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Article in Neuroscience & Biobehavioral Reviews · December 2009

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Inflammation as a psychophysiological biomarker in chronic psychosocial stress

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ARTICLE INFO

Keywords:
- Inflammation
- Psychosocial stress
- Cardiovascular disease
- Burnout
- Life event stress
- Socioeconomic status
- Loneliness
- Autonomic nervous system
- Hypothalamus–pituitary–adrenal axis

ABSTRACT

The measurement of inflammation by biomarkers not only documents clinically relevant infections but also offers an important tool to pin point potentially harmful effects of chronic psychosocial stressors. This article focuses firstly on basic biology of inflammation and lists main biomarkers currently used in psycho-physiologic research. In the second part, the effects of the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system as pathways modulating stress-related inflammation are discussed. Furthermore, current evidence of how chronic psychosocial stressors are related to alterations in inflammatory activity is presented. In summary, job stress, low socioeconomic status, childhood adversities as well as life events, caregiver stress, and loneliness were all shown to exert effects on immunologic activity.

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1. What is inflammation?

1.1. Basic biology of inflammation and outline of the review

Inflammation is a manifestation of biological processes in which the immune system mounts a response to pathogenic
invasion or physical damage. Clinically, inflammation accompanies redness, swelling, rising temperature, and pain. These clinical signs are reflective of increased blood flow and capillary permeability, release of inflammatory mediators, and leukocyte migration to the site of infection/injury. These processes are well orchestrated among leukocytes, platelets, endothelial cells and a myriad of inflammatory mediators such as histamine, complements, chemokines, and cytokines in order to resolve infection or tissue damage without overshooting in inflammation. However, dysfunction of this regulatory system or persistent presence of stimulatory agents leads to chronic inflammation, which is damaging to the local tissue and can lead to pathologies.

This review discusses the literature of inflammatory biomarkers in response to chronic psychosocial stressors. Firstly, we will focus on biomarkers as the basic ingredients of inflammation. Secondly, pathways and factors modulating stress-related inflammation will be discussed and, finally, evidence will be presented about how chronic psychosocial stress may alter inflammatory function. Due to spatial constraint, this last part will not include inflammatory changes related to affective disorders such as depression and posttraumatic stress disorder.

1.2. Biomarkers: the usual suspects

Although any characteristic biological signs that are reliably measured and specific to the biological state can be “biomarkers”, markers in blood are more frequently measured to document inflammation. Among a myriad of blood inflammatory markers, there are a number of “usual suspects” that have mainly been investigated in stress biology research. The most frequently measured is a family of cytokines of which only the representative ones will be discussed in this review.

1.2.1. Cytokines

Cytokines are regulatory glycoproteins produced by a number of different cell types of which leukocytes are a major source. Hence, many cytokines are named as interleukin (IL) with serial number designation (e.g., IL-1, IL-6, etc.). Circulating levels of cytokines are suitable markers of inflammation since they are produced by activated immune cells and lead to activation of other cells (pleotropic) resulting in further synthesis and actions of more cytokines during inflammation. A number of cytokines, such as IL-6, interferons (IFNs), and tumor necrosis factors (TNFs), have been more frequently studied as interface markers between psychology and biology as these cytokines are shown to be associated with or responsive to psychosocial stimuli and also influence psychological states and behavior.

IFN-γ is produced by mostly T and natural killer (NK) cells and TNF-α by macrophages and B lymphocytes. TNF-α and IFN-γ were both shown to be associated with mood state and psychosocial stress (O’Connor et al., 2009). IL-6 is produced by an array of cell types including macrophages, T and B cells, adipocytes, and even myocytes (Pedersen and Febbraio, 2008). IL-6 has been examined more frequently than many other cytokines in the literature of inflammation and psychosocial stress. This might be because in asymptomatic individuals circulating levels of IL-6 are often higher than those of other cytokines and thus also more reliably detectable using high-sensitive assay kits. In addition, associations of IL-6 with psychosocial states and behavior.

