JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2006, 57, Suppl 11, 5–29
www.jpp.krakow.pl

A. K. JOHNSON[1], A. J. GRIPPO[2]

SADNESS AND BROKEN HEARTS: NEUROHUMORAL MECHANISMS AND CO-MORBIDITY OF ISCHEMIC HEART DISEASE AND PSYCHOLOGICAL DEPRESSION

[1]Departments of Psychology, Integrative Physiology and Pharmacology, and the Cardiovascular Center, University of Iowa, Iowa City, IA 52242-1407, USA [2]Department of Psychiatry and the Brain Body Center, University of Illinois at Chicago, Chicago, IL 60612, USA

Heart disease and depression are highly co-morbid. Clinical and experimental research over the past 70 years has led to several neurohumoral hypotheses of causative factors present under the conditions of either heart failure or of psychological depression. Some of these hypothesized factors are common to both disorders and are therefore attractive candidates to account for the high incidence of co-occurrence of depression and heart disease. One experimental approach to study the co-morbidity of heart failure and depression has been to study the behavioral, biochemical and physiological changes in a chronic mild stress model of depression and in heart failure induced by experimental myocardial infarction. Our studies have led us to focus on the pro-inflammatory cytokines, in particular tumor necrosis factor (TNF)-α, and the renin-angiotensin-aldosterone system. Both of these families of humoral factors are elevated in human heart failure and in depression and the two experimental models we have studied. The demonstrated validity of each of these models will be of great value in elucidating the nature of the actions and interactions of these humoral agents as they contribute to the co-morbid conditions of heart failure and depression.

Key words: *renin-angiotensin-aldosterone, pro-inflammatory cytokines, chronic mild stress model of depression, anhedonia, myocardial infarction-induced model of heart failure, tumor necrosis factor (TNF)-α, hypothalamic-pituitary-adrenal axis, brain amine systems*

THE IMPACT OF DEPRESSION AND HEART DISEASE ON PUBLIC HEALTH AND THE CO-MORBIDITY OF THESE DISORDERS

Ischemic heart disease is currently the leading worldwide cause of death and is projected to remain so for several decades (1). In 2002, in terms of disability adjusted for life years, unipolar depressive disorders were fourth in the world, but are predicted to become the second-ranked disorder by the beginning of the third decade of this century (1). Clearly both heart disease and psychological depression represent major health concerns currently and well into the future. However, what is now recognized as a compelling and perplexing fact is that having either depression or heart disease increases the likelihood of developing the second disorder (2).

Early studies (see 3 - 6 for review) investigating the co-morbidity of cardiovascular disease and mood disorders indicated that patients with heart disease are more likely to suffer from depression than otherwise healthy individuals. About 5% of American adults have major depression, but the prevalence of this psychological disorder at any point in time is on the order of 33 (7) to 45% (8) in those patients who survive a myocardial infarction (MI) and is approximately 50% in patients with congestive heart failure (CHF) (9). This type of co-morbidity is of particularly serious concern because major depression doubles the risk that within 12 months a given patient with newly diagnosed coronary artery disease will experience an adverse cardiovascular event (*e.g.*, MI; stroke) (10). Compared to non-depressed patients, those with low mood are found to be at greater risk for cardiac-related death up to 10 years following the diagnosis of coronary artery disease (11). Additional studies indicate that major depression is a significant predictor of mortality in patients at both 6 (12) and 18 (13) months following MI. In other terms, the impact of depression on subsequent morbidity and mortality in patients with heart disease is equivalent to that of left ventricular dysfunction (12), a history of previous MI (13), or smoking (14).

Importantly, depression is also associated with cardiovascular pathology in patients with no history of heart disease. Pratt and colleagues (15) found that in 1,551 people who were free of heart disease, those that had a history of depression were 4 times more likely to suffer a heart attack in the next 14 years than those who did not have the mood disorder. These results confirm earlier work indicating that there is a higher than expected incidence of depression before there is any apparent cardiovascular disease in patients who later go on to develop the latter pathology (16). Specifically, depression is an established risk factor for heart disease (17). It is worth noting that depression is not a predisposing factor for all types of major disorders; for example, as a recent review concludes depressed individuals are not at higher risk for cancer (18).

The cause or causes of the high co-morbidity of depression and heart disease are unknown. However, it seems reasonable to hypothesize that there are points of convergence in the etiology or pathological progression of each illness which produce factors common for both disorders. The identification of candidate mediators common to heart disease and depression can serve as an important source of hypotheses to generate research investigating why these disorders are so frequently co-morbid.

Three relationships between heart disease and depression and the factors that potentially may relate the two are presented in *Fig. 1*. One model proposes that each of the two disorders gives rise to a different by-product (*e.g.*, physiological state or humoral factor) that in turn can produce the second disorder. A second suggests that one common factor gives rise to both disorders. Finally, a third proposes that either depression or ischemic heart failure gives rise to one or more factors that are common to both disorders and that induces the second disorder. Such a common factor may also lead to the further progression of both diseases. This review will identify several of the primary candidate mechanisms and factors that have been proposed to cause or mediate the progression of heart disease or depression. It will then provide examples of experimental strategies which the authors have employed to begin to identify and explore the roles of candidate humoral factors and mechanisms that may be responsible for the co-morbidity of heart failure and psychological depression.

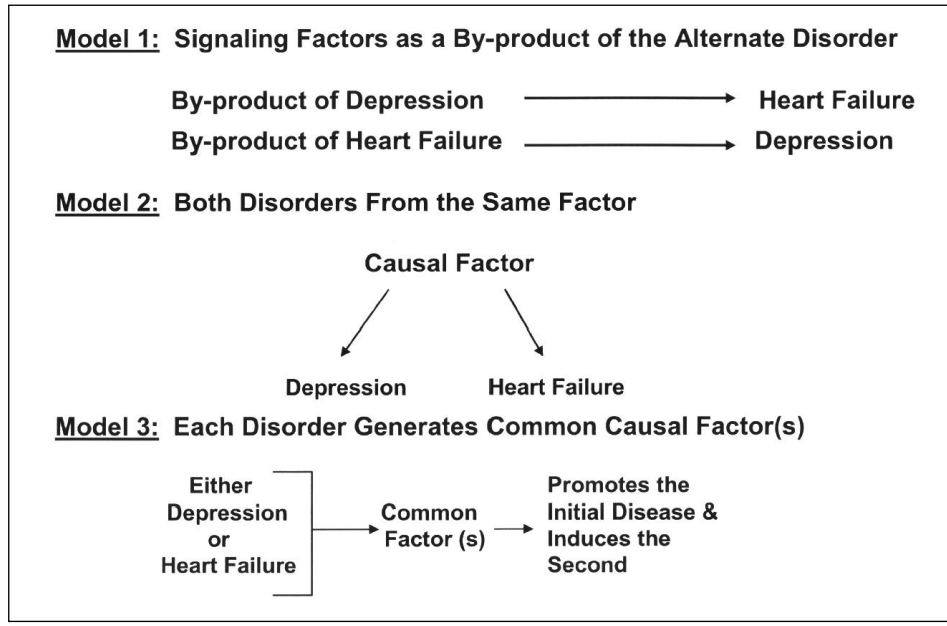

Fig. 1. Three alternative hypotheses to account for the co-morbidity of heart disease and depression.

DEPRESSION IS NOT MONOLYTIC BUT CAN BE CHARACTERIZED ON THE BASIS OF A CONSTELLATION OF ALTERED BEHAVIORAL, PHYSIOLOGICAL AND BIOCHEMICAL ENDPOINTS

The current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (19) defines *major depressive disorder* by the occurrence of at least one depressive episode. There are two essential criteria that must be met for a depressive episode. First, it is necessary to have a minimum of one of two core symptoms — either anhedonia or depressed mood - present for at least 2 weeks (19). Second, it is necessary to have at least five of eight other signs or symptoms. These are: 1) a change in body weight or hunger, 2) a change in sleep pattern, 3) a change in psychomotor activity, 4) fatigue or loss of energy, 5) diminished concentration, 6) feelings of worthlessness or guilt, 7) recurrent thoughts of death or suicide, or 8) the presence of both of the core symptoms (*i.e.*, anhedonia plus depressed mood).

Beyond DSM-IV-TR criteria there are additional physiologic and endocrine changes that accompany depression. For example, there is evidence of increased sympathetic nervous system activity, decreased parasympathetic activity, decreased heart rate variability, and increased cardiovascular reactivity (see 20 for review). In addition, several endocrine changes such as altered regulation of the 1) hypothalamic-pituitary-adrenal (HPA) system, 2) pituitary-thyroid axis, or 3) somatotropic system (21) may accompany depression. The endocrine changes in the HPA axis are the most common hormonal changes and have received the most extensive attention (see below) from both diagnostic and etiogenic perspectives.

