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Stress, depression, and cardiovascular dysregulation: A review of neurobiological mechanisms and the integration of research from preclinical disease models

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Abstract

A bidirectional association between mood disorders such as depression, and cardiovascular diseases such as myocardial infarction and congestive heart failure, has been described; however, the precise neurobiological mechanisms that underlie these associations have not been fully elucidated. This review is focused on the neurobiological processes and mediators that are common to both mood and cardiovascular disorders, with an emphasis on the role of exogenous stressors in addition to: (a) neuroendocrine and neurohumoral changes involving dysfunction of the hypothalamic-pituitary-adrenal axis and activation of the renin-angiotensin-aldosterone system, (b) immune alterations including activation of pro-inflammatory cytokines, (c) autonomic and cardiovascular dysregulation including increased sympathetic drive, withdrawal of parasympathetic tone, cardiac rate and rhythm disturbances, and altered baroreceptor reflex function, (d) central neurotransmitter system dysfunction including dopamine, norepinephrine and serotonin, and (e) behavioral changes including fatigue and physical inactivity. We also focus specifically on experimental investigations with preclinical disease models, conducted to elucidate the neurobiological mechanisms underlying the link between mood disorders and cardiovascular disease. These include: (a) the chronic mild stress model of depression, (b) a model of congestive heart failure, a model of cardiovascular deconditioning, (d) pharmacological manipulations of body fluid and sodium balance, and (e) pharmacological manipulations of the central serotonergic system. In combination with the extensive literature describing findings from human research, the investigation of mechanisms underlying mood and cardiovascular regulation using animal models will enhance our understanding of the association of depression and cardiovascular disease, and can promote the development of better treatments and interventions for individuals with these co-morbid conditions.

Keywords

Animal Models; Baroreceptor Reflex; Central Nervous System; Chronic Fatigue; Chronic Mild Stress; Congestive Heart Failure; Interleukin; Heart Rate Variability; Mood Disorders; Renin-Angiotensin-Aldosterone System; Serotonin; Tumor Necrosis Factor-Alpha; Ventricular Arrhythmias

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Introduction

Converging evidence from both experimental and epidemiological studies indicates that there is a bidirectional association between depression and cardiovascular disease. Cardiovascular disease, characterized by changes in homeostatic and neuroendocrine function, is a significant risk factor for disordered affective states, such as depression (Schleifer et al., 1989; Freedland et al., 2003). Also, depression, characterized by depressed mood, the reduced responsiveness to pleasurable stimuli (anhedonia), and feelings of hopelessness, is a recognized risk factor for heart disease-related morbidity and mortality (Frasure-Smith et al., 1995; Barefoot et al., 1996; Barefoot and Schroll, 1996; Everson et al., 1996; Penninx et al., 2001; Carney and Freedland, 2003; Van der Kooy et al., 2007). The association between mood states and cardiovascular diseases has been shown to be independent of traditional cardiovascular risk factors such as hypertension, high cholesterol, increased body mass index, history of cardiac-related problems, and disease severity (Anda et al., 1993; Barefoot and Schroll, 1996; Penninx et al., 2001; Frasure-Smith and Lespérance, 2003), and exists in individuals with (Frasure-Smith et al., 1995; Barefoot et al., 1996; Carney and Freedland, 2003; Frasure-Smith and Lespérance, 2003) and without (Anda et al., 1993; Barefoot and Schroll, 1996; Everson et al., 1996; Penninx et al., 2001) a history of cardiac pathophysiology.

During the past decade, increasing attention has been devoted to studying the link between mood states and cardiovascular diseases (Musselman et al., 1998; Nemeroff et al., 1998; Carney and Freedland, 2003; Frasure-Smith and Lespérance, 2003; Freedland et al., 2003; Johnson and Grippo, 2006; Freedland et al., 2006; Glassman, 2007), as well as attempts to disseminate information about this relationship to the general biomedical community and the lay public. In 2001, the National Institute of Mental Health presented a summary of recent data linking depression to cardiovascular disease and stated its commitment, along with the National Heart Lung and Blood Institute, to supporting research on the basic mechanisms involved in the co-morbidity of mental and physiological disorders (National Institute of Mental Health, 2001). The American Psychological Association's Practice Directorate has a similar initiative to highlight the role of psychologists in contributing to research and treatment on the overlap of mental and physical well-being (see American Psychological Association, 2004; Stambor, 2006). A 2002 article appearing in *My Generation*, a periodical marketed toward individuals over 50 years of age, discussed the importance of cardiovascular diseases in producing depression (Doner, 2002). Similar articles have appeared recently in *Newsweek* (Miller, 2005), *US News and World Report* (Szegedy-Maszak, 2003) and *Chicago Tribune* (Kotulak, 2006).

In spite of the evidence that depression is associated with heart disease, the pathophysiological mechanisms underlying the association remain unclear. In combination with research that is focused on human populations, experimental approaches that focus on animal disease models provide novel and useful methods for investigating causal and common mechanisms underlying the link between mood and cardiovascular regulation. In particular, the utilization of reliable and valid methodological procedures in animal models can produce results that have translational potential for understanding the association of depression and heart disease in humans.

The purpose of the present review is to provide a summary of common mechanisms in depression and altered cardiovascular regulation. For the past several years our laboratories have been investigating potential causal and common mechanisms that may be involved in this association using model systems in rodents. Our focus here is on clinical and experimental research, coupled with recent findings involving integrative research methods in rodent models. Additionally, we provide some recommendations for future mechanistic research involving animal models and multi-disciplinary studies.

Evidence for the Association of Depression and Cardiovascular Disease

The bidirectional association between mood disorders and heart disease is multifaceted, involving an integration of several central and peripheral processes. The presence of cardiovascular disease or dysfunction can directly and indirectly influence affective states, including signs of both anxiety and depression. Compared to a prevalence of approximately 2–3% (men) and 5–9% (women) of depression in the general population (American Psychiatric Association, 2000), its prevalence in patients following a myocardial infarction may be approximately 45% (Schleifer et al., 1989), and might be even higher in patients with chronic cardiovascular conditions such as congestive heart failure (CHF) (Freedland et al., 2003). Cardiovascular disease-induced depression can result from psychological processes (e.g., contemplation of one's mortality or dealing with significant lifestyle changes) or physiological processes (e.g., changes in visceral afferent neural input or humoral factors released during states of cardiovascular pathophysiology), however it is likely that both psychological and physiological mediators contribute to the association of cardiovascular disease and mood changes.

Aside from cardiovascular pathophysiology influencing depressive signs and symptoms, the presence of depression increases the likelihood of experiencing detrimental cardiac events in patients with established cardiovascular disease. Depending on the study, approximately 20 to 50% of patients who die from myocardial infarction may have experienced an episode of depression prior to the infarction (Lebovits et al., 1967; Greene et al., 1972; Glassman and Shapiro, 1998). The presence of depression doubles the risk that patients with newly diagnosed cardiovascular disease will experience an adverse cardiovascular event within one year (Carney et al., 1988a). Depressed individuals are at a greater risk of death due to cardiac-related events for up to 10 years following the diagnosis of established cardiovascular disease, relative to non-depressed control subjects (Barefoot et al., 1996). Also, independent of risk factors such as arrhythmias and history of previous myocardial infarction, major depression is a significant predictor of mortality in patients at both 6 and 18 months following myocardial infarction (Frasure-Smith et al., 1993; Frasure-Smith et al., 1995). The predictive ability of depression on subsequent cardiovascular events is similar to that of left ventricular dysfunction, history of previous myocardial infarction and smoking (Booth-Kewley and Friedman, 1987; Frasure-Smith et al., 1993; Frasure-Smith et al., 1995), and the risk associated with this condition is independent of other cardiovascular risk factors including smoking, left ventricular ejection fraction, and severity of cardiovascular disease (Carney et al., 1988a).

Depression predicts incidence of cardiovascular disease, as well as cardiac-related morbidity and mortality, in individuals with no prior history of cardiac pathophysiology. For instance, Carney and colleagues (1995a) have estimated that approximately one-half of patients who are depressed at the time cardiovascular disease is initially diagnosed have had one or more prior depressive episodes. Penninx and colleagues (2001) showed that both major and minor depression increase the risk of cardiac-related mortality in patients without cardiac diseases at baseline, however the excess mortality risk was twice as high for major depression versus minor depression. Anda et al. (1993) showed that symptoms of depression, including depressed affect and moderate-to-severe hopelessness, predicted an increase in fatal and nonfatal heart disease in patients without a history of cardiac pathophysiology, independent of baseline medical variables, education, marital status, physical activity and smoking. Similarly, Barefoot et al. (1996) showed that symptoms of depression predicted acute myocardial infarction and total mortality in a community sample of individuals. Furthermore, in this patient sample, the level of cardiovascular risk was directly related to the severity of depressive symptoms, suggesting that individual differences in the vulnerability to psychopathology, pathophysiology, or both may be important in the link between depression and cardiovascular disease. Additional

prospective studies, reviewed elsewhere (Rudisch and Nemeroff, 2003), have found similar effects as those described here.

The Role of Exogenous Stressors, Neuroendocrine Changes and Immune Dysfunction

Responsiveness to stressors interacts with neuroendocrine and immune function

The presence of exogenous stressors influences both mood and cardiovascular regulation. Specifically, chronic stressors, which do not favor behavioral or physiological adaptation, have been discussed in the context of depressive signs and symptoms (Anisman and Zacharko, 1990; Grippo et al., 2003a) and cardiovascular dysregulation (Sgoifo et al., 2001). The predisposing influence of stressors on depression has been reviewed in detail elsewhere (Anisman and Zacharko, 1982; Anisman and Zacharko, 1990; Anisman and Zacharko, 1992; Swaab et al., 2005). Environmental stressors can lead to altered neurochemical function, such as disruptions in the synthesis and utilization of norepinephrine, changes in dopamine activity and altered synthesis of serotonin (5-HT) (Herman et al., 1982; Joseph and Kennett, 1983; Irwin et al., 1986; Adell et al., 1988). Environmental stressors in humans, including marital conflicts, health problems and work overload, have been shown to be associated with depressive disorders (Bidzinska, 1984). Additionally, exposure to acute stressors in rats leads to disrupted exploration, impaired escape performance and reduced appetitive responses to stimuli (see Anisman and Zacharko, 1992). These findings, considered together, provide a long history of evidence linking responsiveness to stressors with depressive syndromes. Hippocampal damage due to stress has been posited as a central nervous system mechanism leading to depressive symptoms via its influence on hypothalamic-pituitary-adrenal (HPA) axis activity (Vaidya, 2000).

