A Hassle a Day May Keep the Doctor Away: Stress and the Augmentation of Immune Function

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SYNOPSIS. Stress may be defined as a sequence of events, that begins with a stimulus (stressor), that is recognized by the brain (stress perception), and which results in the activation of physiologic fight/flight/fright systems within the body (stress response). Many evolutionary selection pressures are stressors, and one of the primary functions of the brain is to perceive stress, warn of danger, and enable an organism to respond. We hypothesized that under acute conditions, just as the stress response prepares the cardiovascular and musculoskeletal systems for fight or flight, it may also prepare the immune system for challenges (e.g., wounding) which may be imposed by a stressor (e.g., an aggressor). Initial studies showed that acute (2h) stress induced a significant trafficking of immune cells to the skin. Since the skin is an organism’s major protective barrier, we hypothesized that this leukocyte redistribution may serve to enhance skin immunity during acute stress. We tested this hypothesis using the delayed type hypersensitivity (DTH) reaction, which mediates resistance to various infectious agents, as a model for skin immune function. Acute stress administered immediately before antigen exposure significantly enhanced skin DTH. Adrenalectomy (ADX) eliminated the stress-induced enhancement of DTH while administration of physiological doses of corticosterone and/or epinephrine to ADX animals enhanced skin DTH in the absence of stress. These studies showed that changes in leukocyte distribution and circulating stress hormones are systemic mediators of the immunoenhancing effects of acute stress. We recently identified gamma interferon as a local cytokine mediator of a stress-induced immunoenhancement. Our results suggest that during acute stress the brain sends preparatory warning signals to the immune system just as it does to other fight/flight systems of the body.

INTRODUCTION

“Stress” is a term that means different things to different people but generally has a negative connotation. Yet, stress is a familiar aspect of life, being a stimulant for some individuals, but a burden for many others. We have defined “stress” as a constellation of events, comprised of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), which subsequently activates physiologic fight/flight/fright systems in the body (stress response) (Dhabhar and McEwen, 1997, 1999). The stress response results in the release of neurotransmitters and hormones that serve as the brain’s messengers to the body. It is often overlooked that the consequences of a stress response are adaptive in the short run (Dhabhar and McEwen, 1996, 1997) although they can be harmful when stress is chronic and long-lasting (Dhabhar and McEwen, 1997; McEwen, 1998). It is also overlooked that physiologic stress is activated during pleasurable experiences involving sexual stimulation (Colborn et al., 1991) and orgasm (Kruger et al., 1998) although it is typically assumed to be activated only during noxious or dangerous conditions. An important distinguishing characteristic of stress is its duration. We define acute stress as stress that lasts for a period of minutes to hours, and chronic stress as stress that persists for several hours a day for weeks or months. An important marker for deleterious amounts of chronic stress is a dysregulation of the circadian corticosterone rhythm in rodents (Dhabhar and McEwen, 1997) and cortisol rhythm in humans (Sephton et al., 2000).

Stress has long been suspected to play a role in the etiology of many diseases, and numerous studies have shown that stress can be immuno-suppressive and hence may be detrimental to health (Munck and Naray-Fejes-Toth, 1992; Herbert and Cohen, 1993; Marrucha et al., 1998; Sheridan, 1998; Kiecolt-Glaser, 1999; Ader et al., 2001). Moreover, glucocorticoid stress hormones are regarded widely as being immuno-suppressive (Munck et al., 1984), and are used clinically as anti-inflammatory agents (Schleimer et al., 1989). In contrast to the generally accepted idea that stress and stress mediators are harmful, this paper examines the potentially beneficial effects of stress and stress hormones in preparing the immune system for dealing with immunologic challenges (e.g., wounding or infection) which may be imposed by the actions of a stressor (e.g., a predator).

