EDITORIAL COMMENT

Acute Psychological Stressors and Short-Term Immune Changes: What, Why, for Whom, and to What Extent?

A series of recent studies (1–9) have assessed the effects of psychological short-term stressors on the immune response. In this paper we briefly review the results of these studies, comment on the nature of the stressors and other methodological parameters, discuss issues related to the time course and specificity of the phenomena, and consider the clinical implications of transient immunological changes.

What Changes?

Table 1 summarizes the nine studies we found, grouped according to the stressors used. An increase in natural killer (NK) cell numbers and a decreased mitogen response, particularly for concanavalin A (Con A), were the most consistent changes noted: NK cell numbers increased in four out of five studies, and Con A decreased in three out of three. The proliferative response to phytohemagglutinin (PHA) decreased in three studies, and was not significantly changed in two. Changes in CD8 numbers were inconsistent, but seemed to increase in studies with longer and/or more intensive stressors (i.e., those that produced larger heart rate increases). B cells and monocytes produced inconsistent results. No differences in CD3 numbers were reported across five studies, and CD4 numbers were unchanged in six out of seven studies. Overall, it is clear that short-term stressors can produce transient immunological alterations, with some facets of the immune response appearing more susceptible than others.

Why: Possible Mechanisms

The immunological changes observed following short-term stressors are very similar to those that have been described following epinephrine injections: increased percentages of NK cells, decreased blastogenic responses to mitogens (PHA, Con A, and pokeweed), and decreased percentages of CD4 cells; total T cells and monocytes did not change (10, 11). These epinephrine-induced changes are thought to reflect transient alterations in lymphocyte migration from lymphoid organs and peripheral blood mediated through adrenergic receptors on lymphocytes or via the sympathetic innervation of lymphoid organs (10–13). Splenectomized patients show much smaller changes in response to an epinephrine infusion than normal subjects (14). Thus, stress-related catecholamine increases provide one mechanism for short-term immunological changes.

Does this mean that immune assays are simply a proxy for the measurement of epinephrine? Data from Crary et al. (10)

suggest not: leukocytes incubated with substantially larger epinephrine concentrations than levels expected in vivo did not affect mitogen stimulation. In addition, a recent review (12) suggests five general pathways through which the central nervous system (CNS) might influence lymphocyte migration, including the actions of other endocrines and neuropeptide transmitters.

For Whom?

Responses to stressors show considerable variability among individuals and across situations. Individual differences in cardiovascular reactivity have been studied extensively (15); since cardiovascular and catecholaminergic reactivity tend to covary when assessed under the same conditions (2, 15), researchers have analyzed immunological changes in relationship to cardiovascular reactivity (2, 3, 9). High reactivity subjects demonstrated greater immunological change than low reactivity subjects, with the latter showing little or no change (2, 3, 9). Table 1 also provides data on the magnitude of the changes in heart rate and blood pressure; by way of comparison, a single injection of 0.2 mg of epinephrine produced mean increases of 10 beats per minute in heart rate, 17 mm Hg in systolic blood pressure, and 12 mm Hg in diastolic blood pressure (10). Plasma epinephrine levels measured 30 to 60 minutes after the injection fell within a normal physiological range (11).

While low reactors showed little change, an individual's classification as low in heart rate reactivity could stem from low sympathetic reactivity, high vagal activation, or low to high coactivation

of the sympathetic and parasympathetic controls on cardiac chronometry; on the other hand, an individual's classification as high in heart rate reactivity could reflect elevated sympathetic reactivity, strong parasympathetic withdrawal, or moderate to strong reciprocal sympathetic activation to the heart (16). Moving beyond conceptualizations of heart rate reactivity as a unidimensional (i.e., sympathetic activation) vector to consider individual differences in the autoimmune origins of heart rate reactivity may provide a way of better quantifying these individual differences (16).

In general, a better understanding of individual differences will also require more consistent attention to methodological issues in future studies. Medication use (especially cardiovascular-altering drugs), dietary factors, age, recent caffeine intake, smoking, aerobic conditioning, and alcohol, in addition to genetic factors, can all have significant consequences for reactivity (15), and yet several studies did not report data for these factors. Independent, e.g., self-report data, verifying the efficacy and strength of the experimental stressor, are necessary to demonstrate that experimental manipulations were successful and should facilitate comparisons across studies. All subjects need to be studied at the same time of day to minimize error variance associated with diurnal variation in both neuroendocrine and immune parameters (12); several studies staggered data collection across the day. When repeated blood samples are collected over a period of several hours, use of an indwelling catheter avoids the additional stress of repeated venipuncture; adaptation periods of 30 minutes or more are advisable following catheter insertion (15). Comparisons of the average heart rate increases across

