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Stress and the "extended" autonomic system

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Abstract

This review updates three key concepts of autonomic neuroscience—stress, the autonomic nervous system (ANS), and homeostasis. Hans Selye popularized stress as a scientific idea. He defined stress variously as a stereotyped response pattern, a state that evokes this pattern, or a stimulus that evokes the state. According to the "homeostat" theory stress is a condition where a comparator senses a discrepancy between sensed afferent input and a response algorithm, the integrated error signal eliciting specific patterns of altered effector outflows. Scientific advances since Langley's definition of the ANS have incited the proposal here of an "extended autonomic system," or EAS, for three reasons. (1) Several neuroendocrine systems are bound inextricably to Langley's ANS. The first to be described, by Cannon in the early 1900s, involves the hormone adrenaline, the main effector chemical of the sympathetic adrenergic system. Other neuroendocrine systems are the hypothalamic-pituitary-adrenocortical system, the arginine vasopressin system, and the renin-angiotensin-aldosterone system. (2) An evolving body of research links the ANS complexly with inflammatory/immune systems, including vagal anti-inflammatory and catecholamine-related inflammasomal components. (3) A hierarchical network of brain centers (the central autonomic network, CAN) regulates ANS outflows. Embedded within the CAN is the central stress system conceptualized by Chrousos and Gold. According to the allostasis concept, homeostatic input-output curves can be altered in an anticipatory, feed-forward manner; and prolonged or inappropriate allostatic adjustments increase wear-and-tear (allostatic load), resulting in chronic, stress-related, multi-system disorders. This review concludes with sections on clinical and therapeutic implications of the updated concepts offered here.

Keywords

Autonomic; Stress; Homeostasis; Allostasis; Dyshomeostasis

INTRODUCTION

This review updates three classic concepts in autonomic neuroscience—stress, the autonomic nervous system (ANS), and homeostasis. These have figured prominently in thinking about numerous acute and chronic disorders. Each can be viewed simply

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or complexly, as evidenced by myriad internet-based media reports and published peer-reviewed original research articles. A concept-driven approach to stress, the ANS, and homeostasis may be beneficial, especially given that multi-disciplinary, multi-system disorders of regulation are prevalent and likely will become increasingly so in the future.

STRESS AS A SCIENTIFIC IDEA

Stress is engrained in folklore and the mass media. Previous publications have traced the evolution of stress as a scientific idea (Goldstein, 1995b; Goldstein et al., 2007) and in particular the contributions of Hans Selye (Jackson, 2014). This section extracts some of the main points.

Selye and stress

Hans Selye introduced and popularized the stress concept. He defined stress variously as a stereotyped response pattern (the General Adaptation Syndrome, with three sequential stages of alarm, adaptation, and exhaustion), a condition or state that evokes this response pattern, or a stimulus that evokes the state ("stressor") (Selye, 1956). This definitional ambiguity weakened his theory. Ffrangcon Roberts famously remarked that according to Selye, "… stress, in addition to being itself and the result of itself, is also the cause of itself" (Jackson, 2014).

Kagan has questioned the usefulness of Selye's stress concept, arguing that "*stress* should be limited to select events that pose a serious threat to an organism's well-being or discarded as too ambiguous to be theoretically useful" (Kagan, 2016)

According to the "homeostat" theory (Goldstein, 1995a), discussed in more detail below, stress is a condition or state in which a comparator homeostat senses a discrepancy between perceived or anticipated afferent input to the brain and a set-point or other algorithm for responding, the integrated error signal resulting in generation of relatively specific patterns of altered effector outflows (Goldstein, 2019; Goldstein et al., 2017).

Relatively late in Selye's career he defined distress as a form of stress that is unpleasant or harmful, in contrast with eustress, which he defined as pleasant and unharmful (Selye, 1974). These definitions were circular and ambiguous. Subsequently the distress/eustress dichotomy was considered temporally, with acute, adaptive "eustress" associated with immunological enhancement and chronic, maladaptive "distress" associated with immunosuppression (Dhabhar et al., 1997).

A non-circular definition of distress holds that distress is consciously experienced, associated with a perceived inability to cope, aversive (i.e., motivates escape or avoidance), produces instinctively communicated signs, and is associated with adrenocortical and adrenomedullary activation and homeostatic resetting (Goldstein, 2006). According to this definition, emotional excitement that is joyful is not distress, although "happy heart syndrome" can have acute adverse consequences (Ghadri et al., 2016).

Selye emphasized the role of glucocorticoids in the stress response. This was expanded by his colleagues and students to the pituitary gland and then to the hypothalamic-

pituitary-adrenocortical (HPA) axis. According to the General Adaptation Syndrome idea, catecholaminergic systems would be involved in the first, alarm, stage.

Selye's doctrine of non-specificity (the "General Adaptation Syndrome")

Selye's doctrine of non-specificity states that stress is the non-specific response of the body to any demand imposed upon it (Selye, 1974). About a half century went by before the doctrine of non-specificity underwent experimental evaluation. The testing was based on stressors eliciting HPA, sympathetic noradrenergic system (SNS), and sympathetic adrenergic system (SAS) responses. The doctrine of non-specificity predicts that at different stress intensities ratios of increments in neuroendocrine responses should be the same; however, when arterial plasma corticotropin (ACTH), norepinephrine (NE), and epinephrine (EPI) were measured simultaneously in conscious rats exposed to cold, intravenous insulin, hemorrhage, or immobilization, all of which increased ACTH levels, cold evoked large NE responses, insulin large EPI responses, and hemorrhage small NE and EPI responses, while immobilization elicited large increases in levels of both NE and EPI. These results were inconsistent with Selye's doctrine of non-specificity and the existence of a unitary "stress syndrome" and were more consistent with the concept that each stressor has a particular HPA, SNS, and SAS "signature" (Pacak et al., 1998b). A variety of other studies have supported the notion of stressor specificity (Kvetnansky et al., 1998; Pacak et al., 1998a; Pacak et al., 1998c).

HPA responses are especially pronounced in distressing situations that are novel. With repeated exposure, the magnitude of the response decreases (Dobrakovova et al., 1993). Habituation is a characteristic of even primitive animals, although whether HPA adaptation to repeated stressors follows "rules of habituation" has been questioned (Rabasa et al., 2015).

