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Histories of sexual abuse are associated with differential effects of clonidine on autonomic function in women with premenstrual dysphoric disorder

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Abstract

In women meeting strict criteria for premenstrual dysphoric disorder (PMDD), we examined whether clonidine, an α2-adrenergic receptor (AR) agonist, would have different effects on sexually abused versus non-abused PMDD women for measures of autonomic nervous system function. Twelve women meeting prospective, DSM-IV criteria for PMDD, five of whom had a history of sexual abuse, participated in a randomized, placebo-controlled, double-blind, cross-over design study, comparing 2 months of on oral clonidine (0.3 mg/day) with 2 months on active placebo. During the luteal phase that preceded randomization and following each two-month challenge, women were tested for cardiovascular measures at rest and in response to mental stress, and for resting plasma norepinephrine (NE) concentrations as well as β1 and β2-AR responsivity using the isoproterenol sensitivity test. Results revealed that in comparison to placebo, clonidine significantly reduced plasma norepinephrine concentrations, increased both β1- and β2-AR responsivity, and reduced resting and stress heart rate (HR) and blood pressure (BP) ($p < 0.05$) in all PMDD women. With clonidine, sexually abused PMDD women exhibited greater decreases in resting and stress-induced HR ($p < 0.01$) and stress-induced systolic BP ($p < 0.05$), while non-abused PMDD women exhibited greater reductions in plasma NE concentration ($p = 0.07$), and greater increases in β2-AR responsivity ($p < 0.05$) than abused PMDD women. These results suggest PMDD women with and without a history of sexual abuse respond differently to a clonidine challenge in measures reflecting

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autonomic nervous system functioning, indicating that abuse may modify presynaptic α2-AR function in PMDD.

Keywords: Premenstrual dysphoric disorder; Sexual abuse; Clonidine; Sympathetic nervous system; Adrenergic function

1. Introduction

Premenstrual dysphoric disorder (PMDD) is estimated to afflict 5 to 8% of women in their reproductive years (American Psychiatric Association, 1987). Dysfunction in a variety of neurotransmitters has been implicated in PMDD, including norepinephrine (NE) (Halbreich, 2003). Evidence suggests that women with severe premenstrual syndrome (PMS) and/or PMDD exhibit dysregulation in centrally-mediated adrenergic activity (Schrijver et al., 1987; Parry et al., 1991), adrenergic receptor (AR) functioning (Halbreich et al., 1993), and increased serum norepinephrine (NE) concentration at rest and during mental stress (Odink et al., 1990; Girdler et al., 1998).

Despite the overwhelming evidence that PMDD women report more stressful life events (Girdler et al., 1993; Fontana and Badawy, 1997), including more frequent sexual abuse (Golding et al., 2000; Golding and Taylor, 1996; Paddison et al., 1990), there exists only one study assessing autonomic function in PMDD in relation to a history of severe stress such as physical or sexual abuse (Girdler et al., 2003). In prior research on sexual abuse and autonomic function in non-PMDD women, it has been difficult to assess the independent role of abuse history on neuroendocrine functioning, since many of the abused women had co-morbid post-traumatic stress disorder (PTSD) (Stein et al., 1997). Indeed, it was reported (Lemieux and Coe, 1995) that only those women with abuse who present with PTSD exhibit greater NE levels relative to healthy controls, whereas abused women with no PTSD have normal concentrations of NE. Other studies of abuse and autonomic function are confounded by the fact that a large proportion of the abused cohort had current major depression and/or were using psychotropic agents (Heim et al., 2000a,b; Orr et al., 1998; Metzger et al., 1999). We recently reported that in PMDD women with no current PTSD or other psychopathology, and who were not using medication, a history of abuse is associated with altered sympathetic function as reflected in resting NE levels and heart rate, AR responsivity to isoproterenol challenge, and NE reactivity to mental stress (Girdler et al., 2003, 2004).

Another strategy for investigating alterations in sympathetic function is to employ an adrenergic agent as a challenge test. Clonidine, a selective partial α2-AR agonist, has multiple effects on noradrenergic function. The rapid action of clonidine is mediated by stimulation of postsynaptic α2-AR and has been used as a challenge test in psychiatry as a means of measuring sensitivity of α2-AR in the brain, evident by increased growth hormone release from pituitary after clonidine (Siever, 1987). In contrast to a rapid action, longer-term effects of clonidine are mediated by stimulation of presynaptic α2-AR, where stimulation mediates biofeedback inhibition of noradrenergic activity (MacMillan et al., 1996). Such an inhibition in central sympathetic outflow is observed