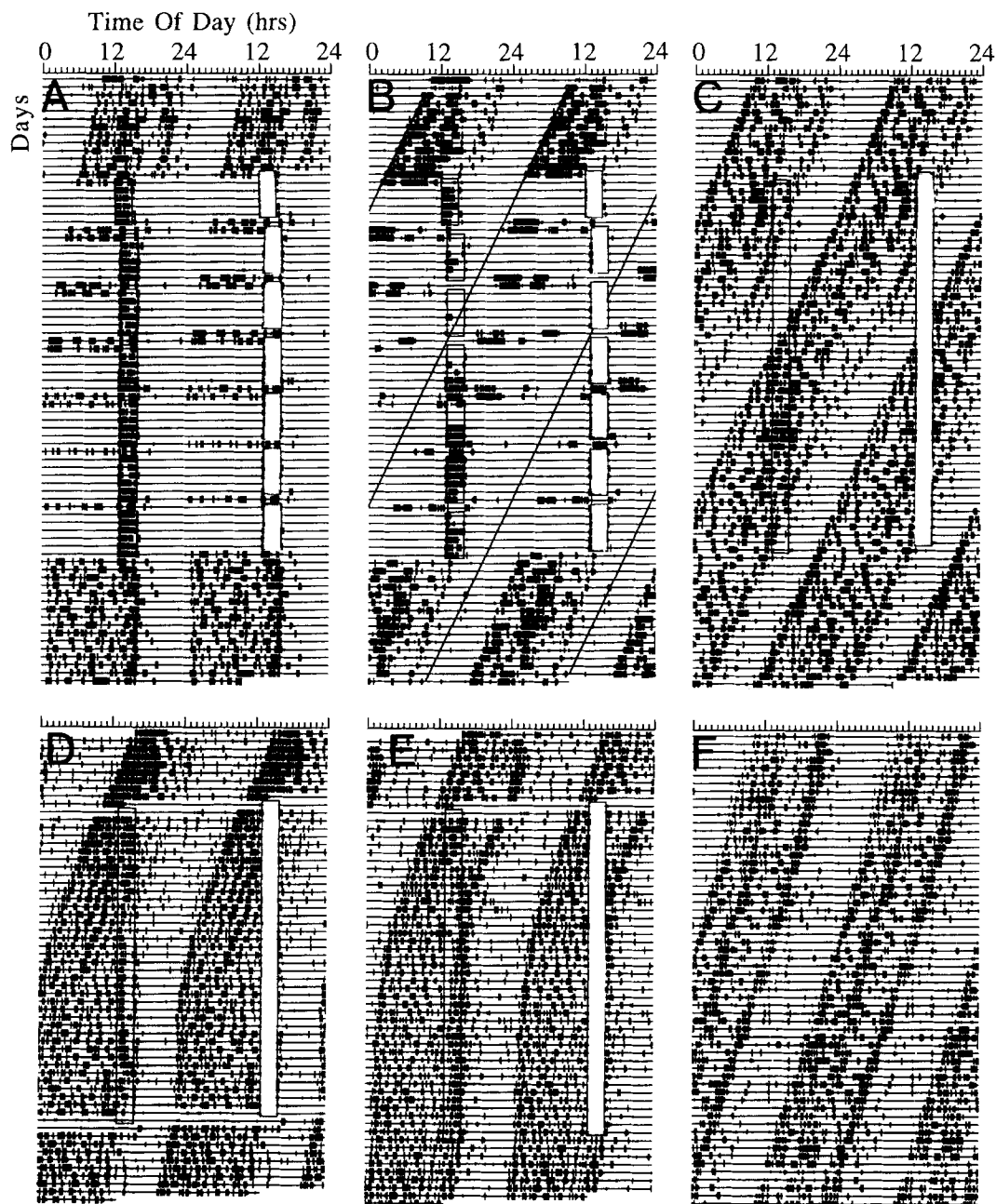


FIG. 2. (A) Double-plotted wheel running chart of a mouse from group 2a that entrained to 3 h/day access to home cage wheel. (B) Wheel-running rhythm of a mouse that did not entrain to wheel restriction, but that exhibited τ changes (illustrated by forward extrapolation of a regression line fit to activity onsets prior to wheel restriction). (C) Mouse that did not entrain to scheduled daily water access. (D–E) Drinking records from two mice from group 2b that did entrain to scheduled daily wheel access. (F) Wheel running of control mouse. Plotting conventions as in Fig. 1.

