

Review

Stress hormones and immune function

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Abstract

Over the past 20 years we have demonstrated both in animal models and in human studies that stress increases neuroendocrine hormones, particularly glucocorticoids and catecholamines but to some extent also prolactin, growth hormone and nerve growth factor. We have also shown that stress, through the action of these stress hormones, has detrimental effects on immune function, including reduced NK cell activity, lymphocyte populations, lymphocyte proliferation, antibody production and reactivation of latent viral infections. Such effects on the immune system have severe consequences on health which include, but are not limited to, delayed wound healing, impaired responses to vaccination and development and progression of cancer. These data provide scientific evidence of the effects of stress on immune function and implications for health.

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1. Introduction

For many years it has been known that stress is detrimental to health. In 1974 Hans Selye defined stress as “the non-specific response of the body to any demand imposed upon it” [1]. This definition of stress was later modified in 1992 by Chrousos and Gold and the term “non-specific” replaced by the hypothesis that above a threshold intensity any stressor would elicit the “stress syndrome” [2]. Stress can occur in a variety of forms, physical or psychological, acute or chronic. It is possible and probable that different forms of stress will have different effects on the stress hormones released and on immune function. Stress is known to cause the release of several stress hormones—primarily glucocorticoids though activation of

the hypothalamic–pituitary–adrenal (HPA) axis and catecholamines through the sympathetic nervous system. For over two decades we have investigated the effects of various forms of stress, both in human studies and in animal models, on neuroendocrine hormones and on cellular aspects of both the innate and adaptive immune responses. The findings of these studies are reviewed here.

2. Models of stress

Over the years we have used numerous models of stress in our studies. In human subjects these have included laboratory-induced stressors such as a speech stress test and mental arithmetic stress test [3], life stressors such as medical students undergoing examination stress, marital stress, physical training stress in West Point Cadets, caregivers of Alzheimer’s or dementia patients, breast cancer patients, pain following surgery, and psychological stressors such as feelings of loneliness, depression and even aging. In animals a number of stress models have been used. These include rotational stress, footshock, restraint stress and

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social disruption stress. For rotational stress the animal’s cage is slowly rotated to induce mild spatial disorientation [4]. This increases plasma corticosterone and epinephrine levels but has no effect on norepinephrine [5,6]. Signaled footshock involves a light stimulus followed by a mild electric shock to the foot pads [7]. This increases plasma corticosterone and decreases hypothalamic norepinephrine [8,9]. Restraint stress involves physically restraining animals in a well ventilated tube [10]. This increases plasma corticosterone [11,12]. Social disruption stress involves social reorganization following addition of an “aggressor” to a group of mice [12]. This also increases plasma corticosterone [12].

3. Neuroendocrine responses to stress

Stress, both physical and psychological, results in neuroendocrine signals being released from the brain that can affect immune function. The main two neuroendocrine pathways activated in response to stress that control the immune system are the HPA axis which results

in release of glucocorticoids, and the sympathetic nervous system which results in release of catecholamines, epinephrine and norepinephrine. However, there are other neuroendocrine factors that are released following stress that also regulate the immune system, including prolactin, growth hormone (GH) and nerve growth factor (NGF) (Fig. 1). We have published both human studies and animal studies which show that these immune-modulating hormones are released following a variety of stressors.

3.1. The hypothalamic–pituitary–adrenal (HPA) axis

One of the main mechanisms by which the brain controls the immune system is through activation of the HPA axis. Upon stimulation, either physical from the periphery via cytokines or psychological, corticotrophin releasing hormone (CRH) is secreted from the paraventricular nucleus (PVN) of the hypothalamus. This then stimulates the anterior pituitary to secrete adrenocorticotropin hormone (ACTH) into the systemic circulation.

