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Psychoneuroimmunology

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Introduction

Stressful life events have been linked to a range of immune-related disorders, including autoimmune diseases, infectious diseases and cancer. Some of the most compelling evidence for stress and disease associations stems from viral challenge studies, in which volunteers are exposed to a cold or influenza virus and then monitored in quarantine for the development of infection and illness. These studies find that individuals with more life stress, as measured by a higher number of recent stressful life events, higher perceived stress and more negative affect are more likely to develop colds than individuals with lower levels of stress (Cohen *et al.*, 1991), and that stressful events lasting a month or more are better predictors of developing colds than those of a briefer duration (Cohen *et al.*, 1998). In addition, individuals who are more sociable and have a diverse social network are less likely to develop a cold (Cohen *et al.*, 2003; Cohen *et al.*, 1997), possibly because such factors may be able to decrease the frequency of stressful life events or buffer deleterious effects of stress.

In addition to disease outcomes, stressful life events may also delay the healing of wounds. Recent studies have shown that long-term care givers who were caring for a severely ill family member experienced greater emotional distress and took nine days longer to heal a dermal punch biopsy wound than age- and income-matched controls (Kiecolt-Glaser *et al.*, 1995). Similar findings were observed in dental students, whose punch biopsy wounds healed 40% more slowly during an examination period than during vacation (Marucha *et al.*, 1998). Such decrements in wound repair may have important implications with regard to surgical recovery and clinical wound repair. Broadbent *et al.* (2003) found that in patients undergoing a hernia operation, those with greater perceptions of stress and worry prior to operation had a more painful, poorer and slower recovery. Among patients at a wound clinic, Cole-King & Harding (2001) found that the healing of leg ulcers was delayed in individuals with higher levels of anxiety and depression (see also 'Life events and health' and 'Stress and health').

Potential mechanisms linking stress and immune disease

One means by which stress may lead to increased susceptibility to disease is by altering the function of the immune system. This hypothesis is one of the central concerns of the field of psychoneuroimmunology (PNI) which attempts to elucidate the relations between psychosocial factors, nervous, endocrine and immune

Table 1. Cells of the immune system

Cell type	Function
White blood cells (WBCs)/Leukocytes	Respond to antigens such as bacteria or viruses and altered host cells such as tumour or infected cells; 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

systems and health. How stress may influence the immune system is not entirely clear. Stress may alter 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. Sympathetic nerve fibres innervate lymphoid organs, and immune cells, which migrate between lymphoid organs and the peripheral bloodstream, contain receptors for numerous hormones and neurotransmitters that are produced during stress (Plaut, 1987).

In PNI research, the most commonly measured component of the immune system is the immune cells, which are collectively 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.

Leukocytes also produce substances called cytokines. Cytokines which are produced by a subset of T-helper cells, called Th1 cells, include IL-2, TNFβ and INFγ. These cytokines selectively activate T-cytotoxic cells and NK cells and thus promote cellular immunity. Cytokines produced by Th2 helper-cells include IL-4, IL-5, IL-6 and IL-13; they selectively activate B-cells and induce antibody production, thus promoting humoral immunity. For a description of measurements of immunocompetence in PNI research see the chapter on 'Psychoneuroimmunology assessments'.

Psychological stress and immunity

A substantial literature in both humans and animals supports associations between immunologic changes and psychological and physical forms of stress (for a recent review, see Segerstrom & Miller, 2004). While the most frequently reported consequence of stressful events is the suppression of immune responses, other research suggests that some forms of stress may be able to both enhance and suppress aspects of the immune response by altering patterns of cytokine secretion (Marshall *et al.*, 1998). Because the cytokines of Th1 and Th2 cells antagonize each other, a suppression of one response may result in enhanced production of the other.

Naturalistic stressors and immunity

Academic stressors

Some of the most commonly examined stressors in relation to immunologic status have been examinations and other forms of academic stress. 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 changes in cytokine production (Kennedy *et al.*, 1988; Marshall *et al.*, 1998). Increased levels of circulating antibodies to Epstein–Barr and other herpes viruses have also been observed during examination periods, indicating, perhaps, the reactivation of latent virus by either direct neuroendocrine influences or weakened immunocompetence.

