Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study

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Objective: To evaluate emotional processing in women with insulin-resistant polycystic ovary syndrome (IR-PCOS) and its relationship to glucose regulation and the mu-opioid system.
Design: Case-control pilot.
Setting: Tertiary referring medical center.
Patient(s): Seven women with IR-PCOS and five non-insulin-resistant controls, aged 21–40 years, recruited from the general population.
Intervention(s): Sixteen weeks of metformin (1,500 mg/day) in women with IR-PCOS.
Main Outcome Measure(s): Assessment of mood, metabolic function, and neuronal activation during an emotional task using functional magnetic resonance imaging (fMRI), and mu-opioid receptor availability using positive emission tomography (PET).
Result(s): We found that insulin-resistant PCOS patients [1] had greater limbic activation during an emotion task than controls (n = 5); [2] trended toward decreased positive affect and increased trait anxiety; [3] after metformin treatment, had limbic activation that no longer differed from controls; and [4] had positive correlations between fMRI limbic activation during emotional processing and mu-opioid binding potential.
Conclusion(s): Patients with IR-PCOS had greater regional activation during an emotion task than the controls, although this resolved with metformin therapy. Alterations in mu-opioid neurotransmission may underlie limbic system activity and mood disorders in IR-PCOS.
Clinical Trial Registration Number: NCT00670800. (Fertil Steril® 2013;100:200–7. ©2013 by American Society for Reproductive Medicine.)
Key Words: Emotion, functional magnetic resonance, insulin resistance, imaging (fMRI), mu-opioid neurotransmission, polycystic ovary syndrome (PCOS)

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Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting approximately 10% of reproductive aged women, is characterized by hyperandrogenism and menstrual disorders (1, 2). Women with PCOS are at increased risk for mood and metabolic disorders, with insulin resistance (IR) found in up to 70% of women with PCOS (3, 4). A recent study by Rassi et al. (5) showed that up to 60% of women with PCOS met the diagnostic criteria for major depression, bipolar disorder, and/or anxiety disorder. Although that study

did not report the prevalence of insulin resistance in their study population, women with diabetes mellitus were excluded. The relationship between PCOS and mood disorders is likely complex, and the pathogenesis is poorly understood.

Neurotransmitters, including opioids, mediate the neuromodulatory effects of insulin; animal studies have demonstrated β-endorphin immunoreactivity in up to 90% of cells with insulin receptors (6, 7). Hyperinsulinemia increases oxidative stress and induces an inflammatory state, compromising neuronal and glial survival, which may be associated with the affective symptoms seen in mood disorders (8). Several studies have found an increased incidence of type 2 diabetes in depressed individuals (9), and insulin-resistant individuals show decreased cortical excitation in response to insulin (10). Other central effects of insulin resistance include altered catecholamine reuptake, turnover, and transport (11). Also, common pathways exist for insulin signaling and pharmacotherapy of certain mood disorders, with insulin-sensitizing drugs alleviating mood symptoms in insulin-resistant and diabetic individuals (10, 12).

Altered central endogenous mu-opioid receptor mediated neurotransmission may underlie the relationship between insulin metabolism and mood. Opioid system dysfunction and metabolic disorders, conditions that are associated with PCOS, have been independently linked to mood disorders. Kennedy et al. (13) detected altered mu-opioid neurotransmission in depressed women as compared with healthy control women. We recently reported that women with insulin-resistant PCOS (IR-PCOS) had greater mu-opioid receptor binding potential than control women in the nucleus accumbens, bilaterally, and the left amygdala, which resolved after treatment with metformin (14).

Our current study evaluates emotional processing and its relationship to the opioid system and glucose regulation in women with IR-PCOS. Functional magnetic resonance imaging (fMRI) activation patterns during an emotional processing task were compared between non-IR controls and women with IR-PCOS, both at baseline and after treatment with an insulin-sensitizing drug, metformin. Functional MRI activation patterns were additionally correlated to mu-opioid receptor binding potential using positron emission tomography (PET) in conjunction with [^{11}C]carfentanil, a selective mu-opioid receptor radiotracer. We hypothesized that [1] fMRI activation patterns would differ between the women with IR-PCOS and the non-IR controls in emotion processing regions, [2] treatment with metformin would improve mood measures and normalize activation patterns, and [3] fMRI activation patterns would be associated with mu-opioid receptor availability in limbic brain regions.

MATERIALS AND METHODS

Beginning in January 2008, we screened 21 women (10 with IR-PCOS and 11 control women) from the general population in southeast Michigan for possible enrollment in the pilot case-control study. We included only women who were healthy, right-handed, nonsmokers between 21 and 40 years of age, with no history of significant medical comorbidities (including depression or diabetes). Participants were excluded if they had contraindications to fMRI, were pregnant within 6 months of the start of the study, had a history of substance abuse, used centrally acting medications or corticosteroids, or if they had used hormones within 2 months of the start of the study. We used the National Institutes of Health (NIH) criteria of menstrual irregularity and hyperandrogenism for the PCOS diagnosis because a higher metabolic risk has been seen with these diagnostic criteria (2, 15). Insulin resistance was defined as a homeostasis model assessment (HOMA2)—Glycemia (mmol/L) $\times$ Insulinemia (μIU/mL)/22.5—sensitivity of $\leq$60%. Non-PCOS controls had regular menstrual cycles with no clinical or laboratory evidence of hyperandrogenism and a HOMA2 sensitivity of $\geq$80%.

After we had screened 21 women, 14 women (7 IR-PCOS and 7 control) were enrolled in the study. Three women were excluded for metabolic testing results (one IR-PCOS and two controls), and four women were excluded for abnormal neuropsychiatric screens (two IR-PCOS and two controls). Two controls were excluded from the analysis for insulin resistance, and one woman with IR-PCOS was excluded from the PET analysis for incomplete imaging data.

We used the Beck Depression Inventory (BDI) (16) and the State-Trait Anxiety Inventory (STAI) (17) to measure depressive and anxiety symptoms, respectively. To assess the affective state, we used the Positive and Negative Affect Schedule (PANAS) (18) and the Profile of Mood States (POMS) (19).

The study procedures were approved by the University of Michigan institutional review board and the Radiation Safety Review Committee (HUM00008330), and written informed consent was obtained from all participants. We obtained medical histories and performed physical examinations (including assessing body mass index [BMI], a potential confounder) for each woman. We also measured each woman's levels for fasting glucose, insulin, 2-hour 75-g dextrose oral glucose tolerance test (OGTT) (potential predictors), free and total testosterone (T) (potential confounders), dehydroepiandrosterone sulfate (DHEAS), lipids, blood count, thyroid-stimulating hormone (TSH), electrolytes, and liver enzymes.

To assess outcomes, the women underwent one (controls) or two (women with IR-PCOS) fMRI and PET scans with [^{11}C] carfentanil, during the follicular phase if they were cycling. The PET scan (HR^{+} scanner; Siemens) was in three-dimensional mode (reconstructed full-width/half-maximum resolution, approximately 5.5 mm in plane and 5.0 mm axially), with the septa retracted and scatter correction, during which 28 frames of increasing duration (from 30 seconds to 10 minutes) were collected.

The specific mu-opioid receptor radiotracer [^{11}C]carfentanil was administered in subpharmacologic tracer quantity (10–15 mCi, less than 0.03 μg/kg total mass) via an antecubital intravenous line (50% in initial bolus, and the remainder continuously infused to achieve constant plasma concentrations). We synthesized [^{11}C]carfentanil at high specific