



## Review

# Mechanisms underlying altered mood and cardiovascular dysfunction: The value of neurobiological and behavioral research with animal models

Angela J. Grippo\*

Department of Psychology, Northern Illinois University, Psychology-Computer Science Building Room 357, DeKalb, IL 60115, United States

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## ABSTRACT

A bidirectional association between mood disorders and cardiovascular diseases has been described in humans, yet the precise neurobiological mechanisms that underlie this association are not fully understood. This article is focused on neurobiological processes and mediators in mood and cardiovascular disorders, with an emphasis on common mechanisms including stressor reactivity, neuroendocrine and neurohumoral changes, immune alterations, autonomic and cardiovascular dysregulation, and central neurotransmitter and neuropeptide dysfunction. A discussion of the utility of experimental investigations with rodent models, including those in rats and prairie voles (*Microtus ochrogaster*), is presented. Specific studies using these models are reviewed, focusing on the analysis of behavioral, physiological and neural mechanisms underlying depressive disorders and cardiovascular disease. Considered in combination with studies using human samples, the investigation of mechanisms underlying depressive behaviors and cardiovascular regulation using animal models will enhance our understanding of the association of depression and cardiovascular disease, and will promote the development of improved interventions for individuals with these detrimental disorders.

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## 1. The importance of altered mood and cardiovascular dysfunction

Evidence obtained from epidemiological and clinical investigations in humans and a limited number of experimental investigations in non-human animals suggests that there is a bidirectional

\* Tel.: +1 815 753 7070; fax: +1 815 753 8088.  
 E-mail address: [angelagrippo@niu.edu](mailto:angelagrippo@niu.edu).

association between mood and cardiovascular dysfunction. Cardiovascular pathophysiology, such as coronary artery disease, myocardial infarction and congestive heart failure (CHF), is significantly related to altered mood states, and conversely depressive syndromes are considered to be risk factors for cardiac morbidity and mortality (Penninx et al., 2001; Carney and Freedland, 2003; Freedland et al., 2003; Van der Kooy et al., 2007; Glassman, 2007). The association between altered mood and cardiovascular disease is independent of traditional cardiovascular risk factors (e.g., hypertension, high cholesterol, increased body mass index, history of cardiac-related problems, disease severity), and has been demonstrated in individuals both with and without a history of cardiac pathophysiology (Penninx et al., 2001; Carney and Freedland, 2003; Frasure-Smith and Lespérance, 2003; Wulsin and Singal, 2003).

The influence of affective states on cardiovascular dysfunction is well documented. Previous studies suggest that the presence of depression doubles the risk that patients with newly diagnosed cardiovascular disease will experience an adverse cardiovascular event within 12 months (Carney et al., 1988), and individuals with depression are at a greater risk of cardiac-related mortality for up to 10 years following the diagnosis of established cardiovascular disease, relative to non-depressed control subjects (Barefoot et al., 1996). Similarly, major depression is a significant predictor of mortality in patients at both 6 and 18 months following myocardial infarction, independent of other factors such as arrhythmias and history of previous myocardial infarction (Frasure-Smith et al., 1993, 1995). Depression also predicts incidence of cardiovascular disease and cardiac-related mortality in initially healthy individuals (i.e., those without a history of cardiovascular pathophysiology). For instance, both major and minor depression are related to an increased risk of cardiac-related mortality in patients without cardiac diseases at baseline (however the excess mortality risk is higher for major versus minor depression) (Penninx et al., 2001). Additional prospective studies, reviewed elsewhere (Wulsin and Singal, 2003), have reported similar effects.

Psychological status influences cardiovascular function, and because the cardiovascular system feeds back to the brain, cardiovascular function in turn can directly or indirectly produce altered mood states. For instance, 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 myocardial infarction may be approximately 45% (Schleifer et al., 1989), and might be higher in patients with chronic cardiovascular conditions such as CHF (Freedland et al., 2003).

The bidirectional link between mood disorders and cardiovascular dysfunction represents an important worldwide public health concern. Statistics from *The Global Burden of Disease* (Mathers and Loncar, 2005) describe cardiovascular disease and psychological depression as two of the most detrimental conditions in developed countries, and they are predicted to remain so for several years. Furthermore, it has been estimated that approximately 75,000 deaths each year in the United States among patients discharged following myocardial infarction may be attributable to comorbid depression (Carney et al., 1999). Considered together, these data suggest that understanding the mechanisms responsible for the association of mood and cardiovascular function will have a positive impact on public health and welfare.

Although a large number of studies have indicated the importance of the association between mood disorders and heart disease, the precise pathophysiological mechanisms underlying this association remain unclear. In combination with research

involving human populations, experimental approaches that focus on reliable and valid animal disease models will provide translational results and offer insight into causal and common mechanisms underlying the link between mood and cardiovascular regulation. Given these considerations, the purpose of the present article is twofold. First, it will provide a brief summary of common mechanisms in depression and altered cardiovascular regulation. Second, it will discuss the value of investigating potential neural, physiological and behavioral processes involved in this association using model systems in rodents.

## 2. Potential common mechanisms underlying mood and cardiovascular function

Common mechanisms involved in the link between depression and cardiovascular disease may include reactivity to exogenous stressors, alterations of neurohumoral, immune and autonomic regulation, and dysfunction of neurotransmitter systems. While not an exhaustive list of potential mechanisms, these neurobiological changes will be summarized with a specific focus on clinical and experimental research and the role of integrative processes.

