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Long term sertraline effects on neural structures in depressed and nondepressed adult female nonhuman primates

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for mood and other disorders. However, their neural effects are difficult to study due to patient compliance and drug history variability, and rarely studied in those prescribed SSRIs for non-mood disorders. Here we evaluated SSRI effects on neural volumetrics in depressed and nondepressed monkeys.

Methods: 42 socially-housed cynomolgus monkeys were randomized to treatment balanced on pre-treatment depressive behavior and body weight. Monkeys were trained for oral administration of placebo or 20 mg/kg sertraline HCl daily for 18 months and depressive and anxious behavior recorded. Volumes of neural regions of interest in depression were measured in magnetic resonance images and analyzed by 2 (depressed, nondepressed) × 2 (placebo, sertraline) ANOVA.

Results: Sertraline reduced anxiety ($p = 0.04$) but not depressive behavior ($p = 0.43$). Left Brodmann's Area (BA) 32 was smaller in depressed than nondepressed monkeys (main effect of depression: $p < 0.05$). Sertraline and depression status interacted to affect volumes of left Anterior Cingulate Cortex (ACC), left BA24, right hippocampus (HC), and right anterior HC (sertraline × depression interactions: all p's < 0.05). In the Placebo group, depressed monkeys had smaller right anterior HC and left ACC than nondepressed monkeys. In nondepressed monkeys, sertraline reduced right HC volume, especially right anterior HC volume. In depressed monkeys sertraline increased left ACC volume. In nondepressed monkeys, sertraline reduced left BA24 volumes resulting in smaller BA24 volumes in nondepressed than sertraline-treated depressed monkeys.

Conclusions: These observations suggest that SSRIs may differentially affect neural structures in depressed and nondepressed individuals.

1. Introduction

Depression is prevalent, debilitating, and nearly twice as common in women as men (Kessler et al., 2003). Volumetric differences in neural structures between depressed and nondepressed individuals, as measured via magnetic resonance imaging (MRI), are widely reported. Among the most commonly reported differences are reduced volumes of hippocampus (HC), amygdala, and cingulate cortex in depressed individuals, although there is some variability in these observations (Arnone et al., 2012; Grieve et al., 2013; Koolschijn et al., 2009; McKinnon et al., 2009; Neumeister et al., 2005; Sheline, 1996; Sheline et al., 1999; Tang et al., 2007).

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Factors such as age, sex, life stress history, number of bouts of depression, and medication history may contribute to this variability.

One potential mechanism through which antidepressant therapies promote remission is increased neurogenesis and synaptic connectivity through synaptogenesis and reorganization or reintegration of new neurons into depression neurocircuitry (Duman and Li, 2012; Mahar et al., 2014). A few studies suggest that neural volumes of major depressive disorder (MDD) patients that are medicated may differ from those who are unmedicated. In longitudinal studies following medication both no change and an increase in hippocampal volume have been reported (Frodl et al., 2008; Vythilingam et al., 2004); and an increase in dorsolateral prefrontal cortex has been reported (Smith et al., 2013). In case-control studies increased volumes of neural regions associated with medication have been reported for the body of the hippocampus (Malykhin et al., 2010), and dentate gyrus (Huang et al., 2013), but an apparent decrease in white matter volume in the left dorsolateral prefrontal cortex and left putamen (Zeng et al., 2012).

Selective serotonin reuptake inhibitors (SSRIs), including sertraline HCl (Zoloft®), are the third most prescribed drug in the United States (Pratt et al., 2011). Use of these medications has increased 400% over the past 15 years, in part because antidepressants are prescribed for a number of disorders other than depression (Pratt et al., 2011). It has been estimated that 11% of Americans over 12 years of age take antidepressant medication. Antidepressant usage is most common in middle-aged women (40–59 years of age) (Pratt et al., 2011). Over 60% of those taking antidepressants have taken it for two years or more (Mojtabai and Olfson, 2011; Pratt et al., 2011). In addition to depression, SSRIs are prescribed for bulimia (McElroy et al., 2012), hot flashes (Shams et al., 2014), obsessive compulsive disorder (Chouinard, 2006), stroke recovery (Mead et al., 2012) and sexual dysfunction (Moreland and Makela, 2005). Although widely prescribed for disorders other than anxiety and depression, there are no studies of the effects of SSRI on brain volumes in individuals without psychiatric diagnoses. Thus, antidepressant effects on neural volumes in nonpsychiatric populations may have important implications for public health.

