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Circadian Food-Anticipatory Activity: Formal Models and Physiological Mechanisms

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MISTLBERGER, R. E. *Circadian food-anticipatory activity: Formal models and physiological mechanisms*. NEUROSCI BIOBEHAV REV 18(2) 171-195, 1994. — Rats and other species exhibit food-anticipatory activity (FAA) to daily mealtime under circadian (24 h) food access schedules. A critical review of several explanatory models indicates that hourglass clocks and associative learning processes are inadequate to explain many properties of FAA in intact and suprachiasmatic nuclei ablated rodents. A computational learning model, involving circadian clock consultation and phase memory, accounts for some but not all of these properties. An entrainment model, invoking separate, compound food- and light-entrainable oscillators, provides a more complete account of FAA. However, FAA may be simulated best by a model that combines oscillator entrainment with clock consultation and memory for circadian phase. Species as diverse as bees, birds, and mammals appear to share many features of FAA in common; differences may be explained in terms of oscillator organization and the ability to represent multiple circadian phases memorially. Physiological mechanisms of FAA are largely unknown; strategies for localization of entrainment pathways and oscillators, and a modest data base, are reviewed.

Food restriction Circadian rhythms Entrainment Learning Foraging Wheel running

A PRIMARY task of the foraging organism is to exploit spatial and temporal regularities of food availability in the environment. Many organisms have evolved spatial mapping abilities and endogenous clocks to accomplish the space-time components of this task. This review is concerned with the contribution of circadian (24 h) clocks to the timing of food seeking behavior, and, in particular, to the phenomenon of food-anticipatory activity (FAA) that many animals manifest under daily schedules of restricted food availability. The primary objective is to critically evaluate several formal models of FAA. A second objective is to review what is known of the physiological mechanisms of FAA. Behavioral rhythms constitute the core of this review; the reader is directed to other reviews for more thorough discussion of physiological rhythms synchronized to daily schedules of food availability (24,49,55,125,175).

I. FOOD ANTICIPATION IN THE RAT: FORMAL MODELS

If a rat is maintained on a single daily meal provided at a fixed time of day it will, within a few days, exhibit increased arousal and activity during the hours immediately preceding feeding time (Fig. 1). This anticipation of mealtime can be detected in a range of behaviors, including wheel running (18,130), unreinforced lever pressing (23), activity directed at

an empty feeding trough (16,108), general cage activity (104), and drinking (23). The specific behaviors displayed may vary, depending on the species and individual, the options available, and the type of resource that the animal is anticipating (e.g., food, water, salt, protein; see section V1.b). In rats and many other species, FAA can be expressed to mealtimes scheduled at any fixed circadian phase during the day or night (19). Thus, although the rat prefers to forage and feed at night, it will exhibit diurnal FAA if that is when the food is (e.g., Figs. 1 and 2).

The question to be addressed here is, by what mechanism does the rat anticipate feeding time? Explanations based on external cueing can be rejected because it has been repeatedly demonstrated that rats and other species can anticipate feeding time in artificial environments lacking any variation in light, temperature, or sound that might serve as a signal of imminent food access. The availability of external cues can modulate or replace internal cueing (see section V1.b), but such cues are not necessary for FAA.

Explanations based on internal cueing make reference to timing mechanisms of different kinds, including:

1. An hourglass or interval timer, which consists of a sequence of behaviors or metabolic events associated with an imposed daily cycle of energy depletion and repletion.

Activity is triggered each day when energy depletion reaches some threshold prior to feeding time. Such timers are not true clocks because they are incapable of self-sustained oscillations and must be reset each day by a feeding event. If no feeding event occurs, or if food is provided ad lib, the daily rhythm of FAA should stop.

2. A self-sustaining oscillator or true clock that can persist in the absence of a feeding cycle. These include damped and undamped oscillators that may persist temporarily or indefinitely, respectively, under constant feeding or deprivation conditions.

Explanatory models of FAA based on self-sustaining clocks can be further classified as either entrainment or nonentrainment models. The entrainment model views FAA as the output of an oscillator whose phase and period is controlled (i.e., entrained) by some correlate of the daily feeding event, in a way directly analogous to entrainment by light : dark (LD) of the circadian clock that regulates day : night cycles of activity under ad lib feeding conditions. The model explicitly pos-

tulates the existence of a food-entrainable oscillator (FEO) that may be coupled too, but is separable from a master light-entrainable oscillator (LEO), which, in mammals, resides in the hypothalamic suprachiasmatic nuclei (SCN) (91). This two-oscillator entrainment model has gained wide (but not universal) acceptance within the field of biological rhythms research (9,24,93,134,156).

Nonentrainment models are compatible with an entrainment process, but do not view phase and period control of the clock as necessary for the generation of FAA. Nonentrainment models can be further differentiated as computational or associative. A computational model has recently been elaborated by Gallistel (1990). This model requires only one circadian clock (a master LEO would suffice) and two assumptions: first, that this clock can be used to store in memory a representation of the circadian phase at which a significant feeding event occurs, and, second, that this clock can be consulted to match the current circadian phase with a predicted phase of feeding. The prediction is not a simple reading of the last feeding time; rather, representations of the last few or

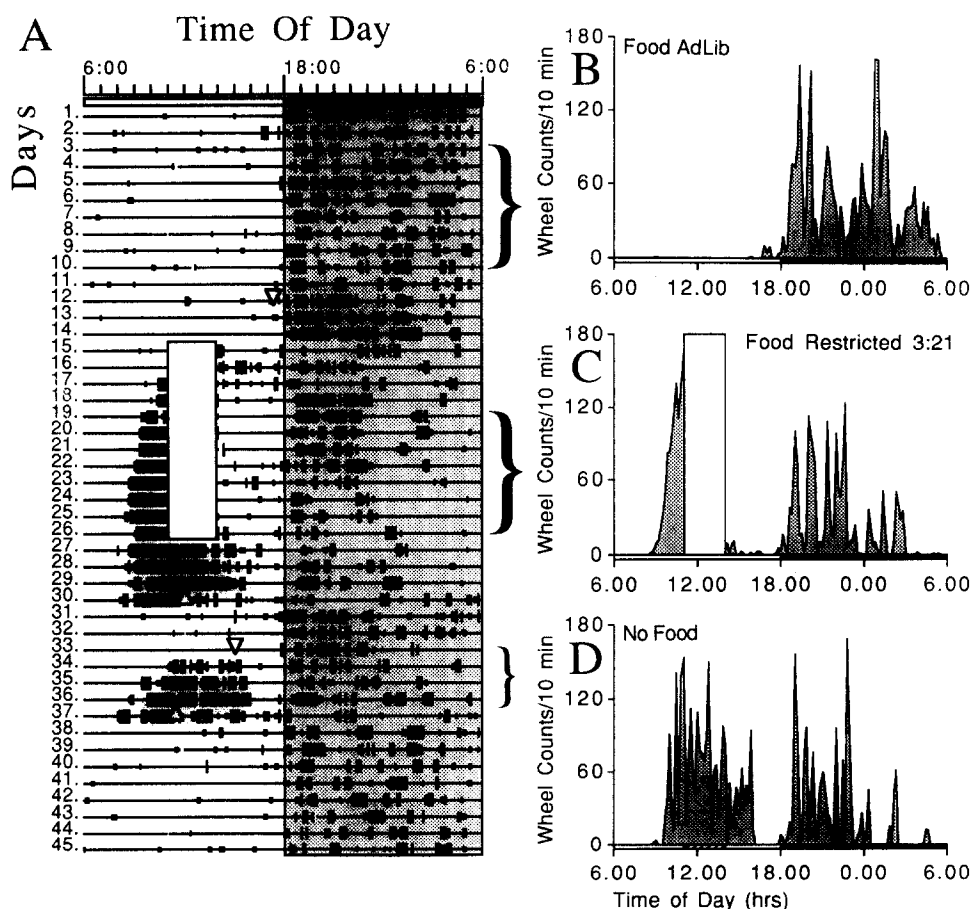


FIG. 1. (A) Standard actogram of wheel-running activity of a rat recorded under LD 12:12 (lights on from 0600-1800 h) during ad lib and restricted food access. Each line represents 24 h, with time in 10 min bins plotted left to right. Time bins during which wheel revolutions were registered are represented by vertical deflections. The hollow vertical bar represents mealtime during the restricted feeding schedule (3 h food, 21 h no-food). Triangles represent the beginning (pointing down) or end (pointing up) of total food deprivation. The rat exhibits little diurnal activity when food deprived prior to the 3:21 feeding schedule. During the feeding schedule, the rat exhibits a robust food anticipatory wheel running rhythm. This rhythm persists during total food deprivation. (B,C,D) Waveforms of wheel running during ad lib food access (7 day average), food restriction (7 day average), and total food deprivation (3 day average), respectively. Unpublished data.

more feeding phases are used to estimate the next feeding phase, with more recent phases being weighted preferentially in the computation.

Associative nonentrainment models of FAA invoke a traditional, noncomputational, associative learning mechanism. One version treats circadian phase as a discriminative stimulus for anticipatory activities that are reinforced by subsequent phase-specific feeding (16). A more common version views fixed daily feedings as a Pavlovian conditioning paradigm in which anticipatory activities represent conditioned responses elicited by the repeated pairing of circadian phase with food presentation (6). Within this framework, circadian phase can be viewed as an incentive stimulus for induction of a conditioned motivational state. Typical restricted feeding procedures may entail both operant and Pavlovian contingencies to various extents. Associative learning explanations of FAA have most often been invoked by physiologists and psychologists studying regulatory processes (e.g., insulin and corticosterone secretion) outside of the traditions of biological rhythms research (35,174,191).

Entrainment and nonentrainment models of FAA can, thus, be distinguished by the role posited for learning in FAA. According to the entrainment model, FAA reflects a phase-angle of entrainment in which the active phase (α) of a clock-controlled rest-activity cycle begins before mealtime. The animal need learn nothing about mealtime, because it is predisposed to express premeal activity by virtue of the phase alignment of its FEO with mealtime (interacting, we assume, with an appetitive motivational state). Within this framework, it is no more meaningful to use the word learning than it would be to say that rats or humans learn to be nocturnal or diurnal. These phase predispositions reflect intrinsic oscillator properties, including period (τ) and phase-response characteristics to the entraining stimulus (the Zeitgeber). True learning models of FAA, as described above, invoke additional, specific learning processes (conditioning or computations) that utilize information provided by the internal clock. Thus, although there has been a tendency to refer to FAA as learning due to a process of entrainment (9), for the purposes of this review these terms will be kept separate because in common usage they imply very different underlying mechanisms, which, as discussed below, are still a matter of contention with respect to FAA.

Given these extant models of FAA, the next objective is to evaluate their success in explaining various properties of FAA as manifest under scheduled feeding paradigms. Discussion will be limited to FAA in rats, because that is by far the most thoroughly studied species in this context. The issue of species generality will be deferred to section IV.

II. PROPERTIES OF FAA IN INTACT RATS

II.a. Dependence of FAA on Circadian Feeding Intervals

Rats do not express FAA to feeding schedules that diverge greatly from 24 h. Thus, intact rats entrained to 24 h LD cycles fail to anticipate daily meal onsets separated by 19 h or 29 h (18,20). The precise range of feeding intervals that LD-entrained rats can behaviorally anticipate has not been thoroughly examined, although preliminary studies indicate that FAA is weak or absent to 23 h schedules but robust to 25 and 26 h schedules [(10); Mistlberger and Marchant, unpublished observations, Fig. 2]. Rats maintained in constant lighting (12) or subjected to SCN ablations [(23,156); see section

III] show a similarly limited range of anticipation that is also significantly asymmetrical with respect to 24 h. Inspection of published figures suggests asymmetry with respect to free-running τ as well, although this requires formal quantification.

This circadian range of anticipation indicates that FAA is based on an internal clock with an intrinsic τ close to 24 h, and is not based on interval timers that can be reset at any arbitrary interval. Such interval timers mediate anticipatory activity (manifest as scalloping activity patterns) on fixed-interval feeding schedules in the seconds-to-minutes range, but there is as yet little evidence in rats that they can time intervals in the range of hours or more. Evidently, these timers cannot support anticipation when meal onsets are separated by as much as 19 h.

According to the entrainment model of FAA, failure to anticipate 19 h and 29 h feeding schedules reflects the limits of entrainment of a circadian FEO. Such limits are a well known property of physical oscillators and reflect the maximum phase shift that the oscillator can undergo in a single cycle. Thus, if an oscillator has an intrinsic τ of 24 h, and can be shifted by as much as ± 2 h per day, then the predicted limits of entrainment would be about 22–26 h.

Within this framework, the observed asymmetry of entrainment limits with respect to 24 h is explained in terms of τ and the phase-response characteristics of the FEO. If FEO τ is 25 h, rather than 24 h, then the upper and lower entrainment limits would be centered at 25 h, not at 24 h. In addition, if the FEO has an asymmetrical phase-response curve (PRC; the function relating size of oscillator phase shift to the circadian phase at which the phase-shifting stimulus is applied) to daily feeding stimuli, in which the maximum possible phase delay exceeds the maximum phase advance, then the observed upper entrainment limit should deviate from 24 h more than does the lower entrainment limit. Note that where appropriate studies have been done in various species, circadian rhythms usually display a non-24 h τ and an asymmetrical PRC to entraining stimuli, i.e., these are reasonable, not esoteric, assumptions for a FEO.

A traditional, associative conditioning explanation of FAA to non-24 h feeding cycles in the 23–26 h range is not available in the literature, but conceivably could be based on a process of generalization across contiguous phases, perhaps in combination with extinction to prior phases no longer associated with feeding. Explanations of observed asymmetric anticipation limits with respect to τ would, however, require the awkward assumption that generalization and/or extinction processes occur more readily in one direction (meals moving later each day) than the other (meals moving earlier).

The computational learning model views anticipation limits as the result of the probability rule that is used to assess the significance of an observed clustering of mealtimes within a circumscribed range of circadian phases (50). Because it usually takes about 3–4 days for FAA to appear under a 24 h feeding schedule in LD-entrained rats, it can be assumed that the rat bases its estimate of feeding time on the last three to four feeding phases. If the feeding cycle is 18 h rather than 24 h, then the last four feeding times would be dispersed over an interval of 24 h, which clearly does not represent a significant phase-specific clustering of mealtimes. If the feeding cycle is 22 h, then the last four meals would be dispersed over a range of only 8 h, which might approach a reasonable phase-clustering on which to base an estimate of the next feeding time. The anticipation limits are, thus, set according to the rule for defining a significant phase cluster.

Although this type of computation can aptly explain anticipation limits without postulating oscillator entrainment, it fails to predict or account for the empirically observed asymmetry of these limits with respect to 24 h in LD entrained rats. Given a certain probability rule for defining a significant cluster of meal onsets, this rule should be applied equally to short-interval and long-interval feeding schedules in the circadian range.