### 2.1. Behavioral and physiological reactivity to exogenous stressors

Exposure to environmental stressors has been shown to be responsible for influencing the development of both mood disorders and cardiovascular diseases. The presence of chronic, unpredictable or uncontrollable stressors does not favor behavioral or physiological adaptation, and therefore may play an important role in the development of depressive signs and symptoms (Anisman and Matheson, 2005) and cardiovascular dysregulation (Sgoifo et al., 2001b). The predisposing influence of environmental stressors on depression has been reviewed in detail elsewhere; several lines of evidence indicate that uncontrollable and unpredictable stressors are associated with depressive syndromes in humans and depression-like behaviors in animal models (Swaab et al., 2005; Anisman and Matheson, 2005; Monroe and Harkness, 2005). Exposure to these types of stressors also contributes to cardiovascular diseases and their antecedent risk factors, such as hypertension, changes in vascular resistance, endothelial dysfunction, altered baroreceptor reflex function and ventricular arrhythmias (Johnson and Anderson, 1990; Sanders and Lawler, 1992; Bairey Merz et al., 2002; Schwartz et al., 2003). Exposure to environmental stressors produces alterations in central processes, including changes in norepinephrine, dopamine, serotonin (5-HT) and corticotropin-releasing factor (CRF), as well as activation of neuroendocrine, immune and autonomic nervous systems (Herman et al., 1982; Joseph and Kennett, 1983; Adell et al., 1988; Vaidya, 2000; Anisman and Matheson, 2005), producing alterations in both mood and cardiac dysfunction (see additional discussion of these systems in Sections 2.2 and 2.3).

### 2.2. The integration of neurohumoral, immune and autonomic function

It is possible that reactivity to exogenous stressors leads to altered mood and cardiovascular regulation via neuroendocrine or neuroimmune systems, or through a disruption of autonomic function. For example, the hypothalamic–pituitary–adrenal (HPA) axis is dysregulated in depressed individuals, including: (1) alterations of CRF, (2) increases in circulating adrenocorticotropic hormone (ACTH), cortisol or corticosterone, and (3) impaired feedback regulation of the axis (Carroll et al., 1976; Raadsheer et al., 1995; Maes et al., 1998; Weber et al., 2000); these changes are not dissimilar to those observed following exposure to chronic

stressors. Similar changes – such as (1) alterations in corticosterone and ACTH, (2) impaired feedback control of HPA axis functioning, (3) impaired glucocorticoid receptor binding in the hippocampus, cortex and dorsal raphe nucleus, and (4) altered CRF input to the dorsal raphe nucleus – have been observed in several animal models of depression (Froger et al., 2004; Maier and Watkins, 2005; Grippo et al., 2005a,b). These changes provide evidence for neuroendocrine dysfunction in depression, which may influence cardiovascular regulation via several potential processes, such as activation of the immune system, release of humoral factors, or activation of the sympathetic nervous system.

The endocrine system interacts with the immune system both within the brain and in the periphery. Depression is associated with activation of immune system factors and disruption of immune processes; this evidence is reviewed in detail elsewhere (Maes, 1995; Zorrilla et al., 2001; Pollak and Yirmiya, 2002; Dantzer, 2006). However, it is not clear whether this activation is a cause or a consequence of altered mood states. For instance, activation of the HPA axis in depression or under conditions of stress can facilitate activation of the immune system via a network involving catecholamine and glucocorticoid actions (see Hawkey et al., 2007). Alternatively, Smith (1991) initially proposed a macrophage theory of depression, suggesting that excessive secretion of monokines such as interleukin (IL)-1, tumor necrosis factor (TNF)- $\alpha$  and interferon, contribute to the pathophysiology of depression. While the precise causal mechanisms involving depression and immune system changes are not entirely elucidated, activation of the immune system also is associated with specific cardiovascular disorders. For instance, pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 are released into the systemic circulation in CHF (Das, 2000). These have adverse effects on the heart and circulation (Kapadia et al., 1998), and therefore may feed back to the central nervous system to induce directly signs and symptoms of depression.

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). Several of these factors interact in the central and peripheral nervous systems, which may influence mood and cardiovascular function. For instance, angiotensin and the pro-inflammatory cytokines both activate the HPA axis to increase circulating glucocorticoids and catecholamines (Pollak and Yirmiya, 2002). These systems interact in the brain, where aldosterone stimulates circulating TNF- $\alpha$  levels, and in the periphery, where cytokines prevent the feedback inhibition of renin release by circulating angiotensin II (Felder et al., 2001). Such interactions can create a cycle whereby immune and other humoral changes during states of cardiovascular pathophysiology influence central nervous system processes, affecting mood states as well as endocrine and autonomic outflow.

Neurohumoral activation, manifest in both generalized and specific HPA axis dysfunction, RAAS activation and altered immune function, interacts with autonomic regulation of the heart (Thayer and Sternberg, 2006). Depression may be characterized by changes in autonomic function, including 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 (Carney et al., 1995; Krittayaphong et al., 1997; Watkins and Grossman, 1999; Pitzalis et al., 2001; Barton et al., 2007). Similar autonomic changes are associated with cardiovascular risk factors such as hypertension, increased body mass index and increased blood glucose, and have been observed in both acute and chronic cardiovascular conditions including atherosclerosis, myocardial ischemia, arrhythmias and CHF (Kannel et al., 1987; Carney et al., 1993; Kristal-Boneh et al.,

1995; La Rovere et al., 1998; Esler and Kaye, 2000). Depression may influence directly the development and/or progression of cardiovascular disease via effects on autonomic imbalance, cardiac rate or rhythm disturbances or ventricular instability; via afferent feedback, these changes can influence neurohumoral and neuroimmune activation. However, there are some discrepancies in the literature regarding the precise autonomic and cardiac changes associated with depressive disorders (see for instance, Watkins et al., 2002; Barton et al., 2007). Additional experimental investigations focused on whole-organism analyses may provide insight into the integration of neurohumoral, immune and autonomic regulation in mood disorders and cardiovascular disease.

