STRESS AND INFLAMMATION

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ABSTRACT

Both acute and chronic stres predisposes to increased inflammatory reactions. Inflammation-promoting changes on multiple levels concur thereto. Stressful conditions in early life may induce changes at the genomic level resulting in an exacerbated inflammatory response to stress later in life. Chronic stress induced alteration in the glucocorticoid level and/or in the glucocorticoid receptor sensitivity may remove the inhibitory effects on cytokine production. The level of inflammatory markers (fibrinogen, C-reactive protein) is increased by both acute and chronic stress. Stress induces a cytokine profile change: an inflammation-prone pattern emerges consisting in higher levels of the pro-inflammatory cytokines paralleled by a decline in the production of the anti-inflammatory ones. This is correlated with a stronger expression of the factors promoting (at the nuclear level) the transcription of the molecules involved in the inflammatory response. Stress boosts the activity of the proteolytic enzymes responsible for the destructive consequences of the inflammation.

Conclusions: Acute stress predisposes to exacerbated inflammatory reactions, while protracted psychological stress may induce a chronic inflammatory process.

Key words: stress, inflammation, cytokine, glucocorticoid, fibrinogen, C-reactive protein, psychogenic fever, transcription factor, complement, metalloproteinase

Abbreviations: CRP = C-reactive protein; DNA = deoxyribonucleic acid; GC = glucocorticoid; GCR = glucocorticoid receptor; HPA = hypothalamus-pituitary-adrenal; IFN-γ = interferon gamma; IL = interleukin; MMP-9 = metalloproteinase-9; NF-κB = nuclear factor kappa B; PTSD = posttraumatic stress disorder; SES = socioeconomic status; SOC = sense of coherence; TNF-α = tumor necrosis factor alpha.

INTRODUCTION

The association of both acute and chronic stress with the pathogenesis and exacerbation of common disease states such as atherosclerosis and asthma appears to be mediated, at least in part, by an enhanced inflammatory responsivity (closely related to immune activation). These changes seem to be independent on the variations in the sympathoadrenal tone.

The link between stress and inflammation is likely to be the consequence of a deliberate pre-programming, as almost all levels of the inflammatory response become activated in demanding circumstances: stress operates on the genetic, mediator, and executive levels, with a corresponding raise in the inflammatory markers.

GENETIC FACTORS

Animal experiments have revealed that a protecting/nurturing maternal attitude early in life may alter the epigenomic state of the genes involved in regulating the inflammatory response to stress. This alteration consists in deoxyribonucleic acid (DNA) methylation and histone acetylation, and may affect the glucocorticoid (GC) receptor (GCR) gene promoter in the hippocampus, with repercussions on the transcription factor binding. These changes may persist into adulthood, but they may also be reversed (e.g. by unleashing the histone deacetylase through the central infusion of an inhibitor). Changing the GCR expression may modify the stress response of the hypothalamic-pituitary-adrenal (HPA) axis (1).

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The offspring that benefited from more signs of maternal care in the first days of life have a dampened hormonal response to acute and chronic stress (decreased production of corticotropin-releasing hormone by the hypothalamus, of adrenocorticotropic hormone by the pituitary, and of GC hormones by the adrenal glands), with a corresponding increase in the hippocampal GCR expression and in the hypothalamic-pituitary sensitivity to GC feedback (2). An enhanced expression GCR means a greater sensitivity to the GC anti-inflammatory effects with a subsequent decrease in the inflammation proneness.

The modified hippocampal expression of the GCR seems to be due to changes in the production of transcription factors, which may be subsequent to the activation of ascending serotoninergic pathways driven by childhood environmental conditions (3).

The changes on the epigenetic level may persist for a long time, altering the individual's response to stress later in life. Even though there are no changes in the DNA structure, the DNA expression is modified, so that negative childhood experiences put their enduring mark on the future adult's ability (or rather disability) to adapt to stress.

