Neuroscience and Biobehavioral Reviews 74 (2017) 433–443

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

The impact of treatment with selective serotonin reuptake inhibitors on primate cardiovascular disease, behavior, and neuroanatomy

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ARTICLE INFO

Article history:
Received 28 February 2016
Received in revised form 12 August 2016
Accepted 29 August 2016
Available online 30 August 2016

Keywords:
Depression
Cardiovascular disease
Coronary atherosclerosis
SSRI
Nonhuman primate
Anterior cingulate cortex
Hippocampus
MRI

ABSTRACT

Selective serotonin reuptake inhibitor (SSRI) use is ubiquitous because they are widely prescribed for a number of disorders in addition to depression. Depression increases the risk of coronary heart disease (CHD). Hence, treating depression with SSRIs could reduce CHD risk. However, the effects of long term antidepressant treatment on CHD risk, as well as other aspects of health, remain poorly understood. Thus, we undertook an investigation of multisystem effects of SSRI treatment with a physiologically relevant dose in middle-aged adult female cynomolgus monkeys, a primate species shown to be a useful model of both depression and coronary and carotid artery atherosclerosis. Sertraline had no effect on depressive behavior, reduced anxious behavior, increased affiliation, reduced aggression, changed serotonin neurotransmission and volumes of neural areas critical to mood disorders, and exacerbated coronary and carotid atherosclerosis. These data suggest that a conservative approach to prescribing SSRIs for cardiovascular or other disorders for long periods may be warranted, and that further study is critical given the widespread use of these medications.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.08.037
0149-7634/

1. Introduction

Coronary heart disease (CHD) is the leading cause of morbidity and mortality of US women, exceeding that of all cancers combined. CHD in women is understudied, and less well understood than in men (Go et al., 2014). Coronary artery atherosclerosis and its sequelae are frequent causes of CHD. The premenopausal life stage is important in determining the extent of postmenopausal coronary artery atherosclerosis and CHD risk because the extent of premenopausal coronary artery atherosclerosis sets the starting point and trajectory for coronary artery plaque progression in the postmenopause (Kaplan et al., 2002).

Depressive disorders are twice as likely and have more serious consequences in women as men (Gorman, 2006; Kim et al., 2015). The lifetime prevalence of depression in women is 20%, occurring most commonly in the reproductive years (Pratt and Brody, 2014). Depression is highly co-morbid with CHD. The relationship between depression and CHD could be one of three natures: CHD may cause depression; depression may cause CHD; or both diseases may be the product of perturbations of common underlying mechanisms. Clinical studies cannot easily discriminate among these three possibilities. However, several studies demonstrate graded relative risk of CHD with depression, suggesting that milder forms of depression in addition to major depressive disorder may be clinically relevant (Leung et al., 2012; Rugulies, 2002; Rudisch and Nemeroff, 2003 Rugulies, 2002; Rudisch and Nemeroff, 2003). Meta-analyses suggest that depression is independently associated with a significantly increased risk of CHD and MI (Gan et al., 2014; Wu and Kling, 2016). Furthermore, development of atherothrombotic CHD is generally predicated by years of coronary artery atherogenesis. These observations suggest a causal role of depression in progression of CHD, although this remains to be evaluated conclusively. When depression may exert its adverse effects during CHD pathogenesis is not well understood. For example, it could be that depression effects CHD rather late in clinical development by precipitating coronary events in the presence of complicated plaques through adverse effects on arrhythmias or platelet reactivity. Depression could also exert adverse effects very early in CHD pathogenesis by promoting atherogenesis. Since CHD is the leading cause of death of women, and women experience twice the prevalence of depression than men, understanding the cardiovascular pathobiology of depression may be particularly important to the cardiovascular health of women (Moller-Leimkuhler, 2010).

Antidepressants are among the most widely used medications in the US, and 60% of those taking antidepressants have done so for 2 years or longer. Women are 2.5 times more likely than men to take antidepressants, and 23% of women aged 40–59 years take antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants (Pratt et al., 2011). In addition to depression, SSRIs are prescribed for a number of other disorders including obsessive-compulsive disorder, bulimia and binge eating, agitation and aggression in dementia and other central nervous system degenerative diseases fibromyalgia, osteoarthritis, and diabetic neuropathy pain, hot flashes, stroke recovery and premature ejaculation (Chouinard, 2006; McElroy et al., 2012; Henry et al., 2011; Pergolizzi et al., 2013; Shams et al., 2014; Mead et al., 2012; Moreland and Makela, 2005 Shams et al., 2014; Mead et al., 2012; Moreland and Makela, 2005). Remarkably little is known about the multisystem effects of SSRIs in those treated for disorders other than mood disorders.