The term, "dishabituation," is used to refer to a return to the initial magnitude of response after habituation has taken place. A related phenomenon is exaggerated responsiveness of adapted organisms to a novel ("heterotypic") stressor. Individuals who have habituated to one form of stress exhibit exaggerated SNS, SAS, and HPA responses to heterotypic stressors (Kvetnansky, 2004; Kvetnansky et al., 2009; Oka, 2018; Uschold-Schmidt et al., 2012). The doctrine of non-specificity does not account for this phenomenon. Clinical laboratory studies have led to the conclusion that specific emotions are associated with patterned ANS responses, with bi-directional influences of emotions on diseases and of diseases on emotional experiences (Levenson, 2019).

Dishabituation is observable even in primitive animals such as *Aplysia* and *Hirudo* and involves the neurotransmitter serotonin (Traina, 2020). Exaggerated responsiveness to a heterotypic stressor requires an ability to recognize that the stressor is novel. Most research on this topic has focused on the involved neurochemical systems including catecholaminergic systems rather than on the central neuroanatomical pathways (Dronjak et al., 2004).

Cannon's doctrine of non-specificity (the "Fight or Flight" response)

Walter B. Cannon was one of the first critics of Selye's theory. Cannon's critique centered on the assumption that a stereotyped response pattern would be adaptive regardless of the character of the stressor. Since a non-specific stress response would not have provided a natural selective advantage, a stereotyped stress response would not have evolved.

This criticism was ironic, because Cannon himself taught that the sympathetic nervous system and adrenal gland act together act as a functional unit, the "sympathico-adrenal" system. The brain was taken to respond to all emergencies the same way, by evoking increased secretion of adrenaline. How could the same response help maintain homeostasis in very different situations? Surely some effects would work against rather than toward homeostasis for at least some body functions at least some of the time. Cannon's answer was that the body's response to emergencies, with adrenaline dominating that response, enhance long-term survival, even if in the short-term aspects of the response moved some of the levels for key variables from the ideal values.

This view is still widely held, although by now there is abundant evidence that the neuronal component, the SNS, and the hormonal component, the SAS, are constitutively active, responsive to activities of daily life, (Lake et al., 1976), and can be activated separately (Goldstein et al., 2001; Goldstein et al., 2008).

Cannon introduced the notion of "fight or flight" (Cannon, 1919). By this term he meant that a rather stereotyped pattern of activation prepares the organism for extreme exertion in emergencies posed by antagonistic encounters. The state of knowledge at the time did not allow for the possibility of different patterns of physiological and biochemical responses that would be coupled to the behavioral and emotional experiences. Experimentally, active avoidance behavior is associated with greater noradrenergic activation and passive freezing behavior with greater adrenergic activation (De Boer et al., 1990). Central neural mechanisms underlying differential responses of the SNS and AHS are poorly understood.

Aggression in rodents has a circadian rhythm. In male mice a daily rhythm in aggression propensity is gated by GABAergic subparaventricular zone neurons, the main post-synaptic targets of the central circadian clock in the suprachiasmatic nucleus (SCN) (Todd et al., 2018). A relay from the SCN to the ventromedial hypothalamus might drive attack behavior and to the dorsomedial hypothalamus fight or flight responses. It has been proposed that abnormal circadian control of aggression may explain "sundowning" in elderly hospitalized patients and those with Alzheimer's disease, but how this would happen has not been explored.

The central stress system

In the 1990s George Chrousos and Philip Gold at the NIH proposed the existence of a central stress system, activation of which would elicit a "stress syndrome," in line with Selye's conceptualization (Chrousos et al., 1992; Sternberg et al., 1992). Key elements of the stress system are the paraventricular nucleus (PVN) of the hypothalamus, from which CRH is derived; and the locus ceruleus (LC) of the pons, from which NE in most of the

brain is derived (Figure 1, left panel). CRH drives pituitary release of ACTH in the HPA axis. Arginine vasopressin (AVP) is another neuroendocrine factor derived from the PVN.

According to the concept of the extended autonomic system (EAS), discussed in the next section, the central stress system is embedded within the CAN (Benarroch, 1993) (Figures 2 and 3).

A recent recapitulation continues these concepts (Tsigos et al., 2020), with key components of the stress system being the HPA axis and autonomic nervous system (ANS), which interact with other vital centers in the brain and periphery to mobilize a successful adaptive response against imposed stressors. The stress system concept continues the tradition begun by Selye, that dysregulation of the stress system (hyper- or hypo-activation) disrupts homeostasis leading to a state of “cacostasis” or allostasis (Chrousos, 2009), resulting in a variety of chronic clinical disorders.

Unlike other autonomic effectors, the parasympathetic nervous system (PNS) is active in situations that are not distressing and tend to build up rather than use up energy (Goldstein, 2006). When the central stress system is activated, PNS outflows generally decrease. Manifestations of PNS inhibition include tachycardia, decreased gastrointestinal motility, decreased production of saliva and tears, and decreased urinary bladder tone.

THE “EXTENDED” AUTONOMIC SYSTEM

The ANS as originally conceptualized by Langley about 120 years ago had three components—the sympathetic nervous system, the PNS, and the enteric nervous system (ENS) (Langley, 1903). In the more than a century that has gone by since then, many discoveries have come to light that justify extending on Langley’s ANS. Three such extensions are neuroendocrinology, inflammation/immunity, and the central autonomic network (CAN) (Figure 2).

Neuroendocrine Extension

The Sympathetic Adrenergic System (SAS)—Cannon added a neuroendocrine component to the ANS when he discovered that adrenaline (synonymous with epinephrine, EPI) is the chemical messenger secreted into the bloodstream during emotional stress (Cannon et al., 1911). One may reasonably claim that EPI was the first identified hormone (Rao, 2019). Cannon viewed the sympathetic nervous system and the adrenal gland to function as a unit, the “sympathico-adrenal system,” which is crucial for maintaining homeostasis (a term he coined) in emergencies.

EPI is a remarkably potent hormone. Probably because of this potency, circulating concentrations of EPI in resting humans are extremely low—in the range of about 100 pM (Kagedal et al., 1988).