Studies conducted on humans proved that a precarious socioeconomic status (SES) in early childhood predisposes to a heightened inflammatory response later in life as reflected in a GCR under-expression, paralleled by an increase in the toll-like receptors (which are assigned a key role in signaling infection) (4).

REGULATORY (HORMONAL) FACTORS

Glucocorticoids are the main hormones involved in checking the intensity of the inflammatory response. The stress-related activation of the HPA axis increases the secretion of GCs, which inhibit the secretion of pro-inflammatory cytokines from the monocytes and macrophages, while the secretion of anti-inflammatory cytokines remains unchanged or is even enhanced. Thus, a decrease in the sensitivity of the GCR may result in an unbridled inflammatory response. Such an effect was detected in women (but not in men) (5) and may be related to the estrogen receptors on monocytes and macrophages. Once activated, these receptors hinder the binding to DNA sites of the transcription factors nuclear factor-κB (NF-κB) and activator protein-1, in a manner reminiscent of the GCs in both mechanism and effect on the cytokine secretion.

On the other hand some chronic stress response patterns such as the posttraumatic stress disorder (PTSD) may lead to a GC secretion decline (with a corresponding increase in the GC sensitivity of the tissues responsible for the pro-inflammatory cytokine production) (6). The hypocortisolism may be interpreted as an adaptive mechanism aimed at reducing the inhibitory effects on cytokine production in situations predisposing to trauma or infection (in which cytokines are required for their fight-and-repair-promoting abilities).

INFLAMMATORY MARKERS

There is presently mounting evidence that some of the usual inflammatory markers (fibrinogen, C-reactive protein) increase in association with both acute and chronic stress (although they are probably not directly involved in the inflammatory process).

Fibrinogen

Acute stress elicits a plasma fibrinogen increase (7) (8), independent of behavioral risk factors such as smoking status (at least in women) (9). Fibrinogen concentration increases in response to acute laboratory mental stressors (for instance an arithmetic task or Stroop color word test). Similar but more pronounced responses may be induced by exercise and adrenaline infusion (10). This response seems to be modulated by female sex hormones, as it is more prominent in the luteal as compared to the follicular phase of the menstrual cycle (11).

Low SES and job strain are two of the most important types of chronic stress for which an association with increased plasma fibrinogen (and a hypercoagulable state) has been proven (12). A low SES is associated with increased plasma fibrinogen level (7). Actually a low SES may have long lasting effects on plasma fibrinogen: low SES in early childhood may have as sequel a higher fibrinogen level later in life (13).

Job stress is another form of chronic stress able to induce an increase in the inflammatory markers: plasma fibrinogen is higher in unemployed than in employed women (14), a finding which may be difficult to interpret as lack of employment may be correlated with the social stress of low income. However, restricting the analysis to employed women, the magnitude of work stress correlates with plasma fibrinogen (14). Also employment grade (considered a SES indicator) is inversely related to fibrinogen level, and so is the individual's control over work decisions (13). Not only low

control is associated with high plasma fibrinogen, but so are high job demands, and high job strain (defined as the ratio between demands and control) (15). Another chronic work stress indicator associated with increased plasma fibrinogen is effort-reward imbalance (high efforts in combination with low rewards – a common indicator of the work-related stress) (16).

Psychosocial stress is one among several factors mediating the association between low educational status and elevated fibrinogen levels (17). Negative social ties (such as being undermined by persons in one's social network) are associated with higher fibrinogen, as is meager social support as a result of social isolation (18). In individuals reporting poor social support, plasma fibrinogen is higher at baseline and increases more after exposure to stress (19).