There has been much discussion over the last several years about whether SSRIs are safe for treating depression in CHD patients (Davidson et al., 2006; Zuidersma et al., 2013). Some have gone so far as to recommend SSRIs to inhibit atherosclerosis progression (Wozniak et al., 2011). These recommendations stem from evidence of increased cardiovascular risk factors in depression such as arrhythmias, platelet reactivity, proinflammatory processes, cortisol concentrations, and low high-density lipoprotein cholesterol (HDLC) concentrations in women (Carney et al., 2002; Shively et al., 2009; Fantidis, 2010; Tedders et al., 2011). Of these risk factors, the available evidence suggests that SSRIs have inhibitory effects on platelet reactivity (de Abajo, 2011) and inflammatory processes (Hannestad et al., 2011; Walker, 2013) although evidence that these affects have cardiovascular significance is scarce. Conversely, SSRIs also have been observed to have adverse effects on CHD risk factors including increasing body weight (BW), body mass index (BMI), waist circumference, fasting glucose, total plasma cholesterol (TPC), low density lipoprotein cholesterol, and triglyceride concentrations (Beyazyuz et al., 2013; Wei et al., 2009; Kesim et al., 2011), all factors that may be affected by food consumption. It is notable that disorders for which SSRIs are commonly prescribed, such as depression, also may affect food consumption. Since all the SSRI-CHD risk factor studies assessed patient populations, the effects of SSRIs on these CHD risk factors are confounded by the disorder for which they were prescribed.

There are no experimental investigations of the effects of SSRIs on coronary artery atherosclerosis extent and severity, and few long term clinical studies of the effect of SSRI use on CHD morbidity and mortality. SADHART (Sertraline AntiDepressant Heart Attack Trial) demonstrated that sertraline was relatively safe and efficacious in depressed patients with ischemic heart disease but was underpowered to detect a mortality difference between sertraline and placebo. Secondary analyses of the ENRICHD (ENhancing Recovery in Coronary Heart Disease) trial suggested that SSRIs in myocardial infarction patients might reduce subsequent morbidity and mortality but the trial was not designed to detect these relationships (Taylor et al., 2005; Joynt and O'Connor, 2005). More recently, increased cardiovascular morbidity and mortality in patients using SSRIs, versus non-SSRIs or no antidepressant, was observed in a 42 month follow up study of CHD patients (Rieckmann et al., 2013). In addition, among women with symptoms of myocardial ischemia, the use of antidepressant medication was associated with subsequent cardiovascular events (e.g. nonfatal myocardial infarction, stroke, congestive heart failure, unstable angina) (Krantz et al., 2009).

Some studies also suggest that SSRI use may increase the risk of ischemic stroke, which is due to atherosclerosis in the cerebral vasculature. A recent meta-analysis of these studies suggests that the use of SSRIs is associated with an odds ratio of 1.48 (CI = 1.08, 2.02) for ischemic stroke (Shin et al., 2014). Likewise, an association between increased carotid intimal-medial thickening, a powerful predictor of myocardial infarct risk (Simon et al., 2002), and SSRI treatment in a study of twins discordant for SSRI has been reported (reported in Shah et al., 2011 American College of Cardiology Scientific Sessions).

Taken together, these observations of associations of worsened cardiovascular risk factors, increased ischemic stroke incidence and carotid intimal-medial thickening, and increased cardiovascular disease (CVD) events in patients with SSRI use suggest a need for better information concerning SSRI effects on the development and progression of atherosclerosis. As long term randomized clinical trials are unlikely due to cost and ethical considerations, we studied these relationships in adult female cynomolgus monkeys (*Macaca fascicularis*) because they are among the best models of depression and atherosclerosis.

2. Monkey model of depression (Fig. 1)

Adult female cynomolgus macaques are a well-established nonhuman primate (NHP) model of depression (Shively and Willard, 2012; Willard and Shively, 2012). Depressive behavior in socially