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Review article

The short-term stress response – Mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity

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ABSTRACT

Our group has proposed that in contrast to chronic stress that can have harmful effects, the short-term (fight-or-flight) stress response (lasting for minutes to hours) is nature's fundamental survival mechanism that enhances protection and performance under conditions involving threat/challenge/opportunity. Short-term stress enhances innate/primary, adaptive/secondary, vaccine-induced, and anti-tumor immune responses, and post-surgical recovery. Mechanisms and mediators include stress hormones, dendritic cell, neutrophil, macrophage, and lymphocyte trafficking/function and local/systemic chemokine and cytokine production. Short-term stress may also enhance mental/cognitive and physical performance through effects on brain, musculo-skeletal, and cardiovascular function, reappraisal of threat/anxiety, and training-induced stress-optimization. Therefore, short-term stress psychology/physiology could be harnessed to enhance immuno-protection, as well as mental and physical performance. This review aims to provide a conceptual framework and targets for further investigation of mechanisms and conditions under which the protective/adaptive aspects of short-term stress/exercise can be optimized/harnessed, and for developing pharmacological/biobehavioral interventions to enhance health/healing, and mental/cognitive/physical performance.

1. Introduction

Chronic or long-term stress has been shown to have numerous adverse effects on health (McEwen, 1998; Ader, 2007). Many of these effects are mediated through stress actions on the immune system (Dhabhar, 2009b; Dhabhar et al., 2012; Padro and Sanders, 2014). It is important to elucidate the psychological and biological mechanisms by which chronic stressors weaken health, exacerbate disease, or inhibit mental and physical performance because that could enable the development of biobehavioral and pharmacological treatments designed to ameliorate or eliminate the harmful effects of chronic stress. However, it is also important to appreciate that the process of evolution did not select for the biological stress response to sicken, handicap, or kill us, but rather to help us survive (Dhabhar, 2012). A psycho-physiological stress response is one of nature's fundamental survival mechanisms. Without a fight-or-flight stress response, a lion has no chance of catching a gazelle, just as the gazelle has no chance of escape. Thus, during short-term stress, multiple physiological systems are activated to enable survival. Dhabhar et al. first proposed that just as the short-term stress response prepares the cardiovascular, musculoskeletal and neuroendocrine systems for fight or flight, under certain conditions, stress may similarly prepare the immune system and the brain for challenges (e.g., wounding, infection, figuring out an escape route, tackling a job interview, running a race, etc.) that may be imposed by a stressor (e.g., predator, or, in modern times, a medical/surgical procedure, professional opportunity, athletic competition, etc.) (Dhabhar et al., 1995, 2001; Dhabhar and McEwen, 1997; Dhabhar, 2014b, 2014a). Since then, numerous studies have shown in humans and animals, that short-term stress experienced at the time of immune activation induces a significant enhancement of the ensuing immune response. Studies have also shown short-term stress induced enhancement of mental performance. We propose that it is important to investigate the adaptive mechanisms and effects of the short-term stress response and to harness the psychological and biological mechanisms of the adaptive stress response, to enhance protection or performance under conditions of threat, challenge, or opportunity.

2. Stress: Definition, mediators, and individual differences

Even though the word "stress" generally has negative connotations,

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stress is a familiar and ubiquitous aspect of life, being a stimulant for some, but a burden for many others. Numerous definitions have been proposed for the concept of stress, each focusing on aspects of an internal or external challenge, disturbance, or stimulus; on stimulus perception by an organism; or on a physiological response to the stimulus (Goldstein and McEwen, 2002; McEwen, 2002; Sapolsky, 2005). *An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physiological fight or flight systems in the body (stress response)* (Dhabhar and McEwen, 1997). Psychological, physiological, physical, or exercise-related stressors all activate biological stress responses involving the release of factors in the systemic circulation and locally within central and peripheral tissues. In the periphery, the stress response consists of the "big three" stress hormones: norepinephrine and epinephrine that are released by the sympathetic nervous system, and cortisol, that is induced following activation of the hypothalamic-pituitaryadrenal axis. Virtually every cell in the body expresses receptors for one or more of these "big three" hormones, that induce changes in almost all cells and tissues and inform them about the presence of a stressor. The peripheral stress response also includes other neuroendocrine factors such as adrenocorticotropin (ACTH), vasopressin (Jezova et al., 1996), and oxytocin (Jezova et al., 1996; Jong et al., 2015), and cytokines (Steptoe et al., 2007) such as interleukin-6 (Puterman et al., 2013) and inteleukin-1beta (Aschbacher et al., 2012). In the periphery, similar biological stress responses are observed under conditions that require protection (e.g. attack by a predator) (Roseboom et al., 2007; Vendruscolo et al., 2006), performance (e.g. making a speech, or taking an exam, running a race) (Kirschbaum et al., 1993; Foley and Kirschbaum, 2010; Henze et al., 2017), or pleasure (e.g. sexual intercourse) (Kotwica et al., 2002; Veronesi et al., 2010; Fox and Fox, 1971; Leuner et al., 2010). However, different types of stressors can differentially affect the relative proportions and the magnitude and duration of elevation of factors induced in the systemic circulation during short-term stress. It is important to recognize, that the biological stress response is the only pathway through which a stressor can affect the body.