Over the past 40 years, there have been several provocative biological theories of depression proposed. Currently, three of the most prominent focus on 1) altered function in brain monoamine systems, 2) the effects of stress on brain-adrenal systems, and 3) altered activity of the immune system.

Monoaminergic theories of depression

Beginning in the 1950's, the actions of several drugs that alter mood were evaluated at the neurochemical level. The antihypertensive drug reserpine induced effects that were considered by clinicians to be the same as naturally occurring depression. It was concluded that these effects were the result of drug-induced inhibition of vesicular storage of monoamines (dopamine, norepinephrine and serotonin). The finding that monoamine oxidase inhibiting drugs reverse reserpine-induced depression supported the monoamine theories of depression which in their simplest formulations are primarily theories of norepinephrine or serotonin deficiencies (22, 23).

The brain serotonin and norepinephrine systems both have divergent structural organizations. That is, relatively few hindbrain aminergic cell bodies project their axon collaterals to diffusely innervate nearly all forebrain structures. At least one of these biogenic amines has been implicated in the control of virtually every

known behavioral, cognitive and physiological response system. Consequently, altered biochemical parameters of even one of the monoamine systems are likely to affect multiple psychological and vegetative functions.

STRESS, THE BRAIN AND THE ADRENALS

The HPA axis and corticotropin releasing hormone [or factor; (CRF)] in depression

The high incidence of depression following the occurrence of a major negative life event (*e.g.*, death of a loved one, loss of a job or bad fortune) has led to the common hypothesis that sustained or repeated exposure to stressors can induces depression. Beginning with the experiments of Selye (24), the concept of stress has been linked to the HPA axis and, later more specifically, with systems associated with neural pathways containing CRF and the nuclei receiving these projections (*e.g.*, locus coeruleus; raphe nuclei). Depressed patients exhibit increased HPA activity. They are hypercortisolemic and many exhibit an impaired suppression of glucocorticoids in response to dexamethasone (25 - 27).

Because of the primary role of CRF in triggering activation of the HPA axis, it has been proposed that hypersecretion/hyperactivity of this peptide might underlie the hypercortisolemia and the symptomatology seen in major depression (28, 29). Elevated CRF levels have been found in the cerebrospinal fluid of depressed patients (29). There is an extensive network of CRF-containing neurons in the central nervous system in addition to the parvocellular neurons in the hypothalamic paraventricular nucleus that project to the median eminence and that control pituitary adrenocorticotropic hormone (ACTH) release. The increase in cerebrospinal fluid CRF in depression may reflect a parallel increase of activity in neurons where this peptide is performing as a classic hypothalamic releasing factor as well as in others where CRF is released in the brain in the manner of a neurotransmitter.

Descending CRF-containing axons from soma in the hypothalamic paraventricular nucleus project to the ventrolateral medulla and the intermediolateral column of the spinal cord. The parabrachial and dorsal motor nucleus of the X^{th} cranial nerve also receive CRF innervation from the central nucleus of the amygdala and the bed nucleus of the stria terminalis (28). These systems are likely to influence autonomic and visceral functions. Central administration of CRF increases blood pressure and heart rate *via* sympathetic activation (30). Intracerebroventricular injections of CRF also produce behaviors resembling those of animals exposed to stressors (31). Such heightened arousal to aversive environments or stimuli may reflect an action of CRF on the noradrenergic neurons of the locus coeruleus (28) or serotonin neurons in raphe nuclei (32). Dysfunction of the locus coeruleus and raphe system has been implicated in both anxiety and depressive disorders. Stress activation of forebrain CRF cell groups leading to altered function of brain stem monoaminergic cell groups may account for many of the vegetative, behavioral and cognitive changes associated with depression.

The renin-angiotensin-aldosterone system

Near the beginning of the modern era of the study of stress neuroendocrinology (24), there was an awareness that in addition to ACTH and glucocorticoids there are in fact many "stress hormones" (see for example 33). Interestingly the CRF-ACTH-cortisol cascade (*i.e.*, the HPA axis) became the prototypic stress hormone system and is synonymous with the concept of stress for many investigators. However, other neurohumoral agents require consideration and integration into the conceptual framework of stress biology. It is particularly notable that in his early investigation of stress Selye was nearly as attentive to the study of adrenal mineralocorticoids as he was to glucocorticoids. In a scholarly review in *Science* in the mid 1950's Selye (34) emphasized the role of ACTH in stimulating the release of both glucocorticoids and mineralocorticoids. He also noted the adrenal corticoids as often having antagonistic actions to one another. In particular, mineralocorticoids were described as *prophlogistic corticoids;* that is, having the capacity to stimulate the proliferative ability and connectivity of connective tissue and enhance inflammatory potential. In contrast glucocorticoids were characterized as *antiphlogistic corticoid*s or those that in his words "…inhibit the ability of the body to put up granulomatous barricades in the path of the invader." Selye had a major research interest in the role of mineralocorticoids in hypertension (35) and cardiomyopathy (36, 37).

It is not entirely clear why the HPA axis became the preeminent, prototypic "stress hormone" in many peoples' thinking, and why the role of aldosterone as a stress mediator received less attention. Perhaps it is because methods for studying the HPA developed more rapidly. Alternatively as is apparent in Selye's (34) review, the control of glucocorticoid release by ACTH was well recognized by the 1950's. However, it was not until the early 1960's that the role of the renin-angiotensin system as primary controller of aldosterone release was discovered (38 - 40).

Although long recognized and studied for their role in cardiovascular pathology (*e.g.*, hypertension), components of the renin-angiotensin-aldosterone system have recently attracted attention as potential mediators of depression. There is evidence to argue that blockade of the renin-angiotensin system improves mood. This work began with brief clinical accounts (41 - 45) in the mid 1980's indicating that patients treated with the angiotensin converting enzyme inhibitors (*e.g.*, captopril) showed improved mood. In larger clinical trials in hypertensive patients (46), it was reported that angiotensin converting enzyme inhibitors improved the quality of life. Systemic angiotensin converting enzyme inhibitors have also been reported to reduce behavioral despair (47, 48) in rat models of depression. More recently, mice lacking angiotensinogen have been reported to have fewer signs of behavioral despair in a swim test (49).

Similarly there is emerging evidence that aldosterone may have a depressivogenic action. A small clinical study by Murck *et al.* (50) reported recently that nighttime aldosterone levels were significantly elevated in depressed patients as compared to controls. This occurred in spite of the two groups having comparable plasma renin concentrations. Emanuele and colleagues (51) recently followed up on these observations with a larger sample that included both patients with major depression and minor depression or dysthymia. After adjusting for potential confounding variables, these investigators found that subjects with depression had 2.77 times higher odds of elevated levels of plasma aldosterone. There were no significant differences in plasma renin levels. There are previous reports of depression being associated with hyperaldosteronism (*i.e.*, Conn's disease or syndrome; 52, 53). However, a concern raised by these earlier studies was that the depression in such cases may have been due to hypokalemia. Depression has been reported as a symptom of hypokalemia and other electrolyte disturbances (54, 55). In this respect, it is important to note that the study by Emanuele and co-workers (51) specifically examined serum potassium (and serum sodium) and found no differences between depressed and control subjects.

The macrophage/pro-inflammatory cytokine (PIC) theory of depression

Early after its inception, the field of psychoneuroimmunology explored the idea that depression might be accompanied by suppression of the immune system. Such logic was probably derived from the assumption that depressed individuals were more susceptible to infectious disease. Some studies have been consistent with this idea. Kronfol and colleagues (56) were the first to demonstrate that subjects with major depression have blunted lymphoproliferative responses as measured in an *in vitro* assay. Major depression was also shown to reduce killer cell activity (57). However, other studies almost immediately began to appear indicating that depressed subjects have enhanced activity in other immune associated factors and components. For example, patients with major depression have higher numbers of leukocytes (58) and elevated humoral factors such as prostaglandins and cytokines that are associated with fever and inflammation (59). Such findings led Smith (60) to posit the macrophage theory of depression. He proposed that excess secretion of PICs (a.k.a. macrophage monokines), such as interleukin (IL)-1, interferon (INF)-α and tumor necrosis factor (TNF)-α, was the cause of depression.

The development of methods to generate pharmaceutical grade polypeptides by using recombinant DNA technology allowed clinical administration of pure PICs. Treatment with INF-α produces depressive symptoms including anhedonia, depressed mood, dysphoria, fatigue, anorexia, hypersomnia, psychomotor retardation, decreased concentration, and confusion (61). Recently it has been shown that treatment with the antidepressant paroxetine significantly reduces the incidence of induced major depression among malignant melanoma patients receiving INF-α therapy (62). Patients receiving IL-2 and TNF-α also exhibit depressive symptoms

(63). Symptoms of depression appear rapidly after the start of treatment with these PICs and usually disappear a short time after termination of administration, suggesting that cytokines play an important role in inducing depression.

