Stimulation of Systemic Low-Grade Inflammation by Psychosocial Stress

Nicolas Rohleder, PhD

Abstract: Psychosocial stress is an important precursor of disease and reduced quality of life in humans. The biological pathways between stress exposure and pathophysiological processes underlying disease have received substantial scientific attention, although the roles of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system remain insufficiently understood. Recent attention has focused on chronic systemic low-grade inflammation as a promising pathway because elevated inflammation often accompanies chronic psychosocial distress. These alterations of inflammatory activity play a key role in the pathophysiology of diseases that are adversely affected by chronic distress, such as cardiovascular disease. Transient increases in systemic inflammation are observed in response to acute psychosocial stress, with larger responses among individuals reporting adverse psychosocial states or conditions such as depression, lower self-esteem, or lower self-compassion. Recent evidence shows that lower subjective social status and perceived purpose in life are associated with sensitization of inflammatory stress responses to repeated stress exposure. The aims of this selective review article are to summarize current knowledge of the role of acute and chronic psychosocial stress on low-grade inflammation in humans and to discuss potential relationships between inflammatory responses to acute psychosocial stress and long-term development of disease. **Key words:** chronic stress, acute stress, inflammation, cytokines, sympathetic nervous system, HPA axis.

CRP = C-reactive protein; **HPA** = hypothalamic-pituitary-adrenal; **IL** = interleukin; **NK** = natural killer; **SES** = socioeconomic status; **SNS** = sympathetic nervous system; **SSS** = subjective social status; **TNF-α** = tumor necrosis factor α; **TSST** = Trier Social Stress Test.

INTRODUCTION

Throughout the life course, organisms, including humans, have to adapt to constantly changing environmental conditions that include both positive and negative experiences. As a consequence, evolution has resulted in the development of physiological and psychological systems that can respond to changing conditions in a way that maximizes optimal development and survival. Research in recent decades has increased our understanding of the role of psychosocial stress in the development of disease. Long-term exposure to negative experiences such as unemployment, work overload, or caring for a family member with chronic disease predicts psychological disorders and medical diseases and is related to reduced life expectancy (see, for example, Ref. (1)).

Traditionally, research aimed at understanding the mechanisms linking stress and disease has focused on the classical stress systems—the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS; e.g., Ref. (2)). However, alterations in HPA axis and SNS are insufficient alone to explain the link between stress and disease (e.g., Ref. (3)); thus, recent attention has been given to other possible mediators. Inflammation is one of these newer and promising mediators, more precisely, a phenomenon called *systemic* or *chronic*, *low-grade inflammation* (4). Of note, chronic low-grade inflammation has to be carefully distinguished from responses to acute infectious stimuli because of at least four major differences. First, chronic inflammation is systemic and not limited to a local site of injury or infection. Second, it is of lower magnitude than other types of inflammation, such as, for example, the inflammation that accompanies acute infection or sepsis. Third, this type of inflammation is typically a longer-term phenomenon, as opposed to the transient nature of inflammatory responses to infection. Finally, there is usually no apparent stimulus, such as infection or injury, that is the clear origin of the inflammatory response. Instead, the circulating levels of inflammatory markers that are termed *low-grade inflammation* increase as we get older (5,6) and have behavioral and psychosocial predictors, such as stress. The association of stress with low-grade inflammation is the topic of this selective review of the literature (7).

Studying chronic, systemic low-grade inflammation in relation to psychosocial stress is of particular interest because inflammatory pathways directly contribute to pathogenesis in health-relevant organ systems. This renders inflammation a more proximal biological pathway than other stress system mediators such as glucocorticoids and catecholamines, which mainly have indirect effects on target systems, for example, as regulators of inflammation. An excellent example of a disease process that is related to stress and influenced by inflammatory factors is atherosclerosis, which is now understood to be the result of immune cell migration into the arterial wall, where local inflammatory responses are the driving force of plaque development and rupture, thereby directly contributing to potentially life-threatening cardiovascular events such as myocardial infarction and stroke. Although atherosclerosis is a local inflammatory event, chronic low-grade inflammation of the entire organism may contribute to the development of atherosclerotic plaques at sites of local arterial microlesions and stimulate further development of already existing plaques (8–10). Many cells and tissues throughout the body are subject to inflammatory influences, and additional consequences of systemic low-grade inflammation include the stimulation of insulin resistance and related risk for Type 2 diabetes (11). Evidence also suggests that inflammation can contribute to tumorigenesis and tumor progression relevant to the development and progression of cancer (summarized, for example, in Ref. (12)). Add to this the proposed role of inflammation in a number of age-related conditions such as Alzheimer's disease and frailty (5), making inflammation one of the most promising biological mechanisms to study as a potential link between psychosocial factors and disease onset and course. Accordingly, the first aim of this review is to summarize

From the Department of Psychology and Volen National Center for Complex Systems, Brandeis University, Waltham, Massachusetts.

Address correspondence and reprint requests to Nicolas Rohleder, PhD, Department of Psychology and Volen National Center for Complex Systems, Brandeis University, 415 South Street, MS062 PO Box 549110, Waltham, MA 02454. E-mail: rohleder@brandeis.edu

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current knowledge regarding the impact of acute and chronic psychosocial stress on low-grade inflammation in humans. The second aim is to discuss potential relationships between inflammatory responses to acute psychosocial stress, chronic low-grade inflammation, and long-term development of disease.

SYSTEMIC LOW-GRADE INFLAMMATION IN CHRONIC STRESS

Chronic exposure to adverse psychosocial conditions comes in different forms and is often characterized by interindividual variability in time course and intensity. It is therefore almost impossible to study in controlled laboratory settings in humans. Although most published studies are cross-sectional assessments at a specific time point during or after the onset of a chronically stressful experience, the number of longitudinal studies is increasing. Different types of enduring adverse psychosocial conditions can be included in the study of chronic psychosocial stress. One commonly studied example of chronic stress is caregiver stress. In this model, individuals, often older adults, who are caring for a partner with chronic illness (e.g., dementia) are compared with matched controls (e.g., Ref. (13)). Other studies examine the association of other forms of stress with low-grade inflammation. For example, in a recent review of the literature, Hänsel et al. (14) present studies on the inflammatory covariates of job stress and burnout, socioeconomic status (SES), childhood adversity, and major life events. In addition, including psychiatric diseases such as depression and posttraumatic stress disorder (PTSD) can provide useful insights because both are related to the experience of stress and show marked alterations in stress system activity (15).

