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Review

Rodent models of depression-cardiovascular comorbidity: Bridging the known to the new

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ABSTRACT

Numerous epidemiological studies have demonstrated a close and bidirectional association between depression and cardiovascular disorders (CVD). This comorbidity places a significant burden on individuals and the healthcare system. Not surprisingly, in the last two decades preclinical research in the field of depression and CVD has rapidly progressed. Multiple studies have demonstrated that aspects of human depression/cardiovascular comorbidity can be modeled in rodents exposed to chronic stress paradigms and that a depressive-like syndrome can be induced in rodent models of CVD. This research has provided insights into neural, autonomic, humoral, immune and circulatory mechanisms linking co-occurring mood and CVD. Recent investigations have started to address gender and individual differences in the vulnerability to both disorders and have begun to explore the efficacy of novel pharmacological interventions for the treatment of these comorbid conditions. This review discusses relatively well-established findings and the latest discoveries from rodent models of depression and CVD, with the aim of providing an up-to-date reference which may guide future studies of the relationship between mood and cardiovascular disturbances.

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1. Introduction

"Depression can break your heart". This was the title of a fact sheet written in 2001 by The National Institute of Mental Health and National Heart Lung and Blood Institute in the wave of a decade of research demonstrating a clear link between depression and cardiovascular disorders (CVD) (National Institute of Mental Health, 2001). Since then not only has a great deal of clinical evidence accumulated in support of this comorbidity but also numerous animal models have been developed in an attempt to reveal basic mechanisms and processes linking co-occurring mood and cardio-

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vascular disorders. It is clear from these studies that depressive-like symptoms and cardiovascular abnormalities can be reliably reproduced in rodent models of chronic stress, and that a depressive-like syndrome can be provoked in rodent models of CVD. Mechanistic investigations have revealed a number of neural, autonomic, humoral, immune and circulatory pathways that could potentially mediate the association between depression and CVD. Moreover, recent work has started to tackle the issue of gender and individual differences in the vulnerability to both conditions, which is a necessary step towards a successful translation of experimental data into clinic. Finally, rodent studies have evaluated the efficacy of conventional antidepressant treatments also in terms of cardioprotection/cardiotoxicity, as well as the potential utility of novel pharmacological interventions for the treatment of these comorbid conditions. The purpose of this review is to integrate relatively well-established findings with the latest discoveries obtained from rodent models of depression and cardiovascular comorbidity, thereby providing an up-to-date reference of the experimental evidence on the relationship between mood and cardiovascular disorders.

2. Comorbidity between depression and cardiovascular disorders

It is quite remarkable that depression is projected to become the leading cause of worldwide disability by 2030 (Mathers et al., 2008). A substantial part of this burden relates to its association with medical illnesses, particularly CVD. Since the landmark study by Frasure-Smith and colleagues in 1993 demonstrating that depression is an independent risk factor for death at six months after myocardial infarction (Frasure-Smith et al., 1993), dozens of epidemiological studies have examined the association between depression and CVD and found it to be complex and bidirectional (Lippi et al., 2009). The bulk of evidence indicates that CVD increase vulnerability to major depression because of their symptom burden, psychological stress, financial hardship, and functional limitations (Egede, 2007; Rudisch and Nemeroff, 2003). Likewise, individuals with major depression are much more likely to suffer coronary artery disease and cardiovascular sequelae such as myocardial infarction, congestive heart failure and hypertension (Lett et al., 2004 Nemeroff and Goldschmidt-Clermont, 2012). In addition, elevated depressive symptoms predict mental stress-induced myocardial ischemia after acute myocardial infarction (Wei et al., 2014) as well as long-term cardiovascular mortality in patients with atrial fibrillation and congestive heart failure (Frasure-Smith and Lesperance, 2010). The association between altered mood and cardiovascular dysfunction is found in individuals both with and without cardiac antecedents, and is independent of traditional cardiovascular risk factors such as body mass index, physical activity, hypertension, hypercholesterolemia, and family history (Lett et al., 2004; Surtees et al., 2008; Whang et al., 2009). Importantly, the presence of chronic stressful life events is widely considered a very important variable influencing the development and progression of both depression and CVD in vulnerable individuals (Grippo and Johnson, 2009; Monroe and Harkness, 2005; Sgoifo et al., 2014). The mechanism or combination of mechanisms involved in this association are not completely understood. Plausible pathways generally fall into two categories: behavioral and biological factors. Behavioral mechanisms include physical inactivity, nonadherence to medications, smoking, dietary indiscretion, and poor social support (Whooley and Wong, 2013). The fact that the association remains significant after taking account of these factors indicates that health behaviors are responsible only in part for mediation. Indeed, many biological processes have been implicated in the link between depression and CVD, including autonomic dysfunction, hyperactivity of the sympatho-adrenalmedullary (SAM) and hypothalamic–pituitary–adrenocortical (HPA) axes, endothelial dysfunction, alterations in the platelet clotting cascade, and increased concentration of proinflammatory cytokines (Grippo and Johnson, 2002; Johnson and Grippo, 2006; Joynt et al., 2004; Seligman and Nemeroff, 2015; Sgoifo et al., 2015; Whooley and Wong, 2013; Wichers and Maes, 2002). However, the identification of precise mechanisms in humans has been hampered by the complexity and bidirectional nature of this relationship, and by substantial differences across studies in the assessment of depression, definition of CVD, and inclusion of covariates for multivariate models (Whooley and Wong, 2013).

