Brain, Behavior, and Immunity 31 (2013) 189–196

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Central autonomic network mediates cardiovascular responses to acute inflammation: Relevance to increased cardiovascular risk in depression?

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ARTICLE INFO

Article history:
Available online 13 February 2013

Keywords:
Cytokines
FDG PET
Peripheral inflammation
Blood pressure
Sympathetic
Heart rate variability

ABSTRACT

Inflammation is a risk factor for both depression and cardiovascular disease. Depressed mood is also a cardiovascular risk factor. To date, research into mechanisms through which inflammation impacts cardiovascular health rarely takes into account central effects on autonomic cardiovascular control, instead emphasizing direct effects of peripheral inflammatory responses on endothelial reactivity and myocardial function. However, brain responses to inflammation engage neural systems for motivational and homeostatic control and are expressed through depressed mood state and changes in autonomic cardiovascular regulation. Here we combined an inflammatory challenge, known to evoke an acute reduction in mood, with neuroimaging to identify the functional brain substrates underlying potentially detrimental changes in autonomic cardiovascular control.

We first demonstrated that alterations in the balance of low to high frequency (LF/HF) changes in heart rate variability (a measure of baroreflex sensitivity) could account for some of the inflammation-evoked changes in diastolic blood pressure, indicating a central (rather than solely local endothelial) origin. Accompanying alterations in regional brain metabolism (measured using ^{18}FDG-PET) were analysed to localise central mechanisms of inflammation-induced changes in cardiovascular state: three discrete regions previously implicated in stressor-evoked blood pressure reactivity, the dorsal anterior and posterior cingulate and pons, strongly mediated the relationship between inflammation and blood pressure. Moreover, activity changes within each region predicted the inflammation-induced shift in LF/HF balance. These data are consistent with a centrally-driven component originating within brain areas supporting stressor evoked blood pressure reactivity. Together our findings highlight mechanisms binding psychological and physiological well-being and their perturbation by peripheral inflammation.

1. Introduction

Inflammation is a risk factor common to depression and cardiovascular disease and is implicated in the increased co-morbidity observed for both these conditions (Panagiotakos et al., 2004). Patients with major depression show activation of inflammatory pathways, manifest as increases in pro-inflammatory cytokines in both the circulation (Alesci et al., 2005) and cerebrospinal fluid (Levine et al., 1999). Some studies also demonstrate a positive correlation between plasma concentrations and symptom severity (Alesci et al., 2005; Thomas et al., 2005).Inflammation even impacts on discrete depression-related symptoms such as fatigue, insomnia and anger/hostility (Dantzer et al., 2008). These motivational and affective changes can be observed in individuals not meeting full criteria for major depression (Suarez et al., 2002, 2004). The link between inflammation and mood symptoms is apparent across the lifespan (Raison et al., 2006).

There is increasing biological understanding of the relationship between physical and psychological health. Functional polymorphisms within pro-inflammatory cytokine genes such as Interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) may increase the risk of depression and are associated with reduced responsiveness to conventional antidepressant therapy (Yu et al., 2003; Jun et al., 2003). Further, experimental induction of acute inflammation using either typhoid vaccine (Harrison et al., 2009a) or lipopolysaccharide infusion (Reichenberg et al., 2001) results in an acute reduction in mood and the therapeutic use of pro-inflammatory cytokines such as Interferon-alpha or IL-2 in the clinical management of medical patients will induce major depressive episodes in up to 50% of patients (Musselman et al., 2001).

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http://dx.doi.org/10.1016/j.bbi.2013.02.001

Inflammation is also implicated in the aetiology of cardiovascular disease (Ridker et al., 1997). Two broad patterns of inflammation-associated cardiovascular risk are recognized: First, an association between chronic low-grade inflammation and gradual accumulation of atherosclerosis and second, an association between acute inflammation (e.g. viral infection) and a transiently increased risk of acute cardiovascular events (Hansson, 2005).This is of particular interest given the association between depression and cardiovascular disease, which remains even after controlling for conventional risk factors such as medication, body-mass index, physical activity, hypertension and hypercholesterolemia (Wulsin and Singal, 2001). Thus understanding the interaction between depression and inflammation is important for mitigating cardiovascular risk (Panagiotakos et al., 2004).

Cardiovascular research has recognised the increased cardiovascular morbidity observed following acute inflammatory episodes such as respiratory or urinary tract infections (Smeeth et al., 2004; Meier et al., 1998) and severe illness requiring intensive care (Quartin et al., 1997). Research into the mechanisms underlying this increased risk has emphasized the role of direct inflammatory effects on endothelial reactivity (Hingorani et al., 2000), as has been observed for other conventional risk factors (Kinlay and Ganz, 1997). Supporting this proposal, experimental induction of acute inflammation using Typhim vaccine suppresses bradykinin- and acetylcholine- induced relaxation of arterial blood vessels (Hingorani et al., 2000). Of note, this impairment in endothelial function follows a very mild systemic inflammatory response (associated with a 2- to 3-fold elevation in pro-inflammatory cytokines) and persists for eight hours after inflammatory challenge (Hingorani et al., 2000).

