Published in final edited form as:
Cell Mol Neurobiol. 2010 ; 30(8): 1433–1440. doi:10.1007/s10571-010-9606-9.

Adrenal Responses to Stress

David S. Goldstein
Clinical Neurocardiology Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5N220, 9000 Rockville Pike, 10 Center Drive, MSC-1620, Bethesda, MD 20892-1620, USA

Abstract

Based on concepts proposed by Langley, Cannon, and Selye, adrenal responses to stress occur in a syndrome that reflects activation of the sympathoadrenal system and hypothalamic–pituitary–adrenocortical (HPA) axis; and a “stress syndrome” maintains homeostasis in emergencies such as “fight or flight” situations, but if the stress response is excessive or prolonged then any of a variety of clinical disorders can arise. The idea of a unitary sympathoadrenal system does not account for evidence that different stressors elicit different patterns of autonomic responses, with exposure to some stressors differentially affecting sympathetic noradrenergic and adrenomedullary hormonal activities. Instead, adrenomedullary responses to stressors are more closely tied to adrenocortical than to sympathetic noradrenergic responses. Distress involves concurrent activation of the HPA and adrenomedullary neuroendocrine systems.

Keywords

Stress; Adrenal; Epinephrine; Norepinephrine; Sympathetic nervous system

Cannon, Homeostasis, and the Sympathoadrenal System

Walter B. Cannon coined the term “homeostasis” to describe the maintenance within acceptable ranges of physiological variables such as blood glucose and core temperature (Cannon 1929a,1939). Cannon extended this concept to include psychosocial threats to homeostasis. In the early 1900s, he described for the first time the acute changes in adrenal gland secretion associated with what he called “fight or flight” responses.

Cannon taught that noxious environmental or internal stimuli threatening homeostasis (e.g., exposure to cold, hypotensive hemorrhage, traumatic pain, insulin-induced hypoglycemia, emotionally distressing antagonistic encounters) concurrently activate the adrenal gland to release epinephrine (EPI, synonymous with adrenaline) and the sympathetic nervous system. He considered the two effectors to function as a unit, which came to be termed the “sympathoadrenal,” “sympathico-adrenal,” of “sympathoadrenomedullary” system. In emergencies, sympathoadrenal activation would tend to restore homeostasis. Indeed, in 1939, Cannon formally and erroneously proposed that the chemical messenger of the sympathetic nervous system was identical to EPI (Cannon and Lissak 1939). Cannon emphasized that disparate threats to homeostasis incite the same sympathoadrenal response (Cannon 1929b, 1939). The notion of a unitary sympathoadrenal system continues in

goldsteind@ninds.nih.gov .
A commentary to this article can be found at doi: 10.1007/s10571-010-9607-8.

medical thinking (Cryer 1980; Shah et al. 1984; Sofuoglu et al. 2001; Kvetnansky et al. 1995).

Selye, Stress, and the General Adaptation Syndrome

Hans Selye, who popularized stress as a medical scientific idea, defined stress as (or a state resulting in) “the non-specific response of the body to any demand upon it” (Selye 1974). By non-specific he meant a shared element regardless of the nature of the demand or stressor. In this regard, his view agreed with that of Cannon.

Selye proposed three universal stages of coping with a stressor—the “General Adaptation Syndrome”—an initial “alarm reaction,” analogous to Cannon’s “fight or flight” response, a stage of adaptation, with resistance to the stressor, and eventually a stage of exhaustion and organismic death. In Selye’s early experiments, after injection of any of a variety of tissue extracts or of formalin into rats, the animals developed a pathological triad of enlargement of the adrenal glands, atrophy of lymphoid tissue in the thymus, spleen, and lymph nodes, and bleeding gastrointestinal ulcers. It was later demonstrated that these changes are associated with and to at least some extent result from activation of the HPA axis. Steroids released into the circulation from the adrenal cortex are required for resistance but are also responsible for pathological changes. Selye’s concept that prolonged stress can produce disease is now widely accepted.

Selye acknowledged that responses to stressors have a specific component that tends to counter effects of the stressor; however, after removal of specific responses from consideration, a non-specific stress syndrome would remain. Chrousos and Gold (1992) modified Selye’s doctrine of non-specificity by proposing that above a threshold intensity, any stressor elicits the stress syndrome.

