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Invited minireview

Stress and the aging immune system

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Abstract

Immune functioning decreases with normal aging and with stress. Social and psychological stressors are a part of daily life and the source of life changing events. Across the lifespan, individuals encounter numerous stressors with effects that accrue at sundry rates due to differential stress exposure, differential stress buffering, differential stress reactivity, differential stress duration (recovery), and differential restorative processes. Research on stress in older adults provides evidence that these processes contribute to effects that mimic, exacerbate, and possibly accelerate the effects of aging on immunity.

Keywords: Immunity; Aging; Stress; Exposure; Buffering; Reactivity; Duration; Recovery; Resilience

1. Introduction

Normal aging has a marked effect on immunity, with the cumulative evidence indicating that cell-mediated immunity consistently shows age-related decrements in function (Castle, 2000; Miller, 1996). Immune functioning is also susceptible to stress, with many of the same immune deficits as are observed in aging (Ader et al., 2001). In this review, we examine the evidence for the hypothesis that stress exacerbates the effects of aging on immune functioning, and that the immune consequences are lasting and deleterious.

The primary change in cell-mediated immunity with aging in adults is a marked decrease in naïve T cells and an increase in memory T cells. The consequences of this shift are widespread. A decrease in naïve T cells of the Th1 (cell-mediated) response is associated with decreased production of interleukin-2 (IL-2) and high-affinity IL-2 receptors, and a reduced T cell proliferative response to novel antigens. With aging, the Th1 response may also include increased production of the pro-inflammatory cytokine, IL-12, which can inhibit the Th2 (antibody-mediated) response. However, an age-related increase in memory T cells of the Th2 response increases production and secretion of interleukin-10 (IL-10) which, in turn, can inhibit the production and release of IL-12 and interferon-γ (IFN-γ), thereby suppressing the cellular inflammatory response (Castle, 2000). In the elderly, the production of Th2 cytokines, IL-4 and IL-10, is greater than it is in the young, whereas production of the Th1 cytokine, IFN-γ, is less, suggesting an age-related shift from a Th1 to a Th2 response (Rink et al., 1998) that may contribute to reduced cellular immunity in older adults. In addition, although the number of natural killer cells (NKC) does not appear to change with age, NKC cytotoxicity is reduced (Castle, 2000).

The naïve humoral immune response also decreases with age; B cells show impaired activation and proliferation, and antibody production is decreased in quantity and quality (i.e., less effective in preventing infection) (Castle, 2000). Diminished $CD4^+$ T cell support for B cell activation and differentiation is thought to be largely responsible for an age-related decline in antibody production to antigens (Miller, 1996). For instance, elderly individuals who exhibited a poor, rather than good, influenza vaccine response were also characterized by greater $CD8^+$ relative to $CD4^+$ clonal expansion (Saurwein-Teissl et al., 2002), indicative of a low CD4:CD8 ratio. Further, the outcome of previous vaccination is a shorter duration T cell memory in older relative to young adults, consistent with the notion that memory T cell function diminishes with age (Miller, 1996).

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Age-related changes are important to understand because they have implications for morbidity and mortality. In a population of individuals aged 86–92 years, the 2-year mortality risk was three times higher (i.e., 60% vs 20%) in individuals identified by cluster analysis to have low T cell proliferative response to mitogens, low B cell number, and low CD4:CD8 ratio (low % $CD4^+$ cells, high % $CD8^+$ cells) than in individuals who exhibited high T cell proliferation, high B cell number, and a relatively high CD4:CD8 ratio (Ferguson et al., 1995). In a follow-up, the high risk immune profile was again found to predict mortality in the ensuing 2-year period in this same population (Wikby et al., 1998).

