Psychoimmunology

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PSYCHOLOGICAL STRESS AND THE IMMUNE SYSTEM IN HUMANS

Stressful life events have been linked to a range of immune-related disorders, including autoimmune diseases, infectious diseases, and cancer (Cohen & Williamson, 1991; Grant *et al*, 1989; Jensen, 1987). One means by which stress may lead to increased susceptibility to these diseases is by altering the function of the immune system This hypothesis is one of the central concerns of the growing field of psychoneuroimmunology (PNI), which attempts to elucidate the relations between psychosocial factors, nervous, endocrine and immune systems, and health.

How stress influences the immune system is not entirely clear. One possibility is that stress alters immune responses through the adoption of coping behaviours, such as smoking or drinking alcohol, that are known to compromise immunity (Kiecolt-Glaser & Glaser, 1988). Alternatively, stress may directly influence immune function through the activation of neuroendocrine pathways that lead to the release of various hormones and neurotransmitters, such as cortisol and catecholamines Direct anatomical links exist between the nervous and immune systems, as evidenced by sympathetic innervation to lymphoid organs, such as the thymus and spleen (Livnat *et al*, 1985). Immune cells, which migrate between the lymphoid organs and peripheral bloodstream, have also been shown to have receptors for numerous hormones and neurotransmitters that are produced and secreted during stress, suggesting that these substances play a role in altering cell function.

MEASUREMENTS OF IMMUNOCOMPETENCE

The function of the immune system is to identify and destroy foreign or non-self materials Such non-self materials include invading foreign agents (or antigens), such as bacteria or viruses or altered host cells such as tumour or infected cells. The immune system is complex and is composed of natural barriers, such as skin and mucous, immune organs, and immune cells In PNI research, the most commonly measured component of the immune system is the immune cells, which collectively work together to mount a response against non-self materials As a group, such cells are known as white blood cells (WBCs) or leukocytes While there are many types of leukocytes, each with distinct functions, such cells are interdependent and perform their functions in an orchestrated fashion to achieve immunocompetence Table 1 lists the different types of immune cells and their primary functions.

Assessments of immune cells fall into two categories, quantifying the number of cells in circulation and assessing their function *in vitro* An overview of the immunological assessments commonly used in PNI research is presented in Table 2

Table 1 *Cells of the Immune system*

Cell type	Function
White blood cells (WBC)	Respond to antigens; include lymphocytes and phagocytes
Lymphocytes	Subset of WBCs that include T- and B-lymphocytes, and NK cells; functions described below
T-helper lymphocytes	Enhance immune responses by stimulating T-cell replication and activating antibody production by B-lymphocytes
T-suppressor lymphocytes	Inhibit immune responses
T-cytotoxic lymphocytes	Destroy virus- , parasite- , and tumour-infected cells; reject transplanted tissue
B-lymphocytes	Produce antibodies
NK cells	Destroy virally infected and tumour cells
Phagocytes	Subset of WBCs that include basophils, eosinophils, neutrophils, monocytes and macrophages; ingest and destroy antigens

In enumerative assays, investigators quantify specific populations of immune cells in the peripheral bloodstream. Typically, these cells include: (i) T-helper lymphocytes (designated CD4), which enhance immune responses through the release of substances promoting the replication and activation of other immune cells; (ii) T-suppressor cells (designated CD8), which down-regulate or suppress immune responses; (iii) T-cytotoxic lymphocytes (also designated CD8), which destroy antigens and play an important role in immune reactions against intracellular parasites and viruses, tumour cells, and tissue transplants; (iv) B lymphocytes (designated CD19), which produce antibodies, proteins that destroy bacteria and prevent viruses from penetrating host cells; (v) natural killer (NK) cells, that destroy certain tumour and virally infected cells; and (vi) phagocytes, such as monocytes and macrophages, which injest and degrade foreign matter and initiate T-lymphocyte activity.