EPI exerts numerous bodily effects. Via beta-2 adrenoceptors on vascular smooth muscle cells there is a fall in skeletal muscle vascular resistance, which tends to shift the cardiac output toward skeletal muscle. Vasoconstriction in the splanchnic bed and kidneys decreases gastrointestinal and renal perfusion. Cutaneous vasoconstriction likely results in the pallor

that characterizes people during distress. Blood flows to vital organs (the heart, brain, and lungs) generally are preserved. EPI increases cardiac rate and contractility (Mezzacappa et al., 1999), increasing cardiac output. EPI increases glucose levels (Darbar et al., 1996) by multiple mechanisms, including anti-insulin effects, breakdown of hepatic glycogen, stimulation of hepatic gluconeogenesis (Sherwin et al., 1984), and stimulation of pancreatic secretion of glucagon (Hamilton et al., 2018). By stimulation of beta-2 adrenoceptors on bronchiolar smooth muscle cells, EPI produces a well known bronchodilator effect. EPI increases hepatic breakdown of lipids to free fatty acids, generating heat, and also evokes thermogenesis via uncoupling protein-1 in brown adipose tissue (Thomas et al., 1997). EPI activates platelets (Mills et al., 1967), via occupation of alpha-2 adrenoceptors (Larsson et al., 1992a; Larsson et al., 1992b). EPI increases sweating (Ogawa, 1976). The combination of cutaneous vasoconstriction, causing skin temperature to decrease, and adrenergic sweating explains the “cold sweat” characterizing people in shock. Finally, EPI intensifies the negative emotional experience of fear (Schachter et al., 1962), probably via afferent information to the brain from physiological changes exerted by occupation of beta-adrenoceptors, although altered vagal afferent traffic (Chen et al., 2012) and delivery to brain regions with a deficient blood-brain barrier (Weil-Malherbe et al., 1959) are other possibilities.

Unlike the SAS, in which plasma EPI levels are infinitesimally low in healthy people during supine rest, the sympathetic noradrenergic system (abbreviated as SNS in this review) is tonically active (Lake et al., 1976). The SNS plays key roles in patterned alterations in the distribution of the cardiac output among the vascular beds during activities of daily life such as standing up (Lake et al., 1976), eating a meal, mild exercise (Seals et al., 1988), the Valsalva maneuver, and adjustments to altered environmental temperatures. In addition to the cardiovascular system, SNS outflows to the irises, sweat glands, gastrointestinal tract, pancreas, and kidneys play important “housekeeping” roles. Such activities are unconscious, automatic, involuntary processes that are tonically active and phasically modulated.

It is important to keep in mind that NE is a neurotransmitter, not a hormone. Increases in renal sympathetic outflow promote sodium reabsorption by proximal tubular cells (Gill, 1979). Both NE and EPI increase cellular uptake of potassium and therefore tend to decrease serum potassium levels (Clausen, 1983).

EPI might evoke psychological effects via afferent regulation of the locus coeruleus (Aston-Jones et al., 1991). If so, regulation via EPI as a hormone is indirect because of the efficient blood-brain barrier for circulating epinephrine (Weil-Malherbe et al., 1959). EPI is synthesized within the brain, such as in C1 neurons of the RVLM that express phenylethanolamine-N-methyltransferase; however, whether EPI actually is a neurotransmitter in the brain has not been demonstrated (Sved et al., 1985).

The Hypothalamic-Pituitary-Adrenocortical (HPA) System—Concepts about functions of the HPA system have evolved over centuries from the discovery of the pituitary gland by Vesalius and of the adrenal gland by Eustachio in the 1600s. Miller has reviewed the history of the field (Miller, 2018). The writings of Selye (Selye, 1950; Selye, 1956),

McEwen (McEwen et al., 2002), and Sapolsky (Sapolsky, 1998) on mechanisms and effects of chronic stress have emphasized the HPA axis.

Stress-related adrenocortical hormones produce numerous bodily effects. Intravenous administration of glucocorticoids can evoke abdominal pain, nausea, and vomiting, disturbed sleep, and neurobehavioral changes such as confusion, irritability, and restlessness (Jongen et al., 2016). Chronically increased glucocorticoid levels, as in Cushing's syndrome from adrenocortical hyperplasia or a pituitary tumor (Cushing's disease), produce truncal obesity, easy bruising, abdominal striae, hyperglycemia, hypokalemia, hypertension, osteoporosis, depressed mood, and susceptibility to non-bacterial infections and viral reactivation.

Corticotropin-releasing hormone (CRH) is expressed in cell bodies of limbic regions of the brain including the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala, as well as in the hypothalamic PVN. CRH derived from the PVN drives corticotropin (ACTH) release from the anterior pituitary gland. CRH, urocortins (UCNs), and CRH receptors (in particular CRFR1) have been viewed as the major effector system for responses to aversive stimuli (Deussing et al., 2018; Yuan et al., 2019). CRH projections to the ventral tegmental area (VTA), the source of the mesolimbocortical dopaminergic system, are derived from the basal nucleus of the stria terminalis (BNST), central nucleus of the amygdala, and PVN (Rodaros et al., 2007).

Although it is established that CRH/CRHR1 signaling mediates aversive responses, including anxiety and depression-like behaviors, recent studies have revealed anxiolytic and appetitive properties of specific CRH/CRHR1 circuits (Dedic et al., 2018). The detailed pathways and molecular mechanisms by which the CRH/urocortin-system translates negative or positive stimuli into integrated biological responses are incompletely understood.

The Renin-Angiotensin-Aldosterone System (RAS)—The renin-angiotensin-aldosterone system (RAS) plays a dominant role in the maintenance of sodium balance, blood volume, and vascular tone.

Dietary sodium restriction potently stimulates RAS activity. Specialized tubule cells of the macula densa monitor the concentration of sodium in the glomerular filtrate. When the amount of sodium falls below a certain level, macula densa cells send a message to nearby juxtaglomerular cells in the walls of the afferent arterioles. The juxtaglomerular cells release into the bloodstream the first effector chemical of the RAS, renin. The juxtaglomerular cells act as sensors themselves. They detect stretch, and therefore the distending pressure, in the blood vessels to the kidneys. A fall in the distending pressure also leads to release of renin.

Renin accelerates the conversion of a protein, angiotensinogen, to a peptide, angiotensin I. Angiotensin I has no known physiological action; however, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II (AII), which is a potent vasoconstrictor. AII stimulates the adrenal cortex to release aldosterone. Aldosterone, the main sodium-retaining hormone of the body, increases reabsorption of sodium from renal tubular cells.

One can conceptualize the RAS as an effector in regulation of both blood pressure and blood volume. Activation of the RAS tends to increase the blood pressure, via the vasoconstrictor effect of AII, and the blood volume, via the sodium-retaining effect of aldosterone.

Circulating AII can reach the brain at sites where the blood-brain barrier is deficient, such as the area postrema (AP) in the dorsal medulla. In addition, there is a brain RAS in which AII is generated via ACE, ACE2 is expressed, and occupation of AT1 receptors within the CAN increases HPA and SNS outflows (Mohammed et al., 2020).

