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Sertraline inhibits increases in body fat and carbohydrate dysregulation in adult female cynomolgus monkeys

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ABSTRACT

Selective serotonin reuptake inhibitor (SSRI) antidepressants are widely prescribed for depression and other disorders. SSRIs have become one of the most commonly used drugs in the United States, particularly by women. Acute effects on body composition and carbohydrate metabolism have been reported, but little is known regarding the effects of chronic SSRI use. We evaluated the effects of chronic administration of a commonly prescribed SSRI, sertraline HCl, on body weight and composition, fat distribution, carbohydrate metabolism, as well as activity, in adult female depressed and nondepressed cynomolgus monkeys (*Macaca fascicularis*; $n = 42$) using a placebo-controlled, longitudinal, randomized study design. Phenotypes were evaluated prior to and after 18 months of oral sertraline (20 mg/kg) or placebo. Over the 18 month treatment period, the placebo group experienced increases in body weight, body fat (visceral and subcutaneous) fasting insulin concentrations, and homeostasis model assessment of insulin resistance scores (HOMA-IR). Sertraline treatment prevented increases in body weight, fat, insulin, and HOMA-IR (all $p < 0.05$), without significantly altering activity levels. Sertraline treatment altered adiponectin in an unusual way — reducing circulating adiponectin in depressed monkeys without affecting fat mass or body weight. Deleterious effects on adiponectin, a potentially insulin-sensitizing and atheroprotective protein, may result in adverse effects on cardiovascular health despite otherwise beneficial effects on body composition and carbohydrate metabolism.

1. Introduction

Obesity, diabetes mellitus, and metabolic syndrome are all major risk factors for cardiovascular disease (CVD) and stroke. In 2012 more than two-thirds of Americans were overweight, and one-third of adults were classified as obese according the criteria set forth by the American Heart Association (National Center for Health Statistics, 2015). This increasing prevalence of obesity, particularly visceral obesity, is most likely also driving an increased incidence of insulin resistance and type 2 diabetes mellitus (Despres and Lemieux, 2006). The clustering of cardiometabolic risk factors related to visceral obesity includes hypertension and perturbations in lipid and carbohydrate metabolism and is known as the metabolic syndrome (Go et al., 2014).

Metabolic syndrome is associated with depression (Kinder et al., 2004; Pan et al., 2012). Depressive disorders are twice as likely in women as men (Gorman, 2006). One in ten women currently suffers from a depressive disorder and women in their late reproductive years have a higher incidence of depression than any other age/sex group (Pratt and Brody, 2014). Depressive disorders can activate the hypothalamic-pituitary-adrenal axis which in turn promotes visceral fat deposition, inflammatory cytokine secretion, and a cascade of biological changes resulting in elevated blood pressure, dyslipidemia, and impaired carbohydrate metabolism (Kinder et al., 2004; Shively et al., 2009). Likewise, the proinflammatory state subsequent to visceral fat deposition may increase depression risk. Thus, the relationship between metabolic syndrome and depression is likely bidirectional (Dunbar et al., 2008; Gragnoli, 2014; Mansur

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et al., 2015; Martinac et al., 2014; Pan et al., 2012). Both metabolic syndrome and depression increase CVD risk, including coronary heart disease, the leading cause of death in women (Despres and Lemieux, 2006).

Antidepressant drugs (ADs) are the third most commonly prescribed medication in America. Women are 2.5 times more likely than men to take ADs, and 23% of women aged 40–59 take ADs. Greater than 60% of Americans taking ADs have taken them for at least 2 years and 14% take them for an excess of 10 years (Pratt et al., 2011). SSRIs are the most commonly prescribed class of ADs (Pratt et al., 2011). In addition to depression, SSRIs were recently approved by the Food and Drug Administration for the treatment of hot flushes and have also shown efficacy in treating migraine headaches and premenstrual dysphoric disorder (Orleans et al., 2014; Stone et al., 2003). This widespread use of SSRIs is an important public health issue because the risks and benefits of chronic SSRI treatment on several biologic systems are unknown.

Published effects of SSRIs on metabolic characteristics are mixed. Clinical studies report beneficial as well as deleterious effects of SSRIs on body weight, waist circumference, insulin secretion and fasting blood glucose (Beyazyuz et al., 2013; Ghaeli et al., 2004; Kesim et al., 2011). Observational studies suggest that SSRI use may be associated with increased waist circumference and impaired glucose handling (Raeder et al., 2006; Yoon et al., 2013). Alterations in glucose and lipids could be due to effects of the drug on body weight, body composition, or behavior. Presently, no data exist regarding SSRI effects on body composition.

To date, the effects of these medications have usually been studied in patient populations with diagnoses of depression or anxiety. This adds a level of complexity in interpreting results because of the associations between depression, obesity and the metabolic syndrome, and difficulties in establishing causality. There is a need for longitudinal, controlled, randomized studies to determine how SSRIs influence body composition and carbohydrate metabolism independently of clinical conditions and syndromes; however, long-term trials evaluating SSRI effects are not ethical in healthy human populations given that SSRI use and discontinuation are both associated with a long list of unpleasant and sometimes serious adverse effects (Cascade et al., 2009; Haddad, 2001).

