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Research report

Large, binge-type meals of high fat diet change feeding behaviour and entrain food anticipatory activity in mice ☆

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ABSTRACT

Male C57BL/6 mice fed *ad libitum* on control diet but allowed access to a palatable high fat diet (HFD) for 2 h a day during the mid-dark phase rapidly adapt their feeding behaviour and can consume nearly 80% of their daily caloric intake during this 2 h-scheduled feed. We assessed food intake microstructure and meal pattern, and locomotor activity and rearing as markers of food anticipatory activity (FAA). Schedule fed mice reduced their caloric intake from control diet during the first hours of the dark phase but not during the 3-h period immediately preceding the scheduled feed. Large meal/binge-like eating behaviour during the 2-h scheduled feed was characterised by increases in both meal number and meal size. Rearing was increased during the 2-h period running up to scheduled feeding while locomotor activity started to increase 1 h before, indicating that schedule-fed mice display FAA. Meal number and physical activity changes were sustained when HFD was withheld during the anticipated scheduled feeding period, and mice immediately binged when HFD was represented after a week of this "withdrawal" period. These findings provide important context to our previous studies suggesting that energy balance systems in the hypothalamus are not responsible for driving these large, binge-type meals. Evidence of FAA in HFD dark phase schedule-fed mice implicates anticipatory processes in binge eating that do not involve immediately preceding hypophagia or regulatory homeostatic signalling.

Introduction

Feeding is driven, in large part, by energy homeostasis – the balance between food intake and energy expenditure. Humans and many mammals consume their energy in the form of periodic bouts or meals. However, the initiation of a meal is not necessarily based on a general energy deficit or a specific need such as an inadequate glucose level. The impulse to initiate a meal may rather be based on factors such as time of the day, eating habits, social environment, or convenience (Woods, 2005). The ability to estimate time and anticipate critical events such as meal time is of relevance in nature, since it has clear implications for survival (Strubbe & Woods, 2004). In laboratory animals, restricted meal-feeding schedules may limit food availability to a single daily meal. Once habituated to these feeding conditions, animals have been shown to anticipate their next meal through adaptations such as increases in locomotor activity, body temperature and hormone release that precede the predicted meals (Verwey & Amir, 2009). The behavioural response is known as food anticipatory activity (FAA), and the 2 h to 3 h period preceding a daily scheduled meal is the relevant time frame (Challet, Mendoza, Dardente, & Pévet, 2009; Mistlberger, 1994; Shibata, Hirao, & Tahara, 2010). FAA is not just limited to restricted feeding schedules, i.e. where food is available for only a short time a day. The reward value of food and its motivational properties have also been implicated in food entrainment since FAA can also be induced in animals fed on palatable feeding schedules, where a stock diet is available for the remainder of the day (Mendoza, 2007; Mistlberger & Rusak, 1987).

A palatable scheduled feeding model, described by Berner et al. (Berner, Avena, & Hoebel, 2008), based on dietary manipulations by Corwin et al. (Corwin et al., 1998; Dimitriou, Rice, & Corwin, 2000) and Mistlberger et al. (Mistlberger & Rusak, 1987), induces

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substantial food intake over short periods of time in rats (Berner et al., 2008). Utilising this model, we provided scheduled access to a solid high fat palatable diet (HFD) for a 2-h period each day, without imposed caloric restriction during the remainder of the day, a manipulation that resulted in consumption of large, binge-type meals in both rats and mice (Bake, Duncan, Morgan, & Mercer, 2013). Interestingly, mice exhibited a more exaggerated response to the scheduled palatable diet manipulation, with about 80% of total daily calories consumed during the 2-h access (Bake et al., 2013). The present study further characterises the large meal/binge-like eating model at a behavioural level in mice, focussing on how palatable scheduled feeding influences food intake microstructure and meal patterns. We also measured activity patterns (locomotor activity and rearing) as markers of FAA in mice on scheduled palatable diet. In addition, we extended the model beyond the habituated response to palatable schedule feeding to assess food intake microstructure, meal patterns and activity patterns when the palatable scheduled feeding on HFD was withdrawn and then reintroduced.

Materials and methods

Animals

Six male C57BL/6 mice (Harlan, Bicester, UK), with initial body weights of approximately 22 g at 7 weeks of age, were placed under a reversed 12 h:12 h light/dark cycle (lights on at 16:00, ZT0; lights off at 04:00, ZT12; ZT, zeitgeber time) immediately upon arrival and were allowed to acclimatise as a group. After 2 weeks, mice were single housed in TSE PhenoMaster/LabMaster feeding/drinking monitoring cages (TSE Systems, Bad Homburg, Germany) and acclimatised for a week further before the start of 1 week of baseline food intake and locomotor activity measurements (phase 1). All mice were fed *ad libitum* standard pellet diet (Special Diet Services, Witham, UK; #871505 CRM (P); 22% protein, 69% carbohydrate, 9% fat by energy, 2.67 kcal/g) unless otherwise noted. Water was freely available at all times during the experiments. The ambient temperature and humidity in the animal room and in the wire-top experimental cages were c. 21°C and c. 50%, respectively. All procedures were licensed under the Animals (Scientific Procedures) Act of 1986 and received approval from the Ethical Review Committee at the Rowett Institute of Nutrition and Health.