greater in these groups (groups 1b and 2b). Similar observations have been made previously with respect to the phase-shifting effects of triazolam in hamsters (24) and the entraining effects of treadmill running in rats (11). The mechanism for this is unclear. In the present study, it is not explained by a difference in τ prior to the running schedules, nor can it be attributed to differences in the amount of experimentally induced running, because all animals in the forced running groups had to run the same distance in the same time (2.8 km/3 h). Whatever the cause, the result

provides confidence that entrainment to forced treadmill running is not dependent on bouts of voluntary, home cage running triggered in mice after they have been returned from daily treadmill sessions. The failure of mice to entrain to daily schedules of water access also suggests that entrainment was not likely due to eating or drinking during or just after daily activity sessions.

Although daily 3-h schedules of treadmill or home wheel activity were clearly effective zeitgebers for entraining free-running rhythms (particularly in mice without free access to home cage

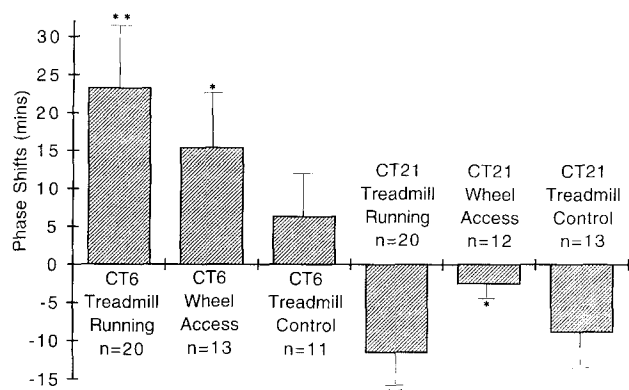


FIG. 3. Mean $\pm$ SE phase shifts induced by 3-h treadmill running, treadmill transfer without running, or home cage wheel access at CT6 and CT21. **Significantly different at $p < 0.001$, * $p < 0.05$.

wheels), single 3-h bouts of treadmill or home wheel running had very modest phase-shifting effects when applied at CT6 or CT21 in mice that did not have free access to home cage wheels. These CTs were selected on the basis of previous studies of nonphotic zeitgebers in hamsters and mice, which suggested that maximal advances to a bout of running should be obtained at about CT4–9, and maximal delays between CT21 and CT3. Of particular relevance, we have previously observed in C57 mice some large phase advances to injections of morphine in the CT3–9 range, an effect that was apparently dependent on the expression of intense, drug-induced cage and wheel activity following the injections [10]. Some results from the first treadmill group were consistent with these expectations; one very large advance was observed when treadmill activity overlapped with CT4–8, one large delay was observed following treadmill activity at CT18–21, and the first three mice entrained within 2–10 days, with treadmill activity producing the requisite phase delays at about CT21. Nonetheless, no similarly large phase shifts were observed in the 3-h activity “pulse” experiment, regardless of the method used to induce activity.

However, in light of the general characteristics of entrainment observed in Experiment 1, this should not be surprising. Apart from the single large phase advance noted, there was virtually no other evidence of advancing shifts or transients when scheduled activity overlapped with CT3–12 (or any CT for that matter). Moreover, when treadmill sessions overlapped with CT13–21, a large number of small delaying transient cycles were evident before steady-state entrainment was achieved, suggesting that the pacemaker is subject to low amplitude (<30 min?) phase delays through this portion of its circadian cycle, culminating in maximal phase delays (30–40 min?) in the CT21–3 range. Larger phase shifts may have been observed if 1) the running stimulus was longer or more intense (although 16 m/min is near maximal for a 3-h session), or 2) other circadian phases had been assessed. For many animals, maximal phase delays may have been more readily obtained in the CT0–3 range, rather than CT21–0, although, again, we saw little evidence for large shifts in animals that ran at these circadian phases without entraining.

