Psychological Stress, Exercise and Immunity

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In terms of cardiovascular, endocrine and immune responses, acute high-intensity aerobic exercise stress may be considered as a subcategory of stressful active coping. The cardiorespiratory responses of both include increases in heart rate, cardiac output, systolic blood pressure, skeletal muscle vasodilation and oxygen consumption. Neurohormonal responses include increases in catecholamines as well as elevations in cortisol under high but not relatively low sympathetic activation. Immune system responses include increases in natural killer (NK) cell number and cytotoxicity and suppressor/cytotoxic lymphocytes as well as decreased proliferative response to mitogens. Task and recovery periods for both acute psychological stress or exercise show biphasic changes in immune response such that immune status is negatively impacted during recovery. Chronic life stressors influence acute cardiovascular, endocrine and immune responses to acute stressors. In addition, both chronic stress and unusually heavy chronic exercise can negatively impact immune status. Given impaired immune status following chronic stress and interactive effects of acute and chronic stressors (e.g. blunted acute NK responses to acute stressors), it is suggested that these factors may extend the window of vulnerability for infectious agents to act following acute psychological (e.g. examinations) or strenuous exercise (competitive athletics) stressors.

Key words: Psychological stress, exercise stress, neuroendocrines, immune status, acute stressors, chronic stressors

Introduction

Selye (58, 59) postulated that the stress response is a general alarm reaction that can be elicited by any of a large number of divergent stimuli. The induced response was believed to follow a specific physiological pattern, which varies only in its particulars among eliciting events. A hallmark of the stress response was thought to be activation of the pituitary-adrenocortical axis.

The notion of a single nonspecific response pattern was challenged by investigators such as Mason (43), who observed differentiated hormonal profiles to such stressors as cold, heat and exercise. Studies from the animal behavior laboratory further showed that mammals confronted by a behavioral stressor tended to reveal one pattern of cardiorespiratory activation if appropriate coping responses are attempted, but a different pattern if coping responses appear to be unavailable. The former pattern is generally associated with movement, whereas the latter pattern is associated with an inhibition of movement (56, 55). This first pattern, known as the defense reaction (1, 15, 30), includes increases in striate muscle activity, heart rate, vasodilation in skeletal muscle, cardiac output, systolic blood pressure and oxygen consumption. The second pattern, which occurs during aversive situations in which an inhibitory motor response is required or an active coping response does not appear to be available or conservation withdrawal seems to be the only adjustment possible, includes an inhibition of movement and increased sympathetic nervous system (SNS) activation associated with peripheral vasoconstriction and an elevation of blood pressure, but also increased vagal tone that restrains heart rate (2, 3).

A similar dichotomy seems to exist when one examines human responses to stressors. Thus, on the one hand, relatively acute *active coping* activities (pattern 1) that involve (representational, anticipated or actual) physical movement tend to elicit responses that resemble the defense reaction; these include mental arithmetic (12), video games (65) and a speech stressor (32). On the other hand, activities that involve *inhibitory coping* (pattern 2), such as the cold pressor test (in which the subject must inhibit the urge to withdraw from the cold stimulus) or mirror tracing (in which the subject must inhibit the tendency to go outside of a designated track because some visual cues are reversed) involve increases in SNS activity and total peripheral resistance (32).

In the present paper we suggest that for conceptual purposes, there appears to be a sufficient number of parallels between emotional stressors that elicit active coping *vis-à-vis* high-intensity, acute respiratory exercise, to consider aerobic exercise as a subcategory of stressful active coping (or pattern 1 response). With this in mind it should be possible to compare

acute stressor-endocrine-immune interactions between aerobic exercise and other active coping responses in order to distinguish contributions made by central command as opposed to those associated with autoregulatory processes. We also suggest that by examining potential interactions between the demands of acute stressors that elicit pattern 1 responses and responses to chronic stressors, some of which possibly involve conservation withdrawal (pattern 2), it may be possible to gain insights into the stressor-endocrine-immune interactions that may influence infectious disease processes.