However some studies failed to provide support for an association between stress and fibrinogen. The discrepancies are possibly due to differences related to gender, age, health status or some other factors. For example, in a study on healthy young women, no correlations have been found between fibrinogen level (and other humoral indicators of an unfavorable metabolic or fibrinolytic risk profile) and work stress (evaluated in terms of job demands, decision latitude, and job-related social support) (20). In a study performed on middle-aged, white-collar workers, the fibrinogen level has not appeared to be related to parameters of work stress, such as effort-reward imbalance or job overcommitment (21). Therefore some authors suggested that it is the social status, as reflected by employment grade, rather than the perceived work stress that correlates with the fibrinogen level (21). An alternative explanation may lie in the unreliability of the declared stress as a measure of the actual stress and of its consequences on health. A better way to objectively gauge stress level is probably the category of stress some particular job (or situation in general) is usually assigned to: one should expect that almost any worker in an emergency department has a significantly higher level of stress than almost any in a dermatology ward.

It is difficult to establish what is the aim of the stress-related increase in fibrinogen – it might be indeed to promote a hypercoagulable state, as others factors involved in coagulation (such as von Willebrand factor and coagulation factor VII) also increase, while the plasma fibrinolytic capacity is reduced. This is rather an adequate response, as stress has been historically associated with injury-predisposing circumstances. It may also be part of a generalized inflammatory response, which is suitable to aggression-prone environments.

C-reactive protein

While fibrinogen is a component of the coagulation system to a greater extent than an inflammatory marker, the C-reactive protein (CRP) is definitely an inflammatory marker.

An increase in the level of perceived stress is independently associated with a higher level of CRP (22). There is generally an increase in CRP plasma level after a stressful task, but this effect is even more evident in persons reporting higher effort-reward imbalance at the work place (23). We can infer that the acute stress-related increase in CRP is even greater in persons exposed to a high level of chronic stress. Depression is another type o chronic psychological disturbance that may potentiate CRP-increasing effect of acute stressors (24).

Stress related to social interactions is correlated with the level of CRP even among healthy adolescents (25). The sense of coherence (SOC) is inversely associated with high-sensitivity CRP (hsCRP) levels, such that lower SOC (indicating higher psychosocial stress) is associated with higher inflammation (at least in men) (26). One of the generally accepted indicators of high social stress is a low SES, which may have several components: a low grade of employment, poor income, deficient education, etc. The level of CRP is higher in individuals with a low SES independently of behavioral, anatomical, demographical, and seasonal risk factors (27).

Another form of stress is that caused by chronic fear of terrorist strikes (fear of oneself or family members being harmed in a terrorist strike) – it has been shown to be correlated with significantly higher levels of hsCRP in women (28).

INFLAMMATION MEDIATORS

Cytokines

Acute stress is associated with an increase in the level of circulating pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, and interferon gamma (IFN-γ), the increase being better defined in individuals with a more intense perception of stress (29). The effect seems to be accentuated in depressed subjects and is correlated with a drop in the sensitivity to the GC anti-inflammatory properties (24).

In circumstances of chronic stress (such as PTSD), the cytokine production is more responsive

to exogenous stimulation (6). For example, a viral illness tends to elicit a stronger cytokine response (correlated with more severe symptoms) in individuals subject to higher levels of psychological stress (30). A further form of chronic stress, and a very common one, is social stress – it, too, is associated with a systemic pro-inflammatory cytokine profile: high level of inflammation-promoting cytokines (IL-6 and TNF-α) and low level of the anti-inflammatory ones (IL-10) (31).

The stress-induced increase in cytokine production is also present in particular/local disease states. One example is gingivitis: it has been shown that a demanding task brings forth an increase in the local concentration of IL-8 (a potent inflammation-promoting cytokine), which may explain the symptom exacerbation in relation with acute stress (32). Another example of chronic inflammatory condition is asthma. In asthmatic children a high level of persistent family stress predisposes to a more prominent inflammatory response to acute events, reflected by an enhanced level of IL-4, IL-5, and IFN-γ, increased susceptibility to airflow obstruction exacerbations, and more severe symptoms (33). A similar result has been reached in a study on asthmatic adolescents differentiated on the basis of their SES: a low SES (usually associated with augmented chronic social stress) correlates with an increased level of cytokines involved in both Th-1 and Th-2 responses (IFN-γ and IL-5, respectively) (34).