### 2.3. The role of central neurotransmitter and neuropeptide systems

Several central nervous system processes are altered in both mood disorders and cardiovascular disease, and can be affected by behavioral, physiological or other neural inputs. Disrupted monoamine function has been implicated in the pathophysiology of depression (Lambert et al., 2000). Evidence from pharmacological studies indicates that monoamine oxidase inhibitors and tricyclic antidepressants have been used previously as effective antidepressants in some patients (see Garlow and Nemeroff, 2004). However, in the context of heart disease, these antidepressants have cardiotoxic effects, including pro-arrhythmic properties (Glassman, 1998). As a result, research has focused more specifically on the role of the serotonergic system in depression. As reviewed elsewhere (Maes and Meltzer, 1995; Lucki, 1998; Berman et al., 1999; Cryan et al., 2005), it has been reported that: (1) 5-HT plays a significant role in behaviors that are disrupted in depression (e.g., mood, sleep, appetite), (2) a decrease in brain 5-HT concentration can precipitate depression in recovering patients, (3) depression is associated with several changes in central 5-HT and 5-HT receptors (e.g., decreased tryptophan concentrations, impaired 5-HT synthesis or release, changes in 5-hydroxyindoleacetic acid, malfunctions at postsynaptic 5-HT receptors, alterations in 5-HT transporter density), and (4) pharmacological agents that alter 5-HT are effective antidepressants. Further, changes in the function of 5-HT type 1A (5-HT<sub>1A</sub>) receptors may play role in the link between depression and cardiovascular disorders (Nalivaiko, 2006).

Central monoamine systems interact with endocrine and autonomic function to influence cardiovascular regulation. The hypothalamic paraventricular nucleus receives serotonergic innervation and also projects to the intermediolateral cell column of the spinal cord, rostral ventrolateral medulla and dorsal vagal complex, which can influence both sympathetic and parasympathetic outflow in depression or during periods of chronic stress (Swanson and Sawchenko, 1980; Badoer, 2001). Also, 5-HT actions in the hypothalamus may regulate hormonal responses to stressors (Van de Kar and Blair, 1999). In related research, altered 5-HT levels have been found in the central nervous system of rodents with myocardial ischemia, and a specific 5-HT transporter gene polymorphism has been associated with a higher risk of myocardial infarction in males who survived an initial heart attack (Sole et al., 1983; Fumeron et al., 2002).

Pharmacological evidence suggests that treatment with the 5-HT reuptake inhibitor fluoxetine increased 24-h heart rate variability in depressed individuals (Khaykin et al., 1998). Similarly, the 5-HT<sub>2A</sub> receptor antagonist, nefazadone, reduced blood pressure and altered sympathetic tone in patients with major depression (Agelink et al., 2001). However, the treatment of depressed patients with 5-HT-altering drugs does not always result in improved autonomic or cardiovascular function; some

studies have found a lack of significant cardiovascular changes in depressed patients treated with 5-HT reuptake inhibitors (Nemeroff et al., 1998; Roose et al., 1998), while others have reported adverse cardiac effects (Dawood et al., 2007). It is possible that central 5-HT may mediate sympathetic outflow to affect heart rate variability through its ultimate effects on discharge of peripheral noradrenergic neurons or by its interactions with other central neurotransmitters such as dopamine.

A neuropeptide that has been receiving increased attention in the context of behavior and autonomic function is oxytocin (OT). In combination with arginine vasopressin (AVP), OT lies at the center of a neuroendocrine network to coordinate social behaviors and responses to various stressors (Carter, 1998; Neumann, 2002). OT may decrease the withdrawal characteristics of fear and anxiety, and increase tolerance for stressful stimuli, protecting the vulnerable mammalian nervous system from regressing into the primitive states of lower brainstem dominance (e.g., freezing, down-regulation of cortical processes) (Porges, 2007).

OT is particularly relevant to the consequences and causes of sociality, and to psychological disorders such as depression (Carter, 1998; Carter and Altemus, 2005; Heinrichs and Domes, 2008). Both OT and AVP have been shown to be altered in depressed patients; while AVP has been consistently increased, it is not clear whether OT's importance is due to an increase or a decrease of this peptide (Purba et al., 1996; van Londen et al., 2001; Carter and Altemus, 2005). Also, of particular relevance are findings from non-human animals showing that social withdrawal and behavioral immobilization in the face of environmental challenges, which are features associated with depressive disorders, are modulated by OT and AVP (Carter, 1998; Porges, 2001). Similarly, 5-HT reuptake inhibitors can cause an increase in OT and a reduction in AVP secretion (see Carter and Altemus, 2005).

While the precise relationship between OT and depression requires further investigation, OT regulates several processes that influence both mood disorders and cardiovascular regulation. This neuropeptide can down-regulate the HPA axis and corresponding affective reactions to stressors in humans (Legros et al., 1987; Heinrichs et al., 2003). In rats, intracerebroventricular OT administration attenuated stressor-induced corticosterone increases and anxiety-like responses (Windle et al., 1997). Neumann (2002) has reviewed evidence for the role of OT in mediating stressor reactivity, suggesting that its involvement is both brain region- and stressor-specific. OT also has several peripheral actions which can influence cardiovascular outcomes. For instance, OT has beneficial effects on blood pressure, and may play a role in regulating autonomic tone (Holst et al., 2002; Michelini et al., 2003). This peptide also has negative inotropic and chronotropic effects in isolated heart preparations, via its actions on cardiac OT receptors (Mukaddam-Daher et al., 2001). Additional studies will elucidate the precise interactions among neuropeptides, alterations in mood and cardiovascular function.

