



Anhedonia and altered cardiac atrial natriuretic peptide following chronic stressor and endotoxin treatment in mice

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Summary Chronic stressors and inflammatory immune activation may contribute to pathophysiological alterations associated with both major depression and cardiovascular disease. The present study, conducted in mice, assessed whether a chronic stressor of moderate severity that induced an anhedonic effect, when coupled with a bacterial endotoxin, lipopolysaccharide (LPS), additively or interactively provoked circulating and heart atrial natriuretic peptide (ANP), a potentially useful diagnostic and prognostic tool in cardiac diseases. As well, given the potential role of inflammatory processes in both depression and cardiovascular disease, we assessed pro-inflammatory mRNA expression in heart in response to the stressor and the LPS treatments. Male CD-1 mice that had been exposed to a chronic, variable stressor over 4 weeks displayed reduced sucrose consumption, possibly reflecting the anhedonic effects of the stressor. Treatment with LPS (10 μ g) provoked increased circulating corticosterone levels in both chronically stressed and non-stressed mice. Moreover, ANP concentrations in plasma and in the left ventricle were increased by both the stressor and the LPS treatments, as were left atrial and ventricular cytokine (interleukin-1 β ; tumor necrosis factor- α) mRNA expression. Further, these treatments synergistically influenced the rise of plasma ANP. A link may exist between stressor-provoked depressive features (anhedonia) and immune activation, with elevated levels of ANP, a potential marker of cardiovascular disturbance. These findings are consistent with the view that chronic stressors and inflammatory immune activation may represent a common denominator subserving the frequent comorbidity between these illnesses.

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1. Introduction

Both chronic stressors and activation of the inflammatory immune response may contribute to the pathophysiological processes that increase vulnerability of depressed patients to cardiovascular diseases (Lesperance and Frasure-Smith, 2000). Consistent with this view, major depressive disorder (MDD) has been associated with increased

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levels of inflammatory factors, including pro-inflammatory cytokines (Maes, 1995), and MDD can be induced by administration of cytokines such as interferon- α (Raison et al., 2006), and to some extent by endotoxin administration (Reichenberg et al., 2001). The processes by which immune activation produces such effects are not fully understood, but it seems that direct or indirect actions of cytokines on brain norepinephrine (NE) and serotonin may contribute to MDD (Anisman et al., 2008b; Dantzer et al., 2008).

It likewise appears that cardiovascular disturbances in rodents and humans may arise in association with immune activation provoked by a bacterial endotoxin, such as lipopolysaccharide (LPS) (Tavener and Kubes, 2006; Zorn-Paully et al., 2007). This endotoxin is a strong stimulus that influences immune cells (Blunck et al., 2001), by directly stimulating toll-like receptor 4 (TLR-4) present on neutrophils and monocytes (Tavener et al., 2004), which may infiltrate cardiac tissues and may promote myocardial dysfunction (Grabie et al., 2003; Tavener and Kubes, 2006). This may, in turn, promote the release of atrial natriuretic peptides (ANP and BNP) by the heart, which have been implicated as hormonal markers in cardiac diseases, including heart failure, cardiac hypertrophy and arrhythmia (Goetze et al., 2004; Mekontso-Dessap and Brochard, 2006). It seems likely that central processes may also contribute to cardiovascular changes. Specifically, the elevated locus coeruleus NE synthesis that occurs in response to stressors and immune activation (Anisman and Merali, 1999) may influence cardiac receptors and increase heart rate, blood pressure and ventricular contraction rate, thereby influencing vulnerability to tachycardia or ventricular fibrillation (Dalack and Roose, 1990).

