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Intermittent access to a sucrose solution impairs metabolism in obesity-prone but not obesity-resistant mice

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HIGHLIGHTS

- Liquid sucrose leads to hyperphagia and body weight gain in obesity-prone (OP) mice.
- This hyperphagia induces fat mass gain, fatty liver and insulin resistance in OP mice.
- Liquid sucrose modulates melanocortin and opioid signaling in the brain of OP mice.
- These effects are reversible after 8 weeks of access to water.
- Obesity-resistant mice are protected from sucrose-induced metabolic consequences.

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ABSTRACT

Consumption of sugar-sweetened beverages is associated with overweight and obesity. In this study, we hypothesized that obesity-prone (OP) mice fed a high-fat high-sucrose diet (HFHS) are more sensitive to consumption of sucrose-sweetened water (SSW) than obesity-resistant (OR) mice.

After 3 weeks of ad libitum access to the HFHS diet (7.5 h/day), 180 male mice were classified as either OP (upper quartile of body weight gain, 5.2 ± 0.1 g, n = 45) or OR (lower quartile, 3.2 ± 0.1 g, n = 45). OP and OR mice were subsequently divided into 3 subgroups that had access to HFHS (7.5 h/day) for 16 weeks, supplemented with: i) water (OP/water and OR/water); ii) water and SSW (12.6% w/v), available for 2 h/day randomly when access to HFHS was available and for 5 randomly-chosen days/week (OP/SSW and OR/SSW); or iii) water and SSW for 8 weeks, then only water for 8 weeks (OP/SSW-water and OR/SSW-water).

OR/SSW mice decreased their food intake compared to OR/water mice, while OP/SSW mice exhibited an increase in food and total energy intake compared to OP/water mice. OP/SSW mice also gained more body weight and fat mass than OP/water mice, showed an increase in liver triglycerides and developed insulin resistance. These effects were fully reversed in OP/SSW-water mice. In the gut, OR/SSW mice, but not OP/SSW mice, had an increase GLP-1 and CCK response to a liquid meal compared to mice drinking only water. OP/SSW mice had a decreased expression of melanocortin receptor 4 in the hypothalamus and increased expression of delta opioid receptor in the nucleus accumbens compared to OP/water mice when fasted that could explain the hyperphagia in these mice. When access to the sucrose solution was removed for 8 weeks, OP mice had increased dopaminergic and opioidergic response to a sucrose solution.

Thus, intermittent access to a sucrose solution in mice fed a HFHS diet induces changes in the gut and brain signaling, leading to increased energy intake and adverse metabolic consequences only in mice prone to HFHS-induced obesity.

Abbreviations: AgRP, agouti-related peptide; AUC, area under the curve; BW, body weight; CART, cocaine- and amphetamine-regulated transcript; CB1-R, endocannabinoid receptor 1; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; DA, dopamine; DIO, diet-induced obesity; DOR, delta opioid receptor; DR, dopamine receptor; FFA, free fatty acids; GLP-1, glucagon-like peptide-1; Gox, glucose oxidation; HDL, high-density lipoprotein; HFHS, high-fat high-sucrose; KOR, kappa opioid receptor; Lox, lipid oxidation; MC4R, melanocortin receptor 4; MOR, mu opioid receptor; NAcc, nucleus accumbens; NPY, neuropeptide Y; NS, non-significant; OP mice, obesity-prone mice; OR mice, obesity-resistant mice; OR, opioid-receptor; POMC, proopiomelanocortin; PYY, peptide YY; SPA, spontaneous physical activity; SSBs, sugar-sweetened beverages; SSW, sugar-sweetened water; TG, triglycerides.

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1. Introduction

In recent decades, increased consumption of sugar-sweetened beverages (SSBs) has been associated with obesity and adverse health outcomes in humans [1–3]. These beverages are often consumed as part of a high-energy diet, especially among young people [4,5]. In this obesogenic environment of fat- and sugar-containing high energy density foods, some individuals are more susceptible (obesity-prone) than others (obesity-resistant) to weight gain [6,7].

Similarly, sucrose-sweetened water (SSW) promotes greater energy intake and/or adverse metabolic effects in laboratory animals fed control diets [8–13]. In addition, intermittent access to SSW is more harmful when ingested with a high-fat diet compared to a control diet [14], highlighting the importance of the combination of obesogenic diets and SSBs. Similar to humans, rodents exhibit a large phenotypic diversity in their sensitivity to obesogenic diet [15–20].

In addition to the association between SSBs and the development of obesity, there is growing support for a link between SSBs and the modulation of neural pathways underlying food intake. The consumption of SSBs alters the expression of neuropeptides involved in the homeostatic control of appetite [8,12] and dopaminergic and opioidergic pathways involved in food reward [14,21,22]. These data suggest that the relationship between SSBs and metabolic dysfunction could be the result of altered brain signaling in areas involved in controlling food intake.