II.b. Persistence of FAA During Food Deprivation

FAA may persist at its usual phase for a week or more when food-restricted rats are fed ad lib (12,43,51,60,158), but in the great majority of cases, it is either completely absent by the second day of ad lib food access or dissipates over 3–4 days (27,51,136,169,170). This failure to persist under constant conditions (i.e., unrestricted food access) could be viewed as the result of strong oscillator damping or a rapid extinction process. However, if a rat expressing FAA to a daily meal is food deprived for 2 or more days, FAA exhibits strong phase-specific persistence (e.g., Fig. 1) (19,23,26,27,97, 119,169,170). In addition, if 3–7 day blocks of food deprivation are repeated after 1 or more weeks of ad lib feeding, FAA reappears at its usual time of day, even 50 or more days following the last daily feeding schedule in rats maintained in LD (19,26,27,119,169,170).

These results are incompatible with hourglass, rapidly damping oscillator, and simple associative learning models. However, they are compatible with the entrainment model given the assumption that coupling between the hypothetical FEO and behavioral effector systems is gated by the animal's motivational state. The computational learning model can also explain FAA persistence and reappearance if it is assumed that the animal retains a memory of circadian phase best correlated with food access in times of privation.

In several studies, the LD cycle was either replaced by constant dark (DD) or light (LL) on the last day of restricted feeding, or was phase-shifted following a number of days of ad lib feeding. In the absence of an LD cycle, the light-entrained rest-activity rhythm (LER) free runs (i.e., persists) with τ usually longer than 24 h in rats (157). Following an acute phase shift of LD, the LER reentrains over a period of days to a week or more, exhibiting transient (i.e., shifting) cycles in the process (168). For both conditions, the computational learning model predicts that if the rat is food deprived, FAA will reappear at the same circadian phase of the LER as it occurred during the original feeding schedule under LD, regardless of external time. The entrainment model, in contrast, need not make a strong prediction as to when FAA will reappear. Most of the results from these studies demonstrate that activity does reappear at roughly the same circadian phase of the LER. However, in many cases there are substantial phase discrepancies that may accumulate with repeated deprivation tests. For example, in two studies conducted in DD, the phase at which FAA reappeared during deprivation drifted earlier with respect to the free-running rhythm (26,27). In a study conducted in LL, the phase at which FAA reappeared also appeared to drift earlier with respect to the free-running rhythm, although in that study FAA was increasingly imprecise with repeated deprivation tests over 80 days, rendering phase assessments equivocal at best (136).

Two studies examined the effects of 8 h or 10 h LD phase shifts on the timing of FAA during food deprivation tests (119,136). In both studies, FAA reappeared at roughly the same phase as was established under the prior feeding cycle. However, in some cases, its timing was very imprecise (136)

or it was absent by the fourth or fifth deprivation test, approximately 80 days after the feeding cycle (119). In a third study (Mistlberger and Marchant, unpublished observations), five of nine rats failed to exhibit FAA during food deprivation following inversion of the LD cycle, although all of these rats showed strong phase-specific FAA during deprivations prior to LD inversion.

These observations indicate that during repeated deprivation tests and intervening periods of ad lib feeding, the phase of FAA with respect to the LER is maximally preserved under LD, possibly perturbed following a shift of LD and, in some cases, progressively offset when rats are exposed to DD or LL. The predictions of the learning models are, thus, not consistently met. One possible reason could be that the remembered or predicted feeding phase is altered by the circadian phase of the first meal following the deprivation tests. Only two of the cited studies reported the time at which re-feeding occurred, and the results do not provide support for the idea (26,27). In those studies, rats were re-fed at the same external clock time following each deprivation test, but this appeared to have no consistent effect on the timing of FAA during subsequent deprivation tests.

The entrainment model can accommodate any observed phase at which FAA reappears during food deprivation. If phase with respect to the LER is preserved after LD shifts or in constant lighting, this can be interpreted in terms of coupling between the hypothetical FEO and the phase-shifted or free-running LEO. If FAA appears to deviate from its original phase with respect to the LER, this can be interpreted as a failure of coupling and an expression of different free-running periods expressed by the separate oscillators. Thus, the entrainment model assumes that coupling between the two oscillators is possibly weak and subject to failure.

Weak mutual (or unidirectional) coupling, particularly from the FEO to the LEO, but also from the LEO to the FEO, may be viewed as an adaptive feature of a two oscillator system, because it would allow the FEO to track a shifting food source without necessarily altering the phase of LERs. Stable photic entrainment may be important for photoperiodic processes, and would ensure a rapid reversion to nocturnal activity when diurnal restricted food access is replaced by free food access.

For the phase of FAA to be retained with respect to LERs following a LD shift, the entrainment model must further assume that the FEO and LEO can couple at any phase relation. This represents an unusual coupling property for two oscillators. However, evidence that FAA phase may not be precisely retained in some studies could indicate that stable coupling does not, in fact, occur at all possible phase relations between FAA and the LER. Further deprivation studies are needed to examine this in more detail. Ideally, such studies should utilize LD shifts, since apparent synchrony of two oscillators under 24 h LD and feeding schedules could reflect similarity of oscillator τ rather than true physical coupling.

In the deprivation studies reviewed there is evidence that FAA dissipates over repeated deprivation tests (119,136). This could reflect gradual FEO damping, analogous to damping of free-running rhythms with prolonged exposure to LL, or it could reflect uncoupling of a FEO from behavioral effector systems. Choosing between these and other alternatives may require physiological analysis of the FEO itself, if such an oscillator can be localized. Learning models would presumably interpret loss of FAA with repeated deprivation tests as a gradual process of extinction, as the previous phase of meal-time is no longer associated with a feeding event.

For the phase of FAA to be retained during deprivation

tests, the FAA timing mechanism must ignore feeding events that occur at other circadian phases during ad lib food access. The problem is equivalent for entrainment and learning models. A possible solution is to assume that the timing mechanism (be it a FEO, associative conditioning or a computation) is insensitive to feeding events during ad lib food access. Sensitivity may be gated by hunger or reduced body weight. If so, then FAA should develop only under schedules that involve caloric restriction. However, this is not necessarily the case. In one study, rats with free access to standard lab chow exhibited anticipatory wheel running to a 10 g supplemental meal of a presumably palatable, chocolate flavored, oily mash (106). FAA was slow to emerge, and was related to the amount of palatable mash consumed (up to 30% of total daily food intake), because rats that were limited to a smaller amount (5 g) did not show anticipation, although they ate all of the mash available. None of the rats lost body weight under these schedules.

More recently, rats have been shown to anticipate daily mealtimes as long as 10–12 h (167). Under these schedules, there is presumably little or no energy deficit. Because these schedules would seem to mimic the natural feeding period of a rat entrained to LD, it is not clear why they should exert phase control over FAA. However, intact rats do occasionally feed during the light, particularly in the hours just preceding dark (135), so it is possible that if light-phase feedings were prevented, then FAA previously associated with a mid-light feeding would be shifted toward dark onset, when the first daily feeding would occur. Together with the palatable food study, such a result would suggest that a necessary and sufficient condition for FAA is a significant concentration of food intake occurring repeatedly at a specific circadian phase, e.g., a 10 g palatable meal in mid-light, or the first meal of the night following a 12 h deprivation interval during the day. Meals occurring at other phases under such schedules may be neither sufficiently large nor as consistently related to circadian phase to influence FAA timing.

II.c. The Latency and Duration of FAA

The typical rat expresses FAA within 3–14 days under a 24 h feeding schedule in which a 2–4 h daily meal alternates with a 20–22 h fast (12,23,26,27,60,107,169,170). The first meal does not seem to influence the timing of activity on the second day of restriction; rats ($n = 12$) food deprived for 2 days and then fed a single 2 h test meal, did not show activity at the test meal time on two subsequent days of total food deprivation that immediately followed (Mistlberger, unpublished observations). This is consistent with an associative learning process, because repeated trials are usually assumed necessary to establish a conditioned response.

According to the computational learning model, the phase of feeding time is recorded with every major feeding event (50). The fact that the rat apparently does not use this information to time its activity following a single test meal after 2 days of food deprivation can be taken as evidence that the organism estimates feeding time on the basis of a significant phase-specific clustering of several past mealtimes. The number of days required for FAA to appear under a 24 h feeding cycle will depend on the significance level that the animal uses in evaluating phase clustering.

Although this conception of latency to FAA is ingenuous, it seems intuitively unsatisfying that the rat should routinely record the circadian phase of all feeding events, including the first meal following 2 days of deprivation, and yet be unprepared or unable to use this information during two subsequent days of deprivation. If an animal is starving, what disadvan-

tage can there be to concentrating activity at the last circadian phase at which a major feeding event occurred, assuming that the animal actually has a record of the time of that event? It is possible that with further deprivation, significant activity at that phase might emerge, although this might be confounded by nonspecific increases in activity throughout the day that occur with severe deprivation. It is also possible that if the rat is food deprived more severely prior to the single test meal, it might express memory of this mealtime more readily during subsequent deprivation, i.e., the probability criteria might be relaxed with increasing privation. Suggestive evidence for this is provided by two studies in which a food-anticipatory corticosterone peak was evident on day 2 of a feeding schedule in rats subjected to 10 days of total food deprivation prior to the first 2 h meal (57,59). Usually, anticipatory corticosterone release does not appear before 7–10 days of restricted feeding. Whether these results reflect metabolic processes specific to corticosterone and independent of circadian timing is not yet clear. Preliminary studies indicate that 4 days of food deprivation does not accelerate the rate at which behavioral anticipation emerges to a daily feeding (Mistlberger, unpublished observations).

For the entrainment model, the significance of the 3–14 day latency to FAA is unclear. In most instances (e.g., Fig. 1), FAA appears to arise *de novo*, in that there is no evidence of existing activity bouts shifting from one circadian phase toward the phase of feeding time (i.e., transient cycles). Occasionally, such transient cycles are evident [e.g., Fig. 2; cf. (104,160)], but there is no convincing evidence yet that these transients are necessary for FAA to occur. In some cases these transients free run through feeding time without entraining.

Although little discussed in the literature, a general assumption seems to be that prior to food restriction, the hypothetical FEO is coupled with the LEO, and contributes to nocturnal activity as part of a multioscillator complex. The data depicted in Fig. 2 would represent evidence in support of such an assumption. The failure to observe transients between nocturnal activity and a diurnal feeding time in most animals could reflect a failure of the FEO to influence behavior until a stable phase of entrainment is achieved. However, this seems unlikely, because robust transients are expressed when the phase of mealtime is shifted by 4–12 h (see section III.c.). Rather, it may be that prior to restricted feeding, the FEO, in most cases, may reside in a damped state, possibly due to desynchrony within a population of suboscillators, and that repeated exposure to the feeding Zeitgeber is necessary to induce sufficient synchrony within the population to influence behavioral effector systems. At present, the lack of information on the status of the hypothetical FEO prior to restricted feeding represents a weakness of the entrainment model of FAA.

When FAA first appears under a typical 24 h feeding schedule, it usually increases in duration for a week or more before stabilizing in the range of 1–5 h. The entrainment model interprets FAA duration as the phase angle at which the FEO is entrained to mealtime. Gradual increases in duration thus represent transients as the FEO settles at a stable phase of entrainment. From the perspective of learning models, the gradual increase in FAA duration is paradoxical. With greater training should come more accurate temporal performance or more confidence in computed estimates of feeding time. If so, FAA duration should shrink with increasing exposure to a particular feeding schedule. Learning models provide no compelling rationale for the opposite result.

The amount of food that the rat consumes during a scheduled mealtime also increases during the first 7–10 days of

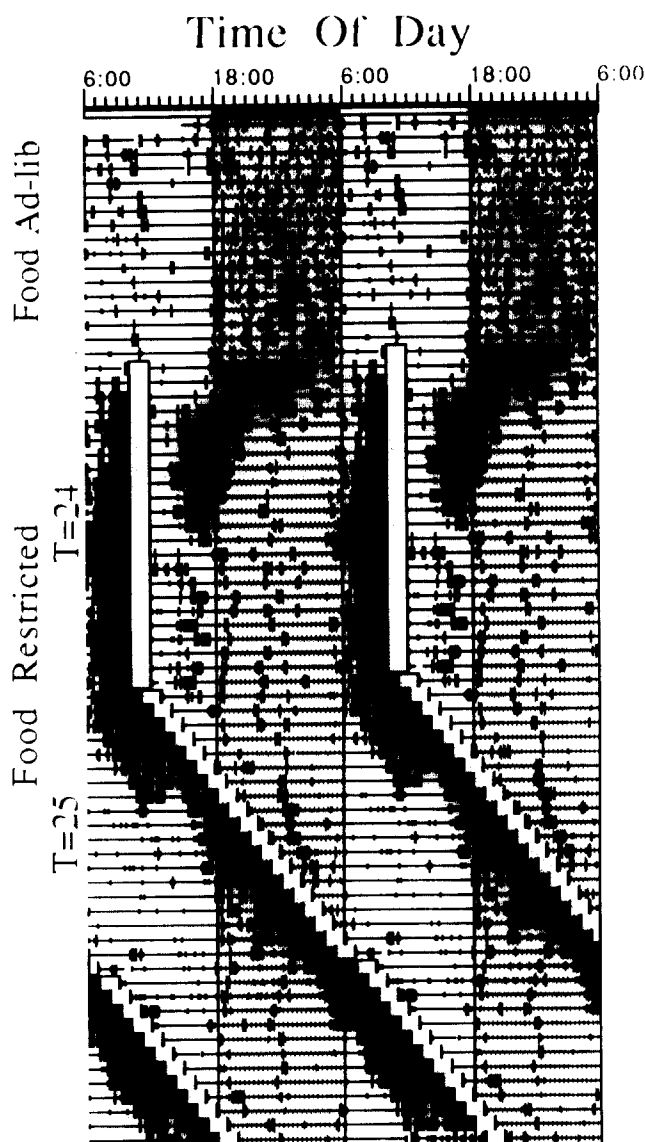


FIG. 2. Double-plotted actogram of wheel running from a rat recorded in LD under ad lib and restricted food access. Same format as Fig. 1, except that consecutive days are plotted left to right and top to bottom, i.e., are repeated to facilitate inspection of non-24 h activity rhythms. The vertically and obliquely running hollow bar represents mealtime during 24 h (2 : 22) and 25 h (2 : 23) restricted feeding cycles, respectively. Strong anticipatory running is evident by the third day of restricted feeding. A dense band of nocturnal activity appears to phase shift toward feeding time, leaving smaller nocturnal activity components. Anticipatory running follows feeding time under the $T = 25$ h schedule. The smaller nocturnal activity components appear to exhibit signs of relative coordination with the anticipatory activity component as it passes through the lights-off period, but they remain nocturnal. Unpublished data.

restricted feeding [cf. (144)]. Presumably, this is related, in part, to initial weight loss and, in part, to synchronization of metabolic and gastrointestinal rhythms to the new feeding time. Whether FAA duration and meal size are causally related is not clear; however, their positive correlation argues against any simple hourglass model that would ascribe FAA duration

to a threshold of energy depletion, because consumption of larger meals should delay rather than advance expression of the threshold.