Pro-ANP is the principal storage form of ANP in the granules of atrial cardiomyocytes. It is cleaved to the inactive N-terminal fragment (NT-pro-ANP) and the active hormone ANP, and then released into the bloodstream by exocytosis (Mekontso-Dessap and Brochard, 2006; Michener et al., 1986; Ruskoaho, 1992). It is mainly produced and secreted by the atrium in response to atrial stretch provoked by volume overload (Mekontso-Dessap and Brochard, 2006; Politi et al., 2007; Shanshan et al., 2005; Weber et al., 2006). Physiological effects of this peptide include natriuresis, diuresis, vasorelaxation and modulation of systems that increase extracellular fluid volume and blood pressure (Mekontso-Dessap and Brochard, 2006; Shanshan et al., 2005).

Although stressors and LPS may induce unfavorable effects on depressive symptoms and on cardiovascular functioning, they may do so through independent pathways. Alternatively, the treatments may engage common processes (e.g., promotion of monoamine and cytokine alterations) so that they additively or synergistically favor the emergence of behavioral disturbances, such as depression, as well as cardiovascular problems (Anisman et al., 2008a). The present study was conducted to assess whether chronic stressors and immune activation (by LPS) would promote signs of cardiovascular disturbances and elicit depressive-like symptoms, and whether the combination of the stressor and LPS treatments would have additive or synergistic effects in this regard.

2. Experimental protocol

Male CD-1 mice ($N = 80$) were obtained from Charles River Canada (St. Constant, Quebec) at about 6–8 weeks of age.

They were allowed to acclimatize to the laboratory setting for 2 weeks before being used as experimental subjects. Mice were housed individually in a temperature-controlled vivarium with lights on from 08:00 to 20:00 h; food and water were freely available. All procedures were conducted in accordance with the guidelines set out by the Canadian Council on Animal Care and were approved by the Carleton University Animal Care Committee.

2.1. Chronic stressor procedure and LPS treatment

Mice were randomly assigned to either a chronic stressor condition or a non-stressed group ($N = 40$ /group). Of these animals all were used for determination of plasma corticosterone. Half the animals were used for ANP determinations and for mRNA expression of ANP and for cytokines.

Stressed mice were exposed to a series of different stressors on each day over 4 weeks. During this time stressors were applied twice a day (different stressors in the morning and afternoon). The stressors were presented on a variable and unpredictable schedule. The animals were returned to their home cages between the two stressor sessions of each day. The chronic stressor regimen included the following stressors: restraint in semicircular Plexiglas tubes (4 cm diameter \times 12 cm long), with tails taped to prevent mice from turning (15 min); exposure to predator odor (rat) by placing the mouse in a cage containing rat soiled bedding (60 min); wet bedding, in which cage bedding was soaked with water (60 min); forced swim in water of 20 °C within a plastic cylinder, 30 cm diameter and 27 cm high (5 min); placement on the open arm of plus maze (5 min); placement in a tight fitting triangular baggie (with a hole for the nose) resulting in complete restraint (15 min), and placing mice in cage with four mice (60 min). These procedures were previously shown to elicit behavioral changes and to altered brain monoamine activity (Anisman et al., 2007; Tannenbaum et al., 2002). Non-stressed mice remained in their home cages, and were not disturbed.

On sacrifice day, which occurred on the morning following the last stressor session, the stressed and non-stressed mice were divided into two subgroups and treated with either LPS (10 μ g, in a volume of 0.3 ml; from *Escherichia coli* 026:B6 $\geq 10,000$ EU/mg; Sigma) or saline.

2.2. Sucrose preference test

The present study was conducted, in part, to determine whether the effects of LPS would be enhanced given a background of chronic stressor exposure that could potentially be associated with depressive-like symptoms. Thus, it was of interest to establish whether the chronic stressor regimen provoked depressive-like behaviors prior to the introduction of the endotoxin. To this end, a sucrose preference test that has been used as a measure of anhedonia (Redei et al., 2001; Willner et al., 1987) was conducted over 24 h periods on three occasions (prior to the stressor regimen being introduced, and then again 2 and 4 weeks after stressor initiation). In this test, mice had access to two 200 ml bottles that contained either tap water or a 1%

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