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Intermittent access to liquid sucrose differentially modulates energy intake and related central pathways in control or high-fat fed mice

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HIGHLIGHTS

- Preference for a 12.6% sucrose solution is greater in high-fat vs normal-fat fed mice.
- Sucrose continuous access increases weight gain in normal and high-fat fed mice.
- Sucrose 2h-intermittent access leads to hyperphagia in high-fat fed mice only.
- Sucrose 2h-intermittent access leads to body weight gain in high-fat fed mice only.
- Sucrose 2h-intermittent access modulates hypothalamic and reward signaling.

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ABSTRACT

Intake of sodas has been shown to increase energy intake and to contribute to obesity in humans and in animal models, although the magnitude and importance of these effects are still debated. Moreover, intake of sugar sweetened beverages is often associated with high-fat food consumption in humans. We studied two different accesses to a sucrose-sweetened water (SSW, 12.3%, a concentration similar to that usually found in sugar sweetened beverages) in C57BL/6 mice fed a normal-fat (NF) or a high-fat (HF) diet in a scheduled access (7.5 h). NF-fed and HF-fed mice received during 5 weeks access to water, to SSW continuously for 7.5 h (SSW), or to water plus SSW for 2 h (randomly-chosen time slot for only 5 random days/week) (SSW-2h). Mouse preference for SSW was greater in HF-fed mice than NF-fed mice. Continuous SSW access induced weight gain whatever the diet and led to greater caloric intake than mice drinking water in NF-fed mice and in the first three weeks in HF-fed mice. In HF-fed mice, 2 h-intermittent access to SSW induced a greater body weight gain than mice drinking water, and led to hyperphagia on the HF diet when SSW was accessible compared to days without SSW 2 h-access (leading to greater overall caloric intake), possibly through inactivation of the anorexigenic neuropeptide POMC in the hypothalamus. This was not observed in NF-fed mice, but 2 h-intermittent access to SSW stimulated the expression of dopamine, opioid and endocannabinoid receptors in the nucleus accumbens compared to water-access. In conclusion, in mice, a sucrose solution provided 2 h-intermittently and a high-fat diet have combined effects on peripheral and central homeostatic systems involved in food intake regulation, a finding which has significant implications for human obesity.

1. Introduction

Consumption of sugar-sweetened beverages (SSBs) is considered to increase energy intake, and has been associated with being overweight in humans [1–6], although a direct relationship between SSB consumption and the prevalence of obesity is debated [7–9]. In rodents fed a control diet, sucrose-sweetened water (SSW) given *ad libitum* at a concentration found in SSBs in mice [10], or with higher concentrations of sucrose in mice [11–13] and in rats [14–17] often induces an increase in caloric intake associated with greater body weight, though to some extent results are contentious [18,19]. In addition, time-limited and scheduled access to SSW can lead to binge-like drinking behavior in rodents fed control diets [20–24], a behavior also reported in rodents offered a palatable food intermittently [25–29].

Food intake control is achieved by appetite signals produced by peripheral circulating hormones and central appetite circuitry [30].

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Circulating hormones such as PYY, ghrelin, leptin and CCK are modulated by high-fat diets [31–33], sucrose solutions [15] and feeding schedule [34]. In addition, studies have shown that changes in the expression of hypothalamic peptides are dependent on diet composition in fat and sugar [35,36]. Central reward pathways are also differentially modulated by consumption of fat and/or sugars [37–39], and mice with binge-like drinking behaviors for sugar solutions have impairments mainly in dopaminergic and opioidergic pathways that regulate reward sensitivity and food intake [20,40]. Hence, as SSBs are often consumed alongside high-fat foods in humans [41], it is important to further examine whether this combination could have a synergistic action on body weight, fat mass [42,43] and on appetite mechanisms [12].

The aim of the present study was to evaluate the effects of a sucrose-sweetened water (SSW) in mice adapted to a normal-fat (NF) or to a high-fat (HF) diet on weight gain, feeding profile and the brain circuitry involved in the control of food intake. Access to the SSW (12.3%) was either continuous – same schedule as the food, in line with other studies [10,15,17,19] – or a 2 h-intermittent access that was made unpredictable (change of time and days of access) because making time of access unpredictable can affect drinking behavior [44]. Similar models of scheduled access to the food (limited in this study to a 7.5 h period of the activity phase) were used in different rodent studies [12,45] to approach human feeding behavior, characterized by a feeding pattern mainly occurring during the light period. In experiment 1, we measured the preference for this SSW (*vs.* water) over 5 weeks in normal-fat (NF) and high-fat (HF) fed mice, to see if the diet affected preference for SSW. In experiment 2, we investigated how continuous or 2 h-intermittent access to SSW affected body weight gain, caloric intake and sensitivity to CCK over 5 weeks in mice adapted to a NF or to a HF diet. A detailed analysis of feeding and drinking patterns was performed in experiment 3 to verify if mice were bingeing on the sucrose solution. We also measured serum levels of peripheral appetite peptides, and the mRNA expression of centrally produced peptides and receptors in the hypothalamus and nucleus accumbens.

