Appetite 103 (2016) 29–37

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Repeated transcranial direct current stimulation reduces food craving in Wistar rats

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ARTICLE INFO

Article history:
Received 23 April 2015
Received in revised form
8 March 2016
Accepted 9 March 2016
Available online 10 March 2016

Keywords:
Craving
Palatable food
Prefrontal cortex
Transcranial direct current stimulation

ABSTRACT

It has been suggested that food craving—an intense desire to consume a specific food (particularly foods high in sugar and fat)—can lead to obesity. This behavior has also been associated with abuse of other substances, such as drugs. Both drugs and food cause dependence by acting on brain circuitry involved in reward, motivation, and decision-making processes. The dorsolateral prefrontal cortex (DLPFC) can be activated following evocation and is implicated in alterations in food behavior and craving. Transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique capable of modulates brain activity significantly, has emerged as a promising treatment to inhibit craving. This technique is considered safe and inexpensive; however, there is scant research using animal models. Such studies could help elucidate the behavioral and molecular mechanisms of eating disorders, including food craving. The aim of our study was to evaluate palatable food consumption in rats receiving tDCS treatment (anode right/cathode left). Eighteen adult male Wistar rats were randomized by weight and divided into three groups (n = 6/group): control, with no stimulation; sham, receiving daily 30 s tDCS (500 μA) sessions for 8 consecutive days; and tDCS, receiving daily 20 min tDCS (500 μA) sessions for 8 consecutive days. All rats were evaluated for locomotor activity and anxiety-like behavior. A palatable food consumption test was performed at baseline and on treatment completion (24 h after the last tDCS session) under fasting and feeding conditions and showed that tDCS decreased food craving, thus corroborating human studies. This result confirms the important role of the prefrontal cortex in food behavior, which can be modulated by noninvasive brain stimulation.

1. Introduction

Palatable foods rich in fat/sugar can trigger an irresistible motivation for consumption known as “food craving”. This behavior can lead to the activation of the reward region in the brain (Murdaugh, Cox, Cook, & Weller, 2012). The dorsolateral prefrontal cortex (DLPFC) may be activated when an individual is given cues that trigger reward memories associated with certain consumptive behaviors inducing craving (Anton, 1999a, 1999b). Imaging studies have shown that the DLPFC is related to cognitive regulation of motivation to eat (Yoshikawa, Tanaka, Ishii, Fujimoto, & Watanabe, 2014). Moreover, deficient prefrontal cortical inhibitory networks have been associated with food craving (Alonso-Alonso & Pascual-Leone, 2007). However, the role of the prefrontal cortex in regulating craving has yet to be fully elucidated.

Human studies suggest that food craving could be a predictor of relapse or weight regain in obese patients, including those who undergo bariatric surgery for weight loss (Budak et al., 2010; Odom et al., 2010). In addition, individuals with intense food craving are more likely to be overweight and/or develop eating-related disorders (Sullivan, Gendall, Bulik, Carter, & Joyce, 1998). Positron emission tomography has shown that food and drug craving have

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http://dx.doi.org/10.1016/j.appet.2016.03.014
0195-6663/

similar neurobiological mechanisms (Wang, Volkow, Telang et al., 2004; Wang, Volkow, Thanos, & Fowler, 2004), which indicates that eating control originates in neural networks associated with decision-making (Pignatti et al., 2006). The above studies underscore the relevance the involvement of prefrontal cortex subregions in food craving, evidence suggests that medial prefrontal cortex is involved in reward processing, while lateral prefrontal cortex is involved in decision-making, and orbitofrontal cortex in behavioral inhibition (for a review, see (Perry et al., 2011). Although several factors can influence the decision of food consumption, one possible approach to regulate food craving might be to interfere with this decision making process by altering the activity of the dorsolateral prefrontal cortex (DLPFC) (Fregni et al., 2008). It is interesting to note that prefrontal cortex is an important nexus where reward seeking and inhibitory control processes are integrated (Kalivas & Volkow, 2005).