Acute infectious illness, such as upper respiratory tract infections, influenza, gastroenteritis, Epstein-Barr virus and cytomegalovirus are associated with a range of depressive symptoms including depressed mood, lost appetite, sleepiness, reduced locomotion, fatigue, lethargy, muscle aches and cognitive disturbances (61). Not only are PICs elevated in infectious diseases, but also in several types of non-infectious conditions such as in autoimmune diseases, stroke, brain trauma, and Alzheimer's disease. A high incidence of depression is reported in such chronic conditions (61). When it was studied, immune dysregulation was found to precede the development of depression. This suggests that rather than being a psychological reaction to medical disorders *per se*, depression is a result of immune activation (64).

CHF IS THE CONSEQUENCE OF A VARIETY OF CARDIOVASCULAR DISEASES INCLUDING MI, CARDIOMYOPATHIES AND VALVULAR DISORDERS

CHF is defined as the inability of the heart to provide adequate blood flow to meet the metabolic demands of the body except by increasing left ventricular end-diastolic pressure. The characteristic course to the syndrome of CHF leads to diminished left ventricular contractility, increased cardiac filling pressure, low cardiac output, and diminished flow to critical vascular beds (*e.g.*, renal). The response of the body to inadequate tissue perfusion is the activation of neural, humoral and behavioral systems that expand vascular volume and raise arterial blood pressure (65). These responses are the same as those that occur during the early phase of hemorrhagic shock (compensated shock or Stage 1 shock) and involve sympathetic activation, mobilization of the renin-angiotensin system, release of the hormones, aldosterone, vasopressin and glucocorticoids, and increased water (thirst) and sodium (salt appetite) intake. From a clinical perspective, the progression of CHF is accompanied by cardiac enlargement, increased fatigue and exertion-induced dyspnea, under-perfusion of key organs, and ultimately right heart failure which produces weight gain with lower extremity and abdominal swelling. Along with increased sympathetic nerve activity, vagal tone is decreased, and as a consequence, resting heart rate increases and heart rate variability is reduced. The result of these autonomic changes is the increased risk of cardiac arrhythmias and sudden death.

The sympathetic nervous system and the renin-angiotensin-aldosterone system in heart failure

For many years the downward course of CHF was regarded to be the result of the progressive decline in the contractility of myocytes. Heart failure was

considered by many to be primarily a hemodynamic disorder. Therapeutic strategies to stem the course of CHF and ultimately death involved attempting to increase the contractility of heart muscle by using drugs such as cardiac glycosides. In other words, attempts were made to correct hemodynamic abnormalities. Drugs such as β-adrenergic receptor blockers which reduce inotropic and chronotropic actions of catecholamines on the heart were thought to be contraindicated in CHF. By the early 1990's after nearly a decade of clinical use of angiotensin converting enzyme inhibitors and new findings that β-blockers actually have salutary effects in the treatment of CHF, a neurohumoral theory of CHF was proposed (66). This hypothesis placed heavy emphasis on the role of reflex activation of the sympathetic nervous system and of the renin-angiotensin system. The consequence of elevated sympathetic nervous system and renin-angiotensin system activity is not only the increase of peripheral resistance which increases the work of the heart, but angiotensin II and catecholamines also directly damage myocytes, induce cardiac remodeling, and depress cardiac function (66, 67). The neurohumoral hypothesis was directed at explaining the reasons for the progressive deterioration in CHF rather than the hemodynamics *per se*. Activation of the sympathetic nervous system and the renin-angiotensin system results in a direct deleterious effect on the heart that is independent from the hemodynamic actions of these neurohumoral agents.

One of the additional neurohumoral actions of the renin-angiotensin system is to enhance secretion of aldosterone, which has its own negative actions in the progression of CHF. Aldosterone has long been recognized for its actions on the renal distal tubules and collecting ducts to promote sodium retention and on the brain to generate salt appetite (see 68 for review). Aldosterone crosses the blood-brain barrier and acts at intracellular mineralocorticoid receptors distributed throughout the limbic system and hypothalamus. Brain mineralocorticoid receptor activation may result in the potentiation of central angiotensin II action by enhancing binding of the peptide to angiotensin type 1 receptors (66, 69). Aldosterone also reduces the sensitivity of arterial baroreceptors (70). Angiotensin converting enzyme inhibitors are not always effective in reducing levels of circulating aldosterone and only suppress secretion transiently (71 - 73). It is important in this regard to note that the mineralocorticoid receptor antagonist, spironolactone, has notable beneficial effects on morbidity and mortality of patients with established CHF (74, 75).

Pro-inflammatory cytokines and heart failure

At about the same time that increased attention was being directed toward the sympathetic nervous system and the renin-angiotensin system as neurohumoral mediators of CHF, the PICs came under scrutiny as being yet another class of potential mediators of this disorder. In CHF, PICs are released into the systemic circulation. The PICs most frequently implicated and measured in heart failure

are TNF-α, IL-1β and IL-6. In the clinical literature, circulating cytokines and their soluble receptors are used as markers of the severity of CHF. TNF-α (76) and soluble TNF receptors (77) in plasma increase in direct proportion to the severity of CHF and correlates well with the outcome of the disease (78).

Blood-borne cytokines stimulate the synthesis and release of more cytokines that can derive from sources in addition to lymphoid tissues. Among major non-lymphoid sources of PICs are heart, liver and brain. In the heart, cytokines can be produced by resident macrophages, mast cells (79) and myocytes (80). Both acute MI and heart failure are accompanied by increases in PICs (80). An initial injury to the myocardium may be the initiating stimulus for generation of coronary derived PICs (81).

The role of cytokines in CHF is not well understood. Both protective and harmful effects have been attributed to PICs (82). Acutely administered cytokines have been reported to have variable effects on sympathetic nervous system activity, blood pressure and heart rate (83, 84). Blood-borne PICs at pathophysiological levels depress myocardial function and induce cardiac remodeling (85).

PICs stimulate the activity of the renin-angiotensin system and interfere with a renal negative feedback system that normally inhibits renin release (86) and aldosterone secretion (87). TNF-α acts to directly upregulate angiotensin type 1 receptors on cardiac fibroblasts (88) and promote apoptosis (82). When TNF-α is overexpressed in mice, they develop dilated cardiomyopathy (89). Considering the actions of PICs, it is clear why there is serious consideration of strategies to inhibit cytokine action in CHF as a means to treat the disease (90).

ANIMAL MODELS OF HEART FAILURE AND OF DEPRESSION ARE USEFUL IN EXAMINING THE ROLE OF NEUROHUMORAL MECHANISMS IN THE CO-MORBIDITY OF THESE DISORDERS

From the previous discussion it is apparent that there are common humoral factors that are elevated in both heart failure and in depression. These factors potentially share common pathways in the central nervous system that trigger the co-morbidity of depression and heart disease. To more carefully investigate the mechanisms to account for the co-occurrence of these disorders, our research has followed two strategies - one which employs a well established *chronic mild stress model of depression* in the rat and a second which makes use of an experimental MI model of heart failure and to combine this with behavioral methods.

Chronic mild stress is a rodent model of depression developed by Katz and colleagues (91), and elaborated by Willner and colleagues (92). By presenting a combination of mild, unpredictable stressors - such as stroboscopic illumination, paired housing, and white noise - chronic mild stress mimics the decreased responsiveness to pleasurable stimuli (anhedonia) seen in depression. Anhedonia is a core component of human depressive disorder, and it is regarded to be one of

its most predominent features (93). In rats, anhedonia is operationally defined as a decrease in responding for a previously demonstrated reinforcer even when the reward is still available. The chronic mild stress model of depression characterizes anhedonia by a reduced consumption of palatable solutions such as sucrose or saccharin, or by decreased responding for rewarding electrical brain stimulation, relative to an experimentally established baseline and as compared to control animals (94, 95). Investigators have used this model of depression to study the effects and mechanisms of pharmacological treatments for the psychological disorder (94, 96). The chronic mild stress model has also been used to examine other specific behavioral signs of depression. For example, Solberg *et al.* (97) found altered circadian rhythms in mice exposed to chronic mild stressors.

The chronic mild stress model has proven to be experimentally robust and very reliable in our hands. We consistently produce anhedonia as measured by decreased sucrose preference (*Fig. 2*, left panel). We have used this "depression" paradigm to study other behaviors and have defined several hormonal, autonomic and cardiovascular changes that accompany the experimentally-induced anhedonia (98 - 102; see *Table I*). A notable behavioral change that accompanies the onset of anhedonia is decreased spontaneous exercise (*i.e.*, wheel running), which recovers, as does a normal hedonic response, once exposure to the mild stressors is stopped (*Fig. 2*, right panel). In addition to the behavioral changes that accompany chronic mild stress-induced "depression," there are several endocrine and cardiovascular changes seen in the anhedonic rats that have also been described in depressed humans. Perhaps among the most relevant to heart disease are increased heart rate and decreased heart rate variability (98 - 100). Both high heart rates and low heart rate variability are common in depressed patients (103).

