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Mind-Body Medicine:

A Model of the Comparative Clinical Impact of the Acute Stress and Relaxation Responses

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Abstract

Although the physiological and biochemical changes that occur during the acute stress response have been well-characterized, the contrasting changes that underlie the relaxation response evoked by various mind-body techniques are less understood. To help guide future mind-body research, we present a conceptual model that integrates patterns of change at the physiological and molecular levels. In addition, we point to future research opportunities and discuss how repeated elicitation of these responses could influence the health of patients.

According to data from the 2007 National Health Interview Survey, the National Centers for Complementary and Alternative Medicine, and the National Center for Health Statistics, 19.2% of the U.S. adult population (more than 55 million people) had used at least 1 form of mind-body therapy during the previous 12 months.[1] Clearly, there is strong interest in mind-body therapies in this country, and this interest is translating into a growing body of research examining the biological basis of this connection.

One of the first attempts to understand the connection between the mind and body occurred nearly 100 years ago when Harvard physiologist Walter Cannon described the fight or flight response, identifying a consistent set of physiological changes that occur when animals, including humans, are exposed to stress.[2] Endocrinologist Hans Selye revised and expanded on Cannon's work 40 years later by describing the “general adaptation response,” a 3-stage model of the body's response to stress.[3] In this article, we will refer to these systemic adaptations as the stress response (SR). The SR consists of an involuntary set of physiological alterations that include increases in heart rate, blood pressure, respiration rate, and metabolic shifts that liberate energy.

More than 30 years ago, cardiologist Herbert Benson, one of the authors of this article, characterized another physiological state, the relaxation response (RR).[4] The RR, which can be voluntarily elicited, is associated with decreases in oxygen consumption, respiratory rate, and blood pressure, along with an increased sense of well-being.[4]

Early investigations mainly examined the physiological changes that occur during both the SR and RR. As new technologies such as biochemical assays have become available, researchers have been able to investigate mechanistic changes that occur during these responses as well, initially focusing on hormones, but more recently on signaling molecules such as nitric oxide (NO). Our primary aim in this article is to present a model that accounts for the physiological and biochemical changes that take place during exposure to acute stressors or elicitation of the RR and the relationship between the 2 responses.

Physiological Changes

The SR triggers a cascade of physiological responses. These include increases in volumetric oxygen consumption (VO_2) and respiration, dilation of the bronchiolar musculature and airways, increased blood pressure caused by increased cardiac output, and increased total peripheral resistance. It also triggers an increase of blood flow to the skin, splanchnic region, muscles, and heart. Together, these physiological responses produce a coordinated series of changes that enable the body to respond to stressful stimuli by providing energy to the areas that need it most. In a similar manner, a coordinated set of reproducible physiological changes have been observed during elicitation of the RR. They include reductions in volumetric oxygen consumption (VO_2), carbon dioxide elimination, a slowing of the heart and respiration rates, a drop in systolic and diastolic blood pressure, and an increase in heart rate variability.[4-7]

Biochemical Changes

Research on the SR has shown that many of the physiological alterations associated with it are brought about by centrally controlled biochemical changes. During situations perceived as being acutely stressful, the 2 main pathways activated are the sympatho-adreno-medullary (SAM) axis and the hypthothalamus-pituitary-adreno (HPA) axis. Both axes are activated by the hypothalamus secreting corticotrophin-releasing hormone (CRH), which causes the pituitary gland to release adrenocorticotropic hormone (ACTH). In the more rapidly acting of these pathways, the SAM axis, ACTH stimulates the adrenal medulla to release the catecholamines epinephrine and norepinephrine.[8] These stress-induced alterations are directly linked to a number of the physiological changes that take place in the body including increases in blood pressure, heart rate, respiration, and oxygen consumption.[8] In the slower-acting HPA axis, blood-borne ACTH acts on the adrenal cortex to release cortisol. Once in the bloodstream, cortisol induces metabolic changes in the liver, resulting in increased glucose concentrations in blood and tissues. The increased glucose produces adenosine triphosphate (ATP) to repair damaged cells and enables metabolically active cells throughout the body to respond to the stressor.[8]

Researchers have also explored whether alterations in these mechanisms underlie the physiological changes observed during the RR. To date, most studies of RR-related biochemical changes have examined those that occur over periods of weeks or months and, thus, fall outside the scope of this review.