In summary, the results of this study indicate that both forced and voluntary running are effective nonphotic zeitgebers for entraining free-running rhythms in mice. However, neither stimulus, at the intensity–duration parameters used, proved sufficient to reliably induce large, readily apparent phase shifts when applied as a single “pulse”. Thus, the entrainment paradigm would clearly seem to be the more useful for further study of the mechanisms

by which nondrug-induced behavioral activity affects the circadian system in mice. In addition, forced treadmill running may offer some special advantages, because it is at least the equivalent of voluntary running in efficacy (percentage of animals entrained), it can be used to generate activity at circadian phases when mice voluntarily may run very little (i.e., CT3–12), and it can potentially overcome deficits in running ability or motivation secondary to experimental interventions used to elucidate neural mechanisms. The drawbacks worth noting are the expense of treadmill equipment, the labor required for transferring animals on a daily basis, and the amount of time necessary to establish entrainment.

Finally, we note that the results do not support previous suggestions that forced running is in some way qualitatively different from voluntary activity in its effects on circadian rhythms [cf. (15)]. The results are instead more consistent with the idea that the stimulus to run is less important for the circadian system than is the intensity, duration or timing of running [also see (13)]. Given the present data, this would seem to be a reasonable work-

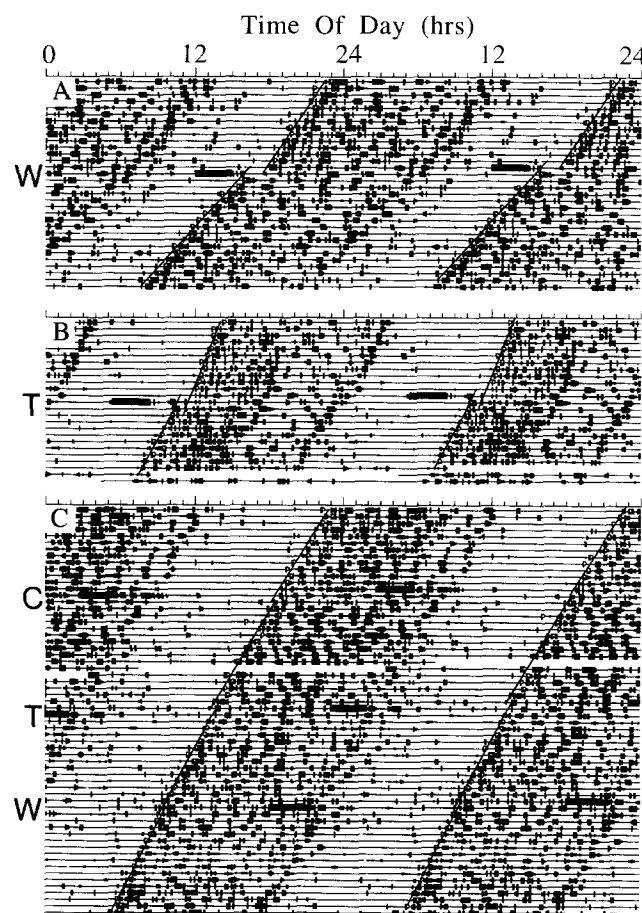


FIG. 4. Drinking rhythms illustrating phase shifts induced by scheduled running (indicated by opaque rectangles). (A) The 110-min phase advance following 3-h access to the home cage wheel (W; mouse ran 3300 half revolutions). (B) The 50-min phase advance following a treadmill session (T) at CT6. (C) The 20-min phase delaying following “control” transfer to treadmill without running (C), 30-min phase delay following a treadmill session at CT21, and 20-min phase delay following 3-h access to the home cage wheel (mouse ran 6000 half revolutions). Plotting conventions as in Fig. 1.

ing hypothesis for mice. Previous observations of relatively weak entrainment effects of treadmill running in rats may be a function of the treadmill parameters used (faster running rates are possible in highly trained rats) or could represent a true species difference, as was argued in that study (11). The absence of reports [and anecdotal negative reports; cited in (15)] of entrainment or phase shifts to forced running in hamsters probably has more to do with the poor response of hamsters to coercion than to properties of forced running per se (unpublished observations). In any case,

more comparative work is needed to evaluate how the circadian systems of different species respond to different methods of evoking behavioral arousal and activity before definitive statements can be made about the motivational and stimulus correlates of running that may be necessary and sufficient for entrainment.

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