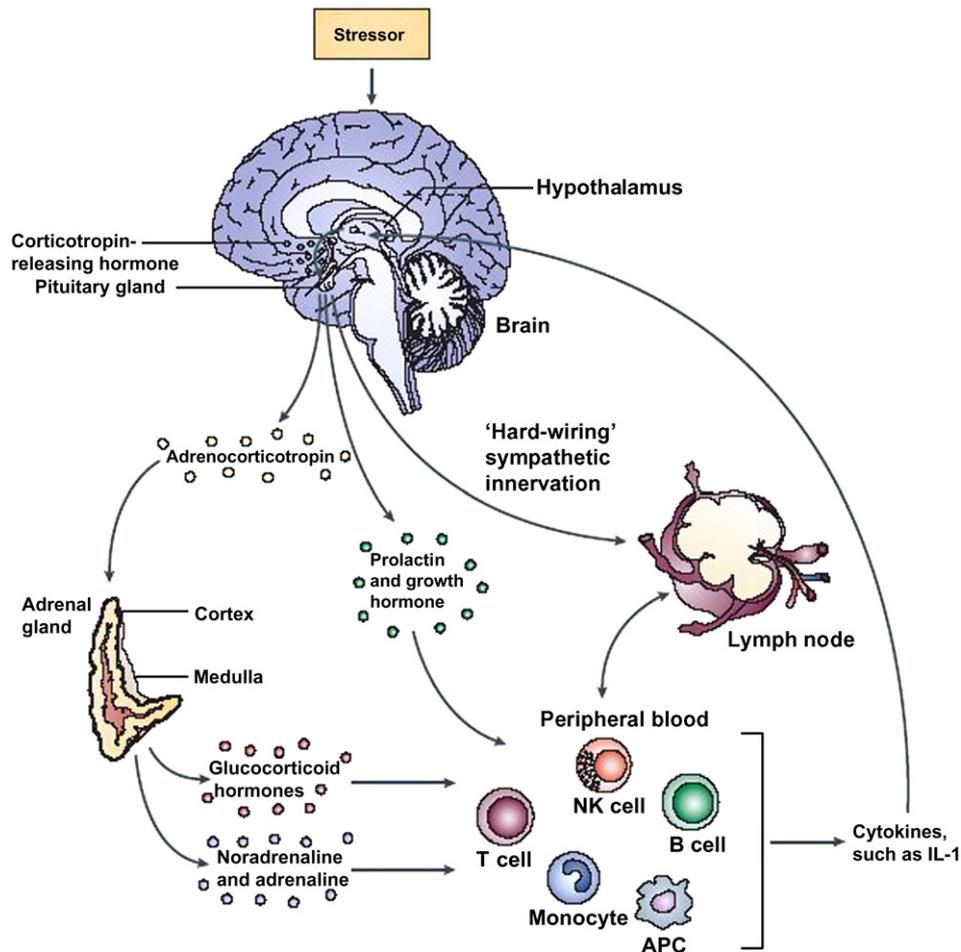


Fig. 1. Stress-associated modulation of the hormone response by the central nervous system. Upon experiencing a stressor, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system are activated resulting in release of glucocorticoids and catecholamines which are able to modulate various aspects of the immune system. In addition, the pituitary hormones prolactin and growth hormone are also released which also can modulate the immune system. Figure reproduced from Glaser and Kiecolt-Glaser [104].

This, in turn, induces the adrenal glands to synthesize and secrete glucocorticoids. In humans, the natural glucocorticoid is cortisol whereas in rodents it is corticosterone. Physiological levels of glucocorticoids are thought to be immunomodulatory whereas stress levels are immunosuppressive. For a review on the mechanisms by which glucocorticoids modulate the immune system, refer to the review by us [13].

As noted earlier both social disruption stress and restraint stress in mice cause activation of the HPA axis resulting in increased serum corticosterone levels [12]. We have also shown that in human studies, a variety of stressors cause increases in plasma ACTH and cortisol levels. Acute stress using a mental math and speech stress test increased ACTH and cortisol in mid-aged and older women [3]. Examination stress in medical students caused an increase in daytime, but not nocturnal, ACTH with no change in cortisol compared to baseline levels taken a month earlier. However, if the group of students was limited to those that perceived the most stress during exams then an increase in plasma cortisol levels was seen during the exam period. Interestingly, the effect of examination stress on daytime ACTH was only observed in the fall and not in the spring, suggesting seasonal variations in HPA axis activation [14]. Extreme exercise stress also increases both ACTH and cortisol [15] and in another study, an increase in cortisol was seen in psychiatric patients who had high scores on the UCLA loneliness scale [16].