II.d. Succeeding Activity

Virtually all rats on 24 h restricted feeding schedules exhibit FAA. In some rats, a second bout of activity, so-called succeeding activity (SA), occurs approximately 3–6 h after mealtime (12,60,166,169). From an entrainment perspective, SA can be viewed as the trailing end of FEO α . This interpretation is supported by the observation that the durations of FAA and SA are negatively correlated across days and across feeding cycles of different periodicities, so that their combined daily duration is conserved (12,60).

From a learning perspective of FAA, SA has no convenient explanation. However, following a daily feeding event, rats do exhibit a period of quiescence and sleep. SA may represent a transient arousal from this due to competing requirements for drinking, grooming, and elimination processes displaced or stimulated by postprandial somnolence. However, the functional significance of the wheel-running component of SA, and of the FAA-SA correlations, is not apparent from this perspective.

II.e. FAA in Constant Lighting: Simultaneous Expression of FAA and Free-Running Rhythms

Richter (130) was the first to report that feeding time can synchronize activity rhythms in rats maintained in LL. Although rats in that study showed anticipation of daily mealtime, it is not clear from the analysis whether the LER was entrained to feeding time or whether it was free running but obscured by the data averaging procedures. Subsequent studies hinted that the LER does not entrain to feeding time. Bolles (17) noted that rats in LL anticipate a daily opportunity to drink (this is essentially a combined feeding and drinking schedule, because rats eat large meals during water access time; see section VI.b.) but also exhibit a second activity component at a different phase that seemed to correspond to a free-running LER. The first clear depiction of FAA concurrent with a free-running rhythm is evident in the data of Edmonds and Adler (43,44) from rats subjected to two meals per day in LL. Subsequent examples abound [e.g., Fig. 3; cf. (12, 23, 51, 60, 103, 104, 160–162, 167, 170, 179)].

The concurrent appearance of two activity rhythms with different periods, one free running and the other phase locked to feeding time, has been taken as strong evidence for a dual FEO-LEO entrainment model of the mammalian circadian system, on the assumption that a single clock cannot readily express two or more periodicities (unless one or more are harmonics of a fundamental period). The same argument applies to the complementary case in which rats express FAA to a 25–26 h feeding cycle concurrent with activity components entrained to a 24 h LD cycle [(10); Fig. 2].

However, the computational learning model does specify a mechanism by which one clock can regulate two rhythms [within limits; (50)]. If the computational rule is to estimate feeding time based on the last three to four feeding phases, with the most recent phase weighted more heavily, then FAA will track a daily feeding cycle, even if its period (T) is different from τ of the LER. The computational model can, thus, explain the concurrent expression of a 24 h FAA and a non-24 h free-running rhythm without recourse to a second oscillator.

In so doing, the model makes an explicit prediction that

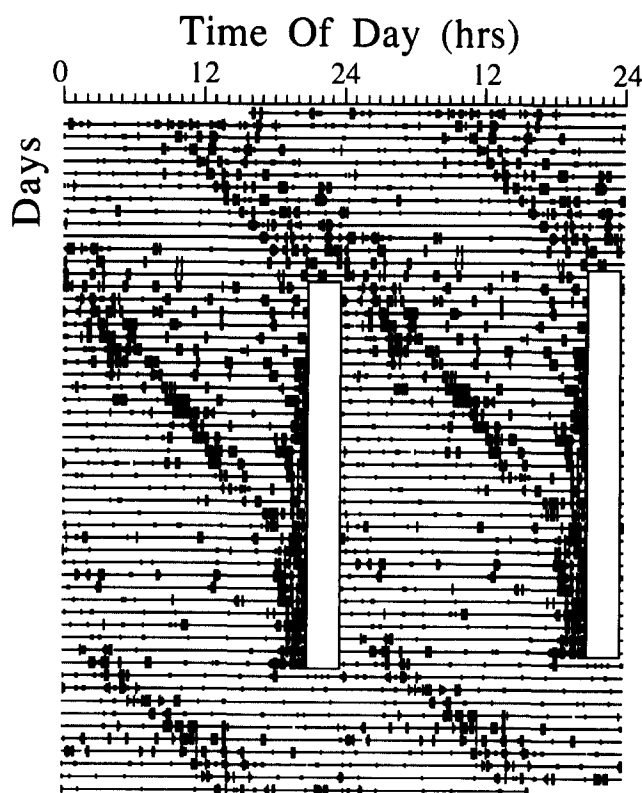


FIG. 3. Double-plotted actogram of wheel running of a rat recorded in constant dim light (LLdim) under ad lib and restricted food access. Same format as Fig. 2. In LLdim, the previously nocturnal circadian rhythm of wheel running free runs with $\tau = 24.7$ h. Under restricted feeding, the rat exhibits food anticipatory wheel running each day, as well as a persisting free-running component of activity. The free-running component shows slight phase and period changes, but does not entrain to the daily mealtime. Unpublished data.

the duration of anticipation should be negatively correlated with τ ; the longer the free-running τ , the shorter should be the duration of FAA to a feeding time that recurs every 24 h. The dual FEO-LEO model makes a similarly strong prediction that the duration of FAA to a 24 h feeding schedule should be unrelated to free-running τ , because in that model FAA duration reflects the phase angle at which a FEO is coupled to mealtime. Because, in the general case, the LEO does not entrain to feeding time, there is no reason to expect that its τ would have a systematic influence on FEO phase.

Although several studies have recorded FAA in rats exposed to 24 h feeding schedules in DD, LL, or after optic enucleation, only one study has examined the relation between FAA duration and free-running τ (161). In that study, separate groups of rats were first entrained to 23 h and 26 h LD cycles, respectively, and upon release into DD, aftereffects of these non-24 h cycles were manifest as short and long free-running τ , respectively. When these two groups were subsequently placed on a 24 h feeding schedule, the short τ rats ($\tau < 24$ h) exhibited an average FAA duration of 7.5 h, a full 3.5 h longer than the long τ rats ($\tau > 24$ h). The direction of this correlation between FAA duration and free-running τ is consistent with the predictions of the computational model.

However, an important caveat with respect to this result is

that FAA duration may vary with the phase of the free-running rhythm; anticipation has been shown to be longer when it overlaps with α of the free-running, LER (19,162). If FAA duration depends on free-running phase, then to gain an unbiased measure of FAA duration, data should be averaged over a full 360° of free run, e.g., if free-running τ is 25 h, data should be averaged over a 25 day segment. Moreover, for this procedure to be meaningful, τ must be stable within the data segment. The analysis performed in the cited study was not intended to meet these criteria and, thus, any conclusions that we would like to extract from it on this issue are at best equivocal.

If the duration of FAA can vary with the phase of the free-running oscillator, independent of τ , and if the α/ρ ratio (for nocturnal rodents, the duration of the daily active period divided by the duration of the daily rest period) varies with τ [Aschoff's rules; (8)], then an observed relation between FAA duration and τ may be secondary to variations in total α time within a given block of days. It might be more meaningful, then, to control for time spent in α in selecting appropriate data segments to compare FAA duration in long and short τ rats. Since α to ρ transitions are often unstable, poorly marked or completely masked in free-running rats under food restriction schedules, such an analysis may be problematic.

The same methodological concerns apply to any analysis of the duration of FAA as a function of the period of the feeding cycle. The entrainment model predicts that FAA duration and feeding cycle period should be positively correlated. For example, the shorter the feeding cycle, the more the oscillator will lag each cycle, and the larger the phase shift that will be required to maintain entrainment. The computational model also predicts a positive correlation, because the computed estimate of feeding time will be incorrect by an amount proportional to the difference between free-running τ and feeding cycle period T .

Results from studies in which the feeding cycle was varied in free-running rats conform to these expectations; FAA was progressively longer as the feeding cycle was lengthened from 23.5 h (the shortest cycle that supported FAA) to 26 h (12). No further lengthening was evident at $T = 27$ h. The slope of the function relating FAA duration to feeding cycle T was estimated at 1.3 [see Gallistel, p. 277; (50)]. It was suggested that the entrainment model demands a slope of 1 for this function, and is, thus, inconsistent with the data (50). The computational model, by contrast, can account for an observed slope greater than 1 by varying the weight given to the most recently recorded feeding phase in the estimate of next feeding phase.

The entrainment model, however, does not demand a slope of 1 for this function. The model assumes that FAA duration reflects the phase-angle of oscillator entrainment to feeding time. Phase-angle of entrainment, in turn, depends on two properties of the FEO, the shape of its PRC to mealtime, and its intrinsic τ . Although the shape of the PRC to feeding events is, at present, unknown, it is known for circadian oscillators generally that τ is modified by entrainment, and changes in the direction of the period of the entraining cycle, as indicated by the previously noted aftereffects on τ when released from entrainment, i.e., free-running τ following entrainment is usually very close to T of the entraining cycle, or closer to T than it was prior to or several weeks after entrainment. Phase angle of entrainment is, thus, not necessarily a linear function of T nor should its change as a function of T necessarily assume a slope of 1.

Another prediction of the computational learning model is

that an acute shift of the free-running oscillator should result in an identical shift of FAA, because there should be a transient mismatch between predicted circadian phase of feeding and external 24 h time (the time domain of the feeding cycle). The entrainment model in the simplest case would predict no response of FAA to a shift of the free-running rhythm. Only one limited test of this has been made; in that study 2 h light pulses produced phase shifts of the free-running rhythm in some rats but in no case was there a detectable change in the phase of FAA (161). However, the number of trials was small.

II.f. Entrainment of Free-Running Rhythms by Feeding Cycles

Although free-running rhythms in rats do not usually entrain to a 24 h feeding cycle, changes in phase and period during restricted feeding are not uncommon (12,23,51,60,103,104,160–162,167,170,179), suggesting that feeding cycles do affect the free-running oscillator. In a modest percentage of cases stable entrainment may occur (51,103,160). In the most thorough study of interactions between feeding cycles and free-running rhythms (160), similarity of free-running τ and feeding cycle T was identified as a necessary condition for entrainment; free-running rhythms synchronized to feeding time only when $\tau - T < 5$ min, although some rats meeting this criterion did not entrain. When entrainment did occur, α onset was usually aligned close to feeding time, although other phase alignments were sometimes evident. However, in many of these latter cases free-running τ during subsequent ad lib feeding was very close to 24 h, suggesting that apparent synchrony of the free-running rhythm to the feeding schedule may have been coincidental. To establish whether phase control (i.e., true entrainment) has been achieved, it would be necessary to alter the phase or period of the feeding cycle.

It thus appears that restricted feeding cycles can function as a Zeitgeber for the free-running LEO in rats. Whether the feeding events have direct access to this oscillator is unclear; Zeitgeber effects could be mediated by coupling with a separate FEO (160) or they could be the result of FAA, because intense novelty-induced, forced, or spontaneous activity has been shown to phase shift or entrain free-running rhythms in rats (95), hamsters (113), and mice (42). This effect is relatively weak in rats, which would account for the extremely narrow τ - T range within which free-running rhythms can entrain to feeding cycles.

Weak entrainment effects of feeding cycles on the LEO are not incompatible with learning models of FAA, but they would seem undesirable. To best estimate feeding time based on circadian phase of past feedings, it is necessary to maintain a stable circadian clock cycle. Within this theoretical framework, it seems paradoxical that the phase or period of the clock should be perturbed by the events that the clock is used to predict. It would clearly be preferable to make the motion of the clock either completely insensitive to or completely determined by feeding events; intermediate effects such as relative coordination would be dysfunctional. However, observations of weak entrainment effects on free-running rhythms may be of little functional consequence because under normal photoperiods the LEO usually remains stably entrained to LD. In some instances, the phase angle of LD entrainment appears to advance (26,27) when rats are maintained on a fixed diurnal meal, but the effect is typically stable, which, for learning models, is all that would be needed to maximize accuracy of food anticipation.

III. PROPERTIES OF FAA REVEALED IN SCN-ABLATED RATS

III.a. Evidence for a Circadian Clock Outside of the SCN

Learning models have tacitly assumed that the light-entrainable, free-running oscillator is the reference clock for the temporal conditioning or computations that underlie FAA. Part of the attraction of the computational model, for example, lies in its ability to explain simultaneous expression of 24 h FAA cycles and non-24 h free-running rhythms without recourse to a second circadian oscillator. However, the food deprivation and light-pulse phase-shift studies reviewed above suggest that motion of the LEO is not always reflected in a corresponding movement of FAA, as is required by learning models. In addition, no attempt has been made to reconcile learning models with the effects of SCN ablations; SCN destruction eliminates or severely disrupts free-running LERs, but neither abolishes nor prevents the expression of FAA (23,87,121,169,170). This has been established for all behavioral and physiological variables known to exhibit anticipatory rhythms under circadian feeding schedules. Thus, if FAA reflects a clock-controlled process in the SCN ablated rat, as it does in the intact rat, then a second oscillator must exist outside of the SCN. If so, then single oscillator learning models in general and the computational model in particular lose the advantage of parsimony that they may appear to hold over the dual oscillator entrainment model.

A variety of studies confirm that FAA in SCN-ablated rats is, in fact, regulated by a self-sustaining clock. These animals are arrhythmic under free-feeding conditions in DD and LD, but anticipate a daily mealtime within a few days of exposure to restricted feeding schedules (23,87,121,169,170). When food is withheld for several days in food-restricted SCN-ablated rats, FAA persists (23,26,141,169). If the feeding schedule deviates greatly from 24 h, no FAA occurs (23,156,170). In some SCN-ablated rats, FAA established to a 23 h schedule became dissociated from feeding time when the schedule was further shortened to 22 h (Fig. 4); during this time, FAA exhibited a persisting free-run for many weeks (156). Although these observations do not distinguish learning from entrainment processes, together they demand recognition that a self-sustaining circadian clock resides outside of the SCN, and that the SCN is not required for FAA.

One recent study disputes this interpretation (141). In that study, SCN-ablated rats were exposed to a standard 24 h restricted feeding schedule and then subjected to 3–4 day blocks of total food deprivation between 6–12 day intervals of ad lib feeding. During restricted feeding, the daily meal was scheduled for 1400, 2300, or 0400 h, labtime, in separate groups of rats. During deprivation, rats previously fed at 1400 showed FAA at about the same clock time as under the feeding cycle. In contrast, rats fed at 0400 h showed a marked delay in the phase at which FAA reappeared, so that it was concentrated around 1200–1600 h, rather than 0400 h. The authors suggest that the reappearance of FAA during deprivation may reflect a direct response to laboratory noise, which presumably is greatest during midday. However, the data presented do not fully support this interpretation; in most cases, resetting of FAA to midday was not immediate but was progressive within and across repeated deprivation tests. This was particularly true for the 2300 h fed rats. Also, there was no evidence of midday activity during restricted feeding in rats fed at night. Thus, exposure to lab noises cannot fully explain the timing of FAA either during a restricted feeding schedule or during subsequent episodes of total food deprivation.