Caregiver Paradigms

Caregiving studies provide strong evidence for an association of stress with low-grade inflammation. Results are relatively consistent and indicate that caregivers show elevated plasma levels of interleukin (IL)-6 (13,16–18) when compared with controls, whereas higher C-reactive protein (CRP) levels are found in some but not all studies (16,17,19). One study revealed that caregivers had higher IL-6 levels 4 weeks after vaccination than did controls (20). Furthermore, it was found that daily stressor experiences partially mediated higher CRP, but not IL-6 concentrations in caregivers (17), and that self-efficacy buffered associations of caregiving with IL-6 (18). In a longitudinal study testing low-grade inflammation in caregivers, Kiecolt-Glaser and colleagues (7) reported that IL-6 concentrations increased more steeply over a 6-year period in elderly caregivers of patients with Alzheimer's disease compared with controls. This was recently confirmed in another longitudinal study of Alzheimer caregivers by von Känel et al. (21), who further found that duration of caregiving was related to higher CRP levels and that, in contrast to the earlier findings, inflammation levels dropped significantly 3 months after the spouse's death. In a recent study of younger caregivers of brain cancer patients, we found linear increases of CRP, but not IL-6, during a 44-week period of diagnosis, treatment, and, in many cases, death of the patient (22). These investigations provide compelling evidence supporting the presence of chronic systemic low-grade inflammation in individuals experiencing the stress of caring for a family member with a chronic disease. This effect is not restricted to older adults, but in older adults, caregiving seems to be related to an acceleration of age-related increases in plasma concentrations of inflammation markers.

Work-Related Stress and Burnout

A few studies have addressed chronic low-grade inflammation in unemployment. In one study, 19 unemployed middle-aged men and women were contrasted with more than 200 employed individuals. Average concentrations of IL-6 and CRP did not differ between the two groups, but the number of individuals with high IL-6 and CRP was higher in the unemployed (59% versus 30%) (23). More evidence is available on burnout, which is frequently discussed as a consequence of work overload. Higher plasma tumor necrosis factor α (TNF-α) was found in school teachers (24) and higher TNF-α and CRP in women from the general population in association with burnout (25,26). In addition, Bellingrath et al. (27) report increased in vitro stimulated production of IL-6 and TNF-α in teachers with high effort/reward imbalance. However, not all studies have found significant relationships between inflammatory markers and burnout (28).

Chronic Stress Related to Low SES

Low SES, usually defined as lower-than-average income or education, and low subjective social status (SSS), which can be assessed, for example, by the MacArthur ladders, have both been found to be related to health and longevity (e.g., Ref. (29)). Nazmi and Victora (30) summarized data from 31 cross-sectional and longitudinal studies and found that most reported inverse associations between social position and CRP, and higher CRP levels in all ethnic groups other than whites. A more recent cross-sectional analysis of the Midlife in the United States study confirmed relationships between low income and education and higher plasma concentrations of IL-6 and other inflammatory markers (31). In a recent article on the results of the prospective Coronary Artery Risk Development in Young Adults study, Deverts et al. (32) report that individuals with lower income and education displayed significantly higher increases in CRP over a 13-year period.

Childhood Adversity and Maltreatment

Low childhood SES is also frequently used as an indicator of early-life/childhood adversity. In these studies, a retrospective assessment of parents' SES during childhood is tested for associations with current psychosocial well-being and markers of inflammation. There is strong evidence linking low childhood SES with higher systemic inflammatory activity in adolescence and adulthood. Miller and Chen (33) and Miller et al. (34), for example, have shown in different studies that indicators of low childhood SES such as home ownership or parental education were significant predictors of inflammatory potential, as evidenced by increased expression of inflammatory genes in circulating immune cells. A similar study by Packard et al. (35)

also showed an increase in plasma concentrations of IL-6 and CRP in adults with low childhood SES. Although the previous studies show that even mild adversity such as lower parental wealth and education is associated with elevated inflammation markers in later life, Danese et al. (36) showed that childhood maltreatment was associated with a 1.8-times higher risk of having CRP concentrations that exceed a cutoff indicating significant risk for cardiovascular disease 20 years later. This relationship apparently remains present into older adulthood, as indicated by the finding that a history of childhood abuse magnifies the relationship of caregiving with IL-6 and TNF concentrations (37).

Depression and PTSD

Some clinical conditions such as PTSD and depression and self-reports of symptoms related to these clinical conditions have sufficient similarities with chronic stress to be included in a review of chronic stressful conditions in relation to inflammation. In a meta-analysis, Howren et al. (38) found overwhelming support for the conclusion that plasma inflammatory markers are positively associated with depression. This was true for four inflammatory molecules (IL-6, CRP, IL-1, and IL-1ra). Furthermore, these relationships were found in clinical and community samples, and data supported a dose-response relationship between symptoms and inflammation. In PTSD, fewer studies are available, but a picture of increased inflammatory activation emerges here as well (for a summary, see Refs. (15,39)). Of interest, Pace and coworkers (40) provide a possible glimpse into intracellular mechanisms underlying inflammation in PTSD by reporting increased nuclear factor κB (NF-κB) DNA binding activity in women with PTSD after childhood abuse.

Self-Reported Chronic Stress and Inflammation

Studies of healthy individuals sometimes report associations between self-rated recent or current stress with inflammatory molecules (e.g., Refs. (41,42)). Similar findings have been reported for self-reported social isolation and/or loneliness, which has been associated with higher plasma IL-6 and CRP, although relationships are stronger in, or sometimes restricted to, older men, while not significant in younger adults or younger women (43–46). Related to these findings is the observed positive relation between self-rated depression, anger, and hostility with CRP levels (47).

Summary of Chronic Stress Associations With Chronic Low-Grade Inflammation

In summary, current evidence is supportive of increased markers of systemic inflammation among individuals experiencing chronic psychological or social stress. The most consistent evidence comes from caregiving paradigms, followed by studies relating early-life adversity or maltreatment to current levels of circulating inflammatory molecules. Current SES and work-related stress are also found to be related to inflammation, but results are less consistent across studies. Nevertheless, psychosocial conditions that fall in the realm of chronic stress seem to associate with chronic low-grade inflammation. Inflammation therefore stands out as a promising biological process to investigate in the association between stress and disease.

