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REVIEW

EMOTION AND IMMUNITY

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Abstract—Earlier studies have suggested that depression is associated with decreased immune function, but a recent literature review has revealed that a majority of studies reached inconsistent or conflicting conclusions. On the other hand, studies on immune function in anxiety disorders are sparse, and their findings are also inconsistent. Despite a few contradictory results, a clinical level of anxiety seems to reduce immune function, whereas a subclinical level of anxiety seems to enhance immunity. The latter may be a transient phenomenon occurring prior to the downregulation of immune function, reflecting the body's defense to a stressor. Thus, research needs to be conducted to elucidate the relationship between those hormones related to hypothalamic–pituitary–adrenal axis and a variety of immune measures at the subclinical level of anxiety. In addition, to confirm the interaction between emotion and immune function, the effectiveness of treatment with medication and psychotherapy on immunity should be investigated. © 1998 Elsevier Science Inc.

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INTRODUCTION

Some studies indicate that anxiety and depression are associated with disease recurrence in patients with genital and oral herpes [1]. Emotional factors (e.g., depression) are thought to play a role in numerous diseases, including Graves disease, rheumatoid arthritis, systemic lupus erythematosus, asthma, and diabetes [2].

Psychosocial factors associated with decreased immune responsiveness produce states of arousal, anxiety, and negative affect [3–7]. These psychological states have been linked to increased neural activity in limbic circuits involving the amygdala and the hippocampus (arousal and anxiety) [8, 9], as well as to imbalances in neocortical activity favoring the right hemisphere(negative affect) [10–12].

It has been suggested that an emotional state, such as anxiety and depression, could play a key role in triggering immune alterations [13, 14]. Theoretically, it can be assumed that negative events (stressors) lead to negative affective states (distress), consequently producing alterations in human immunity [13]. However, mild, brief, and controllable states of challenged homeostasis could actually be perceived as pleasant or exciting, and could be positive stimuli for emotional and intellectual growth and development. The immune response has also been reported to be enhanced when the stressful condition is mild to moderate in intensity [15]. Thus, it is likely to be the more severe, protracted, and uncontrollable situations of psycho-

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logical and physical distress that lead to overt disease states [16], apparently resulting from immunosuppression.

Immunosuppression has been reported in human subjects who experience symptoms of anxiety and depression in response to situations such as examinations, bereavement, separation, and divorce [17–23]. In animals, immunosuppression has also been demonstrated in response to a variety of stressors [15, 17, 24].

The relationship between emotion and the hypothalamic–pituitary–adrenal (HPA) axis has been studied extensively. Dysregulation of the HPA axis is the best documented example of a neurobiological abnormality in depresson. The main findings have been an elevation of cortisol levels, often during the night [25, 26], and a relative resistence of cortisol suppression to dexamethasone administration [26–28]. Thus, hypercortisolemia has been suggested as a possible explanation for reduced immune function in depressed individuals. However, dissociation between the HPA axis and immune function has been reported in depression, with the suggestion that corticotropin-releasing hormone (CRH) and corticoid hypersecretion are not directly responsible for immunosuppression in affective disorders [29, 30].

An anxiety disorder such as panic disorder is accompanied by an activation of the HPA axis, which seems to correlate with the degree of anxiety experienced by the patients. On the other hand, the decrease of anxiety after alprazolam therapy occurs in concert with the normalization of the HPA axis function [31]. In panic disorder, however, there may be a dissociation between HPA axis and immune systems. This hypothesis is reinforced by the observation that administration of CRH with the ensuing ACTH-cortisol hypersecretion failed to modify the lymphocyte proliferative response to PHA [31].

Several methods have been employed to obtain quantitative indices of an individual's immune responsiveness [3, 7, 32–35]. The most frequently used methods include quantification of T-helper and T-suppressor lymphocyte subpopulations; measurement of the ability of lymphocytes to synthesize and release lymphokines; quantification of T-lymphocyte proliferation in response to mitogens such as phytohemagglutinin (PHA), pokeweed mitogen (PWM) and concanavaline A (Con A); quantification of the cytotoxic activity of natural killer cells and other lymphocytes; measurement of total immunoglobulin levels; and measurement of specific antibody titers.

Recently, several prospective studies have addressed the question of whether emotions are accompanied by reduced immune responsiveness [1]. These studies have initiated the following review on the relationship between emotion and immunity.