Nonetheless, that study does raise a methodological point

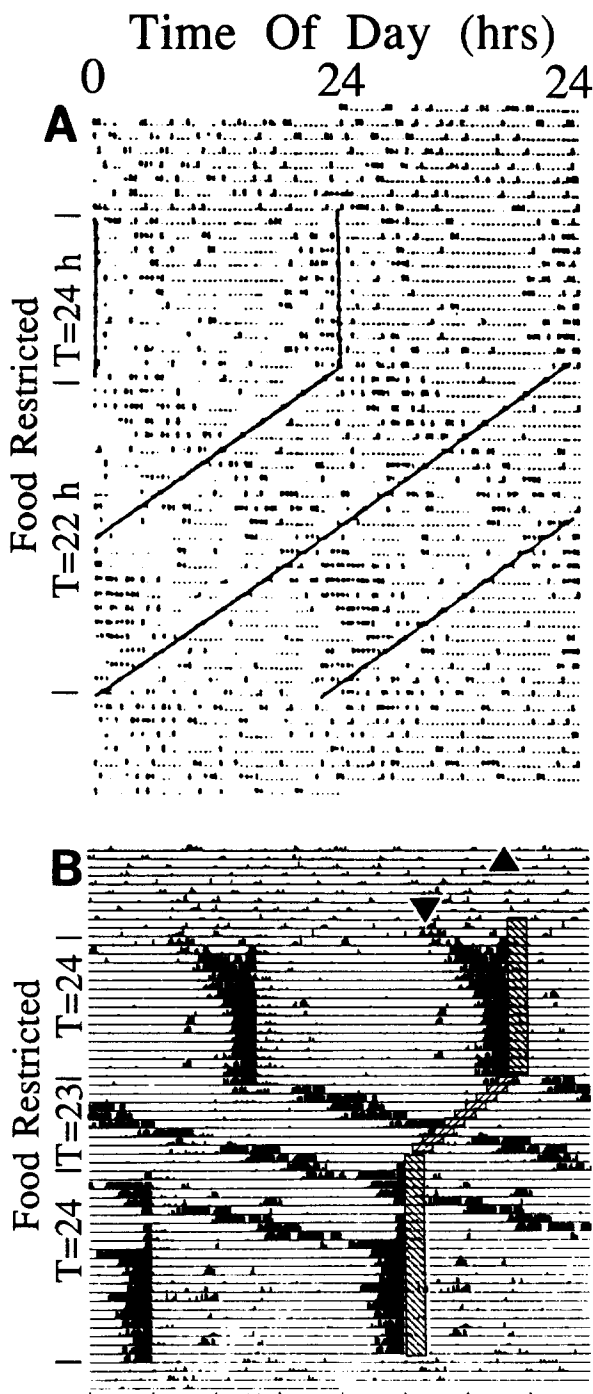


FIG. 4. Double-plotted wheel running activity charts of rats bearing complete SCN ablation. Same format as Fig. 2. Mealtimes during food restriction are indicated by the vertical line (chart A) or the vertical stippled bar (chart B). During ad lib food access, no significant circadian rhythm is apparent, as is typical of rats with complete SCN ablations. During restricted feeding, a food-anticipatory rhythm is generated. When the feeding schedule is shortened to 22 h (A) or 23 h (B), the anticipatory rhythm becomes dissociated from feeding time and free runs with $\tau > 24$ h. In chart B, the free-running rhythm eventually entrains to the feeding schedule when the feeding cycle is again set to 24 h. The solid triangles represent the end (pointing up) and beginning (pointing down) of food deprivation. Modified from Stephan, 1981 (153) and Stephan, 1992 (163).

that may have been inadequately addressed in previous studies. Hungry rats are reactive to noises that signal food access, and this may be accentuated in SCN-ablated rats (132). An accurate assessment of FAA persistence may, thus, require more complete isolation from external cues than is typically attempted or accomplished in most studies. The study also raises the possibility that external noises associated with feeding, and/or the arousal that they induce, may be capable of shifting the phase of the oscillator that mediates FAA. There is little direct evidence on this point and further study seems warranted.

One other feature of the data from that study deserves comment. In a number of cases FAA was weak or absent by the second or third deprivation test which, in some instances, were only 30 days after the last restricted feeding schedule. The authors suggest that the food-anticipatory mechanism is, thus, likely to be a rapidly damping, rather than a self-sustaining oscillator, and that an hourglass mechanism based on competing homeostatic needs for food and sleep cannot be ruled out. However, damping of endogenous circadian rhythms in constant conditions is not limited to FAA. Rats may exhibit free-running rhythms virtually indefinitely in DD or after optic enucleation (131), but these may damp out within weeks to months in LL (41). We have observed many instances of loss of free-running rhythms in mice exposed to dim red light for 2–3 months (Mistlberger and Marchant, unpublished observations). Nonetheless, the free-running LEO in these species is classified as self-sustaining, not rapidly damping, because it is assumed that the underlying mechanism, under optimal conditions, has the structural potential to oscillate indefinitely in the absence of periodic environmental inputs. It is not clear that such conditions can ever be satisfactorily employed in food restriction studies, because food deprivation, an assumed optimal condition, is self-limiting. However, observations of FAA reappearing during deprivation tests scheduled 2–4 months after restricted feeding (26, 27, 119, 136) and of persisting free-running FAA cycles under short feeding schedules [e.g., $T = 22$ h; (156)], indicate that the clock that times FAA in SCN-ablated rats is self-sustaining but, like the LEO, is also susceptible to damping under certain conditions.

A procedural detail that distinguishes the Ruis (141) study from most other deprivation studies conducted in constant conditions was the use of bright LL (100–200 lux) rather than dim LL or DD. Previous studies that used either DD or dim LL all reported more robust reappearance of FAA during deprivation tests up to 80 days after scheduled feeding was replaced by ad lib food access (26, 27, 119, 136). The one exception is a study in which intact rats were exposed to bright LL for 4 months prior to food restriction (100). Although arrhythmic during ad lib feeding, seven of eight rats displayed FAA during restricted feeding. However, during a subsequent deprivation test after 22 days of ad lib feeding, only one rat showed clear reappearance of FAA, while the others showed little or no clustering of activity at any circadian phase. Together with the Ruis study, this seems to suggest that LL may be antagonistic to FAA, at least during deprivation tests or intervening periods of ad lib feeding. Whether this represents an oscillator effect or is due to masking of behavior by light is unclear and requires further study.

III.b. History Dependence of FAA Limits

SCN-ablated rats lack free-running, LERs that might obscure or modulate the expression of FAA; thus, they have

been used extensively as a model system for examining FAA properties. One property of FAA that has been elucidated in SCN-ablated rats is history dependence of anticipation limits (156). SCN-ablated rats do not exhibit FAA to 31 h feeding schedules if the feeding interval is lengthened from 24 to 31 h in a single step. However, if exposed sequentially to schedules with 24, 27, and 29 h cycle durations, some rats do anticipate 31 h and even 33 h schedules.

According to the entrainment model of FAA, the range of feeding cycles that can support FAA reflect the limits of entrainment of the FEO. These limits are determined by two characteristics of the FEO, its intrinsic τ and its PRC to the feeding Zeitgeber. Limits to entrainment are flexible to the extent that τ can be modified during entrainment; thus, if τ is lengthened by entrainment to a 27 h feeding schedule, then the upper limit will be driven above 27 h. Such history dependence of τ and entrainment limits are established properties of circadian oscillators (123).

History dependence of limits to FAA is problematic for learning models. In the computational model, the upper and lower limits to anticipation are set by the probability rule that is used in establishing whether a significant phase-specific clustering of mealtimes has occurred. With longer feeding cycles, meal onsets become increasingly dispersed. To explain an increase in the upper limit following exposure to progressively longer feeding schedules, the computational model, if it is to avoid recourse to oscillator entrainment, must assume a significant relaxation of the probability rule. Whether this is a reasonable assumption or not, it can be evaluated empirically by examining the lower limit of FAA following extension of the upper limit; the entrainment model would predict that the lower limit would be raised due to τ lengthening, whereas the computational model would predict that it would be lowered due to a relaxation of the probability rule.

III.c. Transients in Response to Phase Shifts of Feeding Time

Another characteristic of FAA that has been examined in some detail in SCN-ablated rats are its resetting properties in response to permanent shifts of feeding time. The first study to describe these properties reported that FAA resets not immediately but gradually, in a series of 2-4 h steps (transient cycles) over several days in response to a 12 h shift of feeding time (169). Subsequent studies have shown that FAA usually shows delaying transients, regardless of the direction of the mealtime shift, i.e., if mealtime is advanced by 6 h, FAA resynchronizes by delaying through the 18 h interval between old and new mealtimes, rather than by advancing through the 6 h interval [Fig. 5; (159,166)]. In some cases, FAA resynchronizes to an advanced mealtime without overt transients.

The entrainment model views transients as reflecting the motion of the FEO as it free runs or is phase shifted each day by the displaced mealtime. The size of each daily shift and, thus, the rate of reentrainment, is dependent on oscillator τ and PRC shape.

Transients are not so readily interpreted by learning models. A simple associative temporal conditioning model predicts that, if feeding time is shifted by 12 h, temporal conditioning at the previous mealtime would be extinguished in parallel with the appearance of conditioning at the new mealtime. Transient cycles are neither predicted nor explicable by this simple model.

The computational model fares only marginally better in its treatment of transients. The explanation presumably rests

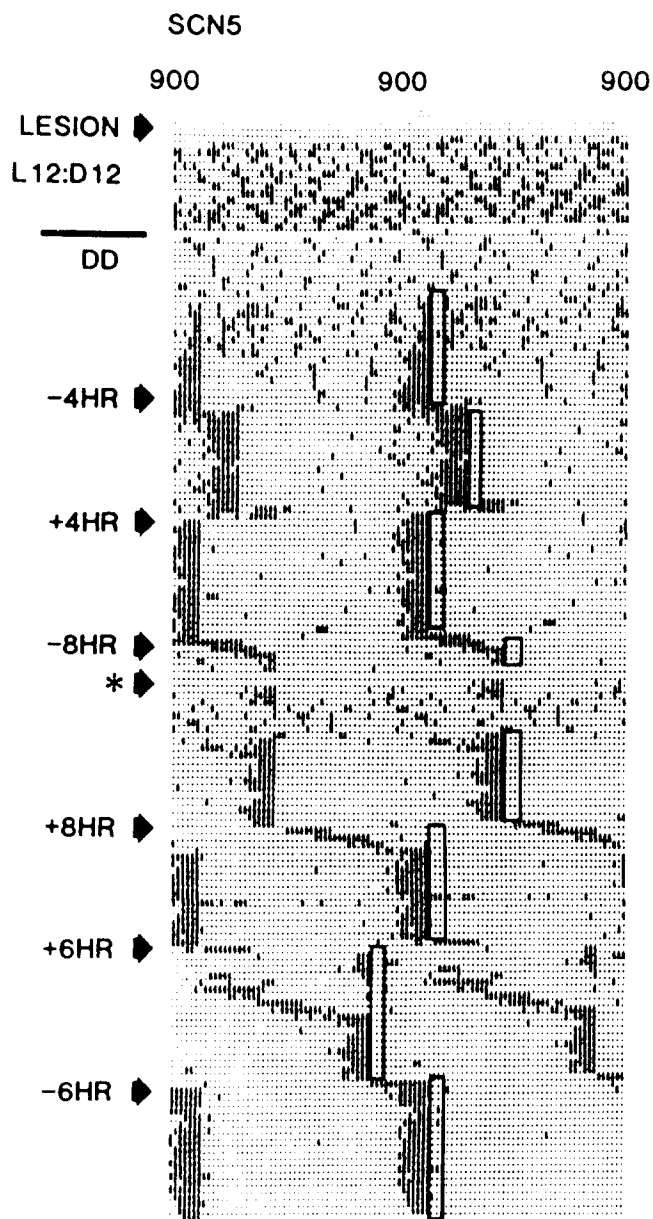


FIG. 5. Double-plotted wheel running activity chart of SCN-ablated rat subjected to phase shifts of feeding time. Plotting conventions as in Fig. 3. Under ad lib feeding, the rat is arrhythmic in both LD and DD. When food is restricted to a single 2-h daily meal (indicated by vertical hollow bars), wheel running anticipates daily mealtime. When mealtime is phase delayed (shifted back) or phase advanced (shifted forward) by 8 h, the anticipatory wheel running rhythm resynchronizes gradually, exhibiting transient (shifting) cycles in the process. Modified from Stephan, 1984 (156).

on the idea that mealtime is estimated based on the last few feeding phases. Thus, if feeding occurs 4 h late, then the computed estimate of the next feeding phase would reflect a compromise position between the last few feeding times (50). In this way, FAA could move systematically in the form of transient cycles from one stable phase to a new stable phase. The number of days required to accomplish this realignment would reflect the number of circadian cycles that are used in the

calculation, the relative weight given the most recent feeding, and oscillator τ (if τ is longer than 24 h then resynchronization to delays of mealtime should be accomplished more quickly than to advances of the same magnitude, because the daily error, i.e., $\tau - T$, would be in the correct direction).

The problem arises in cases where delay transients are observed in response to 6 or 8 h advance shifts of mealtime [Fig. 5; (159,166)]. These are not rare occurrences and, thus, are not likely to represent random computational errors. If mealtime occurs 6 h early, the computational model should predict for the next day a mealtime somewhere within the shortest interval between the last two feeding times. Instead, rats that show delay transients behave as if the best estimate is in the longer intermeal interval, i.e., the animal adjusts its FAA in the wrong direction, and continues to shift in this direction until realigned with the new mealtime. Moreover, the size of each daily shift in many cases appears to be relatively constant, even though FAA is first moving away from and then moving toward the new mealtime. This seems an impossible solution, given the computation that the model proposes. The solution should be for FAA to move earlier toward mealtime in steps that decrease as the difference between the estimated and the true feeding time shrinks.

In some cases, FAA realigns to a 6 or 8 h advance of mealtime without apparent transients (159). In such cases, FAA disappears abruptly at the old mealtime and reappears within 2–3 days at the new mealtime. Advancing transients in these cases could be masked by postprandial somnolence. This interpretation is supported by the observation that, after FAA first appears at the new mealtime, FAA onset time often exhibits transients before stabilizing (i.e., the duration of FAA increases for about a week). Such transients in FAA onset (i.e., FAA duration) are interpretable as stabilization of phase control of a FEO, but, as noted in section II.c, are paradoxical from a learning perspective.

The size and direction of transients following meal shifts could be predicted, from an entrainment perspective, given knowledge of oscillator τ and PRC to feeding Zeitgebers. Unfortunately, neither of these FEO properties are known. However, the response of FAA to mealshifts does provide hints; the prevalence of phase delays suggests a long τ and/or a large phase delay zone in the PRC.

