Stress and Addiction: When a Robust Stress Response Indicates Resiliency

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Abstract

Objective—Stress reactivity research has traditionally focused on the idea that exaggerated responses to stress may have adverse effects on health. Accumulating evidence suggests that attenuated responses to stress and delayed recovery may also be problematic.

Methods—This review focuses on the role of the stress response of the hypothalamic-pituitary-adrenocortical (HPA) axis, the endogenous opioid system (EOS), and the cardiovascular system in hypertension, pain perception, and addictive behaviors. Results from multiple methods of assessment and stress paradigms conducted in our laboratory over the past two decades are integrated with research from other investigators and with existing theories.

Results—Research indicates that exaggerated biological and physiological responses to stress and attenuated pain perception are associated with hypertension and risk for cardiovascular diseases. This research complements work linking reduced stress responses with enhanced pain sensitivity and discomfort. Multiple studies have also demonstrated that an attenuated stress response is linked to exacerbation of withdrawal symptoms and relapse in nicotine addiction. Evidence indicates important moderators (i.e., sex, personality traits, and early life adversity) and HPA- and EOS-related mechanisms in the altered response to stress. We integrate these findings in a conceptual model emphasizing that robust stress responses in the context of addiction and relapse should be considered as a marker of resiliency.

Conclusions—A blunted stress response may indicate long-term physiological dysregulation that could usher harmful consequences for cardiovascular disease, pain perception and addictive disorders. The impact of dysregulation is influenced by multiple individual and situational factors that should be considered in evaluating the clinical significance of stress response dysregulation.

Keywords

Stress; HPA response; endogenous opioid system; addiction; relapse; pain; craving; withdrawal

Introduction

Multiple biological, psychological, and behavioral mechanisms mediate the effects of "stress" on health and disease; and research has identified individual difference factors that

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increase vulnerability to the adverse impact of stress as well as factors that promote coping and resilience. In this paper, we use the term stress as an environmental challenge (also referred to as stressor) and distinguish this construct from the stress-response that has multiple psychological, behavioral and biological components. Although exaggerated stress response has been seen historically as a harmful outcome of exposure to stressful events, research provides strong evidence that a blunted stress response can also be harmful and that the direction of impact of the stress response is influenced by conditions, situations, and dispositional factors. Our research program has focused on understanding how stress produces its harmful effects on health, with a particular focus on hypertension, pain perception, and addictive processes.

Central to the focus of our research are the roles of two stress brain pathways: the hypothalamic-pituitary-adrenocortical (HPA) axis and the endogenous opioid system (EOS). After providing a brief definition of the stress response and a review of HPA-EOS interactions related to the stress response, we review several studies conducted by our laboratory and other research teams over the last two decades. Specifically, the following topics will be reviewed: (1) stress-reactivity hypothesis in hypertension and other cardiovascular diseases; (2) the role of stress reactivity in pain perception and analgesia; (3) the effects of exaggerated and blunted stress responses on nicotine addiction and relapse; and (4) moderators of the stress response in pain perception and nicotine addiction. The converging results of these studies are interpreted within a theoretical framework in which a blunted stress response is considered as a marker of adverse outcomes in addiction, while a robust stress response is considered as an indicator of addiction-related resiliency and effective coping.

The Stress Response

Definition of the stress response

Stressful events normally activate several biological systems, including the HPA axis and the sympathetic nervous system (1–5). The HPA axis performs a central function in directing the neuroendocrine response to stress and it plays a mediating role in stress effects on health (6–9). This axis involves three brain and peripheral structures: the hypothalamus, the pituitary gland, and the cortical part of the adrenals. The HPA axis is activated by the release of corticotropin-releasing factor (CRF) from neuronal cell bodies of the paraventricular nucleus (PVN) of the hypothalamus. CRF stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary and beta-endorphin into the systemic circulation. ACTH is transported via peripheral circulation to the adrenal cortex where it stimulates the synthesis and release of corticosteroids--most notably in humans, cortisol (10, 11). Cortisol triggers a negative feedback loop, where it regulates ACTH and CRF release exerting a bottom-up regulatory effects on the HPA (10, 11).

In addition to the HPA axis, stress activates the EOS. Endogenous opioids are naturally occurring, opiate-like substances that regulate mood, pain, and the reinforcing properties of many drugs of addiction (12, 13). Many of the brain structures that regulate physiological and behavioral components of stress responding, including cingulate cortex, amygdala, and periaqueductal gray, contain endogenous opioids (14–19) that are released in response to

stress and that are directly involved in regulating the HPA stress response (12, 20–23). Preclinical studies have demonstrated that central opioid activity interacts with dopaminergic, serotonergic, adrenergic, and GABAergic pathways in the prefrontal cortex, limbic system, and brain stem (24–28). This wide network of activity demonstrates that this system is involved in multiple downstream effects related to HPA activity, stress response, mood changes, and drug reward.

HPA and opioid interaction

Central regulation of the HPA stress response by the EOS involves three points of interface (29–33) as indicated in Figure 1. *First*, CRF neurons in the hypothalamus receive direct inhibitory input from beta-endorphin neurons in the arcuate nucleus (34); this effect is mediated by activation of μ-opioid receptors (35, 36). *Second*, noradrenergic release from the locus coeruleus is under control of opioid neurons within the brainstem (37–39). Beta-endorphin and other opioid neurons indirectly inhibit CRF activity by inhibiting the CRF-stimulatory norepinephrine neurons (37, 40). *Third*, opioid neurons from the arcuate nucleus innervate the nucleus accumbens and prefrontal cortex, major structures involved in mesolimbic drug-reward pathway.

This innervation leads to activation of dopamine release in the mesolimbic pathway, which involves dopamine-producing neurons within the ventral tegmental area (VTA) projecting to the nucleus accumbens (NA) and engaging other structures involved in stress response regulation including the amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC (41, 42). Reduced opioid stimulatory inputs to the mesolimbic dopaminergic system may lead to reduced basal dopamine activity, which may enhance the acute response and rewarding effects of dopamine-stimulating drugs, such as nicotine. Blocking opioid effects using opioid antagonists should lead to disinhibition of HPA regulatory effects, causing enhanced HPA output, as evidenced by increased ACTH and cortisol production. This pattern of hormonal release has been established as a reliable indicator to test the functional status of hypothalamic opioid tone (43–45). Decreased opioid tone is predicted to diminish effects of HPA axis opioid neurons, thereby attenuating HPA response to opioid blockade challenges. Reduced opioid tone may influence modulation of mesolimbic dopaminergic transmission; and observations that dysphoric states are usually associated with impaired endogenous opioid functions (46–49) suggest that reduced tone may also contribute to increased negative affect.