Stressors also contribute to cardiovascular diseases and their antecedent risk factors (see Knardahl et al., 1988; Johnson and Anderson, 1990). There are several indices of interactions among environmental stressors and hypertension, arrhythmias and sudden death. For example, behavioral stressors have been shown to lower the cardiac threshold for ventricular fibrillation in both normal and acutely ischemic hearts of dogs (Corbalan et al., 1974; Matta et al., 1976), which is a primary mechanism responsible for sudden cardiac death (Verrier and Lown, 1984). Similarly, presenting food beyond the reach of a hungry animal has been shown to affect ventricular arrhythmias in the ischemic hearts of pigs (Carpeggiani and Skinner, 1991). Environmental stressors also influence the pathogenesis of hypertension (see Sanders and Lawler, 1992; Bedi et al., 2000).

While stressors have been demonstrated to influence both mood and cardiovascular regulation, the specific central and peripheral mechanisms that contribute to these changes require further investigation. General and specific changes in neuroendocrine function may play a role in linking responsiveness to stressors, mood states, and cardiovascular function. Endocrine changes associated with depression – including activation of the HPA axis and abnormal feedback in this system – are similar to the body's physiological responses to stressors and have been linked directly or indirectly to cardiovascular regulation. The association of depressive syndromes with dysfunction of the hypothalamic-hypophyseal axis was first described by Carroll (see Carroll, 1976; Carroll et al., 1976a; Carroll et al., 1976b). Alterations in corticotropin-releasing factor (CRF) have been observed in the cerebrospinal fluid (Banki et al., 1992), hypothalamus (Raadsheer et al., 1995), and locus coeruleus (Bissette et al., 2003) of depressed patients. Similarly, central CRF administration induces depression- and anxiety-related behavorial changes both in rodents and non-human primates, including decreased food intake and sexual activity, disturbed sleep, altered motor behavior, and impaired learning (Sirinathsinghji et al., 1983; Krahn et al., 1988; Glowa and Gold, 1991; van Praag,

2004). Several HPA axis-related changes, reviewed previously (Asnis et al., 1987; Maes et al., 1998; Weber et al., 2000), have been associated with depressive disorders, including: (a) dysregulated adrenocorticotropic hormone (ACTH) responses to CRF, (b) enhanced adrenal responses to ACTH, (c) elevated circulating cortisol or cortisone levels, and (d) lack of cortisol suppression in response to dexamethasone. Similar changes, including (a) alterations in corticosterone and ACTH, (b) impaired feedback control of HPA axis functioning, (c) impaired glucocorticoid receptor binding (increased mRNA expression and density of binding sites) in the hippocampus, cortex and dorsal raphe nucleus, and (d) altered CRF input to the dorsal raphe nucleus, have been observed in several validated animal models of depression (Froger et al., 2004; Maier and Watkins, 2005; Grippo et al., 2005a; Grippo et al., 2005b) [but also see (Azpíroz et al., 1999) for negative findings regarding circulating corticosterone levels]; some of these changes are further discussed in the following section.

The endocrine system interacts with the immune system; several of these interactions are common to mood disorders and heart disease and thus might play a role in the association of these conditions. Smith (1991) initially proposed a macrophage theory of depression, suggesting that excessive secretion of monokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α and interferon, contribute to the pathophysiology of depression. Several additional lines of evidence, reviewed in detail elsewhere (Maes, 1995; Connor and Leonard, 1998; Zorrilla et al., 2001; Pollak and Yirmiya, 2002; Kronfol, 2002; Dunn et al., 2005; Dantzer, 2006; Hawkley et al., 2007), suggest that dysfunction of the immune system is associated with depression; however, the precise pathophysiologic mechanisms that link immune dysregulation and depressive syndromes are not clear. TNF-α and α-interferon administered to humans induce depressive signs such as fatigue, malaise, lethargy, psychomotor retardation, irritability and anorexia (Niiranen et al., 1988; Spriggs et al., 1988). Similar changes have been observed following administration of IL-1β (Cunningham Jr. and De Souza, 1993). Interferons and interleukins, such as IL-1β and IL-6, have been reported to be increased in the plasma of some depression patients, however these changes have not been observed consistently across all studies (see for review Dunn et al., 2005).

Experimental evidence, derived from non-human animal studies, may provide additional insight into the associations among immune dysregulation, the central nervous system, and depressive signs. Activation of the immune system, and particularly activation of pro-inflammatory cytokines, are associated with sickness behavior, which includes signs of fatigue, anhedonia, anorexia, and reduced social interactions (Dantzer et al., 1998; Wichers and Maes, 2002; De La Garza II, 2005; Dantzer, 2006). As these signs in animals resemble to some extent depressive signs in humans, sickness behavior may be a useful analog for investigating the precise role of cytokines in depression and cardiovascular dysregulation.

Activation of the immune system is linked directly to specific cardiovascular disorders. In the setting of acute myocardial infarction, the pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 are released into the systemic circulation (Das, 2000). These have adverse affects on the heart and circulation (Kapadia et al., 1998; Ferrari, 1999; Francis et al., 2004), and may act on the central nervous system in parallel to induce signs and symptoms of depression and endocrine and autonomic dysregulation. Peripheral cytokines influence the release and metabolism of several central nervous system neurotransmitters, including dopamine (Jarskog et al., 1997), norepinephrine (Kabiersch et al., 1988) and 5-HT (Clement et al., 1997). These neurotransmitters are involved in sympathetic nerve outflow to the cardiovascular system (Huangfu et al., 1994), and have also been implicated in the pathogenesis of depression (Nosjean et al., 1995) (a further discussion of central neurotransmitter dysregulation is addressed in the section titled “Role of Central Neurotransmitter Systems”). Macrophages secrete ACTH, and can influence HPA axis function (Nathan, 1987). In addition, IL-1, which is produced by macrophages, directly acts on the hypothalamus and pituitary to regulate CRF

and ACTH (Dunn et al., 1999). IL-6 and exogenous interferon-γ also activate the HPA axis (Cassidy and O'Keane, 2000).

In addition to the immune system, the renin-angiotensin-aldosterone system (RAAS) is activated in some forms of heart disease such as CHF, resulting in high circulating levels of angiotensin II and aldosterone (Felder et al., 2001). Angiotensin and the pro-inflammatory cytokines both activate the HPA axis to increase circulating glucocorticoids and catecholamines (Wright et al., 1995; Pollak and Yirmiya, 2002). These two stress-associated humoral systems interact in the brain, where aldosterone stimulates circulating TNF-α levels, and in the periphery, where cytokines prevent the feedback inhibition of renin release by circulating angiotensin II (Felder et al., 2001; Francis et al., 2001a).

Notably, the immune system and the RAAS also are activated in affective states and conditions of stress in the absence of cardiovascular disease (Connor and Leonard, 1998; Pollak and Yirmiya, 2002). For instance, circulating aldosterone levels were found to be elevated in a sample of patients who met formal criteria for major or minor depression (American Psychiatric Association, 2000), compared to age- and gender-matched controls; plasma renin levels showed a slight (but nonsignificant) trend toward being elevated in this sample of depressed patients (Emanuele et al., 2005). Murck et al. (2003) similarly suggest that increased aldosterone levels may be a sensitive marker of depression. The interactions of aldosterone with mineralocorticoid receptors in the brain and periphery may lead to adverse outcomes in depressed patients with a risk of cardiovascular dysfunction. Aldosterone can stimulate increased sympathetic drive and activation of pro-inflammatory cytokines, promoting vascular injury, endothelial dysfunction, myocardial necrosis, catecholamine release and cardiac arrhythmias (Stier Jr. et al., 2002; Francis et al., 2003a; Gomez-Sanchez, 2004). Similarly, blockade of mineralocorticoid receptors with spironolactone reduced both sympathetic drive and circulating TNF-α levels in rats with experimental CHF (Francis et al., 2001a; Francis et al., 2003b), lowered mortality in humans with severe CHF (Pitt et al., 1999), and may improve cardiovascular status in patients with mild CHF symptoms (Baliga et al., 2006). These data suggest a potential pathophysiologic role for central mineralocorticoid receptors in mediating autonomic and cardiovascular dysfunction in the context of cardiovascular diseases such as CHF (a further discussion of autonomic dysfunction in the context of mood and cardiovascular disease appears in the section titled "Role of the Autonomic Nervous System").

Stressor responsiveness interacts with neurohumoral, endocrine, and immune function in valid rodent models of disease

Studies from our laboratories have examined the role of stressor responsiveness, behavior, neuroendocrine dysfunction, and immune alterations both in a rodent model of depression [chronic mild stress (CMS); see for review (Willner, 1997c; Willner, 2005)] and in a rodent model of cardiovascular disease [experimental CHF; see for review (Francis et al., 2001b; Felder et al., 2003)]. These investigations have provided insight into endocrine and immune changes that are common to both depressive disorders and cardiovascular diseases. In a recent study involving the CMS model of depression, we have experimentally validated the hypotheses of neuroendocrine and immune dysfunction in depression (Grippo et al., 2005a). Relative to an undisturbed control group, exposure of adult male rats to 4 weeks of CMS – mild and unpredictable stressors such as strobe light, white noise and damp bedding (refer to Figure 1 for a typical CMS paradigm) – induced experimental anhedonia (reduced sucrose intake), and also led to HPA axis dysfunction, activation of the RAAS, and activation of pro-inflammatory cytokines. For instance, circulating corticosterone, aldosterone and plasma renin activity were elevated in the CMS group versus the unstressed control group. Furthermore, the pro-inflammatory cytokines TNF-α and IL-1β were elevated both in the plasma and in the central nervous system of CMS rats (Figure 2). Interestingly, in this study the cytokine levels

also were systematically correlated with the degree of anhedonia in CMS rats; that is, a higher degree of anhedonia (lower level of sucrose intake) was correlated with higher levels of TNF-α and IL-1β. These relationships indicate that it might be useful to investigate individual differences in the behavioral and physiological vulnerability to environmental stressors using rodent models of depression.

