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Food anticipation depends on oscillators and memories in both body and brain

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ABSTRACT

Despite the importance of learning and circadian rhythms to feeding, there has been relatively little effort to integrate these separate lines of research. In this review, we focus on how light and food entrainable oscillators contribute to the anticipation of food. In particular, we examine the evidence for temporal conditioning of food entrainable oscillators throughout the body. The evidence suggests a shift away from previous notions of a single locus or neural network of food entrainable oscillators to a distributed system involving dynamic feedback among cells of the body and brain. Several recent advances, including documentation of peroxiredoxin metabolic circadian oscillation and anticipatory behavior in the absence of a central nervous system, support the possibility of conditioned signals from the periphery in determining anticipatory behavior. Individuals learn to detect changes in internal and external signals that occur as a consequence of the brain and body preparing for an impending meal. Cues temporally near and far from actual energy content can then be used to optimize responses to temporally predictable and unpredictable cues in the environment.

1. Introduction

The temporal dynamics of foraging, eating, digestion, and metabolism are central to the understanding of energetics. Their study has been approached via research on feeding behavior and metabolism, learning, and circadian timing, although there has been relatively little integration of these areas of interest. In the context of each field, this is understandable. These disciplines have distinct historical roots, different compelling questions, and each is intuitively salient and interesting in its own right. Another reason for the lack of intersection is discrepancy between units of analysis. At the behavioral level, feeding and learning studies focus on the meal, the regulation of meal size, and motivation to obtain a meal. Work on feeding behavior itself is concerned with delineating the cues that signal meal location and time and their relative salience. Studies of the circadian timing system are focused on understanding recurrent physiology and behavior and use eating behavior or the anticipation of eating as a window into oscillator mechanisms. If, however, one considers the body as a dynamically changing system, where change in one aspect produces change in another, the interactions between feeding, circadian oscillators, and learning become significant. In that integrative spirit, we focus on findings in the literature on circadian timing that indicate new mechanisms of interaction among feeding, conditioning, and learning and memory.

The discovery of new mechanisms is always the impetus for a paradigm shift in basic research. In the realm of the circadian timing system, several identifiable shifts have emerged following a rapid series of key discoveries. These enabled exploration of the mechanisms associated with temporal organization in the performance of bodily functions. Specifically, converging studies performed in many laboratories indicated that a master circadian clock was localized to the suprachiasmatic nucleus (SCN) of the hypothalamus [1], the genes and proteins that constitute a core cell-based circadian clock were delineated [2], and circadian oscillators were shown to occur throughout the body, rather than being restricted to the SCN master clock [3]. This led to the detection of oscillators in peripheral organs and tissues that are entrained by food-derived cues [4,5], and highlighted a balance among multiple synchronizing signals in the environment. The discovery of peripheral oscillators also led to the identification of large cohorts of tissue-specific genes whose transcription varies with circadian time. Most recently, it has been discovered that the oscillatory mechanisms underlying circadian rhythms do not require transcriptional mechanisms. This finding is important in the present context because for many years, the great majority of studies of circadian rhythms have been focused on mechanisms associated with cell autonomous circadian oscillation based on cyclical gene and protein expressions requiring transcription

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and translation. This was true even though several important circadian phenomena seemed inexplicable by such mechanisms [6,7]. It is now clear, however, that there exist biochemical pathways, evolutionarily ancient and perhaps highly conserved across taxa, that can drive circadian rhythms in the absence of transcription [8–10]. As a consequence of these discoveries we are now able to explore how these different circadian clocks are linked and the key role played by feeding-associated signals and learning.

The goal of the present paper is to describe areas of overlapping interest in three domains: circadian timing systems, feeding behavior, and learning and motivation. Our perspective is stimulated by evidence that salient cues associated with each of these systems influence circadian oscillators located throughout the body, and that these oscillators, in turn, send signals back to the brain. We do not attempt a thorough literature review, but instead point to review papers and use specific case studies as exemplars of the main points raised.

1.1. Food entrained oscillators (FEOs) and light entrained oscillators (LEOs) in historical perspective

Within the circadian timing system it is well established that in rodents, a discrete population of about 20,000 neurons in the SCN is the locus of a master circadian clock. This clock functions to regulate the phase and period of numerous physiological and behavioral responses, and enables entrainment to daily light–dark (LD) cycles (reviewed in [11]). The evidence for a key role of the SCN derives from years of convergent studies demonstrating that SCN ablation abolishes rhythmicity in most behavioral and physiological measures, that rhythmicity within the SCN is sustained in vitro, and that transplantation of the SCN from one animal to another produces the donor period in the recipient (reviewed in [1]; Fig. 1). Given this solid evidence for a master clock in the brain, it was surprising to find, in the 1970s, that circadian oscillation in food anticipatory behavior (FAA) survives ablation of the SCN [12]. This result led to the possibility, and even the hope that there might be a second nucleus containing a discrete population of oscillators, located within the brain but outside of the SCN, that functioned to sustain circadian rhythms following regularly recurring daily feeding schedules. These putative food entrainable oscillators (FEOs) were thought to be circadian pacemakers independent of light entrainable oscillators (LEOs) of the SCN. Several aspects of food anticipation suggested control by a circadian mechanism.