When viewed as a whole, the diminutions in immune function with aging in adults progress in a slow and indomitable fashion. Individual variations in these downward trajectories are both evident and important, however, as illustrated, for instance, by Ferguson et al. (1995) and Wikby et al. (1998). Although genetic differences account for part of these individual differences, environmental influences are undeniable. Psychological stress, once thought to have no connection to immune function, is now known to affect immunity through specific autonomic and neuroendocrine pathways (Ader et al., 2001). Social and psychological stressors are both a part of daily life and the source of life-altering events. Across the lifespan, individuals encounter numerous life stressors. The frequency, deleterious effects, and cumulative load of these stressors differ across individuals because they differ in their exposure to stressors, the buffering of stressors by others, their reactivity to stressors, the duration of the stressors, and the efficacy of the restorative processes of the body (Cacioppo et al., 2003). Evidence is beginning to accrue that stress exacerbates age-related immune decrements (Kiecolt-Glaser and Glaser, 2001), but less is known about individual differences in the means by which stress affects immunity. In the remainder of this review, we examine the evidence that stress, via each of the portals listed above, mimics, exacerbates, and sometimes accelerates the effects of aging to produce lasting and deleterious effects on immune functioning.

2. Stress and immune functioning in older adults

2.1. Differential stress exposure

Given the social bedrock of human existence, the most stressful experiences people endure are typically those that strain or break social connections. Social isolation, rejection, discrimination, ostracism, and conflict are illustrative. Negative interpersonal events have been shown to be powerful modulators of immune processes (Herbert and Cohen, 1993). For instance, in a sample of older couples married an average of 42 years, negative behavior during a marital conflict was associated with poorer blastogenic responses to two mitogens (reviewed in Kiecolt-Glaser, 1999). This immune decrement mirrors the reduced T cell proliferation to novel antigens observed with aging, and fits the notion that the immune consequences of stress mimic immune aging. The older couples discussed above were relatively happily married; couples in less happy relational circumstances show even greater immune effects (Kiecolt-Glaser, 1999). Repeated immune assaults associated with recurring marital conflicts contribute to a cumulative stress load across the lifespan (i.e., allostatic load; McEwen and Stellar, 1993) and appear to aggravate the normal age-related changes in immunity.

Repeated exposure to stress has a qualitatively different meaning when the stress never relents. Chronic stress (i.e., stress exposure; Fig. 1, first column), such as that associated with caring for a spouse with a progressive dementia (e.g., Alzheimer's disease), has been associated with widespread reductions in immunocompetence including diminished NK cell cytotoxicity, reduced memory T-cell response to Herpes Simplex Virus Type 1, poorer antibody response to influenza virus vaccine, and shortened duration of the IgG antibody response to a pneumococcal bacterial vaccine (reviewed in Yang and Glaser, 2002). As is true for age, these stress-related alterations reflect inadequacies in immune responses to infectious agents and therefore have potential clinical relevance in older adults. The percentage of $IL\text{-}10^+$ lymphocytes in circulating blood was also higher in caregivers than in matched control subjects (Glaser et al., 2001). This stress effect mimics the elevated IL-10 levels seen with the age-related shift to the Th2 response, and could be important because of the inhibitory effect of IL-10 on the Th1 inflammatory response. In addition, a recent 6-year longitudinal study showed that levels of IL-6, a player in the natural immune response that increases with normal aging, increased in caregivers at four times the rate observed in age-matched controls (Kiecolt-Glaser et al., 2003). This result indicates not merely an additive, but an accelerating effect of stress on normal aging of the immune system, at least in terms of IL-6 production.