More than a half century elapsed before Selye’s doctrine of non-specificity underwent experimental testing, which failed to confirm it (Pacak et al. 1998). Even so, modern lay and even scientific literature continues to accept the notions of a unitary stress response, a central neural stress system, and a stress “syndrome.” For instance, a Google search yielded about 4,000,000 hits for “the stress response,” 714,000 hits for “the stress system,” and 202,000 for “the stress syndrome.”

Just as Cannon emphasized activation of the sympathoadrenal system to maintain homeostasis, so did Selye and his students emphasize activation of the HPA axis in the General Adaptation Syndrome.

Systems Concepts of Stress, Allostasis, and Allostatic Load

Modern concepts view stress as a sensed threat to homeostasis (McEwen and Stellar 1993; Goldstein and McEwen 2002), in which the response has a degree of specificity depending on the particular challenge to homeostasis and the organism’s perceptions of the stressor and ability to cope with it (Goldstein 2001).

Concepts of Scientific Integrative Medicine

Scientific integrative medicine is not a treatment method or discipline but a way of thinking that applies systems concepts to conceptualize physiology and pathophysiology. The scientific integrative medicine approach provides a framework for understanding highly complex and dynamic challenges to our integrity as organisms and in turn for developing novel treatments based on this complexity and dynamism (Goldstein 2006). It also leads to systems definitions of stress and allostatic load, as discussed below.

Homeostats

Central to scientific integrative medicine in general and to systems concepts of stress specifically is that the body possesses homeostatic comparators, called “homeostats” (Goldstein 1995). Each homeostat compares information with a set point for responding, determined by a regulator (Fig. 1). A sufficiently large sensed discrepancy between afferent information about the level of the monitored variable and the set point for responding (error signal) elicits altered activities of effectors, the actions of which on the monitored variable decrease the discrepancy.

Homeostatic systems operate according to a few principles that despite their simplicity can explain complex physiological phenomena and might help resolve controversial issues in the area of stress and disease.

Negative Feedback Regulation

Physiological homeostatic systems entail negative feedback regulation of monitored variables such as core temperature, blood pressure, serum osmolality, and glucose levels. Disruption of a negative feedback loop, by preventing afferent information from reaching the brain, inability to process the information and regulate effector functions correctly, or dysfunction or loss of effectors, increases fluctuations in levels of monitored variables (Sharabi et al. 2003).

Positive feedback loops are inherently unstable, and conversion from a negative to a positive neurocirculatory feedback loop presages rapid decompensation. For instance, one can understand transitions from heat stress to heat shock and from compensated to decompensated heart failure in terms of positive feedback loops (Goldstein 2006).

Multiple Effectors

Multiple effectors regulate levels of most monitored variables of the body (Fig. 2). Having available multiple effectors extends the range of control, allows at least some regulation of the monitored variable if a particular effector fails (compensatory activation), and enables elaboration of specific, adaptive effector patterns.

Examples of compensatory activation in physiology include augmentation of sympathoneural responsiveness by adrenalectomy, hypophysectomy, or thyroidectomy (Udelsman et al. 1987; Goldstein et al. 1993; Fukuhara et al. 1996). Compensatory activation of other vasoactive systems after destruction of the sympathetic noradrenergic system helps to explain why many workers, including Cannon, erroneously concluded that the sympathetic nervous system acts only as an “emergency” system (Gauthier et al. 1972; Julien et al. 1990).

Patterning of neuroendocrine, physiological, and behavioral effectors increases the likelihood of adaptiveness to the particular challenge to homeostasis, providing another basis for natural selection to favor the evolution of systems with multiple effectors.

Effector Sharing

Different homeostatic systems can interact by sharing effectors (Fig. 3). This can help understand clinical associations that might otherwise be unexpected. For instance, sharing of the adrenomedullary hormonal system by the barostat and glucostat can explain hyperglycemia in gastrointestinal hemorrhage, and sharing of the vasopressin system by the barostat and osmostat can explain hyponatremia in heart failure.

Primitive Specificity

Beginning soon after adequately sensitive assay methods of plasma levels of norepinephrine (NE) and EPI became available, evidence rapidly accumulated for different noradrenergic versus adrenergic responses in different situations (Cryer 1980; Robertson et al. 1979; Young and Landsberg 1979; Young et al. 1984). These findings did not fit with the notion of a unitary sympathoadrenal system.

