

# Phase Shifts to Refeeding in the Syrian Hamster

## Mediated by Running Activity

RALPH E. MISTLBERGER,<sup>1</sup> S. V. SINCLAIR, E. G. MARCHANT AND L. NEIL

*Department of Psychology, Simon Fraser University, Burnaby, BC V5A 1S6 Canada*

Received 18 April 1996; Accepted 19 August 1996

MISTLBERGER, R. E., S. V. SINCLAIR, E. G. MARCHANT AND L. NEIL. *Phase shifts to refeeding in the Syrian hamster mediated by running activity*. *PHYSIOL BEHAV* 61(2) 273–278, 1997.—Circadian rhythms in hamsters can be entrained by restricted daily feeding schedules. Phase control may be exerted by feeding per se, or by wheel running in anticipation of food access. Phase modulation by feeding was examined here by depriving hamsters of food for 9–24 h and refeeding at 1 of 7 different zeitgeber times on the first day of constant dim light. Significant group mean phase-advance shifts were observed only following 24 h and 17 h deprivations ending in the mid-subjective day, 7 h before the usual time of lights off (mean shifts 28 min and 66 min, respectively). The largest phase shifts were associated with wheel running during the first 6 h of refeeding. When running wheels were locked during this time in an additional group, no phase shifts were observed. A trend for small phase delays was evident for 14 h deprivations ending at the beginning of the subjective night, but no significant group mean or individual shifts were observed at other refeeding times. Refeeding after food deprivation, thus, appears to have minimal effects on circadian phase in hamsters; wheel running associated with refeeding may account for occasional shifts observed. Copyright © 1997 Elsevier Science Inc.

Circadian rhythms    Entrainment    Wheel running    Nonphotic zeitgebers

IN MANY species, circadian rhythms of foraging and feeding are plastic, rather than rigid, and can be shifted to exploit environmental opportunities or exigencies. There are potentially three mechanisms by which the circadian system could adjust behavior to regularities or changes in feeding time: 1. Feeding events might uncouple from the master light-dark (LD) entrainable circadian pacemaker (in mammals, the suprachiasmatic nuclei, SCN) a secondary oscillator or pacemaker that would coordinate behavior with feeding time without necessarily altering the phase of photic entrainment; 2. the phase of the LD-entrained pacemaker (or secondary food-entrained pacemaker) at which feeding occurs may be recognized and recorded, for subsequent use as a discriminative cue to guide foraging in time and place; 3. single feeding events might directly shift the phase of the LD-entrained pacemaker.

There is good evidence for the first two of these three mechanisms. A number of species exhibit a daily rhythm of anticipatory activity to a scheduled feeding time, regardless of when in the LD cycle this meal occurs (6,21). Anticipatory rhythms can track (within limits) non24-h feeding cycles independent of the LD cycle, can persist in the absence of food, and are not disrupted by ablation of the LD-entrainable SCN pacemaker [reviewed in (6,21)]. These and other properties suggest that food-anticipatory rhythms represent the output of a separate food-entrainable pacemaker. In addition to anticipating feeding time, a few species have also been shown capable of discriminating the circadian phase of scheduled feeding times by associating unique feeding places with unique feeding times (4,23,24). In rats, this discrim-

ination process can be mediated by a food-entrainable pacemaker in the absence of the SCN (23).

By comparison, good evidence for the third potential mechanism, direct shifting of the light-entrained pacemaker by feeding, is meager. There are two kinds of relevant experiments, those in which animals are fed at the same time each day for a number of days (i.e., entrainment studies), and those in which animals are food-deprived for some duration and then refeed at a particular circadian phase (i.e., phase-response studies). Entrainment studies are common, and have produced substantial evidence for food anticipation and a food-entrainable pacemaker (6,21), but are confounded in what they can tell us about shifting of the LD-entrained SCN pacemaker by feeding. In some of these studies, rats or hamsters were restricted to a single meal each day in the middle of the light period of the LD cycle (normally their rest phase), and nocturnal activity onset appeared to shift forward, although in most cases this was not explicitly noted or quantified (e.g., 8,9,20,31). This could represent shifting of the LD-entrained pacemaker by feeding, or it could represent a component of activity driven by the food-entrained pacemaker [dubbed “succeeding activity” by Aschoff, and thought to constitute the tail end of “alpha” of this pacemaker (3)]. Moreover, if the LD-entrained pacemaker is shifted in food-anticipating animals, this could be secondary to internal coupling forces between food and light-entrainable pacemakers (34), or to the anticipatory activity and arousal associated with the daily mealtime. Single bouts of running activity in the middle of the usual inactive period can

<sup>1</sup>To whom requests for reprints should be addressed. E-mail: mistlber@sfu.ca

phase-advance or entrain circadian rhythms in rodents, independent of feeding (e.g., 27,29,30,37,38). Running activity and arousal could account for cases in which scheduled feeding has entrained free-running rhythms in rats (rarely) (e.g., 34) and hamsters (more commonly) (e.g., 1,20).