A reasonable strategy to further elucidate a PRC to feeding events would be to assess the phase shifts of FAA that might occur on the day after a single displaced feeding time. Because feeding events on that or subsequent days might induce further shifts or mask the initial shift, a useful design would be to withhold food for several days following the displaced meal. This paradigm is analogous to obtaining a PRC to light by applying light pulses at specific circadian phases on the first day of DD after entrainment to LD.

Recent attempts to use this method have revealed that a single meal displaced by 4, 6, or 9 h is sufficient to induce a 1–1.5 h delay of FAA, but that by the second or third day of total deprivation following the test meal FAA returns to its initial position (166). Similar results were obtained in cases where the rats were exposed to the displaced mealtime for 2 consecutive days before deprivation. If the test meal was repeated for 3 or 4 days before deprivation, complete and stable resetting of FAA was usually apparent.

These results indicate that one or two exposures to a displaced feeding event have little lasting effect on FAA phase. The tendency of FAA to return to its original phase position after a small initial shift could represent a short τ free run. However, during a second deprivation test that followed 8

days of ad lib feeding, FAA reappeared again at this phase, as if τ was very close to 24 h, and not running less than 24 h. In fact, in a number of cases there was a marked tendency for activity to reappear at the original feeding time during deprivations, even if FAA had apparently been reset to a new mealtime displaced by 6 or 9 h. A similar affect was apparent in a companion study, in which rats were subjected to 8, 10, and 12 h phase delays and advances of mealtime; in some cases activity persisted at the original feeding time even while the rat displayed FAA to a new mealtime (165).

Assuming that persistence of FAA at an original mealtime is not an artifact of laboratory noise, these results are problematic for learning and entrainment models. From a learning perspective, circadian phases no longer associated with feeding should, because of extinction processes, lose the ability to elicit FAA, or should play no role in estimates of feeding time once FAA is fully reset to a new mealtime. For entrainment models to explain activity persisting at an original feeding time, a two oscillator organization has been suggested in which the FEO can dissociate (i.e., split) into two oscillating subunits, with one oscillator moving toward the new mealtime and the other retaining a position near the prior feeding time or returning to that position after an initial perturbation (165,166). Such a two-oscillator organization raises several questions: How does one oscillator ignore timing information from the shifted mealtime, and how can it retain a memory of phase displacement that would allow it to return to its original position? A two-oscillator organization has previously been suggested to account for FAA expressed to two meals per day (158,163), and will be discussed further in that context.

III.d. Anticipation of Multiple Meals

Restricted feeding paradigms that employ a single daily meal have proven a powerful tool in elucidating structure and function in circadian timing systems. However, for many species such paradigms may be viewed as lacking ecological validity. Indeed, most organisms feed more than once a day, and may be exposed to multiple feeding sources with unique temporal windows of availability. A clock mechanism for optimal regulation of foraging behavior should, thus, enable the organism to predict and anticipate more than just a single daily feeding event. The earliest studies to examine adaptation to multiple feeding times used bees and birds as model systems. Those data will be discussed separately in section IV; here, discussion is confined to abilities displayed by rats in multiple feeding paradigms.

d1. Two or three meals in one place. Bolles and Moot (19) first reported that rats entrained to LD cycles can anticipate two daytime or nighttime meals, each 1 h in duration and separated by 6 h. This finding is significant for two reasons. First, it demonstrates that FAA is not a simple function of linear metabolic effects of feeding and deprivation, because the duration and peak of FAA was the same for both meals, despite the widely disparate intermeal intervals that preceded each (i.e., 18 h and 6 h). Second, the two intermeal intervals embedded in this design assure that anticipation is not based on learning of a feeding interval; if it were, then the rat should become active every 6 h or every 18 h.

Anticipation of two daily mealtimes should provide no particular difficulty for simple associative learning models; if the rat can be temporally conditioned to one feeding time, there is no reason why it should not be able to learn two feeding phases, assuming that the intermeal interval exceeds the resolution with which reliable internal clock readings can be taken.

For the computational model, anticipation of two daily meals is problematic. If the rat uses the last three to four mealtimes to compute the next circadian phase of feeding, then the best estimate should fall somewhere within the shortest interval between meals. To anticipate two meals using such a mechanism, there must be a rule so that estimations of each feeding time ignore feeding events occurring 6 h or more out of phase.

For the entrainment model, the cost of anticipating more than one daily meal is parsimony, because more than one clock is necessary. This, in itself, is not an usual feature of circadian systems, because it is already well known that the LEO can be induced to split into two independent free-running components that can be modelled as separate oscillators with two stable coupling modes 180° apart (124). By postulating different PRCs to light (or different intrinsic τ s), these two oscillators could entrain to different edges of the daily LD cycle (i.e., dawn and dusk), and could, thus, mediate α expansion and compression effects that parallel seasonal changes in photoperiod. Similar characteristics might permit two oscillators to entrain stably to two mealtimes.

If anticipation of two daily meals separated by 6 h is accomplished by temporal conditioning or computations, then anticipation of three or four meals separated by 6 h should also be possible. However, to date, all of the evidence indicates that rats cannot do this; SCN-ablated rats readily anticipate two meals separated by 8 h, but do not anticipate more than two of three daily meals separated by 6, 6 and 12 h, or 8, 8 and 8 h (164). In many instances, FAA associated with one feeding time jumps or shifts to another feeding time, often displaying transient cycles in the process.

Failure to anticipate three daily meals, and apparent phase jumps of FAA from one to another mealtime, are properties that cannot be explained by extant learning models. Because the meals occur at intervals that can readily support two bouts of FAA, arguments involving the limits of phase resolution can be rejected. Moreover, because FAA may be associated with any two of the three meals, and may jump among the three following periods of stability, arguments invoking masking effects of prior meals (i.e., postprandial somnolence) are unconvincing.

From the entrainment perspective, anticipation of two but not three daily meals suggests that the FEO can decompose to a maximum of two independently oscillating subunits. Movement of FAA from one to another mealtime, particularly prevalent if one intermeal interval is shortened, represents phase jumps analogous to those observed in the LER when the interval between dusk and dawn light pulses under a skeleton photoperiod is shortened to some critical value (122,157). Such jumps are conceived as reflecting coupling interactions between two oscillators which, at certain phase angles, are mutually repellent or attractant; the force of this coupling relation would induce a phase jump if it exceeds the force of the entraining Zeitgeber.

d2. FAA to two meals with different feeding periodicities. A two-oscillator organization has also been suggested based on the observation that rats can anticipate two meals that differ in their periodicity of recurrence (158,163). Although clearly not an easy task, this has been convincingly demonstrated in SCN-ablated rats maintained on two daily meals, one repeating every 25 h and the other every 26 h (163). Under such schedules rats can anticipate both meals, although there appear to be intermeal intervals at which instabilities occur. For example, FAA is suppressed prior to meals that lag the first meal by 1–5 h. Also, at 11–16 h intervals between meals,

FAA to one mealtime may switch to the other, sometimes displaying transients in the process. The challenge for the entrainment model is to formally describe how oscillator subunits can display stable, if temporary, phase coupling to one meal without constant disruption by coupling inputs from the other meal and oscillator. This may involve modulations of oscillator τ and PRC that would promote matching of oscillator characteristics to the feeding cycle, thus facilitating stable phase control by the correct daily meal.

For the computational learning model, the problems of anticipating two meals with different periods are the same as for anticipating two meals with the same period. Moreover, for both types of learning models, the instabilities and jumps noted at 11–16 h intermeal intervals make no sense; at such maximal intervals, discrimination between two feeding phases should be easiest and most stable.

d3. Two meals in different places: Time and place learning. Food varies in two dimensions, time and space, and animals must integrate both dimensions to forage optimally. The ability to associate feeding time with a unique feeding place has been most thoroughly studied in bees and several species of birds. Lab and field studies indicate that these species can learn both the time and place of two or more daily meals. These studies will be discussed further in section IV.

For rats, there is but a single published study documenting similar abilities. In that study, intact and SCN-ablated rats received two meals per day, each associated with a different lever that the rat was required to press to receive 45 mg pellets of food (22). All of the rats showed anticipatory lever pressing prior to both feeding times, but fewer than half showed significant spatial discrimination. In unpublished studies, we have observed similar performance by LD-entrained, intact rats receiving two meals per day, separated by 7 or 10 h, at two automated feeding sites that were positioned at opposite ends of a 1 m square open field enclosure (Mistlberger, unpublished observations). Poor time-place discrimination by some of the rats in these studies may reflect the close proximity of the two feeding places, because there is little cost in shuttling between feeders or levers prior to both scheduled feeding times (22). In preliminary tests, the use of barriers and hurdles positioned between feeding sites did not significantly improve discrimination. Nonetheless, the data from these studies clearly indicate that rats do have the capacity to associate two different feeding locations with two different times of food availability.

The ability of rats to learn feeding places is well established, and the fact that they can associate places with circadian phase is not problematic for learning models of FAA. Indeed, the computational model explicitly postulates that both the time and the place at which events occur are recorded in memory, and can serve as index variables for memory retrieval (50). An alternative conception would be to treat the spatial and temporal discriminations as a form of state-dependent learning, in which each circadian phase represents a unique state. In either case, the problem of using circadian phase as a conditional cue is straightforward if the animal uses a single clock.

The entrainment model, however, postulates that anticipation of two daily meals reflects entrainment of not one but two oscillators, and many of the properties of FAA support such a conception. Assuming that both oscillators have similar entrainment characteristics and couple to mealtime at the same phase angle, then each mealtime will be associated with identical internal clock time. To make a time-place discrimination, a unique time must be associated with each place. Thus, the internal mechanism that consults and records clock

phase would also have to record clock identity, i.e., meal A occurs at phase X of FEO subunit A, meal B occurs at phase X of FEO subunit B (or phase Y of subunit A, if only one subunit is consulted).

Regardless of the number of clocks involved, or whether clock entrainment occurs, time-place discriminations are consistent with the idea that circadian phase is subject to real-time consultation and memorial representation.

IV. OTHER SPECIES

IV.a. Invertebrates

a1. Bees. The earliest studies of food anticipation, conducted by Beling and Wahl in the 1920-30s, were prompted by field observations that fertile bees appear to learn when breakfast is served on the back patio (47). These studies laid important groundwork for a general theory of circadian timing based on internal clocks that was to coalesce by the late 50s (see Cold Spring Harbor Symposium on Quantitative Biology, 1960). A summary of this work is as follows.

1. Bees trained to obtain sugar water at a field station at a fixed time of day anticipate this daily event by 1 h or more (13,183), depending on the circadian phase of training (109,110). Bees trained to receive food every 19 h for 10 days show activity 24 h but not 19 h after the last feeding event (13). Anticipation of 24 h feeding intervals persists in constant light and temperature (13,183), and resets gradually in response to a phase shift of feeding time (128,129).
2. Bees trained to receive a morning meal at one station and an afternoon meal at a second station exhibit strong time-place discrimination in group performance (45,110,183). Individual bees, however, apparently do not readily display two anticipatory peaks; only 16 marked bees in a colony (total number of bees not reported) showed station visits at both feeding times in a two meal paradigm (110). That report appears to be at odds with an earlier study demonstrating that, after a single day of training, individual bees showed variations in food search intensity that corresponded to nine feeding times with 60 min interfeeding intervals (82). The design of this latter study differed, however, in that the bees were food restricted and were not required to forage over a distance. Whether or not this is an ecologically valid procedure, it does effectively reveal timing abilities not readily observed in field studies.
3. Colonies of South African bees (*Apis mellifera capensis*) maintained in LL show free-running circadian rhythms of colony foraging activity that entrain to a 2 h feeding time (48). The onset of group activity each day anticipates feeding time by a duration that is positively correlated with the period of the feeding cycle. Entrainment was evident in all colonies tested at feeding periods of 24 and 25 h, but some colonies did not entrain at periods of 22 and 23 h.

These results highlight fundamental similarities between bees and rats in circadian FAA. Individuals of both species can anticipate one or two daily meals under LD and LL, but cannot anticipate meals presented at intervals outside of the circadian range. The duration of anticipation to a single meal in LL is a function of feeding cycle T, and anticipatory rhythms exhibit transient cycles in adjusting to phase shifts of mealtime.

One apparent difference between rats and bees is that in bees, the free-running LEO is entrained by feeding schedules in LL, whereas in rats the free-running rhythm is usually not

entrained. There is, at present, no evidence that food- and light-entrainable rhythms can be dissociated in bees. Other species can be distinguished on this dimension; in some, food- and light-entrainable rhythms are readily dissociable, whereas in others, dissociation is rare or has yet to be documented. From the perspective of the entrainment model of FAA, this variability is thought to reflect differences in the strength of coupling between FEOs and LEOs. However, in cases where evidence for separate FAA and free-running rhythms is lacking, it remains possible that only a single oscillator exists. In such cases, it will be necessary to evaluate whether FAA is possible following removal of the LEO (e.g., the SCN in mammals).

A second apparent difference between bees and rats is that bees may be capable of discriminating up to nine daily meal-times, whereas rats fail to anticipate more than two meals. These differences could conceivably be secondary to the experimental protocols used. In any case, the ability to discriminate a large number of circadian phases presents difficulty for a strict entrainment model of FAA, because the problem of achieving stable, independent phase control of nine or more circadian oscillators to identical Zeitgebers separated by as little as 1 h would seem forboding. These data may indicate that FAA in bees is mediated by two independent processes, a memory for oscillator phase combined with entrainment of a single master oscillator.

IV.b. Fish

Anecdotal evidence suggests that freshwater fish congregate at pond locations that fishermen bait at a specific time each day. Laboratory studies confirm that in at least some freshwater fish (e.g., Medaka, *Oryzias latipes*), some behaviors (e.g., intraspecies agonistic activity), but not others (e.g., egg-laying or courtship), are synchronized to feeding time under LD, and persist at that time during 3 days of total food deprivation (187). In the caverniculus fish *Nemacheilus evezardi*, feeding time synchronizes phototactic behavior, although the role of food access in this response was confounded with light exposure (126). Several marine fish species have been shown to anticipate feeding time under LD and LL, and may exhibit transients in the resetting response to a shift of mealtime (38). These studies suggest that at least some fish use endogenous clocks to coordinate activity with feeding times, but the contribution of learning and entrainment processes remain to be clarified.

IV.c. Birds

FAA in birds shares many of the characteristics of FAA in bees and rats. The earliest avian study demonstrated that finches anticipate one or two meals per day under LD and LL, but do not anticipate single meals recurring every 26 h (155). Wagner (182) reported that canaries can anticipate a daily meal in DD, and Adler (4) later presented impressive evidence for strong anticipation of four daily meals, distributed at 3 h intervals within the light period, in three starlings (one of the birds skipped the morning activity peak, perhaps due to low natural light at that mealtime). This work has been extended in a series of studies by Biebach, Krebs, and colleagues who have demonstrated convincingly that warblers (14,15,83), as well as starlings (188), can learn the time and place of four daily meals occurring in different locations in a four-chamber apparatus. In starlings, this time-place discrimination persists (free runs) in LL (188).