In the sheltered confines of a laboratory, with controlled temperature and ad libitum water, nutrients, and calories, mammals do not seem to require an intact sympathetic nervous system (Cannon 1931). It is by now clear that even under resting conditions pulse-synchronous bursts of skeletal muscle sympathetic nerve activity are detectable, and NE continuously enters the venous drainage of most organs. Activities of daily life, such as standing up (Lake et al. 1976), digesting a meal (Patel et al. 2002), speaking in public (Gerra et al. 2001), and walking—i.e., not only emergencies—are associated with rapid adjustments in sympathetic nervous system outflows.

Adrenomedullary hormonal system activity, and thereby EPI levels, respond to global or metabolic threats, such as hypoglycemia, hemorrhagic hypotension, exercise beyond an anaerobic threshold, asphyxiation, emotional distress, and shock. Evidence also has accumulated for an association between NE and active escape, avoidance, or attack, and an association between EPI and passive, immobile fear. Thus, in contrast with Selye's doctrine of non-specificity, according to the systems theory of stress activities of effector systems are coordinated in relatively specific neuroendocrine patterns.

Studies of humans exposed to cold or with mild core hypothermia have provided support for the notion of primitive specificity of neuroendocrine stress responses. Cold exposure increases plasma NE levels, with little if any increases in plasma EPI or ACTH levels, consistent with sympathetic neuronal activation and relatively less adrenomedullary and adrenocortical activation. Mild core hypothermia also increases antecubital venous levels of NE but not EPI (Frank et al. 2002). Both NE and EPI levels in arterial plasma increase in this setting, but with larger NE responses (Goldstein and Frank 2001). When these homeostatic mechanisms are overwhelmed and core temperature falls, then increased adrenomedullary secretion results in high circulating EPI levels, increasing generation of calories (Staten et al. 1987) and eliciting cutaneous vasoconstriction, which decreases evaporative heat loss. The adrenomedullary activation is associated with distress, which motivates escape and avoidance learning.

Allostasis

Homeostasis implies set goal values for monitored variables; however, ranges of acceptable values are decidedly inconstant. Levels of physiological activity required to re-establish or maintain homeostasis differ, depending on continually changing conditions in which the organism finds itself—e.g., running versus standing versus lying down. "Allostasis," a term used by Sterling and Eyer in 1988 (McEwen 1998), refers to levels of activity required for the individual to "maintain stability through change"—i.e., to adapt (McEwen 1998, 2000; Schulkin et al. 1998). Regulation around an altered apparent steady state is the essence of allostasis. Adaptations involving allostasis to cope with real, simulated, or imagined challenges are determined by genetic, developmental, and experiential factors.

Homeostat resetting redefines the conditions required to maintain homeostasis. This would be analogous to a different thermostatic setting in the winter compared to the summer. A neuroendocrine example is the hyperglycemia of exercise. Even in anticipation of the need for metabolic fuel, by activation of "central command," the blood glucose level increases to

a new steady-state value. Classically conditioned hyperglycemia provides another example of allostasis (Siegel 1972).

Resetting alters activities of multiple effector systems required to maintain allostasis, at least for short durations. During stress, short-term changes in homeostatic settings generally enhance the long-term well-being and survival of the organism. When superimposed on a substrate of pathology, however, homeostatic resetting can cause harm. For instance, in the setting of ischemic heart disease, global or patterned increases in sympathetic outflows from homeostat resetting would increase cardiac work, and the resulting imbalance between oxygen supply and demand could precipitate angina pectoris, myocardial infarction, or sudden death.

Allostatic Load

While they may be effective over a short interval, allostatic alterations may have cumulative long-term adverse effects. For instance, chronic elevation of blood pressure to ensure adequate blood flow to the brain might eventually lead to heart or kidney failure. “Allostatic load” (McEwen and Stellar 1993) refers to effects of prolonged continuous or intermittent activation of effectors involved in allostasis. In the analogy of the home temperature control system, allostatic load would increase if a window or door were left open. In this situation, one or more effectors might be activated frequently or even continuously. Long-term allostatic load—the wear and tear cost of adaptation—provides a conceptual basis for studying long-term health consequences of stress (Fig. 4).