Endocrine-Immune Interaction

Both pattern 1 and pattern 2 responses are associated with SNS activation (44). Norepinephrine (NE) is released by postganglionic sympathetic neurons, whereas epinephrine (E) is the primary hormone released by the adrenal medulla. Depending upon the intensity, duration and other characteristics of the stressor, the hypothalamic-pituitary-adrenocortical system (HPAC) may also become engaged. Activation of the HPAC system is associated with release of corticotropin releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary and cortisol from the adrenal cortex.

The hormones of the HPAC and sympathoadrenomedullary (SAM) systems are known to influence the immune system. Thus, CRH can inhibit natural killer cell cytotoxicity (NKCC) (52); ACTH impairs the responsiveness of T-lymphocytes to antigenic (CD3 antibody) and mitogenic stimuli such as concanavalin A (ConA) (36); and corticosteroids impair or modify several components of cellular immunity including T-lymphocytes (18), macrophages (51) and NKCC (39). Cortisol and ACTH receptors have been identified in lymphocytes and the interaction of cortisol receptors with appropriate levels of cortisol may inhibit cellular immune responses (see 4 for review). Similarly, increases in peripheral catecholamines influence the immune system. Sympathetic noradrenergic fibers innervate the vasculature as well as the parenchymal regions of lymphocytes and associated cells in several lymphoid organs. Nerve terminals in these organs are generally directed into zones of T-lymphocytes (22). Activation causes the release of these lymphocytes into the peripheral circulation. Administration of beta-adrenergic agonists is associated with reduced NKCC (35) and decreased T-lymphocyte proliferation (54), which is consistent with the presence of beta-adrenergic receptors found on lymphocytes.

In general, catecholamines tend to reduce most immune functions *in vitro*, including NKCC (10, 54). Recently, however, *in vivo* study has shown that acute emotional stressors can lead to an increase in the number of NK cells in the peripheral circulation (8). In the resting state, NK cells are found along the endothelial cell layer of the arterial wall (5). This constitutes the vessel's marginal zone. At rest the adhesive forces between the NK cell and the endothelium is greater than the shear forces that would free NK cells to move into the circulating pool of lymphocytes. During acute stress (which presumably includes intense aerobic exercise), increased flow in the systemic arterial system changes the equilibrium between adhesive and shear forces, permitting NK cells to leave the marginal zone. In addition, β_2-adrenoceptor stimulation of lymphocytes further disrupts interaction of NK cells with the endothelium, additionally decreasing adhesion (8). In this manner, the number of NK cells recruited from the marginating to the circulating pool of lymphocytes is increased. Thus, while SNS activation may reduce NKCC activity *in vitro* (10, 29), stress-induced recruitment of NK cells into the circulating pool would make an increased number of cells available for lysis, particularly once the peak concentration of catecholamines is diminished (9, p. 119). This, of course, could have implications for immune system function during the period after acute exercise during which the lymphocyte count dips below preexercise levels (48).

Stressor-Endocrine-Immune Interactions in Laboratory

Recent laboratory reactivity studies have been used to examine the roles that the endocrine and immune systems play in the acute stress response (6, 14, 42, 46, 63). Results from these types of studies have shown that the endocrine and immune responses to active coping tasks in the laboratory closely resemble the responses made to high-intensity, cardiorespiratory exercise (11, 20, 23, 27). The basic experimental paradigm to examine the effects of behavioral stressors involves presenting stressful stimuli and measuring the various stressor-induced immune changes that ensue.

One laboratory stress study found that women subjected to a 12-min mental arithmetic task produced increases in T-suppressor-cytotoxic (CD8) and NK cell (CD56) lymphocyte enumeration during the task (46). Another investigation observed that CD8 lymphocytes increased in number, but the lymphocyte response to phytohemagglutinin (PHA) was attenuated following exposure to mental arithmetic and a Stroop color-word conflict test, but only in subjects who showed high SNS activity as indexed by plasma catecholamine and cardiovascular reactivity (42). Still another study, conducted on postmenopausal women, found that responses to mental arithmetic and a speech stressor task increased heart rate, decreased pre-ejection period (PEP) and increased plasma catecholamines as well as induced increases in NK cell number and NKCC and a decrease in lymphocyte proliferation to ConA (14). This study also reported that individuals characterized by high, relative to low SNS activity as indexed by cardiovascular measures, showed greater stress-related changes in plasma ACTH and cortisol levels but comparable changes in E and NE concentrations. In the Miami laboratory we have also examined cardiovascular, neuroendocrine and immune responses to speech stressor (pattern 1) and mirror tracing (pattern 2) tasks (63). Both the preparation for the speech and mirror tracing tasks elicited comparable increases in blood pressure, although the blood pressure elevations were supported by different mechanisms (i.e., cardiac output increased during speech preparation and total peripheral resistance increased during mirror tracing).