In enumerative assays, the various populations of immune cells are identified and counted by staining the unique surface molecules of each cell type with specific fluorescent reagents Using this technique, one can quanitify the percentages or absolute numbers of T-lymphocytes (and their subsets), B-lymphocytes, macrophages, and NK cells from the peripheral circulation In addition, the ratio

Table 2 *Immune assessments commonly used in PNI studies*

Measure	What it tells us
Numbers or percentages of WBC populations (lymphocytes and phagocytes)	Composition of WBC populations in the peripheral bloodstream
Lymphocyte proliferation	Ability of lymphocytes to divide in response to a stimulating mitogen, such as PHA, Con A, or PWM *in vitro*
Natural killer cell activity	Ability of natural killer cells to destroy tumour cells *in vitro*
Lymphokine and interleukin production	Ability of activated lymphocytes and monocytes to produce and release molecules that serve as regulating signals between immune cells *in vitro*
Antibody levels	Amount of antibody production in response to an antigen *in vitro*

of T-helper to T-suppressor/cytotoxic cells, which is used as an index of immune status, may be determined. Although the interpretation of quantitative immune cell changes in the circulation during stress is not entirely clear, it is likely that such alterations reflect the redistribution of immune cells between the peripheral blood and lymphoid organs (O'Leary, 1990) Migratory shifts in lymphocyte populations may influence immunocompetence by determining whether lymphocytes will encounter an environmental antigen in a particular location in a timely fashion (Ottaway & Husband, 1992).

In addition to quantitative assessments, functional assessments of immunity can be made using a variety of *in vitro* assays One of the most fundamental functions of immune cells is to divide, or proliferate in response to antigens In proliferation assays, lymphocytes are exposed, *in vitro*, to chemicals or plant extracts that stimulate cell division These stimulants are called mitogens The most commonly used mitogens in PNI research are phytohaemagglutinin (PHA) and Concavalin A (Con A) which stimulate the division of T-cells, and Pokeweed mitogen which stimulates division of both T- and B-cells.

The ability of NK cells to destroy tumours by rupturing their membranes (cell lysis) can also be assessed *in vitro* In the chromium-release assay, NK cells are incubated with tumour cells that contain a radioactive substance, such as radioactive-labelled chromium Natural killer cell activity is reflected by the extent of tumour cell lysis, which in turn, is determined by the amount of radioactivity released from the lysed cells into the culture medium.

Other functional assays are designed to measure levels of antibodies in saliva or serum Antibodies are specialized proteins that carry out a number of immune functions and they are produced by B cells in response to antigens Greater antibody response is usually interpreted as better immunocompetence However, elevated antibody levels to latent viruses, such as herpesviruses may reflect a weakened ability of the immune system to keep such viruses from becoming active Therefore, higher antibody levels to latent viruses are often interpreted as indicating *poorer* immunocompetence (Kiecolt-Glaser & Glaser, 1987)

Finally, *in vitro* functional assays are also used to measure sub-

stances produced and secreted by lymphoyctes and monocytes, called cytokines In these assays, immune cells are first activated by mitogens, such as PHA or Con A After incubation, the cell mixture is exposed to labelled antibody that attaches to the specific cytokine in question The quantity of cytokine secreted by these cells is then determined by the degree of binding between the specific cytokine and labelled antibody

PSYCHOLOGICAL STRESS AND IMMUNITY

A growing literature in both humans and animals supports associations between immunological changes and psychological and physical forms of stress (for extensive reviews involving humans, see Herbert & Cohen, 1993; O'Leary, 1990) Changes in the immune system have been found to accompany exercise, exams, confronting a phobic stressor, bereavement and divorce, occupational stress, unemployment, and the ongoing uncertainty associated with living near Three Mile Island (TMI) several years after the nuclear accident

Perhaps the most commonly examined stressors in relation to immunological status have been examinations Indeed, several indices of immunosuppression have been observed among medical students during final exams Compared to test-free periods, students undergoing exams have shown decrements in lymphocyte response to mitogenic stimulation, reduced NK cell activity, alterations in T-cell populations, increased plasma levels of circulating antibodies, and decreased cytokine production (Kennedy, Kiecolt-Glaser & Glaser, 1988; Glaser *et al*, 1986) Increased levels of circulating antibodies to Epstein–Barr and other herpesviruses have also been observed during examination periods, indicating, perhaps, the reactivation of latent virus by either direct neuroendocrine influences or weakened immunocompetence In some cases, the most extreme immunological changes were found to occur in subsets of students with the highest levels of overall life stress, loneliness, or tendency to ruminate about stressful events during the examination period (Kiecolt-Glaser *et al*, 1984; Workman & La Viá, 1987)