Chronic effector system activation might alter the efficiency of the homeostatic system itself. For instance, chronic sympathetic nervous stimulation of the cardiovascular system could promote cardiovascular hypertrophy, “splinting” arterial baroreceptors in stiff blood vessel walls, in turn contributing to systolic hypertension and the risk of heart failure, kidney failure, and stroke. Moreover, an inappropriately large adrenomedullary response to a stressor might exaggerate the experience of distress (Schachter and Singer 1962). Exaggerated distress responses might increase the risk of worsening an independent pathologic process, such as in panic-induced angina pectoris (Wilkinson et al. 1998; Mansour et al. 1998).

Recently, panels of specific indices have been proposed as biomarkers of allostatic load (Juster et al. 2010). Because of the primitive specificity of stress response patterns, one might question the universal applicability of such panels. On the other hand, in chronic distress, a set of indices might reflect consequences of persistent activation of the adrenal cortex and medulla.

Systems Definitions of Stress and Distress

Even a simple homeostatic reflex reflects stress when a perceived discrepancy between a set point for a monitored variable and information about the actual level of that variable elicits compensatory responses that decrease the discrepancy.

Thus, one way of looking at stress is as a condition where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match current or anticipated perceptions of the internal or external environment, and this discrepancy between what is observed or sensed and what is expected or programmed elicits patterned, compensatory responses (Fig. 4).

Distress is *aversive* to the organism, as evidenced by motivation for learning to escape or avoid the stressor. Selye characterized distress as unpleasant or harmful (Selye 1974),

without separating these two very different characteristics. The systems theory of stress does not assume an equivalence of noxiousness (i.e., negatively reinforcing properties) with production of pathological changes; that is, the theory does not assume that distress causes disease.

Selye's theory emphasized the non-specificity of the stress response, whereas according to the systems theory, the experience of distress depends on the character, intensity, and meaning of the stressor as perceived by the organism and on the organism's perceived ability to cope with it. This is in line with Lazarus's views on emotional stress and psychological coping (Somerfield and McCrae 2000). For an organism to experience distress therefore seems to require *consciousness*, to interpret the situation in terms of the ability to cope. This notion can help explain the finding that sedation with the benzodiazepine, alprazolam, attenuates the ACTH and EPI responses to glucoprivation (Breier et al. 1992).

Distress responses, as all stress responses, have a "purpose," mitigating effects of a stressor in some way. This applies not only to neuroendocrine aspects of those responses (such as the glucose counter-regulatory actions of pituitary-adrenocortical and adrenomedullary stimulation during insulin-induced hypoglycemia) but also to psychological aspects (such as conditioned aversive and instrumental avoidance learning).

Distress responses evolved and continue to be expressed even in higher organisms, including humans who actually are only rarely exposed to truly "fight-or-flight" agonistic encounters, partly because of the importance of those responses in instinctive communication. Selye's theory did not consider the *communication* function of distress.

An Adrenal Distress System

A fourth characteristic of distress is *adrenal activation* (Goldstein 1995, 2001).

A sufficient number of studies have been published in which adrenomedullary, adrenocortical, and sympathetic noradrenergic activities have been monitored simultaneously to enable a meta-analysis of the literature, to examine inter-relationships among alterations in activities of these key effector systems upon exposure to different stressors and reassess long-standing concepts about these inter-relationships.

A recent study based on computer searches of PubMed (Goldstein and Kopin 2008) retrieved publications describing original data about plasma EPI, ACTH, and NE levels measured before and during or after exposure to stressors. Magnitudes of responses were categorized according to the following criteria. If there was no significant change in plasma levels of the dependent variable, a score of 0 was assigned. If there were a statistically significant increase but less than a doubling of the pre-stress baseline level, a score of 1 was assigned. If there were at least a doubling of the baseline value, up 3 times the baseline value, a score or 2 was assigned. If there were a large increase, from 3 up to 10 times the baseline value, a score of 3 was assigned. If there was a massive increase to ≥10 times the baseline value, a score of 4 was assigned. A total of 15 different stressors were identified for which the available literature satisfied the above criteria.

Mean EPI responses were strongly positively correlated with mean ACTH responses (Fig. 5) and less strongly with NE responses. Plasma EPI responses were larger than expected for NE responses during hypoglycemia and smaller than expected for NE responses during cold exposure with-out hypothermia, orthostasis, and active escape/avoidance. Plasma NE responses were larger than expected for ACTH responses during cold exposure without

hypothermia and severe/exhausting exercise and smaller than expected for ACTH responses during hypoglycemia.