The findings from this study suggest that interactions of cytokines and the RAAS with central processes, such as activation of the HPA axis, may be important mechanisms that influence both cardiovascular function and affective states. This intercommunication can influence downstream functions such as the release of corticosterone or catecholamines, regulation of circulating pro-inflammatory cytokines, and alterations in renin and aldosterone secretion (Bataillard et al., 1992; Wichers and Maes, 2002; Francis et al., 2003b), in turn providing a potential physiological link between affective states and cardiovascular dysfunction.

Although pro-inflammatory cytokines are elevated both in mood disorders and cardiovascular diseases, it is not clear whether these changes are a cause or consequence of the conditions. Therefore, we sought to examine the causal relationship of TNF-α in mediating a depression-like behavior in adult male rats with CHF, which involved experimental occlusion of the left descending coronary artery (Grippo et al., 2003b). Serum levels of TNF-α are increased in rats with experimental CHF (Francis et al., 2004) and may be increased in humans with CHF associated with ischemic heart disease (Levine et al., 1990). This cytokine has been shown to contribute in part to left ventricular dysfunction, cardiomyopathy and pulmonary edema (Kapadia et al., 1998). Similar to previous studies (Felder et al., 2003; Francis et al., 2003b), we found that experimental CHF, compared to sham occlusion procedures, produced a significant increase in circulating TNF-α levels. Furthermore, experimental CHF led to a significant reduction in responding for rewarding electrical brain stimulation into the lateral hypothalamus, indicative of anhedonia. When plasma TNF-α levels were lowered with the TNF-α antagonist etanercept (Adis International Limited, 1999), the behavioral responding for rewarding electrical brain stimulation was restored to baseline values, indicating a reversal of the CHF-induced anhedonia (Figure 3). These results suggest that CHF can induce anhedonia via a physiological mechanism involving activation of TNF-α.

Central TNF-α was not measured in this study, however it is possible that its behavioral effects were due in part to its actions in the brain. Receptors for TNF-α and IL-1, -2 and -6 have been found in the hippocampus and hypothalamus (Hopkins and Rothwell, 1995; Rothwell and Hopkins, 1995). The precise pathways of communication between the heart and brain involving the pro-inflammatory cytokines have not been elucidated and various routes have been proposed. For example, cytokines produced in the periphery may gain access to the central nervous system by way of the circumventricular organs, through the blood-brain barrier by selective saturable transport systems, actions on brain perivascular cells, or via neurally-mediated mechanisms involving visceral sensory nerves (Dantzer, 1994; Banks et al., 1995; Maier and Watkins, 1998; Schlitz and Sawchenko, 2002; Felder et al., 2003). TNF-α may act directly or indirectly to affect neurotransmitters that are involved in reward mechanisms and the display of depressive signs, including dopamine and 5-HT (Connor et al., 1998; Dunn et al., 1999).

Role of the Autonomic Nervous System

Autonomic dysfunction influences cardiac changes associated with depression

Activation of neuroendocrine systems, manifest in both generalized and specific HPA axis dysfunction and RAAS activation, can induce autonomic nervous system changes that are common to both depression and cardiovascular disease. Depression may be characterized by changes in autonomic regulation of the heart, such as activation of the sympathetic nervous

system, withdrawal of vagal tone to the heart, elevations in heart rate, reductions in heart rate variability, and altered baroreceptor reflex function (Esler et al., 1982; Rechlin et al., 1994a; Rechlin et al., 1994b; Carney et al., 1995b; Krittayaphong et al., 1997; Watkins and Grossman, 1999; Pitzalis et al., 2001; Barton et al., 2007; Hausberg et al., 2007). Similar autonomic changes are associated with cardiovascular risk factors such as hypertension, increased body mass index and increased blood glucose, and are observed in both acute and chronic cardiovascular conditions including atherosclerosis, myocardial ischemia, arrhythmias and heart failure (Ryan et al., 1976; Dyer et al., 1980; Gordon et al., 1981; Billman et al., 1982; Beere et al., 1984; Kannel et al., 1987; Schwartz et al., 1988; Carney et al., 1993; Kristal-Boneh et al., 1995; Palatini and Julius, 1997; La Rovere et al., 1998; Esler and Kaye, 2000; Tapanainen et al., 2002).

Autonomic imbalance is characterized by elevated sympathetic tone, decreased parasympathetic tone, or both. Previous research suggests that increased sympathetic and/or decreased parasympathetic tone are predisposing factors for ventricular fibrillation (Lown and Verrier, 1976; Kjekshus et al., 1981; Kleiger et al., 1987). Disrupted autonomic balance can mediate cardiovascular states during behavioral challenges. Sgoifo et al. (1998) showed that autonomic imbalance, characterized by exaggerated sympathetic tone and lower parasympathetic antagonism of sympathetic activation, may mediate ventricular arrhythmias during an acute social challenge (resident-intruder test).

Activation of the sympathetic nervous system and withdrawal of the parasympathetic limb lead to elevations in resting heart rate. An increase in basal heart rate is a prognostic indicator for morbidity and mortality related to heart disease (Ferrari et al., 2003). Elevated heart rate has been observed in depressed patients both with and without cardiovascular disease (Forbes and Chaney, 1980; Carney et al., 1988b). Both hypertensive (Goldstein, 1983) and normotensive (Lechin et al., 1995) depressed patients have been shown to exhibit higher heart rates than nondepressed individuals. Also, patients with both depression and cardiovascular disease display higher heart rates than nondepressed patients with cardiovascular disease (Carney et al., 1993). Heart rate may be altered in depression via norepinephrine and epinephrine acting on cardiac β-adrenergic receptors at the sinoatrial node, or from an increased sensitivity of β-adrenergic receptors on the heart (Kannel et al., 1987). While not all studies in depressed populations have shown significant end-organ changes, such as increases in heart rate (see Dawood et al., 2007; Barton et al., 2007), it is likely that neural control of cardiac function is altered in depression. Indeed, elevations in catecholamines have been reported in the plasma and cerebrospinal fluid of patients with melancholic depression. Gold and colleagues (2005) have observed significant increases in mean 24-hour levels of cerebrospinal fluid norepinephrine, plasma norepinephrine, and plasma epinephrine in severely depressed patients, versus controls. The authors also reported that plasma norepinephrine levels in severely depressed, unmediated patients were high enough to be capable of increasing mortality in CHF. Also important, even mild-to-moderately depressed patients in this study displayed clinically-relevant increases in arterial norepinephrine appearance rate.

Neural control of autonomic and cardiac function associated with depression may also be manifest in the form of altered heart rate variability. A reduced variability in heart rate is a sign of impaired autonomic control of cardiovascular regulation. For example, a decreased variability in heart rate is found in patients with cardiovascular disease (Ryan et al., 1976; Kristal-Boneh et al., 1995), and has prognostic value for predicting outcomes in myocardial infarction and CHF (Kleiger et al., 1987; Wolk, 1996; Tapanainen et al., 2002).

Heart rate variability has been shown to be reduced in depressed patients both with and without cardiovascular disease, compared to nondepressed individuals (Rechlin et al., 1994a; Rechlin et al., 1994b; Carney et al., 1995b; Pitzalis et al., 2001), however some studies have reported

negative findings in this variable (see Yeragani et al., 1991; Dawood et al., 2007). Differences in heart rate variability reported across studies may be related to the severity of depressive symptoms. For example, patients with higher depression scores on the Minnesota Multiphasic Personality Inventory-Depression [MMPI-D (Hathaway and McKinley, 1967)] showed lower heart rate variability than patients with lower scores on this instrument (Krittayaphong et al., 1997). Recent pharmacological data suggest that central serotonergic mechanisms may influence heart rate variability in depressed individuals (Khaykin et al., 1998). Furthermore, treatment of depressed patients with 5-HT reuptake inhibitors has been reported to lower sympathetic activation, evidenced by a reduction in whole body norepinephrine spillover (Barton et al., 2007). However, some studies have reported no significant cardiovascular changes (neither positive nor negative) in depressed patients treated with 5-HT reuptake inhibitors (Nemeroff et al., 1998; Roose et al., 1998a; Roose et al., 1998b), whereas others have reported adverse effects (see for instance Dawood et al., 2007).

Cardiac reflex mechanisms, mediated in part by the autonomic nervous system, are important in regulating cardiovascular function, and may play a role in the link between cardiovascular disease and depression. A reduction in baroreceptor reflex (i.e., baroreflex) sensitivity has been shown to differentiate high- from low-risk patients recovering from myocardial infarction and CHF (Mortara et al., 1997). Also, the combination of both reduced baroreflex sensitivity and reduced heart rate variability was of additional prognostic value in a sample of post-myocardial infarction patients, compared to that of either marker alone (La Rovere et al., 1998). In animal models of heart disease, reduced baroreflex sensitivity is associated with an increased risk of ventricular fibrillation during a brief ischemic episode (Billman et al., 1982; Schwartz et al., 1988). Also, coronary artery occlusion has been shown to attenuate the baroreflex control of heart rate both in anesthetized dogs and in humans (Trimarco et al., 1987; Airaksinen, 1999).

A few studies have demonstrated that depression in humans may be associated with reduced baroreflex sensitivity. Watkins and Grossman (1999) reported that baroreflex sensitivity was altered in cardiac patients with depression. However, baroreflex dysfunction in depressed individuals has not been consistently demonstrated in all studies. A more recent study from Watkins and colleagues (2002) found no association of baroreflex sensitivity with symptoms of depression in a sample of patients following acute myocardial infarction, however symptoms of anxiety were associated with reduced baroreflex sensitivity in this patient sample. It is possible that symptoms of anxiety may mediate the apparent link between depression and altered baroreflex sensitivity that has been reported in some studies. However, Dawood and colleagues (2007) showed no association between state or trait anxiety and altered baroreflex function in patients with major depression. Therefore, further studies are required to validate this hypothesis. An increase in cardiac sympathetic tone may be an important mechanism underlying the reduced baroreflex sensitivity in depression, as reduced baroreflex sensitivity has been observed in unmedicated depressed patients, but not in depressed patients treated with β-adrenergic receptor antagonists, following myocardial infarction (Pitzalis et al., 2001).