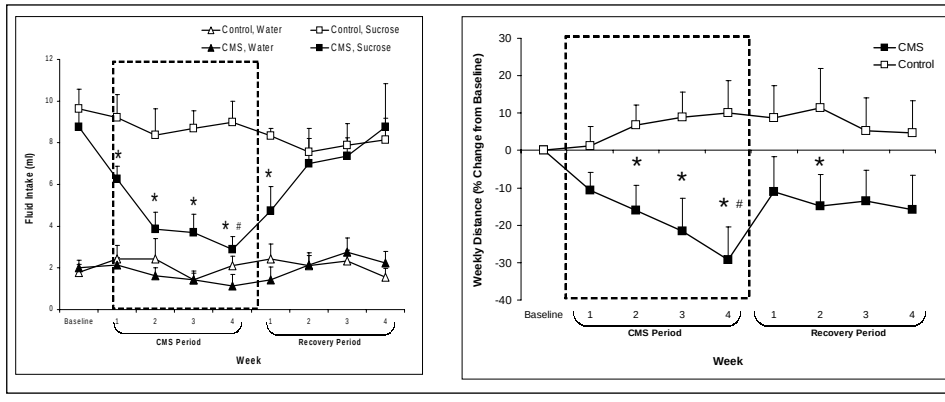

Fig. 2. Behavioral changes in control and chronic mild stress (CMS) rats during CMS and after CMS. (Left) 1% sucrose and water intake (ml). (Right) Percentage of baseline running wheel activity. #P<0.05 with respect to baseline; *P<0.05 with respect to control group. Adapted from (99); with permission.

Table 1. Chronic mild stress (CMS) produces behavioral, physiological and biochemical changes related to heart disease and depression

Behavioral Changes
- Anhedonia (95, 98-102, 113)
- Psychomotor retardation (99)

Cardiovascular Changes (98-100, 102)
- Elevated resting heart rate
- Reduced heart rate variability
- Increased cardiovascular reactivity
- Elevated sympathetic activity
- Increased vulnerability to cardiac arrhythmias

Neurohumoral Changes (101)
- Elevated pro-inflammatory cytokines
- Activation of the renin-angiotensin-aldosterone axis
- Elevated glucocorticoids

Dissociation of Behavioral and Cardiovascular Changes during Recovery from CMS (99)
- Behavioral changes recover 2-3 weeks after cessation of CMS
- Cardiovascular changes do not recover within 4 weeks after cessation of CMS

Dissociation of Behavioral and Cardiovascular Changes during Selective Serotonin Reuptake Inhibitor Treatment in CMS (102)
- Fluoxetine treatment prevents anhedonia
- Fluoxetine only partially attenuates cardiovascular changes

Interestingly, heart rate variability is also low in post-MI patients, and the degree of reduction in variability is correlated with the likelihood that a post-infarct patient will suffer another negative cardiovascular event. Decreased heart rate variability is a predictor of the likelihood of post-myocardial survival (104, 105). Chronic mild stress exposed rats also evidence elevated sympathetic nervous system activity, enhanced cardiovascular reactivity (98, 99, 102), and importantly, an elevation of several stress-related factors (101). Anhedonic chronic mild stress rats, as compared to controls, also show increased vulnerability to premature ventricular complexes, salvos and ventricular tachycardia when challenged with an arrhythmia-inducing drug (100; *Fig. 3*).

The chronic mild stress model has excellent predictive validity for its capacity to identify antidepressant drugs that will prevent or reverse the anhedonia (106). Because of the high incidence of depression accompanying heart disease, it is important to identify antidepressants, that are safe for the cardiac patient. The tricyclic and monoamine oxidase inhibitor classes of antidepressants are regarded as cardiotoxic, a fact that is likely to limit their use in heart patients (107). Although the use of selective serotonin reuptake inhibitors may still raise some concerns for their use in depressed, heart failure patients (*e.g.*, see 108), they may be a better choice than the classic antidepressant drugs. In order to examine the effects of selective serotonin reuptake inhibitors on both the behavioral and cardiovascular

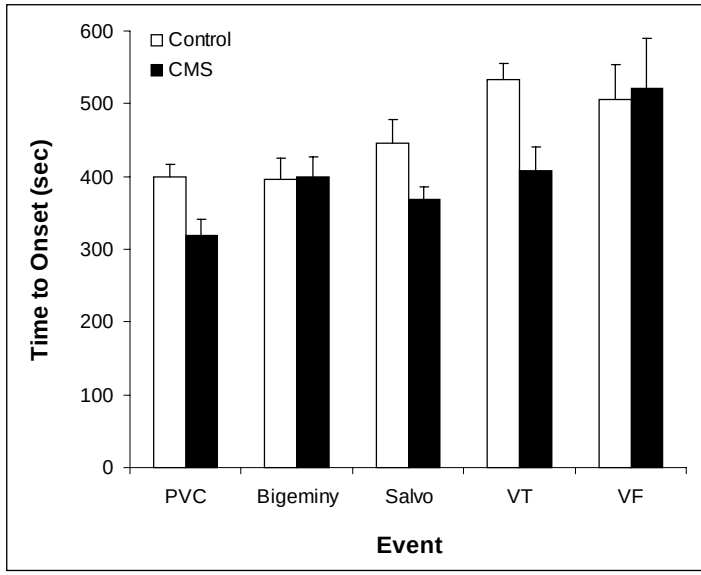

Fig. 3. Mean times for onset of premature ventricular contraction (PVC), bigeminy, salvo, ventricular tachycardia (VT) and ventricular fibrillation (VF) following intravenous aconitine in control and chronic mild stress (CMS) rats. *P<0.05 *vs.* control. Adapted from (100); used with permission.

effects of chronic mild stress, we chronically administered fluoxetine daily over the four-week period that we exposed animals to the battery of stressors (102). Chronic fluoxetine treatment prevented anhedonia. However, the effects of chronic mild stress on cardiovascular variables - specifically elevated resting heart rate, exaggerated pressor responses to an acute air jet stressor, reduced cardiac output and stroke volume, and exaggerated responses to β-adrenoceptor antagonist treatment - were only partially reversed by the fluoxetine treatment.

Taken together, studies in the chronic mild stress model have given us further insights into candidate factors that may contribute to the causes of mood disorders and the pathogenesis of heart disease. We now recognize the importance of sympathetic activation and release of key neurohumoral agents that are common to experimental models of both heart disease and depression.

ANHEDONIA AND IMPAIRED LOCOMOTOR ACTIVITY IN HEART FAILURE

We have used a MI heart failure model to study behavioral changes indicating anhedonia (109) and the effects of heart failure on “voluntary” or “spontaneous” exercise. In these experiments, anhedonia was assessed in male, Sprague-Dawley rats by using intracranial rewarding self-stimulation. Bipolar stimulating electrodes were implanted into a brain “reward area” (i.e., lateral hypothalamus). Rats were then trained in an operant chamber to lever-press in order to deliver a train of electrical stimulation of 200-500 ms pulses at 60-120 Hz through the hypothalamic electrodes. Current-response curves were generated by varying the current level in

a descending series from 350 to 50 μA in 25 μA decrements. The animals were permitted to respond for 1 minute at each intensity. An MI (or control surgery; *i.e.*, sham operated rats) was induced by coronary artery ligation, and self-stimulation rates were tested 7 days following surgery. Anhedonia was operationally defined as a reduction in the response rate for electrical stimulation (*i.e.*, a parallel shift of the current-response curve to the right). Compared to baseline values and to sham-operated rats, experimental MI produced a reduction in self-stimulation rates 7 days after ligation (*Fig. 4*; Note: The current required to produce bar pressing at 50% of the maximum value is defined as the Effective Current 50 or EC_{50}). It is important to note that animals with infarcts (*Fig. 4*) retained the capacity to attain maximum rates of responding. This fact rules out the likelihood that non-specific motor