Phase-response studies of refeeding in mammals have been uncommon and less systematic, and we have found only 3 examples, each using a different species. One study of the marsupial *S. m. froggatti* reported large phase shifts ranging from 1–7 h in magnitude following 3-day bouts of food deprivation in constant dark (DD) (11). All of the shifts were advances, and there was no apparent relation between the shift and the phase at which refeeding occurred, although the number of data points at the circadian phases sampled was small. The animals were previously subjected to a 3 h/day restricted feeding schedule; thus, it is possible that shifts were due to refeeding, to increased activity, or some other consequence of food deprivation, or to some interaction between the light-entrainable free-running pacemaker and a separate, previously food-entrained pacemaker. Three-day bouts of food deprivation were also used in a study of rats free-running for several weeks in DD and constant light (LL) (10). No phase shifts were detected to refeeding at a range of circadian phases in DD, but large delays and advances, again in the 1–7 h range, were observed to refeeding in LL. Phase dependency was unclear, but a general trend was for phase delays following refeeding in the late subjective day (usual inactive phase for rats), and phase advances following refeeding in the late subjective night (active phase), a phase response profile more similar to photic than nonphotic stimuli (27). The differential effect of DD and LL may be related to pacemaker amplitude, because rhythm amplitude, in rats, attenuates more rapidly in LL (e.g., 12) and amplitude may be one determinant of phase-shift magnitude (16). One final study of hamsters also utilized a 3-day deprivation period and refeeding at a range of circadian phases, with a consequent small *n* (26). Small (<1 h) phase changes, primarily advances, were observed and, again, there was no relation to circadian phase. Activity levels were significantly increased during food deprivation, and this may have contributed to the shifts observed.

It has recently been proposed that acute feeding episodes might directly phase-shift the LD-entrainable pacemaker in hamsters via activation of growth hormone-releasing hormone afferents to the SCN (36). Given the paucity of evidence that feeding can shift the SCN pacemaker independent of activity, and the general interest in identifying true nonphotic zeitgebers for phase resetting of mammalian rhythms, we conducted an additional phase-response study of refeeding in fasted hamsters. We first evaluated a range of deprivation durations and circadian phases of refeeding and then focused on refeedings in the middle of the subjective day, which was the only phase at which we saw significant shifting. When the hamsters were prevented from wheel running during the first 6 h of refeeding at this phase, no shifts were observed. The results suggest that phase shifts to refeeding are dependent on the expression of wheel-running activity and, thus, provide no support for the idea that feeding can directly shift the phase of LD-entrained rhythms by a feeding-specific pathway to the SCN pacemaker.

#### METHODS

Adult, male Syrian hamsters (*n* = 86, 2–4 months old, Charles River, Montreal, Canada) were housed individually in plastic cages (45 × 25 × 20 cm) equipped with 17-cm running wheels and wire-mesh floors. The cages were maintained in isolation cabinets with controlled lighting (LD 14:10; 20 lx lights

on) and ventilation fans. Wheel-running activity was detected by microswitches and recorded continuously by computer (Activity Counting System, Simon Fraser University).

Phase shifts were assessed using a modified version of the Aschoff Type II procedure, in which the test stimulus (i.e., refeeding) occurs on the first day of DD (2). This procedure has several advantages; It avoids changes in pacemaker properties with prolonged exposure to constant conditions, it has better ecological validity than prolonged DD or LL, and it is convenient (28). Hamsters show minimal aftereffects on the first few days of DD, and these are accounted for by appropriate control DD tests (i.e., no test stimulus). After at least 2 weeks of acclimation to home cages and the lighting schedules, the hamsters were placed in DD (dim red light, 1 lx) for 4–6 days. Food was removed either prior to or during the first night of DD, and replaced at a selected zeitgeber time 9–24 h later (ZT; corresponding to clock time, where dark onset under LD 14:10 is designated ZT12 by convention). Seven different refeeding ZTs were examined, with 10–17 hamsters per test (see Fig. 1; deprivation duration in brackets); ZT0 (20 h), ZT3 (15 h), ZT5 (24 h and 17 h), ZT9 (21 h), ZT12 (14 h), ZT15 (9 h), ZT18 (21 h). The timing of these deprivations is illustrated in Fig. 2A–D. To evaluate the contribution of wheel running to phase shifting, an additional 17-h deprivation test ending at ZT5 was conducted, in which the running wheels were locked for the first 7 h (ZT5–12) after refeeding. Individual hamsters were subjected to one control DD test without food deprivation and either 1 or 2 food-deprivation tests. All tests were separated by at least 5 days of exposure to LD. In this first study, no attempt was made to match deprivation duration across ZT condition. Hamsters exhibit circadian rhythms of food intake and wheel running (39); thus, it is difficult in principle to match food-deprivation duration and energy expenditure for deprivations ending at different ZTs.