We hypothesized that combining fat- and sugar-containing obesogenic diets with SSBs would have greater metabolic consequences in mice already prone to diet-induced obesity (DIO) compared to obesity-resistant mice, and that the observed differences could reflect an altered gut and/or brain signaling. In the present study, we demonstrate that intermittent access to SSW with a sugar concentration similar to soda increases body weight and fat mass gain and leads to insulin resistance and fatty liver only in mice that are already sensitive to a high-fat high-sucrose diet. These metabolic consequences are fully reversed by removal of the SSW, and are accompanied by a decreased expression of the melanocortin 4 receptor in the hypothalamus and increased expression of delta opioid receptor in the nucleus accumbens.

2. Materials and methods

2.1. Animals

180 male C57Bl/6J mice (Harlan Laboratories) aged 5 weeks (19.2 ± 0.4 g) were housed individually in cages with grid floor in a temperature-controlled room (22 ± 1 °C) with a reversed 12:12-hour light–dark cycle (lights off at 09:30). After arrival, mice were habituated to the laboratory conditions for one week with ad libitum access to chow and water. During the experimental period, mice were fed a modified AIN93M high-fat high-sucrose diet (HFHS) (Table 1) that was moistened (70/30 ratio of powder/water) to minimize spillage. To consolidate feeding behavior (and better assess the consequences of adding access to SSW), the HFHS diet was only available for a 7.5 h period beginning at the onset of the dark period (09:30–17:00) throughout the study, as previously published [14]. In a preliminary study, we also controlled that this schedule did not affect BW gain in chow-fed mice and therefore that this 7.5 h time window was long enough to allow a normal caloric intake (unpublished data). Water was available ad libitum with the food throughout the experiment for all mice. This study was approved by the French National Animal Care Committee (number 12/087) and conformed to European legislation on the use of laboratory animals.

2.2. Selection of obesity-resistant (OR) and obesity-prone (OP) mice

OP and OR mice had the same BW (18.7 ± 0.2 g) and fat mass (2.8 ± 0.1 g) at the beginning of the study. Mice were classified as OR or OP based on their gain in body weight (BW) (3.2 g ± 0.1 for OR mice (lower quartile) < 5.2 g ± 0.1 for OP mice (upper quartile), $P < 0.001$) and fat mass (4.2 g ± 0.1 for OR mice (lower quartile) < 5.3 g ± 0.2 for OP mice (upper quartile), $P < 0.001$) during the first 3 weeks of HFHS feeding. OP mice had larger visceral (1.4 g ± 0.1 vs. 0.8 g ± 0.04 for OR, $P < 0.001$) and subcutaneous fat pads (1.4 g ± 0.1 vs. 0.8 g ± 0.04 for OR, $P < 0.001$) compared to OR mice.

Table 1
Composition of the high-fat high-sucrose (HFHS) diet.

Ingredients	g/kg	% energy
Milk protein	170	13.5
Cornstarch	254	40.8
Sucrose	253.7	
Soybean oil	10	45
Lard	215	
Salt mix	35	
Vitamin mix	10	0.8
Cellulose	50	
Choline chloride	2.3	
Energy content, kJ/g	19.6	

2.3. Experimental design

After the 3 week selection period, OR and OP mice were divided into three weight-matched groups (n = 15/group) and continued to receive the HFHS diet for 16 weeks (Fig. 1). Mice had also access to either i) water ad libitum as previously (OR/water, OP/water), ii) water ad libitum plus access to SSW (12.6% w/v sucrose in water, 2.1 kJ/mL) for 2 h/day (at a randomly-chosen time during the 09:00–17:00 time window when access to HFHS was also provided; hereafter referred to as '2 h-intermittent access') on 5 randomly-chosen days/week (OR/SSW, OP/SSW), or iii) water ad libitum plus 2 h-intermittent access to SSW for the first 8 weeks, then access to only water for the last 8 weeks (OR/SSW-water, OP/SSW-water). Access to the SSW was restricted (2 h) and unpredictable (change of time and days of access) to mimic human environment.

2.4. Body weight and body composition

Mice were weighed twice a week. Body fat and lean mass were determined in vivo by dual energy X-ray absorptiometry every 4 weeks (Lunar Piximus, GE Medical System).

2.5. Energy expenditure and food/drink intake

Food and SSW intake were measured twice a week by determining changes in the weight of individual food cups (placed on a grid floor). Data were corrected for spillage by weighing the food that went through the grid, moistening of the solid food and evaporation and converted to kJ. Detailed recordings of HFHS and SSW ingestion patterns, spontaneous physical activity (SPA) and VO_2 and VCO_2 were obtained using individual metabolic cages during weeks 14 and 15, for 2 or 3 consecutive days, during which access to HFHS was available from 09:00 to 17:00 as usual. Day 1 in the metabolic cage was used for habituation. Recordings were taken during day 2 for all groups, and for standardization, SSW was made available between 11:00 and 13:00 for OR/SSW and OP/SSW mice. Recordings were taken during day 3 only for SSW mice to study their feeding and SPA patterns in the absence of access to SSW. Food intake, drink intake and SPA data, initially recorded at 5 s interval, were pooled into 10-min intervals. Food/drink intake data were then analyzed to extract the following parameters: meal numbers, meal size (kJ), meal duration (min), ingestion speed (kJ/min) and inter-meal interval (min) (as described previously [14]). Glucose oxidation (Gox) and lipid oxidation (Lox) profiles were computed in Watts (J/s) from VO_2 and VCO_2 (mL/min) [23].