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Neuroendocrine Markers of Stress

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Although universally experienced, stress is difficult to define. One reason for this difficulty is the diversity of stimuli which serve as stressors; pain, surgery, hemorrhage, infection, noise, examinations, and public speaking are all examples of stressors. Similarly, the compensatory physiologic events elicited by stressors, termed stress responses, are also diverse in nature. Numerous physiologic measures have been evaluated for their role in the stress response; pulse, blood pressure, sweating, and cortisol, epinephrine, and norepinephrine levels are all examples of stress responses. This paper reviews one class of physiologic responses, the neuroendocrine responses to stress.

Neuroendocrine substances play a key role in initiating and coordinating behavioral, cardiovascular, metabolic, and immunological responses to stressors. Numerous neuroendocrine factors have been evaluated[1–4] for their role in organizing physiologic responses to stress (Table 1). These substances differ in their structure (e.g., peptides, biogenic amines, steroids, etc.), function, and origin (e.g., glands, nerves, other tissue). In addition, they also differ as markers of stress; the composite secretory profile of these substances varies according to the stressor and other factors (Table 2). Accordingly, measurement of these substances provides a means of assessing the magnitude and spectrum of various physiologic responses to stress. This is an important area of research because successful adaptation to stressors requires coordinated physiologic responses. These measures may be of value in the diagnosis and evaluation of treatment outcome in chronic pain patients.

NEUROENDOCRINE MARKERS OF STRESS

Neuroendocrine responses to stressors can be categorized by their tissue of origin (Table 1). This division, although arbitrary, provides some insight into basic differences in the physiology of substances originating from endocrine and neural sources.[5,6] For example, neurally derived factors generally respond to a stressor with a quick increase in circulating levels and a relatively short duration (e.g., norepinephrine), while endocrine-derived factors generally respond with a slower onset and a longer duration in elevated levels (e.g., cortisol). This division, between endocrine and neural origin, will be used to review neuroendocrine markers of stress.

Activation of the pituitary-adrenal axis is a prominent neuroendocrine response to stressors, promoting survival under extreme conditions.[7] Stimulation of this axis in response to a variety of stressors results in hypothalamic secretion of corticotropin releasing factor (CRF). In turn, CRF stimulates the pituitary corcitotroph cell to cosecrete adrenocorticotropin (ACTH), β-lipotropin (B-LPH) and β-endorphin (B-END). In humans, plasma levels of these hormones can increase 2- to 5-fold during stress. Although the physiologic properties of ACTH are recognized (i.e., adrenocortical steroidogenesis), the contributions of B-END and B-LPH, if any, to the adaptive response to stress are not known. However, results from several studies suggest that pituitary B-END may modify the perception of pain. For example, blood levels of immunoreactive B-END (iB-END) are inversely related to pain report in patients after oral surgery,[8] laparotomy,[9] and major burns.[10] Additional studies have demonstrated that stimulation of B-END secretion by administration of CRF to oral surgery patients is associated with decreased postoperative pain,[11] whereas blockade of B-END secretion with low doses of dexamethasone results in increased levels of postoperative pain.[12] A potential target site for analgesic activity of circulating opioid peptides is peripherally inflamed tissue.[13,14] These results indicate that activation of the pituitary-adrenal axis alters metabolic,[15] immunologic,[15] and, possibly, nociceptive responses to stressors.

The pituitary-adrenal axis is stimulated in response to acute stressors such as intraoral injections of local anesthetics,[16] oral surgery,[8,12,17] abdominal surgery,[18] retinal photocoagulation,[19] acute postoperative pain,[11,12,17] anesthesia reversal/recovery,[20] cardiac arrest,[21] and exercise.[22] The response of this axis to chronic pain is more complicated, with hormone levels reported as elevated,[23,24] nor-

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Table 1. Peripheral Neuroendocrine Markers of Stress

	Increase Over Baseline Levels
Endocrine	
1. Pituitary adrenal axis: (e.g., ACTH, B-END, B-LPH, cortisol)	2–5*
2. Prolactin	8–20
3. Growth hormone	2–10
4. Pituitary thyroid axis (e.g., TSH, T4, T3, rT3)	0?
4. Pituitary gonadal axis (e.g., LH, FSH, Testosterone, E2)	0?
5. Glucagon	0.5–1
6. Insulin	0?
7. Renin-angiotensin	2–3
8. Aldosterone	2–3
Neural	
1. Sympathoneural (e.g., NE, NPY?)	0–32
2. Adrenomedullary (e.g., EPI, DA, M-ENK)	0–300
3. Vasopressin	2–15
4. Primary afferents (e.g., SP, CGRP)	?