Catecholamine systems of the body interact with the RAS in several ways. First, stimulation of both the SNS and SAS increases renin secretion (Gordon et al., 1967). Second, AII acts in the brain to increase SNS outflows. Third, there are abundant AII receptors in the adrenal medulla, and AII can evoke release of adrenaline directly (Zimlichman et al., 1987). Meanwhile, EPI increases renin secretion. Fourth, dopamine (DA) attenuates the amount of aldosterone secretion from the adrenal cortex in response to AII. Angiotensin II is a potent vasoconstrictor and in concert with EPI would be expected to augment splanchnic and renal vascular resistance.

Aldosterone, the body's main mineralocorticoid, promotes sodium reabsorption and renal potassium loss. EPI decreases serum potassium and magnesium levels (Darbar et al., 1996; Nayyar et al., 2017), via augmentation of Na/K ATPases that mediate transmembrane cation influx (Baron et al., 1985). The fall in serum potassium may help to explain a dissociation of stimulated plasma renin activity and less clear effects on plasma aldosterone (Kruse et al., 1994).

The Arginine Vasopressin/Anti-Diuretic Hormone (AVP/ADH) System—Arginine vasopressin (AVP), acting as the anti-diuretic hormone (ADH), promotes renal retention of water. In acute illnesses this can manifest with decreased serum osmolality and hyponatremia (Friedman et al., 2013). AVP acting as a pressor contributes to vasoconstriction and blood pressure; however, the effects may be masked by other determinants of systemic vascular resistance. In addition, in the brain AVP shifts the arterial baroreflex to lower blood pressures, reducing the maximum amount of sympathetic activation for a given decrease in blood pressure (Hasser et al., 1997).

PACAP—Pituitary adenylate cyclase-activating polypeptide (PACAP) was first identified in hypothalamus, based on its ability to increase cyclic AMP generation in the anterior pituitary. PACAP also has been proposed to be a "master stress hormone," especially with regard to SAS activation (Eiden et al., 2018). Acetylcholine and PACAP acting as neurotransmitters at adrenomedullary chromaffin cells release EPI for given rates of splanchnic sympathetic nerve firing. PACAP is also expressed at several brain sites in the CAN such as the PVN, amygdala, and prefrontal cortex.

Modern neuroendocrinology refers rather specifically to peptides secreted by hypothalamic neurons into the circulation. Even in this restricted sense the neuroendocrine and autonomic systems clearly interact. For instance, thyroidectomy, which increases thyrotropin secretion, also increases plasma levels of the sympathetic neurotransmitter norepinephrine (NE)

(Fukuhara et al., 1996). Infusion of the beta-adrenoceptor agonist isoproterenol into humans decreases plasma levels of ACTH and EPI (Eisenhofer et al., 1987). Hypopituitarism and adrenocortical failure decrease plasma EPI and increase plasma NE (Rudman et al., 1981; Sverrisdottir et al., 1998). AVP inhibits sympathetic noradrenergic responses to hemorrhage (Hasser et al., 1997).

Inflammatory/Immune Extension

The ANS and inflammatory/immune system affect each other. Immune cells express neurotransmitter receptors, and neurons express cytokine receptors. Additionally, immune cells can synthesize and release neurotransmitters such as catecholamines themselves, probably via autocrine-paracrine mechanisms. Natural killer cells are innate lymphocytes that are important for early and effective immune reactions. Their activities are regulated by all the major effector chemicals of the EAS, including glucocorticoids, EPI, serotonin, and DA (Capellino et al., 2020).

Whereas the roles of afferents (e.g., via vagal and somatic sensory nerves) and ANS and HPA efferents in inflammatory reflexes have been studied intensively, central pathways mediating inflammatory reflexes remain poorly understood.

Catecholamines and immunity—It has been proposed that overactivity of myocardial beta-adrenoceptors by SNS activation exerts pro-inflammatory effects and thereby contributes to the pathogenesis of atherosclerotic cardiovascular disease (Karakas et al., 2018). This concept does not take into account that there are three types of peripheral catecholamine system—the SNS, where NE is the locally acting neurotransmitter, the SAS, where EPI is the hormone, and the DOPA-DA autocrine-paracrine system (Goldstein et al., 1995), in which DA is produced in, released from, and acts locally on parenchymal cells that take up DOPA from the circulation and decarboxylate the amino acid to form the catecholamine. The latter mechanism is by definition an activity of “APUD” cells (APUD standing for amine precursor uptake and decarboxylation) that release polypeptides hormones in a diffuse neuroendocrine system (Modlin et al., 2006).

In primary human monocytes, alpha-1 adrenoceptor stimulation by phenylephrine has been reported to suppress the NLRP3 inflammasome (Horstmann et al., 2016); however, the same drug has been reported to induce cardiac dysfunction and inflammation in vivo as evidenced by increased expression of IL-6 and NLRP3 (Xin et al., 2020).

Across a variety of stressful situations increases in EPI levels are associated with elevations of the pro-inflammatory cytokine IL-6 (Danobeitia et al., 2012; Hashizaki et al., 2018; Jan et al., 2009; Koelsch et al., 2016; Kulp et al., 2010; Papanicolaou et al., 1996; Piira et al., 2013); however, bases for this relationship have not been systemically studied.

It has been proposed that during restraint stress, activation of catecholaminergic and glutamatergic C1 neurons in the RVLM stimulates a splenic anti-inflammatory pathway, which may protect tissues against ischemic injury (Stornetta et al., 2018).

A program consisting of meditation, cyclic hyperventilation followed by breath retention, and cold exposure has been reported to increase plasma EPI levels substantially; and during subsequent endotoxin administration, the intervention group had more rapid increases in plasma levels of the anti-inflammatory cytokine IL-10, lower levels of pro-inflammatory cytokine TNFα, IL-6, and IL-8, and milder flu-like symptoms, suggesting that voluntary activation of the SAS suppresses in vivo innate immune responses in humans (Kox et al., 2014)..

Although most research on effects of catecholamines on immunity has focused on adrenoceptors on immune cells, vasoconstriction from SNS activation decreases the exit of B and T lymphocytes and leukocytes (Devi et al., 2021). This may explain elevated neutrophil counts in critical illness.

C1 neurons of the rostral ventrolateral medulla (RVLM) may be a key way-station in catecholamine-immune interactions. Experimental neural manipulations of C1 neurons mediate restraint stress-induced anti-inflammation (Abe et al., 2018).