The loss of an intimate relationship from either death or divorce has also been associated with altered immunity, including suppression of lymphocyte responses to mitogenic stimulation, reduced NK cell activity, and changes in T-cell subpopulations Early investigations found lowered mitogenic lymphocyte proliferation in bereaved subjects following the loss of a spouse, as compared to both non-bereaved controls (Bartrop *et al*, 1977) and the pre-bereavement period (Schleifer *et al*, 1983) Subsequent findings indicated that the degree of immune change among bereaved persons was related to the severity of depressive response before and after the loss (Irwin *et al*, 1987)

Separation and divorce have similarly been associated with immune alterations Kiecolt-Glaser, Glaser, and colleagues found that recently separated or divorced women demonstrated lower percentages of circulating NK and T-helper cells, decreased proliferative responses to PHA and Con A, and higher antibodies to Epstein–Barr virus than a comparison group of married persons (cited in Kennedy, Kiecolt-Glaser & Glaser, 1988) Similar findings were reported in a subsequent investigation comparing separated or divorced men to matched married controls As in the previous study, separated or divorced men had higher antibody levels to latent viruses (here, Epstein–Barr virus and herpes simplex virus)

T-lymphocyte populations, however, did not differ between the two groups. Finally, both studies showed that, for married couples, poorer marital quality was related to higher levels of distress, loneliness, and latent virus antibody response (cited in Kennedy, Kiecolt-Glaser, & Glaser, 1988).

Immunological changes accompany other prolonged stressors, as well, such as long-term unemployment, occupational stress, caregiving for a terminally ill patient, and residing near a damaged nuclear power plant. In an examination of the immune-related effects of caregiving for a family member with Alzheimer's Disease, Kiecolt-Glaser and colleagues found that caregivers exhibited lower percentages of total lymphocytes and T-helper cell subsets, and higher antibody titres to Epstein–Barr virus (Kiecolt-Glaser et al, 1987).

Heightened distress and higher latent antibody levels were also observed in TMI residents more than 6 years after the nuclear accident, as compared to demographically comparable controls (McKinnon et al, 1989). Living near TMI was also associated with enumerative immune alterations, including higher numbers of circulating neutrophils, and lower numbers of B lymphocytes, T-suppressor/cytotoxic lymphocytes, and NK cells (McKinnon et al, 1989).

Both job stress and long-term unemployment have been linked to lowered lymphocyte reactivity to PHA (Arnetz et al, 1987; Dorian et al, 1985). In one study, immunological function was found to remain depressed throughout the study interval, despite the inclusion of a psychosocial intervention programme designed to assist the unemployed (Arnetz et al, 1987).

Taken together, most studies involving stress and immunity indicate that psychological stressors are associated with changes in immune cell numbers and functions (Herbert & Cohen, 1993). The most consistent alterations include reduced NK cell activity and lymphocyte proliferation to PHA and Con A, and increased antibody levels to latent herpesviruses. Decreases in percentages or absolute numbers of circulating B cells, T cells, T-helper cells, T-suppressor/cytotoxic cells, and NK cells are also frequently reported stress-related immune responses. Moreover, such alterations may persist (i.e. fail to habituate) with prolonged stressor exposure. However, because the aforementioned studies document *correlational* relations between stress and immunity, causal interpretations cannot be made. Even if stress, itself, does lead to changes in the immune system, it is not clear whether this occurs because stress influences health behaviours or neuroendocrine parameters. Few investigations have examined relationships between health practices or neuroendocrine factors and immune alterations during stress (Herbert & Cohen, 1993). Whereas extreme modifications in health practices result in altered immunity, it is not yet clear if more modest changes similarly influence the immune system. Although few PNI investigations with humans measure concomitant changes in hormonal or catecholamine levels, the small number of naturalistic studies that have included neuroendocrine variables suggest that the sympathetic nervous system may play a significant role in stress-induced immune alterations (e.g. McKinnon et al, 1989).