An evolutionary perspective

An evolutionary perspective has guided our approach to the study of stress and immune function. When viewed from this perspective, suppression of immune function under all stress conditions does not appear to be adaptive because stress is an intrinsic part of life for most organisms, and dealing successfully with stressors is what enables survival. Environmental challenges and most evolutionary selection pressures, are stressors which may be psychological (fear, anxiety), physical (wounding, infection), or physiological (food or water deprivation). One of the primary functions of the brain is to perceive stress, warn of danger,
and enable an organism to deal with the consequences. This function is accomplished through the release of stress-responsive neurotransmitters and hormones. For example, when a gazelle sees a charging lion, the gazelle’s brain detects a threat and orchestrates a physiologic response which first prepares, and then enables, the gazelle to flee. We have suggested that under such conditions, just as the stress response prepares the nervous, cardiovascular, musculoskeletal, and neuroendocrine systems for fight or flight, it may also prepare the immune system for challenges (e.g., wounding or infection) which may be imposed by the stressor (Dhabhar et al., 1994, 2000; Dhabhar and McEwen, 1999, 2001). A focus of our research has been to elucidate the cellular and molecular mechanisms mediating the beneficial versus harmful effects of stress on the overall health of an organism.

Paradoxical observations regarding the effects of stress on immune function

Three paradoxes present themselves when one reviews the extensive literature examining the relationship between stress, immune function, and health: First, as the preceding discussion suggests, it is paradoxical that organisms should have evolved to suppress immune function at a time when an active immune response may be critical for survival, for example, under conditions of stress when an organism may be injured or infected by the actions of the stress-inducing agent (e.g., an attacking predator). Second, on the one hand stress is thought to suppress immunity and increase susceptibility to infections and cancer (Ben-Eliyahu et al., 1991; Cohen et al., 1991; Glaser et al., 1994; Kiecolt-Glaser et al., 1996; Sheridan, 1998), while on the other, it is thought to exacerbate inflammatory diseases (Solomon and Moos, 1964; Mei-Tal et al., 1970; Amkraut et al., 1971; Thomason et al., 1992; Al’Abadie et al., 1994; Pawlak et al., 1999) like psoriasis, asthma, arthritis and lupus erythematosus (which should be ameliorated by a suppression of immune function). Third, stress is known to exacerbate autoimmune and inflammatory diseases (Solomon and Moos, 1964; Mei-Tal et al., 1970; Thomason et al., 1992), however, stress hormones (glucocorticoids) are used clinically to treat these diseases (Schleimer et al., 1989).

Keeping these paradoxical observations in mind, and based on our initial studies on the effects of stress on blood leukocyte distribution, we hypothesized that under certain conditions, stress may enhance rather than suppress immune function. The studies described here were designed to test this hypothesis.

Stress-induced changes in leukocyte numbers in the blood

Immune cells or leukocytes circulate continuously from the blood, into various organs, and back into the blood. This circulation is essential for the maintenance of an effective immune defense network (Sprent and Tough, 1994). The numbers and proportions of leukocytes in the blood provide an important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood. Stress-induced increases in plasma corticosterone are accompanied by a significant decrease in numbers and percentages of lymphocytes, and by an increase in numbers and percentages of neutrophils. It has been shown that stress-induced changes in blood leukocyte distribution are apparent within 30 min of applying the stressor and are accounted for by a large decrease (45–60% lower than baseline) in total blood leukocyte numbers (Dhabhar et al., 1995). FACS analyses revealed that absolute numbers of peripheral blood helper T cell (Th), cytolytic T cell (CTL), B cells, natural killer (NK) cells, and monocytes all show a rapid and significant decrease (40 to 70% lower than baseline) during stress (Dhabhar et al., 1995). Further experiments revealed that stress-induced decreases in blood leukocyte numbers are rapidly reversed with leukocyte numbers returning to pre-stress baseline levels within three hours after the cessation of stress (Dhabhar et al., 1995). Similarly, stress-induced decreases in blood leukocyte numbers have been reported in fish (Pickford et al., 1971), mice (Jensen, 1969), rats (Johns, 1967; Rinner et al., 1992; Dhabhar et al., 1994; Stefanski et al., 1996), rabbits (Toft et al., 1993), horses (Snow et al., 1983), non-human primates ( Morrow-Tesch et al., 1993), and humans (Herbert and Cohen, 1993; Schedlowski et al., 1993). This suggests that the phenomenon of stress-induced leukocyte distribution has been conserved through evolution, and that perhaps this redistribution has an important adaptive and functional significance.