Stress Reactivity and Pain in Hypertension

Our research was initially grounded in the stress reactivity hypothesis, which is that enhanced physiological responses to acute stress increases risk for health problems, particularly cardiovascular diseases (50, 51); and we assumed that reduced response to stress would be beneficial to health. Work in this area assumes that responses to acute stressors in the laboratory provide an accurate indication of how individuals respond to stressful events in their daily life. Therefore, the stress reactivity hypothesis is typically studied using laboratory protocol wherein individuals are exposed to acute challenges, such as public

speaking, mental arithmetic, or cold pressor tests, and their cardiovascular and physiological responses are measured (52–54).

Overall, there is mixed support regarding the generalizability of laboratory-based stress research (52, 53, 55), some longitudinal studies provide evidence of an association between the magnitude of responses to acute stress tasks (laboratory) and increases in blood pressure levels over time (56–60) as well as cardiac morphological changes, including increased left ventricular mass (51, 61, 62). Despite many researchers focusing on negative implications of enhanced stress response, and despite the underlying linear function implied by the stress reactivity hypothesis, much of the subsequent sections of this paper will address the need to consider the significance of a reduced or blunted stress response.

HPA stress response in hypertension

Early stress reactivity research focused primarily on autonomic and cardiovascular measures (e.g., (50, 63–65)), which tend to be responsive to various activating tasks rather than to specific tasks that are emotionally distressing. During the 1990s, more research was conducted focusing on other biological and neurochemical measures. Our research in the 1990s (e.g., (66–69)) contributed to expanding the definition of stress reactivity by incorporating new stress challenges (e.g., situational novelty, pharmacological challenges, and medical exam stress) and by incorporating additional biological measures, primarily the HPA hormones, prolactin, beta-endorphin, and dehydroepiandrosterone (DHEA) (70–74). The approach to expand the biomarkers of stress in the laboratory complemented an established approach to the assessment of sympathetic, hemodynamic, and cardiac structural changes associated with stress, especially in hypertensives and hypertension prone individuals (75–81).

The introduction of additional socially-relevant stressors to laboratory human research broadened the scope of our sampling of the stressful experiences people may encounter in daily life. This approach enhanced the generalizability of the results (64, 82–84) while reducing the artificial and academic natures of the acute laboratory stressors that dominated stress reactivity research up to that point (84–87). In addition, integration of multiple physiological systems in assessing the stress response enabled us to better capture the broad effects of stress and enhanced the validity of laboratory stress research.

For instance, in one study, we examined the effects of exposure to a novel experimental setting on resting, morning blood cortisol concentrations in men with borderline hypertension (66) to test the hypothesis that increased central nervous system activation among individuals with borderline hypertension would predict enhanced anticipation and cortisol secretion in a novel experimental situation. We found that participants with hypertension had higher cortisol concentrations than normotensive participants during the first and second days of exposure to the lab, but this difference disappeared on the third and fourth days. In another study, we assessed cortisol levels in individuals with hypertension before and after exposure to stressful challenges (67). Stress protocols included two levels of demand (intermittent reaction time with brief rests vs. reaction time alternating continuously with mental arithmetic); and we found that high-demand (continuous), but not moderate-

demand (intermittent), mental stress produced enhanced cortisol response in participants with hypertension relative to normotensive participants.

To better define alterations of the psychobiological stress response in individuals with hypertension, we continued our research by evaluating the impact of a pharmacological challenge on the stress response in this group. In one study, we administered a dietary dose of caffeine (3.3 mg/kg, equivalent to 2 to 3 cups of coffee) and examined the effects of such a dose on HPA responses to stress in hypertensive and normotensive individuals (69). Although both hypertensive and normotensive participants showed significant cortisol responses to caffeine combined with the stress tasks, only participants with hypertension exhibited a significant cortisol response to the caffeine challenges during rest, indicating enhanced sensitivity of this stress hormone to this stimulant substance. We replicated and expanded these findings in a larger sample of normotensives who had a parental history for hypertension (88). In all, these observations reinforced the utility of adrenocortical measures in studies of stress reactivity among individuals at risk for cardiovascular diseases. They also demonstrated, for the first time, the combined effects of caffeine plus stress in hypertension-prone individuals.

Our research on the HPA axis in individuals with hypertension provided translational evidence of earlier work in animal models, as indicated by a review of the literature that integrated animal and human findings to evaluate the glucocorticoid hypothesis of hypertension (5). Overall, glucocorticoids (primarily corticosterone in rats and cortisol in humans) affect several blood pressure (BP) regulating processes and they influence expression of genes involved in BP (5). These effects may contribute to at least one subtype of the heterogeneous and multifactorial polygenic condition of hypertension. Furthermore, studies have examined cortisol tissue sensitivity, cortisol production and cortisol metabolic rate in hypertension-prone persons (89–91); the results of which provide support for the hypothesis that elevated cortisol levels may serve as an intermediate phenotype of hypertension risk. Incorporating HPA measures and non-invasive hemodynamic assessment in stress reactivity research and expanding the types of stress challenges used in the laboratory and in ambulatory settings (92–94) has enabled us to learn a great deal about manifestations of vulnerability and risk. This research also produced greater convergence of evidence related to the role of stress in hypertension risk.

In summary, we conducted a series of lab studies using different types of acute and natural stressors and using pharmacological challenges. The results of these studies demonstrate that vulnerable populations (primarily hypertensive and hypertension-prone individuals) consistently experience enhanced HPA activity and enhanced cardiovascular response to stress.

Stress and pain perception

The complex organization of the stress response involving multiple cortical, subcortical, and peripheral systems is also essential in pain reception and regulation of pain response. It is possible that processes involved within both stress response and pain regulation are integrated at multiple central nervous system (CNS) levels (95–97). Multiple brain structures, including the amygdala, prefrontal cortex, multiple nuclei in the hypothalamus,

insula, anterior cingulate, locus coeruleus, and other structures within the limbic system are involved in both pain and stress response regulation (97–99). This integration may account for the reciprocal influences between stress and pain. Acute stress suppresses pain perception (100–102), and mechanisms may involve central opioid system (71, 103, 104) and peripheral baroreceptor activation (105, 106).