The enhanced level of inflammatory markers and the cytokine burst appear to be correlated events, endorsing the idea of a concerted reaction of the organism with the aim of being prepared to mount a strong inflammatory response in conditions of high stress.

There is also some evidence that the stress-induced increase in the inflammatory markers and the cytokine surge are related events. Indeed, the A allele of the TNF-α-308 G/A polymorphism appears to be involved in mediating the CRP raise associated with the state of exhaustion generated by unrelenting stress (35).

Prostaglandins

It is known that in some individuals fever may have a psychological determinism – the term psychogenic fever has been coined to designate this phenomenon. In such patients acute stressors might increase core body temperature without the intervention of pyrogenic cytokines. However, the process is not merely the consequence of heat production through increased muscle activity. The primary event is the rise in the hypothalamic thermoregulatory set point. The mechanism is similar to that of infection-induced fever, being a brain controlled active hyperthermia mediated by an up surge in the plasma level of prostaglandin E2 and interleukin-6 (more precisely, by their action on the hypothalamus) (36). As expected, this process may be hindered by the prostaglandin synthesis blocking effect of the cyclooxygenase inhibitors. Interestingly, there is still another mechanism through which stress exerts its core temperature increasing effect. Special types of stress such as that associated with anticipatory anxiety choose a 5-HT-mediated pathway. This mechanism is insensitive to cyclooxygenase inhibitors, but responds to benzodiazepines and serotonin Type 1A receptor agonists (37).

Nuclear factor-κB

In the search for the molecular mechanisms of increased stress-related inflammatory response, one potential candidate is NF-κB, a transcription factor that has (besides various other effects) pro-inflammatory activity. In a recent study it was pointed out that relational stress enhances the expression of NF-κB, which is inconsequential in the basal state, but results in an amplified inflammatory response to exogenous intruders (38).

Inflammatory executive factors

What I called executive factors (executors) of the inflammatory process are actually the various humoral and cellular agents that make up the innate and adaptive immune system. In a previous article, we reviewed the way stress influences the antibody production, the macrophages, and the leukocytes (39). Now we shall examine the sparse existing information about the stress impact on some of the proteolytic enzyme systems acting as final links of the inflammatory events chain: the complement system and the metalloproteinases.

Complement

It has been shown that stress (at least acute stress) enhances complement activation, as evidenced by the C3a, C5a, and Bb increased levels associated with the completion of a demanding task. Complement cascade activation may be one of the mechanisms explaining the stress-related exacerbation of the inflammatory processes (40).

A presumably stress-provoked inflammation worsening has also been noticed in specific disease states, such as systemic lupus erythematosus, where it is associated with an aggravation of the perceived

symptomatology and an increase in the C3 and C4 levels (41).

Matrix metalloproteinase

The activity of the proteolytic enzyme matrix metalloproteinase-9 (MMP-9) increases during inflammatory processes, and is another component of the defense and adaptation systems that is correlated with psychosocial factors without the intervention (as mediators) of the usual risk factors (42). Interestingly, when an increase in MMP-9 activity is supposed to benefit the organism, psychological stress has the opposite effect: instead of increasing, it decreases the enzyme's activity. This behavior was observed in patients recovering from a surgical intervention: the stress-related drop in the enzymatic activity impairs the connective tissue matrix remodelling process resulting in protracted and poorer wound healing (43).

CONCLUSIONS

In both acute and chronic over-demanding situations an inflammation-prone pattern of response emerges. This pattern consists in changes on all levels of the inflammatory system, starting from the genomic level and going all the way down to the executive level, and including hormonal regulatory factors, inflammatory markers, and inflammatory mediators.

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