Marital stress increases plasma cortisol and ACTH levels but the interactions are complicated with differences occurring between the wives and husbands and also differences in newly married couples compared to couples who have been married for a number of years. ACTH but not cortisol was increased during marital stress in newly married couples and correlated with hostile behavior [17] and troubled marriages 10 years later [18]. Interestingly, relative power in the relationship in newly married couples determined endocrine responses following a conflict. The wives showed increased ACTH responses to conflict only when the husband was the more powerful partner in the relationship. In addition, cortisol declined when they were more powerful or had equal power in the relationship. When the husband has power there was no decline in cortisol following conflict. ACTH levels following conflict decline in the husbands but when the wives were more powerful or if power was shared this decline in ACTH took longer to occur. Likewise cortisol levels in the husbands declined following conflict but in the case of equal power this decline took longer to occur [19]. In older couples, marital stress increased plasma cortisol [20], which correlated with “wife negative-husband withdrawal” behavior during conflict [20,21]. Lower marital satisfaction and negative behavior during conflict correlated with higher levels of cortisol and ACTH following conflict in the wives of older couples but not the husbands [22]. These studies

show that a number of different stressors result in the activation of the HPA axis and release of glucocorticoids, an affect that has been observed in many different situations by different researchers [23–26].

Cortisol elicits its many actions through a cytosolic receptor, the glucocorticoid receptor (GR). Upon ligand binding, GR dissociates from a protein complex, translocates to the nucleus where it binds to specific DNA sequences to modulate gene transcription [27,28]. In addition, GR can also interfere with the signaling pathways of other transcription factors such as NF κ B and AP-1 to repress transcription of many inflammatory molecules [29]. Examination stress in medical students decreased the peripheral blood leukocyte glucocorticoid receptor mRNA compared to 1 month prior to exams, although protein levels were not measured [30]. The observation of decreased glucocorticoid receptors during stress when there is an increase in the ligand, cortisol, has also been shown by other researchers [31–33] and may be a result of homologous down regulation [34].

3.2. The sympathetic nervous system

Activation of the sympathetic nervous system results in secretion of acetyl choline from the pre-ganglionic sympathetic fibers in the adrenal medulla. This induces secretion of epinephrine into the systemic blood supply. Norepinephrine is released from the nerve terminals in the vicinity of immune cells. These catecholamines have many immunomodulatory effects which have been the subject of many recent reviews [35–37] and will not be discussed here.

The sympathetic nervous system is also activated by stress resulting in the release of norepinephrine and epinephrine. A mental math and speech stress test increases epinephrine and norepinephrine [3,38]. Increased epinephrine and norepinephrine were correlated with hostile behavior and with “wife negative-husband withdrawal” behavior during conflict in newly married couples [17,21] and correlated with divorce or troubled marriages 10 year later [18]. In older couples, increased norepinephrine correlated with lower marital satisfaction and negative behaviors during conflict in the wives, but not in the husbands [22]. These results show that various forms of stress activate the sympathetic nervous system and result in catecholamine release.

Catecholamines bind to the β_2 -adrenergic receptor and stimulate activation of a G-coupled protein which results in increased intracellular cAMP [39]. Over the period of a year with 3 examination periods, plasma and intracellular cAMP increased with continued examination stress. There was no difference in the first exam period in first year medical students but there was a significant increase in the 2nd and 3rd examination periods in that year [40]. These data suggest that increased catecholamine release during examination stress results in increase β_2 -adrenergic receptor activation.

3.3. Prolactin

Prolactin is secreted from the anterior pituitary gland and from many extra-pituitary sites including immune cells [41]. It is immunostimulatory and is proposed to act as a counter measure to glucocorticoids [42–44]. In the rat, prolactin has been shown to be released during stress, although stress-induced decreases in prolactin can occur under certain stress conditions, such as during the proestrous afternoon surge or during the nocturnal surge of pseudopregnancy [45]. Examination stress in medical students had no effect on plasma prolactin [46] but serum prolactin decreased with hostile behavior during conflict in newly married couples who also reported high marital satisfaction [17]. These data suggest that some forms of stress may increase prolactin release. Prolactin has been shown to be increased by stress in other studies [47–49] but is not as well studied as glucocorticoids and catecholamines.

3.4. Growth hormone (GH)

Growth hormone (GH), like prolactin, is also secreted from the anterior pituitary gland but can also be produced by immune tissues thereby having an autocrine/paracrine effect on immune cells [43,50]. It is also immunostimulatory and suggested to counteract the effects of glucocorticoids [43,44]. GH has also been suggested to act as a cytokine promoting cell cycle progression of lymphoid cells [50]. Many of the effects of GH are mediated through GH-induced production of insulin-like growth factor-1 (IGF-1). Examination stress in medical students does not affect plasma GH levels [46]. Interestingly, GH secretion was higher in the fall than in the spring [46], suggesting a seasonal effect on this immune-related hormone. Plasma GH levels were increased with hostile behavior during conflict in newly married couples who claimed high marital satisfaction [17]. However, in caregivers of Alzheimer's patients GH mRNA levels in PBMCs and B lymphocytes was decreased compared to controls [51,52]. These data show that GH is increased by stress as has been shown by other researchers [49].

