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A mouse model for binge-like sucrose overconsumption: Contribution of enhanced motivation for sweetener consumption

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HIGHLIGHTS

- We developed a simple mouse model for binge-like sweetener overconsumption.
- Limited access to sucrose or saccharin and chow was given in food restricted-mice.
- Trained mice increased sucrose or saccharin consumption during brief time periods.
- Trained mice exhibited binge-like behavior even when they were not hungry.
- The binge-like behavior may be due to enhanced hedonic motivation for sweetener.

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ABSTRACT

Behavioral and neural features of binge-like sugar overconsumption have been studied using rat models. However, few mouse models are available to examine the interaction between neural and genetic underpinnings of bingeing. In the present study, we first aim to establish a simple mouse model of binge-like sucrose overconsumption using daytime limited access training in food-restricted male mice. Trained mice received 4-h limited access to both 0.5 M sucrose solution and chow for 10 days. Three control groups received (1) 4-h sucrose and 20-h chow access, (2) 20-h sucrose and 4-h, or (3) 20-h chow access, respectively. Only the trained group showed progressively increased sucrose consumption during brief periods of time and developed binge-like excessive behavior. Next, we examined whether the present mouse model mimicked a human feature of binge eating known as "eating when not physically hungry." Trained mice consumed significantly more sucrose or non-caloric sweetener (saccharin) during post-training days even after they nocturnally consumed substantial chow prior to daytime sweetener access. In other trained groups, both a systemic administration of glucose and substantial chow consumption prior to the daytime limited sucrose access failed to reduce binge-like sucrose overconsumption. Our results suggest that even when caloric consumption is not necessarily required, limited access training shapes and triggers binge-like overconsumption of sweetened solution in trained mice. The binge-like behavior in trained mice may be mainly due to enhanced hedonic motivation for the sweetener's taste. The present study suggests that our mouse model for binge-like sugar overconsumption may mimic some human features of binge eating and can be used to investigate the roles of neural and genetic mechanisms in binge-like overconsumption of sweetened substances in the absence of physical hunger.

1. Introduction

Binge eating in humans is characterized by features such as the excessive consumption of food in a brief period of time and in the absence of physical hunger [1–4]. Increased consumption of sugar-sweetened beverages and binge-like sugar overconsumption are related to health and behavioral problems including affective disorder, substance abuse, obesity, diabetes, and metabolic syndromes [5–10]. Recent studies in rat models have clarified behavioral and neurological mechanisms and the consequences of binge eating [2–4]. To our knowledge, however, only a few mouse models for binge-like behaviors involving the consumption of high-fat [11] and high-fat and high-energy chow [12] and palatable food [13] (i.e., Nabisco Oreos) have been reported. Only one mouse model of excessive sucrose consumption has been developed [14]. Thus, neural and genetic mechanisms for binge-like overconsumption of sweet substance(s) remain largely unknown because of the lack of a suitable mouse model.

The first aim of the present study was to establish a simple mouse model for binge-like sugar overconsumption by using a limited access procedure under food restriction [cf., 15–20]. Developing a tractable mouse model of binge-like sucrose overconsumption could allow the

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development of a number of mutant and knockout/in strains to investigate the neurobiological mechanisms of binge-like behavior associated with sugar intake. Such studies may provide us with clues regarding the neurogenetic basis of cravings or the compulsive features [21,22] of binge-like sugar overconsumption. Mouse models would also help understand obesity due to the binge-like behavior [23–25]. In this study, we chose the C57BL/6J mouse strain because it is widely used as a genetic control strain in neurobiological and physiological studies and has a common genetic background shared with a variety of genetically engineered strains.

Using the limited access procedure, we addressed two aspects of binge-like behavior in our mouse model. A history of footshock stress and limited access to food under caloric restriction [26] successfully evokes binge-like behavior in rats; however, it has been debated whether stressful treatment and food restriction is similarly effective in mice [12,13]. We thus tested whether a limited access protocol under food restriction is effective in mice. Second, like non-food deprived rat models [2,17,27,28], previously established mouse models without food restriction [12,13] required longer time periods to establish stable binge-like behavior, apart from the model described by Halpern et al. [11]. Therefore, we examined whether shorter periods of training effectively produce stable binge-like behavior in our mouse model.