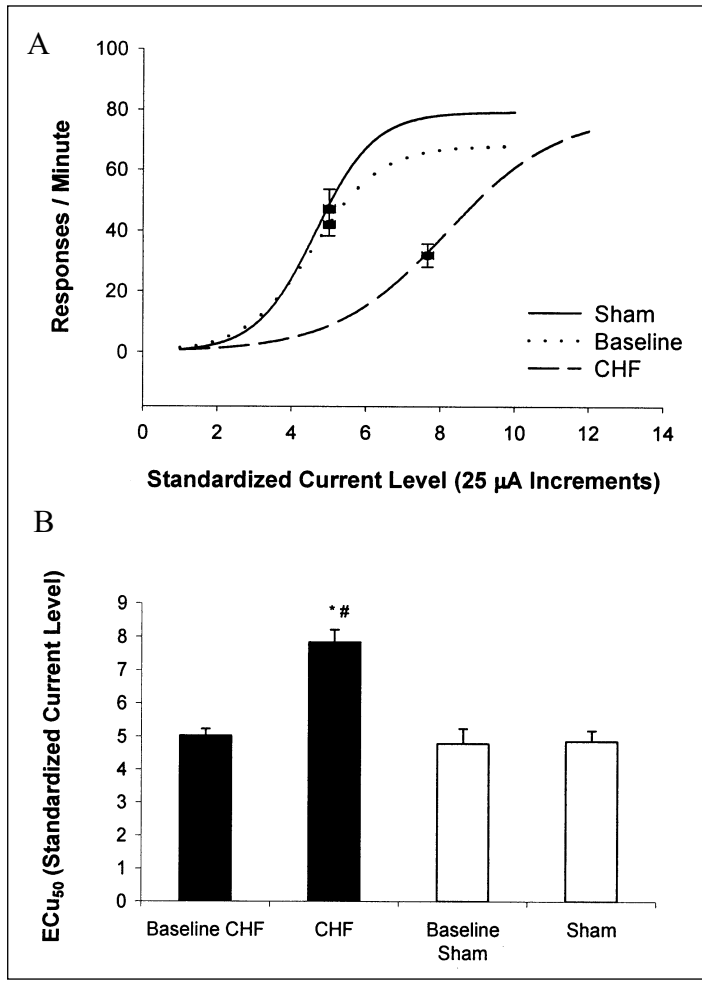

Fig. 4. Current-response functions (A) and Effective Current 50 (EC_{50}) values (B) in congestive heart failure (CHF) and sham heart failure (sham) groups. *P < 0.05 *vs*. Baseline CHF. #P < 0.05 *vs*. Sham. Reprinted from (109); used with permission.

deficits from the MI or heart failure produced the impairment in responding for reward. The results suggest that rats with heart failure are anhedonic.

Because the PIC TNF-α is elevated in our model of CHF and because the PIC IL-1β has been shown to decrease responding for rewarding electrical brain stimulation (110), we tested whether the TNF-α antagonist, etanercept, would reverse the anhedonia associated with experimental MI (109). *Fig. 5* shows the self-stimulation rates 24 hours following administration of etanercept (0.25 mg/kg, i.p.) or vehicle in rats displaying anhedonia on Day 7 after induction of experimental heart failure. The results of these experiments demonstrate that the measure of experimental CHF-induced anhedonia is reversed by treating the animals with an inhibitor of TNF-α.

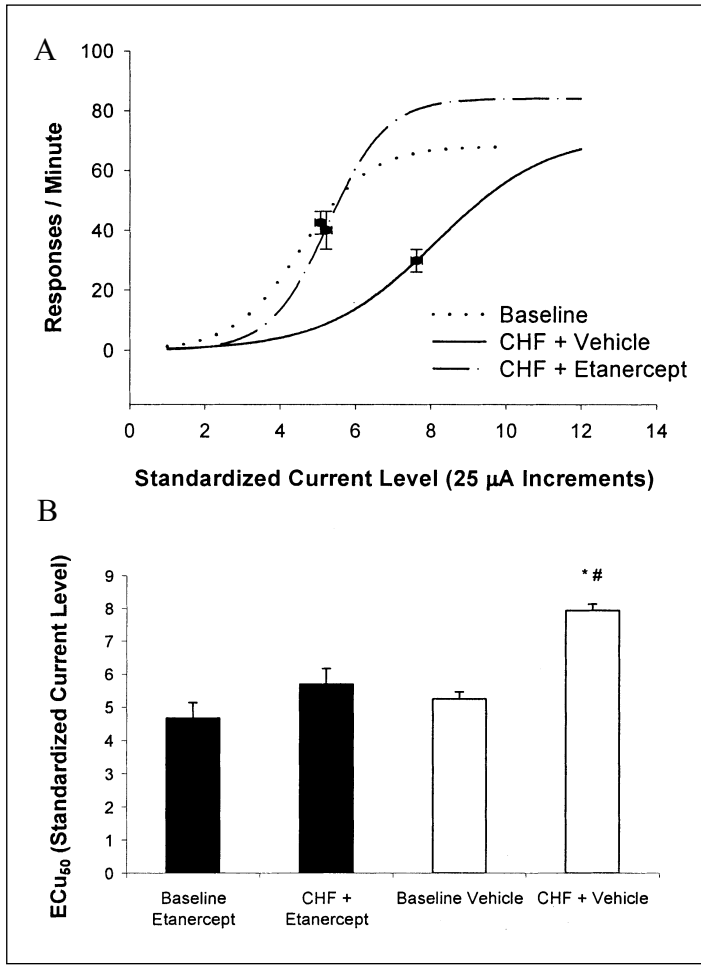

Fig. 5. Current-response functions (A) and effective current 50 (ECu_{50}) values (B) in congestive heart failure (CHF) rats before and 24 hours following etanercept or vehicle treatment. *P < 0.05 *vs*. Baseline Etanercept. #P < 0.05 *vs*. CHF + Etanercept. Reprinted from (109); used with permission.

A well recognized change in humans with heart failure is a reduction of voluntary locomotor behavior and reluctance to exercise. The resulting poverty of psychomotor behavior in patients with heart failure may in part reflect cardiovascular deconditioning, but also might be attributable to impaired motivational processes. Anergia is also a common symptom associated with psychological depression (19). In light of the demonstrated improvement in the health status of heart patients when they engage in increased exercise, it is important to understand the reasons why such patients decrease their exercise. Potentially the decrease in willingness to exercise may not be entirely due to reduced physical capacity but may also involve central motivational or drive mechanisms as well.

We have examined the effects of experimentally-induced MI on "spontaneous" wheel running in rats. In order to assess the effects of heart failure on animal-initiated exercise, wheel running was monitored in rats until stable daily levels were observed. Then, the rats either received experimental MIs or sham ligations. Rats were returned to their cages with running wheels and monitored for another three weeks. The extent of heart failure was assessed by echocardiogram at 2 and 23 days after surgery. This measure confirmed the presence of massive damage to the cardiac muscle of the left ventricle in the ligated group, but none in the sham ligated group. Both groups of rats showed a complete cessation of running immediately following the surgery. The rats that received sham ligations returned to the pre-surgery baseline by the 6th day post-surgery. In contrast, the rats with heart failure reached stable post-surgery levels of activity by the 6th day, but this was only 10 to 20% of their pre-ligation baseline (*Fig. 6*). These results indicate that reduced psychomotor activity, another behavioral change frequently seen in humans with heart failure and in depressed patients, is also present in rats with experimental heart failure.

MINERALOCORTICOID RECEPTOR AGONIST-INDUCED ANHEDONIA

Both chronic mild stress and heart failure induced by experimental MI activate the renin-angiotensin-aldosterone system (101, 111; Dr. Robert Felder, personal communication). That is, both plasma renin activity and aldosterone are elevated in these experimental models. As discussed earlier in this review, there is evidence for components of the renin-angiotensin-aldosterone system contributing to both the progression of heart failure and to depressive illness. In order to more directly determine if chronic elevation of a mineralocorticoid receptor agonist will induce anhedonia, we (112) treated rats with daily injections of the mineralocorticoid, deoxycorticosterone acetate (DOCA). We chose a dose and treatment regimen that we frequently use to induce sodium appetite. Rats were trained to self-stimulate and current-response curves were generated by varying current level in a descending series. After establishing self-stimulation baselines, rats were given daily DOCA (10 mg/kg; n=12) or vehicle (n=7) injections. After 4 days of DOCA

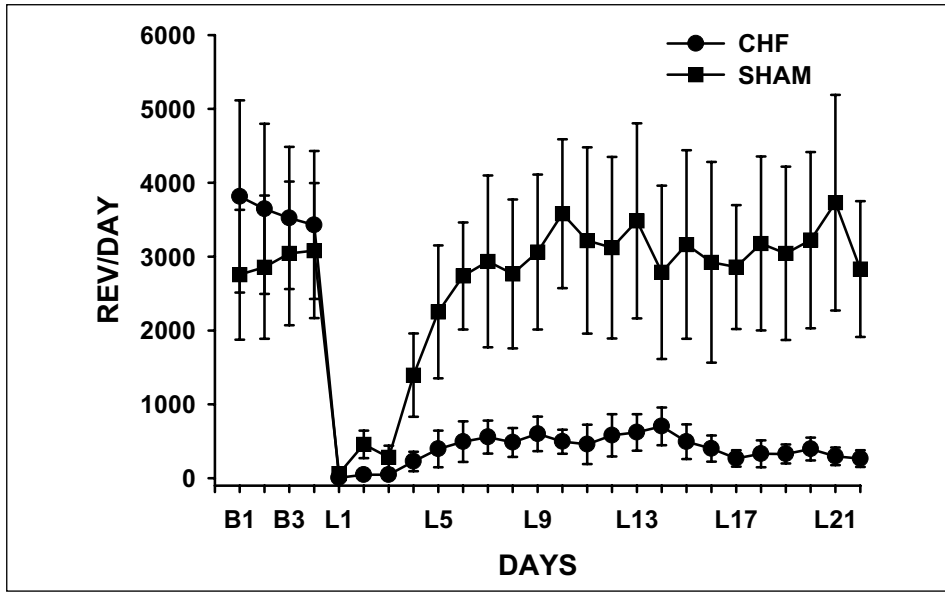

Fig. 6. Spontaneous running-wheel activity (revolutions/day) in rats before (B1-B4) and after (L1-L22) experimental heart failure. CHF = congestive heart failure.

treatment, self-stimulation testing was then conducted over the next 3 days. DOCA-treated rats without access to NaCl displayed a rightward shift of their current-response functions relative to their baseline (*Fig. 7*, bottom panel), whereas vehicle-treated rats did not (*Fig. 7*, top panel). After establishing current-response functions, rats were given access to 0.3 M saline and intakes were recorded to determine if DOCA had induced a significant sodium appetite. A DOCA-induced sodium appetite was evident by the first day that intakes were recorded, and intakes remained significantly elevated relative to the vehicle-treated group until DOCA treatment and testing were concluded. These results provide evidence that mineralocorticoid directly or indirectly may contribute to depressive behaviors in states in which they are elevated.