Dhabhar et al. have shown that the stress-induced changes in leukocyte distribution are mediated by hormones released by the adrenal gland (Dhabhar et al., 1996; Dhabhar and McEwen, 1999). Thus, the magnitude of the stress-induced changes in blood leukocyte numbers is significantly reduced in adrenalectomized animals (Dhabhar et al., 1995, 1996). Cyanoketone, a steroid synthesis inhibitor, acts on 3 β-hydroxysteroid dehydrogenase to significantly reduce stress-induced elevations in plasma corticosterone while leaving intact secretion of permissive levels of the hormone during the circadian cycle (Spona, 1981). Interestingly, stress-induced decreases in blood lymphocyte numbers are significantly reduced, and stress-induced increases in blood neutrophil numbers are significantly enhanced in cyanoketone-treated animals (Dhabhar et al., 1996). Several studies have shown that glucocorticoid treatment induces changes in leukocyte distribution in mice (Dougherty and White, 1945; Spain and Thalhimer, 1951; Cohen, 1972; Zatz, 1975), guinea pigs (Fauci, 1975) rats (Ulich et al., 1988; Miller et al., 1994; Dhabhar et al., 1996), rabbits (Van Den Broek et al., 1983), and humans (Fauci and Dale, 1974; Fauci, 1976; Onsrud and Thorsby, 1981).
It has been shown in rats that both adrenalectomy (which eliminates the corticosterone and epinephrine stress response) (Jensen, 1969; Keller et al., 1983; Dhabhar et al., 1995, 1996), or cyanoketone treatment (which eliminates only the corticosterone stress response), virtually eliminate the stress-induced redistribution of blood leukocytes (Dhabhar et al., 1996).

Since adrenal steroids act at two distinct receptor subtypes which show a heterogeneity of expression in immune cells and tissues (Dhabhar et al., 1993, 1995), we investigated the role played by each receptor subtype in mediating changes in leukocyte distribution (Dhabhar et al., 1996). Acute administration of aldosterone (a specific Type I adrenal steroid receptor agonist) to adrenalectomized animals did not have a significant effect on blood leukocyte numbers. In contrast, acute administration of corticosterone (the endogenous Type I and Type II receptor agonist), or RU28362 (a specific Type II receptor agonist), to adrenalectomized animals induced changes in leukocyte distribution which were similar to those observed in intact animals during stress. These results suggest that corticosterone, acting at the Type II adrenal steroid receptor, is a major mediator of the stress-induced decreases in blood lymphocyte and monocyte distribution. Taken together, these studies show that stress and glucocorticoid hormones induce a significant decrease in blood lymphocyte numbers when administered under acute or chronic conditions.

In apparent contrast to glucocorticoid hormones, catecholamine hormones have been shown to increase blood leukocyte numbers in rats (Harris et al., 1995) and humans (Landmann et al., 1984). On closer examination it is observed that following adrenaline or noradrenaline administration, neutrophil and NK cell numbers increase rapidly and dramatically whereas T and B cell numbers decrease (Tonnesen et al., 1987; Landmann, 1992; Schedlowski et al., 1993; Benschop et al., 1996). Therefore, the absolute number of specific blood leukocyte subpopulations may be significantly affected by the ambient concentrations of epinephrine, norepinephrine and corticosterone. Differences in concentrations and combinations of these hormones may explain reported differences in blood leukocyte numbers during different stress conditions (e.g., short-versus long-duration acute stress, acute versus chronic stress) and during exercise (Herbert and Cohen, 1993; Brenner et al., 1998).