ACUTE STRESS–INDUCED INCREASES IN PERIPHERAL INFLAMMATION

In addition to the evidence reviewed above regarding the association of chronic stress, depression, and related psychiatric conditions with chronic low-grade inflammation, studies have also shown that acute stress exposures are followed by increases in plasma levels of inflammation markers. Such increases are important to the understanding of central nervous system involvement in the regulation of inflammation, and also because stable differences between individuals in response patterns to daily stressors might contribute to long-term inflammatory regulation, with consequences for health and longevity. Numerous studies have consistently found increases in plasma concentrations of inflammation markers in response to acute laboratory psychosocial stress tasks, such as the Trier Social Stress Test (TSST; (48)), and other tasks such as Stroop and Mirror Tracing tasks under time pressure and/or social evaluation (see, for example, Ref. (49)). A meta-analysis by Steptoe et al. (50) published in 2006 summarized early studies and came to the conclusion that the most consistent increases were found for the proinflammatory cytokines IL-6 and IL-1β, whereas increases in TNF-α and CRP were not statistically significant. Since then, these findings have been replicated and extended. Taken together, these studies show that acute stress–related increases in peripheral inflammatory markers are relatively slow, even in comparison with cortisol, with peak concentrations reached at the 2-hour poststress time point. No studies have attempted measurements at later time points, which essentially means that it is not known when peak and recovery occur. Several factors have been shown to be associated with individual differences in the magnitude of this response. For example, larger stress-induced increases in inflammatory markers have been associated with depressive symptoms. Pace et al. (51) report higher IL-6 responses in patients with early-life adversity and major depression. Subclinical depressive symptoms are also related to higher IL-6 responses in one study using the Center for Epidemiologic Studies Depression Scale (52), but not in an earlier study using the Beck Depression Inventory (53). Early-life adversity assessed with the Childhood Trauma Questionnaire, in the absence of depression, has also been associated with IL-6 reactivity (54). Furthermore, low self-esteem (55), high hostility (56), and increased loneliness (in women only) (57) were found to be associated with higher stress-related increases in plasma inflammatory markers. Higher inflammatory responses to stress have also been reported in individuals with lower SES (58,59) and lower SSS (60), as well as in those with higher work stress (effort/reward imbalance; (61)) and in individuals showing higher state anger and anxiety in response to the stress paradigm (62). We have recently found that IL-6 responses to stress are higher in individuals with lower self-compassion (90) (see Fig. 1).

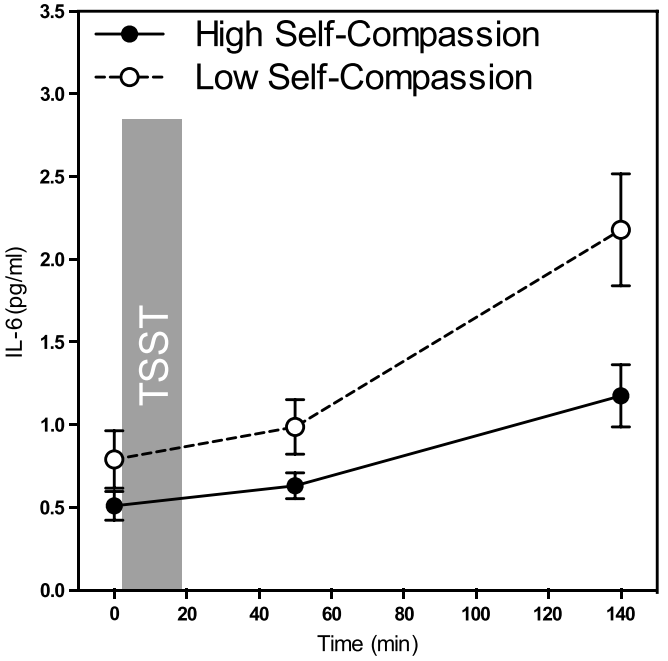

Figure 1. IL-6 levels at baseline and 30 and 120 minutes after exposure to the TSST for participants above and below the mean on self-compassion (*n* values = 20 and 21 for the high and low self-compassion groups, respectively). Reproduced with permission from Breines et al. (90). IL-6 = interleukin-6; TSST = Trier Social Stress Test.

Inflammatory stress responses were also found to be higher in those with lower fitness (63) and higher abdominal fat (as measured by waist-to-hip ratio; (64)) and with higher carotid stiffness (65). These results show that there is now a convincing body of evidence supporting the notion that acute stress exposure stimulates a slow but steady increase in plasma concentrations of inflammatory markers and that these increases tend to be higher in individuals with less favorable trait or state measures of psychosocial functioning and well-being.

The evidence reviewed above shows that acute psychosocial stress exposure results in increases in inflammation markers and psychosocial background factors (e.g., depression, low SES) are associated with the magnitude of these stress-induced inflammation responses, but it is currently unclear what drives this response and where the increased circulating inflammation markers originate.

Regulation by Stress System Mediators

Early animal-based research has shown that stress-related activation of the HPA and SNS axes may result in the observed increases in peripheral inflammatory markers. For example, rodent studies show that the increase in circulating IL-6 that follows the physical stress of surgery or experimentally induced fever is prevented by administration of β-blockers and induced by β-adrenergic agonists (66). Furthermore, experimental administration of epinephrine in rats induced a dose-dependent increase in plasma IL-6, with a peak after 2 hours and recovery at 4 hours, which was blocked by β-adrenergic antagonists (67). Studies in humans have revealed similar results, with positive correlations between catecholamine and inflammatory responses to acute mental challenge and exercise (68,69). Interestingly, the administration of glucocorticoids blocked these responses (68).