HPA system and immunity—In interpreting the literature about the HPA system and immunity one must separate reports about effects of exogenously administered glucocorticoid from effects of alterations in endogenous glucocorticoid release resulting from increased HPA system activity. One might presume that in the “alarm phase” of stress (see the section on Stress as a Scientific Idea) high circulating levels of cortisol blunt inflammatory/immune functions. Instead, acute stress, via HPA activation, seems to if anything augment immune responses. Studies by Dhabhar, McEwen, and colleagues have suggested that acute stress exposure redistributes leukocytes from the blood to organs such as the skin and lymph nodes (Dhabhar et al., 1997). Based on pharmacological blockade experiments, the redistribution depends on actions at type II (glucocorticoid) adrenocortical hormone receptors (Dhabhar et al., 1996). Subsequently the investigators reported that rats subjected to immobilization have rapid mobilization of neutrophils, lymphocytes, helper T cells, cytolytic T cells, and B cells into the blood, followed by a decreased trafficking of all cell types out of the blood, with the exception of neutrophils, numbers of which continue to increase (Dhabhar et al., 2012). A limitation in the latter experiments was that trunk blood samples were assayed, and even in the first sample plasma levels of NE and EPI were drastically increased. This means the immediate mobilization and subsequent decline could have reflected direct effects of high circulating catecholamine levels or indirect effects of local catecholamine-induced circulatory changes, especially in the skin. In general, over the course of 2 hours, acute restraint decreases lymphocyte and increases neutrophil counts (Dhabhar et al., 1996).

After infection, HPA system activation augments production and release of glucocorticoids; however, the multiplicity of effects of the hormones on functions of immune cells makes it difficult to delineate specific roles in vivo. Quatrini et al. (Quatrini et al., 2018) found that the regulation of natural killer cell function by the glucocorticoid receptor is required for surviving mouse cytomegalovirus infection. Endogenous glucocorticoids produced shortly after infection induce selective, tissue-specific expression of the checkpoint molecule PD-1 on natural killer cells. The glucocorticoid–PD-1 pathway limits the production of

the cytokine interferon-γ by splenic natural killer cells, which in turn prevents lethal immunopathology—without compromising viral clearance. HPA axis activation in response to viral infection therefore preserves tissue integrity without impairing pathogen elimination.

The cytokine IL-6 not only activates the HPA axis but also directly stimulates production of aldosterone, cortisol, and androgenic steroids (Path et al., 1997). In conscious, unrestrained rats, TNFα administration increases plasma levels of glucagon, corticosterone, ACTH, NE, and 3,4-dihydroxyphenylglycol (DHPG, the main neuronal metabolite of NE) (Darling et al., 1989).

Pro-inflammatory cytokines increase expression of CRH and AVP in the hypothalamus (Chikanza et al., 2000), probably via vagal afferents (Gaykema et al., 1995). In critically ill patients, non-survivors have been reported to have higher ACTH levels in response to exogenously administered CRH and longer release of cortisol, associated with higher levels of IL-6 and IL-8 (Dimopoulou et al., 2007). In patients with sepsis or ARDS, high dose corticosteroid administration does not improve survival; however, low doses of corticosteroids alleviate inflammation and improve survival (Chadda et al., 2002).

A key example of neuroimmune-autonomic interactions is co-regulation by CRH of the HPA axis and the adrenal medulla. Corticosteroid synthesis by cultured adrenocortical cells is increased 10-fold by co-culture with adrenomedullary chromaffin cells (Haidan et al., 1998). Across a variety of stressors plasma EPI responses are more closely tied to ACTH responses than to NE responses (Goldstein et al., 2008); however, effects on immune cell populations of stressors that specifically stimulate SNS outflow (cold exposure) or SAS outflow (glucoprivation) do not seem to have been studied.

The vagus/inflammasome system—An example of autonomic-immune interactions is regulation of cytokines and the “inflammasome” by the vagus nerve (Koopman et al., 2016; Woody et al., 2017). In the cholinergic anti-inflammatory pathway (Tracey, 2007), efferent nerve traffic from the dorsal motor nucleus of the vagus nerve increases delivery of acetylcholine to α7 nicotinic receptor subunits on celiac-superior mesenteric post-ganglionic neurons that terminate in the spleen and act on splenic immune cells to decrease TNFα generation (Koopman et al., 2016; Lerman et al., 2016; Rosas-Ballina et al., 2008; Yi et al., 2016) A randomized, blinded, healthy control pilot trial of non-invasive transcutaneous vagal stimulation reported down-regulation of inflammatory cytokine release (Lerman et al., 2016).

The inflammasome concept is based on the NOD-, LRR- and pyrin domain-containing protein 3, or NLRP3 (Swanson et al., 2019). NLRP3 is conceptualized to be an intracellular sensor that can detect a wide variety of microbes, including RNA viruses. NLRP3 inflammasome formation leads to release of the pro-inflammatory cytokines IL-1beta and IL-18 and to cell death by pyroptosis. Pyroptosis is a form of programmed cell death that may remove intracellular viral replication niches in the tissue. The sulfonylurea oral hypoglycemic drug glyburide is a NLRP3 inhibitor (Voet et al., 2019); however, effective doses may be high enough to produce cardiovascular side effects.

Dopamine—DA, via the type-1 DA receptor-1 (DRD1) and cyclic AMP signaling inhibits the NLRP3 inflammasome (Yan et al., 2015). This introduces the possibility of modulating cytokine "storm" by a DRD1 agonist. Fenoldopam is a catechol-containing DRD1 partial agonist that does not cross the blood-brain barrier. The drug also exerts vasodilator effects in coronary, renal, mesenteric, and peripheral arteries and is used intravenously clinically as an anti-hypertensive agent.

The sources of endogenous DA outside the brain are relatively poorly understood. In the kidneys DA is formed from uptake and decarboxylation of circulating 3,4-dihydroxyphenylalanine (DOPA) (Wolfovitz et al., 1993) by proximal tubular cells and acts as an autocrine-paracrine substance (Goldstein et al., 1995) that promotes natriuresis (Baines, 1990). In patients with decompensated congestive heart failure, levodopa treatment increases urinary sodium excretion (Grossman et al., 1999). Whether intravenously administered DOPA or DA affects the NLRP3 inflammasome is unknown.

The Central Autonomic Network

A hierarchy of brain regions collectively called the central autonomic network (CAN) (Benarroch, 1993) determines ANS outflows (Figure 3). The CAN involves all levels of the neuraxis. At the cortical level the CAN includes the medial prefrontal cortex, anterior cingulate, and insula. In addition, trans-neuronal tract tracing with pseudorabies virus has revealed that the motor cortex is connected multi-synaptically to the adrenal gland (Strack et al., 1989).