Stress, pain, and hypertension risk

Findings of exaggerated stress response in hypertensive and hypertension-prone individuals intersected with observations of blunted pain perception (i.e., hypoalgesia) in these populations (105, 107–109). This was particularly intriguing when examining the association of BP with pain perception in normal, healthy young individuals (108, 109) and in young individuals with parental history of hypertension (108, 109). To explain this phenomenon, we conducted a series of studies in collaboration with colleagues at Ohio University and the University of Birmingham, United Kingdom (110–114) in which we focused on two possible mechanisms.

One potential mechanism was enhanced baroreceptor stimulation (105, 106) that may result from increased cardiovascular response in this population (62, 69, 93, 115–117). We examined effects of baroreceptor stimulation on nociceptive responding in men and women with positive (high risk) or negative (low risk) parental history of hypertension. Subjective pain and nociceptive responding were evaluated during electrocutaneous sural nerve stimulation and under three baroreceptor conditions (stimulation, inhibition, and control). Although both stimulatory and inhibitory baroreceptor conditions were associated with reduced pain reports relative to control, this effect was comparable in low and high risk groups (112). This finding suggested that attenuated pain perception in hypertension-prone individuals may not be due to enhanced baroreceptor activity.

The second mechanism that we examined to explain hypoalgesia in hypertension-prone individuals was a blunting of normal opioidergic inhibitory regulation of hypothalamic activities. This work was based on previous opioid blockade research (118–120); therefore, we examined the effect of opiate blockade on HPA responses to a painful stressor in individuals with and without a parental history of hypertension. In this research, we used a double-blind, counterbalanced design to administer the blockade (placebo or naltrexone) prior to assessing nociceptive flexion reflex threshold. Results showed increases in salivary cortisol levels following pain assessment after the ingestion of naltrexone, but not after placebo. Although pain threshold and tolerance were higher among high-risk men relative to low-risk men, there was no difference in the influence of opioid blockade between the two groups (121).

In summary, these studies confirmed attenuated pain sensitivity in persons at high risk for hypertension, but they did not support a role for the EOS nor for enhanced baroreceptor activation as explanatory mechanisms for the hypoalgesia observed in hypertension-prone individuals. In light of the earlier observations that this group exhibits stress-response dysregulation, we speculated that alterations within the stress response systems could contribute to pain alteration in this population. Next, we briefly review studies that provided initial support for this hypothesis.

Stress response systems and pain

In our efforts to examine the role of the stress response in regulating pain perception, we conducted multiple studies. For example, we examined the extent to which basal cortisol concentrations and hemodynamics during rest predicted level of pain experienced during exposure to the hand cold pressor test (CPT) (122). To examine these relationships, we used a design that involved examining immediate and delayed pain, wherein participants were asked to rate their pain every 15 seconds during a 90-second CPT and during a 90-second post-CPT (recovery) period (109); participants also reported pain using the McGill Pain Questionnaire. Salivary cortisol samples and cardiovascular measures were collected prior to, during, and after the CPT. The results revealed that higher pre-CPT cortisol concentrations predicted lower pain reports during and after the CPT. We also found that systolic BP and stroke volume correlated negatively with pain.

Though our cardiovascular findings were consistent with previous research, the cortisol-pain connection was novel and suggested that HPA activation may contribute to, or be a marker of, attenuated pain perception seen during acute stress events. The role of increased CRF in pain has been proposed (123); and although early pharmacological studies indicated analgesic effects of CRF in dental patients (124), direct effects of CRF on pain sensitivity have not been consistently observed (125).

Our findings also extended previous observations of reduced adrenocortical activity in individuals with chronic pain conditions, such as fibromyalgia, rheumatoid arthritis (126, 127), chronic fatigue syndrome (128, 129), and child abdominal pain (130). Indeed, early research on chronic pain syndromes showed an association between ongoing pain and adrenocortical hyporesponsiveness (131–134). For instance, cortisol was inversely associated with pain intensity and number of pain sites (135); and chronic headache was associated with decreased cortisol concentrations in serum and cerebrospinal fluid (134). Other researchers found that women with chronic pelvic pain showed lower morning cortisol levels relative to normal controls (133); and others found that low back pain was associated with smaller cortisol variation between morning and midday levels (136). These findings, in combination, support the possibility of adrenocortical involvement in regulating pain and increasing risk for chronic pain syndromes. The immuno-regulatory effect of cortisol and its influence on inflammation, including its inhibitory effects on prostaglandins (137, 138), may play a role in explaining this phenomenon. Early experimental evidence with the Lewis rat, a model characterized by a genetically deficient glucocorticoid production, demonstrates consistent results, showing high susceptibility of this animal model to inflammatory diseases (139).

Stress-induced analgesia—One manifestation of the influence of stress on pain regulation is stress-induced analgesia. Stress (e.g., electric footshock) in rats suppresses pain behavior (140). Specifically, intermittent, uncontrollable footshock produces analgesia mediated by opioid mechanisms, whereas exposure to continuous footshock produces non-opioid analgesic effects (141). On the other hand, clinical research indicates the role of stress in exacerbating pain perception (142–144). Yet, research in healthy humans indicates the possibility that acute stress may attenuate pain perception (102, 145). These effects are

likely mediated by physiological, peripheral, and descending opioid mechanisms. For example, there are indications that baroreceptor stimulation (105, 146), peripheral opioid peptides (147), and cardiovascular reactivity (148) may play a role (149).

Informed by this literature, we examined the extent to which psychophysiological and adrenocortical responses to acute stress predicted subsequent pain perception in a relatively large sample of healthy participants (100). Participants were assigned to one of two conditions: rest followed by pain induction (using the CPT) or stress (public-speaking challenge) followed by pain. Stress exposure was associated with reduced pain during CPT; and this effect was mediated by systolic BP level during stress. Mood changes were independent predictors of pain. This evidence further implicated stress-related pressor effects in altering pain perception. The findings provided additional support for the hypothesis that attenuated pain perception in hypertension may be due to altered stress response and BP changes.