2.2. Stress buffering

Social factors are not only a source of stress, but they can also play a role in moderating the effects of stress. For example, having other people readily available as a source of emotional, appraisal, or instrumental support can minimize or prevent perceiving an event or situation as stressful (i.e., stress buffering; Fig. 1, first column). The stress-buffering effect, which was first articulated by Cohen and Wills (1985), explains in part why social support is associated with better immune functioning (e.g., greater NKC lysis, stronger proliferative responses

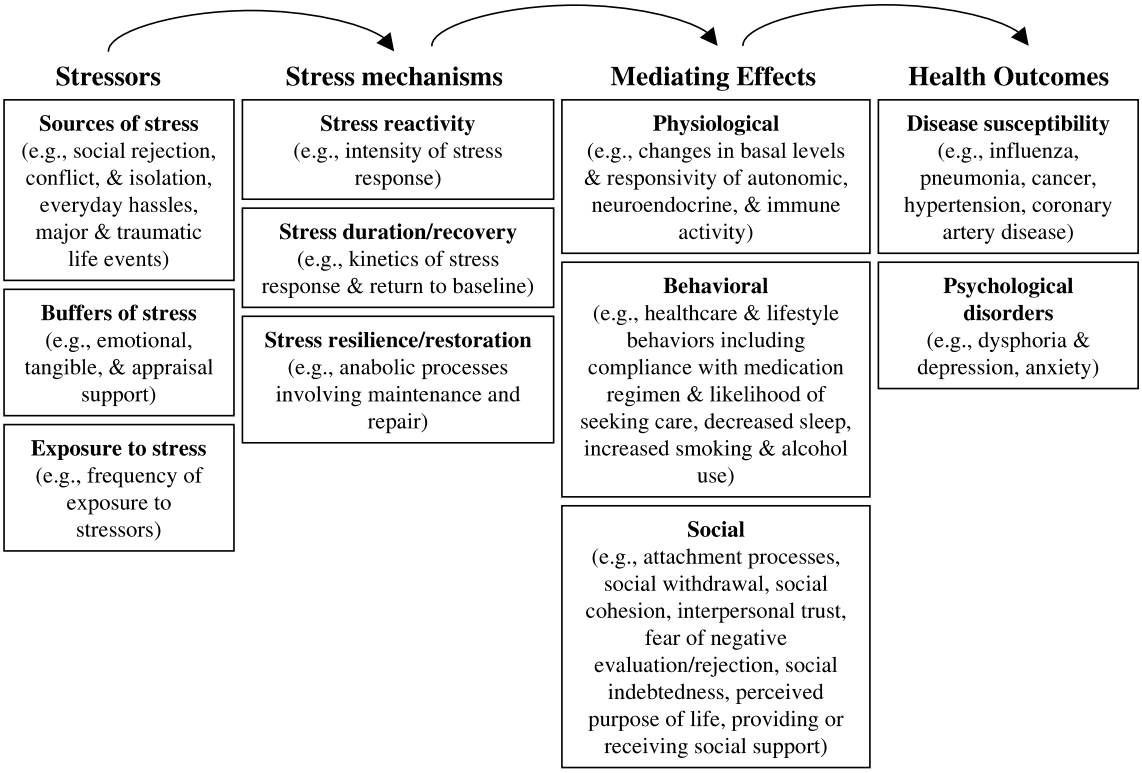

Fig. 1. Portals by which stress can exacerbate aging effects on immune function. Psychological stress, once thought to have no connection to immune function, is now known to have marked effects on immunity. Social and psychological stressors are both a part of daily life and the source of life-altering events. Across the lifespan, individuals encounter numerous life stressors. The frequency, deleterious effects, and cumulative load of these stressors differ across individuals because they differ in their exposure to stressors, the buffering of stressors by others, their reactivity to stressors, the duration of the stressors, and the efficacy of the restorative processes of the body (Cacioppo et al., 2003). Research on stress in older adults provides evidence that increased stress exposure, inadequate stress buffering, exaggerated stress reactivity, extended stress duration, and possibly diminished restorative processes have effects that mimic, exacerbate, and possibly accelerate the effects of aging on immunity. (*Note*. The processes above are depicted as unidirectional to highlight the effects attributable to stress per se.)

to mitogens; Uchino et al., 1996). Although older adults are generally as satisfied with the support they experience in their relationships as are young adults (Carstensen, 1992), caregivers of spouses with a dementia report fewer and less supportive relationships with others than do age-matched controls. Consistent with an additive effect of stress and aging on immune functioning, the less the social support reported by caregivers, the lower the likelihood of stress buffering and the greater the declines in immune function across time. An example of immune decline was decreased responsivity to IL-2 and IFN-γ by the NK cells of low-support caregivers (reviewed in Kiecolt-Glaser, 1999). The relative inability of NK cells to increase their activity upon stimulation is consistent with an age-related decrease in NKC cytotoxicity.