SHORT-TERM LABORATORY STRESSORS AND IMMUNITY

While associations between naturally occurring stressors and alterations in immune function are well documented, only recently have investigators utilized controlled, experimental studies to examine stress–immune interactions. Experimental manipulations where subjects are randomly assigned to stressor exposure or non-exposure (i.e. control groups) are required for clarifying causal interpretations about stress-immune relations. Experimental studies are also useful for the investigation of potential neuroendocrine mechanisms associated with immunological changes during stress, since they eliminate other potential influences, such as changes in health behaviours.

There are now several studies demonstrating immunological alterations following exposure to standardized laboratory stressors, including challenging computer tasks, mental arithmetic, electrical shocks, loud noise, unsolvable puzzles, graphic films depicting combat surgery, marital discussions involving conflict, and interviews eliciting the recollection of positive and negative experiences and mood states (for a recent review, see Kiecolt-Glaser et al., 1992). Exposure to these tasks has been shown to evoke a variety of enumerative immune changes; the most consistent findings include increases in the numbers of circulating NK cells and T-suppressor/cytotoxic lymphocytes, and a decrease in the ratio of T-helper to T-suppressor cells (primarily as a function of augmented T-suppressor lymphocytes, rather than altered T-helper cells) (Bachen et al., 1992; Brosschot et al., 1992; Naliboff et al., 1991). Most of these studies failed to demonstrate significant stress-induced changes in numbers of total T-lymphocytes, T-helper lymphocytes, or B cells (Brosschot et al, 1992; Manuck et al, 1991; Naliboff et al, 1991).

In studies examining changes in percentages of lymphocyte subsets, rather than absolute numbers, findings are mixed. Some investigations have shown significant shifts in the proportions of circulating immune cells (Naliboff et al., 1991), whereas others have failed to detect such changes (Knapp et al, 1992; Sieber et al, 1992; Weisse et al, 1990).

Changes in functional measures of immunity, including diminished lymphocyte mitogenesis (Bachen et al, 1992; Knapp et al, 1992; Manuck et al, 1991; Weisse et al, 1990; Zakowski et al, 1992) and altered NK cell activity (Naliboff et al, 1991; Sieber et al, 1992) also occur following exposure to brief psychological stress. The specific effects of acute stress on NK cell activity are less clear, and studies have demonstrated increases as well as decreases in this parameter (Naliboff et al, 1991; Sieber et al, 1992). It is possible that the different task characteristics employed by these experiments may have accounted for the discrepant findings. Naliboff et al (1991) observed increases in NK cell activity following active attempts to perform a mental arithmetic task, whereas Sieber et al (1992) found reduced NK cell activity following passive exposure to uncontrollable bursts of loud noise. Because active coping strategies frequently accompany sympathetic arousal, it is possible that enhanced sympathetic activation associated with effortful attempts to perform well on mental arithmetic may have resulted in the increased NK cell activity observed by Naliboff et al.; indeed, the infusion of catecholamines have previously been shown to elicit increases in NK cell activity in humans (Buske-Kirschbaum et al, 1992).

The appearance of immunological changes in response to acute psychological stress is rapid, occurring as early as 5 minutes from stressor onset (Herbert et al, 1994). Increases in NK cell and T-suppressor/cytotoxic lymphocytes return to baseline levels by 15 minutes after stressor termination (Brosschot et al, 1992). The immediate effects of short-term stressors may not necessarily reflect

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longer-term changes seen during exposure to naturalistic stressors, which are of more chronic duration. Whereas acute stressors elicit immediate elevations in NK and T-suppressor/cytotoxic cell numbers, naturalistic stressors tend to be associated with reductions in these cell types (Herbert & Cohen, 1993) The reasons for these discrepancies are not yet clear, but may reflect complex differences in the hormonal environment surrounding immune cells (Herbert & Cohen, 1993). Interestingly, long-term sympathetic activation, induced by the drug terbutaline, results in a similar reduction of circulating T-suppressor/cytotoxic lymphocytes and NK cells in humans (Maisel et al., 1990)

