Stress and Immunity: Age Enhances the Risks

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Abstract

A competent immune response is central to good health. There is good evidence that both aging and psychological stress can dysregulate immune function, resulting in changes in various aspects of the immune response that are large enough to have consequences for health. Older adults appear to show even greater immunological impairments associated with stress or depression than younger adults. Thus, the data suggest that aging interacts with stress and depression to enhance risks for morbidity and mortality among older adults.

Keywords

stress; immune function; aging; social support

A well-functioning immune system is central to good health. The immune response serves as the primary defense against infectious disease and certain cancers. Autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis reflect dysregulations in immune function in which the immune system attacks certain of the body's own cells because it cannot distinguish self from nonself. Maladaptive immunological alterations may influence the etiology, progression, and severity of a variety of disorders and diseases, from ulcers to atherosclerosis. Wound healing, particularly the initial phases, is an immunologically mediated process. Given its centrality, it is not surprising that conditions or processes that influence immune function can have diverse consequences for health. Both aging and psychological stress are notable in this regard; we first consider their individual contributions, and then their interactive effects.

AGE AND IMMUNE FUNCTION

Certain aspects of the immune response decline with age, and there are clear health risks associated with these age-related changes. For example, although influenza is rarely fatal among healthy younger adults, pneumonia and influenza together constitute the fourth leading cause of death among individuals who are 75 years of age or older (Yoshikawa, 1983). Moreover, for each death officially attributed to influenza, there are two and a half times as many additional influenza-related deaths, primarily among people for whom heart disease or lung disease is the reported cause of death (Sprenger, Mulder, Beyer, VanStrik, & Masurel, 1993).

Other types of infection also make notable contributions to morbidity and mortality among older adults. The aging immune system is thought to be a significant factor in the increased incidence of shingles (herpes zoster) among older adults. Tuberculosis, often underdiagnosed among the elderly, has its highest incidence in individuals who are 65 and older (Yoshikawa, 1983). Diabetes mellitus, a substantial health problem among the aged, is associated with increases in a number of infectious diseases. The prostate enlargement that accompanies aging is a risk factor for urinary tract infections.

Wound infections clearly increase with age, and the elderly have a heightened risk for mortality associated with surgery, including much greater jeopardy from postsurgical infections (Yoshikawa, 1983). The fact that hospital-acquired infections are three times higher in the elderly than the general population poses a particular risk, because older adults have both more frequent and longer hospital stays than younger individuals. Rates for pneumonia, urinary tract infections, and surgical wound infections are all elevated among the elderly.

Finally, the incidence of a number of different cancers increases with age. Immune function is likely a primary defense against only a subset of malignancies; however, cancer treatments such as chemotherapy and radiation enhance the risk for infection, and treatment can also be complicated by infection. In addition, some cancers (e.g., chronic lymphocytic leukemia and multiple myeloma) are associated with pneumonia and certain bacterial infections (Yoshikawa, 1983). Thus, the functioning of the immune system clearly has notable implications for morbidity and mortality among the elderly.

PSYCHOLOGICAL STRESS AND IMMUNE FUNCTION

Evidence from the past two decades has demonstrated the re-

sponsiveness of the immune system to psychological stress. Some of the earliest work, a series of studies of medical students' responses to examinations, showed transient changes in multiple facets of the immune response (Kiecolt-Glaser & Glaser, 1991). Like most professional students, these medical students were "experts" at taking tests—they had long histories of performing well under these very conditions. The fact that something as transient, predictable, and relatively benign as examination stress had significant consequences for immune function suggested that other everyday stressors could produce similar alterations.

Subsequent work with chronic stressors provided evidence of long-term immune dysregulation. Marital studies provided provocative evidence that close personal relationships can affect physiological functioning. A laboratory paradigm was used to study hormonal and immunological responses to marital conflict in 31 older couples (mean age = 67) who had been married an average of 42 years (Kiecolt-Glaser et al., 1997). Consistent with data obtained from newlywed couples, both hormone levels and immunological function showed significant relationships to negative or hostile behavior during marital conflict in these older couples. Among wives, marital satisfaction and escalation of negative behavior during conflict showed strong relationships to changes in hormone levels, accounting for 16% to 21% of the variance in the rates of change of three stress hormones. In contrast, husbands did not show significant relationships between hormones and negative behavior or marital quality. Both men and women who demonstrated relatively poorer immunological responses across three laboratory assays displayed more negative behavior during conflict; they also characterized their usual marital disagreements as more negative than individuals who showed better immune responses. The data demonstrate that abrasive marital interactions have physiological consequences even among older adults in long-term marriages, and suggest that wives are at greater risk than husbands. In fact, the data may underestimate the actual physiological impact of marital discord, because the older couples were generally quite happy, and their marriages had endured.

A number of studies also suggest that caregiving for a family member with dementia, another persistent interpersonal stressor, can have hormonal and immunological consequences. One series of studies from our laboratory involved men and women who were providing long-term care for a spouse or parent with Alzheimer's disease; typically, such families report high levels of distress as they attempt to cope with the patient's problematic behaviors, and a variety of adverse immune changes have been associated with this stressor. For example, we assessed changes in depression, immune function, and health in 69 spousal caregivers who had already been providing care for an average of 5 years (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Between the start of the study ("intake") and follow-up 13 months later, these caregivers showed decrements relative to 69 sociodemographically matched control subjects on three measures of cellular immunity[2]; the caregivers also reported significantly more days of infectious illness, primarily upper respiratory tract infections.