Several studies have found that some individuals are more susceptible to immune alterations during exams than others. For example, the largest immunologic changes were found to occur in students with the highest levels of overall life stress, anxiety, loneliness or tendency to ruminate about stressful events (Glaser *et al.*, 1992; Kiecolt-Glaser *et al.*, 1984; Marshall *et al.*, 1998; Workman & La Via, 1987). Personality styles associated with greater positive affect and adaptive coping strategies may attenuate stress-related immune alterations. Segerstrom *et al.* (1998) observed that optimistic first-year law students had higher levels of T-helper cells and NK cell cytoxicity during their first semester of law school than did pessimistic students (see 'Personality and health').

While most studies support an effect of immune suppression from examination stress, other recent findings suggest that exams and other brief naturalistic stressors may increase Th2 cell-mediated humoral immunity and macrophage activity, and concurrently decrease Th1 cell-mediated cellular immunity. In a recent meta-analytic review of the PNI field, Segerstrom and Miller (2004) found that examinations are often associated with increases in IL-6 and IL-10, and decreases in IFN-γ. The decreased Th1 cytokine production is consistent with observed decreases in T-cell proliferative responses and NK cell activity, and increased antibody production to latent viruses. It is also possible that an increase in humoral activity during stress might contribute to an increased incidence of type-2-mediated conditions, such as allergic/asthmatic reactions and heightened autoimmune activity (Marshall *et al.*, 1998).

Bereavement

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 sub-populations. Early investigations found lowered mitogenic lymphocyte proliferation in bereaved subjects following the loss of a spouse (Bartrop *et al.*, 1977) and that the degree of immune change was related to the severity of depressive response before and after the loss (Irwin *et al.*, 1987). In men infected with the human immunodeficiency virus (HIV), the death of an intimate partner or close friend has been found to result in lowered NK cell activity and proliferative responses to PHA compared with nonbereaved, HIV-infected men (Goodkin *et al.*, 1996; Kemeny *et al.*, 1995). Findings relating bereavement to numbers of T-helper (CD4) cells in HIV-positive men have been mixed, with some studies showing no relationship (Goodkin *et al.*, 1996; Kemeny *et al.*, 1995), and others linking bereavement to an enhanced CD4 decline (Kemeny & Dean, 1995) (see 'Coping with bereavement').

Separation, divorce and marital conflict

Separation, divorce and marital conflict 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 (see Kennedy *et al.*, 1988). Higher antibody levels to latent viruses were also found in separated or divorced men and couples reporting poorer marital quality (Kennedy *et al.*, 1988). Finally, studies from this research group have found that marital conflict that includes hostile interactions may evoke fairly persistent immune changes, even when couples report being happily married (Kiecolt-Glaser *et al.*, 1993; Kiecolt-Glaser *et al.*, 1997). In a study of newly-wed couples, those who exhibited more hostile or negative behaviours during a brief conflict resolution task were found to exhibit greater declines in functional immune measures 24 hours later (Kiecolt-Glaser *et al.*, 1993). Similar results were found in couples who had been married an average of 42 years (Kiecolt-Glaser *et al.*, 1997).

Other prolonged stressful events

Immunologic changes accompany other prolonged stressors, as well, such as long-term unemployment, occupational stress and care giving for a terminally ill patient. In an examination of the immune-related effects of care giving 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 titers to Epstein Barr virus (Kiecolt-Glaser *et al.*, 1987). In addition, care givers demonstrated lower antibody responses to both influenza virus and pneumococcal pneumonia vaccines compared with age-matched controls (Glaser *et al.*, 2000; Kiecolt-Glaser *et al.*, 1996; Vedhara *et al.*, 1999). In two of these studies, fewer care givers achieved the four-fold increase in antibody titre (used as a marker of vaccination success) than did controls (Kiecolt-Glaser *et al.*, 1996; Vedhara *et al.*, 1999). Given the increased morbidity and mortality among the elderly after exposure to influenza viruses, such findings may be of clinical importance. Finally, there is evidence that chronic stress and depression may contribute to the greater production of cytokines (Anisman & Merali, 2002) or a dysregulated cytokine response to vaccination (Glaser *et al.*, 2003). Higher levels of plasma IL-6 were observed in a group of care givers compared to individuals who were anticipating a housing relocation or community controls (Lutgendorf *et al.*, 1999). In older adults receiving an annual influenza vaccination, those with more depressive symptoms showed an increase in plasma IL-6 by two weeks after vaccination, whereas there was little change in adults reporting few or no symptoms of depression. Such findings suggest that depressed mood may be related to an amplified and prolonged inflammatory response after vaccination (Glaser *et al.*, 2003).