No attempt has yet been made to determine whether the

free-running rhythm in these birds entrains to a 24 h feeding schedule. However, free-running rhythms in pigeons (3) and house sparrows (56) can be entrained to a single daily feeding time. In house sparrows, restricted to 12 h daily food access, the limits of entrainment to feeding cycles in LL appear quite narrow, within the range of 23.5 to 25 h, possibly due to the long duration of food access utilized (56).

In studies of rats, restricted feeding times are routinely scheduled during the rat's inactive period (lights on), so that FAA is not obscured by the high levels of activity normally expressed in the dark. This procedure is a convenient means of assessing whether FAA can be dissociated from the active phase of the LEO. Most bee and bird studies have not used this design, possibly because these diurnal species will not forage in the dark. In the one exception to these studies (3), pigeons were restricted to food for 2 h in the dark (0.1 lux) of a 12:12 LD cycle, during which time pecking of a key provided food reward. The birds showed modest levels of unrewarded pecking behavior during the light period, but during the dark all key pecks were restricted to the 2 h mealtime. Because the access time was not signalled by an external cue, the rewarded pecking must have been timed by an internal clock, i.e., the first few pecks can be viewed as anticipatory or time-sampling behavior. What is noteworthy is that when the LD cycle was reversed, the LER of pecking appeared to display transients as it realigned with the new daytime (now overlapping with feeding time). This suggests that although feeding time controlled the phase of the LEO under DD and LL, it did not control its phase under LD. Thus, food anticipation in the pigeon may not be dependent on entrainment of the LER, as has been suggested for bees. These particular results are consistent with a FEO-LEO entrainment model, with or without an additional learning process, but require further substantiation [which may be contained in a recent study by Phillips et al., 1993, although we have not yet seen the data; see (120)].

IV.d. Mice

In the earliest mouse study [(92); see also (9)], white mice of an unspecified strain showed anticipation of a daily meal provided at lights on under LD, and a second peak of activity at lights off. Under DD, the FAA persisted, but the lights-off peak advanced, i.e., showed a short τ free run. The number of days recorded was inadequate to assess whether this advancing activity peak would have entrained to feeding time, but the study does constitute the first demonstration of FAA concurrent with a free-running activity component.

More recent studies suggest significant interstrain differences in response to food restriction in mice. The C3H mouse, for example, appears to be a rigidly nocturnal feeder; when food access was shifted abruptly to a 4 h diurnal mealtime, these mice failed to eat, and died within days (34,64). By extending the mealtime to 12 h, and shifting the access time by 1 h per day until it was entirely diurnal, all of the mice survived. However, unlike C57BL/6J mice, which readily adapted to diurnal feeding, the C3H mice did not show a shift of peak body temperature toward the feeding time, suggesting that the phase of the LEO was not affected by the inverted feeding cycle.

A second comparative study revealed that while both C57 and CS mice anticipate a 2 h daily feeding time in DD, free-running rhythms persisted in all C57 mice, but were entrained to feeding time in 11/13 CS mice (1). However, among the CS mice, there is clear evidence for stable FAA concurrent with

up to 2 weeks of transients in the free-running rhythm before a stable phase angle of entrainment was achieved. In this respect, the two strains are similar, because both can show coexisting FAA and free-running activity components.

IV.e. Hamsters

Hamsters are a herbivorous species that forage nocturnally but eat every few hours throughout the day and night, primarily utilizing hoarded food stocks. Hamsters exhibit a limited capacity for hyperphagia in response to food deprivation and, thus, cannot adapt to daily feeding schedules in which food is restricted to 2, 6, or even 12 h durations (139,153). Several recent studies, however, have used limited-amount rather than limited-duration feeding schedules to demonstrate that hamsters can anticipate the onset of daily food access, and that this can entrain their free-running rhythms in DD or LL. In LL, 5 of 11 intact hamsters maintained at 70% body weight anticipated meal onset, but in no case was the free-running rhythm entrained (2). Another study observed entrainment of free-running or disrupted rhythms in 26 of 31 hamsters in LL [Fig. 6A; (98)]. In DD, using a presumably palatable diet, free-running rhythms in 8 of 15 hamsters entrained to feeding time (2). In LD, only 5 of 31 hamsters maintained at about 82% body weight anticipated daily feeding beginning in mid-light, and each of these continued to express nocturnal activity, but when LD was replaced by DD, nocturnal activity shifted toward and was entrained by feeding time in 19 cases [Fig. 6B; (98)]. During the shifting process, stable FAA coexisted with transient cycles of the previously LER.

These data indicate that hamsters can simultaneously express FAA and light-entrained or free-running rhythms. Ablation studies further show that FAA in hamsters is not dependent on the SCN, and may, in fact, be more readily expressed in its absence (2,96). In addition, FAA in SCN-ablated hamsters shows circadian limits and can persist under constant feeding conditions (99). The similarity of these FAA properties in rats and hamsters suggests that the mediating mechanisms are a common feature of mammalian circadian systems.

IV.f. Rabbits

The rabbit is another herbivorous species that shows FAA in response to restricted feeding schedules. In one study, free-running rhythms of Himalayan rabbits maintained in LL were entrained to a 4 h daily meal with a positive (i.e., anticipatory) phase (75). The results were interpreted in terms of a single light- and food-entrainable pacemaker. However, in some of the data illustrated, it appears that the phase at which free-running rhythms resume during ad lib feeding following the feeding cycle is consistent with its phase prior to the feeding schedule, and not with its apparent phase during the schedule. Moreover, in published figures from a previous study by the same lab, free-running activity components are clearly coincident with strong FAA (74). The data are thus consistent with a two oscillator FEO-LEO model.

IV.g. Mammalian Carnivores

The ability to track temporal regularities of prey availability would seem to have considerable adaptive significance for carnivores. Thus, it is not surprising that FAA has been observed in each of the four carnivore species studied to date. The most extensive studies have involved two nocturnal marsupials, the Kowari and the Quoll. Kowari maintained on a feeding schedule in which food was replenished each day at a

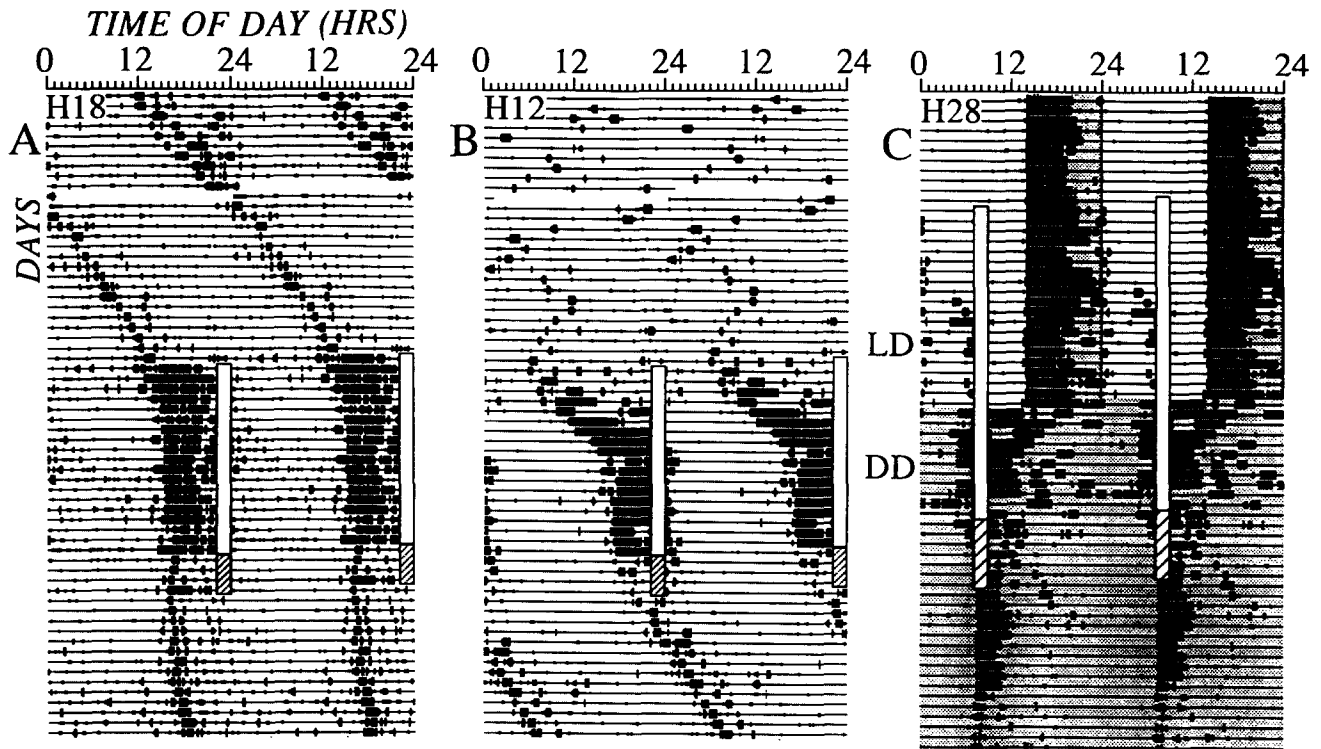


FIG. 6. Double-plotted wheel running activity charts of intact Syrian hamsters. Hollow vertical bars indicate time of water access and food replenishing during water and food restriction. Enough food was provided each day to maintain body weight at about 85% of baseline. Striped vertical bars indicate restricted water access with ad lib food access. (A) Hamster recorded in LLdim exhibits free-running activity rhythm that entrains to water and food access time. This pattern is similar to SCN-ablated hamsters, except that the food-entrained rhythm in most cases doesn't persist as clearly during subsequent ad lib food and water access. (B) Hamster in LLdim with disrupted activity rhythm shows recovery and entrainment of rhythm to feeding time. (C) Hamster in LD followed by DD. Under LD, some water/food anticipatory activity was evident. During DD, anticipatory activity was expressed more robustly, and the previously light-entrained activity rhythm exhibits transient (shifting) cycles as it entrains to water/food access time. Modified from Mistlberger, 1993 (98).

fixed time, but was not restricted in amount, showed variable responses (79). In LD, some individuals showed FAA to a midday meal, some showed a phase shift of the LER toward mealtime, and some showed intermediate responses. In DD, some animals showed strong FAA coexistent with a free-running rhythm, and in only one case was the free-run possibly entrained to mealtime. In a second study, a limited-duration feeding schedule was utilized, with much stronger effects (80). Nine of 10 individuals showed FAA to a midlight meal under LD and, when transferred to DD, the LER in eight cases became entrained to mealtime. The process of entrainment took as long as 3 weeks, during which time the animals displayed stable FAA coexisting with a phase shifting or free-running rhythm. Strong persistence of FAA was demonstrated during 3 day intervals of total food deprivation.

Similar results have been obtained from limited-duration feeding studies of the Quoll (117). Under LD, Quoll anticipate a 2 h daily meal, while retaining nocturnal activity. When transferred to DD, FAA was unperturbed, whereas the LER free ran in some cases, and may have entrained to feeding time in other individuals. In a second experiment conducted in LL, free-running rhythms exhibited much longer τ and did not entrain to mealtime, presumably reflecting the limits to entrainment of the free-running oscillator. These marsupials, thus, show mixed responses to restricted feeding; in all cases

FAA is strong, but entrainment of the LEO to feeding time is variable across individuals.

The remaining study of carnivores reported FAA in minks and weasels subjected to limited-amount (85% of baseline) feeding schedules in DD and LL (194). However, FAA was quite slow to develop, requiring at least 20–30 days exposure to the feeding schedule before appearing, and was weak and variable by comparison to the other species discussed. These features may reflect the use of a limited-amount feeding schedule; the animals may distribute their feeding over a considerable duration, or may make metabolic adjustments that reduce the motivational impact of a reduction in available calories. Free-running rhythms were indistinct in most individuals and the recordings were not maintained sufficiently long to establish whether the free-running rhythm could be entrained to food onset time.

IV.h. Primates

Primate studies have focussed almost exclusively on the squirrel monkey, a diurnal omnivore with a monophasic sleep-wake rhythm similar to humans. An early case study ($n = 1$) purportedly showed synchronization of activity rhythms to feeding time, but was confounded by the use of a self-selected lighting schedule (33). Several subsequent studies also

reported that a single daily feeding synchronized free-running activity rhythms of squirrel monkeys in LL (176–178). Under these schedules, activity and drinking behavior anticipated feeding by 1 h or more, and free ran from that phase during subsequent ad lib food access. The results are, thus, compatible with an interpretation of entrainment.

More recent studies suggest that social cues, in the form of human contact each day for delivery and removal of food, may have provided the dominant cues that entrained these animals. When food was provided by automation, entrainment of free-running rhythms did not occur, with the exception of one case, in which the period of the feeding cycle closely matched free-running τ (11); note that cues associated with manual delivery of food are neither necessary nor sufficient for FAA in any other species yet examined]. Nonetheless, modulations of τ suggestive of relative coordination were not uncommon in the three animals tested, suggesting a weak effect of feeding cycles on the free-running LEO. Similar results were reported in a second study, in which only two of eight monkeys under automated restricted food access showed clear entrainment of free-running activity rhythms, while several others showed relative coordination (21).

Both of these latter studies also reported anticipatory activity to feeding time, with some discrepancies possibly related to the activity measures used. In one study, anticipation was evident in food cup activity and interruption of tree-climbing prior to mealtime during testing in LD. In LL, however, these anticipatory responses were not apparent (11). The other study, in contrast, reported that FAA in lever pressing (an instrumental response necessary for food acquisition) was evident in all animals in LL, although it was often less robust during the inactive phase of the free-running rhythm (21). Anticipation was weak or absent in perch-hopping activity. The evidence, thus, indicates that squirrel monkeys can generate FAA concurrent with free-running rhythms, and that this is best revealed in instrumental, appetitive behaviors. Primates, thus, appear to share circadian FAA properties in common with other mammals.

There are no studies yet available to assess whether humans can anticipate scheduled feeding times under constant conditions, or whether such feedings can entrain free-running rhythms. A few studies [e.g. (46,53,90)] have examined the effects of morning and evening feedings on various metabolic and hormonal variables, but none have been conducted in temporal isolation, or have assessed standard circadian phase markers such as deep body temperature, plasma melatonin, or sleep and wake onsets.

V. SUMMARY

The following conclusions can be drawn from the literature reviewed.

1. External cues are not necessary for FAA.
2. Hourglass or interval timer models can be ruled out as possible mediating mechanisms of FAA. Such timers are completely inadequate to explain the 22–31 h limits to anticipation, the persistence of FAA cycles during deprivation, the reappearance of FAA cycles during deprivation after apparent damping under ad lib feeding, the appearance of transient FAA cycles in response to phase shifts of mealtime, the similarity of FAA duration, and intensity to two daily meals separated by 6 h, despite the significantly different deprivation intervals that precede each meal, and other more subtle features of FAA.
3. Evidence for sustained free runs of FAA cycles under 22–

23 h feeding schedules, and for reappearance of FAA during bouts of total food deprivation after weeks or months of ad lib food access, indicates that FAA is regulated by a self-sustaining oscillator, and rules out involvement of a rapidly damping oscillator subtype.