Researchers examining potential relationships between the RR and HPA changes have tended to focus on the release of cortisol. However, their studies differ in the methods of measurement, the time of day the studies took place, and the extent of participant experience with eliciting the RR. To control for these variations, we selectively reviewed only those studies that measured acute changes in serum cortisol levels while controlling for diurnal rhythms. Sudsuang and colleagues found Buddhist monks had significantly lower serum cortisol levels following a period of meditation than did members of a nonmeditating control group.[5] Jenving and colleagues examined a group of Transcendental Meditation practitioners and found that participants with 3 to 5 years of experience showed a significant reduction in cortisol concentrations during 40 minutes of practice compared with members of a nonmeditating control group.[9]

Beyond the Classic Markers—Nitric Oxide

Technological advancements now make it possible to study a growing number of biochemicals, including nitric oxide (NO). Nitric oxide is a short-lived nitrogenous free radical that has been shown to mediate diverse physiological processes including cardiovascular, immune, and nervous system function.[10] The extremely short half-life (subsecond) and gaseous nature of

NO make this molecule difficult to measure and has led to the development of multiple indirect measurement strategies. These include the measurement of NO in exhaled breath, the measurement of nitrites and nitrates (NO degradation products) in plasma, and the measurement of flow-mediated dilation (FMD) in arteries.

In blood, NO is oxidatively metabolized to nitrite (NO2-) and nitrate (NO3-), together called (NOx).[11] These degradation products are more stable than NO itself. However, the usefulness of these measures of in situ responses to stress and the RR is limited by the fact that NOx levels in blood are influenced by several extraneous factors such as dietary nitrate intake and nitrate inhalation (from polluted air).[11] It is estimated that 70% to 90% of the nitrites present in plasma are derived from NO synthesized by the constitutive isoform of nitric oxide synthase (NOS), endothelial NOS or eNOS.[12]

Flow-mediated dilation can provide an indirect measure that represents the presence of NO, as there is a strong correlation between FMD and plasma nitrite levels.[12] NO was first characterized as an endothelium-derived relaxing factor and is now known to play a prominent role in vascular dilatation, which affects blood pressure.[13, 14] In addition, NO plays a central role in a number of other cardiovascular processes including the regulation of platelet function, vascular smooth muscle cell proliferation, and leukocyte interactions with vascular endothelial cells. Through these processes, NO is thought to play an integral role in the development of atherosclerotic plaque.

In terms of the immune system, NO has the capacity to influence the phenotype of inflammatory cells and thus is capable of influencing the character of immune responses.[15] The generation of NO is dependent on the enzyme NOS. Different isoforms of NOS have been identified including some that are constitutively expressed and others whose activation is associated with disease processes. According to a recent hypothesis, constitutive NOS is influenced by elicitation of the RR.[16]

NO and the Stress Response

Recent research shows that mental stress is associated with vasoconstriction in healthy adults. For example, Lind and colleagues have shown that having healthy volunteers engage in 5 minutes of mental arithmetic impaired FMD in the brachial artery.[17] Given the prominent role that NO plays in modulating vascular tone, it has been hypothesized that a change in the NO level may be important to the FMD impairment observed during exposure to mental stress.

In Lind's study, the effects of stress on FMD were examined only once at the end of a 5-minute period of mental stress. However, Ghiadoni and colleagues had volunteers watch a videotape of a stress-inducing speech to indirectly investigate NO-related changes several hours afterward.[18] The results showed that while the gross hemodynamic response associated with the acute stressor resolved rapidly, changes in FMD were significantly altered for more than 90 minutes after participants heard the speech. This work suggests that the acute mental stressors we regularly encounter may have subtle physical effects that persist well beyond the duration of the event.

NO, HPA Axis, and SAM Interactions

In addition, it is becoming apparent that NO interacts with chemicals released as part of both the SAM and HPA responses to acute stress (Figure). Within the SAM axis, research shows that bidirectional influences occur. When healthy humans are subjected to sympathetic stimulation, FMD is markedly attenuated.[19] Research also shows that NO inhibits aspects of the SAM axis. For example, in an experiment that exposed healthy humans to mental stress and used L-NG-monomethyl-arginine (L-NMMA) to block NO release, Lindqvist et al. showed

that plasma norepinephrine levels increased to a higher degree when NO release was blocked than in the control condition, showing that NO likely exerts inhibitory effects on the SNS during stress.[20]

Research also shows that bidirectional patterns of influence exist between NO and components of the HPA axis. For example, glucocorticoids reduce the presence of NO by inhibiting NOS. When present within the adrenal glands, NO inhibits the initial biosynthetic step in steroid production, which leads to decreases in hormones such as cortisol. Research also suggests that NO modulates the release of other stress hormones including ACTH.[21] It has been shown that simulated public speaking tasks decrease the surrogate measure of NO presence, FMD; these FMD changes are known to be influenced by a cortisol-related pathway because blocking cortisol production, through metyrapone administration, prevents the stress-stimulated FMD reductions.[22]