In contrast to quantitative alterations, reductions in lymphocyte proliferation persist up to at least 90 minutes after stressor termination (Weisse et al , 1990; Zakowski et al., 1992). With respect to NK cell activity, decreases persist as much as 72 hours after the exposure to laboratory stress (Sieber et al., 1992). As the authors note, it is not yet known if these changes represent a sustained decrease in NK cell function or a conditioned response elicited by a return to the laboratory setting

The aforementioned studies also suggest that immune changes elicited by short-term mental stress may be modulated by sympathetic activation. First, the rapid appearance of lymphocytic changes during mental stress makes it unlikely that other, slower-responding hormones (e.g. cortisol) are contributing to the effects. Indeed, two studies found immune alterations in the absence of concomitant cortisol responses to the stressors (Manuck et al., 1991). Zakowski et al (1992) reported enhanced cortisol levels following exposure to a stressful film, but found that proliferative reductions preceded the cortisol response by 30 minutes. Secondly, infusion of catecholamines invoke functional and enumerative immune alterations that are similar to those seen during acute mental stress (van Tits et al , 1990). Finally, only those subjects with the most pronounced sympathetic activation in response to laboratory stressors display suppression of mitogenic stimulated lymphocyte proliferation (Manuck et al , 1991; Zakowski et al , 1992).

Laboratory manipulations of mood states are similarly associated with increased sympathetic arousal and altered immune function. Knapp et al. (1992) reported that decreased proliferation during interviews eliciting negative mood states were related to increases in heart rate ($r = .56$) In addition, the tendency for NK cell activity to rise was also associated with increases in heart rate ($r = .51$), as well as systolic blood pressure ($r = .49$) Interestingly, Knapp et al (1992) observed decreases in lymphocyte proliferation during the induction of both positive and negative mood states; such findings are consistent with a catecholamine-mediated hypothesis, since both positive and negative emotions have been linked to elevations in urinary levels of catecholamines (Levi, 1972).

Overall, experimental studies indicate that psychological stressors of a short-term nature elicit reliable and transient alterations in immune cell numbers and function While functional immune

changes following acute stress are similar to those accompanying chronic naturalistic stress, the direction of quantitative changes in some lymphocyte subpopulations differ in the two forms of stress Whereas increases in NK cell and T-suppressor/cytotoxic lymphocytes are typically seen following laboratory stressors, decreases in these cell types occur during chronic stress. Studies assessing indices of sympathetic activity through cardiovascular and catecholamine responses to stress offer compelling evidence for the role of the sympathetic nervous system in at least some of these immune modifications

IMPLICATIONS

Stressors of various types do induce a wide range of immunological alterations in humans. It is through such changes in immune system functioning that stressors may ultimately be linked to subsequent disease. Before these firm conclusions can be reached, however, several remaining gaps in our knowledge of stress–immune–disease relationships must be empirically addressed. One of the foremost gaps concerns the clinical significance of observed immunological alterations. It is not yet clear that either the nature or magnitude of immunological change found in PNI research bears any relevance to increased disease susceptibility Indeed, immune responses of stressed persons generally fall within normal ranges (Rabin et al , 1989) Furthermore, the immune system is complex and one or even several measures of immune function may not provide an adequate representation of host resistance (Palmblad, 1981) Finally, stress-related changes in immune parameters may not be linked to disease in a straightforward manner. For instance, a decrease in one parameter could result in an increased risk for one type of disease (i e. acute viral infections), but decreased risk for another (i.e. autoimmune disease) (Irwin, Daniels & Weiner, 1987)

It is also possible that a number of other variables, such as age and genetic factors, interact with stress exposure and immune response to determine health outcomes. It is well known, for instance, that ageing, itself, is associated with a decline in immune function, as indicated by decreases in the proliferative response to mitogens, natural killer cell activity, antibody production, and phagocytic activity (for a discussion, see Scapagnini, 1992). Stress-related immune alterations may have more important consequences for individuals with already compromised immune systems, such as the elderly or those with autoimmune disorders or HIV-infection (Kiecolt-Glaser & Glaser, 1987).

Over the last 20 years, PNI research has made great strides in establishing links between psychological stressors and altered functioning in the immune system This remains one of the most promising pathways through which stress may alter host resistance to disease onset or exacerbation. Carefully designed prospective studies, measuring all three aspects of the stress–immune–disease model are needed to more fully understand these associations

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