Autonomic and baroreflex mechanisms are associated with depressive signs in animal models

The discrepant findings from human studies regarding the specific autonomic and cardiac disturbances associated with depression highlight the need for well-controlled, experimental investigations involving valid and reliable animal model systems. Because the CMS model of depression possesses both face and predictive validity (Willner, 1997a; Willner, 1997c), it is a useful tool for investigating autonomic and cardiac dysfunction associated with depressive signs.

Recent studies with the CMS model indicate that specific autonomic mechanisms are likely to link depressive signs and cardiovascular dysregulation. Compared to unstressed control

groups, exposure to 4 weeks of CMS in adult male rats induced several basal cardiac alterations, including elevated resting heart rate and reduced heart rate variability (Grippo et al., 2002; Grippo et al., 2003a). Furthermore, when animals were perturbed with air jet stress (a novel stressor), we observed exaggerated pressor and heart rate reactivity in rats that were previously exposed to CMS versus the respective control groups. While the behavioral changes associated with CMS are shown to recover within a few weeks following cessation of the CMS protocol, these cardiovascular disruptions persist for a longer period, suggesting that simple removal of the depressive signs is not associated with alleviation of the underlying cardiovascular pathophysiology. Consistent with these findings are those from Carney and colleagues (2000), who suggest that while heart rate and heart rate variability may improve in treated depressed patients, they may never return to baseline levels.

Based on our initial experiments, we have concluded that exposure to CMS induces several basal cardiac changes and exaggerated cardiovascular reactivity to environmental stressors. The elucidation of the underlying mechanisms for these changes will be extremely useful for developing novel and effective treatments for patients with depression and heart disease. Thus, we have investigated specifically the potential autonomic and cardiac mechanisms underlying these basal and stress-reactive changes in the CMS model, showing that basal cardiac disturbances associated with CMS are mediated by elevated sympathetic drive (Grippo et al., 2002; Grippo et al., 2003a). Protocols involving selective pharmacological autonomic blockade have demonstrated that CMS is associated with a greater attenuation of heart rate following β-adrenergic receptor blockade with propranolol (2 mg/kg, iv), relative to an unstressed control group (Figure 4). β-adrenergic receptor blockade with propranolol also abolished heart rate variability differences between CMS and control groups. These results suggest that cardiac sympathetic tone is elevated in CMS, mediating directly the elevated basal heart rate and heart rate variability changes observed in this animal model of depression.

We have likewise investigated a potential cardiac mechanism, vulnerability to ventricular arrhythmias, in the link between depressive signs and cardiac dysregulation. Using the CMS model of depression, we examined the types and time course of ventricular arrhythmia development associated with anhedonia (Grippo et al., 2004). This study was conducted with an experimental protocol involving intravenous administration of aconitine, a pro-arrhythmic agent that induces ventricular arrhythmias by preventing the inactivation of sodium channels following generation of the action potential (Catterall and Ray, 1976; Honerjager and Meissner, 1983). Following exposure to 4 weeks of CMS or control conditions, aconitine was infused into anesthetized male rats over a period of several minutes, and the time to onset of different arrhythmias was recorded. Both simple (premature ventricular contractions) and complex (salvos and ventricular tachycardia) arrhythmias developed earlier in the CMS group relative to the control group (Figure 5). A re-examination of these data also indicates that a larger percentage of animals in the CMS group exhibited ventricular tachycardia versus those in the control group in response to aconitine administration (80% versus 42%, respectively), suggesting that CMS is associated with an increased susceptibility to ventricular arrhythmias when the cardiovascular system is perturbed. These results are especially important when considered in the context of findings from human populations. Carney and colleagues (1993) showed that patients with coronary artery disease and depression had a higher prevalence of ventricular tachycardia versus those patients without corresponding depression. Similarly, post-myocardial infarct patients are at a greater risk of mortality if they have a combination of premature ventricular contractions (greater than 10 per hour) and a high score on the Beck Depression Inventory [BDI (Beck et al., 1961)] relative to patients with fewer premature ventricular contractions or those with a low BDI score (Frasure-Smith et al., 1995). Taken together, the findings from humans and rodents suggest that signs and symptoms of depression may be directly associated with ventricular electrical instability, which can in turn influence cardiovascular function and disease outcomes.

Role of Behavioral Mechanisms

Behavioral mechanisms, including physical inactivity, may underlie depression and heart disease

Common behavioral mechanisms, only some of which can be modeled in animals, can underlie mood disorders, altered cardiovascular function, and potentially the links between these conditions. While not an exhaustive list, research from human studies and a limited number of non-human animal studies suggests that potential behavioral mechanisms can include: (a) poor adherence to medical regimens (Bollini et al., 2006; Rieckmann et al., 2006; Fenton and Stover, 2006), (b) negative health behaviors such as smoking, alcohol use or poor diet (Everson-Rose et al., 2004; Pelloux et al., 2005; Fenton and Stover, 2006), and (c) fatigue or physical inactivity (Appels and Mulder, 1988; van Deist and Appels, 1991; Bruce et al., 1994; Mendes de Leon et al., 1998; Kop, 1999). For the purpose of the present discussion, we will focus on physical inactivity as a behavioral mechanism that is common to both mood disorders and cardiovascular disease.

Chronic fatigue – a syndrome which can be characterized by persistent fatigue that is not substantially relieved by rest, sleep that is not refreshing, poor memory or concentration, frequent or recurring sore throat, headache of a new type, swelling of lymph nodes, muscle or joint pain, and/or depression (Straus et al., 1985; Centers for Disease Control and Prevention and National Center for Infectious Diseases, 2001) – is sometimes found in patients with depression (Puffer and McShane, 1992). Some of the behavioral similarities of depression and chronic fatigue syndrome suggest that these two conditions may share aspects of the same physiologic abnormalities. The antidepressant fluoxetine, for instance, is a successful treatment for some chronic fatigue patients (Klimas et al., 1993). Chronic fatigue syndrome may occur in individuals with a premorbid vulnerability to depression; however, psychological disturbances may be a consequence, rather than a cause, of chronic fatigue (Hickie et al., 1990).

Excess fatigue, particularly in elderly individuals, may play an important role in underlying the association of altered mood and cardiovascular dysregulation. In a study comparing the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV)* classification of major depression with exhaustion in American patients with cardiovascular disease, over half of the exhausted patients did not meet criteria for depression, whereas nearly all patients meeting criteria for depression also met criteria for exhaustion (Kop, 1999). Somatic symptoms of depression, including fatigue, may be responsible for affecting daily functioning in depressive disorders (Bruce et al., 1994). Also, the relationship between depressive symptoms and physical functioning may play an important role in the risk of cardiovascular disease in older women but not in older men (Mendes de Leon et al., 1998).

Excess fatigue also may be a precursor to myocardial infarction and sudden cardiac death (Rissanen et al., 1978; Appels and Mulder, 1988). “Vital exhaustion” includes loss of vitality and libido, listlessness, tiredness and increased irritability (Appels and Mulder, 1988; van Deist and Appels, 1991). Exhaustion may be a short-term risk factor for recurrent myocardial infarction, and is predictive of future myocardial infarction independent of blood pressure, smoking, cholesterol, age and the use of antihypertensive medications (Appels and Mulder, 1988). The possibility that fatigue and physical inactivity influence the relationship between depression and cardiovascular disease is supported by the finding that physical exercise is often included as a component of treatment programs for both depression (Perski et al., 1999; Paluska and Schwenk, 2000) and heart disease (McCartney, 1998; Braith, 1998). Strength training has been shown to improve both mood and self-esteem in cardiac rehabilitation patients (Beniamini et al., 1997). Further, exercise training has been shown to significantly improve heart rate variability, baroreflex sensitivity, blood pressure and vascular function (Kristal-Boneh et al.,

1995; Collins and DiCarlo, 1997; Zoeller Jr., 2007), which has implications for both cardiovascular disease and depression.

Some (but not all) patients with chronic fatigue show similar immune deficiencies to depressed patients, including elevated levels of cytokines (IL-1 and TNF-α), reduced natural killer cytotoxicity and impaired cell-mediated immunity (Klimas et al., 1990; Partarca et al., 1993). Additionally, some immune abnormalities in chronic fatigue patients are normalized following fluoxetine treatment (Klimas et al., 1993). Further, IL-1 has been shown to cause prolonged slow-wave sleep in both rats (Tobler et al., 1984) and rabbits (Krueger et al., 1984). These findings indicate that the condition of fatigue is associated with immune dysfunction, which may mediate both depressive signs and cardiovascular dysfunction. However, it will be necessary to systematically investigate interactions of fatigue and activity level, mood states, and cardiovascular function to elucidate the precise immunologic pathways involved in this link.

Physical inactivity and neurohumoral changes are observed in animal models

Previous studies from our laboratory have attempted to delineate the mechanisms underlying the associations among behavioral signs of depression, cardiovascular dysfunction, and fatigue or physical inactivity. For instance, in the CMS model, we have observed a reduction in spontaneous locomotor activity in adult male rats exposed to 4 weeks of CMS (Grippo et al., 2003b). This behavioral sign recovers approximately 3 weeks following cessation of the CMS protocol, which is similar to the time course in recovery of disrupted appetitive responses for rewarding stimuli (anhedonia) in the CMS model.