At the level of the limbic system there are the amygdala and hippocampus. Hypothalamic regions include the paraventricular nucleus (PVN), lateral hypothalamus, the dorsomedial hypothalamus (involved with stress-induced hypothermia (Oka, 2018)), and the hypothalamic area controlling emotional responses (HACER), which is also called the peri-fornical area (Smith et al., 1984). Midbrain components include the peri-aquaductal gray and ventral tegmental area (VTA), and pontine components the locus ceruleus (LC, the main source of norepinephrine in the brain), the parabrachial nucleus (PBN), and A5 noradrenergic cell groups.

There are several medullary nuclei in the CAN, including the raphe serotonergic cell groups, C1 adrenergic neurons and respiration-related neurons (respiratory pattern generator (RPG), pre-Botzinger complex, retrotrapezoid nucleus) in the rostral ventrolateral medulla (RVLM), A1 noradrenergic neurons in the caudal ventrolateral medulla (CVLM), the ventromedial medulla (VMM), the nucleus ambiguus (NA) the dorsal motor nucleus of the vagus nerve (DMNX), and the nucleus of the solitary tract (NTS), which is the main site of initial synapse formation in the baroreceptor and chemoreceptor reflexes.

Other regions associated with the CAN include the circumventricular regions with an imperfect blood-brain barrier (e.g., the area postrema (AP) of the dorsal medulla, subfornical organ, organum vasculosum of the lamina terminalis (OVLT), and median eminence.

Signals from interoceptors related to blood volume and pressure connect with many brain sites in the CAN. Structures along the lamina terminalis include the subfornical organ

(SFO), median preoptic nucleus (MnPO), organum vasculosum of the lamina terminalis (OVLT), and PVN. The SFO is the primary forebrain target for angiotensin II (AII), while cells in the OVLT function as osmoreceptors. The MnPO, which lies inside the blood–brain barrier, receives input from both the SFO and the OVLT and probably processes information about the status of intracellular and extracellular fluid compartments and blood pressure.

SFO, MnPO and OVLT provide input to the PVN, which directly and indirectly (e.g., via the RVLM) connects to preganglionic sympathetic neurons. The area postrema (AP), caudal ventrolateral medulla (CVLM), nucleus of the solitary (NTS), and parabrachial nucleus (PBN) all also directly or indirectly influence activity in the RVLM. A conceptualization of the "stress system" has adopted more of a mind-body approach (Charmandari et al., 2005). According to this view, the stress response is subserved by components located both in the brain and periphery. The principal effectors are CRH, AVP, the proopiomelanocortin-derived peptides alpha-melanocyte-stimulating hormone and beta-endorphin, glucocorticoids, and the catecholamines NE and EPI.

Ding et al. recently used resting-state brain functional magnetic resonance imaging to assess CAN functional connectivity and baroreflex measures at rest (Ding et al., 2020). Functional connectivity between the left amygdala and left medial frontal gyrus, bilateral post-central gyri, and bilateral paracentral lobules was found to be associated with baroreflex-cardiovagal gain and with low-frequency power of heart rate variability, the latter thought to be a measure of the ability to modulate cardiac autonomic outflows via baroreflexes (Goldstein et al., 2011).

The definition of structures subsumed under the heading of CAN is somewhat arbitrary. For instance, the motor cortex has not been considered to be a component of the CAN, despite multi-synaptic anatomic links to the adrenal gland (Strack et al., 1989) (Recall the etymology of the term, "emotion," from the French *émouvoir*, "to move emotionally," and the antecedent Latin *emovere*, "to move.") Neither has the mesolimbocortical system, an intensively studied catecholaminergic system involved with reward-related motor function learning; and the nigrostriatal dopaminergic system, which is crucial for locomotion. It should be noted that anatomic organization and neurotransmitter pathways in the brain are far from congruent.

In conclusion, the EAS concept provides a framework for the complex, integrative, interacting, dynamic nature of the ANS, neuroendocrine systems, and inflammatory/immune systems in daily life, numerous stressful situations, and several distress-related clinical conditions. The reciprocal inter-relationships of the SAS, HPA axis, and other neuroendocrine systems with inflammatory/immune systems is especially complex and ripe for future applications of systems biologic approaches.

HOMEOSTASIS AND THE NOTION OF PURPOSE

Homeostasis is a founding principle of integrative physiology. In systems biology, however, homeostasis is almost invisible. In integrative physiology homeostasis is a key *goal* that

drives body processes. In systems biology homeostasis is a *result* that emerges from continual adjustments in the operations of complex networks (Goldstein, 2019).

In the 1800s the French physiologist Claude Bernard introduced the idea of the internal environment, the *milieu intérieur*. In the face of the vicissitudes of the external environment, organisms maintain a constant fluid environment that bathes cells of the body. Even more meaningful, he proposed a purpose for body processes: "The constancy of the internal environment is the condition for free and independent life…All the vital mechanisms, however varied they might be, always have one purpose, that of maintaining the integrity of the conditions of life within the internal environment" (Bernard, 1974).

In the 1900s Walter B. Cannon took up Bernard's theme. Cannon wrote, "My first article of belief is based on the observation, almost universally confirmed in present knowledge, that what happens in our bodies is directed toward a useful end." (Cannon, 1945) His *Bodily Changes in Pain, Hunger, Fear and Rage*, includes the statement, "It has long been recognized that the most characteristic feature of reflexes is their "purposive" nature, or their utility either in preserving the welfare of the organism or in safeguarding it against injury (Cannon, 1919).

The common denominator in Bernard's and Cannon's concepts is the notion of *purpose*. Bernard's assertion about the purpose of body processes and Cannon's about the "useful end" are teleological. Teleology refers to a purpose or goal as the reason for something. To a systems biologist, teleological explanations are unnecessary. Physiological phenomena do not occur because they have the purpose of maintaining homeostasis. Instead, homeostasis is an emergent consequence.

Different writers refer to homeostasis of the entire organism, in line with Cannon, or the maintenance of levels of particular physiological variables or biochemical compounds within bounds, while levels of others can vary—e.g., blood pressure homeostasis, sodium homeostasis, glucose homeostasis, and temperature homeostasis.

The evolutionary biologist and philosopher Ernst Mayr proposed the existence of "teleonomic" forms of goal-directed processes that depend on the operation of a program, "coded or prearranged information that controls a process (or behavior) leading it toward a goal. The program contains not only the blueprint of the goal but also the instructions of how to use the information of the blueprint. A program is not a description of a given situation but a set of instructions persisting toward an end point under varying conditions, where the end state of the process is determined by its properties at the beginning" (Mayr, 1992). Mayr emphasizes that "the goal of a teleonomic activity does not lie in the future, but is coded in the program" (108).

