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Behavioral characterization of a model of differential susceptibility to obesity induced by standard and personalized cafeteria diet feeding

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HIGHLIGHTS

- Balb/c mice fed a cafeteria (CAF) diet become obesity prone (OP) or resistant (OR).
- OP and OR mice differ in snack preference (sweet vs savory).
- OP mice decrease their sucrose preference and OR increase their physical activity.
- A personalized CAF diet causes hyperphagia but not obesity in OR mice.

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ABSTRACT

Despite the increase in obesity prevalence over the last decades, humans show large inter-individual variability for susceptibility to diet-induced obesity. Understanding the biological basis of this susceptibility could identify new therapeutic alternatives against obesity. We characterized behavioral changes associated with propensity to obesity induced by cafeteria (CAF) diet consumption in mice. We show that Balb/c mice fed a CAF diet display a large inter-individual variability in susceptibility to diet-induced obesity, such that based on changes in adiposity we can classify mice as obesity prone (OP) or obesity resistant (OR). Both OP and OR were hyperphagic relative to control-fed mice but caloric intake was similar between OP and OR mice. In contrast, OR had a larger increase in locomotor activity following CAF diet compared to OP mice. Obesity resistant and prone mice showed similar intake of sweet snacks, but OR ate more savory snacks than OP mice. Two bottle sucrose preference tests showed that OP decreased their sucrose preference compared to OR mice after CAF diet feeding. Finally, to test the robustness of the OR phenotype in response to further increases in caloric intake, we fed OR mice with a personalized CAF (CAF-P) diet based on individual snack preferences. When fed a CAF-P diet, OR increased their calorie intake compared to OP mice fed the standard CAF diet, but did not reach adiposity levels observed in OP mice. Together, our data show the contribution of hedonic intake, individual snack preference and physical activity to individual susceptibility to obesity in Balb/c mice fed a standard and personalized cafeteria-style diet.

1. Introduction

There are large differences in susceptibility to diet-induced obesity among individuals, but the mechanism(s) governing this variation remains unknown [1,2]. Like humans, rodents exhibit large individual differences in propensity for obesity induced by high-fat diet intake [3–7], and studies suggest that adaptations in energy expenditure and control of hedonic food intake may play a key role [8–10].

High levels of spontaneous physical activity (SPA) correlate with resistance to diet-induced obesity [11–13]. SPA describes low intensity physical activity, executed in the absence of an immediate reward [14]. In humans, SPA is defined as all physical activity excluding formal exercise and describes a series of movements such as ambulating and standing [13,14]. In rodents, SPA includes all locomotor activity in an open field or home cage after an acclimation period to eliminate novelty-induced locomotion [15]. In humans, SPA inversely correlates with weight change during diet-induced obesity whereby people that remain lean spend more time performing SPA compared to those who

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become obese [12,13]. Evidence from animal models also shows SPA can decrease severity of diet-induced obesity. Outbred rats with higher SPA are resistant to obesity induced by high-fat diet compared to rats with low SPA [16] and rats bred for resistance against diet-induced obesity have higher SPA levels compared to rats bred for susceptibility to weight gain when fed high-fat diet [11,17]. Furthermore, SPA was included in statistical models that predict propensity to obesity induced by high-fat diet consumption in inbred C57 mice [4]. However, the relative contribution of SPA to susceptibility to diet-induced obesity in humans and rodents appears to be dependent on the diet type, duration of the over-feeding period and in the case of animal models, of rodent species and/or strain [16,18,19].

In addition to low SPA, excessive intake of energy-dense foods is another major contributor to obesity prevalence [20,21]. Energy-dense foods, such as those rich in fat or sugar alter neuronal circuits regulating reward behavior, thus promoting their over-consumption and facilitating the emergence of obesity [22]. However, there is large inter-individual variability in preference for high-energy dense foods [23,24] that modulates neurobiological adaptations of reward systems and food choice [25]. Furthermore, how obesity alters reward-behavior in relation to food is unclear. In rodents, diet-induced obesity can either increase or decrease food-motivated behaviors such as sucrose pellet self-administration or conditioned place preference for sucrose [26–31]. Animal studies suggest that a higher motivation to obtain energy-dense foods predicts susceptibility to diet-induced obesity [26], which is consistent with neuroimaging studies demonstrating that higher susceptibility to reward effects of energy-dense foods leads to over-eating [32]. Yet, obese rats and humans have lower dopamine tone and release following food intake [33–35], suggesting that over-eating is a compensatory behavior, which seeks to capture the experience of rewards associated with consumption of energy-dense foods [36,37]. Together, these data illustrate that the relative contribution of reward-based behavior to individual susceptibility to obesity remains largely unknown.