To measure phase shifts, activity data were transferred to a Macintosh computer for analysis using Circadia (Simon Fraser University). Activity onsets were detected automatically according to the following definition; An onset was one 10-min time bin during which wheel revolutions exceeded 100 counts after 240 min during which this threshold was not exceeded. The average activity onset time for the last 3–5 days of LD prior to DD was calculated, and this was subtracted from the activity onset times on days 1–5 of DD following refeeding to obtain a phase-shift measure corrected for prior phase-angle of entrainment to LD. The same analysis was conducted for the control DD tests

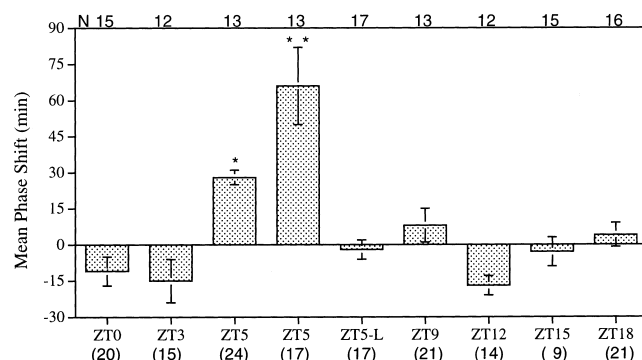


FIG. 1. Group mean ( $\pm$  SE) phase shifts to bouts of food deprivation ending at 7 different zeitgeber times (ZTs). Duration of deprivation is indicated in brackets below the abscissa. *n* per ZT is indicated above the mean bars. \**p* = 0.006; \*\**p* < 0.001 by comparison to within-group control tests.