We extended these findings by examining the role of endogenous opioid mechanisms in pain via a double-blind, counterbalanced study using placebo or 50 mg of naltrexone (for opioid blockade) (71). This study demonstrated consistent responses to opioid blockade as indicated by increased plasma cortisol, ACTH, beta-endorphin, prolactin, and salivary cortisol levels. One intriguing observation resulting from this study is that women in the blockade condition reported reduced pain and BP. This was opposite to the expected effects; and it indicates differential effects of the opioid system on pain perception and BP in men and women, further supporting the sex-specific pattern of interactions between hemodynamic and central regulation of pain and hypertension risk (71, 150, 151).

In summary, results from this series of studies indicate that differential baroreflex, endogenous opioid activation, and descending pain modulation did not explain observed hypoalgesia in hypertension-prone individuals. Studies examining the role of the stress response and systems involved in this response provide evidence that altered stress-response may be involved in modifying pain sensitivity among hypertension-prone individuals. These studies also provide evidence that attenuated stress response may be associated with adverse effects, including increased pain sensitivity and discomfort. Therefore, it is possible that reactivity to stress is not only a manifestation of demands on the body, but that it may also shape how we process and respond to subsequent stressors or emotional challenges. Next, we relate these findings to a growing literature on the clinical significance of the blunted stress response.

Blunted Stress Response as a Risk Factor for Addiction Relapse

The role of stress in the maintenance of and relapse to drug abuse is well established (6, 152–163). For example, stress is one of the most commonly cited triggers of tobacco use and relapse (6, 164–168). Stress increases the frequency of smoking and accelerates progression towards a full relapse among abstinent smokers (169–173). These risks are particularly high in the presence of other negative affective states, including anxiety, irritability, depression, and craving (174–178).

Observations from other literatures provide examples of when hypoactivation of the stress response systems can be associated with adverse symptoms, including negative affect, distress, and pain perception. For example, blunted HPA stress response has been observed in individuals with alcoholic addiction and other substance over-users (179–181). Our hypertension studies excluded heavy alcohol and other drug users and we applied specific dietary instructions to limit potential confounding effects on the stress response (69, 182, 183). We also excluded smokers to avoid the acute effects of tobacco, or the distressing effects of withdrawal (if smokers were asked to abstain from smoking), on the stress response. This led us to question the impact of abstinence from smoking and whether it could serve as a natural stressor for people who are dependent on tobacco. Therefore, we set out to conduct a series of studies to examine the effects of withdrawal stress on mood, psychobiological response to acute stress, and performance measures under these conditions.

Nicotine withdrawal as a stressor

Abstinence from smoking is associated with numerous distressing symptoms, including craving, anxiety, depression, restlessness, irritability, and difficulty concentrating (184). Intensity of withdrawal symptoms is influenced by multiple factors, including: 1) length of time since the last cigarette; 2) level of nicotine dependence; 3) situational demands (e.g., acute stressors, demanding challenges, or smoking-related cues); and 4) the person's disposition and skills (e.g., coping resources, history of psychopathology). Smoking abstinence may also lead to acute changes in various neurobiological systems, although their characteristics and consequences are not well understood. The detrimental effects of abstinence on mood are possibly modulated by these biological systems and they likely exacerbate the experience of stress and increase the probability of smoking resumption (165, 185). Therefore, we decided to test the hypothesis that psychophysiological responses to behavioral challenges are enhanced by short-term abstinence from smoking.

In one study, we collected physiological, cognitive, and self-report measures during rest and in response to acute stress among smokers after a period of smoking abstinence (18 hours) or after ad libitum smoking (186). We found that withdrawal produced significant distress symptoms and greater BP responses to the acute speech challenges. Withdrawal was also associated with worse cognitive performance. This set of results demonstrated a stress-like cluster of symptoms during nicotine withdrawal, as evidenced by changes in mood, performance, and BP responses (186). Yet, it was not known how long-term smoking and dependence alter these stress response systems and how withdrawal may influence long-term stress-related changes.

Acutely, nicotine stimulates adrenocortical and cardiovascular functions (187–189); and an additive effect of nicotine and acute stress has been documented. Chronic nicotine administration may lead to prolonged HPA activation, but little was known about long-term effects on stress response or how these responses may be modified by short-term abstinence. The latter question is important for elucidating the role of stress-related physiological changes in exacerbating withdrawal symptoms and in altering the rewarding properties of nicotine (190). Therefore, we examined differences in adrenocortical, cardiovascular, and mood reports during rest and in response to acute psychological stress (a combination of

public speaking and mental math) among three groups: abstinent smokers, smokers who continued to smoke at their normal rate, and non-smokers (191). We compared these data to those obtained during a control session, when participants rested for the entire time in the lab, and found that smokers (smoking ad libitum or abstinence) showed attenuated systolic BP responses to public-speaking stressor when compared to non-smokers. Compared to non-smokers, smokers also exhibited a blunted cortisol response to stress (191).

These diminished systolic BP and cortisol responses to stress in smokers, independent of acute exposure to nicotine, indicate alterations in the stress response resulting from chronic exposure to nicotine that are independent of withdrawal. Frequent and prolonged stimulation of the HPA by repeated exposure to nicotine may lead to enhanced HPA activation, but reduced sensitivity to effects of other stimuli not related to nicotine (192); therefore, disrupting the ability of the HPA system to mount a normal response to acute stress. Mechanisms mediating the effects of chronic tobacco use on stress response systems likely involve multiple processes, including reduction of the number or affinity of nicotinic receptors mediating effects of nicotine in the PVN and other central nervous system structures (191). It is not clear if such changes may be normalized by long-term abstinence.

In summary, these initial studies demonstrated that smoking deprivation was associated with deterioration of mood and with exaggerated stress response, indicating a stress-like effect of abstinence. Furthermore, the long-term effects of smoking appear to be associated with dysregulation of the stress response, characterized by blunted HPA and other biological responses to stress. The relevance of these processes within clinical contexts were not known. The role of dysregulated stress response in increasing vulnerability for smoking relapse was investigated subsequently.

Blunted stress response and addiction relapse

Building on research demonstrating altered stress response among smokers (191–196), we conducted a series of studies to examine the extent to which this altered stress response predicts early smoking relapse (197–202). In one study (203), we tested smokers interested in quitting during a day when they were still smoking at their usual rate (ad libitum) and during the first day of their abstinence. Salivary cortisol levels and mood reports were assessed during the evening and morning over 24 hours of ad libitum smoking and during the first 24 hours of abstinence. Not surprisingly, participants reported significant withdrawal symptoms on the first day that they were abstinent. Smokers who relapsed during the first week of abstinence reported greater craving for cigarettes and greater overall distress during the first 24-hour period of abstinence than those who maintained abstinence over the same period. Though all participants showed the expected diurnal changes in cortisol levels, smokers who relapsed within the first week of the quit attempt exhibited a greater decline in cortisol levels on the abstinence day compared to the ad libitum day.