Physical inactivity may lead directly or indirectly to changes in autonomic and cardiovascular function. However, it is also possible that depression and heart disease share common features that are manifest in fatigue or associated with changes in physical activity. By using a model of disrupted sodium homeostasis, we have studied RAAS mechanisms associated with behavioral signs of depression and cardiovascular dysfunction (Grippo et al., 2006b). Disruption of body sodium and water balance has many behavioral, endocrine and autonomic effects, reviewed elsewhere (Johnson and Thunhorst, 1997; Johnson and Thunhorst, 2007). We demonstrated that sodium depletion in rats, induced by 2 injections of the diuretic agent furosemide combined with a sodium-deficient diet, reduced responding for rewarding electrical brain stimulation into the lateral hypothalamus, indicative of anhedonia. In a parallel experiment, the same sodium depletion paradigm led to a significant elevation of resting heart rate and blood pressure, and a reduction in heart rate variability. Related research suggests that rats with experimental CHF display a sodium appetite (Francis et al., 2001b). In the clinical setting, hyponatremia has been reported in patients with CHF, and has been shown to possess prognostic value for cardiovascular outcomes (LeJemtel and Serrano, 2007; Gheorghiade et al., 2007a; Gheorghiade et al., 2007b). Further, improved outcomes in acute heart failure are related to an improvement of circulating sodium levels (Rossi et al., 2007). These data provide additional evidence for the interrelatedness of sodium intake and balance, activation of the RAAS and cardiovascular regulation.

Activation of the RAAS may play a role also in the hedonic deficit in animals with a sodium deficit. For instance, in a related series of experiments, administration of the mineralocorticoid agonist deoxycorticosterone acetate (DOCA), which induces a sodium appetite in the absence of any sodium deficiency, produced anhedonia in rats measured via two independent operational tests (responding for lateral hypothalamic rewarding electrical brain stimulation and ingestion of 2% sucrose) (Morris et al., 2006). Of particular importance in this study was the finding that DOCA-treated rats that were allowed ad libitum access to saline did not significantly reduce their responding for either rewarding electrical brain stimulation or sucrose, suggesting that a persistent sodium appetite (e.g., “craving” for sodium) may be

capable of altering the behavioral sensitivity to other rewarding stimuli. Consistent with this hypothesis are findings from a study conducted by Willner and colleagues (1998), showing that induction of depressive signs in both humans and rats led to an increased appetite (e.g., "craving") for sweet rewards.

Role of Central Neurotransmitter Systems

Central neurotransmitter system dysregulation is associated with depression and altered cardiovascular regulation

Central nervous system processes are ostensibly changed in both mood disorders and cardiovascular disease; evidence for some of these changes has been discussed in the preceding sections. In the current section we will discuss the role of specific neurotransmitter system dysfunctions, with evidence derived primarily from pharmacological and anatomical studies.

Disrupted norepinephrine and dopamine function is implicated in the pathophysiology of depression (Lambert et al., 2000; Garlow and Nemeroff, 2004), and increased norepinephrine levels may play a role in the elevated risk of CHF in some depressed patients (Gold et al., 2005). Treatment with the antihypertensive drug reserpine, which depletes monoamine stores, may induce depression (Duman, 1999). Also, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) increase synaptic levels of monoamines in the central nervous system. Individuals who are dexamethasone test non-suppressors exhibit higher basal plasma concentrations of norepinephrine, as well as exaggerated levels of norepinephrine in response to a cold challenge, versus patients who are suppressors (Roy et al., 1987). Pharmacologic agents that affect central dopaminergic actions also are effective antidepressants (Muscat et al., 1992; Cheeta et al., 1994; Willner, 1995; Willner, 1997b; Foley et al., 2006). It is likely, therefore, that the pathophysiology of depression involves some dysregulation of monoamine systems in the brain. The precise central mechanisms involved in the pathogenesis of depressive syndromes, however, are not well understood.

For several years, research has focused on the role of the serotonergic system in depression. As reviewed elsewhere (Meltzer, 1990; Maes and Meltzer, 1995; Lucki, 1998; Ressler and Nemeroff, 2000), it has been reported that (a) 5-HT plays a significant role in behaviors that are disrupted in depression, such as mood, sleep and appetite, (b) a decrease in brain 5-HT concentration can precipitate depression in recovering patients, and (c) depression is associated with multiple changes in central 5-HT metabolism and 5-HT receptors, including decreased tryptophan concentrations, impaired 5-HT synthesis or release, changes in 5-hydroxyindoleacetic acid, malfunctions at postsynaptic 5-HT receptors and alterations in 5-HT transporter density. Furthermore, several classes of pharmacological antidepressants, including MAOIs, TCAs and 5-HT reuptake inhibitors, as well as electroconvulsive shock therapy, increase serotonergic neurotransmission (Owens and Nemeroff, 1994; Berman et al., 1999), and produce specific antidepressant-like effects in drug-screening models of depression such as the forced swim test (Cryan et al., 2005).

However, the precise central nervous system mechanisms of antidepressant treatments, and exactly how they act to alter depressive signs and symptoms, are not fully understood. Impaired function at the level of 5-HT type 1A (5-HT_{1A}), 5-HT type 1B (5-HT_{1B}) and 5-HT type 2 (5-HT_2) receptors has been identified in several neurological and psychological disorders, including depression (Roth, 1994; Lucki, 1998). For instance, an enhancement of 5-HT_2 receptor function has been described in depressed individuals (Mikuni et al., 1991), which may result from an increase in affinity or concentration of these receptors (Pandey et al., 1990; Kusumi et al., 1991). 5-HT_{2C} receptor gene polymorphisms and altered editing of 5-HT_{2C} receptors have been implicated in the pathophysiology of affective disorders (Lerer et al., 2001; Gutiérrez et al., 2001). Recent studies with a transgenic mouse model misexpressing an

RNA editing enzyme that affects the 5-HT_2 receptor indicate changes on behavioral tests that are consistent with endogenous depression and anxiety (Singh and Johnson, 2007). Also, it has been suggested that an impaired balance between 5-HT_{1A} and 5-HT_{2A} receptors may underlie depressive disorders (Berendsen, 1995; Blier, 2001).

5-HT reuptake inhibitors alter 5-HT neurotransmission and 5-HT receptor function in the brain. However, the effects of 5-HT reuptake inhibitors may differ depending on the brain region and the method of measurement. Daily injections of the 5-HT reuptake inhibitor fluoxetine for 3 weeks enhanced 5-HT synthesis and turnover in the hypothalamus, hippocampus and frontal cortex of the mouse brain; the mechanism for these changes may involve alterations at 5-HT_{1B} autoreceptors (Stenfors and Ross, 2002). In a more recent study, treatment of panic disorder patients with a 5-HT reuptake inhibitor led to a decrease in 5-HT turnover, using a measure of whole-brain turnover levels via 5-hydroxyindoleacetic acid spillover (Esler et al., 2007). Research from Van de Kar and colleagues (Van de Kar, 1989; Zhang et al., 2000; Sullivan Hanley and Van de Kar, 2003) suggests that functional changes at postsynaptic 5-HT_{1A} receptors are important in the mechanisms underlying 5-HT reuptake inhibitors and in the development of depressive signs and symptoms. These functional changes may provide a partial explanation for the delay in clinical effectiveness in some depressed individuals, despite potentially rapid inhibition of the 5-HT transporter with 5-HT reuptake inhibitors.

The serotonergic system interacts with endocrine and autonomic function to influence cardiovascular regulation. In addition to the antidepressant properties, drugs that alter brain 5-HT function can alter circulating concentrations of ACTH and cortisol or corticosterone (Fuller, 1996; Murphy et al., 1996). These effects are likely mediated by serotonergic innervation of CRF-containing neurons in the hypothalamic paraventricular nucleus (Bagdy and Makara, 1994). 5-HT actions in the hypothalamus may play a role in regulating hormonal responses to stressors (Van de Kar and Blair, 1999). For instance, antidepressant treatment restores the feedback inhibition of cortisol on the HPA axis that is dysregulated in some depressed patients (Barden et al., 1995). Similarly, destruction of hypothalamic 5-HT neurons with 5,7-dihydroxytryptamine has been shown to enhance the inhibitory effect of dexamethasone on the adrenocortical response to ether stress (Feldman and Weidenfeld, 1991).

The hypothalamic paraventricular nucleus, which receives serotonergic innervation, projects to the intermediolateral cell column of the spinal cord, rostral ventrolateral medulla and dorsal vagal complex to influence both sympathetic and parasympathetic outflow (Swanson and Sawchenko, 1980; Badoer, 2001). Related evidence regarding 5-HT and cardiovascular function suggests that blood vessels which have been damaged by hypertension or atherosclerosis are hypersensitive to the vasoconstrictor effects of 5-HT (van Zwieten et al., 1990). Also, Sole and colleagues (1983) observed altered 5-HT levels in the central nervous system of rodents with myocardial ischemia. More recently, Fumeron et al. (2002) found that a specific 5-HT transporter gene polymorphism was associated with a higher risk of myocardial infarction in males who survived an initial heart attack. Finally, dysfunction of blood platelets, which are regulated in part by 5-HT and can influence the pathogenesis of cardiovascular disease, has been described in depression (Bruce and Musselman, 2005; Mössner et al., 2007; Glassman, 2007). Taken together, these findings point to a possible link between depressive disorders and neuroendocrine and autonomic regulation, which can ultimately affect cardiovascular function.

Central neurotransmitter and receptor dysregulation is observed in animal models

Experimental research, involving whole-animal analyses of behavior and physiology as a result of pharmacological manipulations of the serotonergic system, may increase our understanding of the involvement of 5-HT in mediating mood and cardiovascular function. Recent studies

from our laboratory and our collaborators have focused on specific behavioral, neuroendocrine, and autonomic and cardiovascular effects of manipulation of 5-HT and 5-HT_{1A} receptors in rodent models. Because 5-HT reuptake inhibitors have been an extremely popular class of antidepressants in recent years (Advanstar Communications, 2007a; Advanstar Communications, 2007b), we have focused on the effects of fluoxetine on both behavioral and cardiovascular consequences of CMS in rats (Grippo et al., 2006a). Compared to treatment with saline vehicle, daily administration of fluoxetine (10 mg/kg, sc; administered concurrently with the CMS paradigm) in animals exposed to 4 weeks of CMS prevented anhedonia (i.e., prevented the reduction in sucrose consumption), yet only partially prevented the cardiovascular consequences of the stressors. Specifically, while basal heart rate in the CMS group was significantly elevated (relative to an undisturbed control group), administration of fluoxetine only slightly attenuated this increase in CMS-exposed rats. Similarly, sympathetic drive was elevated in rats exposed to CMS, but fluoxetine administration only partially attenuated this increase (Figure 6). These findings have implications for understanding the role of 5-HT in mediating depressive signs and cardiovascular dysfunction. Further, they provide additional evidence for the hypothesis that reduction of depressive signs does not automatically lead to a reduction in the underlying cardiovascular pathophysiology associated with this condition. However, reductions in heart rate have been described in patients with depression and cardiovascular disease treated with fluoxetine (Roose et al., 1998a), suggesting that this antidepressant may improve cardiac function in certain contexts.