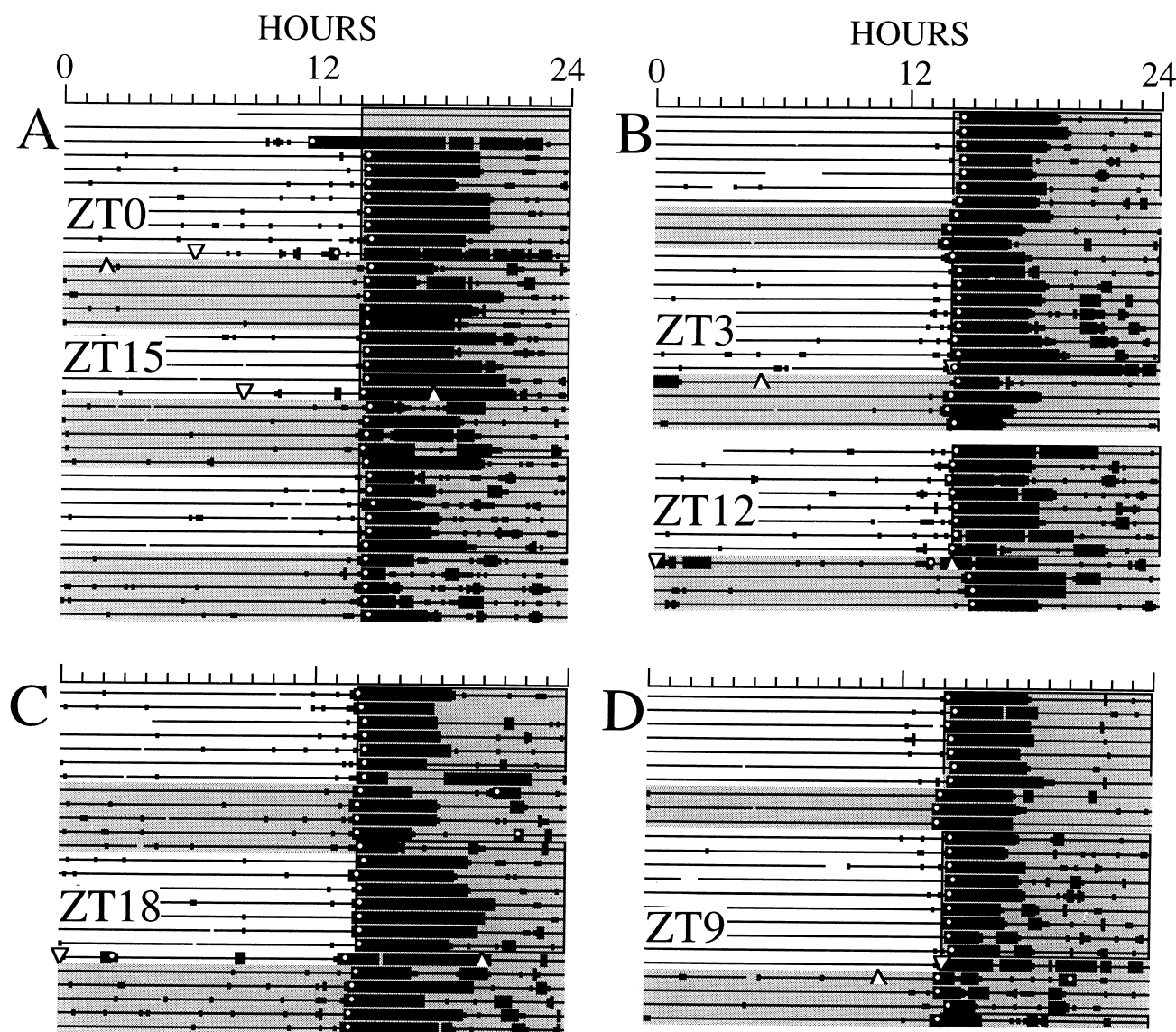


FIG. 2. Wheel-running activity of individual hamsters subjected to food deprivation ending at 6 different ZTs. Horizontal lines within each chart consist of 144 consecutive 10-min time bins plotted from left to right. Consecutive days are aligned top to bottom. Vertical deflections from each line represent bins during which wheel-running counts were registered (3 levels: 1–9 counts, 10–19 counts, and > 19 counts). (▽) the beginning of food deprivation; (△) the end of deprivation; (•) activity onset as detected by computer. Shaded area represents dim red light during LD and DD. (A) ZT0 and ZT15; (B) ZT3 and ZT12; (C) ZT18; (D) ZT9.

(no food deprivation). Phase shifts were evaluated statistically by paired *t*-tests (Bonferroni adjusted significance level,  $p < 0.006$ ), and expressed as difference scores for each animal (food-deprivation test – control test). The relation between phase shifts and activity during deprivation or after refeeding was assessed by Pearson product moment correlations. Inspection of the data indicated that phase shifts, where evident, were not preceded by transients. Consequently, day 2 of DD was used for tests of means and correlations. All means are reported  $\pm$  SE.

#### RESULTS

##### Phase Shifts

Mean phase-shift responses to food deprivation and refeeding are summarized in Fig. 1, and examples of the largest or typical

phase shifts for each ZT are illustrated in Figs. 2 and 3A–C. In the control tests, activity onsets on day 2 of DD generally occurred within –30 min to +40 min of activity onset during LD (grand mean =  $19 \pm 3$  min,  $n = 86$ ; Fig. 4A). Following food deprivation, the mean and range of activity-onset times on day 2 of DD was greater, but the distribution was otherwise similar (grand mean =  $24 \pm 4$  min,  $n = 126$ ; Fig. 4B). Group mean phase shifts were not significantly different from the control tests for food deprivations ending at ZT0, 3, 9, 15, and 18 ( $p > 0.1$  in all cases; Fig. 2). Within these groups, there was little variability and no exceptional cases. A trend toward a significant phase delay by comparison with the control test was evident for 14-h deprivations ending at ZT12 ( $-17 \pm 4$  min,  $t = 2.79$ ,  $p = 0.018$ ; e.g., Fig. 2B). Small, but significant, group mean phase