McEwen and Wingfield (McEwen et al., 2010) and McEwen and Lasley (McEwen et al., 2002) have offered examples of what seem to be teleonomic processes.

> …a cow that begins lactation undergoes morphological, physiological and behavioral changes so it can raise a calf. None of this is essential for the maintenance of homeostasis of the cow, although homeostatic set points will

> have changed… Another example is the migration of a songbird from Mexico to Alaska in spring and back again in autumn. Here again, there are major changes in morphology, physiology and behavior that allow this animal to complete a journey of almost 5000 km in less than a month. But none of this is essential for maintenance of homeostasis. In both examples, the process of preparing for lactation or migration involves regulation of gene expression
>
> (McEwen et al., 2010).

McEwen and Lasley especially emphasize the role of cortisol in one of the more spectacular examples of a teleonomic process—that determining the migration, spawning, and death of salmon.

> The whole reason for the migration is to produce the next generation of salmon, so in the cortisol-soaked salmon, unlike other chronically stressed animals, reproduction is not a luxury system to be put on hold. Far from it; the sex glands continue to mature and the sex hormones skyrocket. In fact, biologists consider death by cortisol to be programmed into the salmon
>
> (McEwen et al., 2002).

Homeostats

Hierarchical networks involving input-output relationships continuously orchestrate and learn adaptive patterns of observable behaviors, cognition, memory, mood, and autonomic systems. Taken together, these networks determine levels of internal variables and act as if there were homeostatic comparators–i.e., “homeostats” (Goldstein, 2019).

Homeostats are unnecessary, simplistic, and teleological, so what good are they?

First, lumping the complex networks that make up the metaphorical regulators and conceptualizing purposes in controlling the regulated variables enable definitions of otherwise difficult ideas—such as stress. According to the homeostatic theory (Goldstein, 1995a), in stress a homeostat senses a discrepancy between afferent information about the regulated variable and the setpoint for arousing a response. Stress is then the condition, and the error signal is the measure of the extent of stress.

The integrated error signal could correspond to a kind of “memory” that would more be more efficient than the instantaneous error signal in returning the regulated variable to the setpoint value (Goldstein, 2008). Reference to the analogy of a modern home heating system conveys the idea about where memory may fit in here (Goldstein, 2013). With “proportionate control” the response of the furnace to a decrease in room temperature is proportionate to the magnitude of the error signal. The level of the monitored variable reaches a steady state, but unless the system has infinite gain the steady-state level never completely reaches the thermostatic setting. With “integrated control” added to proportionate control, not only does the magnitude of the error signal itself drive the effector but so does the integral of the error signal. That is, the thermostat responds not only to the error signal but also to how the error signal has accumulated over time.

Second, the homeostat theory lends itself straightforwardly to computer models that define homeostatic resetting, compensatory activation of alternative effectors, effector sharing, allostatic load, and induction of pathophysiologic positive feedback loops (Goldstein, 2006; Goldstein, 2008; Goldstein, 2013).

Third, the homeostat idea helps explain clinical phenomena in autonomic medicine. For instance, a patient had “complex” sleep apnea, meaning that his condition worsened rather than improved with continuous positive airway pressure. He brought with him and used during his hospitalization a modified continuous positive airway pressure device that administered CO2 via the mask. Inhaling CO2 produces a metabolic acidosis. The patient’s “chemostat” sensed the hypercarbia and metabolic acidosis, and this released the sympathetic noradrenergic and adrenergic systems from restraint by the “barostat,” resulting in extreme hypertension and high plasma catecholamine levels (Goldstein, 2019).

Homeostats are metaphorical comparators that sense discrepancies between afferent information a set-point for responding, implying a goal optimal state. Hu et al. recently reported by studying a neural network model of the pre-frontal cortex that the optimal performance of working memory co-occurs with the critical dynamics at the network level and the excitatory/inhibitory balance at the level of individual neurons, suggesting the existence of a unified, multi-scale, optimal state modulated by DA (Hu et al., 2019).

Allostasis and Allostatic Load

Sterling and Eyre introduced the concept of allostasis (Sterling et al., 1988), from the Greek *allos* (“other”) and *stasis* (“standing, stoppage”). Whereas homeostasis refers to processes that maintains physiological and biochemical regulated variables within narrow operating ranges, in allostasis values for these variables are altered.

Schulkin and Sterling have emphasized that allostatic changes importantly reflect anticipatory, “feed-forward” regulation as opposed to reactive, negative feedback regulation (Schulkin et al., 2019; Sterling, 2020). Even in echinoderms, which lack a brain and spinal cord, evidence has been reported for immune responses not only in reaction to but also in anticipation of stressors. Remarkably, such animals produce cortisol, and cortisol levels increase in the hydrovascular fluid of the Polian vesicle in response to the scent of a predator (Hamel et al., 2021).

Cannon’s classic monograph, “Organization for Physiological Homeostasis” (Cannon, 1929), contained only one figure, which depicted opposing roles of the “sympathico-adrenal” system in raising and the “insular or vago-insular” system in lowering blood glucose. The actions of these opposing effectors would keep blood glucose within bounds (Figure 1A). Allostasis can be conceptualized in terms of homeostatic resetting manifested by shifts in input-output curves (Goldstein et al., 2002). The low-grade fever attending a flu-like illness is an example of allostasis. This seems to correspond to an acute alteration in the optimal state.

Allostatic adjustments use up more energy than do homeostatic adjustments, and the input-output curves generally become flatter, implying decreased homeostatic efficiencies.

Allostatic states that are temporary are thought to be beneficial (McEwen et al., 2002). Once the individual recovers, the input-output curves revert to those before the acute illness, with no apparent harm done. Allostatic states, however, also increase wear and tear—allostatic load, defined as the cumulative biological burden on the body as a whole due to attempts to adapt to life's demands (Seeman et al., 2001).

Quantitative indexes of allostatic load have been based on prediction of mortality and declines in cognitive and physical functioning (Seeman et al., 2001). Recently, the allostatic burden among adults in the United States was assessed across race/ethnicity, gender, and age groups over a 30-year time period, based on data from the National Health and Nutrition Examination Survey from 1988 through 2018. The allostatic load score was calculated from the sum total of abnormal measures for serum albumin, body mass index, serum C-reactive protein, serum creatinine, systolic and diastolic blood pressure, glycated hemoglobin, total cholesterol, and serum triglycerides. Among adults aged 18 or older, the prevalence of high allostatic load increased from 34% in 1988–1991 to 49% in 2015–2018. Adults aged 40 years old and older had over 2-fold higher risks of elevated allostatic load than did adults 18–29 years old.