SUMMARY AND CONCLUSIONS

It is well established that heart failure and depression co-occur with a much greater frequency than would be anticipated on a statistical basis. It is easy to assume that depression that follows an event such as MI might arise because of heightened awareness of one's own mortality. However, it is also not unreasonable to posit that there may be more fundamental, common psychological and/or physiological processes contributing to both of these disorders.

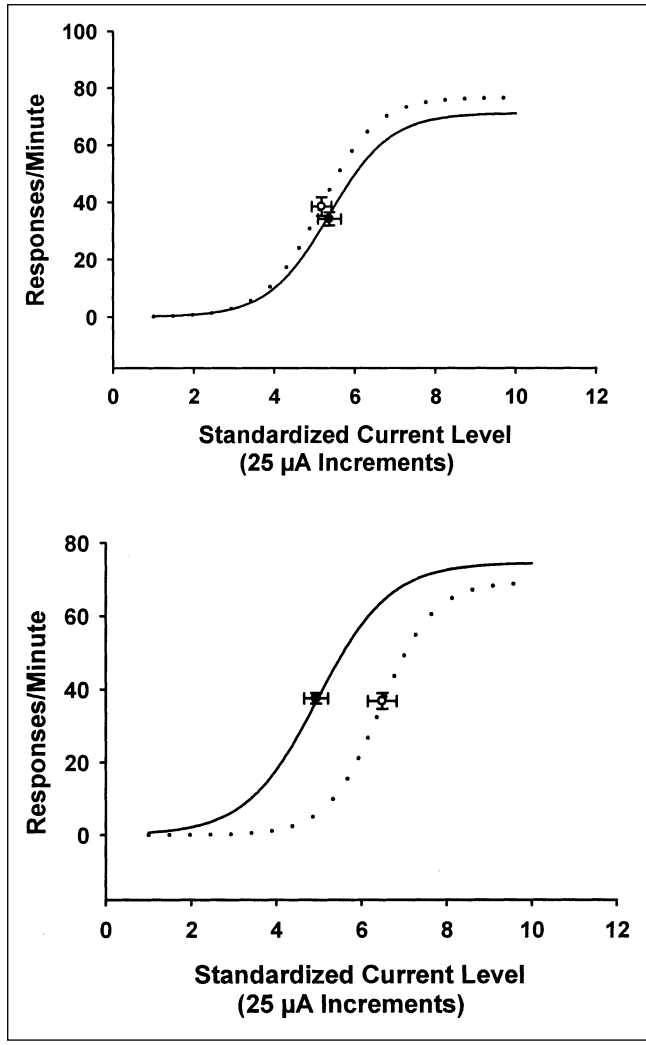

Fig. 7. (Top) Mean self-stimulation current-response curves for vehicle-treated rats without access to NaCl. (Bottom) Mean self-stimulation current-response curves for DOCA-treated rats. Data are shown as sigmoid curves fit to mean values. Black dots indicate the midpoint [Effective Current 50 (EC_{50})] of each curve. Baseline *vs*. vehicle EC_{50} values were not significantly different. DOCA treatment produced elevated EC_{50} values relative to baseline [$t(11) = 3.45$ $P<0.05$]. DOCA = deoxycorticosterone acetate. Solid line = baseline; dotted line = vehicle (top panel) or DOCA (bottom panel) treatment. Reprinted from (112); used with permission.

An overall strategy to attempt to understand the reason for the high co-morbidity between heart disease and depression is to consider the current experimental literature related to hypothesized mechanisms of depression and heart disease and to identify common factors and then investigate candidate mechanisms. Some common factors, namely, pro-inflammatory cytokines and the adrenal hormones, glucocorticoids and mineralocorticoids, and their primary hormonal controllers, CRF-ACTH and renin-angiotensin, respectively, are activated in both heart failure and in depression. Broadly defined, these factors can be considered as major "stress hormones." Stressful

life events have long been postulated as contributing to the pathogenesis of psychological depression.

In studies employing an experimental model of depression, anhedonia produced by chronic mild stress, we have found many of the physiological (*e.g.*, reduced heart rate variability; increased heart rate; increased sympathetic tone) and humoral changes reported in depressed humans to be present in animals evidencing anhedonia.

Also, we have found that animals with experimental heart failure exhibit anhedonia and reduced psychomotor responses, both behavioral indices of depression. The similarities in physiological and humoral changes accompanying both experimental heart failure and experimental depression support the hypothesis that there are common factors generated by heart failure and by stressors that induce depression. This observation provides insight into why having one of these illnesses serves as a risk for the genesis of the second disorder.

Fig. 8 depicts the nature of events that can trigger heart failure and depression. The physiological stressors of heart failure and the psychological stressors of exogenous psychosocial challenges lead to activation of similar

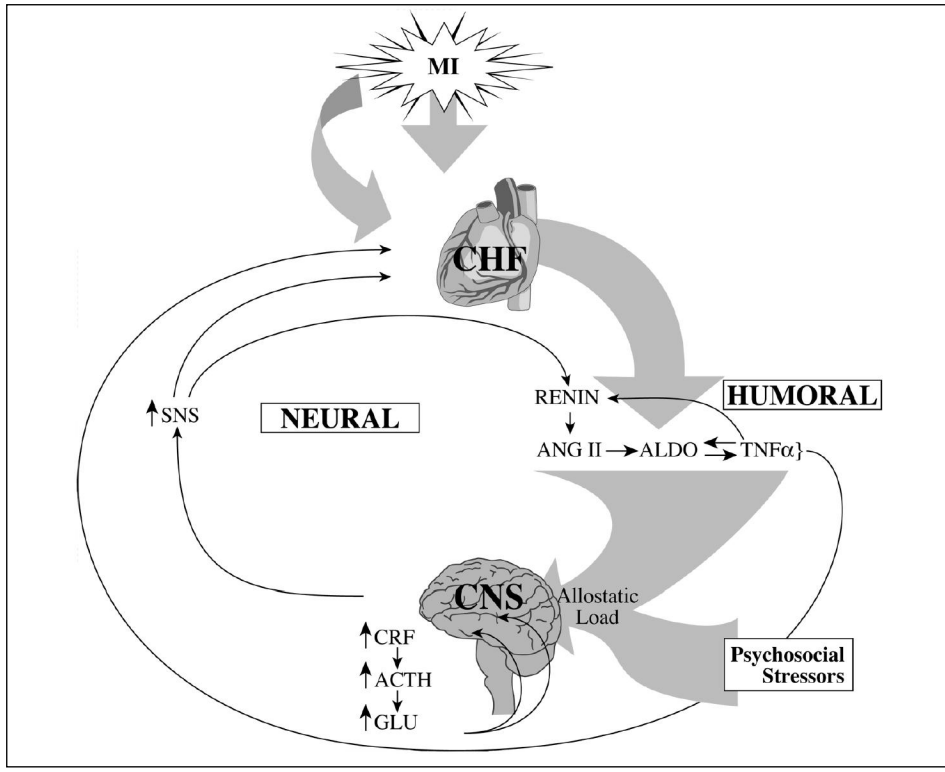

Fig. 8. Neurohumoral factors and the vicious cycle of heart failure and psychological depression.

humoral/endocrine patterns. The appreciation that similar mediators may be activated by both disorders serves to provide new strategies for intervention and treatment of these illnesses. Of particular utility in studying common and causal mechanisms in depression and cardiovascular disease are animal models of depression and heart failure. Experimental investigations with these have provided insight into the important associations between mood disorders and heart disease.

Acknowledgement: This work was supported by the National Heart, Lung, and Blood Institute HL-14388 and HL-57472, National Institute of Diabetes and Digestive and Kidney Diseases DK-066086 (AKJ), and National Institute of Mental Health MH-65839 (AJG).