It should be noted that synthesis and release of different cytokines coordinate with each other; a subset of cytokines (i.e., anti-inflammatory ones such as IL-4 and IL-10) are released in response to the elevation in cytokines promoting inflammation (i.e., pro-inflammatory ones such as IFN-γ and TNF-α). In addition, cytokine receptors and antagonists are crucial in biological actions of cytokines for their high-affinity binding properties. For example, receptors of TNF-α and IFN-γ or IL-1 receptor antagonist can neutralize the ligand by blocking its access to intact receptors. Meanwhile, soluble IL-6 receptors form a IL-6/sIL-6R complex to stimulate cells such as neuronal cells (Heinrich et al., 2003). As levels of some soluble receptors (e.g., TNF receptor) rise in response to the corresponding cytokine levels (e.g., TNF), the receptor levels in circulation are used as pro-inflammatory markers (Bower et al., 2002), even though they may be functionally antagonistic to the cytokines.

1.2.2. Acute phase proteins/reactants

In response to the release of inflammatory cytokines acute phase proteins, particularly C-reactive protein (CRP), are produced. CRP is considered a reliable marker of inflammation since its rapid production by the liver is in response to inflammation (i.e., especially a rise in IL-6 levels) and infection and its half-life is constant as CRP levels in blood are solely determined by its production (Pepeys and Hirschfeld, 2003). In addition, CRP levels in blood are also a useful diagnostic marker for cardiovascular pathology.

1.2.3. Leukocyte migration

As mentioned, leukocyte migration to the affected sites is a critical process in inflammation. In humans, the literature consistently reports trafficking of immune cells to the peripheral blood compartment during acute stress (Hong et al., 2005). Circulating leukocyte subpopulation numbers, however, were altered in individuals of chronic stress (Cole, 2008). Although the measurements of cellular components are more complicated than soluble factors in blood, leukocyte trafficking in the context of psychosocial stress is a promising biomarker of inflammation and immune system reactivity to stress. Leukocyte migration and homing are largely mediated by cellular adhesion molecules (CAMs) that include families of selections and integrins being expressed on immune and endothelial cells.

1.3. How are inflammatory biomarkers assessed?

The development of commercially available high sensitivity assay kits greatly contributed to the proliferation and expansion of the inflammation and psychosocial stress literature. Mostly, circulating levels of cytokines are assessed by enzyme-linked immunosorbent assay (ELISA) in serum or plasma. Serum or plasma samples for measuring cytokines are stored at −80 °C immediately upon harvest. It should be noted that cytokines are susceptible to freeze-thaw.

Leukocyte trafficking during inflammation is assessed using flow cytometry by labeling cells with fluorochrome-conjugated antibodies against surface phenotypic or migration markers. Flow cytometry techniques also enable investigators to assess intracellular cytokine production by different cell types before they are released into the blood stream.

2. Pathways and factors modulating stress-related inflammation

2.1. The hypothalamic-pituitary-adrenal (HPA) axis

Following psychological stress, the hypothalamic paraventricular nucleus synthesizes and secretes corticotrophin releasing
hormone (CRH) into the pituitary portal vein system. CRH stimulates the pituitary to release adrenocorticotropic hormone (ACTH) into the systemic circulation which prompts the secretion of glucocorticoids (GCs), predominantly cortisol, from the adrenal cortex. GC modulate physiologic, metabolic, and immunologic processes to restore homeostasis (Chrousos and Gold, 1992).

