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The Effect of Depo Medroxyprogesterone Acetate (DMPA) on Cerebral Food Motivation Centers: A Pilot Study using Functional Magnetic Resonance Imaging

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Abstract

Objective: The primary objective is to examine activation of food motivation centers in the brain before and 8 weeks after depo medroxyprogesterone acetate (DMPA) administration.

Study design: This prospective experimental pilot study examined the effects of DMPA on food motivation centers utilizing functional magnetic resonance imaging (fMRI) in eight nonobese, ovulatory subjects. fMRI blood oxygen level dependent (BOLD) signal was measured using a 3-Tesla Scanner while participants viewed images of high-calorie foods, low-calorie foods and nonfood objects. fMRI scans were performed at baseline and 8 weeks after participants received one intramuscular dose of DMPA 150 mg. fMRI data were analyzed using the FMRIB Software Library. Changes in adiposity and circulating leptin and ghrelin levels were also measured.

Results: There was a greater BOLD signal response to food cues in brain regions associated with food motivation (anterior cingulate gyrus, orbitofrontal cortex) 8 weeks after DMPA administration compared to baseline ($z>2.3$, $p<.05$ whole-brain analysis clustered corrected). No statistically significant change was detected in circulating leptin or ghrelin levels or fat mass 8 weeks after DMPA administration.

Conclusion: Analysis of differences in food motivation may guide the development of interventions to prevent weight gain in DMPA users.

Implications: These data support a neural origin as one of the mechanisms underlying weight gain in DMPA users and may guide future research examining weight gain and contraception.

Keywords: DMPA; MRI; Cerebral food motivation centers; Weight gain

1. Introduction

Depo-medroxyprogesterone acetate (DMPA) is a contraceptive method used worldwide by millions of women. According to the 2006–2008 National Survey of Family Growth, 22% of American women between 15 and 44 years of age who have ever been sexually active have used DMPA; however, weight gain is a common complaint among DMPA users with approximately 2.1% of users discontinuing this method due to weight increase [1,2]. Studies of weight gain and DMPA have shown mixed results. Prospective controlled studies evaluating weight gain in normal weight women showed no relationship between DMPA use and energy intake, energy expenditure or body weight [3,4]. Other studies reported substantial mean weight gain with DMPA [5–9].

DMPA-associated weight gain has been demonstrated to be due to an increase in fat mass; however, the mechanism of action is unknown [10]. It is hypothesized that DMPA may contribute to weight gain by an action similar to glucocorticoids. The androgenic action of DMPA exerts an anabolic effect on lean mass and may regulate fat deposition, particularly in the abdominal region [10–12].

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Neural mechanisms are central to the regulation of motivationally mediated behaviors, thus the increasing concern surrounding the dramatic rise of obesity has led to research aimed at understanding the neural substrates of appetitive function in humans. The role of the hypothalamus in food motivation is well established [13,14]. Recently, the corticolimbic system which comprises the reward circuitry in the brain has become increasingly implicated in normal appetite as well as abnormal food intake and obesity [12]. Eating palatable food increases activation in regions implicated in reward. Previous studies have demonstrated that hyperresponsivity of reward regions to palatable food images, palatable food television commercials and pictorial cues that predict impending palatable food receipt were predictive of future weight gain [13–15]. Obese compared to normal-weight individuals have greater brain reward activation to visual food cues, especially appetizing, high-calorie foods [16]. The evidence that elevated reward region responsivity to various food cues correlates with future weight gain provides behavior support for association of these reward centers to weight gain.

As regulation of eating behavior spans the range of nonconscious and conscious events, it is believed that functional magnetic resonance imaging (fMRI) provides an increasingly important tool for investigating how different regions of the brain control normal and abnormal eating behaviors. The brain regions that have been implicated in food motivation in previous fMRI studies include the prefrontal cortex, lateral and medial orbitofrontal cortex, anterior cingulate, insula, hippocampus, amygdala, nucleus accumbens (ventral striatum) and fusiform [17–20]. In a study performed in 13 healthy normal-weight adult women, images of high-calorie foods yielded significant activation on fMRI within the hypothalamus, thalamus, corpus callosum and cerebellum compared with images of low-calorie foods [21]. It has been well documented that food ingestion changes during the menstrual cycle, with food intake reaching a nadir around the time of ovulation when estrogen is elevated and progesterone is low and increases following ovulation when progesterone is dominant [22,23].

To date, there are no studies evaluating neuroimaging and food motivation changes associated with use of DMPA or any other type of contraception. Our study aimed to examine a potential central nervous system mechanism for weight gain associated with DMPA use. We hypothesized that the use of DMPA in women alters the brain response to food imaging stimuli and specifically increases activation of areas of the brain responsible for food motivation.

2. Materials and methods

2.1. Study design and participants

This prospective, experimental pilot study was performed on healthy, nonobese right-handed females. Participants were recruited through Internet advertising and at the Los Angeles County/University of Southern California Medical Family Planning clinic. Women between the ages of 18 to 45 years, with a body mass index (BMI) >18.5 and <30 kg/m^2, ovulatory based on a day-21 serum progesterone, who desired to use DMPA were included in the study. Women were excluded if they had a history of psychiatric disorders, any major weight changes in the past 3 months or history of bariatric surgery. In addition, women with prior DMPA use in the last 6 months or other hormonal contraception in the past 3 months, history of diabetes mellitus or currently pregnant were excluded. This study was approved by the Institutional Review Board of the University of Southern California in Los Angeles, California. All participants signed an informed consent prior to enrolling in the study.

2.2. Study procedures

Participants completed a baseline study visit, including a fasting blood draw, measurement of body weight, height, total body fat and an fMRI scan. Participants subsequently received 150-mg im dose of DMPA on the same day. Eight weeks after DMPA administration, participants returned for a follow up visit that included a fasting blood draw, measurement of weight, height, total body fat and an fMRI scan.

All participants had normal to corrected-to-normal vision, were fasting for at least 8 h and were unaware of the food-related nature of the experiment prior to viewing of the stimuli in the scanner. Prior to the scan, participants viewed a slideshow on a computer to become accustomed to the fMRI and the tempo of the images. No images in the slideshow were included in the paradigm, and all sample images were of animals instead of foods to avoid habituation.

2.3. Imaging methods

Each participant had two fMRI sessions (baseline and 8 weeks post-DMPA) with a block design visual stimulus presentation of the three stimulus categories: high-calorie foods, low-calorie foods and nonedible objects. Functional imaging data were acquired using a GE 3 T MRI system located at the USC Health Science Campus at baseline during the participants' luteal phase prior to receiving the DMPA injection and again 8 weeks after DMPA administration. During the fMRI, head motion was minimized by placement of comfortable foam padding around the head. For each participant, anatomical sagittal images ($256\times256\times174$) of 1-mm^3 isotropic spatial resolution were obtained using a 3D FSPGR BRAVO-sequence (TR = 8.86 ms, TE = 3.52 ms, flip angle = 13°). Blood oxygen-level dependent (BOLD) activity was measured with a T2*-weighted echo planar imaging sequence (TR = 2500 ms, TE = 30 ms, flip angle = 90°, inplane resolution = 1.875 mm × 1.875 mm, slice thickness = 3.5 mm with 0.5 mm gap).