The association of exaggerated adrenocortical and mood perturbations during the first 24 hours of abstinence with early relapse indicated that processes underlying these measures may contribute to perceived benefits of smoking (204), possibly enhancing the reinforcing value of smoking after abstinence and increasing risk for early relapse (205). This, in turn, may contribute to early relapse, possibly driven by motivation to self-medicate (169, 206).

Although this study focused on important stress-response systems during a critical period of a quit attempt, and although it prospectively examined the extent to which changes in obtained measures were associated with early relapse, it did not directly address the stress response.

Thus, we performed a subsequent study to examine HPA responses to stress following the first 24 hours of a quit attempt in predicting relapse over a four-week period (198). In addition to ACTH plasma and salivary cortisol concentrations, we collected a battery of cardiovascular measures and mood reports during rest and in response to acute psychological stressors (public speaking and mental arithmetic). After the quit day, participants attended four weekly follow-up sessions to measure relapse and to verify maintained abstinence from smoking. Smokers who relapsed within four weeks showed attenuated ACTH, beta-endorphin, cortisol, and BP responses to stress relative to those who successfully abstained over the same period. Those who relapsed also reported exaggerated withdrawal symptoms and mood deterioration during the initial withdrawal period. The link between stress response and relapse is further moderated by several additional factors, some of which I review below.

Moderators of the Blunted Stress Response in Nicotine Addiction

To identify factors that moderate the link between stress response and intensity of withdrawal and risk for relapse, our research has focused on both biological and situational factors. Specifically, we have examined sex differences, individual differences in emotional dispositions, adverse early experiences, and exposure to multiple substances.

Sex differences—There is accumulated evidence demonstrating sex differences in hormonal and cardiovascular responses to stress (71, 151, 207). Clinical and epidemiological reports also indicate that stress is more frequently reported by women, compared to men, with addiction problems; and stress is more frequently cited as a reason for drug use and relapse by women than by men (208–211). Environmental context and smoking-related cues (e.g., smell and taste) play a greater role in determining the perception of smoking effects in women than in men (166, 178, 212–216). Compared to men, women who smoke are more likely to use smoking to cope with negative affect and discomfort (217, 218). Women also report more distress after exposure to acutely stressful situations and to smoking-specific stimuli (176, 177, 219–221); and they are less likely to maintain long-term abstinence (222–228). Sex differences in the role of the opioid system in the stress response (229–233) and in responses to opioid blockade have also been reported, with women exhibiting greater HPA response to opioid blockade challenges (45, 234). Preclinical evidence also indicates sex differences in the sensitivity, quantity, and ratio of different classes of opioid receptors (231, 233, 235).

Our laboratories have examined sex differences in HPA and emotional dysregulation within the area of nicotine addiction. Our findings indicate that during withdrawal (early abstinence), women experience greater negative symptoms than men, especially during exposure to stress; and men exhibit enhanced stress and cortisol response (198). Our studies also document sex-related moderation of relapse predictors. For instance, blunted ACTH and

cortisol responses to stress predict relapse among men, but not among women (166). In a recent study with a relatively large sample of smokers, we demonstrated that elevated salivary cortisol during the early abstinence phase predicted quicker relapse for women, while the opposite was true for men (214).

Emotional dispositions—Knowing that drugs may be used to manage intense emotions, and informed by research indicating that smokers with high levels of hostility may use cigarettes to cope with anger-provoking situations (236–238), our laboratories examined the roles of various factors related to emotion regulation and dispositions in shaping the stress response among smokers and other stimulant users during withdrawal. Through this research, we found that smokers who have a high level of trait anger tend to experience more anger during withdrawal and in response to stress (200). We also found that high anger was associated with increased withdrawal symptoms and craving during the first 24 hours of abstinence as well as with blunted ACTH stress response. Furthermore, we found evidence that high trait anger was associated with increased risk for early relapse. These findings are consistent with acute effects of stress in smokers and other substance users (178, 239, 240); and the findings indicate that high levels of trait anger predispose individuals to experience greater emotional intensity during withdrawal, possibly contributing to mood difficulties and vulnerability for drug use and early relapse.

Life adversity—Considerable research has linked adverse childhood events to substance use and to long-term effects of stress (241–243); and our research has examined the influence of adversities on smoking relapse among habitual smokers using prospective observations. In this research, we followed participants from pre-quit ad libitum smoking to four weeks post-quit; and a non-smoking group was included for comparisons. The results provide evidence that early life adversity not only predicts smoking but also increases challenges (i.e., increased craving) in abstinence and vulnerability for relapse. In addition, we found sex differences in the connection between life adversity and risk for relapse such that female relapsers tended to report experiencing greater life adversity than their male counterparts (244).

Overall, this research complements our and others' research on stress response dysregulation in this vulnerable group of smokers. Indeed, previous research demonstrated that individuals who have a history of high adversity exhibit dysregulated responses to stress, characterized by blunted HPA responses and blunted diurnal fluctuation (245–248). It is possible that this blunted response is accentuated by exposure to substances contributing to increased vulnerability to relapse.

Polysubstances use—Co-use of multiple substances is a highly prevalent clinical challenge. Indeed, in the area of tobacco addiction, co-use of other substances, such as alcohol, cannabis, and other stimulants, is a significant impediment for cessation and a risk for relapse (157, 166, 249–252). Our laboratories recently conducted a series of studies focusing on the adverse effects of concurrent use of tobacco and the psychostimulant khat, a plant widely used in east Africa, the Middle East, and among immigrant communities around the world (253), on the stress response, affect regulation, and intensity of withdrawal symptoms. These studies demonstrate parallel findings to studies that focused on tobacco

smokers. Furthermore, these studies indicate that co-use of tobacco and khat is associated with significant neuropsychological deficits, particularly working memory and attention deficits (254–256). These deficits appear to be related to the hypoactive stress response systems in this co-using population (257–259).