In our studies on NF-κB DNA binding activity, we found that NF-κB activation in human peripheral blood mononuclear cells, which is a precursor to increased concentrations of inflammatory markers in plasma, was stimulated by norepinephrine, specifically through α_2- and β-adrenergic receptors (70) and that the NF-κB response to psychosocial stress was negatively correlated with salivary cortisol response (71). With regard to plasma concentrations of inflammation markers, Kunz-Ebrecht et al. (72) found higher IL-6 and IL-1ra responses in participants with lower net cortisol concentrations before and after the stress task. Although this relationship was not fully replicated in a study by von Känel et al. (73), they did observe an inverse association of IL-6 and cortisol secretion during the last of three repeated TSST exposures. We recently observed a similar inverse relationship between HPA axis habituation and IL-6 sensitization to repeated stress exposure. In other words, individuals with lower HPA axis habituation showed a larger IL-6 response to the second, relative to the first, TSST exposure (Thoma et al., manuscript in preparation). Of note, von Känel et al. (74) tested whether short-term administration of aspirin or propranolol suppressed stress-induced IL-6 increases and surprisingly found that only aspirin was effective as a suppressor of the inflammatory stress response. An explanation for the missing ability of propranolol to block the stress-induced IL-6 increase might be the timing of propranolol administration.

Taken together, stress-related increases in circulating markers of inflammation seem to be related to activation of the SNS, particularly signaling through β-adrenergic receptors. Inflammatory responses are inversely related to HPA axis activation and can be suppressed by glucocorticoid administration. These mechanisms could be active in different tissues and cell types, that is, immune and nonimmune cells such as adipocytes or endothelial cells, as discussed below.

Intracellular Inflammatory Signaling and the Role of Immune Cell Redistribution

If immune cells are the source of stress-induced inflammation markers, it should be possible to measure activation of the "inflammatory machinery" within immune cells harvested from peripheral blood in humans exposed to acute stress. In fact, in a study investigating the role of the inflammatory transcription factor NF-κB, we discovered a rapid and strong increase in NF-κB DNA binding activity in human participants exposed to the TSST, compared with nonresponses in a no-stress control group. We confirmed this response in a transgenic mouse model, as well as in vitro in the monocytic, human THP-1 cell line, where we also found evidence for a central role of adrenergic receptors as mediators of NF-κB activation (70). We later confirmed this finding in a sample of individuals of varied ages and found that NF-κB responses were smaller in older compared with younger individuals and that they were inversely related to cortisol responses to the same stressor, but not associated with norepinephrine

responses (71). Similar responses were also found by Pace et al. (51) in women with major depression and a history of childhood maltreatment, but not in the group of healthy controls. In addition to, and likely a consequence of, changes in NF-κB DNA binding activity, a study by Brydon et al. (75) revealed increased gene expression of IL-1β but not IL-6 in response to stress induced by a Stroop and mirror tracing task performed under time pressure. Nater et al. (76) used genome-wide microarrays in a smaller study of individuals exposed to the TSST and found increased expression of genes regulated by NF-κB and the JAK/STAT pathways. A significant NF-κB increase had earlier been documented in response to an hour of physical exercise (77). In this study, plasma concentrations of TNF-α and sIL-2R also increased from preexercise to postexercise, but statistical relationships were not reported. In a similar study using a 5-minute bout of exercise to activate stress systems, Richlin et al. (78) also found exercise-related increases in NF-κB DNA binding activity when measured in the entire population of peripheral blood mononuclear cells. Given the well-established change in immune cell distribution that also accompanies exercise, they also examined NF-κB DNA binding activity among different leukocyte subsets, reporting the highest binding activity in natural killer (NK) cells and the lowest in monocytes. Although no significant increases were found in any of the subsets, the overall NF-κB increase was significantly correlated with an increase in circulating NK cell numbers from preexercise to postexercise. Thus, the authors concluded that NF-κB increases in response to exercise were a likely consequence of changes in the distribution of cell subtypes in peripheral circulation and not of changes within specific immune cells. It is possible that cell subset redistribution plays a role; however, we have also shown NF-κB responses to norepinephrine on a per-cell basis in human monocytic cell lines in vitro (70), and although we did find redistribution of immune cells in our later study (71), using these cell number changes as statistical controls did not explain a significant portion of the NF-κB response. It should be noted though that our cell counts did not specifically identify NK cell changes. An explanation for these divergent findings might be that immune cell redistribution was more pronounced in response to intense exercise as compared with psychosocial stress. A further potentially meaningful difference is that exercise of short duration as used by Richlin et al. does not typically activate the HPA axis, so that only part of the effect of stress responses on NF-κB is investigated in exercise studies.

Taken together, there are probably at least two mechanisms at work, redistribution of immune cells stimulated by catecholamines and potentially glucocorticoids, as well as catecholamine-mediated activation of intracellular inflammatory signaling pathways, most prominently NF-κB, with subsequent activation of inflammatory gene expression.

Nonimmune Sources of Inflammatory Markers

The production of inflammatory cytokines is not restricted to cells of the immune system, but it is also observed in other cell types such as adipocytes and endothelial cells. In obesity, increased concentrations of IL-6 are observed, and in vivo studies in humans and mice have revealed larger IL-6 responses to β-agonist infusion in obesity. Interestingly, β-agonists induce significant increases in IL-6 production in cultured human adipocytes while having no effect on peripheral blood mononuclear cells (79). This might indicate a primary role of adipose tissue in stress-induced increases in plasma levels of proinflammatory markers. It remains to be investigated whether this mechanism plays a role in normal-weight individuals. In an ongoing study, we observed that sensitization of IL-6 responses to acute psychosocial stress, that is, responding with higher IL-6 increases to repeated stress exposure, is significantly increased in overweight individuals (manuscript in preparation). Endothelial cells also produce inflammatory cytokines, for example, IL-6 (80), and similar to immune cells, the NF-κB pathway plays a key role in inflammatory gene expression (81,82). This pathway is central to the development of atherosclerotic plaques and may contribute to levels of cytokines in peripheral circulation. Contracting muscle cells have also been shown to produce IL-6, and plasma IL-6 concentrations increase during exercise (83). However, most laboratory stressors (as well as most real-life stress-provoking situations in humans) do not involve physical activity; thus, muscle cells are an unlikely source of the increase in inflammatory markers that accompany acute psychological stress. A further possibility is involvement of the adrenal gland in secretion of inflammatory markers. Different cell types within the adrenal glands express inflammatory cytokines, with secretion of IL-6 stimulated by Lipopolysaccharide and Adrenocorticotropic Hormone (84). In humans, TNF-α and IL-6 are found in the glucocorticoid-producing zona reticulosa of the adrenal cortex (85). This raises the possibility that stress-induced activation of the HPA axis results in increased production of inflammatory markers, yet this seems inconsistent with evidence that the acute inflammatory response is largely driven by catecholamines.