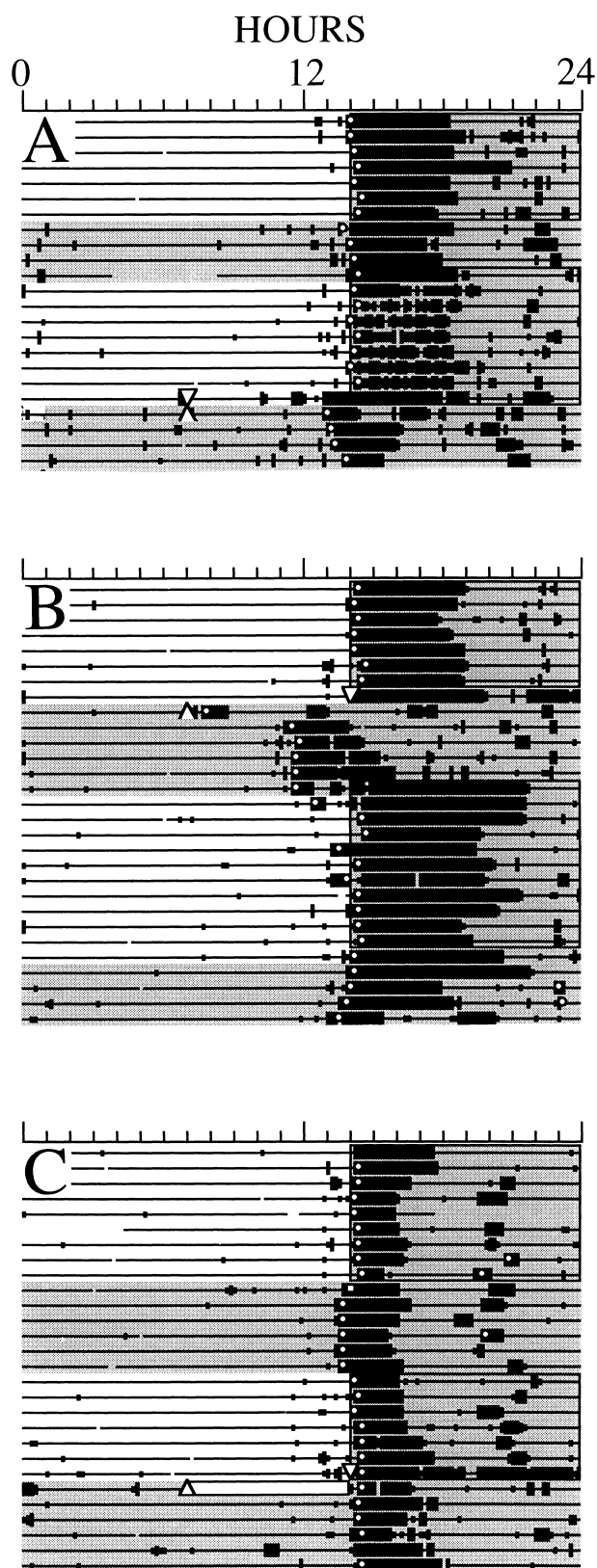


FIG. 3. Wheel-running activity of hamsters subjected to food-deprivation tests ending at ZT5. (A) 24-h food deprivation; (B) 17-h food deprivation; (C) 17-h deprivation, followed by 7-h wheel lock (indicated by the opaque rectangle). Plotting conventions as in Fig. 2.

advances were evident following the 24-h deprivation ( $28 \pm 3$  min,  $t = 7.38$ ,  $p < 0.001$ ; e.g., Fig. 3A) and 17-h deprivation ( $66 \pm 16$  min,  $t = 3.27$ ,  $p = 0.006$ ; e.g., Fig. 3B), ending at ZT5. Differences between these 2 groups were not significant.

#### Relation of Phase Shifts to Activity

Some of the hamsters that were food deprived for 17 h or 24 h and refeed at ZT5 exhibited wheel running during the first 3 h and/or second 3 h of food access. Although the average amount of activity expressed was quite modest ( $203 \pm 72$  revs/3 h and  $83 \pm 48$  revs/3 h, respectively), there was nonetheless a significant relation between wheel running over this 6 h and phase shifts ( $r = 0.78$ ,  $p < 0.001$ ; Fig. 5). This relation is largely accounted for by 2 animals that showed the largest phase shifts (175 and 195 min, respectively, with respect to the control test) and the most wheel running (1638 and 900 wheel revolutions, respectively, in the first 3 h, and another 1134 and 756 revolutions in the second 3 h). No other hamster shifted by more than 75 min or ran more than 700 counts, and most ran less than 200 counts.

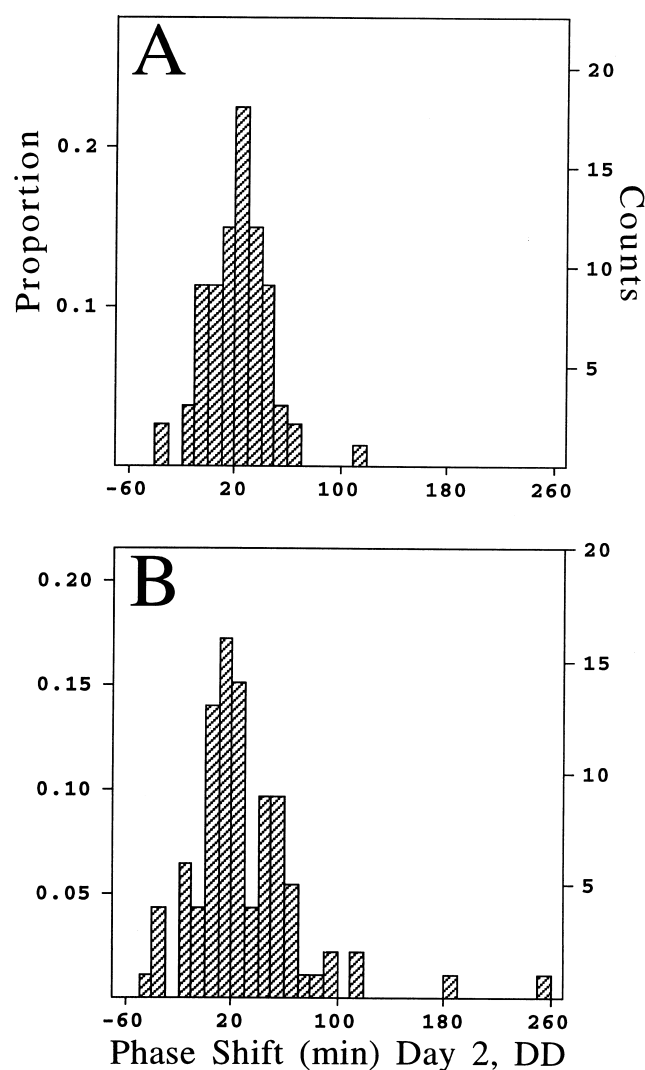


FIG. 4. Frequency distributions of activity onset on Day 2 of DD in the control (nondeprived) condition (A) and after food deprivation of varying duration and refeeding time (B).