Overall, current research suggests that SAM- and HPA-mediated inhibition of NO may be among the factors that cause increases in blood pressure during an acute SR. Recent studies have considered how the operation of the relationships between NO and the hormonal and nervous systems may influence long-term health. In considering the implications of their findings, Ghiadoni et al. hypothesized that the repeating patterns of acute changes that are likely to be experienced during daily life may be among the factors that contribute to the development of some disease states. As an example, they suggested that the persisting changes in FMD that occur in response to daily stressors may be one mechanism through which experiences of repetitive mental stress is linked to atherogenic processes.[18]

NO and the Relaxation Response

Blood pressure reduction is among the changes most consistently observed during studies of the RR. A substantial number of reports have demonstrated this association in both healthy and hypertensive participants.[5,6,23] In terms of mechanism, in addition to the constitutive role of eNOS, in vivo evidence shows that NO-releasing neurons located within the vascular terminals of the autonomic nervous system play a role in regulating vascular tone; NO from both of these sources could potentially be involved in RR-associated blood pressure decreases.[24] Further, the operation of HPA- and SAM-NO feedback loops may also contribute to NO-induced vascular tone changes during RR elicitation.

In 2001, Stefano et al. proposed that NO may mediate some of the physiological effects of the RR.[16] This hypothesis suggested that constitutively derived NO may have a role in the peripheral vasodilation consistently observed in studies of the RR.

Our group recently began experimentally examining Stefano's hypothesis and found that RR elicitation (as measured by decreased VO_2) was associated with an acute increase in the presence of NO.[25] The prominent role that NO plays in the regulation of vascular tone and the recent observation of acute NO increases during RR elicitation led us to the following hypothesis: that NO changes play a role in the consistent pattern of blood pressure reduction that is seen during RR elicitation.

In a subsequent randomized controlled trial, we demonstrated that 8 weeks of RR training significantly reduced systolic blood pressure in individuals with systolic hypertension. Systolic blood pressure decreased by 9.4 mmHg and pulse pressure by 7.9 mmHg on average. With 8 more weeks of RR training, 32% of the study participants were able to eliminate 1 or more of their antihypertensive medications.[6] In our on-going randomized trial, we are examining whether the extent of NO change observed during RR elicitation is related to the extent of blood pressure change that occurs in people with systolic hypertension.

NO in a Model of Acute Stress and Relaxation Responses

The relationships previously described led us to consider where, conceptually, NO changes may fit into a schema that represents relationships between acute stress and relaxation responses and the biochemical and physiological changes that occur. The Figure shows how NO changes might relate to other biochemical and physiological changes. For example, the inhibited NO release during the SR is a consequence of elevated norepinephrine and cortisol levels. In turn, NO inhibition is shown to be among the factors contributing to physiological changes such as elevations in blood pressure. During the RR, the opposite phenomenon potentially contributes to physiological changes such as a decrease in blood pressure.

In summary, the inclusion of NO in our model deepens our understanding of the biochemical processes that underlie the cognitive-to-physiological relations of the RR. Overall, research on the SR and RR is showing that when similar parameters are examined, they tend to show alterations in opposing directions. The Figure represents the changes that occur during the SR and the RR. Its value lies in the fact that it is a comparative view of the 2 responses and that it illustrates the interrelations among physiology, hormones, and signaling molecules.

Future Directions

If we are to more fully understand the health benefits of the mind-body therapies that elicit the RR, future research will need to explore the role of other biochemicals in eliciting the response. For that to happen, several methodological and conceptual issues will need to be addressed.

First, researchers will need to consider the clinical conditions on which they want to focus. The consistently reproduced effect on blood pressure that has been reported in the RR literature plus emerging observations of RR-induced NO changes, coupled with the strong role that NO is known to have in influencing vascular tone, builds support for investigating the contribution that RR elicitation could make to the management of hypertension.

Second, the complexity of biological systems involved suggests that the physical effects of RR will be mediated by patterns of change that involve multiple components that, when present together, alter the organism's capacity to respond to stressful situations.

Finally, future research will need to expand the concept of how acute effects influence the long-term health trajectory of the organism as a whole. Relaxation technique training programs need to include cognitive-behavioral skills to help participants learn to identify habitual thought patterns that increase stress. When mind-body techniques to evoke the RR are integrated into an individual's lifestyle in a manner similar to that suggested by Ghiadoni, there is the potential for a cumulative health benefit.[18] Our recent data is consistent with this concept. We showed that more than 2,000 genes are differentially expressed in long-term practitioners of varied mind-body practices compared with control subjects who did not practice these techniques.[26] Furthermore, when the nonpractitioners received 8 weeks of RR training, expression of more than 1,500 genes was altered when compared with their baseline condition. A core challenge will be to build a body of empiric evidence documenting examples of such relationships and explaining the underlying mechanisms through which they operate.