### 3. The value of experimental investigations using animal models

Difficulties exist in forming comprehensive theories to describe the mechanisms of interaction between mood disorders and cardiovascular disease, in part due to the lack of useful “biological markers” of mood disorders (see Mössner et al., 2007) and the limited experimental research focusing on neural, physiological and genetic processes underlying these conditions. Integrative research using valid and reliable preclinical models of disease, with a focus on whole-organism studies as well as cross-species comparisons, can permit a mechanistic analysis of the factors that influence depression and cardiovascular risk. Research with

animal model systems that includes a specific focus on core behavioral and neurobiological features of the conditions in question – that can be operationally defined, quantified, observed and systematically investigated – will offer the greatest translational potential. For instance, the key feature of anhedonia, which is central to depression (American Psychiatric Association, 2000), is influenced by psychological, neurochemical and physiological factors. This behavioral sign can be effectively mimicked in animal models, and can be combined with the systematic and quantitative evaluation of cardiovascular dysfunction such as autonomic imbalance, vascular changes, arrhythmias or myocardial ischemia.

Several animal models of depression have been developed and reasonably well validated. Non-human primate models involving cynomolgus monkeys (*Macaca fascicularis*) have focused on vascular responsiveness, neurotransmitter functions and social behaviors, among others, in the context of depression and/or cardiovascular disease (Hamm et al., 1983; Shively and Bethea, 2004). In rodents, such as rats or mice, validated models such as learned helplessness (Seligman, 1974; Maier and Watkins, 2005), chronic mild stress (CMS) (Katz, 1982; Willner, 2005) and behavioral despair (Porsolt et al., 1977; Cryan et al., 2005) have focused on behavioral and physiological consequences of depression, mechanisms of antidepressant treatments and potential etiological factors in mood disorders. Newer models in rodents have focused on exploring the role of the social environment in mediating affective signs and autonomic function (Sgoifo et al., 2001b; Bartolomucci et al., 2003; Grippo et al., 2007b). To highlight the utility of model systems involving rodents, the following sections will focus on two models that our laboratories have utilized as tools for investigating mechanisms involved in the link between depressive disorders and cardiovascular dysfunction.

#### 3.1. Example 1: chronic mild stress in rats

The CMS model of depression involves exposing rodents to a chronic period of unpredictable mild stressors such as strobe light, white noise, damp bedding and an empty water bottle; initial studies with this model in rats focused on behaviors related to depression and mechanisms underlying antidepressant treatments (Katz, 1982). The validity, reliability and utility of CMS have been described previously (Willner, 1997, 2005). Given the need for systematic and experimental investigation of the association between depression and cardiovascular disease, we have used the CMS model (Sprague–Dawley rats) to examine behavioral, physiological and central nervous system processes that may underlie these conditions.

Recent studies with the CMS model have provided insight into potential behavioral and physiological processes that are dysregulated in depression and cardiovascular disease. In a series of studies, adult, male rats were exposed to 4 weeks of CMS (versus undisturbed control conditions; see Fig. 1 for a typical CMS paradigm), which produced behavioral changes consistent with depressive syndromes (Grippo et al., 2002, 2003). These changes include reduced physical activity (reduced spontaneous activity in a running wheel) and anhedonia (reduced responsiveness to a previously defined rewarding stimulus), shown by a reduction in the consumption of a palatable sucrose solution (Fig. 2). CMS also produced several cardiac alterations, including elevated resting heart rate and reduced heart rate variability (time-domain analysis). Furthermore, rats that were previously exposed to CMS (versus control) displayed exaggerated pressor and heart rate reactivity when perturbed with a novel acute stressor (air jet stress). While the behavioral changes associated with CMS recover within a few weeks following cessation of the stressors, these cardiovascular disruptions persist across time, suggesting that

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Water Deprivation	1600 → 0800						
Empty Water Bottle		0800-0900					
Continuous Lighting	1600 → 0800				1700 → 1000		
Cage Tilt		1100-1700					
Paired Housing	→ 0800			1800 → 1400		1000 →	
Damp Bedding					1700 → 1000		
White Noise						1000-1300	
Strobe Light	1100-1600			1300-1500			

Fig. 1. Example of a chronic mild stress paradigm. Reprinted from Grippo et al. (2006), with permission, copyright 2006 Elsevier Limited.

simple remediation of the depressive signs is not associated with alleviation of the underlying cardiovascular pathophysiology. Consistent with these findings are those from Carney et al. (2000), suggesting that while heart rate and heart rate variability may improve in treated depressed patients, they may never return to baseline levels.