3.5. Nerve growth factor (NGF)

Nerve growth factor (NGF) is a neurotrophic hormone that can regulate the immune response. NGF can function through the hypothalamus to activate the HPA axis [53]. In addition, NGF can function as an autocrine/paracrine factor to regulate immune cells. It promotes proliferation and differentiation of T and B lymphocytes and acts as a survival factor for memory B lymphocytes [54]. It has also been shown to be increased following stressful life events [54,55]. Caregivers of Alzheimer's patients expressed increased blood NGF levels compared to controls and the amount of NGF also positively correlated with high perceived stress and depression [56].

4. Effect of stress on immune function

Stress has been shown to have detrimental effects on the immune system. These include changes in lymphocyte populations, in the ratio of helper:suppressor T cells, decreased lymphocyte proliferation, NK cell number and activity, impaired antibody responses and reactivation of latent viral infections (Fig. 2).

4.1. Natural killer (NK) cell activity

Natural killer NK cells are a type of cytotoxic T lymphocyte that is part of the innate immune system. They primarily kill viral infected cells and cancer but will also kill bacteria, parasites and fungi. Their activity is tightly regulated and these cells can be activated by interferon γ (IFN γ) and interleukin-2 (IL-2). Thus, increased NK cells and increased activity, as determined by lysis of target cells, is needed to fight infection or cancer. Decreased NK cell number and NK activity occurs following a variety of stressors which would result in decreased responses to infection.

We have shown that in mice, restraint stress decreases NK cell activity following footpad infection with herpes simplex virus-1 (HSV-1) [57]. In addition, we have shown that in human subjects, examination stress decreased NK cell activity compared to a month earlier [58–60]. Students who were higher scorers for stressful life events on the brief symptom inventory (BSI) or loneliness on the UCLA loneliness scale showed a lower level of NK cell activity [58].

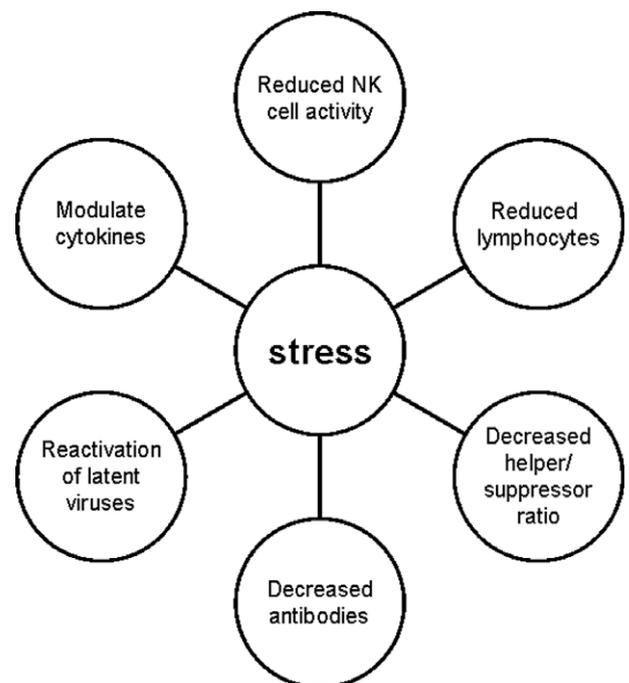


Fig. 2. Stress affects various aspects of the immune system. Stress can reduce NK cell activity, reduce the number of lymphocytes, decrease the ratio of helper to suppressor T cells, decrease antibody production, reactivate latent viruses and modulate cytokine production.

Continuing caregivers of Alzheimer's patients and those that had been bereaved for 2 years or less showed low cytotoxic NK response when stimulated with rIFN γ or rIL-2 [61,62]. In the absence of these cytokines there was no difference between continuing caregiver, bereaved caregiver or controls [61,62]. These results differ from those obtained with medical students, however, there are two major differences, the age of the subject and the type of stressor, acute versus chronic [61].