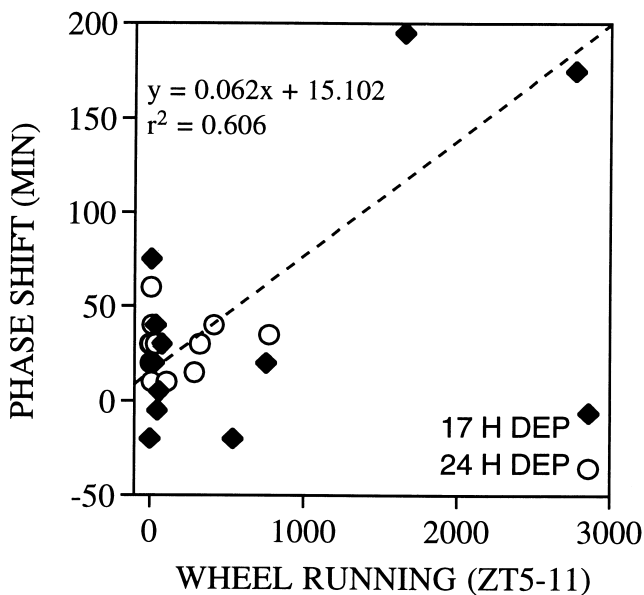


FIG. 5. Scatterplot illustrating the relationship between phase shift on Day 2 of DD (expressed as a difference score with respect to the control test) and wheel running during the first 6 h following refeeding at ZT5.

To examine if activity was necessary for phase shifts to refeeding at ZT5, hamsters ( $n = 17$ ) were food-deprived for 17 h and had their wheels locked from ZT5-12 after refeeding. No significant phase shift was evident by comparison with the control test (mean difference =  $-2 \pm 4$  min; e.g., Fig. 3C).

Increased levels of activity during food deprivation were evident during the subjective day in other ZT groups (e.g., Fig 2A, B, C). However, the amount of activity was generally modest and the timing of activity bouts was variable across animals. In these groups, no relation could be detected between phase on day 2 of DD and total activity or activity within selected h of the subjective day during food deprivation (e.g., ZT0-3, 5-8, or 8-11).

#### DISCUSSION

This study demonstrates that bouts of food deprivation ending at selected ZTs on the first day of DD can phase-shift circadian rhythms in the hamster. However, these effects were quite modest. Only 2 phase shifts exceeding 75 min relative to the control tests were observed in 126 deprivation tests, and significant group mean shifts were observed only following 17-h and 24-h food deprivations ending at ZT5. In addition, phase shifts were related to, and may be dependent on, the expression of wheel-running activity stimulated by refeeding. First, there was a positive correlation between the size of the phase advance following refeeding and the amount of wheel running during the first 3 h and 6 h of food access, although this was largely accounted for by the 2 hamsters with the largest shifts. Second, hamsters in the 17-h deprivation group, in which running wheels were locked for 7 h after refeeding, did not show significant phase shifts by comparison with their own control DD tests. These data appear to add to accumulating evidence that nonphotic stimuli capable of shifting or entraining circadian rhythms may, in many cases, do so indirectly via common effects on arousal and activity levels. The list of such stimuli now includes scheduled access to novel wheels (27,30,38), home wheels (13,18), and treadmills (18,19), litter changes (27), social interactions (27), cold (22), drugs (17,29,37), and fasting or refeeding (present study).

Activity was occasionally observed at ZT5-8 and 8-11 in some of the other groups of food-deprived hamsters, but few, if any, phase shifts occurred in these groups, and no relation between these bouts of activity and phase on day 2 of DD could be detected. The levels of running were generally quite low but, in a few cases, were similar to the levels expressed by hamsters in the ZT5 refeeding group that did show phase shifts. The salient difference between these groups is that the ZT5 hamsters had access to food during this time. It may be that refeeding and wheel running have arousing effects that, in combination, were sufficient to induce a phase shift but, independently, were insufficient.

Alternatively, food deprivation may attenuate the neural signal by which activity shifts the pacemaker. One candidate signal is serotonin (5-HT). The SCN pacemaker receives dense serotonergic innervation (25). Tryptophan (Trp; the 5-HT precursor) uptake and 5-HT synthesis are increased by running activity (7), 5-HT content in the SCN correlates positively with wheel running activity (32), and 5-HT agonists administered during the mid-subjective day can induce phase advances similar to those induced by running activity (14,35). In rats, Trp uptake and 5-HT synthesis stimulated by running are attenuated by food deprivation (7). If 5-HT mediates in whole, or even in part, the phase-shifting effects of activity, and if food deprivation blunts the effects of activity on 5-HT synthesis and release, activity during food deprivation might be a less-effective stimulus for phase shifts. This may be the reason that restricted daily feeding schedules entrain free-running rhythms in relatively few rats (34) and not all hamsters (1,20), despite often intense food anticipatory activity. If the full effects of activity on 5-HT metabolism recover soon after refeeding at ZT5, then the phase-shifting effects of activity might be restored. Similar arguments might be advanced for other neural pathways thought to be involved in nonphotic shifting (e.g., thalamic intergeniculate leaflet neuropeptide Y and the geniculohypothalamic tract) (5), but little information is available on how these might be directly or indirectly affected by food deprivation (e.g., the intergeniculate leaflet receives 5-HT afferents). Thus, although the present study does not provide convincing evidence that food deprivation or refeeding can directly alter circadian pacemaker phase in hamsters, it remains possible that manipulations of food intake could modulate the response of the pacemaker to other nonphotic zeitgebers. Evidence in support of this general concept is provided by recent studies demonstrating attenuation of phase shifting to light pulses in hamsters following TRP loading (15).