* Represents the stress-induced increase from baseline levels. See text for references.

mal,[25–27] or even decreased.[28–30] These studies indicate that interpretation of levels of pituitary-adrenal hormones as markers of stress is relatively simple for acute stressors, such as postoperative pain, and is more complicated for prolonged stressors, such as chronic pain conditions. Potential contributing factors for modifying this stress response are discussed in the next section.

Several other pituitary hormones are also secreted in response to stressors. Prolactin levels can increase 8- to 20-fold during acute stressors such as abdominal surgery,[31,32] burns,[33] retinal photocoagulation,[19] cardiac arrest,[21] exercise,[32] and in some[34] but not all[35] studies on headache patients. However, prolactin levels are often near the normal range during chronic stressors such as several days after major surgery[32] or burns.[36] The physiologic actions of prolactin during stress are unclear; it may participate in enhanced metabolism (via insulin resistance) or modification of nociception.[37]

Growth hormone is also released from the pituitary during stress. In response to acute stressors such as surgery,[19,31,32] fever and exercise, growth hormone levels can increase 2- to 10-fold. However, the duration of growth hormone secretion is short; levels have reported to be near normal a few hours-to-days after major surgery[32] or burns.[36] The physiologic significance of a relatively brief elevation in growth hormone levels is not known, although enhanced metabolic activity may accompany its insulin antagonist properties.

Not all pituitary hormones respond to stress with an increase in blood-borne concentrations. For example, the pituitary-thyroid axis undergoes a complex series of changes to result in a decrease in its functional activity.[1] In addition, gonadotropin levels show little-to-no change during surgical stress,[19,38] and levels may decline below normal in the acute post-operative period.[38]

Hormones from other endocrine glands are also released in response to stressors. Plasma levels of glucagon increase after burns[39] and in some,[40] but not all[19,41] patients after major surgery. One reason for this discrepancy is that glucagon levels often increase by a small magnitude (50%–100% over baseline) with a long lag period (i.e., 12–24 hours). Insulin levels tend to decrease as the perceived magnitude of surgical stressors increases.[42] The decrease in insulin levels, coupled with increased levels of prolactin, growth hormone, glucagon and epinephrine, contribute to the development of a stress-induced hyperglycemia.[43] Insulin levels tend to return to normal, or exceed normal levels, in the initial postoperative period.[4] Plasma renin activity and aldosterone levels have been reported to increase 2- to 3-fold after burns,[45] although results from surgery patients are less consistent.[4,20] These results indicate that numerous hormones are released from several endocrine glands to form a varied reponse to stressors.

A second major category of stress responses consists of neurally derived substances. The primary example of this category is the sympathoadrenomedullary system. Numerous studies indicate that stressors evoke increased circulating levels of epinephrine (EPI), primarily from adrenomedullary secretion and norepinephrine (NE), primarily from sympathetic nerve terminal overflow.[6] Plasma levels of these catecholamines can increase several fold in response to acute stressors such as oral surgery (EPI: 1- to 3-fold; NE: no change[16,46,47]), acute postoperative pain

Table 2. Factors That Modify Physiologic Responses to Stress

Extrinsic factors
1. Type of stress: (e.g., psychologic vs physical)
2. Intensity
3. Time parameters
Duration
Frequency
Time of occurrence
4. Chronicity
Intrinsic factors
1. Age
2. Sex
3. Health status (e.g., concurrent disease)
5. Context (e.g., patient's control over stressor)
6. Concurrent drugs