REFERENCES

1. Mathers CD, Loncar D. Updated Projections of Global Mortality and Burden of Disease, 2002-2030: Data Sources, Methods and Results. Geneva, World Health Organization. http://www.who.int/healthinfo/statistics/bodprojectionspaper.pdf, 2005.
2. Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction. *JAMA* 2003; 289: 3106-3116.
3. Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. *J Clin Psychiatry* 1990; 51 Suppl: 4-9; discussion 10-1.
4. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry* 1998; 155: 4-11.
5. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998; 55: 580-592.
6. Nemeroff CB, Musselman DL, Evans DL. Depression and cardiac disease. *Depress Anxiety* 1998; 8 Suppl 1: 71-79.
7. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996; 58: 99-110.
8. Schleifer SJ, Macari-Hinson MM, et al. The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989; 149: 1785-1789.
9. Freedland KE, Rich MW, Skala JA, Carney RM, Dávila-Román VG, Jaffe AS. Prevalence of depression in hospitalized patients with congestive heart failure. *Psychosom Med* 2003; 65: 119-128.
10. Carney RM, Rich MW, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988; 50: 627-633.
11. Barefoot JC, Helms MJ, Mark DB, et al. Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* 1996; 78: 613-617.
12. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993; 270: 1819-1825.
13. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995; 91: 999-1005.
14. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. *Psychol Bull* 1987; 101: 343-362.

15. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* 1996; 94: 3123-3129.
16. Freedland KE, Carney RM, Lustman PJ, Rich MW, Jaffe AS. Major depression in coronary artery disease patients with vs. without a prior history of depression. *Psychosom Med* 1992; 54: 416-421.
17. National Institute of Mental Health. Depression Can Break Your Heart. Bethesda, National Institute of Mental Health. NIH Publication No. 01-4592. http://www.nimh.nih.gov/publicat/heartbreak.cfm, 2001.
18. Spiegel D. Cancer and depression. *Br J Psychiatry* 1996; Suppl 30: 109-116.
19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 4th Edition, Text Revision. Washington, D.C., American Psychiatric Association, 2000.
20. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev* 2002; 26: 941-962.
21. Holsboer F. Neuroendocrinology of mood disorders. In Psychopharmacology: The Fourth Generation of Progress, FE Bloom, DJ Kupfer (eds). New York, Raven Press, 1995, pp. 957-969.
22. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 1965; 122: 509-522.
23. Coppen A. The biochemistry of affective disorders. *Br J Psychiatry* 1967; 113: 1237-1264.
24. Selye H. A syndrome produced by diverse nocuous agents. *Nature* 1936; 138: 32.
25. Weber B, Lewicka S, Deuschle M, Colla M, Vecsei P, Heuser I. Increased diurnal plasma concentrations of cortisone in depressed patients. *J Clin Endocrinol Metab* 2000; 85: 1133-1136.
26. Maes M, Lin A, Bonaccorso S, et al. Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. *Acta Psychiatr Scand* 1998; 98: 328-335.
27. Asnis GM, Halbreich U, Ryan ND, et al. The relationship of the dexamethasone suppression test (1 mg and 2 mg) to basal plasma cortisol levels in endogenous depression. *Psychoneuroendocrinology* 1987; 12: 295-301.
28. De Souza EB, Grigoriadis DE. Corticotropin-releasing factor: Physiology, pharmacology, and role in central nervous system and immune disorders. In Psychopharmacology: The Fourth Generation of Progress, FE Bloom, DJ Kupfer (eds). New York, Raven Press, 1995, pp. 505-517.
29. Nemeroff CB, Widerlov E, Bissette G, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* 1984; 226: 1342-1344.
30. Fisher LA. Corticotropin-releasing factor: endocrine and autonomic integration of responses to stress. *Trends Pharmacol Sci* 1989; 10: 189-193.
31. Dunn AJ, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Brain Res Rev* 1990; 15: 71-100.
32. Kirby LG, Rice KC, Valentino RJ. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. *Neuropsychopharmacology* 2000; 22: 148-162.
33. Rydin H, Verney EB. The inhibition of water-diuresis by emotional stress and by muscular exercise. *Q J Exp Physiol* 1938; 27: 343-374.
34. Selye H. Stress and disease. *Science* 1955; 122: 625-631.
35. Selye H, Hall CE, Rowley EM. Malignant hypertension produced by treatment with deoxycorticosterone acetate and sodium chloride. *Can Med Assoc J* 1943; 49: 88-92.
36. Selye H. Protection by a steroid-spirolactone against certain types of cardiac necroses. *Proc Soc Exp Biol Med* 1960; 104: 212-213.
37. Selye H. Production of hypertension and hyalinosis by desoxocortisone. *Br Med J* 1950; 1: 203-206.

38. Laragh JH, Angers M, Kelly WG, Liberman S. Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *JAMA* 1960; 174: 234-240.
39. Genest JE, Korw E, Nowaczynski W, Sandor T. Study of urinary adrenocortical hormones in human arterial hypertension. First International Congress of Endocrinology, Copenhagen, 1960.
40. Davis JO, Carpenter CCJ, Ayers CR, Holman JE, Bahn RC. Evidence for secretion of an aldosterone-stimulating hormone by the kidney. *J Clin Invest* 1961; 40: 684-696.
41. Germain L, Chouinard G. Treatment of recurrent unipolar major depression with captopril. *Biol Psychiatry* 1988; 23: 637-641.
42. Germain L, Chouinard G. Captopril treatment of major depression with serial measurements of blood cortisol concentrations. *Biol Psychiatry* 1989; 25: 489-493.
43. Zubenko GS, Nixon RA. Mood-elevating effect of captopril in depressed patients. *Am J Psychiatry* 1984; 141: 110-111.
44. Cohen LM, Anderson G, White RF, Griffing G, Melby J. Enalapril and hypertension. *Am J Psychiatry* 1984; 141: 1012-1013.
45. Deicken RF. Captopril treatment of depression. *Biol Psychiatry* 1986; 21: 1425-1428.
46. Croog SH, Levine S, Testa MA, et al. The effects of antihypertensive therapy on the quality of life. *N Engl J Med* 1986; 314: 1657-1664.
47. Giardina WJ, Ebert DM. Positive effects of captopril in the behavioral despair swim test. *Biol Psychiatry* 1989; 25: 697-702.
48. Martin P, Massol J, Scalbert E, Puech AJ. Involvement of angiotensin-converting enzyme inhibition in reversal of helpless behavior evoked by perindopril in rats. *Eur J Pharmacol* 1990; 187: 165-170.
49. Okuyama S, Sakagawa T, Sugiyama F, Fukamizu A, Murakami K. Reduction of depressive-like behavior in mice lacking angiotensinogen. *Neurosci Lett* 1999; 261: 167-170.
50. Murck H, Held K, Ziegenbein M, Kunzel H, Koch K, Steiger A. The renin-angiotensin-aldosterone system in patients with depression compared to controls - a sleep endocrine study. *BMC Psychiatry* 2003; 3: 15.
51. Emanuele E, Geroldi D, Minoretti P, Coen E, Politi P. Increased plasma aldosterone in patients with clinical depression. *Arch Med Res* 2005; 36: 544-548.
52. Malinow KC, Lion JR. Hyperaldosteronism (Conn's disease) presenting as depression. *J Clin Psychiatry* 1979; 40: 358-359.
53. Khurshid KA, Weaver ME. Conn's syndrome presenting as depression. *Am J Psychiatry* 2005; 162: 1226.
54. Enya M, Kanoh Y, Mune T, et al. Depressive state and paresthesia dramatically improved by intravenous MgSO4 in Gitelman's syndrome. *Intern Med* 2004; 43: 410-414.
55. Fletcher AJ, Standen SM. A multi-centre study of potassium deficiency in the elderly. *Curr Med Res Opin* 1973; 1: 584-590.
56. Kronfol Z, Silva J, Jr., Greden J, Dembinski S, Gardner R, Carroll B. Impaired lymphocyte function in depressive illness. *Life Sci* 1983; 33: 241-247.
57. Irwin M, Gillin JC. Impaired natural killer cell activity among depressed patients. *Psychiatry Res* 1987; 20: 181-182.
58. Kronfol Z, House JD. Lymphocyte mitogenesis, immunoglobulin and complement levels in depressed patients and normal controls. *Acta Psychiatr Scand* 1989; 80: 142-147.
59. Lieb J, Karmali R, Horrobin D. Elevated levels of prostaglandin E2 and thromboxane B2 in depression. *Prostaglandins Leukot Med* 1983; 10: 361-367.
60. Smith RS. The macrophage theory of depression. *Med Hypotheses* 1991; 35: 298-306.