4. A dual FEO-LEO model, in which both oscillators can dissociate into two independently oscillating subunits, is consistent with most of the known properties of FAA as manifest by intact and SCN-ablated rodents. The major challenges for this model include a) specifying the status of the hypothetical FEO prior to restricted feeding, b) specifying how coupling between the FEO and effector systems for specific rhythms is regulated by the animal's deprivation state, c) describing formally how two FEO subunits can entrain, even temporarily, to two feeding cycles with different periods, in the face of competing influences of the second daily meal and oscillator subunit, and d) describing formally how a FEO subunit can manifest a memory for phase displacement, if such a phenomenon is substantiated by further work.
5. A simple temporal conditioning learning model does not explain many properties of FAA. The computational learning model, by contrast, was explicitly designed to explain certain properties of FAA based on a general principle that animals record the phase of occurrence of feeding and other significant daily events. Much of the appeal of such a model rests in its ability to account for these properties in terms of a single LEO. However, this advantage of parsimony is lost in view of the well established independence of FAA from the master LEO located in the SCN. In addition, the model fails to adequately account for many features of FAA including a) asymmetry of FAA limits with respect to 24 h, b) history dependence of FAA limits, c) asymmetry of FAA resetting properties in response to phase shifts of mealtime, d) failure of rats to anticipate more than two of three or four daily meals despite equivalent intermeal intervals, e) FAA phase jumps or shifts with transient cycles between two of two or three daily meals, and f) instabilities of FAA at certain intermeal intervals under two meal per day schedules.

Nonetheless, the general principle on which the computational model is based may have considerable merit. Evidence that animals can learn time-place associations is consistent with the idea that circadian clocks can be consulted and that circadian phase can be represented in memory. The ability of birds and bees to discriminate four and nine daily feeding phases, respectively, makes a literal memory for circadian phase an attractive alternative to a strict entrainment model that would postulate four and nine independent mediating oscillators. Given the current literature base, a model combining a single light- and food-entrainable oscillator with memory for phase would seem to most economically simulate FAA in bees and perhaps also in some birds [but see (120)], whereas a dual FEO-LEO circadian organization, with at least some capacity for phase memory, may be required to best simulate FAA in mammals. Further work is necessary to substantiate the extent to which mammalian species are capable of memorial representation of circadian phase.

VI. PHYSIOLOGICAL MECHANISMS OF FAA

VI.a. Strategies for Localizing Function in Circadian Systems

The literature reviewed has clearly established that FAA is regulated by a self-sustaining oscillator that, in rats and

hamsters, can function in the absence of the SCN LEO. However, the physiological substrates of this oscillator are unknown. A guide to oscillator localization is provided by the converging set of experimental procedures that led to confirmation of the SCN as a self-sustaining, master LEO. These procedures, and some of the results obtained, include:

1. Ablations; SCN-ablations disrupt or eliminate light-entrainable, free-running rhythms [(40,111,142,172); but see (81)].
2. Neural recording; SCN neurons exhibit circadian variation in multiple (69–71,77,147) and single (52,54,150,151) unit activity, in vivo and in vitro.
3. Metabolic activity; SCN neurons exhibit circadian variation in glucose metabolism, in vivo (148) and in vitro (116).
4. Neural stimulation; electrical (144) and chemical (91) activation of SCN neurons phase shifts free-running rhythms.
5. Pharmacology; SCN applications of cholinergic (78) and excitatory amino acid receptor antagonists (29,30) can block phase-shifting responses to light pulses.
6. Gene expression; light pulses that shift free-running rhythms induce *c-fos* expression in the SCN [reviewed in (7)].
7. Neural transplants; fetal SCN transplants can restore free-running rhythms in SCN-ablated rats and hamsters (89, 127).

As an initial approach to oscillator localization, neural ablation has traditionally played an important role. Potential targets for such studies include known afferent and efferent connections of the SCN (on the assumption that a FEO is coupled to the SCN LEO), as well as brain and endocrine structures that exhibit neural, metabolic, or molecular (e.g., gene expression) rhythms or responses coordinated with daily feeding cycles.

VI.b. Identifying the Zeitgeber for FAA

The ablation studies critical to discovery of the LEO were guided by the reasonable assumption that a LEO must receive information about LD, and that this information must be retinal in origin because, in mammals, the eyes are necessary for photic entrainment. A similar strategy of identifying the Zeitgeber, its transduction site(s) and afferent (entrainment) pathway(s) may suggest target sites amenable to the localization procedures listed above.

It has been assumed that the oscillator mediating FAA is entrained exclusively by feeding related stimuli (9,93), in part due to observations that rats do not anticipate a daily opportunity to ingest water or salt, despite experimentally induced thirst or salt hunger. However, this assumption was premature, as more recent evidence has revealed that anticipation of other resources is possible but may be behavior specific. Thus, although thirsty rats do not anticipate water access time in wheel-running (97) or general cage activity (105), they do show anticipatory activity directed at a water-delivery site (97). Similarly, salt-hungry rats fail to exhibit salt-anticipatory wheel running (137), but can express anticipatory lever pressing for salt (138). Certain properties of food anticipation may also be measurement dependent; in rats, the magnitude and duration of FAA is generally greatest in wheel-running, lever-pressing, and food-bin approaches, and is less robust and may be absent in nonspecific cage activity or drinking (12,23,107,179). In squirrel monkeys, FAA is most robust in lever pressing or food-cup activity (21,102).

In addition to dependence of anticipatory activity on the

type of behavior measured, two other potential methodological pitfalls were identified in the salt- and water-restriction studies. First, to identify a Zeitgeber for anticipatory activity, the stimulus must be isolated from other potential Zeitgebers. For example, water restricted rats maintained on a dry food diet tend to concentrate food intake around the time of water access (105). Thus, failure to prevent such food intake may result in reports of robust water anticipation in a number of behavioral measures, and inappropriate conclusions concerning the efficacy of water access as a Zeitgeber (39). In practice, separation of putative Zeitgebers may be difficult to achieve [cf. (98)].

Second, external cues may replace internal cues as signals for resource access time and, in so doing, may obviate the need to express anticipatory activities. Thus, salt-restricted rats for which salt access time was signalled by a noise tended not to exhibit anticipatory lever pressing (138). Similarly, pigeons restricted to a 2 h daily meal did not express anticipatory food-key pecking if the food key was lit only during the access time (3). When the key was then lit continuously, anticipatory pecking was immediately expressed, suggesting that learning or entrainment processes were already engaged despite the absence of overt anticipatory responses. Food anticipation in rats is evidently less susceptible to such effects, since, with few exceptions, food restriction studies have used automated (sliding doors, rotating bins) or hand-delivered feeding methods that provide obvious auditory and visual cues of food access time. Auditory cues that precede food access by 0.1–4 h may delay the daily rise of FAA, but do not block its expression (179).

The observation that rats can anticipate resources other than food is interpretable in two ways: anticipation may be mediated by separate, resource specific oscillators, or by a single oscillator sensitive to different ingestive events or some stimulus common to all such events. We assume for the sake of parsimony that a single oscillator is involved. Suggestive evidence for this is provided by a study in which rats were maintained on 1 h daily water restriction schedules, in some cases combined with 1 h daily food access (97). Low-amplitude water anticipation was evident in most rats when water was restricted to 1 h in the middle of the light period and food was available throughout the 12 h dark period. However, water anticipation was minimal or absent when food and water were restricted to separate 1 h intervals separated by 7, 10, or 12 h. All of these animals showed FAA, suggesting that food access competes with and dominates water access as a Zeitgeber for common anticipatory oscillators.

We also assume that this common oscillator is entrained by a set of stimuli specific to ingestive events, rather than by nonspecific stimuli such as stress or arousal. Rats subjected to a restraint stress procedure (118) or 2 h forced treadmill running or swimming (95) at a fixed time each day do not show the anticipatory increases in plasma corticosterone or behavioral activity that they exhibit under restricted feeding schedules. Free-running rhythms in hamsters are entrained by a scheduled daily 2–3 h bout of novelty-induced wheel running (113,115), but hamsters typically also do not show activity in anticipation of this event, as they can to a daily mealtime (94,115). Thus, nonspecific arousal does not seem to be a sufficient stimulus for anticipatory activity in the intact rat or hamster.

Nonetheless, after SCN-ablation, some hamsters do show synchronization of activity components to a daily bout of novelty-induced wheel running, and the phase of synchrony is positive, i.e., anticipatory, suggesting that some correlate of

stimulated running may have access to a common anticipatory oscillator outside of the SCN (96). However, it remains to be determined whether anticipatory activity in this paradigm is independent of changes in feeding patterns that might be associated with 3 h of stimulated running without food.

Feeding-related stimuli that could function as Zeitgebers for FAA could be a) preingestive (auditory, visual, olfactory), b) cephalic (gustatory, somatosensory), c) gastric-duodenal (mechanoreceptors, chemoreceptors), and/or d) postabsorptive (chemoreceptors). Critical endocrine or neural signals may be elicited at any of these levels (e.g., cephalic insulin response triggered by sight, smell, taste or ingestion of food).

The contribution of these potential Zeitgeber transduction sites to the generation of FAA can be assessed by procedures that remove, bypass, or activate discrete sensory components of the total response to food acquisition and intake. A modest literature base permits the following tentative conclusions:

1. Preingestive stimuli do not provide cues necessary for FAA; blind (51,160) or anosmic rats (28) exhibit normal FAA to a daily meal (although the combination has not been tested). Whether such cues are sufficient for FAA has not been formally tested.
2. Cephalic stimuli do not appear to provide cues that are sufficient for FAA; rats exhibit FAA to a 10 g supplemental meal of palatable mash, but not to a 5 g meal or a 10 g nonnutritive substitute matched approximately for sweetness, taste, and texture (106). Meals (10 g) of protein, fat, or carbohydrates are similarly ineffective stimuli for FAA in nonfood-deprived rats, although they are effective if the rat is calorically restricted (101).
3. Cephalic stimuli may also not be necessary for FAA, because transections of the vagus (necessary for cephalic insulin response to food) or the trigeminal nerve complex (orosensory and gustatory afferents) do not affect FAA [(32, 102,112); Mistlberger and Houpt, unpublished observations].

A stronger test of the role of cephalic stimuli is to bypass these responses altogether by direct intragastric (IG) feeding. One study of cyclic IG feeding in squirrel monkeys reported some instances of relative coordination of free-running activity rhythms to feeding time, but no evidence of meal anticipation (5). This could be due to the feeding procedure, which involved a 12 h IG infusion by remote pump. A better test, in view of findings reviewed above, would be to shorten the mealtime and make IG feeding contingent on an instrumental response.

Cyclic IG feeding has yet to be employed in a study of rat FAA. However, there are three published reports of cyclic intravenous (IV) feeding. In one study, a 12 h daily meal delivered IV was sufficient to synchronize daily rhythms of several pancreatic digestive hormones (e.g., sucrase) that are released in anticipation of feeding time in oral fed rats (173). A second study utilized an 8 h IV delivered meal and reported no anticipatory rhythm of sucrase (175). However, the raw data from these two studies look similar, and the different conclusions may reflect differences in the numbers of animals or time points sampled. A third study found that 8 h IV-delivered meals abolished the daily plasma corticosterone rhythm, which exhibits a strong food-anticipatory rhythm in oral fed rats (145).

Unfortunately, none of these IV feeding studies recorded behavioral variables. Due to the small size and high metabolic rate of rats, a minimum 8 h of IV feeding is required to deliver an adequate daily nutrient supply. Feeding schedules employ-

ing such long meal durations may not affect all circadian variables equally. For example, although 6 h daily mealtimes induce behavioral anticipation, they may not synchronize anticipatory corticosterone rhythms [(57); but see (145,173, 175)]. These different responses of behavioral and physiological variables may reflect two functionally separate adaptations that the rat must make to restricted feeding schedules. First, there are those adaptations related fundamentally to the acquisition of food; the rat must anticipate when food will be available and be prepared to interact with its environment at that time to ensure food acquisition. Second, there are those adaptations related to the regulation of body weight. If food is available for a short time or in a small amount, the rat must accelerate ingestion and/or enhance the efficiency of nutrient digestion and utilization. If food is available for a more extended duration, these metabolic adjustments may be attenuated or absent. Thus, it is perhaps not surprising if behavioral and digestive/metabolic variables are differentially affected by the temporal parameters of food availability schedules. The data available on enzyme and hormone rhythms in IV fed rats, thus, do not permit any substantive conclusions on the importance of cephalic and intragastric stimuli for food anticipatory behaviors.

VI.c. Ablation Studies

Afferent pathways that supply timing information necessary or sufficient for FAA remain to be identified, and thus provide no explicit clues to candidate substrates of a FEO. Nonetheless, if it is assumed that the oscillator mediating FAA receives information concerning the timing of food intake, then a set of candidate structures can be obtained from the literature on neural mechanisms of ingestive behavior. Another set of candidate structures can be obtained if one also assumes that a FEO is anatomically coupled with the SCN LEO. Ablation studies to assess the role of these candidate structures carry a third implicit assumption, which is that the FEO is contained within a single structure, analogous to the LEO in the SCN.

Neural and endocrine substrates implicated in various aspects of ingestive behavior and metabolism are widely distributed, and only a subset of these areas have been examined for a role in FAA. The first structure to be examined was the adrenal gland, since adrenal corticosterone secretion exhibits prominent food anticipatory release and shows a persisting circadian rhythm of responsivity to ACTH *in vitro* [i.e., the adrenal may be an oscillator; (37,181), but see (189)]. However, adrenal excision has no effect on FAA, despite eliminating plasma corticosterone rhythms (23).

Four studies have examined effects of ventromedial hypothalamic lesions on FAA; three reported loss of food anticipatory behavioral or corticosterone rhythms (67,85,146). However, the fourth study found that behavioral anticipation, although attenuated during the first few weeks after surgery, recovers during subsequent weeks (104). Recovery of anticipatory corticosterone rhythms has since also been reported (62). The nature and significance of the early attenuation of FAA is unclear. A preliminary report indicates that hypophysectomy can also transiently attenuate FAA, and incidental damage in that region could mediate VMH effects on FAA (171).

Two other hypothalamic areas involved in the regulation of ingestive behavior include the paraventricular (PVN) and lateral hypothalamus (LH). Radiofrequency ablations of the PVN in some rats eliminated food anticipatory nonspecific cage activity, but not anticipatory food-bin activity (107).

