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The effect of high-fat diet consumption on appetitive instrumental behavior in rats

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ABSTRACT

Evidence now indicates that the chronic consumption of high-calorie foods, such as a high-fat diet (HFD), is associated with impaired control over food-seeking, yet the extent of this alteration is not fully understood. Using different reinforcement schedules, we evaluated whether HFD intake from weaning to adulthood modifies instrumental responding and induces a shift from goal-directed actions to habitual responding. We first observed reduced instrumental performance and motivation for a food reward in HFD-fed rats trained under schedules of reinforcement that facilitate habitual responding [Random Interval (RI)]. However, this deficit was alleviated if rats trained under RI were subsequently trained with reinforcement schedules that promote goal-directed strategies [Random Ratio (RR)]. Using an outcome devaluation procedure, we then demonstrated that consumption of a HFD promoted habitual behavior in rats trained under RI but not RR schedules. Finally, extended HFD exposure did not interfere with the ability of RR training to overcome impaired RI instrumental performance and to favor goal-directed behavior. These results indicate that chronic consumption of a HFD changes the co-ordination of goal-directed actions and habits and that alteration of food-seeking may be reversed under particular behavioral conditions.

1. Introduction

Extended consumption of palatable, energy-dense foods has recently been associated with a variety of undesirable effects on food-related behaviors, including deficits in learning about food-predictive cues (Reichelt, Morris, & Westbrook, 2014; Zhang, Manson, Schiller, & Levy, 2014), alterations in food motivation (la Fleur et al., 2007; Tracy, Wee, Hazeltine, & Carter, 2015) and resistance to changes in food value (Furlong, Jayaweera, Balleine, & Corbit, 2014; Horstmann et al., 2015; Kendig, Boakes, Rooney, & Corbit, 2013). Indeed, appropriate food-seeking in both humans and animals is modulated by the current motivational or incentive value of the food; increases in incentive value promote food-seeking actions whereas decreases inhibit this behavior. The effective control of eating behavior therefore requires that subjects can flexibly adapt their actions in response to fluctuations in the value of the food. A failure to adapt to changes in incentive value leads to inflexible, habitual food-seeking.

Recent evidence from studies in humans (Horstmann et al., 2015) and animals (Furlong et al., 2014; Kendig et al., 2013) indicate that high-fat diet (HFD) intake is associated with reduced sensitivity to the current food value. Specifically, rats with chronic restricted access to 10% sucrose (Kendig et al., 2013) or sweetened condensed milk (Furlong et al., 2014) during adulthood fail to selectively reduce their instrumental responding for a food that is no longer valuable. Importantly, in these studies, rats were trained to acquire the food-seeking response using a random interval (RI) schedule in which reinforcement occurs, on average, after *n* amount of time, contingent on a lever press. Such schedules of

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reinforcement are known to promote the development of habitual actions by minimizing the perceived correlation between behavior and reward (Dickinson, 1985). In contrast, random ratio (RR) schedules of reinforcement arrange that each response will be rewarded according to a fixed probability thus, a strong behavior-reward correlation is maintained throughout training. Ratio schedules therefore favor the execution of flexible, goal-directed behavior (Dickinson, 1985). At present, it is unclear how diet affects instrumental learning *per se* using different schedules of reinforcement. While some studies have reported no effect of diet on instrumental training (Furlong et al., 2014; Kendig et al., 2013) others have observed a decrease in performance for obese mice maintained on a HFD (Davis et al., 2008; Finger, Dinan, & Cryan, 2012; Harb & Almeida, 2014).

Here, we investigated the effect of chronic HFD intake from weaning to adulthood on food-seeking behaviors. First, we compared the effect of a HFD on instrumental learning using RI versus RR schedules of reinforcement and then assessed motivation on a progressive ratio task. Finally, we used RI and RR schedules, typically used to establish habitual versus goal-directed food-seeking respectively, to evaluate sensitivity to changes in food value.

2. Materials and methods

All experiments were conducted in agreement with the French (Directive 87–148, Ministère de l'Agriculture et de la Pêche) and international legislation (directive 2010–63, September 22, 2010, European Community) and were approved by the local ethics committee (agreement number 5012047-A).