A stress-induced decrease in blood leukocyte numbers represents a redistribution rather than a destruction or net loss of blood leukocytes

From the above discussion it is clear that stress and glucocorticoid hormones induce a rapid and significant decrease in blood lymphocyte, monocyte, and NK cell numbers. This decrease in blood leukocyte numbers may be interpreted in two possible ways. The decrease in cell numbers could reflect a large-scale destruction of circulating leukocytes. Alternatively, it could reflect a redistribution of leukocytes from the blood to other organs in the body. Several studies have shown that this decrease reflects a redistribution rather than a destruction of immune cells (Dougherty and White, 1945; Spain and Thalhimer, 1951; Cohen, 1972; Zatz, 1975; Lundin and Hedman, 1978; Cox and Ford, 1982).

We conducted experiments to test the hypothesis that acute stress induces a redistribution of leukocytes from the blood to other compartments in the body (Dhabhar et al., 1995; Dhabhar, 1998). The first series of experiments examined the kinetics of recovery of the stress-induced reduction in blood leukocyte numbers. It was hypothesized that if the observed effects of stress represented a redistribution rather than a destruction of leukocytes, one would see a relatively rapid return of leukocyte numbers back to baseline upon the cessation of stress. Results showed that all leukocyte subpopulations which showed a decrease in absolute numbers during stress, showed a complete recovery with numbers reaching pre-stress baseline levels within 3 hr after the cessation of stress. Plasma levels of lactate dehydrogenase (LDH), a marker for cellular damage, were also monitored in the same experiment. If the stress-induced decrease in leukocyte numbers were the result of a destruction of leukocytes, one would expect to observe an increase in plasma levels of LDH during or following stress. No significant changes in plasma LDH were observed, further suggesting that a redistribution rather than a destruction of leukocytes was primarily responsible for the stress-induced decrease in blood leukocyte numbers (Dhabhar et al., 1995).

**Stress-induced redistribution of blood leukocytes—functional consequences**

Dhabhar et al. (1994) were the first to propose that a stress-induced decrease in blood leukocyte numbers represents an adaptive response that may increase immune surveillance/response in organs to which leukocytes traffic during stress (Dhabhar et al., 1994, 1995, 2000; Dhabhar and McEwen, 1996, 1999). These authors have suggested that such a decrease in blood leukocyte numbers represents a redistribution of leukocytes from the blood to other organs such as the skin, mucosal lining of gastro-intestinal and urinary-genital tracts, lung, liver, and lymph nodes which may serve as “battle stations” should the body’s defenses be breached. They have also suggested that such a leukocyte redistribution may enhance immune function in compartments to which leukocytes traffic during stress (Dhabhar et al., 1995, 2000; Dhabhar and McEwen, 1996, 1997).

Thus, an acute stress response may direct the body’s “soldiers” (leukocytes), to exit their “barracks” (spleen and bone marrow), travel the “boulevards” (blood vessels), and take position at potential “battle stations” (skin, lining of gastro-intestinal and urinary-genital tracts, lung, liver, and lymph nodes) in preparation for immune challenge (Dhabhar et al., 1994, 1995, 1996, 2000; Dhabhar and McEwen, 1996, 1997).
In addition to “redistributing” leukocytes to potential “battle stations” stress hormones may also better equip them for “battle” by enhancing processes like antigen presentation, phagocytosis, and antibody production. Thus, a hormonal alarm signal released by the brain upon detecting a stressor, may “prepare” the immune system for potential challenges (wounding or infection) which may arise due to the actions of the stress-inducing agent (e.g., a predator or attacker).

**Stress-induced enhancement of immune function**

While a majority of studies in the field of psychoneuroimmunology have focussed on the immunosuppressive effects of stress, several studies have also revealed that under certain conditions, stress can be immunoenhancing. In general, acute stress is found to be immunoenhancing whereas chronic stress is found to be immunosuppressive, (in some cases the effects of stress on leukocyte numbers and proportions in the compartment being assayed need to be taken into consideration for this statement to hold). Dhabhar et al. have suggested that a stress-induced enhancement of immune function may be an adaptive response which prepares an organism for potential immunologic challenges (e.g., a wound or infection inflicted by an attacker) for which stress perception by the brain, and subsequent stress hormone and neurotransmitter release, may serve as an early warning (Dhabhar et al., 1995; Dhabhar and McEwen, 1996, 1997, 1999).