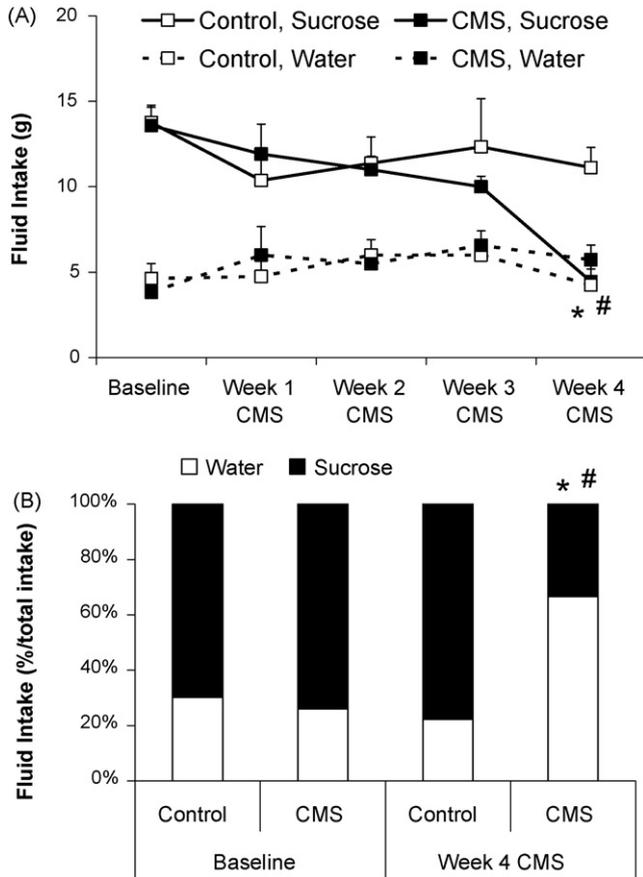
The elucidation of specific mechanisms underlying cardiovascular changes in the CMS model will be useful for developing novel and effective treatments for patients with depression and heart disease. To this end, we have investigated potential autonomic and cardiac mechanisms underlying the basal and stressor-reactive changes in the CMS model. Autonomic blockade with the  $\beta$ -adrenergic receptor antagonist, propranolol hydrochloride (2 mg/kg, i.v.), indicated that sympathetic drive is elevated following exposure to CMS (Grippo et al., 2002, 2003). Direct lumbar sympathetic nerve measurement suggested also that sympathetic activity is increased in the CMS model (Grippo et al., 2008a). Activation of the sympathetic nervous system mediates directly the elevation in heart rate and decrease in heart rate variability observed in this animal model of depression, and is consistent with autonomic changes in humans with depression and/or heart disease (e.g., Section 2.2).

CMS also may be associated with an increased vulnerability to ventricular arrhythmias. Following 4 weeks of CMS in adult, male rats, we examined the types and time course of ventricular arrhythmia development following intravenous administration of the pro-arrhythmic agent, aconitine (Grippo et al., 2004). CMS (versus control) was associated with a decreased threshold for the development of premature ventricular contractions (PVCs), salvos and ventricular tachycardia (Fig. 3). Further, an increased incidence of ventricular tachycardia was observed in the CMS group versus the control group, following aconitine administration. These findings suggest that signs of depression may be associated with ventricular electrical instability, which can in turn influence cardiovascular function and disease outcomes. These results are especially significant when considered in the context of findings from human populations. Carney et al. (1993) showed that patients with coronary artery disease and depression had a higher

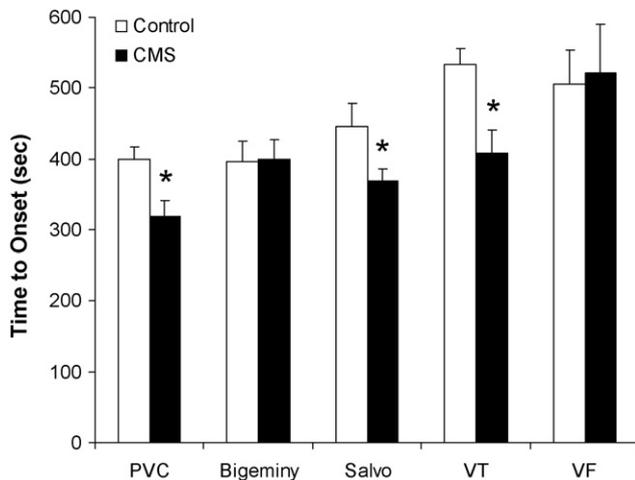
prevalence of ventricular tachycardia versus patients without corresponding depression. Similarly, post-myocardial infarct patients are at a greater risk of mortality if they have a combination of PVCs (greater than 10 per hour) and a high score on the Beck Depression Inventory (BDI) relative to patients with fewer PVCs or those with a low BDI score (Frasure-Smith et al., 1995). Further study of ventricular electrical instability in animal models, such as measures of the amount and type of arrhythmias in response to acute and chronic stressors, will provide additional insight into electrical instability as a mechanism underlying signs of depression and cardiovascular disease.

In addition to investigations of specific autonomic and cardiac responses, a related study involving the CMS model has experimentally investigated neuroendocrine and immune function associated with depression (Grippo et al., 2005a). 4 weeks of CMS exposure produced several neurohumoral and immune changes versus undisturbed control conditions, including: (1) increased circulating aldosterone and plasma renin activity, (2) increased circulating corticosterone, and (3) activation of the pro-inflammatory cytokines, TNF- $\alpha$  and IL-1 $\beta$ , in the plasma and in key central nervous system structures. These changes mirror those observed in human depression, and also are common in individuals with cardiovascular disease (e.g., Section 2.2). The findings from this study suggest that interactions of cytokines and the RAAS with central processes, such as activation of the HPA axis, might influence downstream functions such as the release of corticosterone or catecholamines, regulation of circulating cytokines and alterations in renin and aldosterone secretion, providing a potential physiological link between affective states and cardiovascular dysfunction.