The behavioral challenges induced distinctly different patterns of changes in absolute numbers of lymphocyte subpopulations, and in immune cellular function. Specifically, during the speech preparation period (pattern 1 protocol) the subjects exhibited increases in NK cell number and NKCC, total number of lymphocytes, CD4, CD8 and B cells, a decrease in proliferative response to the mitogen PHA, and a decline in CD4/CD8 ratio. In contrast, the mirror tracing challenge (pattern 2 protocol) elicited an increase in NK and B cells, and a decline in

CD4 cells. The differences in the immune response patterns to the two stressors cannot be accounted for by stressor duration, which was equivalent (i.e., 4 min). Moreover, it is unlikely that the differences in immune response patterns could be accounted for by differential stressor-induced SNS response magnitude *per se*, since the evoked blood pressure and heart rate elevations to these challenges did not differ.

Significant increases in ACTH and cortisol occurred to the speech stressor, but not to the mirror tracing task. The latency of the immune responses occurred concomitant with the blood pressure and other cardiovascular changes, but prior in time to the increases in ACTH and cortisol. Our findings suggest that acute trafficking patterns of cellular immune responses vary as a function of the stressor (pattern 1 vs. pattern 2) and are sympathetically mediated. In a recent study Bachen et al. (6) used mental arithmetic, a Stroop test and a speech stressor to elicit cardiovascular and immune responses. They observed significant increases in NK cell number and cytotoxicity, lower mitogenic responses to PHA and ConA, and a diminished CD4/CD8 ratio in response to the stressors. Nonselective adrenoceptor blockade with labetolol eliminated the immune system changes except that group differences in NKCC were not significant after controlling for differences in NK cell number. These findings provide strong evidence that the immunologic responses to acute pattern 1 psychological stressors are dependent on activation of the SNS.

Interaction of Chronic Stress and Acute Stressors

Chronic life stress has been associated with increased SNS activation (57), engagement of the HPAC axis (34) and changes in cellular immune function (7) although changes in stress hormones are not universally found in persons undergoing chronic stress. In order to examine the interaction of chronic and acute stressors on immune function, several investigators have begun to study this problem in the laboratory. Two studies, for example, have shown that prior life stress is related to increased cardiovascular reactivity (24, 50), and another found that self-report of life stress was associated with a blunted stressor-induced increase in NK cells (13). Although the exact physiological mechanisms by which chronic stress can blunt acute immune responses to stress is unknown, it is conceivable that chronic stress may change both adrenergic agonist and receptor physiology (45).

Interactions between chronic stress and the physiological responses to acute stressors may also be modified by individual differences in reactivity. Thus, for example, Manuck et al. (42) found that individuals who showed relatively high rather than low cardiovascular and catecholamine reactivity to an acute psychological stressor also revealed larger decreases in lymphocyte proliferation in response to PHA and a larger increase in CD8 enumeration. More recently, Sgoutas-Emch et al. (60) selected high heart rate and low heart rate reactor men in a prescreening session and subsequently exposed the subjects to mental arithmetic and a noise stressor during a different session. The high vs. low heart rate reactors did not differ from each other in terms of resting cardiovascular measures. One major finding of the study, however, was that acute stressor-induced increases in NKCC was greater in the high than in the low heart rate reactors. A second major finding in the study was that stress-related elevations in plasma cortisol concentration occurred in the high but not in the low heart rate reactor group. The data reviewed in this section therefore suggest that: (a) even when resting cardiovascular levels are comparable among individuals, those individuals' chronic predispositions may influence endocrine and immune responses; and (b) chronic life stress can influence acute cardiovascular and immune responses to acute stressors.