Both job stress and long-term unemployment have been linked to lowered lymphocyte reactivity to PHA (Arnetz *et al.*, 1987). In contrast to stress and burnout at work, a high sense of personal accomplishment at work may be associated with higher numbers of peripheral lymphocytes, particularly T-cell subsets (Bargellini *et al.*, 2000).

Traumatic events

Fewer studies have examined immunologic changes associated with exposure to extreme traumatic stressors, such as natural disasters, and accidental and deliberate man-made traumatic events. Such studies, however suggest that immune alterations may persist for long periods of time, particularly if symptoms of rumination, anxiety or post-traumatic stress disorder (PTSD) result. In an early study, persistent distress over the nuclear accident at Three Mile Island was associated with higher latent antibody levels and enumerative immune alterations in community residents more than six years after the accident (McKinnon *et al.*, 1989). Symptoms of PTSD were also related to lower NK cell cytotoxicity in residents of neighbourhoods that were damaged by Hurricane Andrew and this effect appeared to be mediated by the development of sleep disturbances associated with the trauma (Ironson *et al.*, 1997).

Two studies have investigated immune alterations in released male prisoners of war and women living in a refugee camp during the Bosnian and Croatian wars (Dekaris *et al.*, 1993; Sabioncello *et al.*, 2000). Both studies found higher numbers of activated lymphocytes in these individuals, compared with laboratory staff controls, along with an increase in proliferating lymphocytes in the female refugees (Sabioncello *et al.*, 2000). Although neither study included assessments for PTSD, other research suggests that the development of PTSD following war and other catastrophic events may be associated with elevated serum IL-6 and IL-1β concentrations (Maes *et al.*, 1999; Spivak *et al.*, 1997), and NK cell activity (Laudenslager *et al.*, 1998). In addition, there is preliminary evidence that veterans with current PSTD or anxiety mount greater cutaneous delayed hypersensitivity test reactions than do veterans without PTSD, suggesting that exposure to disasters and the development of PTSD may be associated with enhanced cell-mediated immunity (Boscarino & Chang, 1999). Despite the methodological

difficulties in this area, these findings remain interesting because they counter evidence that chronic stress suppresses immune functions. These disparate results may be due, in part, to a dysregulation of the HPA axis in PTSD, whereby persistent activation of the HPA axis and enhanced negative feedback of this system lead to lower plasma and urinary cortisol concentrations (Yehuda *et al.*, 1990).

Taken together, most studies involving stress and immunity indicate that psychological stressors are associated with changes in immune functions. The most consistent alterations include reduced NK cell activity and lymphocyte proliferation to PHA and Con A, and increased antibody levels to latent herpes viruses. Changes in percentages or absolute numbers of lymphocyte populations are also frequently reported stress-related immune responses, although these changes are weaker and not as reliable across studies (Segerstrom & Miller, 2004). Preliminary studies also suggest that brief forms of stress may lead to cytokine changes that promote a shift from cellular (Th1) immunity to humoral (Th2) immunity and that traumatic events such as disasters might be linked to enhanced immune function, perhaps in the context of post-traumatic stress disorder and diminished cortisol levels.

Short-term laboratory stressors and immunity

During the last decade, many laboratory studies have been conducted to examine stress-immune interactions. Such investigations are advantageous because they approximate the effects of transient daily life stressors and provide a means to investigate potential endocrine mechanisms underlying associated immunological changes. A number of standardized laboratory stressors have been used in these experiments, including challenging computer tasks, mental arithmetic, electrical shocks, loud noise, unsolvable puzzles, graphic films depicting combat surgery, marital discussions involving conflict and mood manipulation tasks. Exposure to these stressors has been shown to evoke a variety of enumerative immune changes, the most consistent of which are 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. Decreases in lymphocyte mitogenesis and increased NK cell activity are also commonly reported (for a review, see Kiecolt-Glaser *et al.*, 1992). Less is known about cytokine responses to acute psychological stressors, but preliminary reports indicate that such tasks can evoke increases in serum levels and mitogen-induced production of certain cytokines, such as IL-6 and TNF-α (Kunz-Ebrecht *et al.*, 2003; Steptoe *et al.*, 2001), although negative findings have also been reported (Heesen *et al.*, 2002).