61. Yirmiya R, Weidenfeld J, Pollak Y, et al. Cytokines, "depression due to a general medical condition," and antidepressant drugs. In Cytokines, Stress, and Depression, R Dantzer, EE Wollman, R Yirmiya (eds). New York, Kluwer Academic/Plenum, 1999, pp. 283-316.
62. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; 344: 961-966.
63. Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* 1998; 62: 583-606.
64. Yirmiya R, Pollak Y, Morag M, et al. Illness, cytokines, and depression. *Ann N Y Acad Sci* 2000; 917: 478-487.
65. Parmley WW. Neuroendocrine changes in heart failure and their clinical relevance. *Clin Cardiol* 1995; 18: 440-445.
66. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 1992; 20: 248-254.
67. Fyhrquist F, Metsarinne K, Tikkanen I. Role of angiotensin II in blood pressure regulation and in the pathophysiology of cardiovascular disorders. *J Hum Hypertens* 1995; 9 Suppl 5: S19-S24.
68. Johnson AK, Thunhorst RL. The neuroendocrinology of thirst and salt appetite: visceral sensory signals and mechanisms of central integration. *Front Neuroendocrinol* 1997; 18: 292-353.
69. De Nicola AF, Seltzer A, Tsutsumi K, Saavedra JM. Effects of deoxycorticosterone acetate (DOCA) and aldosterone on Sar1-angiotensin II binding and angiotensin-converting enzyme binding sites in brain. *Cell Mol Neurobiol* 1993; 13: 529-539.
70. Wang W, McClain JM, Zucker IH. Aldosterone reduces baroreceptor discharge in the dog. *Hypertension* 1992; 19: 270-277.
71. Borghi C, Boschi S, Ambrosioni E, Melandri G, Branzi A, Magnani B. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. *J Clin Pharmacol* 1993; 33: 40-45.
72. Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol* 1981; 91: 457-465.
73. The RALES Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996; 78: 902-907.
74. Schwinger RH. (The aldosterone antagonist spironolactone prolongs the survival of chronic heart failure patients. The results of the RALES study. The Randomized Aldactone Evaluation Study) in German. *Dtsch Med Wochenschr* 1999; 124: 987-988.
75. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709-717.
76. Dibbs Z, Kurrelmeyer K, Kalra D, et al. Cytokines in heart failure: pathogenetic mechanisms and potential treatment. *Proc Assoc Am Physicians* 1999; 111: 423-428.
77. Nozaki N, Yamaguchi S, Shirakabe M, Nakamura H, Tomoike H. Soluble tumor necrosis factor receptors are elevated in relation to severity of congestive heart failure. *Jpn Circ J* 1997; 61: 657-664.
78. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 2001; 103: 2055-2059.
79. Frangogiannis NG, Burns AR, Michael LH, Entman ML. Histochemical and morphological characteristics of canine cardiac mast cells. *Histochem J* 1999; 31: 221-229.
80. Das UN. Free radicals, cytokines and nitric oxide in cardiac failure and myocardial infarction. *Mol Cell Biochem* 2000; 215: 145-152.

81. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res* 2002; 53: 31-47.
82. Ferrari R. The role of TNF in cardiovascular disease. *Pharmacol Res* 1999; 40: 97-105.
83. Morimoto K, Morimoto A, Nakamori T, Tan N, Minagawa T, Murakami N. Cardiovascular responses induced in free-moving rats by immune cytokines. *J Physiol (Lond)* 1992; 448: 307-320.
84. Saindon CS, Blecha F, Musch TI, Morgan DA, Fels RJ, Kenney MJ. Effect of cervical vagotomy on sympathetic nerve responses to peripheral interleukin-1beta. *Auton Neurosci* 2001; 87: 243-248.
85. Bozkurt B, Kribbs SB, Clubb FJ, Jr., et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. *Circulation* 1998; 97: 1382-1391.
86. Antonipillai I, Wang Y, Horton R. Tumor necrosis factor and interleukin-1 may regulate renin secretion. *Endocrinology* 1990; 126: 273-278.
87. Bataillard A, del Rey A, Klusman I, Arditi GM, Besedovsky HO. Interleukin-1 stimulates aldosterone secretion: involvement of renin, ACTH, and prostaglandins. *Am J Physiol* 1992; 263: R840-R844.
88. Gurantz D, Cowling RT, Villarreal FJ, Greenberg BH. Tumor necrosis factor-alpha upregulates angiotensin II type 1 receptors on cardiac fibroblasts. *Circ Res* 1999; 85: 272-279.
89. Bryant D, Becker L, Richardson J, et al. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circulation* 1998; 97: 1375-1381.
90. Lisman KA, Stetson SJ, Koerner MM, Farmer JA, Torre-Amione G. Managing heart failure with immunomodulatory agents. *Cardiol Clin* 2001; 19: 617-625.
91. Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. *Pharmacol Biochem Behavior* 1982; 16: 965-968.
92. Willner P, Sampson D, Papp M, Phillips G, Muscat R. Animal models of anhedonia. Anxiety, Depression, and Mania. In Animal Models of Psychiatric Disorders, P Soubrie (ed.) Basel, Karger 1991, pp. 71-99.
93. Loas G. Vulnerability to depression: a model centered on anhedonia. *J Affect Disord* 1996; 41: 39-53.
94. Moreau JL, Jenck F, Martin JR, Mortas P, Haefely WE. Antidepressant treatment prevents chronic unpredictable mild stress-induced anhedonia as assessed by ventral tegmentum self-stimulation behavior in rats. *Eur Neuropsychopharmacol* 1992; 2: 43-49.
95. Willner P, Towell A, Sampson D, Sophokleous S, Muscat R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology (Berl)* 1987; 93: 358-364.
96. Muscat R, Papp M, Willner P. Reversal of stress-induced anhedonia by the atypical antidepressants, fluoxetine and maprotiline. *Psychopharmacology (Berl)* 1992; 109: 433-438.
97. Solberg LC, Horton TH, Turek FW. Circadian rhythms and depression: effects of exercise in an animal model. *Am J Physiol Regul Integr Comp Physiol* 1999; 276: R152-R161.
98. Grippo AJ, Moffitt JA, Johnson AK. Cardiovascular alterations and autonomic imbalance in an experimental model of depression. *Am J Physiol Regul Integr Comp Physiol* 2002; 282: R1333-R1341.
99. Grippo AJ, Beltz TG, Johnson AK. Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiol Behav* 2003; 78: 703-710.
100. Grippo AJ, Santos CM, Johnson RF, et al. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. *Am J Physiol Heart Circ Physiol* 2004; 286: H619-H626.

101. Grippo AJ, Francis J, Beltz TG, Felder RB, Johnson A.K. Neuroendocrine and cytokine profile of chronic mild stress-induced anhedonia. *Physiol Behav* 2005; 84: 697-706.
102. Grippo AJ, Beltz TG, Weiss RM, Johnson AK. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. *Biol Psychiatry* 2006; 59: 309-316.
103. Krittayaphong R, Cascio WE, Light KC, et al. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosom Med* 1997; 59: 231-235.
104. Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991; 68: 434-439.
105. Kleiger RE, Miller JP, Bigger JT, Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59: 256-262.
106. Willner P. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl)* 1997; 134: 319-329.
107. Glassman AH. Cardiovascular effects of antidepressant drugs: updated. *Int Clin Psychopharmacol* 1998; 13 Suppl 5: S25-S30.
108. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT, Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry* 1998; 155: 660-665.
109. Grippo AJ, Francis J, Weiss RM, Felder RB, Johnson AK. Cytokine mediation of experimental heart failure-induced anhedonia. *Am J Physiol Regul Integr Comp Physiol* 2003; 284: R666-R673.
110. Anisman H, Kokkinidis L, Borowski T, Merali Z. Differential effects of interleukin (IL)-1beta, IL-2 and IL-6 on responding for rewarding lateral hypothalamic stimulation. *Brain Res* 1998; 779: 177-187.
111. Francis J, Weiss RM, Wei SG, Johnson AK, Felder RB. Progression of heart failure after myocardial infarction in the rat. *Am J Physiol Regul Integr Comp Physiol* 2001; 281: R1734-R1745.
112. Morris MJ, Na ES, Grippo AJ, Johnson AK. The effects of deoxycorticosterone-induced sodium appetite on hedonic behaviors in the rat. *Behav Neurosci* 2006; 120: 571-579.
113. Grippo AJ, Na ES, Johnson RF, Beltz TG, Johnson AK. Sucrose ingestion elicits reduced Fos expression in the nucleus accumbens of anhedonic rats. *Brain Res* 2004; 1019: 259-264.
114. Grippo AJ, Moffitt JA, Beltz TG, Johnson AK. Reduced hedonic behavior and altered cardiovascular function induced by mild sodium depletion in rats. *Behav Neurosci* 2006; 99: 758-766.

Received: November 21, 2006
Accepted: November 24, 2006

Author's address: Alan Kim Johnson, Ph.D., Department of Psychology, University of Iowa, 11 Seashore Hall E, Iowa City, IA 52242-1407. Telephone: (319) 335-2423; Fax: (319) 335-0191; e-mail: alan-johnson@uiowa.edu