At present little data are available concerning the possibility that immune changes associated with chronic stress can influence the onset or progression of disease. A provocative experiment conducted by Cohen et al. (17), however, found a dose-response relationship between self-reported life stress and common cold symptoms when subjects were experimentally exposed to a rhinovirus. And in the Miami laboratory, we have observed that the psychosocial variable of excessive denial in response to a diagnosis of HIV seropositivity correlated $r = -0.69$ with CD4 number and $r = -0.68$ with lymphocyte response to PHA stimulation 1 year after diagnosis even after adjusting for CD4 level at diagnosis (33). We also found that the 1-year immune status, in turn, was reliably correlated with 2-year disease progression. The correlation between CD4 with symptoms was $r = -0.58$ and with AIDS, $r = -0.73$; correlation between PHA response with symptoms was $r = -0.62$ and with AIDS, $r = -0.49$. It would thus appear that some progress is being made in linking behavioral stressors with endocrine and immune measures as well as with disease processes.

Psychological Stress and Athletic Participation

Kiecolt-Glaser and Glaser (37) have suggested that individuals most at risk for negative health consequences mediated by psychological stress are those who are already compromised by their health status or by their behavior. Athletes' behavior of high-intensity and high-volume training (which may become a chronic stressor) has been hypothesized to create favorable conditions for contraction of viral illness via immunosuppression (40, 49, 68). It is possible that psychological factors may also influence athletes' chronic and acute neuroendocrine and immune responses. In this section, we review stressor characteristics and immune responses to exercise.

Acute aerobic exercise presents an active coping task challenge causing increased catecholamine output via SAM activation, increased cardiac output, and decreased total peripheral resistance (38, 48, 55). Norepinephrine is preferentially released over E during exercise, although both increase, whereas psychological stress evokes an opposite preferential catecholamine release (44).

In most cases, cortisol release is dependent on exercise intensity (16, 21). Cortisol, however, may initially decrease and not increase above resting levels until the participant achieves a vigorous exercise level approaching exhaustion (64). Following high-intensity exercise (greater than 80% of functional capacity), cortisol recovery to preexercise levels will vary, at times remaining elevated for hours or even days (48, 67). However, among elite aerobic athletes, cortisol levels immediately following exhaustive exercise may decrease significantly or remain unchanged from baseline (53, 62, 64). These findings suggest that psychological factors in addition to physiological demand may play a role in HPAC regulation among athletes.

Immunologic sequelae of high-intensity exercise include a general rapid increase of immune cells, particularly CD8 and NK cells, with a concomitant decrease in lymphocyte response to ConA and an increase in NKCC followed by transitory decreases in NKCC and ConA below basal levels (23, 26, 48, 66). In contrast, moderate intensity exercise elicits modest shifts in immune cell counts without either a sustained increase in cortisol or epinephrine, and in some cases increases in NK, NKCC, or TLPR (47, 48, 61, 66).

Considering the increased risk of upper respiratory infections among aerobic athletes, particularly following an exhaustive exercise period (49, 68), it has been suggested that high-intensity training may create a window of susceptibility to viral infection (40, 49, 61). It has further been suggested that a portion of the variability in exercisers' endocrine and immune response may be linked to psychological stress, potentially widening a window of susceptibility among competitive athletes (40, 41, 53, 61). Summarizing a series of studies, Frankenhaeuser (25) has shown that catecholamine and cortisol patterns in response to stressors are largely dependent on perception of distress rather than physical effort. As previously mentioned, exercise to exhaustion may in some cases lead to decreased cortisol response among elite athletes (64, 53). Life-event stress has also been associated with prolonged cortisol recovery for up to 1 day and subsequent symptomatology following a maximal graded exercise test (53).

Several interpretations of these data are possible. Having been trained repeatedly to exercise to exhaustion, elite athletes, in contrast to recreational or sub-elite athletes, may display a physiological toughening or adaptive training response (19, 64) such that exhaustive exercise no longer elicits a cortisol response reflecting distress. Alternatively it is possible that preexercise cortisol values may be elevated either because the collections occur within the context of a competitive environment (e.g. apprehension before competition) or because the presumed resting baseline levels already reflect prolonged exercise training as a stressor. In any event, the findings of decreased cortisol response to high-intensity exercise suggest that psychological or physical factors that may serve as acute or chronic stressors can be reflected in what is presumed to be a resting baseline measure.