Studies evaluating neural changes following prolonged antidepressant use are difficult to do under controlled experimental conditions in human subjects because of difficulties with compliance to treatment, and complex drug histories. Here we report the evaluation of the effects of long term SSRI treatment on volumes of specific brain regions in adult female cynomolgus monkeys (*Macaca fascicularis*), a well-established nonhuman primate (NHP) model of depression (Shively and Willard, 2012; Willard and Shively, 2012). Briefly, depressive behavior in socially housed female cynomolgus monkeys occurs in captivity without experimental manipulation. Socially subordinate females are more likely than dominants to display depressive behavior; however not all subordinates display depressive behavior and some socially dominant animals do also (Shively and Willard, 2012; Willard and Shively, 2012). Behavioral depression in adult female cynomolgus macaques appears similar to 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). The menstrual cycles of cynomolgus macaques are similar to those of women in terms of length and hormonal fluctuations. Behaviorally depressed monkeys have low concentrations of ovarian steroids, with preserved menses (Shively and Willard, 2012; Willard and Shively, 2012). The macaque hippocampus (HC) more closely parallels the cellular organization and connectivity patterns of the human hippocampus than does that of the rat (Amaral and Lavenex, 2007), and macaques have complex and differentiated cortical areas, similar to those of human beings, that are important in human depression (Carmichael et al., 1994; Machado et al., 2008). Our group has previously reported reduced anterior hippocampal volume in untreated, behaviorally depressed female cynomolgus macaques. Postmortem *in vitro* analysis (Willard et al., 2009) and pre-mortem *in vivo* MRI measures (Willard et al., 2011) demonstrated region-specific reductions in hippocampal volume in depressed versus nondepressed females. The goal of the present study was to determine the effects of long-term treatment using a commonly prescribed antidepressant, sertraline HCl (Zoloft®), on the volume of depression-related neural regions in depressed and nondepressed NHPs. Examining the effects of sertraline in both depressed and nondepressed monkeys allowed us to test the hypothesis that sertraline treatment has differential effects on brain volumes depending on depression status.

2. Materials and methods

2.1. Subjects

Forty-five adult, reproductive-aged female cynomolgus macaques were imported directly from Indonesia (Institut Pertanian Bogor, Bogor, Indonesia) and quarantined in single cages for one month. Following quarantine, the monkeys were housed in social groups of n = 4–5, in indoor pens (3.05 m × 3.05 m × 3.05 m), in a climate-controlled building with outdoor exposure, 12/12 light/dark, and water *ad libitum*. All monkeys were fed a Western-like diet, designed to be similar to that consumed by some Americans, with 44% of calories from fat, and 0.29 mg/Cal cholesterol which is approximately equal to a human consumption of 500 mg cholesterol/2000 calories (Groban et al., 2014; Shively et al., 2014). The monkeys were all of reproductive age, approximately 15.7 ± 0.3 years of age, estimated from dentition, which approximates a human age of about 45 years. Over the course of the 3.5 year study, three animals died of causes unrelated to the experiment resulting in a sample size of 42. MRI images were not available for one animal, leaving a final sample size of 41. All procedures involving primates were conducted using protocols approved by the Institutional Animal Care and Use Committee of Wake Forest University Health Sciences and were in compliance with all institutional, state, and federal laws for the usage of primates in laboratory settings.

2.2. Experimental design

The monkeys lived in these stable social groups for 18 months, during which depressive behavior was recorded. At the end of the 18 months, the monkeys were assigned by social group to either placebo (n = 20) or sertraline (n = 21) treatment balanced on body weight (BW), body mass index (BMI) and the rate of depressive behavior during the pretreatment period using stratified randomization (Table 1). This approach provides balance on variables that were measured as well as those that were not measured, because these variables are correlated with many other physiological characteristics (Kernan et al., 1999; Lachin et al., 1988). There was also no difference in the groups in total plasma cholesterol, high density lipoprotein cholesterol, quality of ovarian function, and age, all of which could affect brain morphometry (Shively et al., 2015). The monkeys were treated with sertraline for 18 months.

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