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Editorial

Editorial introduction: The effects of somatic disease and environmental insults on the stress response

The majority of work examining relationships between stress and medical illness has focused on the impact of stress and alterations in HPA axis function on the development of diseases and disorders [15,3]. Although it is well accepted that toxic stress can have profound and protracted consequences on numerous systems in the brain and body contributing to a number of medical, neurologic or mental illnesses, there is also substantial evidence that development of these illnesses can have equal consequences on the stress response and hypothalamic pituitary adrenal (HPA) axis function. Illness-induced dysregulation of stress systems may then influence other physiological systems creating a feed-forward cycle and leading to exacerbation of the primary disease or contributing to development of comorbid medical, neurologic or mental disorders. Furthermore, ecological or societal exposures such as environmental toxins, drugs of abuse, and poor nutrition also exert effects on the HPA axis that may further increase risk for development of disease secondary to these exposures (Fig. 1). Therefore, this edition integrates a body of work from experts in various fields of somatic or neurologic illness, drug addiction, metabolism and nutrition, and environmental toxins to discuss the consequences of these diseases or exposures on the HPA axis and the stress response.

Major medical illnesses that involve pathophysiological processes such as inflammation can affect the stress response and HPA axis function to contribute to increased risk for behavioral comorbidities like depression. For example, cancer and its treatments have been associated with increases in inflammatory markers at rest and in response to stress in association with alterations in HPA axis function, which is thought to contribute to behavioral symptoms of depression, fatigue and cognitive dysfunction in cancer patients and survivors [4,14,24]. In this special issue, Leah Pyter reviews recent clinical and translational evidence that cancer can impact endocrine, immune, or behavioral responses to stress. Whereas the clinical work in this area has focused primarily on the effect of cancer therapies (e.g. radiation and chemotherapy), this review presents a unique perspective on how the tumors themselves may perturb physiological systems beyond their local microenvironment to contribute to alterations in immune, nervous, and metabolic systems [17,23]. Relevant literature from rodent cancer models are presented and integrated with the clinical literature, which indicate overall elevations in baseline glucocorticoids and decreased HPA axis responses to acute stressors, to make the case that alterations in stress responses by the cancer itself may interact with psychological and physiologic stressors during diagnosis and treatment to influence behavioral and physical health outcomes in cancer patients.

In addition to cancer, inflammation as a result of chronic viral infections and their treatments has also been associated with increased risk for depressive symptoms, which may occur in part due to effects on the stress response and HPA axis function. Indeed, patients with chronic hepatitis C virus infection who are treated with the inflammatory and anti-viral cytokine interferon (IFN)-alpha experience a range of depressive symptoms including anhedonia, anxiety, sleep disturbances and fatigue [19,6], all of which are found to correlate with induction of other cytokines and inflammatory signaling pathways [20,5] and with evidence of reduced glucocorticoid sensitivity [18]. These findings have included increased evening plasma cortisol concentrations and a flattened diurnal cortisol slope that correlated with increased inflammatory markers including the cytokine tumor necrosis factor (TNF) and its soluble receptor 2 (sTNFR2) [18]. Herein, new data from Felger and colleagues extend these findings by assessing glucocorticoid negative feedback to dexamethasone (DEX). An IFN-alpha-induced increase in sTNFR2 was associated with significant increases in post-DEX cortisol, which in turn correlated with both flattening of the diurnal cortisol slope and increased depression scores. Therefore, inflammation-related flattening of the diurnal cortisol slope might be secondary to reduced glucocorticoid receptor sensitivity, which may in turn lead to failure to regulate inflammation, ultimately contributing to depressive symptoms in medically ill patients.

Epilepsy is a common neurological disease that has profound effects on physiology including neuroendocrine and stress responses, and is associated with increased prevalence of depression and anxiety [11]. As reviewed by Wulsin and colleagues, and similar to that described above for cancer and IFN-alpha therapy for hepatitis C virus, recent evidence suggests that glucocorticoids are elevated in patients with temporal lobe epilepsy (TLE), one of the most frequent forms of epilepsy in adults. For instance, findings indicate that in addition to post-seizure elevations in cortisol, TLE patients fail to suppress cortisol release in response to DEX or exposure to psychosocial stressors [25,1]. Stress is a commonly reported trigger of seizures, and excess glucocorticoids may promote seizure susceptibility by increasing neuronal excitability and epileptiform activity. Further understanding potential mechanisms by which TLE may lead to abnormal stress responses has implications for the development of therapeutic strategies to reduce vulnerability to seizures and to psychiatric comorbidities.