In summary, a combination of different mechanisms is likely responsible for the observed stress-induced increase of inflammatory markers in plasma. There is strong evidence for a central role of catecholamine signaling as the activating factor and for glucocorticoids as the controlling or regulating factor. More specifically, catecholamine signaling affects both intracellular inflammatory pathways, that is, NF-κB activation, and immune cell redistribution, leading to higher numbers of cells with inflammatory activity in circulation to result in higher plasma levels of inflammatory markers. Similarly, glucocorticoids exert their anti-inflammatory effects through mutual antagonism with the NF-κB pathway, but also contribute to immune cell redistribution by reducing the number of proinflammatory cells in circulation. Thus, it is likely that both per-cell activation and redistribution contribute to plasma levels of inflammatory markers. Of the nonimmune cells, adipocytes are the most likely to contribute to circulating inflammatory markers, whereas we know less about the role of endothelial cells and other cell subtypes. It remains to be determined whether muscle or adrenal cells contribute to stress-induced increases in low-grade inflammation.

Determinants and Consequences of Acute Inflammatory Stress Responses

Another important question to address with regard to the acute inflammatory response to stress is its biological purpose. The increases in IL-6 that accompany exercise seem to result from activation of muscle cells and seem to serve regulatory purposes and help in long-term adaptation to increased energy demands (e.g., Ref. (86)). In contrast, the purpose of increased peripheral inflammation in response to acute psychological stress is less clear. This reaction is frequently discussed in the context of other immune changes that accompany acute psychosocial stress and are interpreted as anticipatory up-regulation to protect against injury and subsequent infection that can be contracted during fight-or-flight responses. Because most psychosocial stress in modern humans occurs without injury and infection, such a response might turn out to be maladaptive, at least if not terminated quickly. This, in turn, suggests that an acute increase in plasma concentrations of inflammatory molecules in response to stress is an antiquated response that is no longer of health benefit. Certain conditions would need to be present (i.e., activation of regulatory functions) to prevent dangers to health associated with stress-induced increases in inflammation markers. In line with theories such as the allostatic load model (87), it can be assumed that a strong response to stress exposure followed by rapid termination of the response after the stress situation has passed represents a healthy, adaptive response. As described above, stress-induced activation of the plasma inflammatory response seems to be stimulated by the SNS, whereas the magnitude and duration of this response seem to be controlled by glucocorticoids. The exact trajectory of the inflammatory response and factors that influence recovery remain to be determined in studies that include longer follow-up times. However, it is known that people differ substantially in the magnitude of their inflammatory response to external challenges, with adverse psychosocial states (or traits), and some markers of cardiovascular disease such as carotid stiffness (65), predicting larger responses. This raises the possibility that higher inflammatory responses are in fact signs of a maladaptive response. However, the health significance of these individual differences remains unclear. To date, only one study provides evidence for a prospective relationship of higher acute inflammatory responses with adverse health outcomes (88): Brydon and Steptoe report that higher stress-induced increases of IL-6 and fibrinogen are related to higher ambulatory blood pressure in a 3-year follow-up.

Individual differences in one-time stress exposure are only one potential pathway from stress to disease. In real life, humans are exposed to repeated stressful events, some of different and varying nature and others recurring and largely similar. It has been proposed that an adaptive way to respond to repeated exposures to the same stressful stimuli is to habituate, that is, to show lower psychosocial and biological responses to re-exposure. In this regard, the magnitude of the HPA axis response to the TSST has been shown to habituate, with lower response on a second exposure to the experimental stressor (e.g., Ref. (89)), but at the same time, the SNS was found to not habituate. This difference in response patterns likely reflects different biological functions in stress-provoking situations, which might (SNS) or might not (HPA axis) be necessary to retain physiological functions.

With regard to inflammation, a constant up-regulation, with rather long-term increases in inflammatory markers, might carry negative health consequences because it might lead to higher average daily concentrations, and it might also stimulate feed-forward inflammatory signaling loops. Of interest, in this context, are findings from von Känel et al. (73) showing that IL-6 responses to repeated acute stress exposure did not show any signs of habituation. In this study, salivary cortisol responses showed the same pattern of habituation already established in the literature, but no reductions in IL-6 reactivity were observed between the first and the third exposure to the TSST. We recently confirmed this finding in a study using two repeated TSST exposures (90). We further found in our study that although inflammatory responses to repeated stress exposures do not habituate, there is a substantial amount of variation, with approximately half of the participants showing habituation and a large proportion even showing sensitization, that is, displaying higher IL-6 responses to the second compared with the first stress task (Thoma et al., manuscript in preparation). Although it has not been tested whether this sensitization of inflammatory responses to acute stress is predictive of negative health developments in the future, we do have some preliminary cross-sectional evidence indicating that sensitization of inflammatory stress responses might be maladaptive. We found, for example, that lower self-ratings of SSS, as well as lower perceived purpose in life, were significantly related to higher sensitization of IL-6 responses to repeated TSST exposure. In the same study, we also found relations with physical health. Overweight individuals showed significantly higher sensitization than did normal-weight participants, despite normal pre-stress levels of IL-6 (Rohleder et al., in preparation; see Fig. 2 for a schematic summary of these relationships).