As discussed above, acute stress induces a significant redistribution of leukocytes from the blood to other organs (e.g., skin and lymph nodes) in the body (Dhabhar et al., 1995; Dhabhar, 1998), and adrenal stress hormones are major mediators of this leukocyte redistribution (Dhabhar et al., 1996). Since the skin is one of the targets to which leukocytes traffic during stress, Dhabhar & McEwen hypothesized that a stress-induced leukocyte redistribution may increase immune surveillance in the skin and consequently enhance immune function should the skin be exposed to antigen following acute stress (Dhabhar and McEwen, 1996).

To test this hypothesis, they examined the effects of acute stress on skin immunity, using a rodent model for a skin delayed type hypersensitivity (DTH) response (Dhabhar and McEwen, 1996). In order to induce DTH, animals were initially sensitized to 2,4-dinitro-1-fluorobenzene (DNFB) by administering the chemical antigen to the skin of the dorsum. The sensitization phase of a DTH reaction is one where the organism develops an immunologic memory (through the generation of memory T cells) for the antigen with which it is immunized. Following sensitization, the ability of the animals to mount a DTH response against DNFB was examined by administering DNFB to the dorsal aspect of the pinna. The DTH response was subsequently measured as an increase in pinna thickness which is proportional to the intensity of the ongoing immune reaction (Phanuphak et al., 1974; Kimber and Dearman, 1993). This phase, also known as the elicitation or challenge phase, involves recruitment of memory T cells and effector cells such as neutrophils, macrophages, CTLs and NK cells which mount an immune response against the antigen to which the animal was previously sensitized. Acute restraint stress administered immediately before either sensitization or challenge with antigen, resulted in a large and long-lasting enhancement of skin DTH (Dhabhar and McEwen, 1996, 1999). Histological analysis revealed significantly larger numbers of leukocytes in the skin of stressed animals both before and after exposure to antigen, and suggested that a stress-induced redistribution of leukocytes was one of the factors mediating the stress-induced enhancement of skin immunity (Dhabhar and McEwen, 1996). Moreover, it has recently been shown that gamma interferon is a local cytokine mediator of a stress-induced enhancement of skin DTH (Dhabhar et al., 2000).

Similarly, acute stress has similarly been shown to enhance skin DTH in mice (Blecha et al., 1982). Wood et al. have shown that exposure to footshock stress enhances humoral as well as cell-mediated immunity to keyhole limpet hemocyanin (KLH) (Wood et al., 1993). These investigators administered a single acute footshock session on days −1, 0, 1 and 3 relative to sensitization (day 0). They observed that compared to non-stressed controls, animals stressed on days 0 or 1 showed enhanced immune responses with respect to serum anti-KLH IgG levels, splenocyte proliferation, and skin cell-mediated immunity to KLH antigen. Interestingly, non-stressed animals failed to show a significant increase in serum antibody titers and in KLH-stimulated splenocyte proliferation relative to non-immunized animals (Wood et al., 1993). Similarly, Persoons et al. have shown that acute stress administered prior to intrathecal immunization with trinitrophenyl keyhole limpet hemocyanin (TNP-KLH) significantly enhanced the primary humoral response in rats (Persoons, 1995). They also showed that acute stress administered prior to antigen administration to previously immunized animals resulted in a significant enhancement of a secondary humoral response (Persoons et al., 1995). In another study, Carr et al. reported that cold stress enhanced IgG and IgM production by splenocytes and that this enhancement was mediated by the alpha adrenergic receptor (Carr, 1992).