No attempt was made to measure food intake during refeeding in this study, because disruptions caused by weighing food could have induced or contributed to phase shifting. However, visual observations in this and previous studies (20) indicate that the latency to eating after deprivation is minimal (on the order of s or min) and that a bout of feeding was initiated at the scheduled refeeding ZT. Thus, the failure of most animals to exhibit phase shifts is probably not due to a failure to eat, particularly for those deprivations ending in the subjective night (i.e., ZT12, 15, and 18), when feeding is normally maximal. This was confirmed in a pilot study, in which hamsters deprived of food for 17 h and refed at ZT5 consumed  $1.2 \pm 0.03$  g in the first 3 h of food access, and  $2.4 \pm 0.09$  g during the first 6 h. Previous studies have shown that hamsters have a limited capacity to gorge following a food deprivation; thus, it is not likely that food intake during the first 3-6 h of refeeding could be greatly enhanced by subjecting the hamsters to longer periods of food deprivation (33). Hamsters with running wheels tolerate extended food deprivation poorly, and a more likely result would be excessive wheel activity during the subjective day and night, and possible debilitation.

The timing of food intake is of obvious adaptive significance for many organisms, and specializations of the circadian system, in the form of a separate food-entrainable pacemaker for antici-

pating mealtime and phase discrimination permitting time-place learning, have evolved to facilitate optimal foraging (4,6,21,23, 24). The results of the present study, however, detract from the proposal that the circadian system in at least one species, the hamster, can be acutely phase-shifted by a feeding-specific signal to the light-entrainable pacemaker (36). Rather, it may be that phase shifts and entrainment of circadian rhythms to feeding time are mediated by a nonspecific signal associated with the activity and arousal that accompany feeding schedules. This may be a

mechanism by which free-running rhythms in other species, such as rats, occasionally entrain to scheduled feeding (1,20,34). If so, we may find that entrainment of free-running rhythms to feeding schedules in hamsters and rats is dependent on the opportunity to express vigorous activity in running wheels.

#### ACKNOWLEDGEMENTS

This study was supported by operating and equipment grants (R. E. M.) and Graduate Fellowships (S. V. S and E. G. M) from NSERC, Canada.