Summary of Acute Stress–Induced Increases of Systemic Inflammation

Although we do not know the precise mechanism and tissue source of the increase in circulating markers of inflammation that follows acute psychological stress, the response seems related to catecholamine and glucocorticoid stress responses

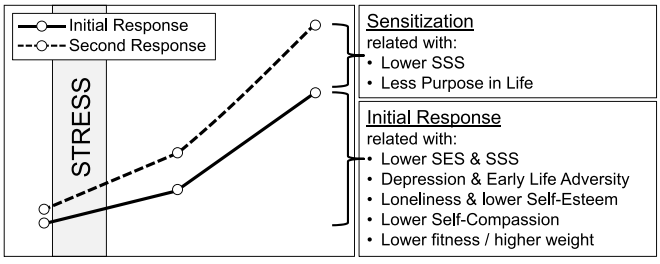

Figure 2. Schematic representation of plasma inflammatory response to initial and repeated acute psychosocial stress (left) and associations of initial response with psychosocial and other conditions, as well as with sensitization upon repeated exposure with psychosocial conditions (right). SSS = subjective social status; SES = socioeconomic status.

and, in general, is higher among individuals experiencing and/or reporting less favorable psychosocial conditions. However, habituation–and especially lack of habituation–of inflammatory responses across repeated stressors is more complex and difficult to explain. Our recent findings suggest that failure to habituate and sensitization of IL-6 responses to repeated stress are also associated with less favorable psychosocial conditions. However, it is not clear how the HPA and SNS pathways contribute to this effect, especially given that glucocorticoid responses habituate, whereas catecholamine responses do not. In theory, this would result in a higher inflammatory response to repeated stress exposure; however, this is not compatible with our findings or those of von Känel et al. showing that individuals with stronger HPA axis habituation also show more habituation (or less sensitization) of inflammatory stress responses. To explain this relationship, further assumptions have to be made about additional mediators or regulatory mechanisms. A candidate mechanism might be altered glucocorticoid sensitivity of inflammatory mediator producing cells and tissues in response to repeated stress (see, for example, Ref. (91)).

GENERAL SUMMARY AND FUTURE DIRECTIONS

The literature reviewed here underscores the importance of focusing on peripheral inflammation in our quest toward understanding pathways between psychosocial stress and physical or psychological health risk. An important question that is currently unresolved is how acute stress responses are related to the longer-term changes that accompany chronic stress, or more precisely, if and how acute stress responses are predictors of long-term dysregulation even in the absence of other chronic stressors. A number of theories of stress address these issues. For example, in the cascade hypothesis, it is suggested that repeated increases of cortisol would induce decreased hippocampal feedback sensitivity, which, in turn, would result in further and higher cortisol increases, leading to a vicious cycle of increasing cortisol concentrations (92). Although human aging is not characterized by higher basal HPA axis activity (e.g., Ref. (93)), the proposed mechanism could play a role in HPA axis changes during long-term stress or after trauma. The allostatic load model also makes specific predictions about acute stress response patterns (94), with a failure to habituate contributing to accumulation of damage and increasing risk for disease. Systemic low-grade inflammation fits into this as one of several secondary systems but is of exceptional importance because of its strong relationships with disease-relevant pathophysiological mechanisms.

However, empirical studies testing the prospective relationship of acute stress response patterns such as nonhabituation with development of disease are missing. It will be important in future research to aim for a better understanding of maladaptive acute stress response patterns, for example, by asking why some individuals do not habituate and whether failure to habituate contributes to increased health risk. We have begun addressing the question of why individuals differ in their ability to show HPA axis habituation, or less pronounced inflammatory sensitization under repeated stress, and found preliminary evidence for factors related to more or less efficient habituation of HPA axis or IL-6 responses, for example, stress appraisals, poststress rumination, SSS, experience of purpose in life, or self-rated depressive symptoms. This will have to be extended to the investigation of trait and state factors, as well as trait by state interactions.

To understand the consequences of maladaptive stress response patterns, we will need to move to multisystem assessments of biological responses to repeated acute stress events. Prospective studies are needed that test not only the stability of specific stress response patterns but also whether specific patterns predict long-term decline in function and development of disease.

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REFERENCES

1. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA 2007;298:1685–7.
2. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull 2007;133:25–45.
3. Miller AH. Inflammation versus glucocorticoids as purveyors of pathology during stress: have we reached the tipping point? Biol Psychiatry 2008;64:263–5.
4. Danesh J. Smoldering arteries? Low-grade inflammation and coronary heart disease. JAMA 1999;282:2169–71.
5. Ershler WB, Sun WH, Binkley N. The role of interleukin-6 in certain age-related diseases. Drugs Aging 1994;5:358–65.
6. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004;39:687–99.
7. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A 2003;100:9090–5.
8. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–72.
9. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol 2006;6:508–19.
10. Kop WJ, Cohen N. Psychoneuroimmunological pathways involved in acute coronary syndromes. In: Ader R, editor. Psychoneuroimmunology. 4th ed. Amsterdam: Academic Press; 2007:921–43. Chapter 43.
11. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860–7.
12. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
13. Lutgendorf SK, Garand L, Buckwalter KC, Reimer TT, Hong SY, Lubaroff DM. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. J Gerontol A Biol Sci Med Sci 1999;54:M434–9.
14. Hänsel A, Hong S, Camara RJ, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev 2010;35:115–21.
15. Rohleder N, Wolf JM, Wolf OT. Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder. Neurosci Biobehav Rev 2010;35:104–14.