Several other studies have reported stress-induced enhancement of humoral immune responses. For example, cold stress has been shown to accelerate antigen removal in mice (Sabiston et al., 1978). Other stressors have been shown to increase antigen-specific antibody titres in rats, mice, and pigs (Solomon, 1969; Blecha and Kelley, 1981; Berkenbosch et al., 1991; Cocke et al., 1993; Wood et al., 1993; Persoons et al., 1995). It has also been proposed that glucocorticoids may shift the balance of an ongoing immune response in favor of humoral immunity (Danes and Araneo, 1989; Gajewski et al., 1989; Mosmann and Coffman, 1989; Mason, 1991), and physiological doses of glucocorticoids have been shown to enhance immunoglobulin production by mitogen- (Grayson et al., 1981) and...
IL-4 (Wu et al., 1991) stimulated human lymphocytes in culture.

Stress-induced suppression of immune function

Numerous studies have shown that stress can be immunosuppressive and hence may be detrimental to health (for review see: Ader et al., 2001). Since these studies have been reviewed and discussed extensively, the reader is referred to these reviews for a more detailed account of the subject. It may be worth noting here that most stress conditions which are found to be immunoenhancing involve acute stress, and those which are found to be immunosuppressive involve chronic stress (with the effects of stress on leukocyte distribution being an important factor to be taken into account). It has been shown that in contrast to acute stress, chronic stress suppresses the skin DTH response (Basso et al., 1993; Dhabhar and McEwen, 1997). A chronic stress-induced decrease in leukocyte mobilization from the blood to other body compartments is thought to be one of the mediators of this stress-induced suppression of skin DTH (Dhabhar and McEwen, 1997). Similarly in human and animal studies, chronic stress has also been shown to suppress different immune parameters.

Adrenal hormones mediate the bi-directional effects of stress on skin immune function

In contrast to the well-known immunosuppressive effects of glucocorticoids, several studies have revealed that glucocorticoid hormones also exert immunomodulating (for review see: Wilckens and DeRijk, 1997) and immunoenhancing effects (for review see: Dhabhar and McEwen, 2001). In general, pharmacological concentrations of glucocorticoids exert immunosuppressive effects, whereas under different conditions, physiologic concentrations may exert immunomodulatory, immunoenhancing, or immunosuppressive effects. It is important to recognize that the source (natural versus synthetic) and concentration (physiologic versus pharmacologic) of glucocorticoid hormones, the effects of other physiologic factors (hormones, cytokines, and neurotransmitters), and the state of activation of an immune parameter (naïve versus activated leukocyte, early versus late activation, etc.), are all important factors which ultimately determine the nature of the effects of glucocorticoids on a given immune response.

It has been demonstrated that the acute stress-induced enhancement of skin DTH is mediated by adrenal stress hormones (Dhabhar and McEwen, 1999). Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of skin DTH (Dhabhar and McEwen, 1999). Low dose corticosterone or epinephrine administration significantly enhanced skin DTH and produced a significant increase in T cell numbers in lymph nodes draining the site of the DTH reaction (Dhabhar and McEwen, 1999). Moreover, simultaneous administration of these two stress hormones, produced an additive increase in the skin DTH response. These results showed that hormones released during an acute stress response may help prepare the immune system for potential challenges (e.g., wounding or infection) for which stress perception by the brain may serve as an early warning signal (Dhabhar and McEwen, 1999). In contrast to the effects of physiologic doses of natural hormones, high dose corticosterone, chronic corticosterone, or low dose dexamethasone administration, all significantly suppressed skin DTH (Dhabhar and McEwen, 1999).

Thus, adrenal stress hormones mediate the bi-directional effects of stress on skin immunity: Low doses of acutely administered corticosterone and epinephrine have immunoenhancing effects, whereas high doses of corticosterone, chronic corticosterone, or low doses of the synthetic steroid, dexamethasone, all exert immunosuppressive effects (Dhabhar and McEwen, 1999). Moreover, dexamethasone shows a significantly greater immunosuppressive potency than corticosterone (Dhabhar and McEwen, 1999). The cellular and molecular mechanisms mediating these bi-directional effects of stress hormones on skin immune function need to be investigated further.

