Search for the feeding-entrainable circadian oscillator: a complex proposition

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Working in the laboratory of John B. Watson in the early 1920s, Curt P. Richter first observed the phenomenon of rats engaged in what would later be called food-anticipatory activity: “It is seen that immediately following the daily feeding period there is a period of relative inactivity lasting from four to five hours. . . . During the last two to three hours of the twenty-four the activity increases very rapidly up to the time of the next feeding period” (24).

More recently it has become clear that food-anticipatory activity (FAA) exhibits the defining characteristics of a circadian rhythm. Circadian rhythms are oscillations of physiological or behavioral functions that are timed by biological clocks, the best studied of which is found in the hypothalamic suprachiasmatic nucleus (SCN). Although these clocks can operate in the absence of external input, to be useful in the anticipation of expected environmental changes, they must be synchronized by the environment in response to cues called zeitgebers (German for time-giver). Light is the strongest zeitgeber for the SCN. Working through specialized retinal photoreceptors (10), light causes an adjustment to the phase of the clock in the SCN each day to maintain a precise 24-h period. However, the effect of this light exposure each day is limited; the SCN takes several transient cycles to fully resynchronize to abrupt large changes in environmental time, a process we experience as jet lag. FAA also displays transients for several cycles following an abrupt change in feeding time (29). Furthermore, FAA persists during several days of total food deprivation (1, 25), the equivalent to constant darkness for rhythms synchronized by light exposure.

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While the SCN is established as the main light-entrainable circadian oscillator in the mammal, it is not the source of the timing signal that triggers FAA (31) [for a detailed discussion see Landry et al. (14), in this issue of American Journal of Physiology - Regulatory, Integrative and Comparative Physiology]. Determining the anatomic location of the food-entrainable oscillator (FEO) (25, 30) has been surprisingly difficult. The attempts to do so are well reviewed in Refs. 19 and 28 and again in the comprehensive introduction to the Landry et al. report (14). The most valid conclusion we can draw from this literature is that we know more about where the FEO is not, rather than where it is.

In a recent article, Gooley and Saper study (11) also reports on some experiments in which they fail to reproduce the abolition of FAA following lesions of the brain stem parabasal nuclei (PBN). This finding stands in stark contrast to those reported by me and my colleagues a few years earlier (4) in which FAA was abolished after PBN lesions. This latter study indexed FAA with two different measures of feeder-approach behavior.

The disparate findings on PBN lesions (see Refs. 11 vs. 4) and on DMH lesions (see Refs. 11 vs. 14) do not stand alone as examples of inconsistent findings in this area. An earlier report by Mistleberger and Mumby (20) showed that large limbic system lesions, including the accumbens core and shell, failed to affect FAA in rats using feeder approaches as the behavioral measure. However, Mendola et al. (18) reported that more specific excitotoxic lesions of the core region of nucleus accumbens reduced the intensity of FAA. The Mendola study used infrared beam breaks as their measure of activity. Furthermore, while lesions of the hypothalamic paraventricular region abolished anticipation measured by tilt-cage activity, food-bin approach measures revealed that the rats were still predicting mealtime (21).

A common feature among these pairs of seemingly inconsistent results is the difference in the specific behavioral measurements being made. Although parabasal lesions abolish food-directed behavioral anticipation (4), they do not abolish the increase in general cage activity before mealtime. While PVN lesions abolish tilt-cage anticipation, they do not block more meal-directed activity (21). Likewise, while FAA is eliminated by DMH lesions when measured by general cage activity and even wakefulness (11), the findings published in this issue show that rats still exhibit anticipation when measured using food-bin-directed behavior and in the presence of a sleeping tube that may increase the selectivity of the behavior being measured (14).