Physiological doses of GC suppress the release of pro-inflammatory cytokines as IFN-γ, IL-2, and TNF-α by stimulating GC receptors on T-helper (Th)1 lymphocytes and thereby promote cellular immunity (Barnes, 1998). GC also trigger the release of anti-inflammatory factors such as IL-4, IL-10, and IL-13 by Th2 lymphocytes and thereby enable humoral immunity (Adcock and Ito, 2000). By inhibition of the release of pro-inflammatory IL-12 and TNF-α in antigen presenting phagocytes, GC induces a shift of differentiation of Th0 precursor cells towards Th2 (DeKruyff et al., 1998). Additionally, cytotoxic cells, natural killer cells, and Th1 cells express less IL-12 receptors under the influence of GC (Wu et al., 1998). In summary, GC cause a series of systemic interactions leading mainly to an anti-inflammatory response (see Fig. 1). At low physiological concentrations, however, GCs are permissive and, under certain conditions, act even pro-inflammatory (Sternberg, 2001). It should be noted, although beyond the scope of this review, that the communication between the HPA-axis and the immune system is bidirectional (Miller et al., 2009).

2.2. Autonomic nervous system (ANS)

Stress stimulates sympathetic noradrenergic fibers, mainly in the paravertebral ganglionic chains and prevertebral ganglia, and it also stimulates the release of catecholamines (CAs) by the adrenal medulla directly.

Virtually all leukocytes except Th2 lymphocytes express β-adrenergic receptors (β-ARs), mostly β2 receptors (Sanders, 1998). Systemic CA effects are similar to those of GC resulting in inhibition of pro-inflammatory IFN-γ, IL-2, as well as IL-12 and TNF-α (Panina-Bordignon et al., 1997). IL-8 is highly chemotactic for neutrophil granulocytes and thus activates inflammation (Linden, 1996). As aforementioned, acute stress leads also to transient but significant leukocytosis, which is largely mediated by CA (Hong et al., 2005). Catecholamines may lead to detachment of leukocytes that are loosely attached to the endothelium and their trafficking to the circulation (Ottaway and Husband, 1994). Individuals with higher catecholamine levels after a speech stressor showed significantly larger increases in Tc and NK cell numbers (Hennig et al., 2000).

Immune modulation of the parasympathetic system is primarily mediated by fibers of the vagus nerve (Borovikova et al., 2000). The vagus’ primary neurotransmitter acetylcholine (ACE) inhibits the release of the pro-inflammatory cytokines TNF-α, IL-1, IL-6, IL-18, high-mobility group box 1, and prostaglandin E2 by macrophages through nicotinic cholinergic receptors, mainly the subtype α7 (Thayer, 2009). The communication between the ANS and the immune system is bidirectional (Elenkov et al., 2000).

2.3. How do chronically activated HPA-axis and ANS trigger inflammatory responses?

It seems obvious that diminished vagal activity under chronic psychosocial stress increases inflammatory action (Tracey, 2002). Fig. 2 presents five not mutually exclusive models on how chronic psychosocial stress might additionally induce heightened inflammatory activity through primary increase in HPA and sympathetic activity.

Models 1 and 2 point at a decreased anti-inflammatory feedback. This could result from systemic overload with subsequent exhaustion of adrenal glands, autonomous nerve fibers, or hypothalamic-medullar structures (model 1) (Elenkov and Chrousos, 1999). An example for HPA-axis “fatigue” is diminished HPA