Further studies from our lab and others have found additional evidence that caregivers have poorer immune function than well-matched control subjects (Kiecolt-Glaser, 1999). Moreover, the immunological dysregulation of this chronic stressor can continue at measurable levels even several years after the spouse dies and caregiving activities have ended; the persistent distress in our bereaved caregivers differs from the typical pattern of improved mood within 1 to 2 years following bereavement for noncaregivers (Kiecolt-Glaser, 1999). The fact that former caregivers continue to be more distressed than control subjects may account, in part, for the persistent maladaptive changes.

However, although the immune dysregulation can be explained by such psychosocial processes, there are also important biological processes to consider. Indeed, it is possible that the continuing immune dysregulation reflects other mechanisms. In particular, chronic stress may accelerate the process of immune dysregulation associated with aging (Sapolsky, Krey, & McEwen, 1986). Thus, chronic stressors may also serve to accelerate the aging of the immune response.

INTERACTIONS AMONG STRESS, AGING, AND IMMUNE FUNCTION: HEALTH IMPLICATIONS

Older adults appear to show greater immune dysregulation associated with stress or depression than younger adults (Herbert & Cohen, 1993; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). The immunological decrements associated with stress or depression are of particular concern because older individuals' age-related immunological impairments have important health consequences: Respiratory infections such as influenza and pneumonia are major causes of morbidity and mortality among the elderly, and many older adults do not respond to influenza virus vac-

cines as efficiently as younger adults (Burns & Goodwin, 1990). Adults who show poorer responses to vaccines also experience higher rates of illness, including influenza (Burns & Goodwin, 1990).

In one study (Kiecolt-Glaser et al., 1996), we compared response to an influenza vaccine among spousal caregivers and well-matched noncaregiving control subjects. The conventional standard for determining a significant response to a viral vaccine is a 4-fold rise in levels of antibody. By this criterion, the caregivers exhibited significant deficits in their responses compared with the control subjects: Only 38% of caregivers had responded 1 month after vaccination, compared with 66% of control subjects. However, these differences were magnified in older subjects: Among subjects younger than 70, 53.8% of the caregivers responded, compared with 75% of the control subjects, and among those older than 70, only 26.3% of the caregivers responded, compared with 60% of the control subjects. These data suggest that caregivers are more vulnerable than their age-peers to influenza virus infection and, potentially, to other infectious agents (Burns & Goodwin, 1990), with older caregivers showing the greatest risk.

Stress also alters another immunologically mediated process, wound healing (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). Aspects of the immune response play a key role early in wound healing by helping to prepare injured tissue for repair and enhancing recruitment of certain key cells to the site. For example, people providing care to family members with dementia took an average of 9 days longer to heal a 3.5-mm wound than control subjects; in other words, it took them 24% longer to repair a small, standardized wound (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Further research demonstrated that even a transient, commonplace stressor, academic examinations, could substantially delay wound repair: Wounds placed on the hard palate 3 days before a major test healed an average of 40% more slowly than those made in the same individuals during summer vacation.

Some evidence suggests that surgical stress interacts with both age and psychological stress to heighten risk for older adults. For example, in one study, older and younger subjects did not differ immunologically prior to elective surgery for hernia repair; however, the former had a poorer response on two immune measures 5 days after the operation (Linn, Linn, & Jenson, 1983). When the older and younger groups were subdivided on the basis of their preoperative anxiety, highly anxious older subjects had significantly more complications than the other three groups. Thus, morbidity and mortality following surgery are substantially greater among older adults than younger adults; further suppression of the immune response by psychological stress may put older adults at even greater risk.

If psychological stress has negative immunological consequences, might interventions that reduce stress have positive effects? In one well-controlled study, 45 older adults were randomly assigned to one of three protocols, relaxation training, social contact, or no intervention (Kiecolt-Glaser et al., 1985). Relaxation subjects showed significant positive changes on two different immune measures; the other two groups showed nonsignificant changes.

Positive benefits are not limited to formal interventions; as might be predicted from the ample literature on social support, supportive personal relationships dampen stress-related immune changes, whereas social isolation and abrasive interactions promote immune dysregulation. Familial ties are an especially powerful source of social influence in relation to endocrine and immune function (Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

A key question throughout much of the psychoneuroimmunology literature has been the extent to which stress-induced immunological changes have consequences for morbidity and mortality. The data on susceptibility to infectious disease and wound repair have already provided clear evidence of important health effects in two domains, but these represent a small subset of the potential range; given the centrality of the immune response for good health, results thus far are likely only the tip of the iceberg, and continued exploration should be very productive. A better understanding of how psychological states influence immune function and health will aid in the promotion and development of behavioral applications for both older and younger adults.

Recommended Reading

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Notes

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2. The cellular immune response, the non-antibody-producing arm of the immune response, is important for defense against virus-infected cells, transplanted tissue, cancer cells, fungi, and protozoans.

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