Psychiatric patients who had high scores on the UCLA loneliness scale, also showed decreased NK cell activity [16]. Lower NK cell activity was also seen in subjects who exhibited more negative or hostile behaviors following a discussion on marital problems [63]. In a group of patients who had recently undergone surgery for breast cancer, reported stress correlated with lower NK cell activity and diminished responses of NK cells to IFN γ [64]. However, the acute stress of a mental arithmetic stress test increased NK cell numbers and cytotoxicity [38]. Interestingly relaxation techniques, but not social contact, in a study of geriatric people in an independent-living facility significantly increased the NK cell activity [65]. These data show that stress decreases NK cell activity, thereby removing the protective effects of these cells and possibly leading to increased viral infections and even cancer. Reduced NK cell activity has been found in other studies on the effects of stress on immune function [66,67].

4.2. T lymphocyte populations

Lymphocytes play an important role in cell-mediated immunity. They can be differentiated from NK cells and B lymphocytes by the presence of the T cell receptor on the cell surface. T lymphocytes can be divided into subgroups: cytotoxic T cells (CTL) (also known as CD8+ T cells) which destroy cells that are recognized as foreign or non-self; helper T cells (also known as CD4+ T cells) which secrete cytokines and prompt B lymphocytes to synthesize antibodies; memory T cells which are antigen-specific T cells that may be either CD4+ or CD8+; regulatory T cells (also known as suppressor T cells) which act on helper T cells to suppress antibody production.

We have shown that examination stress in medical students causes a decrease in total T lymphocytes, helper T lymphocytes and suppressor T lymphocytes compared to 6 weeks earlier [59,68]. There was also a decreased ratio of helper T lymphocytes to suppressor T lymphocytes [59]. Such a decreased ratio of helper to suppressor T cells was also seen in men with poor marital quality [69]. Interestingly, employment of relaxation techniques in medical students increased the percentage of helper T lymphocytes [59]. Mental arithmetic stress test also increased CD8+ (cytotoxic) T lymphocytes [38]. Memory T cell killing of Epstein-Barr virus (EBV) transformed autologous B lymphocytes was decreased in medical students experiencing exam stress during a series of 3 examination periods over a year compared to baseline measurements taken 1 month

before each exam [40]. The ability of memory T cells to proliferate in response to 5 of 6 purified EBV polypeptides was also decreased during examination stress compared to a month prior [70]. Caregivers of dementia patients also exhibited poor memory T cell proliferation in response to a HSV-1 antigen compared to controls [71].

Caregivers of Alzheimer patients have an increase in IL-10+ in both CD4+ and CD8+ T lymphocytes but no change in IFN γ +/CD8+, IFN γ +/CD4+, IL-2+/CD8+, or IL-2+/CD4+ cells. The difference in the percentage of IL-10+ cells between caregivers and age-matched controls was also dependent on age, with there being a greater difference at a younger age and diminished differences as age increased [72]. This indicates that stress increases the Th2 cells that produce the Th2 cytokine IL-10, possibly through the actions of glucocorticoids that are known to induce a shift from Th1 to Th2 cytokine production [73].

4.3. B lymphocytes and antibodies

B cells are involved in the humoral immune response. When a B cell comes into contact with a foreign antigen, it engulfs the antigen and digests it and then displays fragments of the antigen on MHC molecules. These then attract T cells which recognize the specific MHC-peptide complex. Cytokines secreted by the T cell activate the B cell and trigger its proliferation and differentiation into a plasma cell. Plasma cells produce antigen-specific antibodies. We have shown that stress affects different serum immunoglobulins in the absence of infection. In one study, plasma IgA increased during examination stress compared to 1 month earlier but IgG, IgM, and salivary IgA did not change [58]. However, in another study, examination stress caused significant increases in IgG, IgM and IgA [74]. In mice, we have shown that footshock decreased serum IgM produced against HSV-1 compared to controls [7].

4.4. Lymphocyte proliferation

During infection lymphocytes proliferate. The proliferation of lymphocytes following stimulation by a mitogen (blastogenesis) can be used as an *in vitro* measure of the body's response to challenge by an infectious agent. Phytohemagglutinin (PHA), a plant lectin, primarily stimulates T lymphocytes whereas pokeweed mitogen (PWM) stimulates B lymphocytes and concanavalin A (Con A) stimulates both T and B lymphocytes. Stress reduces lymphocyte proliferation following infection in animal models and mitogen stimulated proliferation in human studies.