The results of this meta-analysis therefore support a close association between adrenomedullary and HPA responses across a variety of stressors, an association that is stronger than that between adrenomedullary and sympathetic noradrenergic responses. The findings favor the concept of an adrenal distress system and support the notion of "primitive specificity," according to which stress responses occur in relatively specific neuroendocrine patterns. By promoting homeostasis, such patterning would have provided clear advantages in natural selection and therefore evolved. In contrast, Cannon's and Selye's theories, based on stereotyped responses regardless of the stressor, do not account adequately for outliers in the scatter plots relating EPI to NE and NE to ACTH responses. For instance, plasma EPI and ACTH responses to hypoglycemia are much larger than expected for NE responses, and plasma NE responses to cold exposure without hypothermia are much larger than expected for EPI or ACTH responses.

Thus there seems to be at least as good a justification for the concept of coordinated adrenocortical–adrenomedullary responses as for coordinated adrenomedullary–sympathoneural responses in stress. This coordination may involve corticotropin releasing hormone driving adrenocortical and adrenomedullary outflows (Yoshida-Hiroi et al. 2002) as well as interactions between adrenocortical and adrenomedullary chromaffin cells (Zuckerman-Levin et al. 2001; Ehrhart-Bornstein and Bornstein 2008).

References

Breier A, Davis O, Buchanan R, et al. Effects of alprazolam on pituitary-adrenal and catecholaminergic responses to metabolic stress in humans. Biol Psychiatry 1992;32:880–890. [PubMed: 1334713]

Cannon WB. Organization for physiological homeostasis. Physiol Rev 1929a;9:399–431.

Cannon, WB. Bodily changes in pain, hunger, fear and rage. D. Appleton & Co.; New York: 1929b.

Cannon WB. The effects of progressive sympathectomy on blood pressure. Am J Physiol 1931;97:592–595.

Cannon, WB. The wisdom of the body. W.W. Norton; New York: 1939.

Cannon WB, Lissak K. Evidence for adrenaline in adrenergic neurones. Am J Physiol 1939;125:765–777.

Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. J Am Med Assoc 1992;267:1244–1252.

Cryer PE. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med 1980;303:436–444. [PubMed: 6248784]

Ehrhart-Bornstein M, Bornstein SR. Cross-talk between adrenal medulla and adrenal cortex in stress. Ann N Y Acad Sci 2008;1148:112–117. [PubMed: 19120098]

Frank SM, Cattaneo CG, Wieneke-Brady MB, et al. Threshold for adrenomedullary activation and increased cardiac work during mild core hypothermia. Clin Sci 2002;102:119–125. [PubMed: 11749669]

Fukuhara K, Kvetnansky R, Cizza G, et al. Interrelations between sympathoadrenal system and hypothalamo-pituitary-adrenocortical/thyroid systems in rats exposed to cold stress. J Neuroendocrinol 1996;8:533–541. [PubMed: 8843022]

Gauthier P, Nadeau R, De Champlain J. Acute and chronic cardiovascular effects of 6-hydroxydopamine in dogs. Circ Res 1972;31:207–217. [PubMed: 4340389]

Gerra G, Zaimovic A, Mascetti GG, et al. Neuroendocrine responses to experimentally-induced psychological stress in healthy humans. Psychoneuroendocrinology 2001;26:91–107. [PubMed: 11070337]

Goldstein DS. Stress as a scientific idea: a homeostatic theory of stress and distress. Homeostasis 1995a;4:177–215.

Goldstein, DS. Stress, catecholamines, and cardiovascular disease. Oxford University Press; New York: 1995b.

Goldstein, DS. The autonomic nervous system in health and disease. Marcel Dekker, Inc.; New York, NY: 2001.

Goldstein, DS. Adrenaline and the inner world: an introduction to scientific integrative medicine. The Johns Hopkins University Press; Baltimore, MD: 2006.