The differences in cortisol response patterns to maximally exhaustive exercise are consistent with Frankenhaeuser's (25) suggestion that cortisol response may be significantly dependent upon cognitive appraisal of the stress situation. Moreover, while the acute cortisol response to aerobic exercise may be part of a normal, adaptive response to task demands, prolonged HPAC activation may reflect a deleterious adjustment (55, 19). This is especially likely to be the case considering the immunosuppressive effects of cortisol.

In considering the interactions between acute and chronic stressors, it is important to consider the long-term apprehensions that may occur prior to a competitive event plus the stringent demands placed upon multiple organ systems by prolonged training. After a competitive event, psychological factors may also influence the endocrine and immune systems. Thus, while winning or exceeding performance expectations may lead to one pattern of adjustments, increased negative mood and feelings of failure may follow a poor performance, leading to a different pattern. Although no direct investigations of neuroendocrine or immune responses either to competitive anxiety or psychological factors associated with performance outcome have yet been conducted, prior research has documented increased cortisol and decreased immunoglobulin A levels as athletes move from noncompetitive to competitive portions of their seasons (31, 41).

Conclusions

Recent epidemiologic data suggest that unusually heavy chronic exercise may be associated with an increased risk of upper respiratory tract infections (49). Similarly, Cohen et al. (17) found a dose-response relationship between self-reported chronic stress and common cold symptoms when subjects were experimentally exposed to a rhinovirus. Both chronic stress (34, 7) and unusually heavy chronic exercise (49) have been associated with elevation of stress hormones and/or negative changes in immune function. Thus, the relationship between unusually heavy chronic exercise and risk of upper respiratory tract infections may occur either because prolonged exercise training is a major stressor or because the endocrine and immune changes induced by the chronic exercise regimen may interact with other chronic stressors to increase the risk of infection.

Before turning to interactions that may occur between acute and chronic stressors, let us briefly summarize the findings that we reviewed suggesting that cardiovascular, endocrine and immune responses occurring to acute psychological stressors involving active coping are similar to those elicited by acute aerobic exercise. The cardiorespiratory responses of both, for example, include increases in heart rate, cardiac output, systolic blood pressure, skeletal muscle vasodilation and oxygen consumption. Neurohormonal responses include increases in norepinephrine and epinephrine as well as increases in cortisol under high SNS but not relatively low SNS activation. Immune system responses include increases in NK cell number and NKCC, total number of lymphocytes and CD8 cells as well as a decrease in proliferative responses to plant mitogens. Given these parallels and the literature on the defense reaction in animals, it may be useful to consider acute high-intensity aerobic exercise stress as a subcategory of stressful active coping.

Although pattern 1 responses have been studied extensively, the endocrine and immune responses to pattern 2 have been less well investigated. To the extent that pattern 2 responses tend to be more chronic than pattern 1 responses (56, 55), the consequences of interactions between the effects of short-term active coping stressors (e.g. examinations; aerobic exercise competitions) superimposed upon long-term stressors (e.g. high level of hassles; chronic academic stress; unusually heavy chronic exercise) should be examined.

The literature that we have reviewed concerning the interaction of acute and chronic stressors suggests that chronic life stressors can influence acute cardiovascular, endocrine and immune responses to acute stressors (13, 24, 50). This is particularly interesting given that both chronic stress (7) and unusually heavy chronic exercise (49) can negatively impact immune status. The task and recovery periods for both acute exercise (23, 27, 28) and psychological stressors (13, 46) show biphasic changes in immune responses such that immune status is

negatively impacted during the recovery period. Given changes in basal immune levels following chronic stress and the interactive effects of acute and chronic stressors (13, 24, 50) on immune function (e.g. chronic stress blunts acute immune response to stressors), it is conceivable that the interaction may extend the window of vulnerability for infectious agents to act following strenuous, competitive exertion. In any event, future research should examine stress-endocrine-immune-upper respiratory infection interactions particularly as they are moderated by chronic stressors, acute stressors and their interactions. It may be that the anecdotal reports of increased likelihood of upper respiratory infections following examination stress or competitive exercise stress possess scientific validity and have more in common with each other than has previously been suspected.

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