2. Material and methods

2.1. Animals (experiments 1–3)

The study was approved by the French National Animal Care Committee (numbers 11/033 and 12/038) and conformed to the European legislation on the use of laboratory animals. Seven week-old male C57BL6/J mice (Harlan Laboratories, France) were housed individually on a 12 h reversed light/dark cycle (lights off at 09:30). In the three experiments mentioned below, mice received either access to a normal-fat (NF) diet or to a high-fat (HF) diet enriched in lard that were AIN90M modified diets (UPAE-INRA, Jouy-en-Josas). The NF diet provided 14.6 kJ/g of energy (14% protein/energy, 74% carbohydrate/energy and 10% fat/energy) and the HF diet provided 19.6 kJ/g of energy (14% protein/energy, 40% carbohydrate/energy and 45% fat/energy). The composition of these two diets is described in Table 1. The NF and HF diets were moistened (60/40 ratio of powder/water) to minimize spillage. The sucrose-sweetened water (SSW) used in the three experiments described below is a solution of 12.3% w/v sucrose in water (2.4 kJ/mL) that was prepared fresh every two days. The time for feeding and drinking was limited from the onset of the dark period (09:30) until 17:00 (7 h 30-period), and mice were habituated to this feeding protocol one week before the beginning of experimental procedures (during which mice had access to either NF or HF diet plus water in this schedule).

Table 1
Composition of NF and HF diets used in the 3 experiments.

	Normal-fat diet	High-fat diet
Ingredients, g/kg		
Milk protein	140	170
Cornstarch	623	437
Sucrose	100	71
Soybean oil	40	10
Lard	0	215
Salt mix	35	35
Vitamin mix	10	10
Cellulose	50	50
Choline chloride	2	2
Energy content, kJ/g	14.6	19.6

2.2. Experiment 1: preference for the SSW solution

14 male C57BL6/J mice were split into two groups matched for body weight and fed the NF or HF diet (n = 7/group). Both groups had access to both water and SSW (12.3% w/v sucrose in water) from 9:30 to 17:00. All mice were maintained on their respective diets and drinks for 5 weeks. Food and drink intake were measured 3 times per week throughout the study by measuring daily weight changes of food cups placed on the cage floor. Data were corrected for spillage (easy to monitor since mice were housed in cages with grids), food moistening and evaporation (measured with a food cup placed in an empty cage) and converted to kJ.

2.3. Experiment 2: effects of SSW-access on body weight, caloric intake and CCK sensitivity

2.3.1. Procedure

36 male C57BL6/J mice were split into six groups (n = 6/group) matched for body weight. Three groups were fed the NF diet and three groups the HF diet. Two groups had access to only water (NF-water and HF-water) and two groups had access to only SSW (NF-SSW and HF-SSW) (12.3% w/v sucrose in water). Access to water or SSW was limited to the period during which food was also available, because if we had let fluid be accessible in the light cycle, some mice would have drunk only water but others would have ingested calories from the SSW. The two remaining groups had access to water in the same timeframe as the food and had access to SSW for only 2 h at random in this period, five randomly-chosen days per full 7-day week, so including weekends (NF-SSW-2h and HF-SSW-2h). In these two groups, random access to SSW was made available at least 1 h after presentation of the food/water to avoid overconsumption due to hunger or thirst, and water was available at the same time as the SSW. All mice were maintained on their respective diets and drinks for 5 weeks.

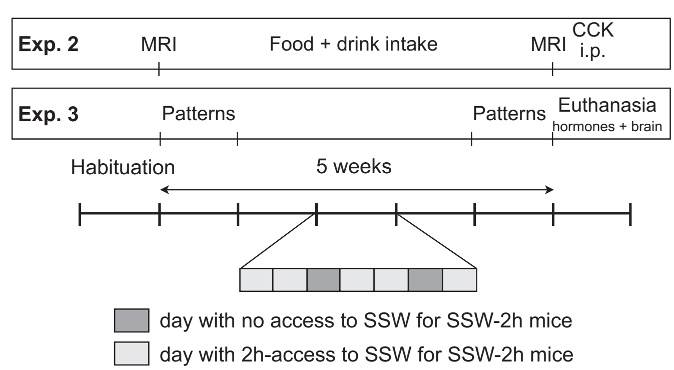

Fig. 1. Design of experiments 2 and 3. Mice were habituated for 1 week to their feeding schedule. Mice with access to water and mice with continuous access to SSW had access to water or SSW everyday (accessible in the same schedule as their NF or HF diet). Mice with access to SSW 2 h-intermittently had access to water in the same schedule as the food and access to SSW for 2 h only 5 days per week (chosen randomly). For example, in week 3 of experiment 2, SSW-2h mice had access to SSW for 2 h on Monday, Tuesday, Thursday, Friday and Sunday. Feeding and drinking patterns were measured during weeks 1 and 5 in experiment 3 (on days with and without SSW access for SSW-2h mice).