2.1. Animals and diets

Male naïve Long-Evans rats (Janvier, France), aged 3 weeks on arrival, were housed in groups of two in polycarbonate cages in a climatized (22 ± 1 °C) room maintained under a 12 h light/dark cycle (lights on at 7:00 A.M). Rats had *ad libitum* access to food and water from arrival until the beginning of the behavioral procedures. The food provided was either a control diet (CD) offering 2.9 kcal/g (consisting of 2.5% lipids and 60% carbohydrate, mostly from starch; A04, SAFE, Augy, France) or a high-fat diet (HFD) offering 4.7 kcal/g [consisting of 24% lipids (45 kcal), mostly saturated fat from lard, and 41% carbohydrates (35 kcal); D12451, Research Diets, New Brunswick, NJ, USA]. Behavioral experiments began after 3 months (Experiments 1a, 1b and 2) or 6 months (Experiment 3) of diet exposure, starting at weaning. The duration of the HFD exposure was chosen based on our previous work (Boitard et al., 2012, 2014, 2015). Body weight was measured once per week from arrival. Rats were submitted to a food deprivation schedule five days before behavioral procedures and a sufficient amount of food (either CD or HFD) was made available to maintain them at approximately 90% of their *ad libitum* feeding weight.

2.2. Behavioral apparatus

All experimental phases took place in eight identical conditioning boxes (40 × 35 × 30 cm, Imetronic, Pessac, France) enclosed in sound and light-attenuating wooden chambers. The conditioning boxes were made of grey polyvinyl chloride on three sides and transparent Perspex on the opening face, with a stainless-steel grid floor (27 parallel 0.5 cm diameter stainless-steelbars; 1.5 cm apart) above a sawdust tray. Each chamber contained a ventilation fan producing a background noise of 55 dB and four light-emitting diodes on the ceiling for illumination of chamber. In the middle of the left wall, a magazine received food pellets (45 mg; Bioserv) from a dispenser located outside the operant chamber. The magazine was equipped with infrared cells to detect head entries. Each chamber was also equipped with a pump that was fitted with a syringe that, when activated, delivered a 20% sucrose solution (0.1 ml). During instrumental training and testing, a retractable lever could be inserted on either side of the magazines. All stimuli were delivered by a computerized interface (Imetronic) that also recorded lever presses.

3. Experiment 1a: impact of HFD intake on instrumental training under an interval schedule of reinforcement

3.1. Behavioral procedures

Behavioral experiments began after 3 months of diet exposure (CD: n = 14, HFD: n = 18). Before the experiments, rats were handled every day for 5 days. They were then given two 30 min magazine training sessions during which food rewards (grain-based pellets) were delivered on a random time 60 s schedule.

3.1.1. Random interval training

Each training session began with the illumination of the house light and insertion of an active and inactive lever. Twelve training sessions were given in total with two 30 min sessions per day, approximately 2 h apart. During the first session, each press on the lever resulted in the delivery of a grain food pellet. For the remaining 11 sessions, lever presses were rewarded according to a Random Interval 30 schedule (RI-30). Presses on the inactive lever were without consequence. Each session ended after 30 min, with a maximum of 60 rewards earned.

3.1.2. Progressive ratio

To assess whether the different pattern of lever pressing behavior observed in interval schedules in rats fed a HFD is also associated with altered motivation, a progressive ratio (PR) test was performed. In this test, the first press was reinforced and then the rat was required to increase its responses by three lever presses for each subsequent reward delivery. For example, an animal was rewarded after 1 press, then after 4 presses, 7 presses, and so on. The test ended after 60 min. The last completed ratio before the session ended was defined as the breaking point.

3.2. Plasma measurements of metabolic parameters

A subset of rats (CD: n = 10, HFD: n = 15) used for RI training and PR were sacrificed for metabolic analyses after the behavioral tests, that is, after 4 months of CD or HFD exposure. The metabolic status of the rats was evaluated by measuring plasma cholesterol, triglycerides, insulin, and leptin using specialised kits (cholesterol RTU and triglycerides enzymatique PAP 150; Biomerieux, France) or milliplex (rat serum adipokine kit; Millipore).

4. Experiment 1b: impact of HFD intake on instrumental training under a ratio schedule of reinforcement

Experiment 1A demonstrated that HFD intake impairs instrumental performance under interval schedules of reinforcement. Here, we investigated if a similar impairment is observed when rats were subsequently trained on a ratio schedule of reinforcement, where the correlation between behavior and reward is greater. Two groups of rats were first trained as above on an interval schedule of reinforcement (CD: n = 13, HFD: n = 16). Then, rats received random ratio (RR) training followed by a PR test.