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Food restriction-induced hyperactivity: Addiction or adaptation to famine?

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Wheel running

Summary Increased physical activity is present in 30—80% of anorexia nervosa patients. To explain the paradox of low food intake and excessive exercise in humans and other animals, it has been proposed that increased physical activity along with food restriction activates brain reward circuits and is addictive. Alternatively, the fleeing-famine hypothesis postulates that refusal of known scarce energy-low food sources and hyperactivity facilitate migration towards new habitats that potentially contain new energy-rich foodstuffs. The use of rewarding compounds that differ in energy density, such as the energy-free sweetener saccharin and the energy rich sucrose makes it possible to critically test the reward-addiction and fleeing-famine hypotheses. The aims of the present work were to study if sucrose and/or saccharin could attenuate food restriction-induced hyperactivity, weight loss, increased plasma corticosterone, and activation of brain structures involved in neuroendocrine control, energy balance, physical activity, and reward signaling in rats. Its major findings are that access to sucrose, but not to saccharin, attenuated food restriction-induced running wheel activity, weight loss, rises in plasma corticosterone, and expression of the cellular activation marker c-Fos in the paraventricular and arcuate hypothalamus and in the nucleus accumbens. These findings suggest that the energy-richness and easy availability of sucrose interrupted a fleeing-famine-like hyperactivity response. Since corticosterone mediates food restriction-induced wheel running (Duclos et al., 2009), we propose that the attenuating effect of sucrose consumption on plasma corticosterone plays a role in reduced wheel running and weight loss by lowering activation of the nucleus accumbens and arcuate hypothalamus in these animals.

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1. Introduction

Increased physical activity is present in 30—80% of anorexia nervosa patients (Davis et al., 1994; Klein et al., 2007) and is generally considered as a strategy to lose weight. However, food restriction by itself can lead to increased physical activity in anorexia nervosa (Holtkamp et al., 2004). In addition, several reports indicate that increased physical activity is linked to a compulsive component (Davis et al., 1995; Holtkamp et al., 2003) suggesting that it is not under cognitive control. The interactions between low food intake and excessive physical activity can be addressed in animals using behavioral paradigms, known as activity-based anorexia (Burden et al., 1993) and food restriction-induced hyperactivity (Broocks et al., 1990; Duclos et al., 2005). In these paradigms, rodents with free access to food display spontaneous wheel running that is covered by energy intake, whereas animals for which access to food is limited in amount or in time engage in excessive running that leads to denutrition and ultimately to death (Siegfried et al., 2003).

To explain the paradox of low food intake and excessive exercise in humans and other animals, it has been proposed that increased physical activity along with food restriction activates brain reward circuits (Bergh and Sodersten, 1996; Fladung et al., 2010). The observations that high scores on addiction scales in anorexia nervosa patients are related to excessive exercising (Davis and Claridge, 1998; Klein et al., 2004) corroborate this reward-addiction hypothesis. Since food restriction is known to increase drug reward (Carr, 2007), it may well be that it also increases the reward of physical activity.

Alternatively, the fleeing-famine hypothesis postulates that refusal of known scarce energy-low or hard-to-assimilate food sources and hyperactivity facilitate migration towards new habitats that may contain new energy-rich or easily-assimilable foodstuffs (Guisinger, 2003). The occurrence of hyperactivity upon reduced energy availability in many animal species suggests that it represents an adaptive response. According to the fleeing-famine hypothesis, initial food restriction to lose weight in humans may activate brain structures underlying this phylogenetically old response and induce regular food refusal and hyperactivity, thus leading to further weight loss (Guisinger, 2003).

Free access to glucose attenuates food restriction-induced wheel running and weight loss in animals (Takeda et al., 2003). In addition, the reinforcement value of wheel running can be substituted to a certain extent by sucrose in food-restricted, but weight-stable, rats (Belke et al., 2006). Finally, limited access to a sweet and high-fat diet prevents food restriction-induced weight loss but without altering daily wheel running (Brown et al., 2008). These findings, however, can be explained both by the reward-addiction and by the fleeing-famine hypotheses, since glucose, sucrose and fat are both rewarding and energy-rich. Interestingly, wheel running decreases cocaine self-administration and *vice versa* (Cosgrove et al., 2002). Furthermore, the reinforcing value of cocaine can be substituted by the artificial energy-free sweetener saccharin (Lenoir et al., 2007). These observations led us to critically test the reward-addiction and fleeing-famine hypotheses by comparing the effects sucrose to those of saccharine on food restriction-induced wheel running.

The main aim of the present work was, therefore, to study if sucrose and/or saccharin could attenuate food restriction-induced hyperactivity and weight loss. Since we have previously shown that corticosterone mediates food restriction-induced hyperactivity (Duclos et al., 2009), we also measured its plasma concentrations and the cellular activation marker c-Fos in the paraventricular nucleus of the hypothalamus (PVH), known to control activity of the hypothalamus—pituitary—adrenal axis. Finally, we studied cellular activation in the nucleus accumbens and arcuate nucleus of the hypothalamus (ARH), two brain structures involved in reward signaling, physical activity and energy balance (Werme et al., 2002; Badman and Flier, 2005).

2. Methods

2.1. Animals

Experiments were conducted on 112 male Lewis rats (Charles River, l'Arbresle, France) known to be sensitive to food restriction-induced activity (Duclos et al., 2005). Four week-old animals were housed four per cage with *ad libitum* access to food (standard laboratory chow OA4; UAR, Villemoisson, France) and water at constant temperature (23—25 °C) and a 12 h light—dark cycle (lights on at 0700 h). They were left undisturbed for two weeks before being housed individually when their body weight reached 175—180 g. Experiments were conducted according to French and European recommendations on animal research (European Council Directive of 24 November 1986 (86/609/EEC)).

2.2. Experimental protocol

On day 1 of the experiment, after 14 days of habituation to the animal colony, rats were placed in individual cages and kept in a temperature (23—25 °C)- and light (lights on 0700—1900 h)-controlled room that housed all cages, running wheels and recording equipment necessary for the experiment. To address the effects of food restriction and running wheel activity, animals were housed individually and randomly assigned to one of the four experimental conditions: *ad libitum* access to food, but not to a running wheel (AL), *ad libitum* access to both food and a running wheel (ACT), food restriction in the absence of a running wheel (FR) and food restriction with access to a running wheel (FR-ACT). Rats in the FR-ACT group had access to the running wheel for 22.5 h during which they were food-deprived. During the remaining 1.5 h animals were locked out of the wheels and given free access to food starting at 1500 h. Animals in the FR group were given a daily food allowance corresponding to the meal of a previously assigned FR-ACT rat. The effects of sucrose or saccharin consumption were studied by providing half of the rats with a two-bottle choice consisting of plain water and 0.88 M sucrose (SUC) solution and the other half with plain water and 0.002 M saccharin (SAC) solution. Since saccharin is 300—500 times sweeter than sucrose (Wiet and Beyts, 1992) and the concentration of saccharin was 440-fold lower than that of sucrose, the saccharin and sucrose solutions used in the present study were comparably sweet. Thus, the experimental design included three independent variables each with two levels: (1) food intake: restricted or *ad libitum*