Acute stress enhances innate and adaptive immune responses

It is important to bear in mind that most in vivo immune responses involve a combination of innate as well as adaptive cellular and cytokine mechanisms (Abbas et al., 2000). It has been suggested that stress enhances innate immunity but suppresses adaptive immunity (Fleshner et al., 1998). However, evidence shows that a stress response can enhance innate immunity (Rhinehart et al., 1975; Lyte et al., 1990; Renz et al., 1992; Broug-Holub and Kraal, 1996) as well as the humoral and cellular (Wood et al., 1993; Dhabhar et al., 2000; Dhabhar and McEwen, 2001) arms of an adaptive immune response (Moynihan and Stevens, 2001). The determining factor is whether the physiological conditions established during a stress response favor immunoenhancement around the time of exposure to antigen, pathogen, or wounding. The mechanisms involving leukocyte trafficking and activation that are discussed above apply to neutrophils, monocytes, NK cells, T cells and B cells (Fig. 1). Thus, a stress-induced redistribution of monocytes and lymphocytes to the skin and lymph nodes would enhance an innate (role of monocytes or NK cells) or an adaptive immune response (role of monocyte antigen presentation, memory T or B cell function, effector monocyte, T cell, and NK cell function). Similarly, an acute stress-induced neutrophilia would favor immunoenhancement by mobilizing neutrophils into the blood stream and making them available for recruitment and activation at sites of inflammation. Since neutrophils are critical for most inflammatory reactions, an increase in neutrophil recruitment could enhance the inflammatory phase of both innate and adaptive immune responses. Mechanisms involving leukocyte activation
Fig. 1 Schematic describing the relationship between different parameters of stress and glucocorticoid hormones (GCs), and their bidirectional effects on immune function (for review see: Dhabhar and McEwen, 2001). While this figure discusses the role of glucocorticoid hormones, it is important to bear in mind that catecholamines and peptide hormones are also released during stress and these mediators also influence immune responses. A) IMMUNOENHANCEMENT: A stress-induced redistribution of leukocytes within the body may result in enhanced immune function within compartments to which leukocytes traffic during stress and suppressed immune function in compartments which are relatively depleted of leukocytes. In addition to affecting leukocyte distribution, acute stress, or acute exposure to physiological levels of glucocorticoid hormones may also enhance leukocyte activation and effector function. Immunoenhancement may be mediated by an increase in innate, cell-mediated, or humoral immunity. The beneficial effects of such immunoenhancement may include increased resistance to infections or cancer. The harmful effects of such immunoenhancement may include exacerbation of autoimmune or inflammatory disorders. B) IMMUNOSUPPRESSION: Chronic stress, pharmacological doses of glucocorticoid hormones, or synthetic glucocorticoids such as dexamethasone all suppress immune function. Chronic stress to physiological concentrations of endogenous glucocorticoids, or physiological concentrations of glucocorticoid hormones acting at later stages of an immune response may also suppress immune function. Stress- or glucocorticoid hormone-mediated immunosuppression may increase susceptibility to infections or cancer, but may protect against autoimmune or inflammatory reactions. Factors such as coping style, gender, genes, and age are also likely to influence the relationship between stress and immune function.
corticoid hormones play as modulators of an immune response. The immunoenhancing effects of stress can be placed into context with its well-known immunosuppressive effects if one considers the following factors: 1) The effects of stress on leukocyte distribution. 2) The duration of exposure (acute versus chronic) to stress. 3) The concentration (physiologic versus pharmacologic) and source (endogenous versus synthetic) of stress hormones. 4) The timing of stress exposure relative to the stage of development of the immune response.

Much work remains to be done. The precise characteristics of the different conditions described above and their interactions with psychological, physiologic, and genetic factors need to be further investigated and defined. A determination of the physiologic mechanisms through which stress and stress hormones enhance or suppress immune responses may help our understanding and treatment of diseases thought to be affected by stress. Therefore, the psycho-physiologic, cellular and molecular mechanisms by which stress and stress hormones up- or down-regulate an immune response merit further investigation.

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