3. Rodent models of depression and cardiovascular comorbidity

In combination with findings from human studies, the use of well-validated, reliable, and relevant preclinical models offers several advantages for the study of the comorbidity between depression and CVD. Research using animal models allows for a high level of experimental control as well as integrative methods and analyses. Given the established stress dependence of both diseases, rodent research has implemented stress paradigms for investigating common and causal pathophysiological mechanisms underlying this comorbidity. Chronic paradigms like social defeat (SD), social isolation (SI) and chronic mild stress (CMS) imply the exposure of adult rodents to natural stressors mimicking stressful events of everyday human life, and are currently considered the most realistic models for reproducing aspects of human depression/cardiovascular comorbidity (Grippo, 2009, 2011; Sgoifo et al., 2014). Their construct, face, and predictive validities have been comprehensively presented elsewhere (Grippo, 2009, 2011; Grippo et al., 2008b; Hollis and Kabbaj, 2014; Sgoifo et al., 2014; Willner, 2005). In the CMS and SD models, rats or mice are exposed sequentially, over a period of weeks, either to a variety of mild stressors (CMS) (Willner, 2005) or to brief episodes of aggression and social subordination by a larger and more aggressive conspecific (SD) (Miczek, 1979). These paradigms are by far the most used for exploring the behavioral and cardiovascular consequences of chronic stress exposure. On the other hand, prolonged (2–4 weeks) SI from either a same-sex sibling or an opposite-sex partner is often used as a chronic stress model in the monogamous prairie vole, a highly social species that exhibits social behaviors that parallel those observed in humans (Carter et al., 1995). Chronic stressors applied to rodents during the prenatal (i.e., prenatal stress) or postnatal (i.e., maternal separation) period or during adolescence (i.e., chronic social stress, repeated restraint stress or chronic variable stress) do increase vulnerability to a depressive-like phenotype later in life (Wulsin et al., 2016), but have only moderate effects on basal cardiovascular function in adulthood (Cruz et al., 2016; Duarte et al., 2015; Mastorci et al., 2009; Trombini et al., 2012) and therefore will not be considered here. On the other hand, rodent models of heart failure, myocardial infarction and cerebral ischemia have been proven to be equally useful in studies of the association between cardiovascular dysfunction and altered mood. In the following sections, we will summarize established and new findings obtained from rodent studies that have addressed the bidirectional association between depression and CVD from both a psychological and cardiovascular point of view.

3.1. Depressive-like syndrome in chronically stressed rodents

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V; American Psychiatry Association) diagnosis of major depressive disorders in humans requires the presence of