![Fig. 1](image-url). Physiologic effects of glucocorticoids on immune cell activity and cytokine balance. Thin solid lines = direct activation but indirect inhibition; thin dashed lines = inhibition; thick solid lines = activation; thick dashed lines = direct inhibition but indirect activation; double lines = probably the most potent mechanism. Abbreviations: APC = antigen presenting cells; Bdiff = differentiation of B-lymphocytes; HIST = eosinophile granulocytes and mast cells; IFN = interferon; IL = interleukin; NK = natural killer cells; TOX = cytotoxic T-cells; Th0 = naive Th1 and 2-precursor cells; Th1 and 2 = T-helper lymphocytes 1 (cellular, pro-inflammatory) and 2 (humoral, anti-inflammatory); TNF-α = tumor necrosis factor-α.
activity documented in patients with multiple sclerosis (Wei and Lightman, 1997) or atopic dermatitis (Buske-Kirschbaum et al., 2002). A meta-analysis found an inverse relationship between time since onset of chronic stress and daily cortisol volume (Miller et al., 2007). Onset and exacerbation of rheumatoid arthritis are accompanied by diminished production of GC. Moreover, progressive disintegration of sympathetic nerve fibers during the course of this disease is an example for exhaustion of autonomous nerve fibers (Straub et al., 2005). Model 2 shows an increased receptor expression followed by resistance at the receptor level as the main contribution to decreased anti-inflammatory feedback (Elenkov and Chrousos, 2002). This model is supported by augmented β-AR in asthma patients (Goleva et al., 2006) and in lymphocytes of MS patients (Arnason et al., 1988; Karaszewski et al., 1990). It is further supported by increased GR expression in asthma (Sousa et al., 2000), GC-resistant inflammatory bowel disease (Honda et al., 2000; Orii et al., 2002; Towers et al., 2005), and rheumatoid arthritis (Derijk et al., 2001).

Another hypothesis (model 3) posits recurrent infections as the basis of inflammatory activity (Eskandari et al., 2003) since chronically elevated GC levels come along with enhanced susceptibility to viral infections and decreased antibody production (Rozlog et al., 1999).

Model 4 suggests disease-specific alterations of stress-immune interactions (Elenkov et al., 2000). In Crohn’s disease, Th1 abnormalities involve overproduction of IL-12, IFN-γ, and TNF-α (Bouma and Strober, 2003). Higher incidence of mutant alleles of β-AR was reported in asthma (Hawkins et al., 2004), signalizing that genetic influences play a role in disease-specific alterations of stress-immune interactions.

Model 5 assumes locally harmful effects as a result of pro-inflammatory effects of stress hormones (Elenkov, 2008).

Further mechanisms could help explain increased inflammatory activity under chronic stress, like, for instance, alterations of responses to acute stress on top of chronic stress. Reactivity of epinephrine and cortisol to speech and arithmetic tasks was stronger in women with familiar risk of breast cancer than in women without this form of chronic life stress (Gold et al., 2003). Exhaustion, a potential marker of long-term chronic stress, was associated with attenuated habituation of the cortisol response to repeated Trier social stress testing in healthy adults (Kudielka et al., 2006).

3. Chronic psychosocial stress and inflammation

3.1. Definition of chronic psychosocial stress

A chronic psychosocial stressor normally pervades one’s life and shows stability followed by various adaptations. These adaptations include one’s behavior, social role, and individual psycho-physiologic reactivity (Chida and Hamer, 2008). To present the evidence of chronic psychosocial stress effects on inflammation the literature on job stress/burnout, low socioeconomic status, childhood adversity and life event stress, caregiver stress, and loneliness is presented.

3.2. Job stress and burnout

The burnout syndrome comprises symptoms of emotional exhaustion, lack of accomplishment, and depersonalization (Maslach et al., 2001). High levels of these symptoms independently predict high levels of TNF-α and lower levels of the anti-inflammatory IL-4 in school teachers (von Kanel et al., 2008). Similarly, Grossi et al. (2003) reported higher TNF-α in women with severe burnout. Burnout in women also seems to be associated with elevated levels of CRP (Toker et al., 2005).

Burnout may affect HPA-axis function as workers with chronic burnout show higher cortisol levels during the work day (Melamed et al., 1999). Grossi et al. (2005) found higher awakening cortisol in women with burnout. Burnout symptoms consistently to be associated with a lower level and smaller increase of the cortisol-awakening response. This group also found a stronger HPA-axis suppression in subjects with burnout after dexamethasone administration.

However, current evidence of significant alterations in the HPA-axis and in pro-inflammatory factors in the burnout syndrome is not conclusive. Some studies did not find any differences in HPA-axis function among burnout patients (Onen Sertoz et al., 2008;
Another study on burnout did not find an increase in pro-inflammatory cytokines after stimulating T-cells, but it found that the production of anti-inflammatory IL-10 was significantly increased (Mommersteeg et al., 2006).