In mice, footshock stress and restraint stress decreased CTL responses in spleens and lymph nodes of HSV-1-infected mice [7,11,57] and reduced HSV-1-induced lymphadenopathy (swelling of the lymph nodes) in a mouse model of HSV infection. Adrenalectomy had no effect on the restraint stress decrease observed in HSV-induced lymphadenopathy suggesting that this occurs through an adre-

nal-independent mechanism. However, adrenalectomy did reverse restraint stress prevention of expansion of CTL [11]. Exogenous corticosterone alone was unable to suppress CTL expansion. However, when combined with restraint stress in these adrenalectomized animals corticosterone was able to suppress CTL expansion. This suggests that CTL development is dependent on two factors—one adrenal-dependent and one adrenal-independent [11]. RU486, a glucocorticoid receptor antagonist, prevented the restraint stress decrease in lymphocyte proliferation in the lymph nodes following footpad HSV-1 infection. Nadolol, a β -adrenergic antagonist, was unable to prevent restraint stress decrease in lymphocyte proliferation in this model and a combination of both RU486 and nadolol had a similar effect of RU486 alone suggesting that β -adrenergic receptors do not modulate lymph node cellularity in this model of HSV-1 infection. However, nadolol was able to partially reverse restraint stress suppression of HSV-1-specific CTL activation suggesting that β -adrenergic receptors were involved here. In this study RU486 alone had no effect on CTL activation but RU486 and nadolol together fully reverse restraint stress suppression of HSV-1 CTL activation suggesting that both glucocorticoids and catecholamines are involved in stress-induced suppression of CTL activation [10].

We have also shown a poor T lymphocyte proliferation response to PHA or Con A in psychiatric patients who had high scores on the UCLA loneliness scale [16], in patients who had recently undergone surgery for breast cancer [64,75], in caregivers of dementia patients [76], in medical students undergoing exam stress [68], in women with poor marital quality [77], in subjects who exhibited more negative or hostile behaviors following a discussion on marital problems [63], and following a mental arithmetic stress test [38].

Interestingly intervention therapy in small group sessions reduced stress, improved mood, changed health behaviors and helped compliance in the maintenance of cancer treatment. The intervention resulted in either a stable or an increase in T cell proliferation over the 4 month period in patients who had undergone breast cancer surgery [75]. In medical students the use of hypnotic-relaxation techniques protected the ability of T lymphocytes to proliferate from the effects of examination stress [78]. Active coping or avoidance coping strategies enhanced PHA or Con A proliferation of lymphocytes during stress [79]. These data show that stress can reduce the proliferation of T cells in response to mitogens and antigens, resulting in the reduction of the number of circulating cytotoxic T cells and helper T cells.

4.5. Cytokines

Cytokines are inflammatory molecules that are released by many cell types and are important in both the innate and adaptive immune responses. Cytokines can act in an autocrine, paracrine or endocrine fashion and are highly

pleomorphic. Cytokines can be subdivided into Th1 and Th2 cytokines, which are produced by type 1 and type 2 helper T cells respectively. Th1 cytokines include IL-1, IL-2, IL-6, IFN γ and tumor necrosis factor α (TNF α) whereas Th2 cytokines include IL-4, IL-5, IL-10 and IL-13. IL-1 and IL-6 are pro-inflammatory cytokines that are amplifiers of T and B lymphocyte proliferation. IL-2 is important in the defense against microbial infection. TNF α is involved in systemic inflammation.

Caregivers of Alzheimer patients have increased plasma IL-6 compared to controls [80,81]. In a longitudinal study over a period of 6 years, caregivers and former caregiver's showed an increase in plasma IL-6 levels that increased at a rate four times faster than those of age-matched controls [80]. Local IL-6 production at the site of dermal wounds was lower in couples experiencing marital stress. However, plasma IL-6 levels were higher in high-hostile couples the morning after a conflict [82]. People with more depressive symptoms had an increase in plasma IL-6, which was further increased following vaccination with an influenza virus vaccine [83]. Peripheral blood leukocytes from caregivers produced lower levels IL-2 and IL-1 β in response to the influenza virus HA protein but there was no change in serum IL-6 levels [84]. Examination stress was associated with a decrease in IL-2 receptor (IL-2R) mRNA levels and protein expression in peripheral blood leukocytes compared to baseline [85]. Examination stress was also associated with a decrease in the production of IFN γ by peripheral blood leukocytes stimulated with Con A or PHA in medical students compared to 1 month prior to exams [30,40,60]. As for IL-6, local TNF α production at the wound sites was lower in couples experiencing marital stress. However, plasma TNF α levels were higher in high-hostile couples the morning after a conflict [82]. As already described, stress appears to increase serum IL-6 levels in chronically stressed older adults. IL-6 is a marker of inflammation and it has been previously noted that stress hormones can induce IL-6 [73]. Generally, glucocorticoids are thought to cause a shift from Th1 to Th2 cytokines by downregulating Th1 cytokines such as IFN γ and upregulating Th2 cytokines such as IL-10 [73].