1.2. Food anticipatory activity — the phenomenon that stimulated the search for FEOs

The weight of evidence supports the view that the body uses an endogenous circadian timing system under the control of food-entrainable oscillators to predict the availability of food. These FEOs activate food-seeking behaviors and facilitate the synthesis and secretion of hormones necessary for digestion before mealtime. In the typical experimental paradigm, food is made available for a few hours daily, sufficient to ensure that the animals have no reduction in total caloric intake or body weight (reviewed in [13,14]). The increased activity seen in anticipation of a meal serves as a convenient measure of anticipatory behavior and generally supports a role for circadian timing mechanisms. When animals are entrained to a light:dark cycle and restricted to a single meal at a fixed time each day they exhibit increased locomotor activity beginning 1–3 h prior to mealtime. This behavior is established in about a week following repeated exposure to the regularly scheduled restricted feeding times. Importantly, the timed, daily expression of food anticipatory activity (FAA) continues even when meals are omitted for several days, indicating a memory for the time of day. Several aspects of the response suggest that it involves a circadian but non-SCN based oscillatory mechanism (reviewed in [14]). First, when SCN-lesioned rats are shifted from a food restriction schedule to total food deprivation, the expression of FAA continues for several days and free-runs with a circadian period. Second, FAA rhythms are most readily observed in feeding schedules with periodicity in the circadian range, indicating limits of entrainment [15].

Such evidence, among other suggestive studies, led to extensive searches for an FEO outside the SCN with the hope of finding a nucleus entrained by food that was parallel to the light entrained SCN. Note that despite limits of entrainment for a single food presentation, rats with SCN lesions can anticipate 2 meals per day [16,17]. This raises the

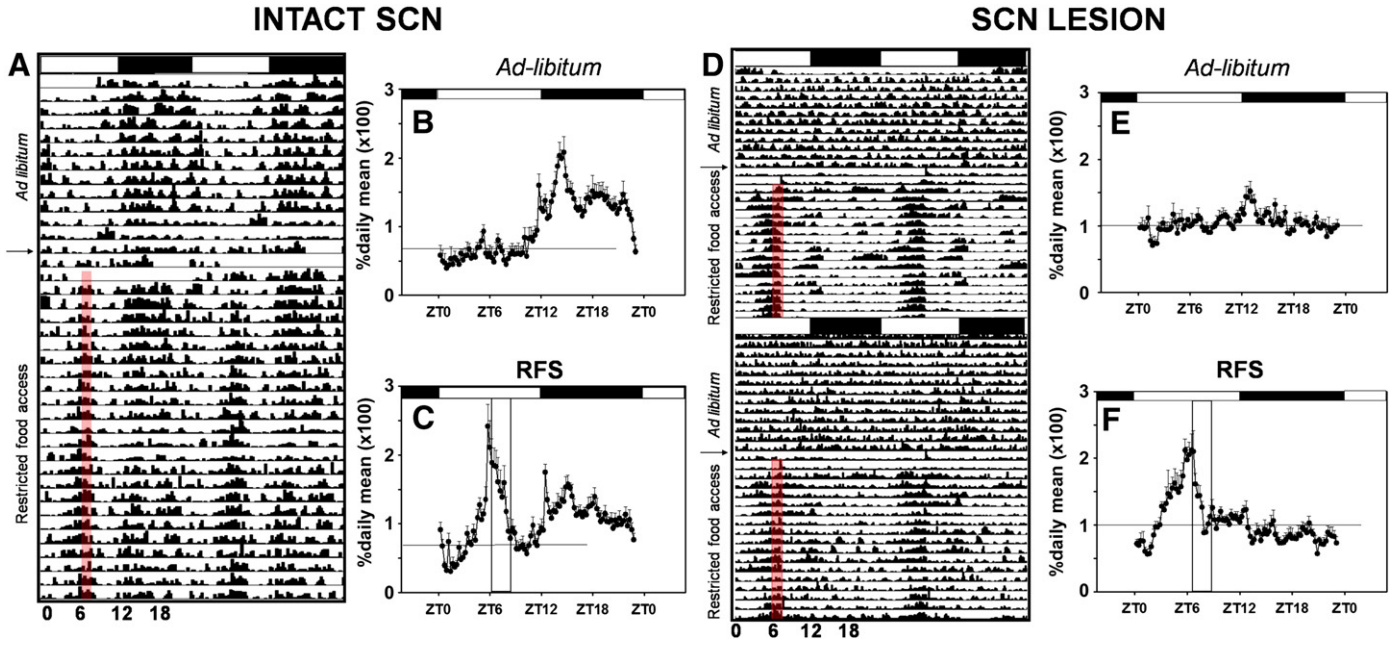

Fig. 1. Comparison of general activity of intact (A, B, C) and SCN-lesioned rats under ad lib (B, E) and food restricted (C, F) conditions. Vertical shaded regions indicate time of food availability. General activity of representative animals is shown in the double-plotted actograms. Mean activity profiles in ad libitum feeding and during 3 weeks food restriction are displayed (horizontal lines indicate mean activity level during the light phase). Note that FAA is maintained following ablation of the SCN.
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