16. von Känel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, Grant I. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C reactive protein, and D-dimer. J Gerontol A Biol Sci Med Sci 2006;61:963–9.
17. Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. Health Psychol 2012;31:264–8.
18. Mausbach BT, von Känel R, Roepke SK, Moore R, Patterson TL, Mills PJ, Dimsdale JE, Ziegler MG, Ancoli-Israel S, Allison M, Grant I. Self-efficacy buffers the relationship between dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. Am J Geriatr Psychiatry 2011;19:64–71.
19. Lovell B, Moss M, Wetherell M. The psychosocial, endocrine and immune consequences of caring for a child with autism or ADHD. Psychoneuroendocrinology2012;37:534–42.
20. Segerstrom SC, Schipper LJ, Greenberg RN. Caregiving, repetitive thought, and immune response to vaccination in older adults. Brain Behav Immun 2008;22:744–52.
21. von Känel R, Mills PJ, Mausbach BT, Dimsdale JE, Patterson TL, Ziegler MG, Ancoli-Israel S, Allison M, Chattillion EA, Grant I. Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. Gerontology 2012;58:354–65.
22. Rohleder N, Marin TJ, Ma R, Miller GE. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. J Clin Oncol 2009;27:2909–15.
23. Hintikka J, Lehto SM, Niskanen L, Huotari A, Herzig KH, Koivumaa-Honkanen H, Honkalampi K, Sinikallio S, Viinamaki H. Unemployment and ill health: a connection through inflammation? BMC Public Health 2009;9:410.
24. von Känel R, Bellingrath S, Kudielka BM. Association between burnout and circulating levels of pro- and anti-inflammatory cytokines in school-teachers. J Psychosom Res 2008;65:51–9.
25. Grossi G, Perski A, Evengard B, Blomkvist V, Orth-Gomer K. Physiological correlates of burnout among women. J Psychosom Res 2003;55:309–16.
26. Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. J Occup Health Psychol 2005;10:344–62.
27. Bellingrath S, Rohleder N, Kudielka BM. Healthy working school teachers with high effort-reward-imbalance and overcommitment show increased pro-inflammatory immune activity and a dampened innate immune defence. Brain Behav Immun 2010;24:1332–9.
28. Mommersteeg PM, Heijnen CJ, Kavelaars A, van Doornen LJ. Immune and endocrine function in burnout syndrome. Psychosom Med 2006;68: 879–86.
29. Adler NE, Boyce T, Chesney MA, Cohen S, Folkman S, Kahn RL, Syme SL. Socioeconomic status and health. The challenge of the gradient. Am Psychol 1994;49:15–24.
30. Nazmi A, Victora CG. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health 2007;7:212.
31. Friedman EM, Herd P. Income, education, and inflammation: differential associations in a national probability sample (The MIDUS study). Psychosom Med 2010;72:290–300.
32. Deverts DJ, Cohen S, Kalra P, Matthews KA. The prospective association of socioeconomic status with C-reactive protein levels in the CARDIA study. Brain Behav Immun 2012;26:1128–35.
33. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom Med 2007;69:402–9.
34. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A 2009;106:14716–21.
35. Packard CJ, Bezlyak V, McLean JS, Batty GD, Ford I, Burns H, Cavanagh J, Deans KA, Henderson M, McGinty A, Millar K, Sattar N, Shiels PG, Velupillai YN, Tannahill C. Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive performance: a cross sectional, population-based study. BMC Public Health 2011;11:42.
36. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A 2007;104:1319–24.
37. Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med 2011;73:16–22.
38. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171–86.
39. Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. Brain Behav Immun 2011;25:6–13.
40. Pace TW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM. Increased peripheral NF-kappaB pathway activity in women with childhood abuse related posttraumatic stress disorder. Brain Behav Immun 2012;26:13–7.
41. Ranjit N, Diez-Roux AV, Shea S, Cushman M, Seeman T, Jackson SA, Ni H. Psychosocial factors and inflammation in the multi-ethnic study of atherosclerosis. Arch Intern Med 2007;167:174–81.
42. McDade TW, Hawkley LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. Psychosom Med 2006;68:376–81.
43. Hafner S, Emeny RT, Lacruz ME, Baumert J, Herder C, Koenig W, Thorand B, Ladwig KH. Association between social isolation and inflammatory markers in depressed and non-depressed individuals: results from the MONICA/KORA study. Brain Behav Immun 2011;25:1701–7.
44. Loucks EB, Sullivan LM, D'Agostino RBS, Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. J Biosoc Sci 2006;38:835–42.
45. Ford ES, Loucks EB, Berkman LF. Social integration and concentrations of C-reactive protein among US adults. Ann Epidemiol 2006;16:78–84.
46. Loucks EB, Berkman LF, Gruenewald TL, Seeman TE. Social integration is associated with fibrinogen concentration in elderly men. Psychosom Med 2005;67:353–8.
47. Suarez EC. C-reactive protein is associated with psychological risk factors of cardiovascular disease in apparently healthy adults. Psychosom Med 2004;66:684–91.
48. Kirschbaum C, Pirke K-M, Hellhammer DH. The "Trier Social Stress Test"—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28:76–81.
49. Steptoe A, Willemsen G, Owen N, Flower L, Mohamed-Ali V. Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. Clin Sci (Lond) 2001;101:185–92.
50. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun 2007;21:901–12.
51. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry 2006;163:1630–3.
52. Fagundes CP, Glaser R, Hwang BS, Malarkey WB, Kiecolt-Glaser JK. Depressive symptoms enhance stress-induced inflammatory responses. Brain Behav Immun 2013;31:172–6.
53. Benson S, Arck PC, Blois S, Schedlowski M, Elsenbruch S. Subclinical depressive symptoms affect responses to acute psychosocial stress in healthy premenopausal women. Stress 2011;14:88–92.
54. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology 2010;35:2617–23.
55. O'Donnell K, Brydon L, Wright CE, Steptoe A. Self-esteem levels and cardiovascular and inflammatory responses to acute stress. Brain Behav Immun 2008;22:1241–7.
56. Brydon L, Strike PC, Bhattacharyya MR, Whitehead DL, McEwan J, Zachary I, Steptoe A. Hostility and physiological responses to laboratory stress in acute coronary syndrome patients. J Psychosom Res 2010; 68:109–16.
57. Hackett RA, Hamer M, Endrighi R, Brydon L, Steptoe A. Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. Psychoneuroendocrinology 2012;37:1801–9.
58. Steptoe A, Owen N, Kunz-Ebrecht S, Mohamed-Ali V. Inflammatory cytokines, socioeconomic status, and acute stress responsivity. Brain Behav Immun 2002;16:774–84.
59. Brydon L, Edwards S, Mohamed-Ali V, Steptoe A. Socioeconomic status and stress induced increases in interleukin-6. Brain Behav Immun 2004; 18:281–90.
60. Derry HM, Fagundes CP, Andridge R, Glaser R, Malarkey WB, Kiecolt-Glaser JK. Lower subjective social status exaggerates interleukin-6 responses to a laboratory stressor. Psychoneuroendocrinology 2013;38:2676–85.

