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Review

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

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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.

Contents

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

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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