Goldstein DS, Frank SM. The wisdom of the body revisited: the adrenomedullary response to mild core hypothermia in humans. Endocr Regul 2001;35:3–7. [PubMed: 11308990]

Goldstein DS, Kopin IJ. Adrenomedullary, adrenocortical, and sympathoneural responses to stressors: a meta-analysis. Endocr Regul 2008;42:111–119. [PubMed: 18999898]

Goldstein DS, McEwen B. Allostasis, homeostats, and the nature of stress. Stress 2002;5:55–58. [PubMed: 12171767]

Goldstein DS, Garty M, Bagdy G, et al. Role of CRH in glucopenia-induced adrenomedullary activation in rats. J Neuroendocrinol 1993;5:475–486. [PubMed: 8680414]

Julien C, Kandza P, Barres C, Lo M, Cerutti C, Sassard J. Effects of sympathectomy on blood pressure and its variability in conscious rats. Am J Physiol 1990;259:H1337–H1342. [PubMed: 2240238]

Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev 2010;35:2–16. [PubMed: 19822172]

Kvetnansky R, Pacak K, Fukuhara K, et al. Sympathoadrenal system in stress. Interaction with the hypothalamic-pituitary-adrenocortical system. Ann N Y Acad Sci 1995;771:131–158. [PubMed: 8597393]

Lake CR, Ziegler MG, Kopin IJ. Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. Life Sci 1976;18:1315–1325. [PubMed: 933720]

Mansour VM, Wilkinson DJ, Jennings GL, Schwarz RG, Thompson JM, Esler MD. Panic disorder: coronary spasm as a basis for cardiac risk? Med J Aust 1998;168:390–392. [PubMed: 9594949]

McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 1998;840:33–44. [PubMed: 9629234]

McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 2000;22:108–124. [PubMed: 10649824]

McEwen B, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–2101. [PubMed: 8379800]

Pacak K, Palkovits M, Yadid G, Kvetnansky R, Kopin IJ, Goldstein DS. Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. Am J Physiol 1998;275:R1247–R1255. [PubMed: 9756557]

Patel JN, Coppack SW, Goldstein DS, Miles JM, Eisenhofer G. Norepinephrine spillover from human adipose tissue before and after a 72-hour fast. J Clin Endocrinol Metab 2002;87:3373–3377. [PubMed: 12107252]

Robertson DA, Johnson GA, Robertson RM, Nies AS, Shand DG, Oates JA. Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. Circulation 1979;59:637–643. [PubMed: 421304]

Schachter S, Singer J. Cognitive, social, and physiological determinants of emotional state. Psychol Rev 1962;69:379–399. [PubMed: 14497895]

Schulkin J, Gold PW, McEwen BS. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. Psychoneuroendocrinology 1998;23:219–243. [PubMed: 9695128]

Selye, H. Stress without Distress. New American Library; New York: 1974.

Shah SD, Tse TF, Clutter WE, Cryer PE. The human sympathochromaffin system. Am J Physiol 1984;247:E380–E384. [PubMed: 6383071]

Sharabi Y, Dendi R, Holmes C, Goldstein DS. Baroreflex failure as a late sequela of neck irradiation. Hypertension 2003;42:110–116. [PubMed: 12782644]

Siegel S. Conditioning of insulin effects. J Comp Physiol Psychol 1972;78:233–241. [PubMed: 5058460]

Sofuoglu M, Nelson D, Babb DA, Hatsukami DK. Intravenous cocaine increases plasma epinephrine and norepinephrine in humans. Pharmacol Biochem Behav 2001;68:455–459. [PubMed: 11325399]

Somerfield MR, McCrae RR. Stress and coping research. Methodological challenges, theoretical advances, and clinical applications. Am Psychol 2000;55:620–625. [PubMed: 10892204]

Staten MA, Matthews DE, Cryer PE, Bier DM. Physiological increments in epinephrine stimulate metabolic rate in humans. Am J Physiol 1987;253:E322–E330. [PubMed: 3631260]

Udelsman R, Goldstein DS, Loriaux DL, Chrousos GP. Catecholamine-glucocorticoid interactions during surgical stress. J Surg Res 1987;43:539–545. [PubMed: 3695455]

Wilkinson DJC, Thompson JM, Lambert GW, et al. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. Arch Gen Psychiatry 1998;55:511–520. [PubMed: 9633669]

Yoshida-Hiroi M, Bradbury MJ, Eisenhofer G, et al. Chromaffin cell function and structure is impaired in corticotropin-releasing hormone receptor type 1-null mice. Mol Psychiatry 2002;7:967–974. [PubMed: 12399950]

Young JB, Landsberg L. Sympathoadrenal activity in fasting pregnant rats: dissociation of adrenal medullary and sympathetic nervous system responses. J Clin Invest 1979;64:109–116. [PubMed: 447847]

Young JB, Rosa RM, Landsberg L. Dissociation of sympathetic nervous system and adrenal medullary responses. Am J Physiol 1984;247:E35–E40. [PubMed: 6742188]

