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The impact of short-term depot-medroxyprogesterone acetate treatment on resting metabolic rate☆

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Abstract

Objective: This study examines the effect of a progestogen (depot-medroxyprogesterone acetate, DMPA) on resting metabolic rate (RMR) in a cohort of young, normal-weight healthy women. We hypothesize an increase in RMR and nonshivering thermogenesis (NST) resulting in increased body temperature by DMPA.
Study design: We performed a prospective cohort study in 13 subjects tested at baseline, 3 weeks and 9 weeks after 150 mg intramuscular DMPA administration. RMR was determined with indirect calorimetry. Secondary endpoints included changes in body mass index (BMI), body composition, temperature and serum levels of estradiol (E2), luteinizing hormone (LH), progesterone and MPA.
Results: The percent change in RMR from baseline to week 3 (9%) was significantly higher than the percent change from baseline to week 9 (1.6%) ($p = .045$). The greatest percent change from baseline to week 3 compared to baseline to week 9 was seen in women initiating DMPA in the luteal phase of the cycle. Hypothalamic-pituitary-ovarian axis was evident by decreases in E2, LH and progesterone. DMPA resulted in increased body temperature with a significant correlation between the change in body temperature and the change in RMR. No change in body composition was seen.
Conclusions: RMR and NST increased in young healthy women with normal BMI 3 weeks after receiving the initial dose of 150 mg DMPA for contraception. The effect was augmented when the drug was administered during the luteal phase of the menstrual cycle.
Implication: DMPA increases RMR and thermogenesis independent of changes in body mass. An increase in weight with chronic DMPA may result from a combination of hyperphagia and abnormal NST in predisposed individuals.

Keywords: Progestin; Depot-medroxyprogesterone acetate; Resting metabolic rate; Mitochondrial activity

1. Introduction

Several studies of premenopausal women demonstrate an increase in resting metabolic rate (RMR) during the luteal phase of the menstrual cycle, when estradiol (E2) and progesterone levels are elevated, suggesting a role for sex steroids in the regulation of RMR [1–3]. RMR is lower in anovulatory women with hypothalamic dysfunction [4] and higher in pregnancy, especially in the second and third trimesters, with return to prepregnancy levels by 4–6 weeks postpartum [5]. These physiological situations correlate with serum levels of progesterone, being low with anovulation and high in pregnancy. While each of these studies suggests an association between RMR and progesterone levels, alternative explanations inherent to the luteal phase, pregnancy and differing study populations do exist. Additionally, exact mechanisms whereby progesterone may increase RMR are not well established. For example, does an effect by progesterone require the presence of an elevated E2 level? To further evaluate the role of progesterone in modulation of RMR, we investigated healthy, normal-weight young women initiating treatment with parenteral depot-medroxyprogesterone acetate (DMPA) for contraception. We hypothesized that DMPA would increase RMR and nonshivering thermogenesis (NST). DMPA is a potent progestin with a nuclear receptor binding

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affinity of at least twice that of progesterone, a half-life of approximately 50 days and a time to maximum concentration of approximately 3 weeks [6]. It was chosen due to its routine use as a contraceptive, thus negating the need for an investigational drug application and the need for only one injection for the study as opposed to using parenteral progesterone. In addition, DMPA has less absorption variability compared to oral preparations, and it lacks androgen receptor activation seen with progestins derived from 19-nortestosterone.

2. Materials and methods

2.1. Subjects

We enrolled 22 young, healthy women desiring DMPA for contraception. Of these, 17 initiated testing and 13 completed all three sessions. Two of the dropouts were lost to follow-up and the other two were discovered to be pregnant during the study period. We determined recruitment qualifications a priori. Inclusion criteria were age 18–35 years and body mass index (BMI) 20–35 kg/m^2. Exclusion criteria were pregnancy within the previous 6 months, hypertension, thyroid disease, impaired glucose tolerance, use of tobacco or other metabolism-altering drug, planned dietary change during the study period and use of any long-acting hormonal contraceptive within the preceding 9 months or oral contraceptive within the preceding 1 month.