In summary, all of these lesion studies reveal structures that are involved in FAA output but that cannot fully account for the oscillation. One of the elegant aspects of a lesion study is that if it is performed well, a negative result provides a wealth of information. If the rat can still demonstrate the capability, in this case predict mealtime, that structure is not uniquely necessary for that function. The site of the FEO remains elusive!
FEO: Behavioral vs. Physiological Rhythmicity

Despite the failure of lesion studies to unambiguously identify a central site necessary for the generation of FAA, demonstrated, once again, by Landry et al. (14), recent studies suggest that the focus of this search should remain in the central nervous system. Although digestive structures do have independent circadian clocks and these clocks are sensitive to the timing of food access (2, 3, 5, 27, 32), a clear distinction needs to be drawn between these peripheral clocks and the black box we refer to as the FEO. Several lines of evidence suggest functional independence of these systems from one another.

First, while metabolism is clearly altered in restricted-fed rats such that most rhythmic functions reset to mealtime (3, 6–8), entrainment of metabolism is not necessary for FAA. Several studies suggest that FAA can be induced using a highly palatable meal on a background of ad libitum food access (17, 22, 33), eliminating the metabolic rhythms and the catabolic state commonly associated with timed and limited access to food.

Second, while the clock mutant mouse has altered circadian behavioral rhythms in constant conditions (34), behavioral anticipation of mealtime persists (23). However, the livers of Clock/Clock mice exhibit a rapidly damped oscillation in clock gene rhythms once the feeding schedule is terminated (13). Furthermore, whereas Per1 rhythms in digestive tissues, such as liver, stomach, and colon, entrain to daytime feeding in a fashion similar to FAA, these rhythms quickly return to a nighttime peak phase once the rats are released to ad libitum meals (5). In contrast, when the rat is food deprived after 1 wk of this ad libitum access to food, FAA reemerges at the correct daytime phase, while molecular rhythms in all of the digestive tissues remain nocturnal. These findings suggest that molecular rhythms in digestive tissues exhibit different characteristics from the rhythm in behavior.

Because there are clearly a multitude of circadian clocks sensitive to feeding time and these systems may operate independently and serve different physiological functions, I propose that for clarity the term FEO be reserved for the clock system responsible for the generation of FAA, a use of the term consistent with its meaning when it was conceived (25, 30).

Is the FEO a Single Structure?

The failure of lesion studies to identify a single necessary site for FAA suggests that the timing system underlying it may be distributed rather than localized to one site in the brain. Despite the critical differences described above between rhythms in peripheral structures and FAA, the common feature of sensitivity to feeding time among the many oscillating structures in the body is supportive of a distributed or even ubiquitous nature of the FEO; perhaps every neuron in the nervous system or indeed every cell in the organism contributes to this timing function. Certainly, the availability of a circulating energy source is a widely available zeitgeber.

This notion is inconsistent with localization of function, a characteristic of the mammalian nervous system beautifully illustrated by the suprachiasmatic nuclei, a very small structure in the brain with profound functional importance. However, the examples mentioned above of brain lesions where certain behavioral outputs of the FEO can be abolished while others are spared helps to resurrect the idea of localization of function: even if the clock is a distributed or ubiquitous system, its control over physiological and behavioral functions appears to be organized in a highly specific manner.

The Importance of Understanding Entrainment of Circadian Rhythmicity by Food Access

The importance of a thorough understanding of the effects of feeding schedules on circadian rhythmicity cannot be overstated. The ubiquity of the phenomenon underscores its importance in biology. Anticipation of mealtime has been observed in a wide range of species, suggesting a long phylogenetic history. For a thorough review of these studies refer to an excellent chapter by Stephan (28). In addition to those studies covered by Stephan, a recent report describes robust FAA in a species of nocturnal fish (12).

Food restriction dramatically increases life span in many species including laboratory rodents, dogs, and primates (15, 16). The connections between the effects of food restriction on biological timekeeping and on longevity are understudied and may be of great importance. The connection between food restriction and health is reinforced by the recent demonstration that food restriction schedules attenuate tumor development in mice (9, 35). Although this effect may be partially due to caloric restriction, the timing of food intake was clearly important in those studies. Since food intake patterns have been shown to regulate rhythms of cell division (26), it seems that restricted feeding may well prove to be a valuable tool for the control of cancer.

REFERENCES