Although it is impossible to develop a model that totally mimics all the psycho-biological features of human diseases and disorders [29], it needs to be validated whether the present animal model fulfills unique features or objective criteria of binge eating in humans [1–4,29,30] as an isomorphic model of binge-like behavior [17,32]. Like rat models [15–20], we tested whether mice with limited access to a palatable sucrose solution would consume an excessive amount of the sweetened solution in a short period. In the present study, we focused on another feature, that is, persistent eating in the absence of hunger. Humans who binge eat, even after high-caloric intake, show persistent consumption of palatable food [30,31]. Tanofsky-Kraff and Yanovski [31] proposed that more information on the motivation to "eat when not physically hungry" is required. Previous studies [2,24,33,34] suggest that eating when not physically hungry is mediated by non-homeostatic motivation, particularly the hedonic component of highly palatable food. Consistent with these studies, we assumed that the binge-like overconsumption of a sweetened solution in mice was mainly due to non-homeostatic (i.e., hedonic) motivation driven by taste reward/palatability rather than homeostatic motivation driven by physical hunger or metabolic need. We thus tested whether trained mice show persistent motivation to consume sucrose or a non-caloric sweetener, saccharin, even when they are re-fed. For practical reasons, sucrose consumption before (pre-) and after (post-training) the limited access regimen was compared, when the homeostatic motivation to consume sucrose as a caloric source to compensate for an energy deficiency would be greatly reduced. To confirm that the present mouse model shows excessive sugar consumption in the absence of hunger, we also examined the effects of reduction of metabolic need or hunger by systemic administration of glucose and brief preload of chow on binge-like sucrose overconsumption in trained mice

2. Materials and methods

2.1. Animals

C57BL/6J male mice (CREA Japan, Osaka), aged 8–9 weeks at the beginning of the experimental procedures, were housed individually in Plexiglas cages at 22 °C under 12-h light/dark cycles, with lights on at 07:00 h. Water and food were available ad libitum unless otherwise indicated. Pelleted commercial rodent diet (MF, Oriental Yeast Co., Ltd.: 3.6 kcal/g) was used as normal chow throughout the experiments. All behavioral manipulations were carried out in the light cycle. All mice were treated in accordance with the guidelines for the Care and Use of Laboratory Animals (NIH, 1996). The rationale, design, and experimental procedures were approved by the Institutional Animal Care and Use Committee of the Graduate School of Human Sciences, Osaka University, and efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Behavioral procedures

2.2.1. Experiment 1: effect of limited access regimen on sucrose consumption

Mice had ad libitum access to water and chow before the experiment. A high-concentration (0.5 M: 17.1% (wt/vol); 0.67 kcal/g) sucrose (Suc) solution that was more concentrated than those in previous reports [11,20,35] was chosen based on another previous report demonstrating its effective impact in activating gustatory and visceral neuraxes in rats [36]. The sucrose solution and/or water were available to all mice with the two-bottle method.

Five groups of mice ($n = 7$ per group) were assigned feeding conditions as shown in Fig. 1A. The experimental group (Suc4h–Chow4h, trained) was maintained on a 20-h food deprivation schedule followed by 4-h access to the sucrose solution and chow starting at 09:00 h every morning (2 h after lights on). One bottle was filled with the sucrose solution. During the 4-h access period, the group also received water in the other bottle. Mice in this group were placed in the limited access regimen for 10 days. During the limited access period, mice were deprived of water, sucrose, and chow from 13:00 to 17:00 h because of housekeeping maintenance. Two bottles filled with water were available overnight from 17:00 to 09:00 h. To assess the effects of the duration and combination of access to sucrose and chow on the development of binge-like behavior, three additional control groups were also tested in the same schedule except as otherwise noted. A control group (Suc4h–Chow20h) received 4-h daily limited access to the sucrose and chow and additional 16-h nocturnal access to chow, resulting in longer chow access (20 h per day). In this group, water was also given during the 4-h sucrose access. A second control group (Suc20h–Chow4h) received limited 4-h access to chow, sucrose and water with additional 16-h access to the sucrose solution in two bottles overnight, resulting in sucrose access for 20 h and chow access for 4 h with 20-h food restriction. A third control group (Suc20h–Chow20h) received 20-h access to both the sucrose and chow.

All mice were allowed to adapt to drinking water in the two bottles for 7 days before daily limited access session. The Suc4h–Chow4h and Suc4h–Chow20h groups with daily limited access to the sucrose solution received the sucrose solution and water simultaneously at 09:00 and 13:00 h with the two-bottle method. To control for side preference, the left/right position of the sucrose solution and water bottles was alternated daily. Consumption of the sucrose solution and chow during the first hour (09:00–10:00 h), second hour (10:00–11:00 h) and the total 4 h (09:00–13:00 h) was recorded daily. Sucrose consumption was measured by subtracting the final bottle weight from the initial bottle weight. Chow consumption was measured in a similar way but for pellet weight. Both sucrose consumption and chow consumption were also converted into caloric consumption when needed. Daily body weight (BW) was also measured before sucrose/chow access.

To compare sucrose overconsumption in the Suc4h–Chow4h group to the increase in prandial water consumption observed under food restriction, a fourth control group (Chow4h; $n = 7$) received 4-h chow access and water under 20-h food deprivation. The Chow4h group received no sucrose access throughout the experiment, while water was available to this group for 20 h per day. The Chow4h group with no sucrose intake tested the prandial effect on the increase in consumption of the sucrose solution by the Suc4h–Chow4h group.

Four dependent measures were monitored during the course of the experiment, including sucrose, water, and chow consumption, and body weight. For testing procedural differences, data for sucrose and chow consumption were analyzed using mixed two- and three-way repeated measures analysis of variance (ANOVAs). Significant two- and/or three-way interactions were further analyzed by simple effect analyses using