The CMS model has utility for investigating behavioral and physiological changes associated with depressive disorders and the interactions of behaviors with cardiovascular function. In addition, this model may be especially useful for examining central nervous system processes associated with depression, such as the serotonergic system. In an initial study, we investigated the effects of fluoxetine on behavioral and cardiovascular consequences of CMS in rats by administering this 5-HT reuptake inhibitor daily for



**Fig. 2.** Mean (+S.E.M.) absolute water and sucrose consumption (Panel A) and percent preference for sucrose (relative to total fluid intake; Panel B) during a 1-h fluid intake test in chronic mild stress (CMS) and control groups at baseline and during 4 weeks of CMS. The groups did not differ in the amount of absolute fluid intake or sucrose preference during the baseline period. Following 4 weeks of CMS, the CMS group consumed significantly less sucrose, and showed a significantly reduced sucrose preference, vs. the baseline period and the control group ( $^*P < 0.05$  vs. control group at the same time point;  $^{\#}P < 0.05$  vs. respective baseline value). Modified from Grippo et al. (2002), with permission, copyright 2002 American Physiological Society.



**Fig. 3.** Mean (+S.E.M.) time to onset of premature ventricular contractions (PVC), bigeminy, salvos, ventricular tachycardia (VT) and ventricular fibrillation (VF) following intravenous aconitine administration ( $5 \mu\text{g}/\text{kg}/\text{min}$ ) following 4 weeks of chronic mild stress (CMS) or undisturbed control conditions. CMS reduced the onset time to PVC, salvo and VT ( $^*P < 0.05$  vs. respective control value). Modified from Grippo et al. (2004), with permission, copyright 2004 American Physiological Society.

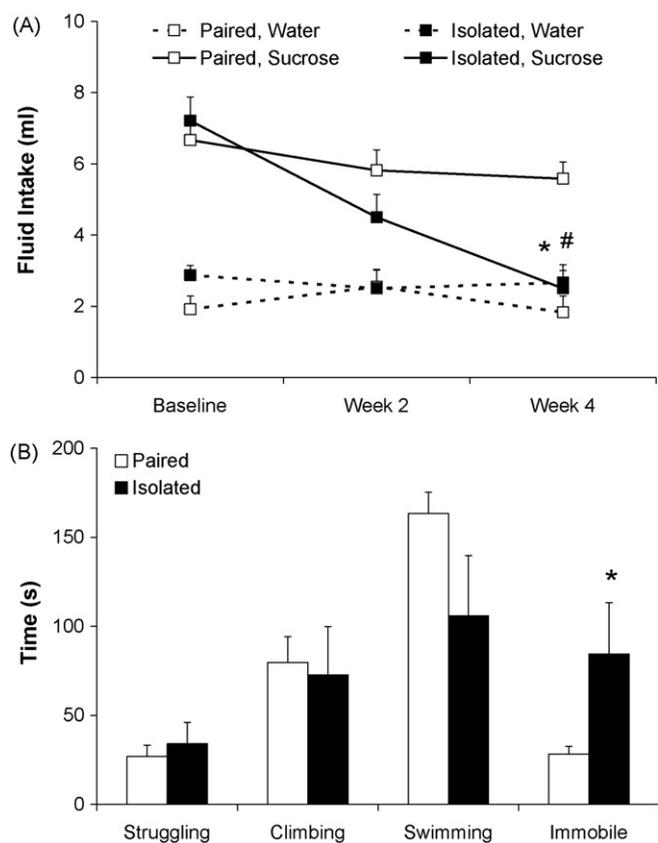
4 weeks (10 mg/kg, s.c.), concurrent with 4 weeks of CMS exposure (Grippo et al., 2006). Versus vehicle, fluoxetine administration in the CMS group prevented anhedonia, but only partially prevented the cardiovascular consequences of the stressors. Specifically, basal heart rate in the CMS group was significantly elevated (relative to control), but administration of fluoxetine only slightly attenuated this increase in CMS-exposed rats. A similar pattern of responses was observed for the elevation of sympathetic tone in the CMS group. These findings have implications for understanding the role of 5-HT in mediating depressive signs and cardiovascular dysfunction, and provide additional evidence for the hypothesis that reduction of depressive signs with traditional therapies does not automatically reduce the underlying cardiovascular pathophysiology associated with this condition. Data regarding fluoxetine administration in humans with depression and heart disease are inconsistent (see Nemeroff et al., 1998; Roose et al., 1998; Khaykin et al., 1998; Dawood et al., 2007); therefore, additional studies with rodent models may provide insight into the role of 5-HT reuptake inhibitor therapy and serotonergic mechanisms underlying mood and cardiovascular dysfunction.

### 3.2. Example 2: disruption of social bonds in prairie voles

The prairie vole (*Microtus ochrogaster*) is a highly social rodent species that is particularly dependent on social interactions for the regulation of behavior, endocrine and autonomic function. Socially monogamous species, such as prairie voles, share with humans a cluster of physiological and behavioral characteristics including the capacity to form social bonds and to develop extended families (Carter et al., 1995). Socially monogamous rodents are especially sensitive to the surrounding social context, and offer a powerful translational model for understanding the mechanisms through which both negative and positive social experiences influence behavior and cardiovascular function. Thus, the investigation of behavioral, physiological and neural consequences of disrupting established social bonds may be very informative in the context of mechanisms underlying mood and cardiovascular dysfunction.