TABLE 1. Studies Assessing the Effects of Short-term Stressors on Immunity

Study	Stressor/Subjects	Group/Conditions	Cardiovascular/ Endocrine Changes	Poststress Immune Changes
Landmann et al. (1)	8 min Stroop; 11 men, 4 women, median age = 20		HR (+8), SBP (+13); DBP (+10), NC: epi, NE, cort	↑NK cells, ↑B cells, ↑mono; NC: CD3, CD4, CD8; leukocytes, granulocytes
Manuck et al. (2)	20 min Stroop, math; 30 men, ages 16–30	High reactors (high) Low reactors (low) No stress controls (C)	HR (High = +18, Low = +7, C = +2); SBP (high = +16, low = +7, C = +2); DBP (high = +18, low = +4, C = 0), epi, NE (High ↑); NC: cort	High: ↓PHA, ↑CD8; NC: CD4, B-cells
Bachen et al. (3)	21 min Stroop; 44 men, ages 19–25	Stress vs. no-stress controls (C)	HR (Stress = +13, C = +1); SBP (Stress = +15, C = 0); DBP (Stress = +12, C = 0)	Stress: ↓PHA, ↓CD4, ↑NK cells; NC: CD3, B-cells
Naliboff et al. (4)	12 min math; 12 younger women, M age = 31; 11 older women, M age = 71	Young vs old; Within subjects, film vs. math	HR (young = +18, old = +7); SBP (young = +14, old = +24); ↑epi (young and old); NC: NE	Young: ↑NKCA, ↑CD8, ↑NK cells; Old: ↑CD8, ↑NK cells; NC: CD3, CD4, B-cells
Brosschot et al (5)	30 min uncontrollable interpersonal stressor; 50 min, M age = 41	Stress vs. no-stress controls (C)	No data	Stress: ↑NK cells, ↑CD8; NC: PHA, PWM, AG, CD3, CD4, HLADR, leukocytes, mono
Weisse et al. (6)	30 min electric shock, noise; 22 men, M age = 28	Controllable (CON) vs. uncontrollable (UC) stressor	No data	CON: ↓Con A, ↓mono ↓B cells; UC: ↓B-cells NC: PHA, CD3, CD4, CD8
Sieber et al. (7)	20 min noise, 30 min rest, 20 min noise; 55 men, ages 18–26	Escapable noise (EN); Inescapable noise/ Response (IN/R); Inescapable noise/ no response (IN/ NR), No noise (NN)	No data	IN/NR: ↓NKCA; NC: NK cells, CD4, CD8, CD25, CD16, B-cells

Knapp et al. (8)	40 min recalls of negative (NEG) and positive (POS) emotional experiences; 10 men, 10 women, ages 18–30	Within-subjects design, 3-day sequence, order randomized	HR (NEG and POS = +5); SBP (NEG = +3)	NEG and POS: ↓PHA, ↓Con A; NC: NKCA, CD3, CD4, CD8, lymphocytes, mono
Zakowski et al. (9)	30 min viewing and recall of a "gruesome" film; 29 men, M age = 31	Film vs. control (C)	SBP (Film = +8, C = −5); DBP (Film = +10, C = +2); cort: higher in film than C	Film: ↓Con A; NC: PHA, IL-1, IL-2

Ag, antigen cocktail; Con A, concanavalin A; cort, cortisol; DBP, diastolic blood pressure change; epr, epinephrine; HR, heart rate change; math, mental arithmetic; mono, monocytes, NC, no change; NKCA, NK cell activity; NE, norepinephrine; PHA, phytohemagglutin; PWM, pokeweed mitogen; SBP, systolic blood pressure change

studies in Table 1 suggest that both the duration and intensity of psychological stressors (as indexed by cardiovascular changes) are related to the breadth and magnitude of immune changes. Obviously, at a minimum, heart rate and blood pressure measurements (and, ideally, plasma catecholamines) are needed to aid comparisons across studies in the future.

To What Extent?

How long do these short-term changes persist? Among the studies that have continued to assess subjects after the stressor ended, the immunological changes appear relatively short-lived (5, 9), although (not surprisingly) more intense stressors such as shock and noise may have somewhat longer-lasting consequences (6). In this regard, the epinephrine injection studies provide helpful data for comparison. The proliferative response to three mitogens was reduced for up to 60 minutes after injection (10), but all responses returned to pre-injection levels 2 hours later.

Could some of the immunological changes reported previously for acute stressors, such as examination stress (17), simply reflect changes in the migration of lymphocytes, rather than more enduring effects? Although some immunological parameters can change quickly, many others have well-characterized time courses; for example, development (or degradation) of antibody (IgG), either to a vaccine (17) or to a latent herpesvirus (17), cannot change over the course of hours. Similarly, changes in gene expression (17) are not transient.

Are the individuals who show greater SNS activity/reactivity also at risk for

more persistent down-regulation of im-
mune function? Do these individuals dif-
fer in the speed with which they return
to baseline? None of the studies reviewed
in this paper provided data relevant to
these important questions. However, re-
cent evidence suggests that chronic stress
may alter both SNS activity and immune
function. Family caregivers of Alz-
heimer's disease (AD) victims who were
low in social support displayed different
patterns of age-related heart rate reactiv-
ity and blood pressure from caregivers
who were high in social support (18). Ear-
lier data from spousal caregivers in this
sample showed that caregivers had poorer
immune function than controls, and low
social support was associated with greater
declines in immune function over the
course of a year (19); importantly, spousal
caregivers had more prolonged infectious
illness episodes (primarily respiratory
tract infections) than controls. Similarly,
Irwin and his colleagues (20) found higher
levels of neuropeptide Y (NPY) in AD
caregivers compared with controls; levels
of NPY, a sympathetic neurotransmitter
released during emotional stress, were in-
versely correlated with NK cell activity.
Longitudinal studies such as these that
evaluate SNS activity and reactivity,
short-term immune and endocrine re-
sponse to laboratory stressors, and longer-
term changes in immunity and health are
clearly needed. These issues may be even
more important in older adults, since ag-

ing is associated with decrements in im-
mune function, enhanced SNS activity,
and changes in noradrenergic innervation
of lymphoid tissues (13, 18–20).

The studies reviewed in this paper sug-
gest a convergence among cardiovascular,
neuroendocrine, and psychoneuroimmu-
nological research and the evaluation of
differences among people who vary in
autonomic activation. A better under-
standing of these individual differences in
response to stress could help identify
those individuals who may be more prone
to long-term health changes.

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