In a related study, we investigated the effects of acute (4 days) fluoxetine administration (10 mg/kg, ip) on regulating sympathetic nervous system activity in a rodent model of cardiovascular deconditioning (hindlimb unloading) (Moffitt and Johnson, 2004). Compared to saline vehicle, short-term administration of fluoxetine (10 mg/kg, ip) in animals exposed to 2 weeks of hindlimb unloading – consisting of elevating the hindlimbs of the animals with a harness – enhanced baroreceptor reflex control of lumbar sympathetic nerve activity. The results from this study suggest that, in animals with a disrupted autonomic balance, fluoxetine administration may reduce sympathetic tone and restore autonomic balance (and consequently baroreflex function). When considered in the context of mood changes and cardiovascular dysfunction, these data indicate that alterations in serotonergic function, particularly via changes at the level of the 5-HT transporter, can influence directly autonomic control of cardiovascular function. Consistent with this hypothesis are data from Sauer and colleagues (2003), demonstrating that the degree of 5-HT transporter affinity of a 5-HT reuptake inhibitor correlated positively with protection against myocardial infarction in users of 5-HT reuptake inhibitors following a first myocardial infarction.

We also have used the CMS model to investigate more directly the role of 5-HT receptor function in the control of HPA axis function (Grippo et al., 2005b). Activation of 5-HT_{1A} receptors in the hypothalamus with the selective 5-HT_{1A} receptor agonist (+)8-hydroxy-N,N-dipropyl-2-aminotetralin hydrobromide (8-OH-DPAT; 40 μg/kg, sc) attenuated the corresponding ACTH response in both female and male rats following 4 weeks of CMS versus control conditions. This finding suggests that 5-HT_{1A} receptor function may be altered in CMS, consistent with evidence from human depression and experimental studies involving the forced swimming model of depression in rodents (see Lucki, 1998). We have not yet extended our findings to investigate the potential autonomic and cardiovascular effects of 5-HT_{1A} receptor activation in CMS; however, because the endocrine and autonomic nervous systems interact within the brain, it is possible that dysfunction of 5-HT_{1A} receptors mediates the association of depressive signs and cardiovascular dysregulation. Future research should focus more directly on the hypothalamic paraventricular nucleus, as this is a site of integration for behavioral, endocrine and autonomic regulation (Swanson and Sawchenko, 1980; Van de Kar and Blair, 1999; Sullivan Hanley and Van de Kar, 2003).

Conclusions and Recommendations for Future Research

Statistics from *The Global Burden of Disease* project (Murray and Lopez, 1996; Mathers and Loncar, 2005) list cardiovascular disease and psychological depression as two of the most detrimental diseases in developed countries. Furthermore, it has been estimated that approximately 75,000 deaths each year in the United States among patients discharged after an initial myocardial infarction may be attributable to co-morbid depression (Carney et al., 1999). The present discussion highlights the significance of the co-morbidity of depression and cardiovascular disease, and underscores the need for understanding the mechanisms responsible for this link to improve public health.

Advancing our understanding of the mechanisms involved in mood and cardiovascular function may be achieved by the systematic investigation of central and peripheral nervous system processes using integrative research techniques. Future research will benefit from a specific focus on factors that are common to both mood states and cardiovascular regulation, including CRF and the HPA axis, the RAAS, pro-inflammatory cytokines and central neurotransmitter systems, as well as the interactions of these systems.

The research described here, including studies from human populations and animal models relevant to depression and CHF, provides a foundation for additional mechanistic investigations of brain-mind-heart interactions. It will prove profitable for future research to continue focusing on relevant animal model systems that have demonstrated validity and reliability. We recommend, similar to recent suggestions from Frazer and Morilak (Morilak and Frazer, 2004; Frazer and Morilak, 2005), that the development of an animal model focused on behavioral signs related to negative affect – i.e., the disposition to experience negative emotional states, including fear, hostility and sadness which underlies symptoms of mood and anxiety disorders (see Watson and Clark, 1984) – can lead to important investigations such as: (a) the neurobiological substrates of co-morbid affective disorders, such as depression and anxiety, (b) mechanisms underlying pharmacological actions in the central nervous system to modify the behavioral dimensions associated with affective disorders, and (c) mechanisms underlying the association of affective disorders with cardiovascular diseases and other general medical conditions. Suls and Bunde (2005) have similarly suggested that generalized negative affect, rather than specific depressed or anxious states, may explain elevated disease risk (e.g., increased risk of cardiovascular disease) in individuals with symptoms of depression or anxiety. To promote further experimental investigations of this construct, recent studies have focused on behaviors relevant to negative affect using novel rodent models (see Overstreet et al., 2003; Grippo et al., 2007).

This discussion also highlights the need for increased collaboration among epidemiologists, health psychologists, physiologists and neuroscientists, similar to the recommendations of Suls and Bunde (2005). Collaborations among clinical and experimental scientists can provide translational findings that have relevance for understanding mood and cardiovascular regulation in humans. This in turn can facilitate research that is focused on the integration of behavior, physiology and brain function in the context of mood and cardiovascular dysregulation. To this end, cross-species comparative studies such as those described by Vaidya and colleagues (2004) and Willner and colleagues (1998), support the utility of parallel studies in human and preclinical disease models.

With continued experimental investigations and increased interdisciplinary and translational collaboration, a greater understanding of and appreciation for the processes that lead to altered mood states and cardiovascular dysregulation can be achieved. The continued focus on animal model systems, in combination with the suggestions recently put forth by Evans et al. (2005) regarding a focus on both human research and clinical practice, will promote the development

of more effective treatments, and ultimately improve the quality of life and physical well-being, in patients with co-morbid mood and cardiovascular disorders.

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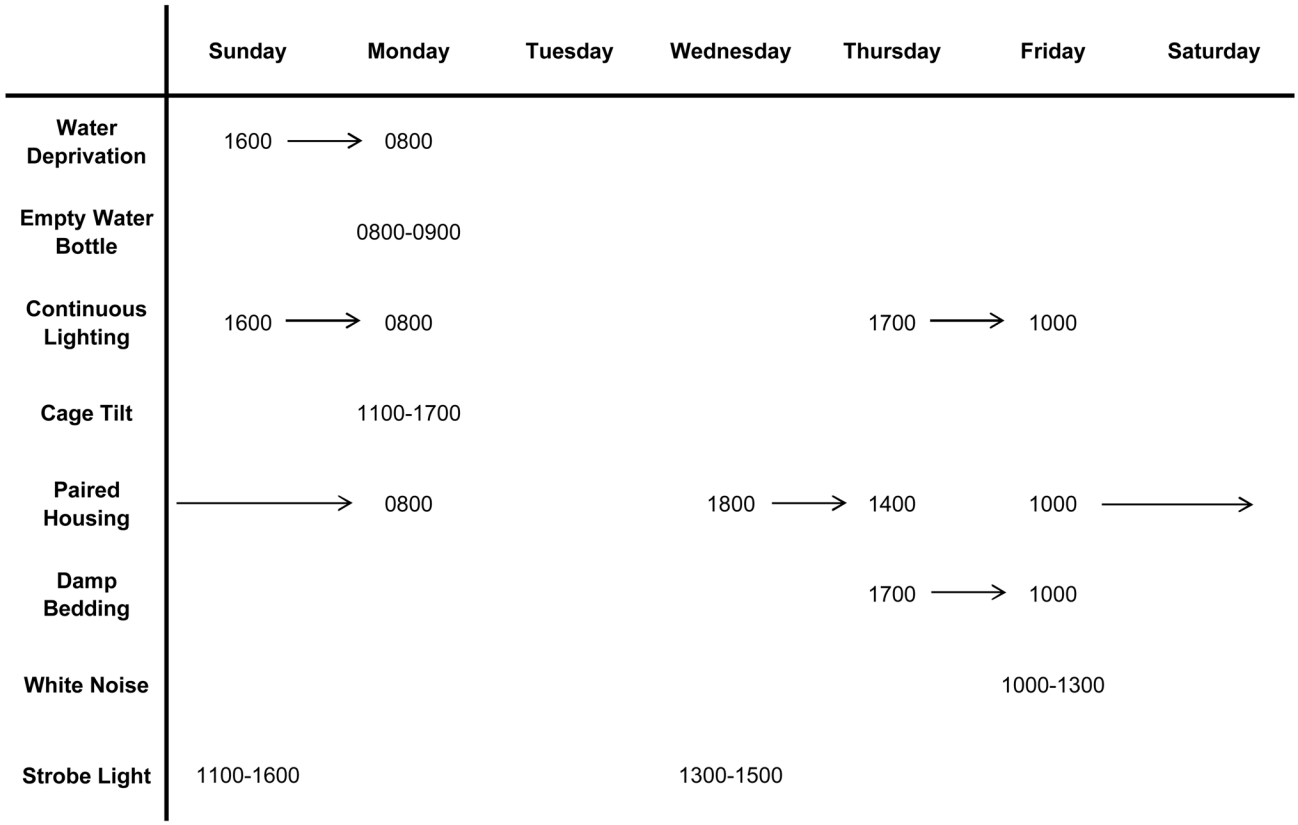

Figure 1.
Example of a chronic mild stress paradigm. Reprinted from (Grippo et al., 2006a); used with permission.