3.3. Low socioeconomic status (SES)

A recent review of studies on circulating CPR levels in relation to socioeconomic factors found a strong inverse association in the majority of studies, even after adjustment of demographic covariates (Nazmi and Victora, 2007). Income and education seem both to contribute to CRP increase as part of low SES. Income at or below poverty level is associated with a CRP value almost twice as high compared to income above poverty level (Alley et al., 2006). In addition, several studies found evidence for a significant CRP increase in people with low education (Rosvall et al., 2006; Lubbock et al., 2005; McDade et al., 2006; Gimenos et al., 2008).

The literature on increased pro-inflammatory cytokines in low SES is more equivocal. Several studies report an inverse association of SES with interleukin-6 levels after controlling for covariates (Hemingway et al., 2003; Gimenos et al., 2007; Koster et al., 2006; Loucks et al., 2006). However, other studies did not find any association between higher IL-6 and low SES after adjustment for behavioral risk factors like smoking and low level of physical activity (Ramsay et al., 2008; Petersen et al., 2008; Dowd and Goldman, 2006). Although low SES might not essentially contribute to an increase in pro-inflammatory cytokines, there is evidence that low SES subjects show a prolonged IL-6 increase after stressful situations (Brydon et al., 2004). Maybe the evidence of the association between CRP and SES is stronger than for individual cytokines because a variety of pro-inflammatory cytokines can induce hepatic production of CPR (Eklund, 2009).

Besides these more traditional inflammatory biomarkers, findings suggest also a role of newer inflammatory parameters in stress research. Hong et al. showed significantly higher soluble intercellular adhesion molecule-1 (sICAM-1) and endothelin-1 (ET-1) levels in low SES subjects (Hong et al., 2006). Another approach to relate SES and regulation of inflammation was proposed by Miller and Chen who measured mRNA for glucocorticoid receptor (GR) and toll-like receptor (TLR) 4 (Miller and Chen, 2007). TLR4 acts as the primary receptor for endotoxin on leukocytes and functions as the interface between pathogen and the immune system. The second and third year of life seem critical for setting the stage for a pro-inflammatory phenotype later in life. Children had relatively higher GR mRNA and lower TLR mRNA during adolescence if their parents were home owner's during early childhood. These effects were neither mediated through on-going economic circumstances, life stress, and health practices nor through changes in current SES.

3.4. Childhood adversity and life event

A prospective birth cohort study found a significantly higher risk of CRP increase 20 years after having experienced childhood maltreatment (Danese et al., 2007). This effect on adult inflammation was independent of co-occurring early life risks, stress in adulthood, adult health, and health behavior. In conclusion, childhood maltreatment may contribute to more than 10% of low-grade inflammation measured by CRP. Experiences of childhood maltreatment also contribute to a reduced ability to control the stress response in hyperactive HPA-axis after acute psychosocial stress in women (Heim et al., 2000). Negative consequences of childhood adversities seem to partly depend on the genetic background as it relates to the amount of short allele of the serotonin transporter gene promoter polymorphism (5-HTTLPR). Caspi et al. reported an association between histories of child maltreatment or recent stressful life events on the one hand and the development of depression on the other only in adults who were carriers of the short but not of the long allel of the 5-HTTLPR (Caspi et al., 2003). It is currently unknown whether this association also predisposes maltreated or traumatized children to an increase in systemic inflammation.

As yet, research suggests an interaction between 5-HTTLPR and stressful life events that predicts heightened endocrine stress reactivity in healthy adults (Alexander et al., 2009).