Social support is also lacking among lonely individuals. Consistent with the research on caregivers, loneliness has been associated with lower levels of NK cell lysis (reviewed in Kiecolt-Glaser, 1999), and higher levels of EBV antibody—a measure used to index deficiencies in cell-mediated immunity (Kiecolt-Glaser et al., 1984). Together, the evidence indicates that chronic stress augments, and the stress buffering provided by supportive others diminishes, the immune decline observed with aging.

2.3. Stress reactivity

Despite their relatively benign nature, even brief psychological stressors are effective elicitors of an immune response (Herbert and Cohen, 1993). In older adults, as in young adults, cellular immune responses to a brief mental arithmetic task (6–12 min) include increased numbers of suppressor/cytotoxic $CD8^+$ cells, increased natural killer cell (NKC) numbers and lytic activity, and decreased leukocyte proliferation in response to the mitogen, concanavalin A (Con A) (Cacioppo et al., 1998). Typically, the magnitude of the physiological response to an acute stressor is related to the objective intensity of the stressor. Physiological stress responses (i.e., stress reactivity; see Fig. 1, column 2) show wide individual differences, however, and these differences may contribute to differential health consequences. Stress intensity also has a substantial subjective component, and differences in perceived stress (another

aspect of stress reactivity; see Fig. 1, column 2) can contribute to differential physiological responses. Differences in psychological stress reactivity may take a long-term toll on immune functioning. This possibility was demonstrated in an animal study in which behaviorally "slow" mice, those which showed greater anxiety in stressful situations, exhibited faster age-related immune declines than did "fast" mice (Guayerbas et al., 2002). Although comparable studies have not been conducted in humans, these findings support the hypothesis that stress accelerates the aging of the immune system.

Psychological stress elicits not only an immune but also an autonomic and neuroendocrine response, and these responses have a discernible impact on immune function. In research examining the relationships among autonomic, neuroendocrine, and immune responses to stress, we found that sympathetic reactivity to psychological stress (as indexed by pre-ejection period, or PEP) predicted poorer T-cell response to influenza vaccination, $r = .68$, $p < .05$, in a sample of older women (Cacioppo et al., 1998). Women who were high sympathetic reactors also exhibited elevated antibody titers to EBV (Cacioppo et al., 2002a), consistent with the notion that exaggerated sympathetic responses to stress are associated with diminished cellular immunity. Importantly, PEP responses to stress among these older women appear consistent across acute psychological tasks (Hawkley et al., 2001) and stable over time (Burleson et al., 2002), suggesting that sympathetic reactivity to everyday stressors and hassles may represent one mechanism by which stress affects immune function. Sympathetic nervous system activity increases with age (Seals and Esler, 2000), and this may exacerbate stress-related immune decrements. The exact mechanism linking exaggerated sympathetic activity and immune decrements is an active area of investigation, but Friedman and Irwin (1995) provide evidence consistent with sympathetic mediation of corticotrophin releasing hormone (CRH) effects, and suggest that abnormal CRH regulation in the brain of the elderly may produce both age-related increases in sympathetic activity and decreases in immune functioning.