Our study sought to determine behavioral adaptations relating to SPA and hedonic food intake in individual susceptibility to diet-induced obesity in mice. We hypothesized that weight change variation among CAF-fed mice would be due to a combination of calorie intake, SPA and hedonic preference. To test this we used Balb/c mice, which have been reported to have a lower susceptibility to diet-induced obesity by high-fat diet consumption compared to other mice strains [3]. Therefore, we fed mice a cafeteria (CAF) diet, which has a higher obesogenic potential compared to homogeneous high-fat diet in pellet form [38,39]. Rodents fed the CAF diet had free access to a rotating selection of energy-dense human snacks plus rodent chow [38,39]. In addition to its higher obesogenic potential, CAF diet is a more translatable model of human unhealthy eating compared to diets rich in a single macronutrient, such as high-fat diets [38,39]. First, we characterized SPA and sucrose preference, before and after CAF diet feeding to determine adaptations of hedonic intake and SPA to individual susceptibility to obesity. Then, we tested whether a personalized CAF diet could induce obesity in mice resistant to diet-induced obesity when fed the CAF diet.

2. Materials and methods

2.1. Animals

Adult male Balb/c mice (8–12 weeks old on arrival, n = 47, Instituto Salud Publica, Santiago, Chile) weighing between 20 and 25 g were housed individually in clear solid bottom cages with corn-cobb bedding and environmental enrichment materials. Mice were maintained on a 12-h light/12-h dark cycle (lights on at 07:00 AM) in a temperature-controlled environment (21–25 °C). For dietary interventions, mice were switched to paper bedding (2:1 mixture of sterilized filter paper and paper towels) to allow precise quantification of food spillage. The control diet was rodent chow (ProLab RMH-3000, Lab Diets, MO, USA, 3.47 kcal/g, with 25.96% kcal from protein, 14.93% kcal from fat and 59.11% kcal from carbohydrates). Supplementary Table 1 shows the nutrient composition of the control diet. Tap water was available *ad libitum* unless noted otherwise. All animal procedures were reviewed and approved by the Institutional Bioethics Committee at Universidad Andres Bello.

2.2. Obesogenic diets

2.2.1. Cafeteria (CAF) diet composition and feeding schedule

The CAF diet contained 6 savory and 6 sweet snacks with an average caloric density of 4.64 ± 0.64 kcal/g and an average macronutrient composition as follows: 8.43% kcal from protein, 45.24% kcal from fat and 46.31% kcal from carbohydrates. Supplementary Table 1 shows the nutrition information for the CAF diet and each snack category. Savory and sweet snacks were classified based on their relative sodium and simple sugar content (Supplementary Table 2).

Mice had continuous access to CAF diet (24-h/d and 7d/week) but snacks were switched 6 d/week every 24 h (Monday–Friday) or 48 h (Saturday to Monday of the following week) with two new randomly selected and pre-weighed sweet and savory snacks. Snacks were placed in a small bowl in a corner of the cage. Mice also had access to standard diet (rodent chow) and tap water *ad libitum* throughout the experiment. To control for changes in food weight due to dehydration, each CAF snack was left at room temperature and weighed daily.

2.2.2. Preferred cafeteria (CAF-P) diet composition and feeding schedule

The CAF-P diet was designed to increase the frequency in which animals were offered their most preferred snacks from CAF diet compared to their less preferred snacks. Following completion of CAF diet feeding, we calculated individual snack preference for each animal by rank ordering based on percent intake throughout the 8 weeks of CAF diet feeding. During CAF-P diet, mice were offered their three most preferred savory and sweet snacks in a ratio of 3:1 relative to their less preferred snacks. The CAF-P diet composition was updated every two weeks in an individual basis, such that the snacks whose consumption represented less than 10% of total snack intake were replaced with the snack that showed the next highest consumption. The CAF-P diet intervention lasted for 6 weeks. All other aspects of the CAF-P dietary intervention were the same as standard CAF diet (Section 2.2.1).

2.2.3. Food intake, body weight and body composition measurements

Food intake from chow and CAF diet snacks (reported as grams (g) or calories (kcal)) were corrected for spillage and dehydration. Body weight (g) was measured every other day. Fat and lean mass (g) were measured weekly (Echo MRI, Houston, TX, USA).

2.3. Spontaneous physical activity (SPA) measurements

Home cage SPA in singly housed animals was recorded continuously using a video camera (SONY CCD 1/3 600 TVL, 15 fps, 352 by 240 pixels) located perpendicular to the longitudinal axis of the cage. To acclimate animals to recording conditions, bedding and enrichment materials were removed 24 h prior to testing, which was necessary for contrast-based detection of the animal. After acclimation, body weight, food intake and spillage were measured. SPA was recorded for 24 h starting 1 h after mice were handled to reduce artificially increasing SPA. Only animals with complete data (i.e. 24 h recordings) were included in the final analysis (OP, n = 16, OR, n = 12, control fed, n = 10). SPA was analyzed with motion tracking software (Any Maze v4.7, Stoelting, IL, USA) and quantified as distance traveled (in arbitrary units) in the horizontal plane based on movement of the animal's center of mass, not including rearing behavior.