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Ketone bodies signal opportunistic food-seeking activity

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Abstract

Food seeking activity at a predictable time of the day is one of the fundamental “opportunistic behaviors” for survival. Neural and molecular basis for such anticipatory activity is not clearly understood. A new report shows liver-derived ketone bodies after several hours of fasting play a key role in this behavior.

Circadian rhythms impart survival advantage by coordinating daily activity-rest cycle with the time of food availability. Such rhythms are generated by a cell autonomous oscillator consisting of CLOCK, BMAL, PER, and CRY proteins [1]. Although the circadian oscillator is present in nearly all cells, ~20,000 neurons of the hypothalamic suprachiasmatic nucleus (SCN) function as master oscillator by driving the daily rhythm in activity and rest under normal condition. Surgical ablation of the SCN abolishes circadian rhythms in activity-rest and feeding-fasting. The SCN oscillator is entrained to the ambient light:dark cycle through light input received from the retina, while the circadian oscillator in the liver is entrained to daily feeding-fasting rhythm through both feeding and fasting signal. Such organization of the circadian system supports daily rhythms in activity-rest in sync with the time of the day or night when food is most probable.

However, if food becomes available exclusively at a different time of the day – e.g. in the morning for nocturnal rodents – the animal must override the circadian drive for nighttime activity to take advantage of the daytime feeding opportunity, yet may sustain the circadian drive to be active at nighttime to prevent being predated during rest of the day. Such transient rise in Food-anticipatory activity (FA) is known for almost a century [2]. To unravel FA, nocturnal rodents are presented with food for only a few hours during late morning when they are usually asleep. Within a couple of days of this restricted feeding (RF) protocol, animals wake up and become active in anticipation of food. Such periodic 24 h rhythm in the timing of FA is maintained even when food is no longer presented in late morning, thus suggesting an intrinsic oscillator that sustains FA.

Surprisingly, FA can be elicited and sustained in SCN-lesioned animals, which lack daily rhythm in activity or feeding. However, when these animals are presented with RF, FA

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emerges after a few days and persists even after food becomes available ad libitum. This led to the hypothesis that a distinct food entrainable oscillator (FEO) may be present outside the SCN [3]. The nature of the FEO has been the subject of numerous investigations. The function of clock genes themselves in FA is not fully elucidated as there are discrepancies in the FA phenotype of different clock mutant mice. *Bmal1*, *Clock*, *Per1* mutant mice show FA whereas FA is absent in *Per2^{Brdm1}* mutant [4]. The role of *Per2* in FA is not clearly understood.

In a recent study, Chavan et al. [5] used tissue specific manipulation of *Per2* expression to examine its role in FA. They generated mice lacking *Per2* in the entire body (*TPer2^{-/-}*), in liver (*LPer2^{-/-}*) or in neurons (*NPer2^{-/-}*), and subjected them to a RF protocol. The mice received 70% of the daily *ad lib* food intake starting at 4 h after lights on (ZT4). As expected, the *TPer2^{-/-}* mice showed no FA. Surprisingly, *LPer2^{-/-}* also lacked FA while the *NPer2^{-/-}* showed normal FA, thus uncovering a role of liver in FA. The absence of FA in *LPer2^{-/-}*, but not in *TPer2^{-/-}* mice was rescued by adenovirus-mediated *Per2* expression in the liver, thus suggesting liver *Per2* expression is necessary but not sufficient (Fig. 1).

The liver transcriptome was examined for signal(s) that transmit food availability information from the periphery to the brain, to “entrain” the FEO to time of food availability. RF protocol caused large transcriptional changes in liver including changes in fatty acids metabolism pathways. In particular *Cpt1a* and *Hmgcs2* induction at ZT4 in the FA protocol is lost in *LPer2^{-/-}* mice. Concomitant activation of *Cpt1a* and *Hmgcs2* can lead to increased ketone bodies synthesis. Accordingly, FA protocol is accompanied by a peak of acetyl-CoA and the ketone body β -hydroxybutyrate (β -OHB) at ZT4 in FA proficient WT or *NPer2^{-/-}* mice that is absent in *LPer2^{-/-}* mice lacking FA. Using a programmable mini-pump, a spike of β -OHB at ZT4 was introduced into *LPer2^{-/-}* mice, comparable in magnitude to β -OHB level observed in WT animals. This led to reasonable rescue of FA.

The role of β -OHB as a signaling molecule fits its known function. Following feeding, the stored glycogen in liver and muscle is gradually depleted during fasting. After a few hours, liver fatty acid oxidation serves as dominant energy source. Fatty acid oxidation in liver produces β -OHB that is secreted into the circulation to supply energy for the brain. β -OHB also signals through a G-protein coupled receptor and can also inhibit histone deacetylase [6]. Such signaling function makes β -OHB a candidate for transmitting the energy status of peripheral organs to the brain.

However, liver derived β -OHB may be insufficient to entrain the FEO. The failure of adenovirally expressed *Per2* to restore FAA in *TPer2^{-/-}* mice combined with intact FA in *NPer2^{-/-}* mice suggests *Per2* expression in other peripheral organs may be necessary. Collaborative systemic signals could originate from other metabolic organs such as the gastrointestinal tract, the adipose tissues, the pancreas or the adrenals. Gut-derived signal such as ghrelin has been described as a potential signal [7] (Fig. 1).

The loss of FA in *TPer2^{-/-}* mice but not in other clock mutant mice raises the question whether *Per2* has a different role in the regulation of *Cpt1* and *Hmgcs* outside its known function as a circadian transcriptional repressor. Nevertheless, the identification of β -OHB as

a signal for FEO has wider implications. The dorsal striatum that receives dopaminergic input has been implicated in generating rhythmic activity of varying frequency from few hours to multiple days, even in the absence of a circadian clock [8]. Dopamine receptor in the dorsal striatum has been implicated in FAA [9]. This raises the hypothesis that the liver derived β -OHB might act in the dorsal striatum to entrain the FEO to time of food availability. Ketone bodies are neuroprotective [10] and are increased in a time-restricted feeding paradigm [11] that also protects against metabolic diseases through pleiotropic effects in multiple organs. The parallel discoveries of candidate FEO in the dorsal striatum, liver derived b-OHB as a potential peripheral signal for FA and the emerging health benefits of TRF makes daily eating pattern an exciting framework to understand how timely interactions among distant tissues maintain metabolic homeostasis, circadian rhythm, and opportunistic food anticipation.

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Figure 1. Liver-derived and *Per2* driven β -OHB is necessary for food anticipatory behavior
 (a) Summary of genetic experiments showing the necessity of *Per2* in the liver for FA. (b) In addition to β -OHB, other peripheral signal may be involved in transmitting food timing to the brain.