The data suggest that most of the immunologic changes following acute stress are rapid and transient, occurring as early as 5 minutes from stressor onset (Herbert *et al.*, 1994). One exception to this rapid response may be stress-induced alterations in serum cytokine levels, which, in some cases, may not be detectable until 45 minutes post-stress (Kunz-Ebrecht *et al.*, 2003; Steptoe *et al.*, 2001). The duration of immunological reactions to acute mental stress may also depend on the parameter in question. Changes in cell redistribution return to baseline within 15 minutes of stressor termination (Brosschot *et al.*, 1992), whereas changes in immune function may persist for at least 90 minutes after challenge (Zakowski *et al.*, 1992).

There is now a great deal of evidence that acute immune responses to psychological stress are largely mediated by activation of the sympathetic nervous system. The most direct evidence for sympathetic mediation is derived from the observation that changes in cellular immune function under stress are ameliorated by the prior administration of an adrenoceptor antagonist (Bachen *et al.*, 1995). Consistent with these findings, studies have also shown that individuals who demonstrate the greatest sympathetic reactions to brief mental stress (as indicated by heightened cardiovascular and catecholamine responses) also produce the greatest immunologic changes (Manuck *et al.*, 1991).

The extent to which individuals differ in their sympathetic, endocrine and immunological responses to stress may have implications for their susceptibility to stress-related illnesses. Recently, investigations have demonstrated that sympathetic and immunologic reactions to brief psychological stress may predict antibody responses to vaccines. Marsland *et al.* (2001) found that medical students who demonstrated the greatest decline in lymphocyte proliferation to PHA following laboratory stress also had the poorest antibody response to a hepatitis B vaccination programme. Cacioppo (1994) also found that sympathetic activation predicted response to an influenza vaccination, with a measured T-cell response declining more quickly in individuals who showed greater cardiac sympathetic activation following a mental task. Similarly, Burns *et al.* (2002) found that individuals who responded to acute stress with a larger cardiac output (reflecting heightened cardiac activation mediated by beta-adrenergic processes), exhibited lower antibody titres to hepatitis B vaccination, compared with those demonstrating a smaller cardiac output. How concominant changes in other stress-related substances, such as cortisol may influence antibody responses to vaccines is currently unclear, but it is noteworthy that positive relationships between the magnitude of sympathetic and cortisol responses to acute stress have been reported (Cacioppo *et al.*, 1994).

Implications and future directions

Stressors of various types do induce a wide range of immunologic 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 gaps in our knowledge of stress-immune-disease relationships must be empirically addressed. Apart from the experimental studies on susceptibility to colds and wound healing in the PNI field, few studies have measured health outcomes. For example, no studies examining the effects of stress on antibody responses to vaccines have included an assessment of vaccine efficacy in terms of disease incidence and severity (Burns *et al.*, 2003). The importance of measuring health outcomes is highlighted by the fact that immune responses of stressed persons generally fall within normal ranges and thus it remains unclear if the nature and magnitude of immunologic change found in PNI research bears relevance to increased disease susceptibility.

Additional research that focuses on populations that may be most susceptible to the influence of stress is also needed. Older people are known to have greatly increased morbidity and mortality from infectious illness and immune alterations

associated with ageing include decreases in proliferative responses to mitogens, natural killer cell activity, antibody production and phagocytic activity (Scapagnini, 1992) as well as increases in IL-6 production (Cohen, 2000). 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).

There is little empirical evidence defining the roles of health behaviours and other mechanisms in evoking immunologic changes to stress. Preliminary evidence indicates that sleep disturbances following stress may play an important mechanistic role (Ironson *et al.*, 1997). Interactive effects between health practices and other variables may also be important to consider, especially for behavioural changes that are moderate. For example, Jung *et al.* (1999) found that mild to moderate levels of cigarette smoking were associated with lower NK cell activity, but only in individuals who were also depressed. Further research on neuroendocrine influences on immune alterations during naturalistic stress is also needed, but is complicated by regulatory processes that accompany prolonged stress, such as negative feedback systems, receptor down-regulation and shifts in circadian rhythms. Despite these complexities, naturalistic studies do suggest that both the sympathetic nervous system and HPA axis play important roles in modulating immune function during stress (Burns *et al.*, 2002; Goodkin *et al.*, 1996; Mckinnon *et al.*, 1989; Vedhara *et al.*, 1999).

In conclusion, during the last 30 years, PNI research has made great strides in identifying relationships 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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