2.1. Protective versus harmful effects of stress

Dhabhar et al., first proposed that short-term or acute stress induced enhancement of immune function may be an adaptive psycho-physiological mechanism that enhances immune protection following wounding, infection, vaccination, and perhaps even in the context of some types of cancer (Dhabhar et al., 1995, 1994; Dhabhar, 2014a; Dhabhar and McEwen, 1996). Although this idea may sound similar to Hans Selye's concept of "eustress," it must be noted that Selye defined "eustress" largely in terms of the nature of the stressor, (i.e., whether it was pleasant as opposed to noxious) but stated that eustress and distress both cause "damage," the former causing less damage than the latter (Selye, 1974). In contrast, Dhabhar et al., have defined "good" versus "bad" stress in terms of the duration of the biological stress response and its adaptive versus deleterious effects, and have stated that stress does not always have deleterious effects, and in some cases can even have beneficial effects on brain, body, and health (Dhabhar, 2009b, 2014a, 2009a; Dhabhar et al., 2012, 1995, 1994, 2007; Dhabhar and McEwen, 1996).

It is known that stress can be harmful when it is chronic or long lasting (McEwen, 1998; Irwin et al., 1990; Glaser and Kiecolt-Glaser, 2005; Chrousos and Kino, 2007), however, it is often overlooked that a stress response has salubrious adaptive effects in the short run (Dhabhar et al., 2007; Dhabhar and Viswanathan, 2005). Therefore, a major distinguishing characteristic of stress is the duration of the biological stress response. *Short-term stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months (Dhabhar and McEwen, 1997). Dysregulation of the circadian cortisol rhythm is one marker that appears to coincide with the deleterious effects of chronic stress (Dhabhar and McEwen, 1997; Sephton and Spiegel, 2003; Saul et al., 2005). The intensity of stress can be gauged by the peak levels of stress hormones, neurotransmitters, and other physiological changes such as increases in heart rate and blood pressure, and could affect the amount of time for which these changes persist during stress and following the cessation of stress.

It is important to note that there are significant individual differences in stress perception, processing, appraisal, and coping (Dhabhar et al., 2007; Gunnar and Quevedo, 2007). Such differences could be the result of genetic as well as experiential factors. Individual differences become especially salient while studying human subjects because stress perception, processing, appraisal, and coping mechanisms can have significant effects on the kinetics and peak levels of circulating stress hormones and on the duration for which these hormone levels are elevated. Studies showing differences in stress hormone receptors, reactivity and peak levels (Dhabhar et al., 1993; Sternberg et al., 1989), adaptation to stress (Dhabhar et al., 1997), and in distribution and activation of adrenal steroid receptors and corticosteroid binding globulin levels (Dhabhar et al., 1993, 1995), suggest that genetic, experiential, as well as environmental factors play a role in establishing individual differences (Dhabhar et al., 1993, 1997, 1995, Gomez-Serrano et al., 2001). The ability of humans to generate and experience psychological stressors even in the absence of external stressors can result in long-term activation of the physiological stress response that often has deleterious effects. The magnitude and duration of elevations in stress hormones can have significant effects on immune function (Dhabhar et al., 2012, 2001; Schwab et al., 2005; Benschop et al., 1996) and on mental and physical performance.

3. Revision of the dogma that immune function is suppressed during stress in order to conserve energy for survival responses

When viewed from an evolutionary perspective, immunosuppression under all stress conditions would not be adaptive because stress is an intrinsic part of life for most organisms, and dealing successfully with stressors enables survival. Moreover, most selection pressures, the chisels of evolution, are stressors. The brain perceives stressors, warns the body of danger, and promotes survival (e.g., when a gazelle sees a charging lion, the gazelle's brain detects a threat and orchestrates a physiological response that enables the gazelle to flee). Stressful experiences often result in wounding or infection. Therefore, immunoenhancement, rather than immunosuppression, would be adaptive during short-term stress because it is unlikely that millions of years of evolution would select for a system exquisitely sculpted to escape the jaws and claws of a lion only to succumb to wounds and microbes (Dhabhar et al., 1995, 1994; Dhabhar and McEwen, 1996). In other words, just as the short-term stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, it should also prepare the immune system for challenges (wounding or infection) that are likely to result from stressful encounters (attack by a predator).

In contrast to the above discussion, it was (and still is) erroneously believed by many that stress-induced suppression of immune function is adaptive because immunosuppression during short-term stress conserves energy that is required to deal with the immediate demands imposed by the stressor. However, most mechanisms of immunosuppression expend, rather than conserve, energy. Moreover, the immune system is often critically needed for responding immediately to the actions of the stress-inducing agent (e.g., wounding by a predator). Thus, while ovulation, copulation, or digestion can wait for the cessation of stress, the immune response is not similarly dispensable during times of stress. Immune activation is critical for responding to the immediate demands of a stressful situation, especially when the situation results in wounding or infection. Furthermore, the time course for many proposed mechanisms for stress-induced immunosuppression, such as