Zuckerman-Levin N, Tiosano D, Eisenhofer G, Bornstein S, Hochberg Z. The importance of adrenocortical glucocorticoids for adrenomedullary and physiological response to stress: a study in isolated glucocorticoid deficiency. J Clin Endocrinol Metab 2001;86:5920–5924. [PubMed: 11739465]

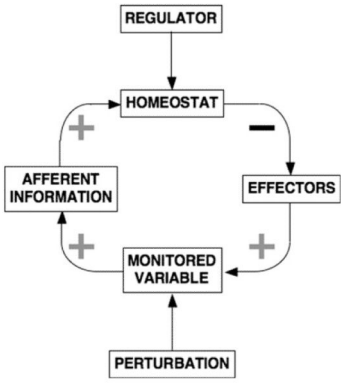

Fig. 1.

A physiological homeostatic system. As the level of the monitored variable changes, afferent information is compared with a set point or other algorithm for responding, and the sensed discrepancy leads to altered activities of effectors. Note the odd number of (–) signs, indicating a negative feedback loop. In response to a continuous perturbation, the level of the monitored variable reaches an apparent steady state

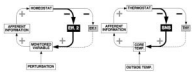

Fig. 2.
Compensatory activation. One advantage of multiple effectors is compensatory activation of alternative effectors if one effector fails, enabling control of the monitored variable. For instance, thyroidectomy augments sympathetic nervous system (SNS) responses to cold exposure

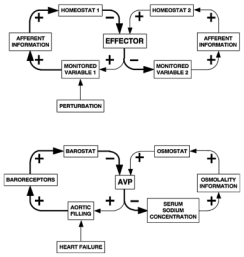

Fig. 3.

Effector sharing. Sharing of an effector by multiple homeostats can explain unpredicted consequences and syndromic features of disease processes. For instance, in heart failure, decreased aortic filling increases levels of vasopressin (AVP), which, as the antidiuretic hormone, promotes retention of free water, explaining hyponatremia attending heart failure

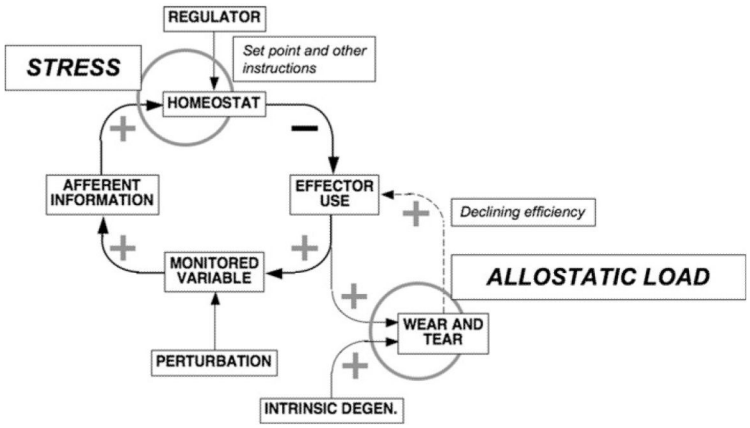

Fig. 4.

Systems definitions of stress and allostatic load. In stress, the organism senses a discrepancy between afferent information about a monitored variable and a set point and other instructions for responding, altering activities of effectors to decrease the discrepancy. Allostatic load reflects wear and tear, which, if sustained and substantial enough, decreases effector efficiency, further activating the effector and accelerating wear and tear. Allostatic load can therefore eventuate in a destabilizing and pathologic positive feedback loop

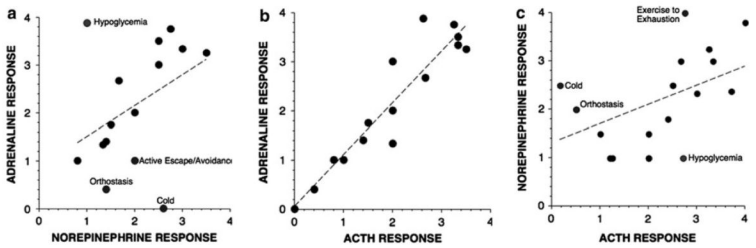

Fig. 5.

Mean values across 15 different stressors for plasma levels of **a** epinephrine (EPI) and corticotrophin (ACTH); **b** EPI and norepinephrine (NE); and **c** NE and ACTH. *Dashed lines* indicate lines of best fit