Dysregulated Stress Response Mediating Nicotine Effects on Appetite

Neurobiological systems involved in the stress response may be involved in regulating appetite as well. During stress, the HPA axis exerts various regulatory actions that influence several survival functions, including appetite regulation and eating behavior. For example, glucocorticoids may influence the reinforcing effects of food by influencing appetite-regulating peptides, such as leptin, orexin, and neuropeptide Y (NPY) (260). In addition, evidence suggests that HPA and other reward-related circuitry may be involved in increasing consumption of calorie-dense food items under conditions of stress (260). As an example, observations in human studies show that participants who exhibit enhanced cortisol response to acute stress tend to consume more calories relative to low cortisol responders. Furthermore, negative affect responses to stress are associated with greater food consumption (261, 262). The mechanisms of this connection between stress and food selection may involve an interaction of reward and stress response pathways. Both stress and palatable food stimulate endogenous opioid release. Peptides modulating HPA axis activity, including the appetite-regulating peptides leptin, ghrelin, orexin, and NPY, are also associated with depressive mood, stress, and addictive behavior (263–266).

A related line of research has established convincing evidence of an inverse association between cigarette smoking and body weight (267–269). Failure to quit smoking is primarily attributed to the addictive properties of nicotine, but the fear of weight gain after cessation of smoking is often a contributing factor (270, 271). The mechanisms mediating the association between smoking cessation and weight gain likely include changes in 1) appetite–related neurobiological and peripheral regulation (272); 2) appetite that leads to increased intake of a high energy diet (e.g., fat and carbohydrates) (273, 274); and 3) metabolic rate (reductions) in the absence of nicotine (275)(276).

Informed by the literature on the long-term effects of nicotine and stress on appetite (277, 278), and encouraged by research linking smoking, craving, and mood with changes in appetite hormones (279, 280), we conducted a series of studies to examine the links between stress response, appetite hormones, and smoking relapse. The results of these studies provide evidence that leptin levels significantly increase following exposure to acute stress (281) and that leptin is associated positively with craving for cigarettes and with other mood states (279). These findings suggest that leptin levels may be a useful marker of the stress response and of craving for smoking. We also found that increased levels of the appetite reducing peptide YY after the first 24 hours of smoking abstinence is associated with decreases in reported craving and increases in positive affect, while higher ghrelin levels are associated with early relapse (282). When we examined changes in leptin from pre to 48 hours post smoking abstinence, we found increased leptin concentrations in women who were successful in cessation for four weeks (283).

Mechanisms for Dysregulated Stress Response in Addiction

Research that focuses on identifying pathways that explain blunted stress response in individuals with addictive problems is a critical step towards identifying potential therapeutic strategies. Our efforts to understand the blunted stress response were guided by three specific criteria: 1) a potential pathway must have a robust basic-science literature demonstrating its role in regulating the stress response, 2) such a pathway should also be directly involved in regulating the effects of substance use, and 3) such a pathway can be studied safely in humans and be subjected to experimental studies in the context of clinical research.

In addition to the HPA axis and the catecholaminergic system, stress activates the EOS (21, 71, 121, 284). Three key points of contact in the central nervous system play a role in the interactions between opioid neurons and structures involved in the stress response and reward regulation (22, 29, 43, 285). These include the locus coeruleus in the brainstem, the PVN of the hypothalamus, and the nucleus accumbens. Opioid neurons typically stimulate dopaminergic neurons, while inhibiting neurons within the PVN and the locus coeruleus, which leads to reduced CRF and catecholamine release (12, 286, 287). These effects indicate a regulatory effect of the EOS on the stress response, emotion regulation, and reward. Considering the role of the EOS in many addictive behaviors (19, 288), it is possible that chronic exposure to substances may alter the functions of this system and, consequently, may influence regulation of the stress response.

Guided by this research and our criteria (outlined above), we conducted a series of studies to examine the integrity of the EOS regulation of the HPA axis during exposure to pain and stress among dependent cigarette smokers and non-smoker controls (70–72, 110, 289–292). In all of these studies, we used the opioid blockade naltrexone within a double-blind crossover design. We hypothesized that because the EOS naturally inhibits HPA activity, naltrexone should increase HPA activity. This was the case across all studies; however, smokers exhibited a blunted HPA response to the EOS blockade, particularly during stress. Furthermore, blunted HPA responses to the EOS blockade and stress were particularly pronounced during smoking withdrawal. Interestingly, in a recent study, we found that smokers who were provided a cigarette to smoke during the laboratory protocol (so that they were not deprived from smoking) showed the most robust response to opioid blockade (see Figure 2). This suggests that availability of nicotine in the system may help normalize the EOS-HPA stress response regulation. Consistent with this idea, it is possible that a rewarding motivation for smoking is to normalize the stress response by normalizing the EOS's regulation of this response.

In addition to the role of the EOS, research has pointed to other factors that may contribute to a blunted stress response, including reduced effort to engage in stress challenges (293, 294), dampened central motivational processes (245, 295), and attenuated response to the rewarding effects of various activities (294). Theoretical discussions of the attenuated stress responses have also incorporated this stress-response dysregulation in the context of broader models of vulnerability (e.g., (296)), suggesting that blunted overall physiological arousal in emotion-related systems may be related to genetic and epigenetic variations that contribute

to alterations in physiological systems involved in the stress response. These changes in the neurobiological systems of the stress response may disrupt affective, cognitive, and interpersonal processes, thereby increasing risk for maladaptive behaviors, such as substance use. Furthermore, social stress and early life adversity may exacerbate these risk-related processes. Early life adversity and certain traits, such as impulsivity, disinhibited temperament, and sensation seeking, may also contribute to both blunted response and to risky behaviors (245, 293–296).

Discussion and Conceptual Model

The research on stress and addiction reviewed above was guided by a heuristic model that links HPA dysregulation and opioid hypoactivity as a result of long-term exposure to nicotine. We hypothesize, as indicated in Figure 3, that acutely smoking and using other drugs of abuse increases indices of the HPA, endogenous opioid, and sympathetic systems.