3.5. Caregiver stress

The burden of providing care to a demented spouse is a well-investigated model of chronic human stress. In a 6-year longitudinal study, spousal dementia caregivers showed an increase in IL-6 four times as large compared to non-caregiving controls (Kiecolt-Glaser et al., 2003). Interestingly, IL-6 change was maintained even after the death of the demented spouse indicating a sort of a “psychophysiological scar”. Similarly, a cross-sectional study found that family dementia caregivers had higher IL-6 levels than healthy age-matched controls (Lutgendorf et al., 1999).

Sequels of spousal caregiver stress are also mirrored in levels of NF-kappaB, a key pro-inflammatory transcription factor. This factor influences the expression of genes coding for several inflammatory mediators, including TNF-alpha and IL-6 (Ahn and Aggarwal, 2005). NF-kappaB can be linked to caregiver stress because stress-associated rise of norepinephrine leads to activation of NF-kappaB and higher norepinephrine has been demonstrated in caregivers under stressful situations (Aschbacher et al., 2007; Bierhaus et al., 2005). Miller recently reported heightened expression of NF-kappaB in familial caregivers of brain-tumor patients (Miller et al., 2008). He also found caregivers’ CPR and IL-1 receptor antagonist to be significantly different from controls.

There is evidence that healthy aging in its own right is accompanied by a decline in the control of immune regulation with increases seen in levels of TNF-alpha, IL-1, IL-6, and CRP (Gouin et al., 2008; Luz et al., 2003; Licastro et al., 2005). This physiology of aging suggests relatively higher susceptibility to pro-inflammatory changes in chronically stressed elderly. To support this notion, we found that the difference in IL-6 between spousal Alzheimer caregivers and non-caregiving controls was moderated by age and that age correlated directly with IL-6 in caregivers but not significantly so in controls (von Kanel et al., 2006).

3.6. Loneliness

Loneliness is defined as individually perceived social isolation (Hawkley and Cacioppo, 2003) and emerged as an important psychosocial aspect of health since individuals who sustain active interpersonal networks are compensated by a buffering effect on their stress parameters (Kikusui et al., 2006). Using data from the third National Health and Nutrition Examination Survey (NHANES III) and after adjustments for cofounders, Ford showed greatest elevation in CRP in men over 60 years who had the fewest social ties (Ford et al., 2006). The CRP increase occurred in a dose-response manner. The Framingham Heart Study yielded similar results in terms of pro-inflammatory activity. Socially less connected men had significantly higher IL-6 levels after adjusting for potential confounders. Women showed similar results on IL-6 levels after adjustment for age (Loucks et al., 2006). Although less apparent than seen for IL-6, there were also inverse associations for CPR and sICAM-1 and social network size. However, these results ceased to be statistically significant in multivariate analyses.

Loneliness is positively associated with the cortisol response over the 30 min following waking even after adjustment for waking cortisol value, sex, SES, smoking, time of waking, and body
mass index (Stetpo et al., 2004). Interestingly, loneliness seems to precede the higher cortisol-alarming response rather than vice versa. A negative affect factor comprising loneliness, sadness, and feelings of being threatened and overwhelmed was associated with a higher next-day cortisol-alarming response, whereas cortisol-alarming response levels measured in the morning did not predict experience of the negative affect factor across the ensuing day (Adam et al., 2006). Although cortisol is mainly considered to have anti-inflammatory effects, chronically elevated cortisol levels seem to involve desensitization of GR pathway that mediates transcriptional response to glucocorticoids (Pace et al., 2007; Miller et al., 2002; Stark et al., 2001).

3.7. Summary and conclusion

Chronic psychosocial stressors have a measurable effect on inflammation although the evidence is not unequivocal. Clinically, chronic psychosocial stressors such as burnout or loneliness are more related to perceptible signs of mental health dysfunction. Impact of low SES, childhood adversities/life events and caregiver stress might be less prominent in a clinical setting and thus in need of active exploration by the physician during the consultation. Further studies are clearly needed to reveal additional inflammatory sequels of chronic psychosocial stressors.

Acknowledgment

We would like to thank Annette Kocher for editorial support.

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