Chronic mild inflammation has also been linked in cross-sectional studies to essential hypertension (Panza et al., 1990), one of the most important risk factors for cardiovascular disease, with family studies suggesting that chronic mild inflammation precedes blood pressure changes (Zizek et al., 2001). Again direct effects of inflammation on endothelium-dependent vascular reactivity have been proposed as the mediating mechanism (Bautista, 2003, Sinisalo et al., 2000). However, subclinical inflammation in healthy middle-aged adults without overt cardiovascular disease is also associated with changes in autonomic tone (a reduction in heart rate variability (Sajadieh et al., 2004)) which itself is a cardiovascular risk factor associated with both depression (Kemp et al., 2010)and risk of coronary heart disease even in physically healthy individuals (Dekker et al., 2000). This suggests that inflammation may mediate the increased risk of cardiovascular disease, not only through direct effects on endothelial reactivity, but also via centrally-mediated effects on autonomic reactivity indexed by heart rate variability.

Heart rate variability (HRV) is a non-invasive index of beat-to-beat changes in heart rate. Overall HRV reflects parasympathetic neural activity interacting with sympathetic influences on the sinus node of the heart and reflects the capacity for parasympathetic inhibition of autonomic arousal. HRV decreases under both physical and emotional stress and increases with rest. High HRVindicates a healthy autonomic nervous system that can respond flexibly to dynamically changing environmental demands while low HRV is frequently a marker of ill-health. Low HRV is an independent risk factor for cardiovascular morbidity and mortality (Tsuji et al., 1996; Dekker et al., 2000) and may precede inflammation-mediated atherosclerosis (Huikuri et al., 1999). Low HRV is also observed in patients with major depressive disorder (Kemp et al., 2010) even without overt cardiovascular pathology though unlike changes in endothelial function (Broadley et al., 2002) has been shown to at least partially reverse following successful treatment (Carney et al., 2000; Narshoni et al., 2001). This state-like association between low HRV and depression is hypothesized to underlie the link between depression and cardiovascular events including sudden cardiac death (Taylor et al., 2010). However, what factors mediate and sustain this reduction in HRV in depression is currently unclear.

Specific brain regions, notably the subgenual cingulate cortex (Drevets et al., 1997) are implicated in the pathogenesis and clinical expression of depression. Inflammation perturbs activity within this region to predict sickness-related changes toward a negative mood (Harrison et al., 2009a). Importantly, there is functional coupling between subgenual cingulate and adjacent ventromedial prefrontal cortices with posterior cingulate cortex within a default mode network implicated in self-directed cognitive processing (Gusnard et al., 2001). Activity within this network is also inversely coupled to dACC activity, both in terms of engagement with external tasks (Raichle et al., 2001) and importantly in effects on cardiovascular physiology (Critchley et al., 2011; Wager et al., 2008) mediated through pons. Increased metabolic activity within dorsal and posterior cingulate and pons also predict response to antidepressant treatment (Mayberg et al., 2000).

Here we investigate the effects of acute inflammatory challenge on blood pressure and sympathetic/parasympathetic balance using a Typhoid vaccine inflammatory challenge previously shown to induce an acute reduction in mood (Harrison et al., 2009a). Central mediators of the relationship between inflammation and change in blood pressure and sympathetic/ parasympathetic balance were investigated using ^{18}Fluorodeoxyglucose (FDG) PET neuroimaging before and 4 h after Typhim or placebo (saline) injection. Specifically we test the hypotheses that (1) direct measures of vascular response to inflammation (blood pressure changes) reflect central adjustments to autonomic control apparent as shifts in LF/HF balance (Mancia et al., 1983); (2) inflammation will induce changes in regional brain activity within the hierarchy of homeostatic brain areas linked to the expression of mood changes and motivation state (e.g. insula, cingulate ventromedial prefrontal cortex (Harrison et al., 2009b) (3) a subset of these areas (cingulate, dorsal pons (Gianaros and Sheu, 2009) will mediate inflammation-induced changes in cardiovascular state.

2. Materials and methods

2.1. Participants

Twenty healthy male participants (mean 24.7 ± 6.8 years) were recruited from advertisements on a local community website. Nineteen were white-Caucasian and 1 black-African. Volunteers were reviewed by a psychiatrist (N.A.H.) and screened for a history of any relevant physical or psychiatric illness. One participant had a history of mild eczema. Four participants rated their general health as excellent, 9 very good and 7 good. No participant rated his or her general health as poor or fair. All were medication free, with no non-steroidal or steroidal inflammatory drug use in the preceding 2 weeks and were non-smokers. Volunteers who had received typhoid vaccine within 3 years or other vaccine within 6 months were excluded. Participants were advised not to consume caffeinated beverages or alcohol, avoid high-fat meals and refrain from excessive exercise for 24 h prior to testing. All were fasted for a minimum of eight hours prior to testing and consumed only water until completion of the study. After complete description of the study to the participants, written informed consent was obtained. Procedures were approved by the Brighton East National Research Ethics Committee.

2.2. Study design

We adopted a randomized, double-blind, repeated measures design in which all participants underwent ^{18}fluorodeoxyglucose