2.4. Stress duration (recovery)

As was described above, providing care for a spouse with a dementia diminishes immunocompetence. The stress of caregiving can last for a long period of time, and consequently, diminished immune function may also persist for an extended period (i.e., stress duration/recovery; Fig. 1, column 2). This could be a temporary immune decrement, however, if immune function rebounds when the stress of caregiving ends (i.e., with bereavement). To the contrary, evidence suggests that the immune effects associated with the chronic stress of caregiving persist long after caregiving has ended. Longitudinal studies have shown that former caregivers do not differ from current caregivers on a variety of measures of immune functioning (reviewed in Kiecolt-Glaser, 1999). For instance, caregivers whose spouse had died during the six years prior to having their immune functioning evaluated showed no difference in age-related changes in IL-6 over the course of the 6-year study when compared to current caregivers. Instead, the rate of increase in IL-6 was four times greater for both current and former caregivers relative to non-caregivers (Kiecolt-Glaser et al., 2003). These data suggest some irreversibility rather than recovery of lost immune function following a stress of long duration, and are consistent with the notion that immune aging can be accelerated through exposure to chronic stress.

2.5. Stress resilience

Importantly, stress exposure, stress buffering, stress reactivity, and stress duration/recovery may not be the complete story. Although research in psychoneuroimmunology has tended to focus on the effects of stressors on catabolic rather than anabolic processes, a comprehensive understanding of stress and aging may require attention to both. For instance, our research on loneliness in young and older adults has made us keenly aware of individual differences in the salubrity of restorative behaviors such as sleep. Briefly, loneliness has been thought to produce poor health outcomes through the selection of poor health behaviors. Health behaviors can impact immune functioning, and caustic behavior changes in response to stressors are well-documented. Our research on loneliness to date, however, has provided scant support for the higher rates of morbidity and mortality in lonely individuals being attributable to health behaviors. Instead, we found lonely individuals tend to be characterized by diminished repair and maintenance (anabolic) processes. For instance, lonely and nonlonely young adults spend equivalent time sleeping, but the sleep of lonely young adults is less efficacious—as gauged by physical evidence (e.g., eye movements) from the nightcap and self reports by the Pittsburgh Sleep Quality Index (Cacioppo et al., 2002b). In a study of elderly adults in an urban metropolitan area, loneliness was again found to be associated with poor sleep quality, sleep latency, and greater daytime dysfunction due to sleepiness (Cacioppo et al., 2002b).

An essential component of optimal functioning consists of the ability to recuperate from daily stressful assaults, to repair cellular damage, and to rebuild the mental, emotional, and physical capacity to respond to and cope with the next day's stressors (i.e., stress resilience; Fig. 1, column 2). A significant opportunity for restoration occurs during sleep. Inadequate sleep has adverse consequences, *including suppression of cellular*

immune responses (Irwin, 2002). Aging is associated with decrements in sleep quality, including increases in time spent awake at night and decreases in sleep depth (Floyd, 2002). As many as 50% of adults over age 65 complain of sleep problems (Foley et al., 1995), making sleep-related immune changes a serious concern among the elderly. Stress, loneliness, and depression all may make sleep less restful and restorative, therefore diminishing the effectiveness of nightly restorative processes. We are currently conducting longitudinal research to examine the extent to which the diminution of restorative processes (e.g., sleep) due to stress contributes to the aging of the immune system across the lifespan.

3. Aging, stress, and immune functioning: a summary

Individuals 65 and older account for a growing proportion of the population and a disproportionate share of days of doctor care and hospital stays. Infectious illnesses (e.g., influenza, pneumonia, septicemia) rank among the top 10 causes of mortality in these older individuals, and play a part in the increased use of health care resources in this population. Aging contributes to the immune deficits that give rise to the prevalence of infectious illnesses in older adults, and the immunosuppressive effects of stress compound this risk factor. Research on stress in older adults provides evidence that increased stress exposure, inadequate stress buffering, exaggerated stress reactivity, extended stress duration, and possibly diminished restorative processes have effects that mimic, exacerbate, and sometimes accelerate the effects of aging on immunity. It is therefore imperative that the specific nature of these combined effects, as well as the salubrious effects of sleep (and associated anabolic processes) and stress buffering, be determined.

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