4.6. C-reactive protein (CRP)

C-reactive protein (CRP) is a plasma protein that is produced in the acute phase response by the liver. CRP is increased during inflammation and can be used as a marker of inflammation. Caregivers of Alzheimer's patients have increased plasma CRP compared to controls [81]. Using a structural modeling equation, an association between pain and CRP was only found in caregivers whereas an association between hostility and CRP was found in both caregivers and controls [81]. This suggests that pain together with chronic stress may be detrimental in older adults. During examination stress no change in plasma CRP was seen [58].

4.7. Reactivation of latent viruses

Our laboratory and others have shown that stress can induce the reactivation of latent herpes viruses, as shown by antibody titers to viral proteins and the detection of viral DNA. In mice latently infected with HSV-1, foot-shock induced the reactivation of latent HSV-1 [7] and social disruption stress, but not restraint stress, caused reactivation of latent HSV-1 in latently infected mice [12].

In human studies, we have shown that antibody titers to EBV, HSV-1 and cytomegalovirus (CMV) were increased in medical students with examination stress [40,86], in caregivers of dementia patients [71], in women characterized as high stress reactors [87], in men and women with poor marital quality [69,77], and in subjects who exhibited more negative or hostile behaviors following a discussion on marital problems [63]. A 6 week training of orientation, military training and extreme exercise in West Point cadets undergoing “Cadet Basic Training” (CBT) did not change the steady state expression of latent EBV, however EBV reactivation did occur when the cadets were taking final examinations similar to the results we obtained in our medical students exam studies. No change was observed in HSV-1 or HSV-6 antibodies during CBT or examination stress. These data suggest that different stressors can have different effects on the reactivation of latent EBV [88] and in some ways are similar to the results we obtained in the study with mice latently infected with HSV-1 previously described [12].

In vitro cell culture studies have confirmed that HPA axis hormones, glucocorticoids, ACTH and CRH can reactivate latent EBV [87,89], thereby suggesting the mechanism by which stress can reactivate latent herpes viruses. Interestingly, muscle relaxation techniques and guided imagery, but not social contact, significantly decreased antibody titers to HSV-1 (reflecting better control over the latent virus by the cellular immune response) in older individuals in an independent-living facility [65]. Others have also shown the benefits of behavioral interventions on immune function [90], reactivation of latent herpes viruses [91], and the progression of cancer [92,93].

5. Implications for health

The effects of stress hormones on immune function described above have numerous implications for health. Three of these—vaccination, cancer and wound healing—are discussed below (Fig. 3).

5.1. Stress and vaccination

Since stress has such detrimental effects on the immune system, we investigated the effect of stress on the ability to respond to a vaccination. In the case of a viral vaccine, it is necessary to induce both an antibody response and a virus-specific T cell response for protection, which is not the case for a bacterial vaccine which induces only an anti-

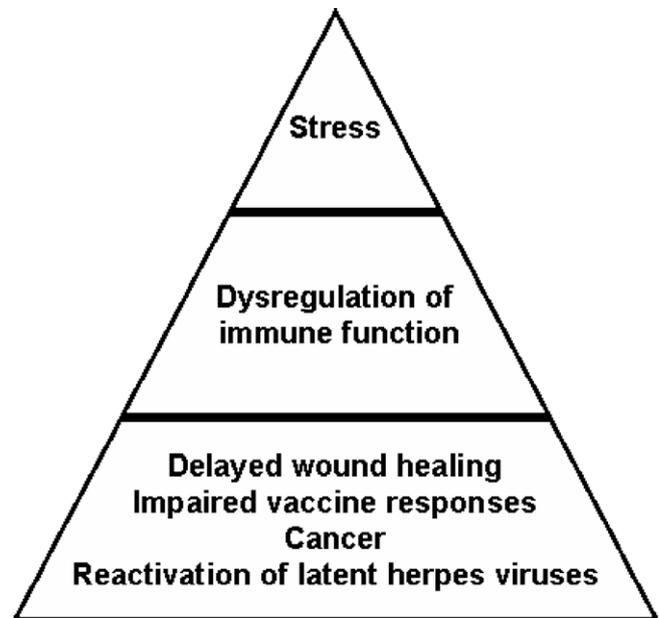


Fig. 3. Stress affects immune function which has implications for health. These include delayed wound healing, impaired vaccine responses, cancer and reactivation of latent herpes viruses.