#### REFERENCES

1. Abe, H.; Rusak, B. Anticipatory activity and entrainment of circadian rhythms in Syrian hamsters exposed to restricted palatable diets. *Am. J. Physiol.* 263:R116–R124; 1992.
2. Aschoff, J. Activity in anticipation and in succession of a daily meal. *Boll. Soc. It. Biol. Sper.* 67:213–228; 1993.
3. Aschoff, J. Response curves in circadian periodicity. In: Aschoff, J., ed. *Circadian clocks*. Amsterdam: North-Holland Publishing Co.; 1965:95–111.
4. Biebach, H.; Falk, H.; Krebs, J. R. The effect of constant light and phase shifts on a learned time-place association in garden warblers (*sylvia borin*): Hourglass or circadian clock? *J. Biol. Rhythms* 6:353–365; 1991.
5. Biello, S. M.; Janik, D.; Mrosovsky, N. Neuropeptide Y and behaviorally induced phase shifts. *Neuroscience* 62:273–279; 1994.
6. Boulous, Z.; Terman, M. Food availability and daily biological rhythms. *Neurosci. Biobehav. Rev.* 4:119–131; 1980.
7. Chaouloff, J. L.; Elghozi, J. L.; Guezennec, Y.; Laude, D. Effects of conditioned running on plasma, liver and brain tryptophan and on brain 5-hydroxytryptamine metabolism of the rat. *Br. J. Pharmac.* 86:33–41; 1985.
8. Clarke, J. D.; Coleman, G. J. Persistent meal-associated rhythms in SCN-lesioned rats. *Physiol. Behav.* 36:105–113; 1986.
9. Coleman, G. J.; Harper, S.; Clarke, J. D.; Armstrong, S. Evidence for a separate meal-associated oscillator in the rat. *Physiol. Behav.* 29:107–115; 1982.
10. Coleman, G. J.; Francis, A. J. P. Food deprivation and reinstatement phase shifts rat activity rhythms in constant light but not constant dark. *Physiol. Behav.* 50:167–171; 1991.
11. Coleman, G. J.; O'Reilly, H. M.; Armstrong, S. M. Food-deprivation-induced phase shifts in *Sminthopsis macroura froggatti*. *J. Biol. Rhythms* 4:49–60; 1989.
12. Eastman, C.; Rechtschaffen, A. Circadian temperature and wake rhythms of rats exposed to prolonged continuous illumination. *Physiol. Behav.* 31:417–427; 1983.
13. Edgar, D.; Dement, W. C. Regularly scheduled voluntary exercise synchronizes the mouse circadian clock. *Am. J. Physiol.* 261:R928–933; 1991.
14. Edgar, D. M.; Miller, J. D.; Prosser, R. A.; Dean, R. R.; Dement, W. C. Serotonin and the mammalian circadian system: II. Phase shifting rat behavioral rhythms with serotonergic agonists. *J. Biol. Rhythms* 8:17–31; 1993.
15. Glass, J. D.; Selim, M.; Srkalovic, G.; Rea, M. A. Tryptophan loading modulates light-induced responses in the mammalian circadian system. *J. Biol. Rhythms* 10:80–90; 1995.
16. Jewett, M. E.; Kronauer, R. E.; Czeisler, C. A. Phase-amplitude resetting of the human circadian pacemaker via bright light: A further analysis. *J. Biol. Rhythms* 9:295–314; 1994.
17. Marchant, E. G.; Mistlberger, R. E. Morphine phase shifts circadian rhythms in mice: Role of behavioral activation. *NeuroReport* 7:209–212; 1995.
18. Marchant, E. G.; Mistlberger, R. E. Entrainment and shifting of circadian rhythms in mice by forced treadmill running. *Physiol. Behav.* 60:657–663; 1996.
19. Mistlberger, R. E. Effects of daily schedules of forced activity on free-running circadian rhythms in rats. *J. Biol. Rhythms* 6:71–80; 1991.
20. Mistlberger, R. E. Effects of scheduled food and water access on circadian rhythms of hamsters in constant light, dark and light:dark. *Physiol. Behav.* 53:509–516; 1993.
21. Mistlberger, R. E. Circadian food anticipatory activity: Formal models and physiological mechanisms. *Neurosci. Biobehav. Rev.* 18:171–195; 1994.
22. Mistlberger, R. E.; Marchant, E. G.; Sinclair, S. V. Nonphotic phase shifting and the motivation to run: Cold exposure reexamined. *J. Biol. Rhythms* 11:208–215; 1996.
23. Mistlberger, R. E.; DeGroot, M. H.; Bossert, J.; Marchant, E. G. Discrimination of circadian phase in intact and SCN-ablated rats. *Brain Res.* (in press).
24. Moore, D.; Siegfried, D.; Wilson, R.; Rankin, M. A. The influence of time of day on the foraging behavior of the honeybee, *Apis mellifera*. *J. Bio. Rhythms* 4:305–326; 1989.
25. Moore, R. Y.; Halaris, A. E.; Jones, B. E. Serotonin neurons of the midbrain raphe: Ascending projections. *J. Comp. Neurol.* 180:417–438; 1978.
26. Morin, L. P.; Blanchard, J. Depletion of brain serotonin by 5,7-DHT modifies hamster circadian rhythm response to light. *Brain Res.* 566:173–185; 1991.
27. Mrosovsky, N. Phase response curves for social entrainment. *J. Comp. Physiol.* 162:35–46; 1988.
28. Mrosovsky, N. Methods of measuring phase shifts: Why I continue to use an Aschoff type II procedure despite the scepticism of referees. *Chronobiol. Int.* (in press).
29. Mrosovsky, N.; Salmon, P. A. Triazolam and phase-shifting acceleration reevaluated. *Chronobiol. Int.* 7:35–41; 1990.
30. Reeb, S. G.; Mrosovsky, N. Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. *J. Biol. Rhythms* 4:39–48; 1989.
31. Rosenwasser, A. M.; Pelchat, R. J.; Adler, N. T. Memory for feeding time: Possible dependence on coupled circadian oscillators. *Physiol. Behav.* 32:25–30; 1984.
32. Shioiri, T.; Takahashi, K.; Yamada, N.; Takahashi, S. Motor activity correlates negatively with free-running period, while positively with serotonin contents in SCN in free-running rats. *Physiol. Behav.* 49:779–786; 1991.
33. Silverman, H. J.; Zucker, I. Absence of postfast food compensation in the golden hamster (*Mesocricetus auratus*). *Physiol. Behav.* 17:271–285; 1976.
34. Stephan, F. K. The role of period and phase in interactions between feeding- and light-entrainable circadian rhythms. *Physiol. Behav.* 36:151–158; 1986.
35. Tominaga, K.; Shibata, S.; Ueki, S.; Watanabe, S. Effects of 5-HT<sub>1A</sub> receptor agonists on the circadian rhythm of wheel running activity in hamsters. *Eur. J. Pharmacol.* 214:79–84; 1992.
36. Vaccarino, F. J.; Sovran, P.; Baird, J. P.; Ralph, M. R. Growth hormone-releasing hormone mediates feeding-specific feedback to the suprachiasmatic circadian clock. *Peptides* 16:595–598; 1995.
37. Van Reeth, O.; Turek, F. W. Stimulated activity mediates phase shifts in the hamster circadian clock induced by dark pulses or benzodiazepines. *Nature* 339:49–51; 1989.
38. Wickland, C. R.; Turek, F. W. Phase-shifting effects of acute increases in activity on circadian locomotor rhythms in hamsters. *Am. J. Physiol.* 261:R1109–R1117; 1991.
39. Zucker, I.; Stephan, F. K. Light-dark rhythms in hamster eating, drinking and locomotor behaviors. *Physiol. Behav.* 11:239–250; 1973.