Neural ablations, thus, may alter the tendency to express certain behaviors without affecting the anticipatory timing mechanism. Neurotoxic lesions of the LH attenuate total daily activity, but do not prevent FAA (107). Other hypothalamic structures destroyed in one or more rats that exhibit normal FAA in these and other studies include the medial preoptic region (median preoptic n., medial preoptic n., medial preoptic area), anterior hypothalamic nuclei, periventricular n., subparaventricular zone, retrochiasmatic area, dorsomedial n., perifornical n., dorsomedial n. (possible subtotal lesions), arcuate, and medial mammillary n. (102,103,107).

Structures outside the hypothalamus that have been examined for a role in FAA include the hippocampal formation (including dentate gyrus, fimbria/fornix, subiculum), amygdala, and n. accumbens. These limbic areas are linked directly and indirectly with the SCN and its primary efferent field, the subparaventricular zone, and have been suggested as possible

sites of an oscillator for anticipatory activity (6,184–186). In addition, the hippocampus exhibits daily rhythms of monoamine transmitters that are phase controlled by feeding time (84,86), and the accumbens exhibits daily rhythms of dopamine release in association with FAA (Blaha and Philips, unpublished observations). However, aspiration and radiofrequency lesions of these structures have no effect on the generation of FAA or its persistence during food deprivation (103; Fig. 7).

Other structures eliminated, usually in combination, in at least some of these animals included the anterior olfactory n., the orbital, infralimbic and dorsal peduncular cortices, the cingulate gyrus, the medial and lateral septum, the vertical limb of the diagonal band, the septohippocampal n., the ventral pallidum, and the bed nucleus of the stria terminalis. Structures that sustained extensive but subtotal damage in those studies include the anterior and ventral caudate, the

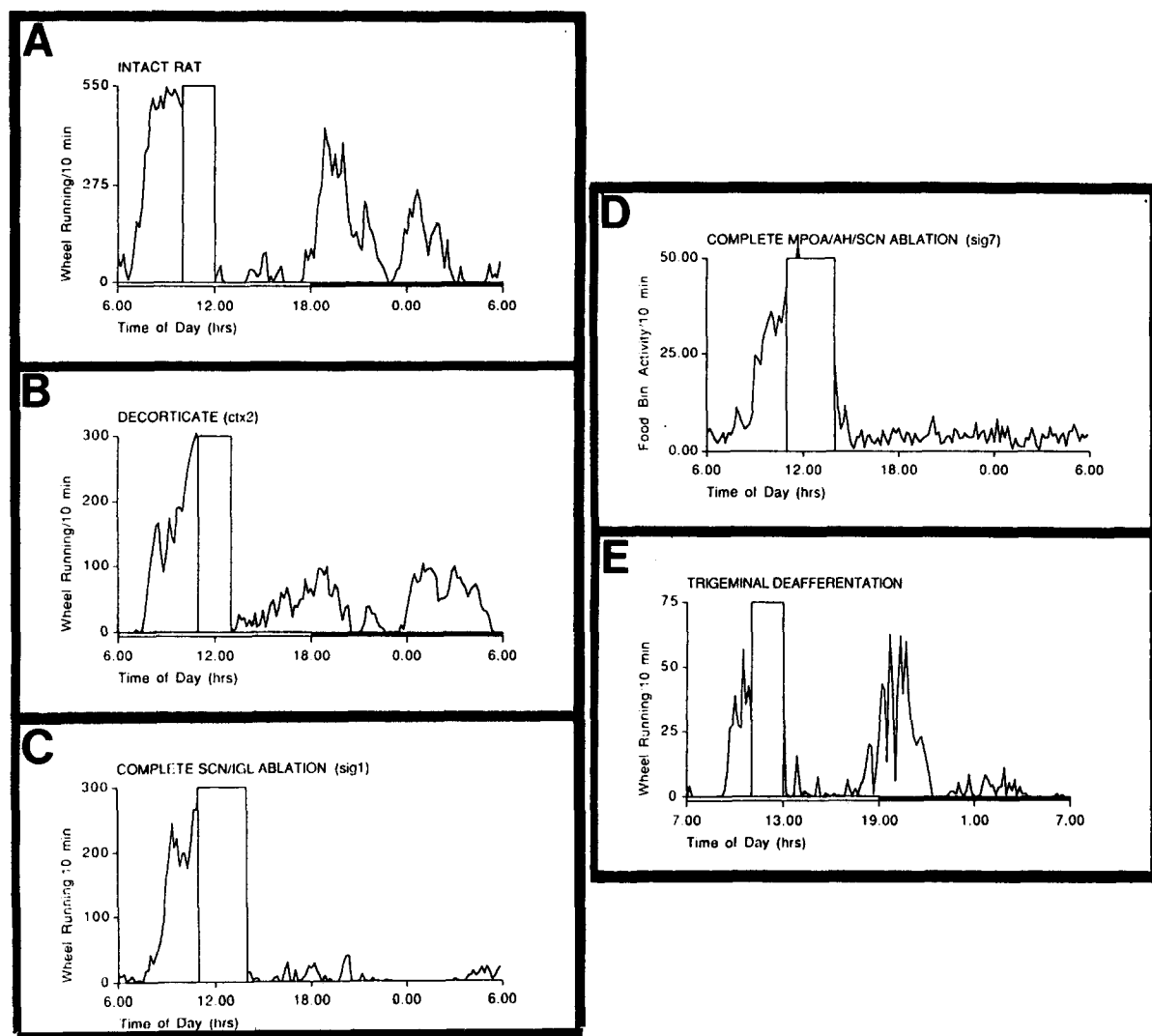


FIG. 7. Average waveforms of wheel running (A,B,C,E) or food-bin (D) activity of rats during food restriction schedules. The hollow vertical bars indicate feeding time. (A) Typical intact rat. (B) Rat in which neocortex was removed by aspiration. (C) Rat bearing combined ablations of the suprachiasmatic nuclei (SCN) and intergeniculate leaflet. (D) Rat bearing complete ablations of the medial preoptic, anterior hypothalamus, and SCN. (E) Rat bearing complete trigeminal nerve deafferentation. All rats were recorded under LD (dark indicated by heavy bar along abscissa), except SCN-ablated rats, which were recorded in LLdim. Unpublished data, Mistlberger, Kippen, Mumby, and Whishaw, 1992.

internal capsule, the lateral preoptic area, the substantia innominata, the anterior claustrum, the anterior third of the thalamic paratenial and paraventricular n., the n. reunions, rhomboid n., and zona incerta. Other studies have shown that combined ablations of the thalamic intergeniculate leaflet (IGL) and SCN (Fig. 7C) or complete aspiration of the neocortex (Fig. 7B) also do not affect FAA (102).

These studies have, thus, established normal expression of FAA despite removal of hypothalamic, basal forebrain, limbic, and cortical structures thought to participate in ingestive processes, or various aspects of learning, memory, and reward. Many of these structures are located within one or two synapses of the SCN. The failure of lesions in these areas to affect FAA may indicate that substrates of FAA are located in caudal diencephalic and brain stem structures that have yet to be evaluated using the ablation method. It remains possible that food-entrainable oscillators are comprised of a population of cells that are distributed across several hypothalamic or extra hypothalamic sites; if there is functional redundancy within this population, then ablations of individual structures may fail to reveal resident components.

VI.d. Neural and Metabolic Activity

Single (149) and multiple unit activity (MUA; 66,68) and 2-deoxyglucose uptake (Mistlberger, unpublished observations; Coleman, personal communication, April, 1992) within the SCN exhibit light-entrainable circadian rhythms that are impervious to restricted daily feeding cycles. In all three of these measures, neural activity is highest during the rest phase of the rat's daily rest-activity cycle. The lack of response of SCN neurons to feeding events, and the dissociation between SCN and behavioral activity during FAA to daytime meals, are consonant with behavioral and lesion evidence that the SCN does not participate in FAA, at least in the rat.

MUA recordings of the LH and VMH in food-restricted rats have revealed daily rhythms of neural activity in phase with feeding time (68,88). The MUA rhythms detected in the LH were sustained for several cycles during food deprivation, whereas those in the VMH were not. However, conclusions that the LH contains a rapidly damping FEO are premature because the rhythm could reflect responses to sensory or motor events or to oscillator signals generated elsewhere in the central or peripheral nervous systems. In any case, ablation studies do not support a necessary role for the LH in FAA (107).

Two studies have demonstrated that smooth muscle activity of rat (31) and hamster (25) duodenum recorded *in vitro* exhibits persisting circadian rhythms that, in rats, are coordinated with daily feeding time. This suggests a hypothesis that FAA is regulated by enteric oscillators. Experimental tests of this hypothesis are few. Jejunal resection has been reported to attenuate but does not eliminate food-anticipatory corticosterone release, suggesting that duodenal activity does not drive that particular food-entrainable hormonal rhythm (76). Behavioral variables were not recorded. Vagal transection eliminates parasympathetic links between the gut and the brain but has no effect on FAA (32,112). Thus, if an enteric oscillator is responsible for behavioral anticipation it must interface with brain effector systems for activity via sympathetic or endocrine routes.

VI.e. Pharmacological Studies

Transmitter systems involved in FAA may be identified by treating rats with specific pharmacological agonists and antagonists prior to daily feeding. This paradigm has been

used to assess the role of dopamine (DA) in FAA (103). Mesencephalic dopamine releasing systems may constitute part of the neural system mediating reward processes, and it may be reasonable to assume that all stimuli capable of generating anticipatory activity, such as food, water, and salt, have strong reward properties. However, pretreating food-restricted rats with haloperidol, a DA receptor antagonist, at moderate to high doses attenuated total daily activity but did not prevent FAA (103). Combined with observations that complete removal of the accumbens nucleus, a major terminal field for midbrain DA neurons, also does not affect FAA, this suggests that DA may have no necessary role in the entrainment or rhythm generating processes underlying FAA (103).

Preliminary reports indicate that daily pretreatment with the opiate antagonist naloxone also does not affect the generation of FAA (Coleman, personal communication, 1992). Another study reported that chronic treatment with naloxone delivered via minipump accentuated food-anticipatory wheel running, but not exploratory activity, in food restricted rats (152). The significance of this result is unclear. Vasopressin pretreatment has also been reported to accentuate the generation and persistence of food anticipatory corticosterone rhythms, but its effects on behavior are unknown (72).

Rats restricted to two meals each day show insulin release conditioned to the sounds of the feeder doors opening; this conditioned response may be related to food entrainment processes, because it did not occur when meals were provided at six fixed times each day (174), a condition under which FAA may not occur. Nicotinic and muscurinic antagonists blocked this conditioned insulin release, indicating that this limb of the food entrainment system may be mediated by cholinergic vagal efferents.

Chronic treatment of SCN-ablated rats with methamphetamine (MA) can induce an immediate restoration of a free-running circadian activity rhythm (58,61). This rhythm can be entrained by restricted feeding but not LD schedules, suggesting that it may represent the output of the FEO responsible for FAA (63). However, the phase angle at which the MA-induced rhythm entrains to feeding time is negative, i.e., activity does not anticipate the daily feeding event under a 24 h schedule (63). Daily rhythms of FAA never assume a negative phase angle in nontreated rats; thus, rhythms associated with MA and FAA may not share a common oscillator substrate. Nonetheless, the absence of FAA under standard food restriction schedules in these studies suggests that MA could alter the period or phase-response characteristics of a common FEO that is revealed by MA treatment. Attempts to replicate and further examine these effects in rat strains available in North America has met with limited success, possibly due to procedural or genetic differences (Rusak, personal communication; Mistlberger, unpublished observations). An hourglass interpretation of MA-induced rhythms has also been presented (140).

VI.f. Gene Expression

Fos, the protein product of the proto-oncogene *c-fos*, is induced in the SCN and IGL of hamsters and rats by light pulses presented at circadian phases that result in phase-shifts of free-running rhythms (7). Novelty-induced wheel running, another stimulus capable of phase-shifting free-running rhythms, induces Fos in the IGL but not the SCN of hamsters (73). This suggests that the IGL may be a transduction site or oscillator for nonphotic Zeitgebers. However, although IGL lesions apparently block phase-shift responses to novelty-induced running (190), they do not prevent FAA in rats or

hamsters (Mistlberger, unpublished observations; Fig. 7C). Brain sites that express Fos or other immediate-early gene products in response to food intake following food deprivation may provide candidate targets for further ablation studies [cf. (65)].

VII. THE RELATION OF RESTRICTED FEEDING TO OTHER NONPHOTIC ZEITGEBERS

The recent discovery that novelty-induced wheel activity can phase shift or entrain free-running rhythms in hamsters has greatly stimulated interest in nonphotic Zeitgebers for circadian rhythms (113,143,180). Unfortunately, there has been a tendency to use the term nonphotic generically, which may foster an impression that all such Zeitgebers operate via a common mechanism. Given present knowledge, such an impression would be premature. There is little convincing evidence in intact hamsters, rats, or mice that daily schedules of novelty-induced, forced, or spontaneous activity can entrain a circadian rhythm component independent of the primary, light-entrainable, free-running circadian rhythm. One recent study provided evidence suggesting that a daily bout of novelty-induced running can split activity rhythms of hamsters under LD, but these findings fall short of demonstrating that one of the activity components can be entrained to the novelty-induced running time while the other activity component free runs (114). Restricted feeding schedules, by contrast, can dissociate an anticipatory activity component from the primary light-entrained or free-running rhythm in hamsters, rats, and mice, suggesting that feeding-related Zeitgebers may entrain an oscillator outside of the SCN, whereas activity-related Zeitgebers may entrain the SCN LEO proper. However, as noted above, SCN-ablated hamsters can exhibit circadian rhythms entrained to daily schedules of novelty-induced activity and to daily feeding schedules, with a similar anticipatory

phase angle (96). Thus, the SCN LEO, at least in hamsters, is apparently not necessary for entrainment to either type of nonphotic Zeitgeber. Gene expression studies suggest that the physiological systems mediating the effects of these two nonphotic Zeitgebers overlap, at most, only partially; as noted above, the IGL exhibits Fos expression to novelty-induced activity (73), but not to postdeprivation feeding [(65); Houpt, personal communication, April, 1993], and IGL lesions block phase shifts produced by novelty-induced activity in hamsters (190), but do not block FAA in rats or hamsters (Fig. 7C). More work will be necessary to establish whether different Zeitgebers share common mechanisms at any level; we speculate that different nonphotic Zeitgebers are carried by separate entrainment pathways that may affect one or more oscillators that are neither SCN nor IGL based. Additional direct effects of either Zeitgeber on the SCN LEO cannot be ruled out.

VIII. CONCLUSIONS

Daily schedules of food availability have long been known to have a profound influence on the circadian timing of behavior and other physiological rhythms. However, many questions still remain concerning the formal analysis and physiological mechanisms of this influence. An assumption that has been implicit in this review is that FAA, as manifest in cage behaviors such as wheel running, lever pressing, and activity directed at feeding locations, represents a laboratory analogue of natural foraging behaviors. Although this assumption may be valid (154), there are remarkably few field studies available by which to better place the properties of FAA in their presumed ecological context [cf. (36,133)].

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