Transcranial direct current stimulation (tDCS) is a non-invasive technique that has emerged as a promising treatment for craving. The importance this technique is that consists of applying a weak, direct, constant and low intensity electric current. The treatment with tDCS is painless, and has been used to treat chronic pain syndromes (DosSantos et al., 2012) and many neuropsychiatry disorders (Brunoni et al., 2012). The mechanisms by which tDCS induces changes across different levels of the nervous system may involve membrane polarization and, consequently, the modulation of neuronal activity (Hunter, Coffman, Trumbo, & Clark, 2013). Moreover, the effects of tDCS on cortical excitability are polarity-dependent. Classically, anodal tDCS enhances, while cathodal tDCS diminishes cortical excitability, within certain parameters of stimulation duration and strength (Nitsche et al., 2003; Nitsche & Paulus, 2000, 2001). An interesting issue is that tDCS modifies not only the activity of cortical areas located directly under the electrodes, but also from distant areas possibly due to primary interconnections (Lang et al., 2005). Many studies using rats have demonstrated the effects of tDCS on memory, Parkinson's disease, and focal epilepsy models (Dockery, Liebetanz, Birbaumer, Malinowska, & Wesierska, 2011; Li, Tian, Qian, Yu, & Jiang, 2011; Liebetanz, Nitsche, Tergau, & Paulus, 2002). Additionally, previous studies of our research group using rats confirmed immediate and long-lasting effects of tDCS treatment on chronic inflammation (Laste et al., 2012) and hyperalgesia induced by chronic restraint stress models (Spezia Adachi et al., 2012). Furthermore, studies in humans have shown that anodal tDCS in the DLPFC (anode right/cathode left) can suppress food craving (Fregni et al., 2008) and enhance the ability to resist foods in healthy subjects during and shortly after treatment (Kekic et al., 2014). However, there is scant animal model research using tDCS in food craving. Studies of this nature could help elucidate the behavioral and molecular mechanisms of eating disorders, including craving. In addition, the ethical impossibility of studying tissue levels of biochemical markers reinforces the need for animal models. To the best of our knowledge, the present study is the first to use rats in animal models of craving.

Several brain regions are related to food intake, but the hypothalamus is the brain structure responsible for the integration of central and peripheral signaling (Schwartz, 2006) and the homeostatic control of food intake (Vucetic et al., 2010). Various hormones and peptides such as leptin, insulin, and neuropeptide Y can modulate hypothalamic activity on food control (Schwartz, 2006). Brain-derived neurotrophic factor (BDNF), a brain neurotrophin, has been reported to play an important role in regulating energy metabolism and feeding behavior (Noble, Billington, Kotz, & Wang, 2011). A recent study by our group has demonstrated that palatable food intake and/or obesity results in decreased BDNF levels (Macedo et al., 2015), which corroborates other studies showing that a reduction in the levels of this neurotrophin can lead to obesity and hyperphagia (Kernie, Liebl, & Parada, 2000; Maekawa et al., 2013; Yi, Heppner, & Tschop, 2011).

In addition, a number of studies have indicated that tDCS can suppress food craving in humans (Fregni et al., 2008), although those studies provided little information regarding the underlying brain mechanism involved. In view of this, the current study was designed to investigate, in an animal model, whether consecutive tDCS sessions would increase the ability to resist foods by reducing food craving. The behavioral parameters herein evaluated were locomotor and exploratory activity, anxiety-like behavior and palatable food consumption test. The objectives of our study were 1) to evaluate the efficacy of eight consecutive tDCS sessions in reducing food craving and 2) to assess the effects of tDCS on brain plasticity in hypothalamic regions regulated by BDNF expression.

2. Materials and methods

2.1. Animals

Eighteen 60-day-old male Wistar rats (weight, 200–250 g) were randomized by weight prior to experiment initiation and housed in 49 × 34 × 16 cm polypropylene cages. The rats were maintained on a standard 12-h light-dark cycle (lights on at 7:00 a.m. and lights off at 7:00 p.m.) in a temperature-controlled environment (22 ± 2 °C), and had access to water and chow *ad libitum*. All experiments and procedures were approved by the institutional Animal Care and Use Committee (GPPG-HCPA protocol No. 110455) and conducted in compliance with Brazilian laws (Brasil, 2008; MCTI, 2013a; MCTI, 2013b) and the Laboratory Guide For The Care And Use Of Animals (The National Academies Press, Eighth Edition, 2011). The husbandry of the animals followed Law No. 11794 (Brazil), which regulates the scientific use of animals. Vigorous attempts were made to minimize animal suffering and decrease external sources of pain and discomfort, as well as to use the minimum number of animals required to produce reliable scientific data. The rats were divided in three animals per cage and acclimated to the vivarium for one week before beginning treatment.

2.2. Experimental design

As shown in Fig. 1, after the acclimation period, the animals were randomly selected for weight and length measurements and subsequently allocated into three groups (n = 6/group): control (CT), sham stimulation (Sham), and transcranial direct current stimulation (tDCS). Before exposure to treatment, the rats were exposed to the open-field apparatus to evaluate locomotor and exploratory activity, and anxiety-like behavior was evaluated on a plus-maze and had access to palatable food during five days for food learning. Forty-eight hours after the learning period, the rats were subjected to a baseline palatable food consumption test. Subsequently, the experimental groups received either active or sham tDCS treatment for eight consecutive days. Twenty-four hours after the last treatment session, all animals underwent a final palatable food consumption test and were killed. The hypothalamus was removed for subsequent analysis of BDNF levels.

2.3. Blinding

To control for possible measurement bias, a number of steps were taken. The hair of all animals across the three groups was shaved in the area of electrode placement. In addition, the researchers responsible for the behavioral ratings were blinded to the numbers assigned to the test boxes, which was done by a third researcher. Therefore, it was impossible for the investigators to distinguish the groups receiving active tDCS treatment from the