Laboratory-housed nonhuman primates may exhibit behavioral depression (Camus et al., 2014; Hennessy et al., 2014; Shively et al., 1997; Shively et al., 2009; Shively et al., 2008; Shively and Willard, 2012) which resembles human depression in physiological, neurobiological, and behavioral characteristics including reduced body mass, hypothalamic-pituitary-adrenal axis perturbations, autonomic dysfunction, increased cardiovascular disease risk, reduced hippocampal volume, altered serotonergic function, decreased activity levels, and increased mortality (Shively and Willard, 2012; Willard and Shively, 2012). Physiological and neurobiological characteristics of monkeys that exhibit behavioral depression have been well characterized (Shively and Willard, 2012) and include dyslipidemia and exacerbated coronary atherosclerosis (Shively et al., 2009; Shively et al., 2008; Shively et al., 2005). Here we evaluated the effects of SSRIs on body composition and carbohydrate metabolism in depressed and nondepressed female cynomolgus monkeys (*Macaca fascicularis*). Since the effects of SSRIs were studied in the presence and absence of depression, depression-associated effects on body composition and carbohydrate metabolism could be separated from those due to SSRI treatment. Female cynomolgus monkeys are uniquely well-suited for this study because, in addition to being a useful and well-characterized model of depression (Shively and Willard, 2012; Willard and Shively, 2012), they are also an established model of diet-induced obesity (Mubiru et al., 2011), and type 2 diabetes mellitus (Shively et al., 2009; Wagner et al., 2006).

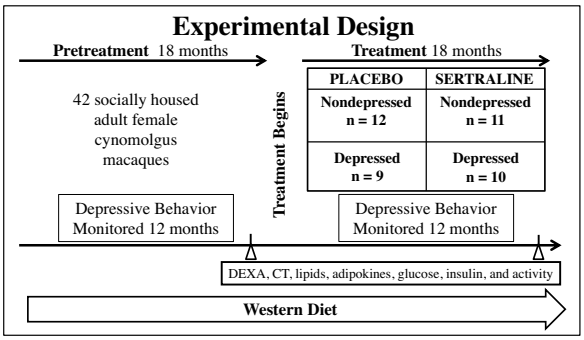

Fig. 1. Experimental Design. 42 adult female monkeys consumed a Western diet for an 18 month Pretreatment Phase, during which behavior and physiology were assessed. The monkeys were assigned to sertraline or placebo treatment groups balanced on Pretreatment rates of depression and body weight. The monkeys continued to consume a Western diet during the 18 month Treatment Phase, during which assessments of behavior and physiology were repeated.

2. Materials and methods

2.1. Animal subjects

These animals were subjects of a study primarily aimed at evaluating the relationship between depression, SSRI treatment, and coronary artery atherosclerosis. Details about the animals; the diet they were fed; and the methods and results have been previously published with regards to cerebrospinal fluid monoamines (Shively et al., 2014), cardiac function (Groban et al., 2014), cardiovascular risk factors and coronary artery atherosclerosis (Shively et al., 2015), and neural structures (Willard et al., 2015). Forty-five adult, reproductively-aged female cynomolgus monkeys were imported from Indonesia (Institut, Pertanian Bogor, Bogor, Indonesia) and quarantined in single cages for a one-month. Following quarantine, monkeys were randomly assigned to social groups of $n = 4–5$ and fed a Western-like diet (containing 44% of calories from fat and 0.29 mg/Cal cholesterol) designed to mimic fat and cholesterol content consumed by Northern Americans (Groban et al., 2014). Monkeys were housed in indoor pens (3.05 m × 3.05 m × 3.05m) with 12/12 light/dark and water *ad libitum*. Monkey ages were estimated from dentition. Monkeys were at least 10 years of age and cycling, thereby approximating premenopausal women in their mid-30s to late-40s. During the 3.5-year study, three animals died of causes unrelated to the experiment resulting in a final sample size of 42. All animal manipulations were performed according to the guidelines of state and federal laws, the US Department of Health and Human Services, and the Animal Care and Use Committee of Wake Forest University School of Medicine. Wake Forest University is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

2.2. Experimental design (Fig. 1)

The monkeys consumed the Western-like diet for an 18-month Pretreatment Phase during which behavior (including depressive behavior) was recorded. Monkeys were trained to run out of their social group pens into a dosing cage and comply with oral dosing. Stratified randomization was used to assign the monkeys by social group to either placebo ($n = 21$) or sertraline ($n = 21$) treatment balanced on Pretreatment rate of depressive behavior and body weight. Thus, depressed and nondepressed monkeys were evenly distributed between the placebo and sertraline groups. Sertraline HCl (Zoloft®) was introduced gradually over a 4-week period to attain a final dose of 20 mg/kg/day; the placebo group received vehicle alone (Shively et al., 2014).