body response. In both situations, at least a four fold increase in IgG antibody is considered the rule for “a take”. Caregivers of patients with dementia showed lower IgG antibody titers following pneumococcal vaccination 3 and 6 months following vaccination compared to former caregivers or controls. No differences were seen earlier at 2 weeks or 1 month following vaccination [94]. This suggests that chronic stress may affect IgG stability or the number of IgG producing cells following vaccination [94]. Caregivers also showed a poorer antibody and very specific T cell responses 1 month after an influenza virus vaccination [84]. In a study with medical students, students were given a series of 3 hepatitis B vaccinations on the 3rd day of a 3 day examination period. Students who were less stressed and anxious had higher antibody titers and a more vigorous T cell response to the vaccine than classmates who were more stressed and anxious six months after the initial injection [95].

5.2. Stress and cancer

Stress effects may influence the incidence and progression of cancer. As already discussed, stress decreases the number and activity of NK cells. These cells are important for their ability to kill tumor cells. In addition, faulty DNA repair can lead to the development of transformed cells. We have shown in an animal model that rotational stress reduced the levels of methyltransferase, a DNA repair enzyme synthesized in response to a carcinogen [4]. In addition, the peripheral blood leukocytes (PBLs) from psychiatric in-patients had poorer DNA repair in response to X-irradiation than cells from normal control subjects. Within the patient group, the high-distress subgroup had

significantly poorer DNA repair than the low distress subgroup [96].

The sympathetic nervous system may also affect tumor progression. We have shown that norepinephrine increases the angiogenic cytokines matrix metalloproteinase-2 (MMP-2), MMP-9 and vascular endothelial growth factor (VEGF) in nasopharyngeal carcinoma (NPC) cell lines which results in increased invasiveness of these cells. Propafenolone, a β -blocker, was able to prevent induction of these genes and prevent invasiveness [97]. Norepinephrine has also been shown to increase the invasiveness of ovarian cancer cells also through induction of MMPs [98]. These data suggest that stress impairs normal DNA repair, and NK cell activity possibly increasing the incidence of cancer and may also increase the invasiveness of at least some cancers through regulation of angiogenesis.

5.3. Stress and wound healing

Wound healing occurs in three overlapping stages. Inflammation plays a role in the early stages of wound healing in which bacteria and damaged tissue are phagocytized and then neutrophils migrate to the site and induce transcriptional activation that regulates cell fate and function and promotes wound healing. We have shown that stress impairs wound healing in dermal blister wounds and in punch biopsy wounds by slowing the wound healing process, through an increase in cortisol which can inhibit the process of cellularization, decrease GH and down regulate the production of pro-inflammatory cytokines at the wound site.

Blister wounds healed more slowly in couples experiencing marital stress and hostile behaviors [82]. In women with higher perceived stress, IL-1 α and IL-8 levels were reduced in blister wounds [99]. Stress also decreased GH levels at blister wound sites and impaired wound healing. Using DNA array technologies, stress was shown to have an overall suppressive effect on the neutrophil transcriptome which caused a shift towards genes involved in cell cycle arrest, death and inflammation [100]. Wound healing of a punch biopsy was found to be delayed in patients experiencing pain following surgery [101] and in caregivers of Alzheimer's patients compared to controls [102]. Interestingly, exercise was found to accelerate wound healing of a punch biopsy wound in older adults [103]. These data show that stress delays wound healing possibly through glucocorticoid repression of local cytokine products and neutrophil accumulation at the site of the wound.

6. Conclusion

Stress, through the actions of stress hormones, has many detrimental effects on immune function which in turn have implications for health. Interestingly, the use of relaxation techniques has been shown to reverse some of these deleterious effects on immune function. Thus, the role of stress in

disease, and the usefulness of practices that reduce stress should not be underestimated.

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