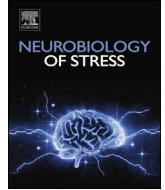




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Neuroinflammation at the interface of depression and cardiovascular disease: Evidence from rodent models of social stress

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ABSTRACT

A large body of evidence has emerged linking stressful experiences, particularly from one's social environment, with psychiatric disorders. However, vast individual differences emerge in susceptibility to developing stress-related pathology which may be due to distinct differences in the inflammatory response to social stress. Furthermore, depression is an independent risk factor for cardiovascular disease, another inflammatory-related disease, and results in increased mortality in depressed patients. This review is focused on discussing evidence for stress exposure resulting in persistent or sensitized inflammation in one individual while this response is lacking in others. Particular focus will be directed towards reviewing the literature underlying the impact that neuroinflammation has on neurotransmitters and neuropeptides that could be involved in the pathogenesis of comorbid depression and cardiovascular disease. Finally, the theme throughout the review will be to explore the notion that stress-induced inflammation is a key player in the high rate of comorbidity between psychosocial disorders and cardiovascular disease.

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List of abbreviations: 5-HT, Serotonin; BDNF, Brain-derived neurotrophic factor; CRP, C reactive protein; CVD, Cardiovascular disease; CRF, Corticotrophin-releasing factor; DA, Dopamine; DR, Dorsal raphe; INF, Interferon; IL, Interleukin; IL-1Ra, Interleukin 1 receptor antagonist; IL-1r2, Interleukin 1 receptor type 2; KYN, Kynurenine; LPS, Lipopolysaccharide; LC, Locus coeruleus; MCP, Monocyte chemoattractant protein; NPY, Neuropeptide Y; NE, Norepinephrine; PTSD, Post traumatic stress disorder; SSRI, Selective serotonin re-uptake inhibitor; TNF, Tumor necrosis factor; Trk, Tyrosine receptor kinase.

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1. Introduction

Depression is one of the most common psychosocial disorders in the United States, affecting nearly 7% of adults and more than 10% of adolescents (National Institute of Mental Health, 2013a,b). Approximately 10–30% of those suffering from depression exhibit treatment resistance (Al-Harbi, 2012), which has been linked to an increase in circulating cytokines (Maes et al., 1997; Musselman et al., 2001b; Miller et al., 2002; Alesci et al., 2005; Motivala et al., 2005; Raison et al., 2013). Although much of what is known about inflammation and depression has been determined by studying cytokine levels in the plasma, elevated pro-inflammatory cytokines are also reported in the cerebrospinal fluid (CSF) of subpopulations of depressed patients (Sasayama et al., 2013; Kern et al., 2014; Devorak et al., 2015). It has only recently been shown for the first time using positron emission tomography that microglial activation is increased in the brains of depressed patients compared to healthy controls, and was positively correlated with severity of depressive symptoms (Setiawan et al., 2015). Together these data indicate that the alterations in inflammatory markers exhibited by a subset of depressed patients represent a complex dysfunction of the immune system incorporating both the brain and the body. Furthermore, suffering from depression greatly increases the risk of developing other inflammatory-related medical disorders such cardiovascular disease (CVD), which may be precipitated by the same systems involved in depression (Seligman and Nemeroff, 2015). A major focus of this review is to elucidate the impact that neuroinflammation can have on neurotransmitters and neuropeptides within the brain that are linked to depression and exhibit neurogenic control of cardiovascular function, thereby providing a window into how inflammation within the brain could not only contribute to psychiatric illness, but also increase risk for CVD.

2. Social stress and coping in humans

Social stress such as bullying, abuse, or taking care of a terminally ill loved one is the most common type of stress individuals will face in their lifetime (Almeida, 2005) and personal perception of a social stressor is predictive of whether one will develop depressive symptoms (Nicolai et al., 2013). Additionally, patients suffering a depressive episode or in remission from depression exhibit increased sensitivity to social stressors encountered in daily life, indicating the robust nature of this stressor (van Winkel et al., 2015). Social stress and depression can affect anyone regardless of age, gender, ethnicity, or socio-economic background; however only a portion of the population is susceptible. The phenomenon by which stress exposure leads to psychosocial disorders in one individual while another remains resilient is well recognized, however, the mechanisms driving these individual differences are not well understood. One factor related to susceptibility and resiliency is the individual coping style adopted to deal with the stressor. In both

animals and humans it has long been suggested that two diverse coping responses to social stress can be distinguished (Henry and Stephens, 1977). Active coping, originally described by Walter Cannon (Cannon, 1915) is characterized as the fight or flight response, while passive coping is characterized by low levels of aggression and heightened immobility (Engel and Schmale, 1972). In humans, the use of passive coping strategies, such as avoidance, withdrawal, and seeking excessive reassurance/negative feedback, has been correlated to a greater susceptibility of developing depression (Cambron et al., 2009; Cairns et al., 2014); while active coping, such as problem solving, seeking support, and engaging in adaptive processes has been related to resiliency (Cairns et al., 2014). In addition, it has been shown that patients who more readily adopt passive coping strategies are not only more susceptible to developing depression, but also exhibit greater lipopolysaccharide (LPS) stimulated IL-6 release from whole blood samples as compared to patients who more commonly adopt active coping strategies (Bouhuys et al., 2004). Thus since different coping strategies result in unique inflammatory responses, coping may be related to the physiological consequences associated with stress exposure and may contribute to comorbid medical disorders such as CVD.

The impetus for this review is to investigate evidence of inflammatory responses that are tightly coupled to individual differences in stress susceptibility. Particular focus will be directed towards reviewing the literature underlying the impact that stress-related neuroinflammation has on neurotransmitters and neuropeptides that could be involved in the pathogenesis of comorbid depression and cardiovascular disease. Given the clinical relevance of studying the inflammatory response under conditions of social stress, our literature review focused mainly on studies utilizing modified resident-intruder models of social defeat stress. It is important to note that the visible burrow system is another highly relevant social stress model that provides significant insight into social stress (Blanchard and Blanchard, 1989; Blanchard et al., 1995; McEwen et al., 2015); however, due to the lack of studies investigating inflammation with this model, it does not fall within the scope of this review.

3. Modeling social stress and coping in rodents using repeated social defeat stress

The resident-intruder paradigm, originally developed by Miczek (Miczek, 1979), takes advantage of the social hierarchy and the continuing struggle for male dominance intrinsic to rodents (rats, mice, prairie voles) in order to model the effects of social stress (Buwalda et al., 1999; Bhatnagar and Vining, 2003; Berton et al., 2006; Trainor et al., 2010, 2011; Wood et al., 2010; Trainor et al., 2011). Social stress, however, is not limited to rodents and has been demonstrated in tree shrews and other non-human primates (Shively and Willard, 2012). Since one of the first descriptions of the resident-intruder model of social stress (Miczek, 1979), many

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