(EPI: 0- to 1-fold; NE: 1- to 2-fold[17,46,47]), cardiopulmonary bypass (EPI: 5-fold; NE: 2- to 3-fold[3]), exercise (EPI: 6-fold; NE: 8-fold[48]), and cardiac arrest (EPI: 300-fold; NE: 32-fold[49]). As suggested by their differential response to these stressors, the adrenomedullary and sympathoneural components can be regulated separately. Recent studies have suggested that adrenomedullary activation is more closely related to stimulation of the pituitary-adrenal axis than to the sympathoneural system.[6,16] In addition, the functional selectivity of these components may differ, because stimulation of adrenomedullary outflow produces increases in systemic plasma levels of epinephrine, whereas stressors can evoke regionally selective sympathoneural release of norepinephrine,[6,50] suggesting a more restrictive locus of control for the latter catecholamine. The physiologic consequence of increased catecholamine levels is increased cardiac output, skeletal muscle blood flow, sodium retention, inhibition of gut motility, cutaneous vasoconstriction (pallor), incraesed glucose availability, bronchiolar dilatation, and behavioral activation.[6]

Several stressors have been reported to evoke vasopressin release from its nerve endings located in the posterior pituitary. Plasma levels of vasopressin increase 2- to 15-fold in response to stressors such as migraine attacks,[51] major surgery,[52,53] and burns.[54] Circulating vasopressin may contribute to altered diuresis, vascular tone (possibly including facial pallor for migraines[51]), and modulation of nociception.[55]

Another example of neurally derived substances is substance P and calcitonin-gene-related peptide. In animals, plasma levels of these immunoreactive peptides have been reported to be elevated by acute stressors such as immobilization[56]; in addition, circulating levels increase in proportion to the magnitude of surgical trauma.[57] However, in humans suffering from conditions such as cluster headache[58] and neuropathies,[59] plasma levels of immunoreactive substance P are reported to be lower than normal. The origin for these circulating peptides remains to be established. One possibility is unmyelinated afferent nerves with conduction velocities in the C fiber range. The physiologic consequences of an increase in circulating substance P and calcitonin-gene-related peptides remains unknown.

FACTORS WHICH MODIFY PHYSIOLOGIC RESPONSES TO STRESS

As proposed in his General Adaptation Syndrome, Selye considered stress responses to be an invariant physiologic defense reaction.[60] However, a more recent model has emerged from the evaluation of a number of stress responses elicited by both physical and psychological stressors. In this model, the profile of stress responses is not invariant; rather, its components are selectively elicited by an integrated central nervous system (CNS) response to the stressor. For example, intraoral injections of a local anesthetic solution to oral surgery patients results in significant increases in circulating levels of epinephrine and immunoreactive β-endorphin (iB-END), with little change in norepinephrine.[16] Conversely, acute postoperative pain in oral surgery patients is associated with increases in plasma levels of norepinephrine and iB-END, with little-to-no change in epinephrine.[17,47] These examples indicate that several factors modify the physiologic responses to a stressor (Table 2). These factors can be classified as extrinsic (i.e., alterations in the stimulus properties of the stressor) or intrinsic (i.e., factors acting within the organism that alter its stress response).

Numerous investigations have focused on extrinsic factors which modify the physiologic responses to stressors. One example of an extrinsic factor is the type, or nature, of the stressor, which covers a spectrum from psychological (e.g., video game competition[61]), to physiological (e.g., hypoglycemia[6]), to physical (e.g., immobilization[62]) stimuli. The composite profile and magnitude of neuroendocrine markers of stress clearly differs according to the type of the stressor.[6,62,63] Even among similar stressors, neuroendocrine responses are often proportional to the magnitude of the stressor.[32,42,64,65] In addition, the temporal parameters of the stressor, its duration, frequency, and time of occurrence, alters the stress response.[62,65–67] Finally, the organism can habituate to the chronic presentation of a stressor, while retaining the ability to respond to novel stressors.[67–71] Thus the type of stressor, its magnitude, temporal patterns, and chronicity all modulate the neuroendocrine response.

Other investigations have evaluated intrinsic factors that modulate neuroendocrine responses to a stressor. For example, several,[66,69,72–74] but not all[75] studies have indicated that age and sex are important intrinsic factors in modifying stress responses. In addition, the relative physical fitness[76] or presence of concurrent disease[1] modifies neuroendocrine responses to stressors. The context of the stressor, for example, the level of ambient noise,[63] or the subject's control over the stressor[77] may also influence physiologic responses. Another major influence on neuroendocrine responses to stress are concurrent medications. Opiates, benzodiazepines, local anesthetics, barbiturates, gaseous anesthetics, glucocorticoids, catecholamines, and nonsteroidal antiinflammatory drugs are only a partial list of drugs which modify stress responses.[2–4,6,11,12,16–18,78,79]

Together, these studies indicate that there is no fixed, invariant stress response as originally proposed in Selye's General Adaptation Syndrome. Rather, the CNS selectively activates various neuroendocrine responses to stress under dynamic, flexible conditions which can be modified by numerous extrinsic and intrinsic factors.