2.2. Design

The Duke Institutional Review Board approved this prospective cohort study. After informed consent, subjects underwent baseline testing, DMPA (Depo-Provera CI; Pfizer Inc., New York, NY, USA) injection and follow-up testing 3 and 9 weeks later. All sessions took place at the same facility, each lasting approximately 1 h, the morning after an overnight fast.

2.3. Outcomes

We considered the primary outcome as longitudinal change in RMR from baseline to week 3 to week 9. Secondary outcomes included longitudinal change in body composition (lean/fat mass), serum E2, luteinizing hormone (LH), P4 and MPA, as well as body temperature, body weight, BMI, blood pressure and pulse.

2.4. Anthropometrics

At the baseline session, we measured subject height to the nearest 0.25 cm. At the beginning of all sessions, body weight was determined in light clothing and without shoes to the nearest 0.1 kg on a digital scale (Scale 5005; ScaleTronix Inc., Wheaton, IL, USA). Body temperature to the nearest 0.1 °F, blood pressure and pulse were recorded using a Dinamap Procare 200 (GE Healthcare, Fairfield, CT, USA).

2.5. RMR

We assessed RMR by indirect calorimetry using a ventilated hood system (TrueMax 2400 Metabolic Cart; Parvomedics, Sandy, UT, USA) in a quiet, darkened, temperature-controlled room. Gas calibration and flow meter calibration were performed at the start of each session. We measured oxygen consumption and carbon dioxide production per minute, for 40 min, with the subject at complete rest. A technician ensured wakefulness. The final 5 min of data was averaged (a common nadir) and RMR was calculated using the Weir formula: $[3.09 \times VO_2 + 1.1 \times VCO_2] \times 1.44$ where VO_2 is the volume of oxygen uptake (mL/min) and VCO_2 is the volume of carbon dioxide output (mL/min) [7].

2.6. Body composition

We measured body composition by air-displacement plethysmography using a Bod Pod (Life Measurement, Inc., Concord, CA, USA) at the first and last testing sessions to gauge fluctuation in lean and fat body mass. The subject first removed all jewelry and changed into tight-fitting spandex athletic shorts and top and a tight-fitting cap to compress the head hair. In-unit testing time was approximately 5 min. Bod Pod calibration, technique and corrections for thoracic gas volume and surface area artifact were conducted as previously described [8]. Intradevice coefficient of variation (CV) and interdevice standard error of estimate are reported to be 1.7% and 1.1%, respectively [9]. All calculations were performed by Bod Pod software, version 1.69.

2.7. Hormonal assays

Serum or plasma was stored at −80°C until batch testing. We determined E2, LH and progesterone levels by automated immunoassay using a mini VIDAS (Biomerieux, Marcy l'Etoile, France). Assay sensitivity and intraassay and interassay CV values for each hormone are as follows, respectively: E2, 9 pg/mL (33 pmol/L), 2.2–7.5% and 3.2–9.5%; LH, 0.1 mIU/mL, 2.7–4.6% and 3.7–6.6%; and progesterone, 0.25 ng/mL (0.79 nmol/L), 3.8–14.3% and 3.1–24.3%. We measured MPA levels by proprietary radioimmunoassay following extraction with ethyl acetate:-hexane (3:2) and subsequent Celite column partition chromatography, with intraassay and interassay CV of 3–11% and 10–13%, respectively. Thyroid-stimulating hormone (TSH) level was determined by automated chemiluminescent immunoassay using a Beckman Unicel DXI 800 (Beckman Coulter, Inc., Brea, CA, USA) with sensitivity 0.015 μIU/mL and intraassay and interassay CV 2.5–5.8% and 2.8–8.9%, respectively.

2.8. Statistical analysis

We analyzed data for the 13 subjects that completed all three testing sessions with IBM/SPSS ver 22. Longitudinal change in mean outcome and covariate values between time points was analyzed using repeated measures analysis of