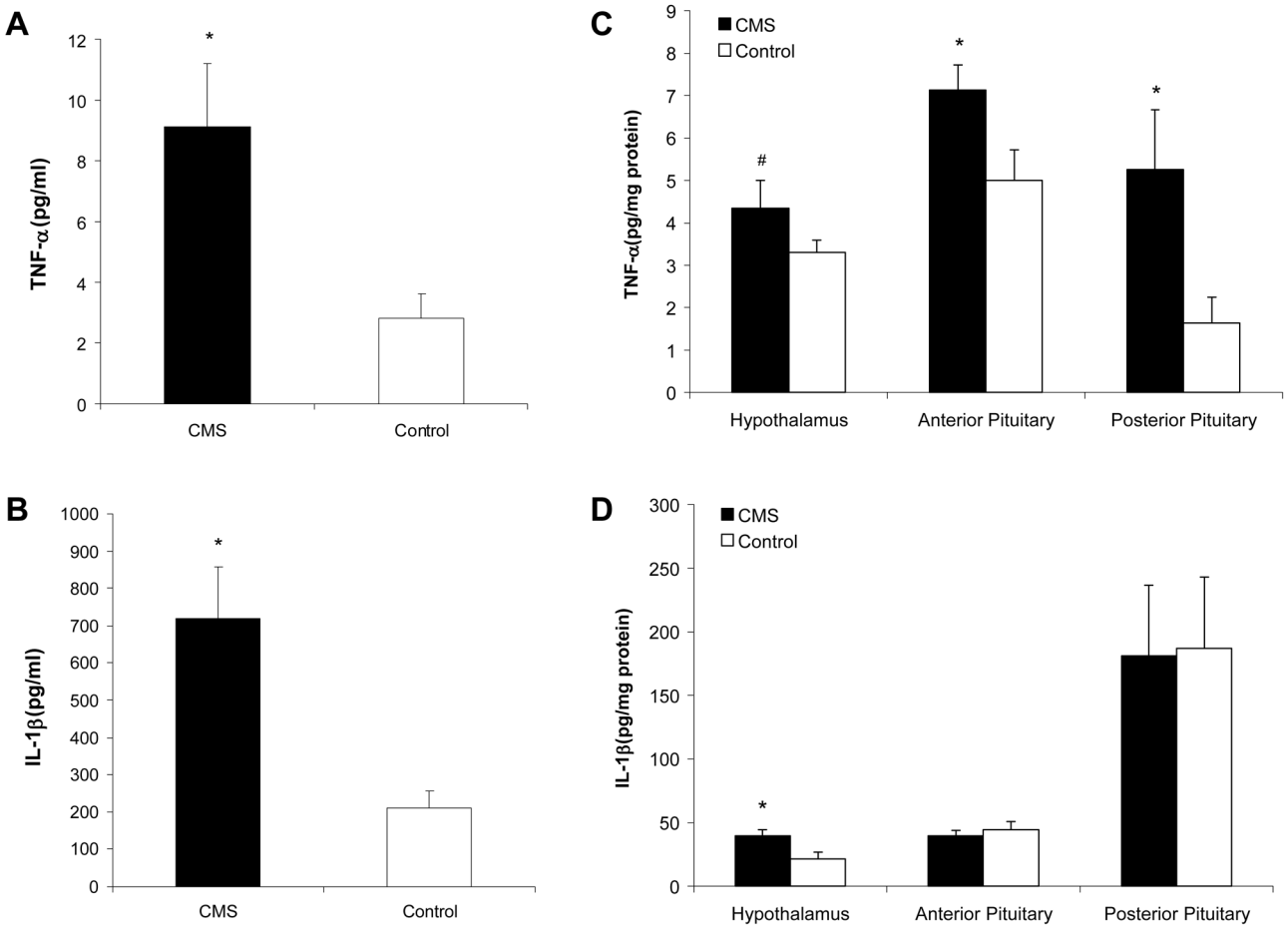

Figure 2.

Mean (+ SEM) levels of tumor necrosis factor (TNF)-α (Panels A and C) and interleukin (IL)-1β (Panels B and D) in the plasma (Panels A and B) and central nervous system (Panels C and D) in chronic mild stress (CMS) and control groups following 4 weeks of CMS. Both cytokine levels were increased in the plasma and specific central nervous system structures (*$P < 0.05$ vs. respective control value; $^{\#}P < 0.1$ vs. respective control value). Adapted from (Grippo et al., 2005a); used with permission.

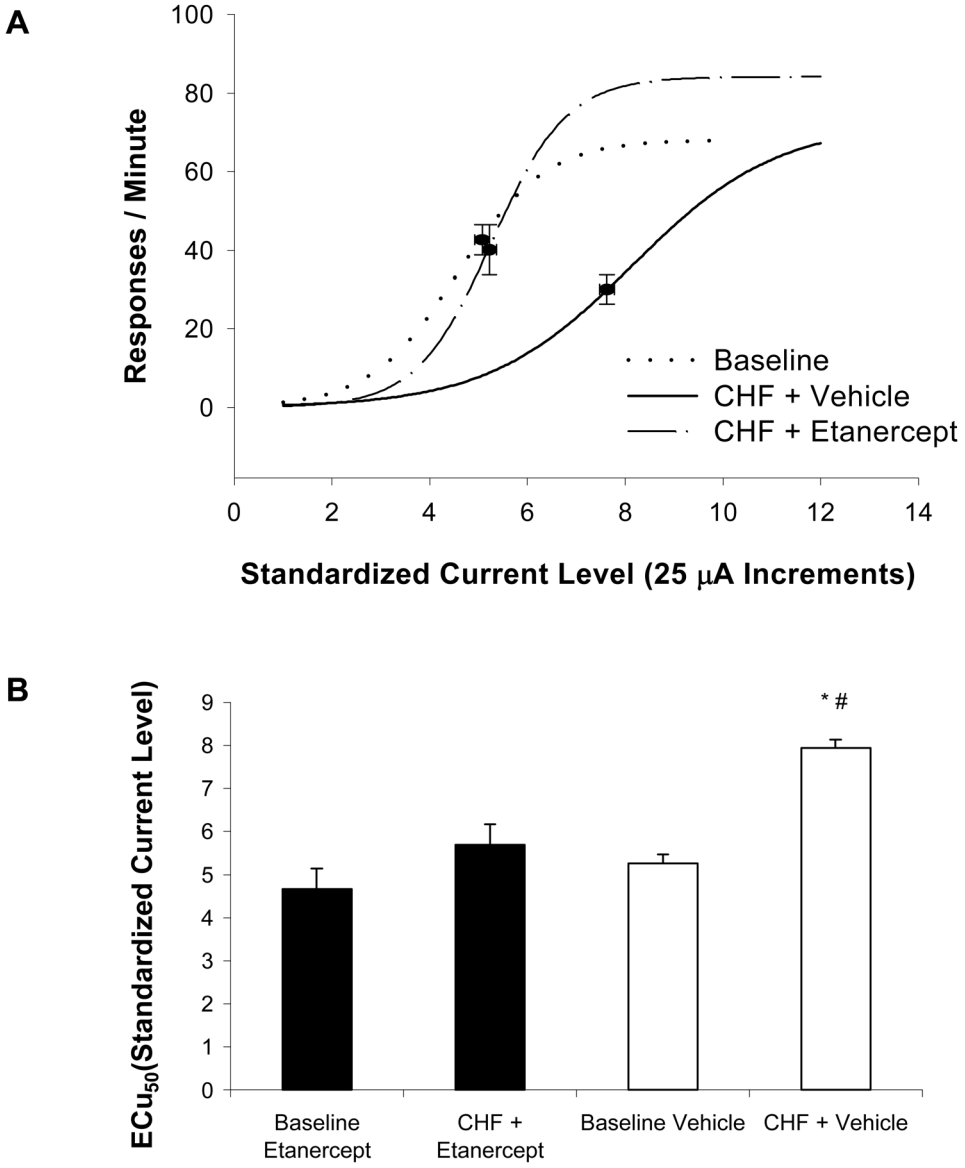

Figure 3.

Current-response functions illustrating the number of behavioral responses per minute at each level of standardized current (Panel A), and corresponding effective current 50 (ECu_{50}) values showing the standardized current intensity that supports 50% of the maximum response rate (Panel B), in rats with congestive heart failure (CHF) before and 24 hours following etanercept or vehicle treatment. CHF animals treated with vehicle displayed a parallel rightward shift in the current-response function and a corresponding increase in ECu_{50} value; CHF animals treated with etanercept displayed values similar to this group's respective baseline values and those of the control group (*$P < 0.05$ vs. Baseline Vehicle; $^{\#}P < 0.05$ vs. CHF + Etanercept). Modified from (Grippo et al., 2003b); used with permission.