SIGNIFICANCE TO DIAGNOSIS AND TREATMENT OF CHRONIC PAIN

Given a bewildering array of neuroendocrine markers of stress, which can be modified by a number of different factors, it is reasonable to ask whether this area of research has relevance for diagnosis or treatment of chronic pain. It is unlikely that different etiologies of chronic pain will have unique patterns of circulating neuroendocrine substances, indicating that knowledge of a patient's neuroendocrine profile may only have adjunctive importance for establishing a diagnosis. Other applications, however, appear more promising.

One application of this area of research is in estimating the chronicity or impact of the patient's pain (i.e., the level of stress). Patients experiencing chronic stress often demonstrate hyperactivity of the pituitary-adrenal axis. The hyperactivity, or degree of stimulation, of the pituitary-adrenal axis can be assessed by the dexamethasone suppression test (DST). The DST is generally administered by ingestion of 1–2 mg of dexamethasone at 1100 hours, with collection of blood samples at 0800 and 1600 hours the next day. Under normal conditions, the pituitary corticotroph cell is suppressed by administration of exogenous glucocorticoids such as dexamethasone, resulting in a prolonged decrease in circulating cortisol levels. For example, only 3.6% of 687 samples from normal subjects had 0800-hour cortisol levels greater than 5 μg/dl.[80] In contrast, 29%–47% of patients with chronic pain[23–25,81,82] or depression[83–86] have post-DST cortisol levels greater than 5 μg/dl. The interpretation of this cortisol nonsuppression has been controversial. More than 8,000 studies have evaluated DST responses in patients with depression or psychiatric illness in an attempt to develop diagnostic criteria.[84] However, this test does not appear selective for psychiatric illness.[83,85,86] Indeed, high percentages (up to 25%) of normal subjects show cortisol nonsuppression before stressors such as surgery,[87] public speaking,[88] and during military basic training.[89] These studies indicate that results of the DST are more of an index of stress than a measure of mental dysfunction.

An additional test for pituitary-adrenal hyperactivity is the administration of corticotropin releasing factor (CRF) to patients. CRF is a endogenous polypeptide that is released from the median eminence of the hypothalamus into the pituitary portal blood supply during stressors such as pain. CRF is a most potent and selective secretogogue for stimulating pituitary corticotroph secretion of β-endorphin and ACTH. Accordingly, the CRF test evaluates corticotroph responsiveness to a stimulus, while the DST evaluates the resistance of the corticotroph to an inhibitor. Both tests are consistent with the concept that chronic stressors result in elevated levels of CRF,[90] which leads to chronic hyperactivity of the pituitary-adrenal axis. Initial studies have evaluated pituitary-adrenal responses to CRF administered to pain patients[11] and depressed patients.[91]

The DST and CRF tests may have implications for pain patients in a fashion similar to the significance that glycosylated hemoglobin levels has for diabetic patients. For diabetic patients, blood sugar levels only reflect recent glycemic control. In contrast, determination of glycosylated hemoglobin provides a measure of glycemic control over the preceding three months. Similarly, for chronic pain patients, measurement of cortisol levels primarily reflects recent levels of stress and is easily influenced (Table 2). In contrast, the DST and CRF tests may provide an index of long-term stress. In this context, these tests may have value for evaluating the long-term efficacy of pharmacological, surgical or behavioral interventions for treating chronic pain.

As emphasized previously, there are numerous neuroendocrine markers of stress that exhibit varied responses due to extrinsic and intrinsic factors. Their physiologic significance for chronic pain remains undetermined; thus the diagnostic and therapeutic implications of most of these substances remains unknown. However, the finding that a large percentage of chronic pain patients exhibit a neuroendocrine correlate of stress (e.g., altered DST values) suggests that this area of research may provide implications in the diagnosis or treatment of chronic pain. In addition, other blood-borne factors serve as indices of tissue inflammation[92,93] and could provide diagnostic information on peripheral contributions to chronic pain conditions.

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