Dietary manipulation

Following baseline measurements (phase 1), all mice underwent the same dietary manipulations, performed with pelleted HFD (Research Diets, New Brunswick, NJ, USA, #D12492; 20% protein, 20% carbohydrate, 60% fat by energy, 5.24 kcal/g). During phases 2 and 3, all mice had scheduled access to HFD for 2 h a day from ZT18 to ZT20 (6 h to 8 h into the dark phase, as employed by (Berner et al., 2008)) and standard pellet diet in the remaining time (phase 2, adaptation; phase 3, habituation). Due to the longitudinal development of binge-type feeding, phases 2 and 3 are termed "adaptation" and "habituation", respectively. After 17 days of HFD scheduled feeding, for phase 4, the mice were switched back to standard pellet diet during scheduled feeding time (i.e. standard diet available 24 h a day; termed "replacement"). After a further 7 days, mice were returned to HFD during scheduled feeding time for 7 more days in phase 5, termed "refeeding". Body weight was measured three times a week.

Food intake measurement and food intake microstructure analysis

During phases 1–5, food intake was measured using the TSE PhenoMaster/LabMaster system, which automatically records the weight of food eaten to a sensitivity of 0.01 g through a calibrated sensor. Food spillage was minimised by a catch tray underneath the food hopper. For assessing HFD intake during scheduled feeding, food hoppers containing the diet were exchanged using the "food refill" menu in the software at ZT18 and then again at ZT20. Food hoppers were also exchanged during baseline and replacement phases to standardise the amount of disturbance each day. Cumulative food intake was recorded at intervals of 5 min and summarised in 1 h bins and then averaged per mouse and study phase.

Meal pattern analysis

Data for meal analysis was collected as binary data every 10 s. Meal analysis was done as "so called" sequence analysis, whereby all meals occurring during the study period were recorded chronologically to allow the evaluation of single feeding episodes. The start of a meal was defined by food removal equal to or larger than 0.05 g and the meal was ended when no further food removal occurred before the end of the inter-meal interval of 15 min. The meal parameters (meal number and meal size) were then summarised over seven time periods – total day (ZT0–24), light phase (ZT0–12), dark phase (ZT13–24), early dark phase (ZT13–15), mid dark phase (ZT16–18), scheduled feeding time (ZT19–20), and late dark phase (ZT21–24), and then averaged per mouse and study phase. A 15 min inter-meal interval is commonly used in defining meals in mice (Atalayer & Rowland, 2011) and rats (Farley, Cook, Spar, Austin, & Kowalski, 2003).

Locomotor activity measurement and analysis

Activity was measured using a multicage activity monitoring system (Ugo Basile, Comerio, Italy). Each cage had a horizontal sensor frame for monitoring locomotor activity such as walking and running, and a vertical sensor frame for rearing and exploratory activity. Activity was measured as infrared beam breaks per 15 min interval, and was recorded via WinDas 2006 software (Ugo Basile). Horizontal and vertical activity data were separately summarised at 1 h intervals and then averaged per mouse and study phase.

Statistical analysis

Statistical analysis was performed with SigmaPlot 12.0 (Systat Software, Chicago, IL, USA). Diurnal differences in food intake microstructure and locomotor activity pattern during baseline were analysed with one-way repeated measures analysis of variance (one-way RM ANOVA). Longitudinal measurements of food intake and physical activity were analysed by two-way RM ANOVA for effect of "study phase" and "time point", and interactions between these factors. Data for meal pattern were analysed by one-way RM ANOVA to reveal overall effects between study phases. When the data were not normally distributed and/or variances were not equal, a non-parametric ANOVA on ranks was performed. *Post hoc* and planned comparisons were assessed with Student–Newman–Keul Tests (SNK). Outcomes were considered statistically significant if P values were lower than 0.05. Data are presented as mean ± standard error of the mean (SEM).

Results

The study consisted of five phases: baseline measurements on standard pellet diet (phase 1), "adaptation" and "habituation" periods when pelleted HFD was fed by scheduled access for 2 h a day with standard pellet diet in the remaining time (phases 2 and 3, respectively), "replacement", when mice were switched back to standard pellet diet during scheduled feeding time (i.e. standard diet available 24 h a day; phase 4), and "refeeding", when mice were returned to HFD during scheduled feeding time (phase 5).