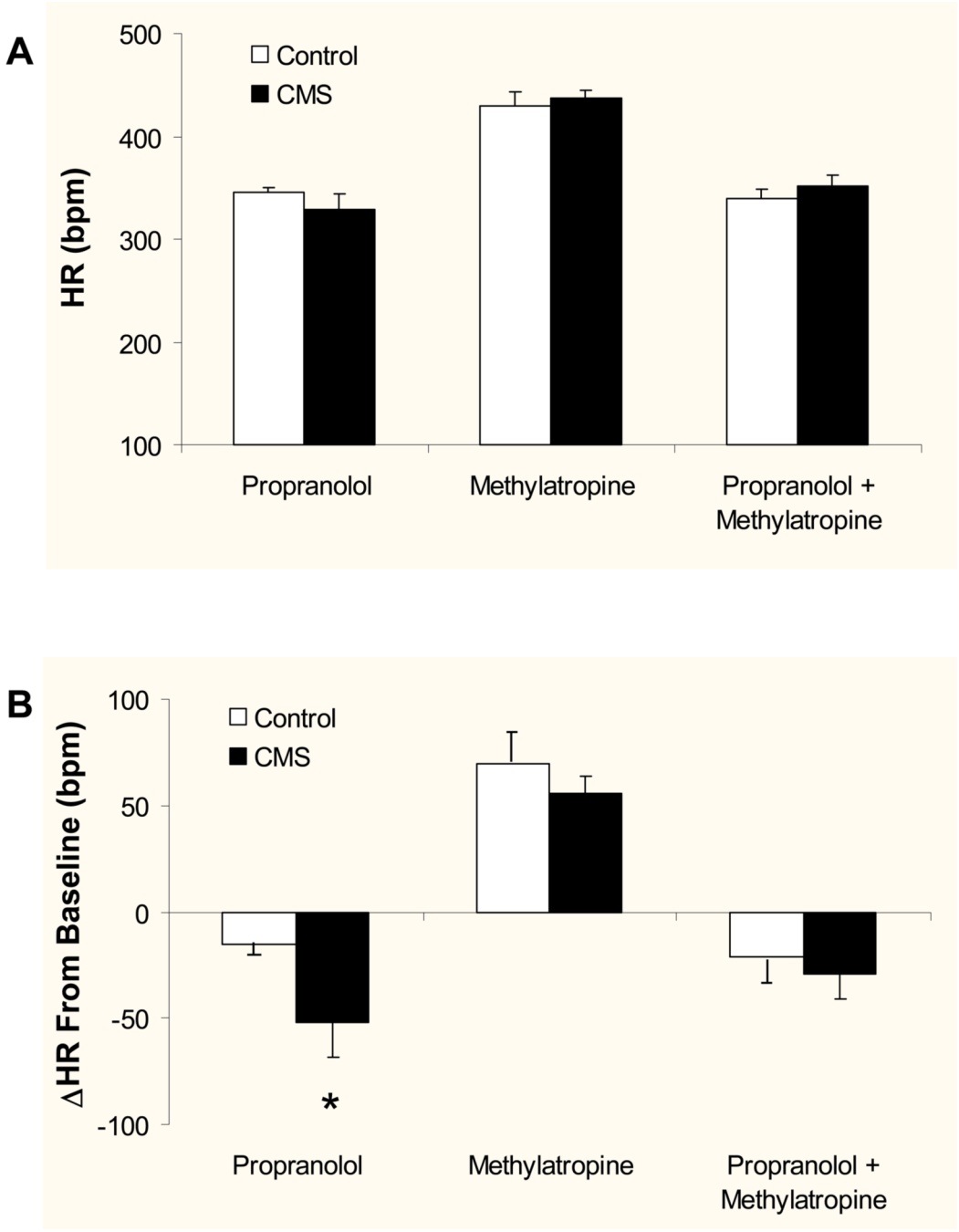

Figure 4.

Mean (+ SEM) absolute resting heart rate (HR; Panel A) and change in HR from baseline (Panel B) following selective and combined autonomic blockade in chronic mild stress (CMS) and control groups. The CMS group displayed a greater bradycardia in response to propranolol administration, compared with the control group (*P < 0.05 vs. respective control value). Reprinted from (Grippo et al., 2002); used with permission.

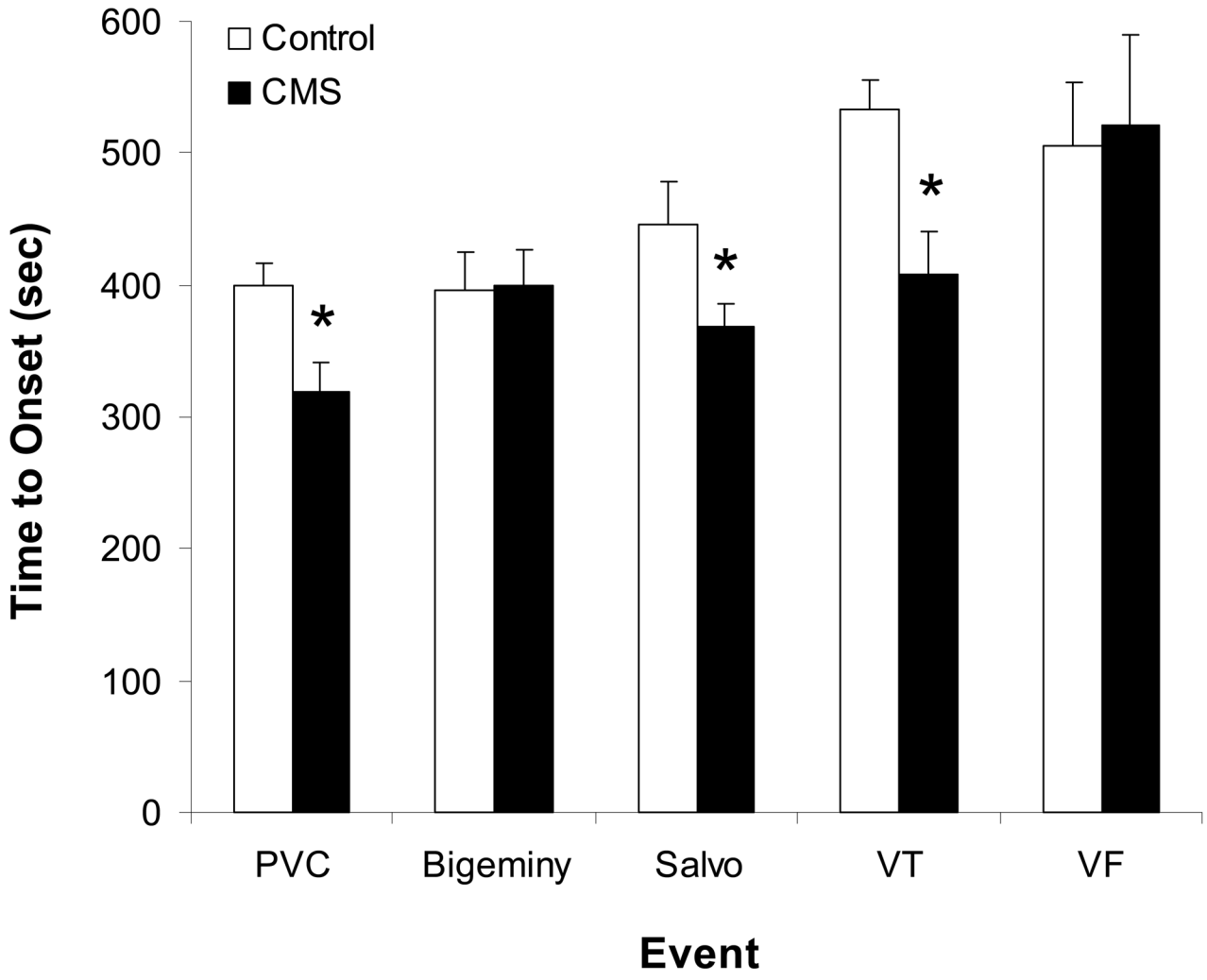

Figure 5.

Mean (+ SEM) time to the onset of premature ventricular contractions (PVC), bigeminy, salvos, ventricular tachycardia (VT) and ventricular fibrillation (VF) following intravenous aconitine administration in control and chronic mild stress (CMS) rats. CMS reduced the onset time to PVC, salvo and VT (*P < 0.05 vs. respective control value) following 4 weeks of CMS. Modified from (Grippo et al., 2004); used with permission.

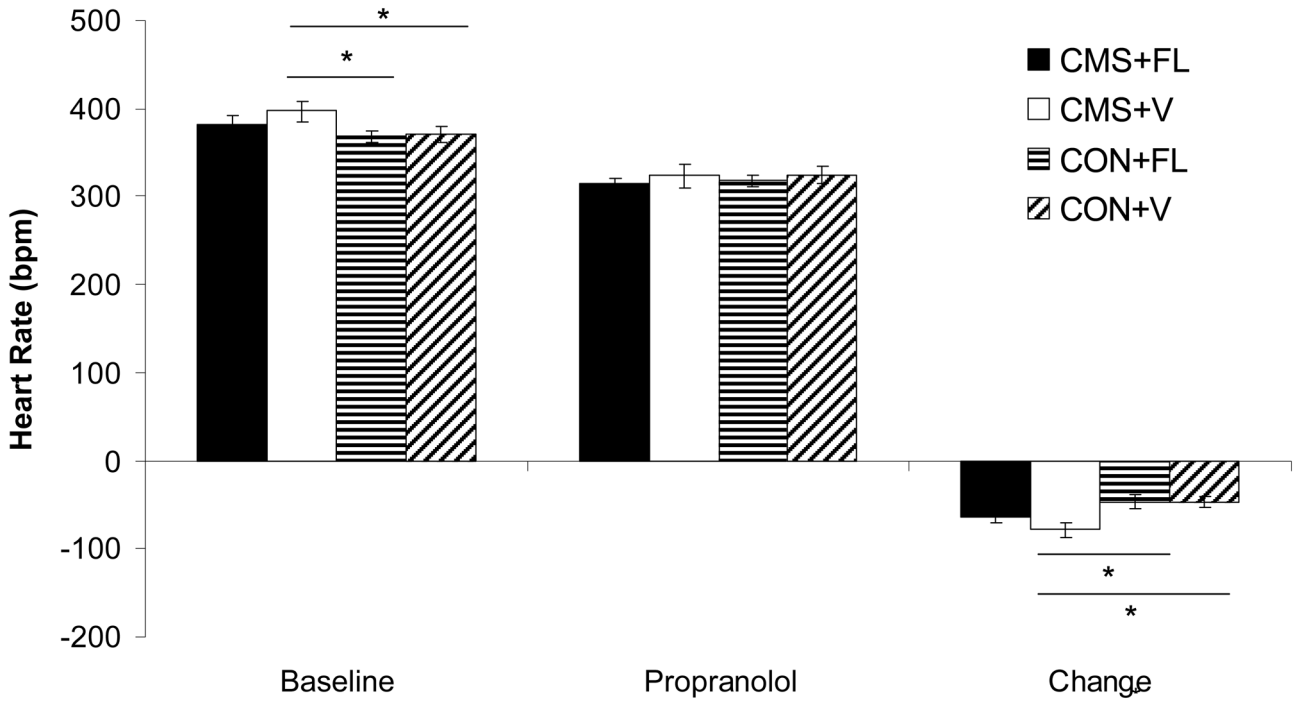

Figure 6.
Mean (+ SEM) absolute heart rate (HR) responses to β-adrenergic receptor blockade with propranolol (2 mg/kg, iv) and change in HR from baseline values, after 4 weeks of CMS, in chronic mild stress (CMS) and control (CON) groups treated with either daily fluoxetine (FL; 10 mg/kg, sc) or vehicle (V). Fluoxetine partially prevented the exaggerated reduction in HR following propranolol administration in the CMS group (horizontal lines denote paired *t*-tests; *P < 0.05 for the indicated comparisons). Reprinted from (Grippo et al., 2006a); used with permission.