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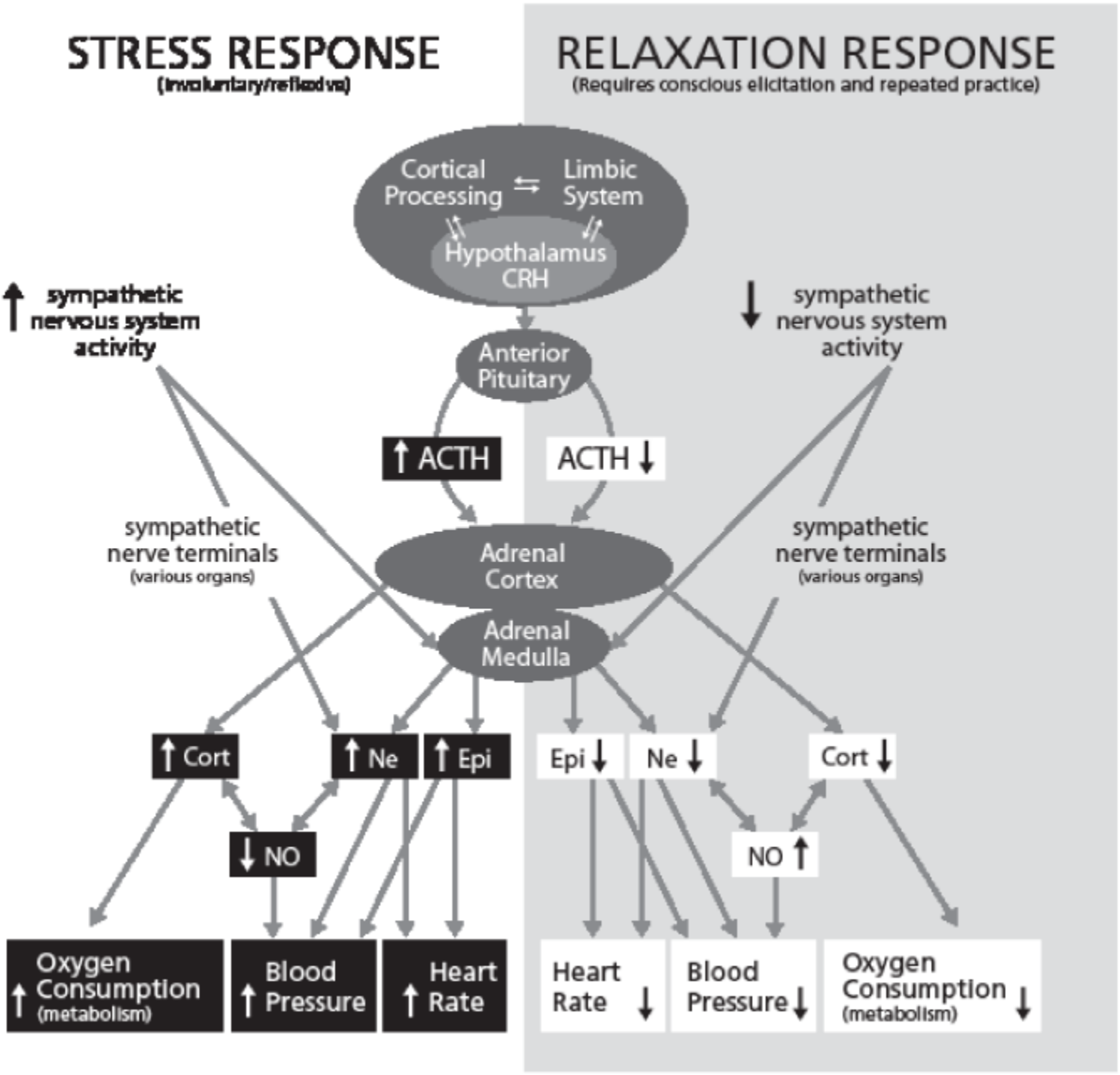

Figure. Comparative Impact of the Acute Stress and Relaxation Responses: Central and Peripheral Nervous System Activities

Using blood pressure as an example, we show how acute stress and relaxation responses alter hypothalamus-pituitary-adrenal (HPA) and sympatho-adreno-medullary (SAM) axis activities. These responses introduce contrasting hormonal and signal molecule changes that in turn influence clinically significant conditions such as high blood pressure.

Epi = epinephrine

Ne = norepinephrine

SAM axis is the adrenal medulla to Ne and Epi

Cort = cortisol

NO = nitric oxide

HPA axis is the adrenal cortex to Cort