Together these findings in cancer, hepatitis and epilepsy indicate that elevated glucocorticoids and decreased regulation of the stress response may be a common feature of a number of medical illnesses. Moreover, decreased ability of the glucocorticoid receptor to inhibit further production of glucocorticoids and inflammatory cytokines may contribute to disease severity and increased risk for behavioral symptoms such as depression. Thus, treatments that target HPA axis

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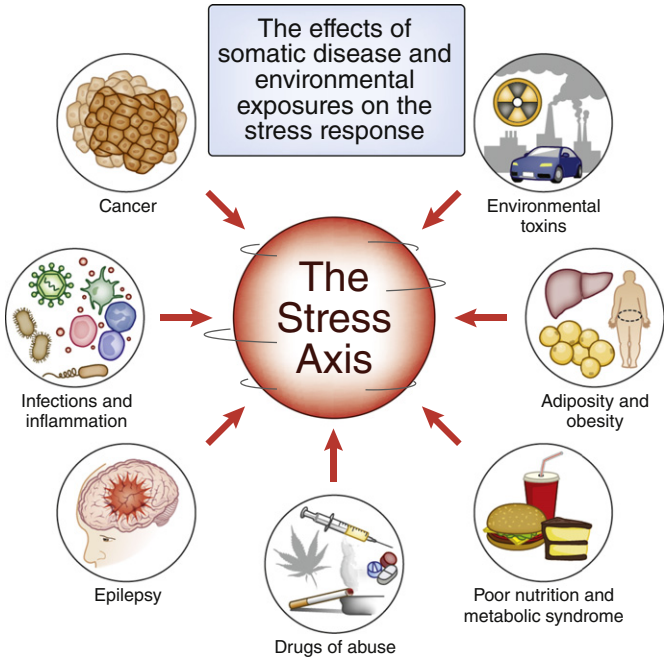

Fig. 1. The stress response is engaged in response to both endogenous and exogenous stimuli. Although we commonly refer to toxic stress impacting the manifestation or course of disease, diseases and disorders can be primary perturbing factors to the stress response. In addition, exogenous stimuli in the environment can both elicit and modify the stress response. The impact of these variables on the stress response, and the possible feed-forward cycle that they can create, are important considerations in the context of studying, preventing, and treating stress-related disorders.

function and glucocorticoid receptor sensitivity may reduce depressive symptoms and improve clinical outcomes in patients with medical illnesses.

In addition to diseases and disorders which can impact the body's response to subsequent stressors, the highly plastic nature of the stress response systems leaves these critical systems vulnerable to alterations induced by exogenous substances. Although it is appreciated that exposure to stressors influences drug seeking and drug taking behaviors [21, 16] and this can be recapitulated in animal models of addiction [12], there is less appreciation for the impact of drugs of abuse on function of the stress response. The contribution by Fosnocht and Briand [7] examines the influence of drugs of abuse on the stress response and delves into the potential mechanisms by which drugs may alter the stress response. Given that drugs can alter the stress response and stress can act as a trigger to further perpetuate drug abuse, it is essential to understand both halves of this relationship in order to effectively treat the addicted brain.

Exogenous substances that can adversely impact the stress response extend well beyond drugs of abuse and are readily available in most kitchens. Much of the point of the stress response is to mobilize energy to adequately respond to the stressor that has been presented [3]; and because of this relationship, diet can be a profound stimulus for the stress response [9]. Harrell, Gillespie, and Neigh [10] propose that changes in energetic state or energetic demands can result in "energetic stress" that can, if prolonged, lead to a dysfunctional stress response. Through their review of the relevant literature, they describe multiple pathways by which diet can reorganize the response to stressors and suggest possible novel therapeutic routes to consider.

Dietary influences on the stress response are further considered in the context of obesity – generally a consequence of prolonged energetic excess. Obesity is a risk factor for both somatic conditions and a range of affective disorders [22]. Given that many of these psychiatric disorders have a stress-reactive component, this further reinforces the proposed relationship between energetic availability and the stress response. This relationship is also influenced by sex as a biological variable. Michopoulos [13] reviews the wealth of data regarding the impact of diet and obesity on function of the hypothalamic pituitary adrenal axis with special emphasis on the influence in females. Collectively, these two reviews highlight the power of diet and energetic balance as both stimulators and regulators of the stress response.

The influence of exogenous substances on responsivity to stress is not limited to ingested agents, but extends to toxins in the environment including pesticides, industrial compounds, and exhaust. The review by Caudle (2016) provides the first collection of findings to date regarding the impact of toxins on the HPA axis and potential mechanisms that mediate these effects. Given the disproportionate exposure of individuals in lower social economic strata to higher levels of environmental toxins [2] and the increased likelihood of trauma exposure in this same demographic [8], an understanding of the influence of toxin exposure on the stress response is a forward-thinking area of research.

Collectively, the primary findings and integrative reviews presented in this issue highlight a commonly underappreciated nuance of stress research. Namely, the influence of conditions and diseases on the stress response, as opposed to the common focuses on the influence of stressor exposure and chronic stress physiological states on response to conditions and diseases. The goal of this special issue is to raise awareness about the bidirectional nature of these interactions and increase sensitivity to these feed-forward cycles among researchers and clinicians focused on stress-related questions.

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