After long-term, intermittent activation by ongoing drug use, changes ensue that lead to neuronal adaptation. This adaptation includes reduced opioid input to the PVN; enhanced basal HPA activation; and reduced stress (HPA), opioid, and sympathetic responses. These alterations become pronounced during cessation, with diminished activity in these systems increasing craving and exacerbating abstinence-related negative affect. This culminates in an increased vulnerability to relapse. Therefore, cessation may unmask underlying dysregulation of the stress response systems, leading to reduced HPA responses to stress and reduced opioid feedback to the PVN. The result is a maladaptive response to stress that may exacerbate withdrawal symptoms and reduce ability to cope effectively with acute stress. Increased sensitivity to negative affect and physical symptoms has recently been linked to low HPA response to stress (297, 298), possibly as a result of poorer counter-regulation by cortisol feedback to critical CRF- and other systems that regulate the stress response (299). These results are consistent with increased craving that may enhance the reinforcing properties of drug use.

In addition to this indirect evidence, our proposed model is supported by neurobiological studies of drug addiction that (a) indicate chronic drug use produces neuronal adaptations in multiple brain systems, and (b) suggest drug deprivation and neurobiological changes after long-term exposure to drugs may produce strong motivational states leading to maintenance of drug use (300–308).

Conclusions

Research reviewed here demonstrates that a blunted stress response may indicate a long-term, adverse effect of substance use on brain functions that may play an etiologic role in various mood, addictive, and cognitive processes. A blunted stress response is likely to contribute to maintenance of addictive behaviors and increase risk for relapse. Psychosocial stress and early life adversity may prime the brain to be sensitive to subsequent exposure to stress and to the impact of substance use. Research suggests that normalizing the biological stress response may help with regulating mood, cognition, and coping with pain and discomfort– all of which are issues associated with blunted stress response. We also propose

that the ability to maintain a robust biological stress response in the face of psychosocial adversity or chronic exposure to substance use should be considered an indicator of resiliency. Indeed, our hormonal findings from multiple studies and populations indicate that a robust stress response buffers negative affect, withdrawal symptoms, craving, and risk for relapse. Accumulating preclinical evidence on neurobiological pathways mediating the stress response provides indirect evidence that a robust stress response is a marker of resiliency (309–314). Future work must probe the role of specific stress-response biological pathways (e.g., blunted HPA and EOS stress responses) in risk for, and maintenance of, substance use and in related mood disturbances. This should facilitate subsequent research into specific therapeutic approaches to address stress-response dysregulation and its impact on mental and behavioral health.

Acknowledgments

List of acronyms

DHEA	dehydroepiandrosterone
CRF	corticotropin-releasing factor
PVN	paraventricular nucleus
BP	blood pressure
VTA	ventral tegmental area
ACC	anterior cingulate cortex
NA	nucleus accumbens
PFC	prefrontal cortex
HPA	hypothalamic-pituitary-adrenocortical axis
ACTH	adrenocorticotropic hormone
GABA	gamma-aminobutyric acid
EOS	endogenous opioid system
CPT	cold pressor test
NPY	neuropeptide Y
DA	dopamine
CNS	central nervous system