61. Hamer M, Williams E, Vuonovirta R, Giacobazzi P, Gibson EL, Steptoe A. The effects of effort-reward imbalance on inflammatory and cardiovascular responses to mental stress. Psychosom Med 2006;68:408–13.
62. Carroll JE, Low CA, Prather AA, Cohen S, Fury JM, Ross DC, Marsland AL. Negative affective responses to a speech task predict changes in interleukin (IL)-6. Brain Behav Immun 2011;25:232–8.
63. Hamer M, Steptoe A. Association between physical fitness, parasympathetic control, and proinflammatory responses to mental stress. Psychosom Med 2007;69:660–6.
64. Brydon L, Wright CE, O'Donnell K, Zachary I, Wardle J, Steptoe A. Stress-induced cytokine responses and central adiposity in young women. Int J Obes (Lond) 2008;32:443–50.
65. Ellins E, Halcox J, Donald A, Field B, Brydon L, Deanfield J, Steptoe A. Arterial stiffness and inflammatory response to psychophysiological stress. Brain Behav Immun 2008;22:941–8.
66. van Gool J, van Vugt H, Helle M, Aarden LA. The relation among stress, adrenalin, interleukin 6 and acute phase proteins in the rat. Clin Immunol Immunopathol 1990;57:200–10.
67. DeRijk RH, Boelen A, Tilders FJ, Berkenbosch F. Induction of plasma interleukin-6 by circulating adrenaline in the rat. Psychoneuroendocrinology 1994;19:155–63.
68. Papanicolaou DA, Petrides JS, Tsigos C, Bina S, Kalogeras KT, Wilder R, Gold PW, Deuster PA, Chrousos GP. Exercise stimulates interleukin-6 secretion: inhibition by glucocorticoids and correlation with catecholamines. Am J Physiol 1996;271:E601–5.
69. Kop WJ, Weissman NJ, Zhu J, Bonsall RW, Doyle M, Stretch MR, Glaes SB, Krantz DS, Gottdiener JS, Tracy RP. Effects of acute mental stress and exercise on inflammatory markers in patients with coronary artery disease and healthy controls. Am J Cardiol 2008;101:767–73.
70. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A 2003;100:1920–5.
71. Wolf JM, Rohleder N, Bierhaus A, Nawroth PP, Kirschbaum C. Determinants of the NFkappaB response to acute psychosocial stress in humans. Brain Behav Immun 2009;23:742–9.
72. Kunz-Ebrecht SR, Mohamed-Ali V, Feldman PJ, Kirschbaum C, Steptoe A. Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. Brain Behav Immun 2003;17:373–83.
73. von Känel R, Kudielka BM, Preckel D, Hanebuth D, Fischer JE. Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. Brain Behav Immun 2006;20:40–8.
74. von Känel R, Kudielka BM, Metzenthin P, Helfricht S, Preckel D, Haeberli A, Stutz M, Fischer JE. Aspirin, but not propranolol, attenuates the acute stress–induced increase in circulating levels of interleukin-6: a randomized, double-blind, placebo-controlled study. Brain Behav Immun 2008;22:150–7.
75. Brydon L, Edwards S, Jia H, Mohamed-Ali V, Zachary I, Martin JF, Steptoe A. Psychological stress activates interleukin-1beta gene expression in human mononuclear cells. Brain Behav Immun 2005;19:540–6.
76. Nater UM, Whistler T, Lonergan W, Mletzko T, Vernon SD, Heim C. Impact of acute psychosocial stress on peripheral blood gene expression pathways in healthy men. Biol Psychol 2009;82:125–32.
77. Vider J, Laaksonen DE, Kilk A, Atalay M, Lehtmaa J, Zilmer M, Sen CK. Physical exercise induces activation of NF-kappaB in human peripheral blood lymphocytes. Antioxid Redox Signal 2001;3:1131–7.
78. Richlin VA, Arevalo JM, Zack JA, Cole SW. Stress-induced enhancement of NF-kappaB DNA-binding in the peripheral blood leukocyte pool: effects of lymphocyte redistribution. Brain Behav Immun 2004; 18:231–7.
79. Mohamed-Ali V, Flower L, Sethi J, Hotamisligil G, Gray R, Humphries SE, York DA, Pinkney J. beta-Adrenergic regulation of IL-6 release from adipose tissue: in vivo and in vitro studies. J Clin Endocrinol Metab 2001; 86:5864–9.
80. Sironi M, Breviario F, Proserpio P, Biondi A, Vecchi A, Van Damme J, Dejana E, Mantovani A. IL-1 stimulates IL-6 production in endothelial cells. J Immunol 1989;142:549–53.
81. Ferran C, Millan MT, Csizmadia V, Cooper JT, Brostjan C, Bach FH, Winkler H. Inhibition of NF-kappa B by pyrrolidine dithiocarbamate blocks endothelial cell activation. Biochem Biophys Res Commun 1995; 214:212–23.
82. Mako V, Czucz J, Weiszhar Z, Herczenik E, Matko J, Prohaszka Z, Cervenak L. Proinflammatory activation pattern of human umbilical vein endothelial cells induced by IL-1beta, TNF-alpha, and LPS. Cytometry A 2010;77:962–70.
83. Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK. IL-6 and TNF-alpha expression in, and release from, contracting human skeletal muscle. Am J Physiol Endocrinol Metab 2002;283:E1272–8.
84. Judd AM, MacLeod RM. Differential release of tumor necrosis factor and IL-6 from adrenal zona glomerulosa cells in vitro. Am J Physiol 1995; 268:E114–20.
85. Ehrhart-Bornstein M, Hinson JP, Bornstein SR, Scherbaum WA, Vinson GP. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. Endocr Rev 1998;19:101–43.
86. Munoz-Canoves P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J 2013;280:4131–48.
87. McEwen BS. Protective and Damaging Effects of Stress Mediators. N Engl J Med 1998;338:171–9.
88. Brydon L, Steptoe A. Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. J Hypertens 2005;23:1001–7.
89. Schommer NC, Hellhammer DH, Kirschbaum C. Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. Psychosom Med 2003;65:450–60.
90. Breines G, Thoma MV, Gianferante D, Hanlin L, Chen X, Rohleder N. Self-compassion as a predictor of interleukin-6 response to acute psychosocial stress. Brain Behav Immun. Epub ahead of print on November 14, 2013. doi: 10.1016/j.bbi.2013.11.006.
91. Rohleder N, Wolf JM, Kirschbaum C. Glucocorticoid sensitivity in humans-interindividual differences and acute stress effects. Stress 2003; 6:207–22.
92. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev 1986;7:284–301.
93. Kudielka BM, Schmidt-Reinwald AK, Hellhammer DH, Schurmeyer T, Kirschbaum C. Psychosocial stress and HPA functioning: no evidence for a reduced resilience in healthy elderly men. Stress 2000;3:229–40.
94. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev 2010; 35:2–16.