

FOOD REWARD WITHOUT A TIMING COMPONENT DOES NOT ALTER THE TIMING OF ACTIVITY UNDER POSITIVE ENERGY BALANCE

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Abstract—Circadian clocks drive daily rhythms in physiology and behavior which allow organisms to anticipate predictable daily changes in the environment. In most mammals, circadian rhythms result in nocturnal activity patterns although plasticity of the circadian system allows activity patterns to shift to different times of day. Such plasticity is seen when food access is restricted to a few hours during the resting (light) phase resulting in food anticipatory activity (FAA) in the hours preceding food availability. The mechanisms underlying FAA are unknown but data suggest the involvement of the reward system and homeostatic regulation of metabolism. We previously demonstrated the isolated effect of metabolism by inducing diurnality in response to energetic challenges. Here the importance of reward timing in inducing daytime activity is assessed. The daily activity distribution of mice earning palatable chocolate at their preferred time by working in a running wheel was compared with that of mice receiving a timed palatable meal at noon. Mice working for chocolate (WFC) without being energetically challenged increased their total daily activity but this did not result in a shift to diurnality. Providing a chocolate meal at noon each day increased daytime activity, identifying food timing as a factor capable of altering the daily distribution of activity and rest. These results show that timing of food reward and energetic challenges are both independently sufficient to induce diurnality in nocturnal mammals. FAA observed following timed food restriction is likely the result of an additive effect of distinct regulatory pathways activated by energetic challenges and food reward. © 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: activity rhythm, circadian thermo-energetics, food entrainable oscillator, nocturnality, palatable food.

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Abbreviations: CTE, circadian thermo-energetics hypothesis; COG, center of gravity; ExT, external time; FAA, food anticipatory activity; FEO, food entrainable oscillator; LD, light–dark; SCN, suprachiasmatic nucleus; TCF, timed chocolate feeding; WFC, working for chocolate protocol; WFF, working for food protocol.

INTRODUCTION

Circadian clocks drive daily oscillations in physiology and behavior allowing organisms to anticipate daily changes in their environment (Pittendrigh, 1993). The main mammalian circadian oscillator in the suprachiasmatic nucleus (SCN) is synchronized with the outside light–dark (LD) cycle by light input from the eye (Reppert and Weaver, 2002). The SCN uses neuronal and endocrine pathways to orchestrate rhythmicity throughout the brain and peripheral tissues (Dibner et al., 2010), leading to nocturnal activity patterns in most small mammals.

Plasticity in circadian organization allows for adaptation to changes in the temporal organization of the environment (Hut et al., 2012). Such plasticity can be observed when access to food is restricted to a limited time during the light phase (Mistlberger, 1994; Stephan, 2002). Food restriction during the light phase results in food anticipatory activity (FAA) accompanied by phase changes in body temperature, corticosterone (Mistlberger, 1994; Stephan, 2002) and liver rhythms (Stokkan et al., 2001), while the SCN remains phase locked to the LD cycle (Stokkan et al., 2001). FAA persists during periods of complete food deprivation, shows transients when entraining to different mealtimes and are expressed in SCN-ablated animals (Stephan et al., 1979). Together, these experiments show that FAA is driven by a SCN-independent ‘food entrainable oscillator’ (FEO).

Time-restricted feeding protocols used to induce FAA typically reduce daily food intake to 60–80% of *ad libitum* levels to motivate animals to eat during their rest phase. Increasing the severity of food deprivation also increases FAA (Mendoza et al., 2005b; Gallardo et al., 2014), suggesting that negative energy balance *per se* might be able to induce diurnal activity in otherwise nocturnal mammals (Hut et al., 2011, 2012). This idea was made explicit in the circadian thermo-energetics (CTE) hypothesis, which predicted that energetically challenged animals become day active, because diurnality is associated with reduced daily energy expenditure under natural conditions (Hut et al., 2012; van der Vinne et al., 2014). The CTE hypothesis was tested in a protocol where mice were energetically challenged by letting them work for food (WFF; Hut et al., 2011). High ‘workloads’ (i.e. running long distances to obtain a food pellet) indeed induce diurnality in mice (Hut et al., 2011) and this effect is augmented by lower ambient temperatures (van der Vinne et al., 2014). The WFF experiments thus confirm that negative energy balance *per se* induces diurnality and hence negative energy balance can partly explain diurnal activity in FAA protocols.

The argument above does not rule out the timing of food availability as an important factor in inducing FAA. Providing a palatable chocolate meal during the light phase in animals with *ad libitum* access to regular chow can induce FAA in rats (Mistberger and Rusak, 1987; Mendoza et al., 2005a; Verwey et al., 2007; Angeles-Castellanos et al., 2008) and mice (Hsu et al., 2010). The length and intensity of FAA, induced without challenging animals energetically, is reduced in comparison to the FAA observed when all food access is restricted to the light phase (Mendoza et al., 2005a; Verwey et al., 2007; Angeles-Castellanos et al., 2008). Taken together, these data show that the FEO-controlled expression of FAA is induced by effects of food timing combined with negative energy balance. This suggests that both the reward system and homeostatic regulation of metabolism are involved in the expression of the FEO.