DEPRESSION AND IMMUNITY

Many studies suggest that, compared with normal controls, patients with depression show reduced immune function in a variety of immune measures. Clinically significant levels of depression are associated with poorer immunocompetence in psychiatric populations. For example, in-patients suffering from depression have a poorer blastogenic response than nondepressed controls [36, 37]. Depressed patients have also been shown to have a lower percentage of helper T-lymphocytes than nondepressed controls [38]. Kronfol et al. [39] reported in their study on lym-

Table I.—The results of the studies on immune functions in depressive disorders compared with normal controls (1978–1990)

	Total number of lymphocytes ($N = 8$)	Lymphocyte response to PHA, Con A, and PWM ($N = 14$)	NK cell activity ($N = 7$)
Increased	0	1	0
Not changed	6	7	2
Decreased	2	6	5

phocyte proliferative response in unmedicated depressed patients that these patients showed markedly reduced responsiveness to PHA, PWM, and Con A when compared with normal controls. It was reported that, when compared with normal controls, major depressive disorder was independently associated with a 50% reduction of natural killer (NK) cytotoxicity [40]. Men troubled by chronic and severe depression over a 2-year period demonstrated a sharper decline in CD4 cells than nondepressed men [41]. However, Schleifer et al. [42] noted that mildly depressed out-patients showed normal immune parameters.

The degree of immunosuppression may be related to the severity of the depression in depressive disorders [37]. Lymphocyte responses to PHA and PWM in patients with melancholic and psychotic depression were significantly lower than those with minor depression [29]. When compared with patients having nonmelancholic depression, patients with melancholia demonstrated reduced *in vivo* cell-mediated immunity as assessed by delayed-type hypersensitivity skin responses [43]. On the other hand, Kemeny [41] found that higher levels of depressed mood were associated with lower numbers of CD4 cells and increased expression of activation markers in lymphocytes in nonbereaved men, but not in bereaved men. These findings suggest that higher depression scores may represent different processes of grief in the bereaved and depressed mood in the nonbereaved, and that the two processes may have different immunological correlates.

In contrast to these findings of immunosuppression in the early studies, immune changes in depressive disorders have not always been clear-cut [44]. A review of the previous studies on depression and immunity [44] (Table I) suggests that, in general, when immune function was assessed by total number of lymphocytes [42, 45–51], lymphocyte proliferative responses to mitogens [19, 49, 50, 52] such as PHA, Con A, and PWM, and NK cell activity [40, 50, 53–55], patients with depressive disorders showed either a decrease or no change in comparison to healthy subjects. Only one study found an increased blastogenic response to PHA [56].

It has been recently reported that depression may be related to a systemic immune activation [57, 58], as indicated by an increase in several lymphocyte subsets, including CD3, CD8, $CD4^+$ CD45RA (memory T-helper cells), and $CD25^+$ [59, 60]. These effects tended to be particularly pronounced when the depression involved melancholia [58]. In another study, major depression and dysthymia were also found to be associated with an increase in the number of NK cells in blood [61]. The increased number of lymphocytes in these depressed patients is likely to represent a change in cell-trafficking patterns stemming from the increased perception of stressors [62].

Moreover, interleukin-1β, which influences CRF secretion, was shown to be in-

creased in depression. Positive relationships between increased IL-1β or IL-6 production and postdexamethasone HPA axis activity were also found in depression [63]. Thus, it was suggested that these cytokines may contribute to the altered HPA functioning associated with depression [64].

As shown in the aforementioned results, the inconsistent findings seem to stem from subtypes of depression (uni- and bipolar) or severity of illness, as well as from the age differences of subjects [14, 58, 65].

It has also been reported that symptom remission may abrogate reduced NK cell activity associated with major depression [66]. On the other hand, antidepressants such as specific serotonin reuptake inhibitors appeared to promote a return of NK cell number to control levels. However, it is likely that antidepressant effectiveness may be related to the subtype of depressive disorder. In particular, it is of interest that, although both major depression and dysthymia were successfully treated with antidepressants, different durations of treatment were required for NK cell numbers to return to control values. In other words, dysthymic patients required a more prolonged period than major depressive patients. Thus, in assessing the relationship between depression and immune status, it is necessary to recognize not only the severity of the illness, but also the duration of the illness and the age of onset.

The experimental designs of a majority of the studies reviewed involved comparison of depressed subjects with healthy individuals, matched for relevant characteristics, such as age, gender, ethnic background, and medication status. These design requirements were often not feasible, and serious confounding variables were introduced into the research [44]. Future studies investigating psychosocial influences, such as depression on immunocompetence, will require more clinically relevant and specific immune measures [44].

LONELINESS AND IMMUNITY

Loneliness is also a construct related to depression. In separate studies, both medical students [32] and psychiatric patients suffering from loneliness [67] have been shown to have lower NK activity. Kiecolt-Glaser et al. [32, 67] assessed lymphocyte responses to PHA and PWM activity and reported that a subgroup of patients with high scores on the UCLA Loneliness Scale showed confluence of hypercortisolism, reduced lymphocyte responses to PHA, and decreased NK cell activity.

In a prospective study [68] that examined the influence of loneliness on herpes virus latency in medical students, those with a higher degree of loneliness had significantly higher Epstein–Barr virus antibody titers than those with a lower degree of loneliness. These data suggest that loneliness-related immunosuppression can significantly modulate herpes virus latency.