Our recent research has focused on the behavioral and neurobiological consequences of long-term social isolation in adult female and male prairie voles. Our findings have demonstrated that at least 4 weeks of isolation from a same-sex sibling induces behaviors relevant to depression using validated operational measures, including anhedonia (reduced intake of sucrose) and learned helplessness (increased immobility in the forced swim test) (Fig. 4) (Grippo et al., 2007b, 2008b). These behaviors mimic those described in human depression (American Psychiatric Association, 2000), and are consistent with behavioral changes observed in the CMS model of depression (e.g., Section 3.1) and other studies using the prairie vole model (Bosch et al., 2004).

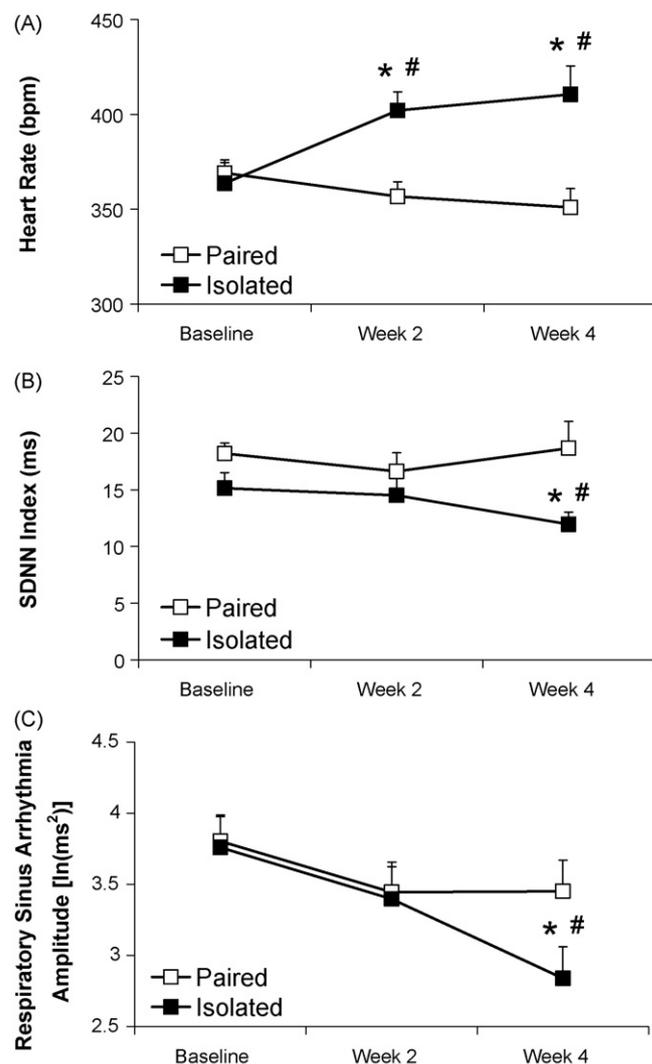
In addition to behavioral changes, we have begun to investigate autonomic and cardiac responses via radiotelemetry in freely behaving, untethered prairie voles as a function of social housing with a sibling versus isolation (Grippo et al., 2007b). 4 weeks of social isolation in adult, female prairie voles induced significant and progressive cardiac disturbances relative to paired conditions, including increased heart rate and reduced heart rate variability (Fig. 5); these changes are similar to those described following 4 weeks of CMS. Social isolation (versus paired conditions) also led to exaggerated tachycardic responses to an acute environmental stressor (5-min resident-intruder paradigm), as well as an increase in cardiac recovery rate following this stressor. These cardiac disturbances appear to be mediated by a significant withdrawal of vagal tone to the heart in isolated prairie voles, evidenced by a reduction in respiratory sinus arrhythmia amplitude (see Fig. 5C) and an attenuation of cardiac responsiveness to cholinergic



**Fig. 4.** Mean (+S.E.M.) water and sucrose intake in female prairie voles during a 1-h fluid intake test at baseline and following 2 and 4 weeks of isolation or pairing (Panel A), and amount of time spent struggling, climbing, swimming and immobile during a 5-min forced swim test following 4 weeks of isolation or pairing (Panel B). Social isolation reduced sucrose intake and increased immobility time in the forced swim test ( $P < 0.05$  vs. respective paired value;  $\#P < 0.05$  vs. respective baseline value). Modified from Grippo et al. (2008b), with permission, copyright 2008 John Wiley & Sons.

receptor blockade with atropine methyl nitrate (4 mg/kg, i.p.). Thus, social isolation has potent inhibitory effects on various behavioral and autonomic measures, providing a potential novel model for the investigation of the association between mood and cardiovascular dysfunction. Related findings from rats suggest that social stressors can influence physiological conditions such as cardiovascular disease, as well as affective behaviors (Sgoifo et al., 2001a).

A related series of studies has focused on behavioral and neuroendocrine regulation in socially isolated prairie voles, and may provide insight into central and peripheral changes relevant to both mood disorders and cardiovascular dysfunction. For example, 4 weeks of isolation from a same-sex sibling (versus pairing) was associated with anhedonia (progressive reduction in sucrose intake) in both female and male prairie voles (Grippo et al., 2007a). Additionally, both female and male isolated animals showed increased circulating OT and increased activation of OT neurons in the hypothalamic paraventricular nucleus following an acute stressor (5-min resident–intruder paradigm). However, isolation alone (without an additional acute stressor) produced an increase in central and circulating OT only in females. It is possible that females are more sensitive than males to the effects of social isolation; females and males may show a different time course of responsiveness to acute and chronic social stressors; or differences in the synthesis and/or effects of central neuropeptides exist between the sexes. Additional studies of social isolation,