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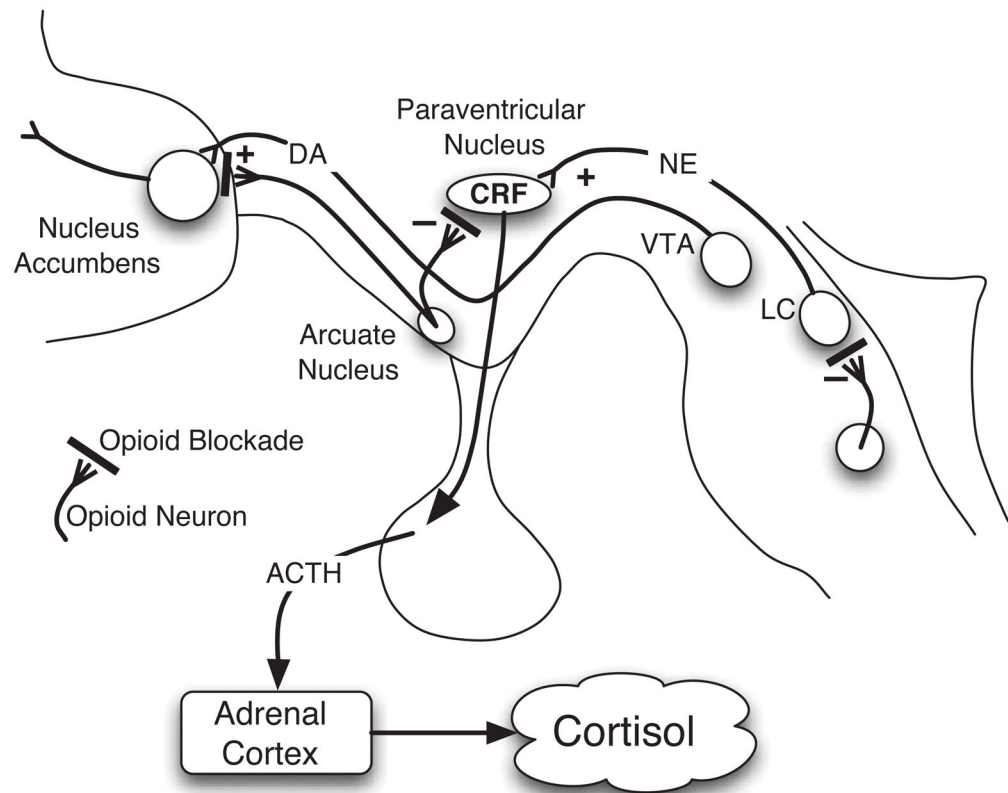
Figure 1.
The interaction of opioid system with multiple pathways involved in the stress response. The figure published originally by Lovallo (33) indicates that areas where opioid blockade acts in three areas: 1) the periventricular nucleus of the hypothalamus (PVN), the locus ceruleus, and the nucleus accumbens. Opioids normally stimulate DA release by the nucleus accumbens, inhibits CRF release from the PVN, and inhibit release of norepinephrine from the locus ceruleus (22). Reprinted from the *International Journal of Psychophysiology*, Vol. 59, Issue 3, Pages 195–202, William Lovallo, Cortisol secretion patterns in addiction and addiction risk (2006), with permission from Elsevier.
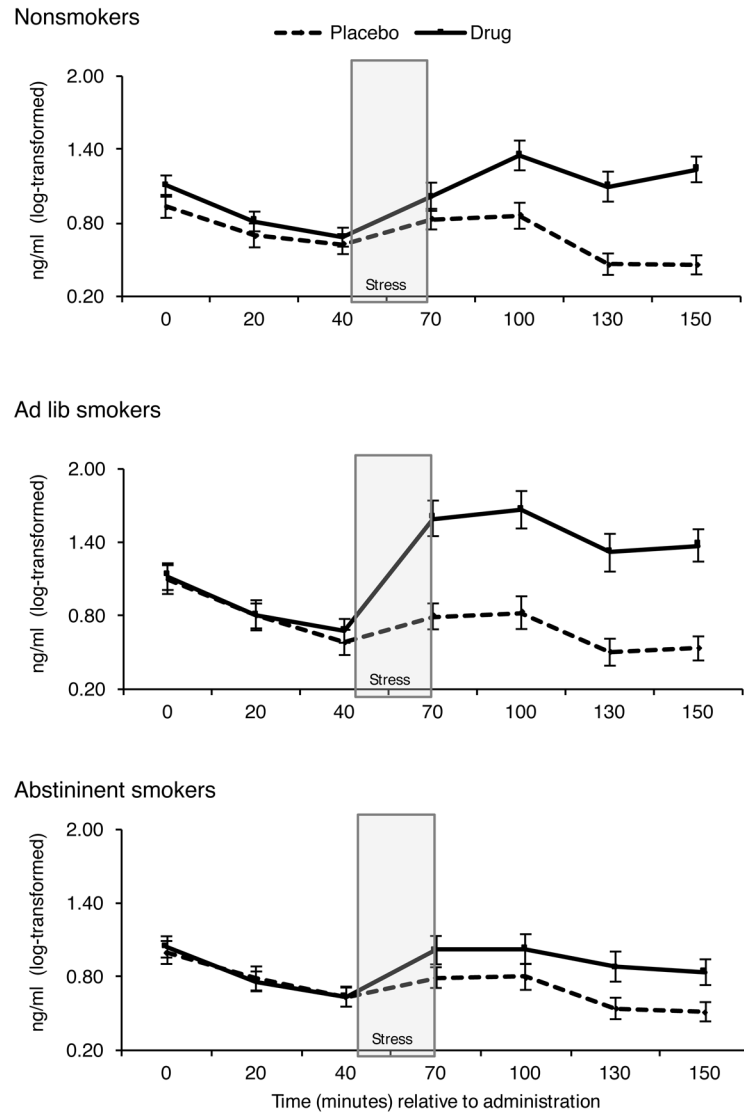
Figure 2.
Effects of opioid blockade on cortisol response to stress was blunted in smokers who were deprived from nicotine, but it was enhanced in smokers who were not deprived from smoking relative to nonsmokers.
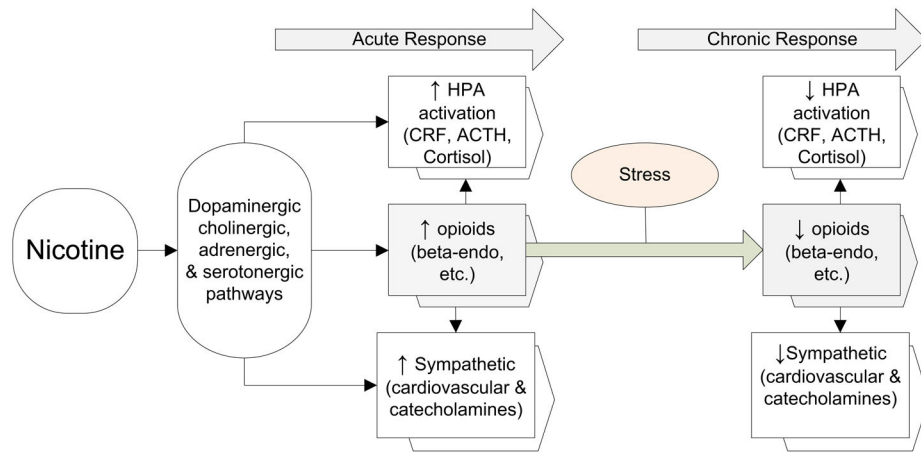
Figure 3.
A heuristic model that depicts effects of drug use on the HPA, endogenous opioid, and sympathetic systems. Long-term effects of drug use may lead to neuronal adaptation that may eventually contribute to neurobiological vulnerability that increase drug use and risk for relapse.

Table 1

Key findings reviewed in this paper

- Implementation of socially-relevant stressors and adrenocortical measures in laboratory research on human subjects enhanced validity and expanded understanding of the stress response.

- Vulnerable populations (primarily hypertensives and hypertension-prone individuals) with enhanced HPA activity and enhanced cardiovascular response to stress.

- Attenuated pain sensitivity is observed in normotensive persons at high risk for hypertension.

- Hypoalgesia in hypertension-prone individuals is not explained by enhanced EOS nor by enhanced baroreceptor activation.

- Altered stress-response may be involved in modifying pain sensitivity among hypertension-prone individuals.

- HPA activation may contribute to, or be a marker of, attenuated pain perception seen during acute stress events.

- Association between ongoing pain and adrenocortical hyporesponsiveness has been demonstrated in multiple chronic pain syndromes.

- Reduced adrenocortical activity in individuals with chronic pain conditions, such as fibromyalgia, rheumatoid arthritis, chronic fatigue syndrome, and child abdominal pain.

- Central regulation of the HPA stress response by the EOS involves three points of interface (locus coeruleus in the brainstem for norepinephrine, the PVN of the hypothalamus for CRF, and the nucleus accumbens for dopamine).

- Individuals with a history of high early life adversity exhibit dysregulated responses to stress, characterized by blunted HPA responses and flatter diurnal fluctuation.

- Nicotine withdrawal produces a stress-like psychological, biological and neurobehavioral effects.

- Leptin levels may be a useful marker of the stress response and of craving for smoking.

- The nexus between stress, addiction, and appetite regulation involves the reward neurobiological pathways.

- Multiple appetite and energy regulating hormones are useful stress markers and addiction relapse predictors.

- Blunted HPA stress response during early smoking abstinence predicts shorter time to relapse.

- Predictors of addiction relapse vary between men and women; biological markers predict relapse better in men, while psychological measures predict relapse better in women.

- Stress hyporesponsiveness is associated with enhanced cognitive deficits among substance co-using populations.

- Blunted physiological arousal in emotion-related systems may be related to genetic and epigenetic variations that contribute to alterations in physiological systems involved in the stress response.