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Testosterone administration attenuates regional brain hypometabolism in women with anorexia nervosa

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Abstract

Abnormalities in brain metabolism have not been consistently well localized in anorexia nervosa (AN), and effects of specific therapies on these functional abnormalities have not been studied. Androgen replacement therapy improves mood, well-being and cognitive function in men with androgen deficiency. We therefore hypothesized that women with AN and relative androgen deficiency would exhibit regional brain hypometabolism compared with healthy controls, and that low-dose physiologic androgen replacement would attenuate the hypometabolism in some of these brain loci. We used FDG PET and statistical parametric mapping methods to investigate regional brain glucose metabolism in (1) 14 women with AN and 20 healthy control subjects of similar mean age and (2) women with AN after randomization to low-dose replacement testosterone therapy or placebo. Cerebral metabolism was decreased in the posterior cingulate, pregenual anterior cingulate, left middle temporal, right superior temporal, and left dorsolateral prefrontal cortex in the AN group compared with controls. In AN patients receiving testosterone, cerebral metabolism increased in the posterior cingulate, subgenual anterior cingulate, premotor cortex, right caudate and right parietal lobes. In conclusion, our data demonstrate distinct loci of regional brain hypometabolism in women with AN compared with controls. Moreover, abnormalities in one of these regions—the posterior cingulate cortex—were attenuated towards normal with low-dose testosterone replacement therapy. Further study is warranted to replicate these findings, as well as to determine their physiological and clinical significance.

Keywords: Androgens; Posterior cingulate gyrus; Positron emission tomography; Women's health; Eating disorders

1. Introduction

Anorexia nervosa (AN), with a prevalence of 0.5–1% of college-age women (Jones et al., 1980; Lucas et al., 1991; Pope et al., 1984; Wakeling, 1996), is a

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psychiatric disorder characterized by self-starvation, impaired body image and amenorrhea (DSM-IV). Neuroimaging studies have demonstrated structural and functional brain abnormalities in women with AN. Structural findings include a generalized decrease in brain volume (Husain et al., 1992; Katzman et al., 1996), which has been shown to normalize with weight gain (Golden et al., 1996; Katzman et al., 1997; Swayze et al., 2003). Functional abnormalities have been identified using positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) in small numbers of patients. PET studies have demonstrated decreased cerebral glucose metabolism in the parietal (Delvenne et al., 1995, 1996, 1997) and superior frontal cortices (Delvenne et al., 1995, 1996) and increased metabolism in the caudate nuclei (Delvenne et al., 1996, 1999; Herholz et al., 1987; Krieg et al., 1991) and inferior frontal cortex (Delvenne et al., 1996, 1999). In addition, cerebral activity has been shown to normalize with weight gain in these patients (Delvenne et al., 1996; Herholz et al., 1987). One small study has suggested a possible role for the anterior cingulate gyrus (Naruo et al., 2001). Exposure to high caloric food stimuli has been shown to cause greater activation within the anterior cingulate gyrus in two studies (Ellison et al., 1998; Uher et al., 2003) and left occipital cortex and right temporo-occipital cortex in another study of young women with AN compared with control subjects (Gordon et al., 2001). However, to our knowledge, the effects of specific therapies on functional abnormalities in AN have not been studied.

Women with AN are at risk for androgen deficiency (Monteleone et al., 2001; Soyka et al., 1999). Although testosterone levels in women are only one-tenth those of men, testosterone deficiency in women may be associated with similar effects. Hypogonadism in men is characterized by depression (Burris et al., 1992; Seidman and Rabkin, 1998; Shores et al., 2004), diminished libido (Bagatell et al., 1994) and poor quality of life (Howell et al., 2000). Moreover, testosterone administration reverses many of these abnormalities (Janowsky et al., 1994; Wang et al., 1996). For example, Grinspoon et al. (2000) reported that testosterone administration in hypogonadal men with HIV-associated weight loss improved indices of depression. In addition, testosterone administration may result in improvement of psychiatric symptoms in men with refractory depression (Perry et al., 2002; Pope et al., 2003; Seidman and Rabkin, 1998).

Although few studies have examined the effects of low-dose androgen therapy in women, the available data suggest that administration of testosterone or testosterone precursors, including DHEA, may result in improvements in libido, mood and well-being in women with androgen deficiency (Arlt et al., 2000; Shifren et al., 2000). Androgen administration may affect brain function directly through androgen receptors and indirectly through conversion to estrogen and dihydrotestosterone, both of which are important neuromodulators capable of stimulating 5-hydroxytryptamine receptors and serotonin transporter protein metabolism (Simerly, 1993; Celotti et al., 1997).

We hypothesized that (1) women with AN would exhibit regional brain hypometabolism compared with control subjects and (2) low-dose testosterone replacement therapy would normalize regional brain hypometabolism in women with relative testosterone deficiency associated with AN. We therefore studied 14 women with AN, using FDG PET, and compared them with 20 healthy control subjects to identify specific regions of cerebral hypometabolism. Twelve of the women with AN were randomized to receive low-dose testosterone by transdermal patch (Intrinsa™, Procter and Gamble Pharmaceuticals, Cincinnati, OH) or placebo to determine whether testosterone therapy attenuated any of the abnormalities observed in the women with AN at baseline.

2. Research design and methods

2.1. Subjects

Fourteen women with AN were recruited for this study. All subjects met the diagnostic criteria for AN, as delineated in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV), including weight loss to less than 85% of ideal body weight (IBW) and amenorrhea for at least 3 months. No patient had received estrogen or other hormones within 6 months of study.

Controls were eligible to participate in the protocol if they had no current axis I psychiatric disorder and no psychotropic medication use or hormone use within the