ANXIETY AND IMMUNITY

Whereas there are numerous immunological studies on depression, studies that examine the relationship between anxiety and immunity are sparse. Recurrent lesions of genital herpes were preceded by higher levels of anxiety and a concomitant blunting of T-cell blastogenesis [69]. In another study, lymphocyte response was

found to correlate negatively with anxiety among hospitalized patients [70]. In a recent study [71], untreated patients with anxiety disorders showed significantly reduced lymphocyte proliferative response to PHA, and reduced PHA-induced interleukin-2 (IL-2) production, when compared with normal controls. However, no significant difference was found in NK cytotoxicity between both groups. The results suggest a reduced cell-mediated immune function in patients with anxiety disorder compared with normal controls, and also a possible interaction between the immune system and anxiety. The findings also suggest that it is imperative that a variety of immune measures are assessed at the same time, when conducting psychoneuroimmunology research. In one study, however, no significant difference in lymphocyte proliferative response to mitogen stimulation was observed between panic patients and healthy controls [72].

It has been reported that subclinical anxiety may be related to decreased cell-mediated immunity. One study found lowered salivary immunoglobulin A (IgA) levels in those who suffered from anxiety when compared with nurses without anxiety [73]. Similar findings in dental students have also been reported [33]. In addition, when compared with less anxious subjects, those with higher anxiety levels had a significantly lower lymphocyte proliferative response to mitogen Con A as well as lower levels of circulating interleukin-1β [74].

On the contrary, a few studies suggest that anxiety can be associated with increased immune function. Preliminary studies reported that anxiety may be associated with immune changes opposite to those found with depression [50, 75], indicating increased immune function in anxiety. In addition, scores on the SCL-90-R anxiety subscale, during an examination period in medical college students, showed a significant positive correlation with NK cell activity [76]. Recently, in another study [77], a significant positive correlation was also observed between scores on the SCL-90-R anxiety subscale and IL-2 production in medical college students 2 weeks before examination. These findings suggest that subclinical anxiety may be associated with increased immune function [76], as opposed to a clinical level of anxiety. Such immune enhancement in subclinical anxiety may be considered a transient phenomenon occurring prior to the downregulation of immune function, indicating the body's defense to a stressor. Thus, these inconsistent but noteworthy findings suggest that these studies need to be replicated to find out whether subclinical anxiety may be different from a clinical level of anxiety in its impact on immune parameters. Very little has been reported on the effects of antianxiety medication and psychotherapy on immunity in anxiety disorder patients. These studies should be conducted to confirm the interaction between anxiety and immunity.

HUMOR AND IMMUNITY

Although the relationship between humor and immune function is an interesting topic, there is limited research available. According to one study, salivary IgA concentration increased significantly after subjects viewed a humorous videotape but did not change significantly after viewing a didactic videotape [78]. Thus, enhancement of the immune system could be one link between anecdotal claims of the relationship between positive emotional state and healing.

LIMITATION IN RESEARCH ON THE RELATIONSHIP BETWEEN EMOTION AND IMMUNITY

The existing literature is highly controversial and fraught with methodologic problems. These problems limit the interpretation and the generalizability of most of the studies. The limitations include diagnostic heterogeneity, sample size, control group composition, and assay techniques [44]. In particular, diagnostic heterogeneity is a potential confounding element that interferes with the attempts to evaluate this body of research.

The sample sizes were small in a majority of the studies, and most did not include age- and gender-matched controls [44]. As there may be age-associated alterations [79] and gender-specific differences [80] in immune function, these factors must be considered in this kind of research.

On the other hand, emotions may lead to unhealthy behaviors that could secondarily impair immunity. If anxiety or depression lead to increased smoking, excessive drinking, drug abuse, disturbed sleep, poor nutrition, or other destructive behavioral changes, then these behaviors themselves may affect NK cell activity, rather than the direct influence of psychological symptoms [1]. In addition, depression-related anorexia, weight loss, and malnutrition, as well as insomnia, may cause impairment of immunity [80–86].

CONCLUSION

Earlier studies have suggested that depression is associated with immunosuppression, but a recent literature review has revealed that many studies reached inconsistent or conflicting conclusions. Few studies have investigated the relationship between anxiety and immunity, in contrast to the numerous immunological studies on depression. Despite a few contradictory reports, a clinical level of anxiety seems to reduce immune function, whereas a subclinical level of anxiety seems to enhance immune function. The latter may be a transient phenomenon occurring prior to the downregulation of immune function, indicating the body defense to a stressor. Thus, research needs to be conducted to elucidate the relationship between the hormones involved in the hypothalamic–pituitary–adrenal axis and a variety of immune measures at the subclinical level of anxiety. In particular, when assessing the relationship between emotion and immune status, it is necessary to recognize not only the severity of the illness, but also the duration of the illness. In addition, the effectiveness of treatment with medication and psychotherapy on immunity should be investigated to confirm the interaction between emotion and immune function.

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