**Fig. 5.** Mean (+S.E.M.) heart rate (Panel A), standard deviation of normal-to-normal intervals (SDNN index; Panel B), and amplitude of respiratory sinus arrhythmia (Panel C) in prairie voles at baseline and following 2 and 4 weeks of social isolation or pairing. Social isolation increased heart rate, and reduced SDNN index and respiratory sinus arrhythmia amplitude ( $P < 0.05$  vs. respective paired value;  $\#P < 0.05$  vs. respective baseline value). Reprinted from Grippo et al. (2007b), with permission, copyright 2007 Elsevier Limited.

behavior and physiological dysfunction are required to determine the precise nature of sex differences in social and neural mechanisms underlying depressive signs and physiological dysregulation. Indeed, as the prevalence of depression is greater in women than in men (American Psychiatric Association, 2000) – which may be a result of sex-based physiological differences, experience-based cultural, behavioral or social differences, or differences in reporting or clinical decision-making practices (among other potential reasons) – it is important to gain a better understanding of sex and gender differences in depression and the association of this condition with cardiovascular dysfunction.

While the precise mechanisms of the changes in OT in isolated female and male prairie voles have not been elucidated, it may be possible that the oxytocinergic system is activated in an attempt to compensate for altered neuroendocrine and autonomic regulation as a result of disrupted established social bonds. This possibility, along with previous findings suggesting that OT may serve to buffer behavioral and physiological responses to stressors (Legros et al., 1987; Windle et al., 1997; Neumann, 2002; Heinrichs et al.,

2003; Heinrichs and Domes, 2008), has led us to investigate the effects of exogenously administered OT on the behavioral and cardiovascular consequences of social isolation using the prairie vole model. Our preliminary findings suggest that daily administration of OT (20  $\mu\text{g}/\text{vole}$ ) during the final 2 weeks of a 4-week isolation period may prevent some of the detrimental behavioral and cardiac effects of isolation in female prairie voles, including anhedonia, increased heart rate and reduced vagal tone (Grippe et al., 2007c). Related findings suggest that OT has antidepressant properties (Arletti and Bertolini, 1987), and may modulate behavioral responses to short-term separation in rats (Insel and Wintink, 1991), however additional analyses are necessary to understand the precise role of the oxytocinergic system in mediating the association between depression and cardiovascular dysregulation.

### 3.3. Summary of findings and limitations from animal model investigations

Studies that focus on animal models can increase our understanding of the mechanisms of stress, autonomic and cardiac dysfunction, and social and neurobiological processes underlying mood and cardiovascular dysfunction. Investigations involving both rats and prairie voles indicate that reactions to the environmental context (e.g., responses to CMS or negative social stressors) can produce important behavioral and physiological changes that mimic the alterations observed in the human conditions. These experimental analyses indicate that sympathovagal imbalance – manifest in the form of altered heart rate and heart rate variability, increased cardiac reactivity both during and following acute stressors, susceptibility to ventricular electrical instability, an increase in sympathetic drive and a withdrawal of vagal tone to the heart – is an important mechanism for understanding the association of depressive behaviors and cardiovascular dysfunction. Additionally, neuroendocrine and immune dysfunction, including activation of the HPA axis, central and peripheral peptides and pro-inflammatory cytokines, play an important role in mediating behaviors, cardiovascular dysregulation and responses to stressors. Finally, administration of pharmacological substances, such as 5-HT reuptake inhibitors or peptides, provide additional insight into potential central processes (e.g., 5-HT or OT) that may underlie the link between depression and cardiovascular disease.

While experimental investigation of animal models can provide useful insight into some of the neurobiological mechanisms underlying the association of depression and cardiovascular disease, inherent limitations exist in animal analog research. Because mental disorders – such as depression – are multifaceted syndromes, including not only physiological and behavioral disturbances but also social and cognitive changes and self-reported symptomatology, it is not possible (or scientifically relevant) to model each aspect of these conditions in non-human animals. To overcome this barrier, it is important for animal model studies to include a focus on species-relevant manipulations (for instance, studies of social isolation in prairie voles because this species, like humans, is socially monogamous), employ validated and translational methodology (such as radiotelemetry for long-term recording of cardiovascular parameters in freely moving, conscious animals), and use observable, quantifiable, reliable and operationally defined dependent measures (such as sucrose intake as an operational definition of anhedonia in rodents). When these practices are employed, the findings from animal model investigations can be interpreted in the context of the empirical data, and the conclusions considered within the larger context of basic science investigations as well as clinical, epidemiological and

experimental studies in human samples. This can lead to a greater understanding of stress, depression, behavior and cardiovascular regulation.

## 4. Considerations for future research

Depression and cardiovascular disease are highly detrimental conditions; the comorbidity of these conditions is an important public health concern. To adequately address the mechanisms underlying these disorders, it will be beneficial to continue investigations of behavioral and neurobiological processes using valid, reliable and useful preclinical animal models in addition to research with community and clinical samples. Additional research will benefit from focusing on the relevance of the models in question and the validity of the methodological procedures to maximize the translational potential of the findings.

Integrative studies involving multi-system and cross-species analyses will enhance our understanding of the link between mood disorders and cardiovascular disease. This will require increased communication and collaboration among varying scientific fields, including clinical and experimental psychology, physiology and neuroscience. To this end, comparative studies conducted by interdisciplinary teams, such as those described by Willner et al. (1998) and Vaidya et al. (2004), support the utility of parallel analyses in humans and preclinical animal models. The continued focus on animal model systems, considered in combination with findings from human samples, will promote the development of more effective treatments and improve the quality of life for individuals with comorbid mood and cardiovascular disorders.

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