To test whether the reward system is also involved in WFF-induced diurnality, we developed the ‘working for chocolate’ (WFC) protocol in which mice with *ad libitum* access to regular chow can obtain a palatable chocolate reward at all times of day by running in a wheel. The daily distribution of activity observed during the WFC protocol was compared to that of mice receiving a chocolate reward in the middle of the light phase to assess the importance of reward timing in re-organizing the daily activity pattern. We expect that in the absence of energetic challenges, daytime activity can be induced by reward timing but not when reward timing is absent in the WFC protocol. Furthermore, the long-term impact of a palatable meal on the daily distribution of activity was assessed by monitoring the daily activity pattern after termination of daytime chocolate feeding.

EXPERIMENTAL PROCEDURES

Animals and activity registration

Male CBA/CaJ mice were moved from our breeding facility (14 h–10 h LD cycle) to the experimental rooms (12 h–12 h LD cycle) at least one week before the start of experiments. Mice were housed individually in standard macrolon cages (15 × 32 × 13 cm) equipped with a running wheel on a sawdust bedding (Lignocel hygienic animal bedding, Rettenmaier, Rosenberg, Germany) on experimental day 0. Standard chow food (AM II diet rodent chow 10 mm, 17.3 kJ/g, Arie Blok, Woerden, The Netherlands) and water were provided *ad libitum* throughout the experiments. Procedures were approved by the Animal Experimentation Committee of the University of Groningen (DEC 5454).

Running wheel activity and activity around the feeding place (only Experiment 2) were recorded in two-minute bins and split in daily intervals starting at lights on (external time (ExT) six). Activity during the light phase was divided by the total daily activity to calculate the percentage of daytime activity. Daily activity onset and offset were calculated as the intersections of a short (10 min) and a long running average (24 h; Hut et al., 1999). Daily center of gravity (COG) was calculated as the time of day where total activity in the preceding and following 8 h was equal. Analyses were performed using

custom build scripts in SciLab 5.5.0, with statistics being performed using mixed-effects general linear models in SAS JMP 7.0. In these statistical analyses, separate analyses were performed for each of the dependent variables (daytime activity, onset, COG and offset) with treatment as independent factor. Animal ID was included as a random factor to our analyses to correct for the repeated measurement of each individual. Tukey HSD post hoc tests were performed when applicable. Data are represented as mean ± SEM in graphs and text.

Experiment 1: WFC

The WFC protocol allowed twelve *ad libitum* fed, five-month-old mice to additionally earn 45-mg chocolate pellets (Dustless Precision Pellets[®], Sucrose, Chocolate Flavor) by running in a wheel. The workload, the number of revolutions needed to obtain a chocolate pellet, started at 500 revs/pellet on day nine and was increased in steps of 20 revs/pellet daily to 700 revs/pellet, where it was kept stable (resulting in 37.3 ± 3.5 chocolate pellets per day). This workload was chosen because it resulted in a chocolate intake that was approximately twice the intake observed when chocolate was provided at a fixed time, ensuring that the lack of a phase shift during WFC was not a result of lowered chocolate intake. The timing of the chocolate reward in the WFC protocol was computer controlled and the mice thus received their food reward each time they reached the workload threshold. Reward timing thus depended solely on the spontaneous activity rhythm of the mice. After the WFC protocol (day 26 until the end), each mouse was provided with 20 pellets daily at the middle of the light phase (ExT 12) to assess the effect of timed chocolate feeding (TCF) on the activity rhythm. Daily checks were performed around one hour before lights off, to confirm that all chocolate pellets had been consumed. The daily distribution of activity was compared for the last 5 days preceding WFC (AL), the last 5 days of WFC (WFC) and the last 5 days of timed chocolate feeding.

Experiment 2: TCF

Eight mice (1.5-month-old) were provided with 20 pellets for two hours, starting at the middle of the light phase (ExT 12). Food was given in a bowl without opening the cage and remaining pellets were removed after two hours to assess the number of pellets eaten. Chocolate pellets were provided on days 9–40. On days 41–60 chocolate was replaced by chow pellets provided between ExT 12 and 14, followed by 20 days of undisturbed *ad libitum* feeding with only regular chow. On experimental days 29–30, the acute effect of termination of daily TCF was assessed by providing mice with chow pellets between ExT 12 and 14. Anticipatory activity around the feeding location was assessed by measuring general locomotor activity using a passive infrared detector placed directly above the feeding place. The effects of TCF were assessed between the last 5 days preceding TCF (pre test), the last 5 days of TCF (Chocolate), the last 5 days of daily provisioning of additional chow pellets (Chow pellets)

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