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REVIEW

Acute and chronic stress induced changes in sensitivity of peripheral inflammatory pathways to the signals of multiple stress systems — 2011 Curt Richter Award Winner

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Summary Exposure to psychosocial stress has been associated with increasing rates of morbidity in humans and in animal models, but the underlying mechanisms are not completely understood. Major stress responsive systems, such as the hypothalamus-pituitary adrenal (HPA) axis and the autonomic nervous system (ANS) are under investigation as underlying pathways, but although acute stress reliably activates these systems, findings of long-term alternations in baseline activity are inconsistent at present. Emerging evidence suggests that stress-related changes in the sensitivity of target systems toward glucocorticoid (GC) regulation, i.e. development of GC resistance, might help explain inflammatory disinhibition and development of disease related to inflammation. More recent findings further show that the autonomic nervous system might play an important role in the regulatory control of the inflammatory cascade. The major argument put forward in this manuscript is that target tissues for stress system modulation, such as the inflammatory cascade, vary in their ability to respond to stress system signaling, and that assessing alterations in this stress signal sensitivity which can be caused by stress or disease processes, might be necessary to understand and explain stress effects on health. This review focuses on the inflammatory system in particular, because anti-inflammatory effects of most stress systems have been documented, but the general assumption might have to be generalized to other target systems. The main conclusion to be made is that reduction in glucocorticoid sensitivity of target tissues is the most consistent finding at present, and that assessing such changes in glucocorticoid sensitivity might be necessary to understand many stress-related changes in physiology.

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1. Introduction

Chronic low-grade systemic inflammation has been identified as one of the major pathophysiological mechanisms underlying life-threatening human diseases such as coronary heart disease and stroke, and it has also been associated with a large array of further diseases or disease processes with significant implications for human life span (e.g. Ridker et al., 1998; Pradhan et al., 2001; Danesh et al., 2000; Hansson, 2005). Furthermore, increases in concentrations of inflammatory markers in blood have been found associated with aging, and such increased concentrations are predictive of morbidity and mortality in later life (Ershler and Keller, 2000).

Because of its major role in many human diseases, and because of the fact that inflammation can be activated not only by infectious but also by non-immunological environmental, behavioral, and psychological stimuli, inflammation is emerging as an important pathway linking stress experience with human health (e.g. Miller and Blackwell, 2006). More specifically, it has been shown that chronic psychosocial stress is prospectively associated with increased concentrations of inflammatory biomarkers in human blood, such as interleukin-6 (IL-6, Kiecolt-Glaser et al., 2003) or C-reactive protein (CRP; Rohleder et al., 2009a).

Candidates for mediating these increases are the two major stress axes and their respective end products: the hypothalamus-pituitary-adrenal (HPA) axis with its glucocorticoid (GC) hormone cortisol, and the sympathetic nervous system (SNS) with its end hormones epinephrine and norepinephrine as summarized repeatedly (Elenkov et al., 2000; Sapolsky et al., 2000). Recently, an additional role of the parasympathetic nervous system (PNS) providing a cholinergic anti-inflammatory pathway has been suggested (Pavlov et al., 2003). The effects of the HPA axis hormone cortisol have been characterized as anti-inflammatory, and although recent findings have shown that not all GC effects inhibit all components of the immune system under all circumstances and at all concentrations (e.g. short-term vs. long-term effects on cell trafficking; Dhabhar, 2002), inflammatory mechanisms are down-regulated by GCs through a well-described mechanism (McKay and Cidlowski, 1999). Effects of the SNS on inflammation have been described as being pro-, and anti-inflammatory, with several factors determining the directionality of the effect. It has for example been shown that catecholamine signaling up-regulates DNA-binding activity of the main inflammatory transcription factor nuclear factor-κB (NF-κB; Bierhaus et al., 2003; Wolf et al., 2009), and that isoproterenol infusion induces increases in IL-6 in healthy humans (Mohamed-Ali et al., 2001). In accordance with this mechanism, acute psychosocial stress induces short-term increases in plasma concentrations of IL-6 in humans (Steptoe et al., 2007). In addition to these pro-inflammatory effects, catecholamines have also been found to act as anti-inflammatory agents, for example suppressing mitogen-stimulated production of inflammatory cytokines in culture (see Elenkov et al., 2000 for a review). These divergent effects might be explained by catecholamine concentration and time of incubation, but also seem to depend on the state of the respective cell or tissue: an already activated inflammatory cascade appears to be suppressed by adrenergic signaling, while in non-activated immune cells, adrenergic signals appear to be able to activate the inflammatory cascade. Taken together, the SNS has the potential to activate inflammatory responses in cells that have not been exposed to infectious antigens, and the HPA axis, as well as later increases in SNS activity and presumably cholinergic PNS signaling act to suppress inflammatory responses.

In light of this mechanism, chronic stress induced increases in circulating inflammatory mediators (Kiecolt-Glaser et al., 2003; Rohleder et al., 2009a) should theoretically be explainable by changes in stress system activity, permitting disinhibition of inflammatory signaling pathways. However, recent studies have not always been successful in documenting differences in basal stress system activity despite increases in inflammation. A possible explanation is that the ability of the inflammatory target tissue to receive stress system signals appears to be subject to inter- and intra-individual variability. In a recent longitudinal study on cancer caregivers, we found increases in CRP over time in caregivers, but not changes in basal HPA axis activity. However, we did observe a gradual decrease in glucocorticoid sensitivity of stimulated inflammatory cytokine production (Rohleder et al., 2009a). Thus it appears that chronic stress induced increases in inflammation cannot be completely understood without taking into account the ability of the target tissue to receive a given stress hormone signal. Indeed, alterations in