Estimating the severity of allostatic load based on combining factors that are known to be associated with increased risk seems to entail an element of circularity.

CLINICAL ASPECTS OF STRESS AND THE EAS

Dyshomeostasis in the Elderly

That resilience declines with aging is part of humankind's evolutionary heritage. In his *The Wisdom of the Body* Cannon devoted an entire chapter to this phenomenon. Cannon summarized already substantial literature that with aging the abilities to maintain body temperature, glucose, blood pH, and circulatory-respiratory delivery of oxygenated blood under baseline conditions are preserved, but for each of these vital functions there are decreased abilities to keep appropriate levels during stress—e.g., heat or cold exposure, glucose ingestion, and exercise.

During cooling by intravenous infusion of cold saline, older people 55–72 years old have larger decreases in core temperature and smaller increments in plasma NE levels, systemic vascular resistance, and heat generation than younger people 18–23 years old (Frank et al., 2000).

After taking a high carbohydrate diet, in young adults postprandial plasma EPI levels follow a biphasic diurnal pattern that is inversely related to glucose and insulin levels. Aging is associated with a dysregulation of this response (Penev et al., 2005). Insulin sensitivity declines with aging; body mass index and mean arterial blood pressure are independent predictors, although age and plasma NE levels are not (Supiano et al., 1993).

Plasma NE levels, NE responses to stress, skeletal muscle sympathetic outflow, and cardiac NE spillover all increase with aging (Davy et al., 1998; Esler et al., 1995; Palmer et al., 1978), probably from a combination of decreased neuronal reuptake of NE and increased

sympathetic nerve traffic. For a given amount of reflexively increased sympathetic outflow there is a blunted vasoconstrictor response (Davy et al., 1998). A potential explanation for this is an aging-related decline in releasable NE stores in sympathetic noradrenergic nerves.

Responses of cardiac NE spillover to exercise are similar in elderly vs. young men, but this is due to an aging-related decline in neuronal reuptake of released NE, meaning that the increment in cardiac sympathetic outflow probably is blunted (Esler et al., 1995).

As people age the efficiency of immune responsiveness also generally declines. Depending on genetics, epigenetics, and life experiences “immune age” can be estimated and is correlated with all-cause mortality (Alpert et al., 2019).

The ability of catecholamines to break down triglycerides to free fatty acids decreases with aging. This may increase susceptibilities to exercise intolerance, decreased ability to maintain core body temperature during cold exposure, and reduced ability to survive starvation, as well as increase visceral adiposity and indolence. Unbiased whole-transcriptome analyses of adipose macrophages has revealed that aging upregulates the gene encoding monoamine oxidase-A (MAO-A) in an NLRP3 inflammasome-dependent manner, and MAO-A inhibition restores NE-induced lipolysis (Camell et al., 2017). It should be noted, however, that MAO-A plays only a small role in sympathetic neuroeffector function, and beneficial effects of MAO-A inhibition might reflect decreased formation of hydrogen peroxide and of the autotoxic catecholaldehydes 3,4-dihydroxyphenylacetaldehyde and 3,4-dihydroxyphenylglycolaldehyde (Goldstein et al., 2014; Kang et al., 2020; Panneton et al., 2010).

Acute Illness

Virtually all acute, severe illnesses are associated with several physiological and biochemical changes that can be traced to alterations in activities of components of the EAS. These include hyperglycemia (Brealey et al., 2009; Ding et al., 2019; Gearhart et al., 2006; Halter et al., 1984; Ritsinger et al., 2019; Shahid et al., 2020), hypokalemia (Darbar et al., 1996; Nayyar et al., 2017), hyponatremia (Friedman et al., 2013; Riegger et al., 1982; Szatalowicz et al., 1981), hyperthermia (Oka, 2018)), hypertension, arrhythmias, baroreflex inhibition, platelet activation or intravascular thrombosis (Bentur et al., 2018; Golaszewska et al., 2021), and stress-related heart failure (e.g., *takotsubo* cardiomyopathy (Akashi et al., 2008)). Acute immunity-related changes include IL-6 generation (Herold et al., 2020; Qing et al., 2020). A concept for relating the EAS to pathophysiological mechanisms in the pandemic viral illness COVID-19 is presented in Figure 4.

The neuroendocrine pattern accompanying fainting reactions illustrates an acute allostatic patterned response. In a distressing situation where an individual cannot fight and cannot flee, the brain can evoke a particular response characterized by SAS activation (Benditt et al., 2003; Kikushima et al., 1999; Takase et al., 2001) and SNS inhibition (Jardine et al., 2002; Mosqueda-Garcia et al., 1997) or attenuated NE release (Evans et al., 2001; Fritsch-Yelle et al., 1996; Vaddadi et al., 2011). We call this “sympathoadrenal imbalance,” or SAI (Goldstein et al., 2003). In this situation, EPI-induced skeletal muscle vasodilation that is unopposed by NE-induced vasoconstriction shunts the cardiac output toward the

limbs and away from the brain. Concurrently, there are substantial increases in circulating AVP (Jardine et al., 1997; Meck et al., 2004; Nilsson et al., 2016), which may be relevant to the mechanism of SNS inhibition in that AVP augments baroreflexive restraint of SNS outflows, probably at the level of the area postrema (Bishop et al., 1987; Hasser et al., 1997).

Chronic Disorders of Regulation

Decreased efficiency of regulation of monitored variables of the body's inner world threatens homeostasis. The homeostasis theory encompasses integration of autonomic nervous with behavioral, endocrine, autocrine/paracrine, and cytokine effectors. The general proposal is that all these systems mediate automatic adjustments that maintain health, and disintegration of these systems causes disorders of regulation in disease (Figure 5). Some of these are post-traumatic stress disorder (Preston et al., 2021), cardiovascular (Esler, 2017; Grassi et al., 2016; Silva et al., 2019; Templin et al., 2019), metabolic (Deussing et al., 2018; Wulsin et al., 2018), and gastrointestinal (Kano et al., 2017; Levinthal et al., 2020) disorders, and neurodegeneration (Foffani et al., 2018; Fornai et al., 2021; Ren et al., 2021; Wu et al., 2016).

Hypertension provides an example of a chronic disorder of regulation. A role for increased SNS outflow in hypertension has long been suspected (Goldstein, 1981). Elevated SNS outflow seems especially prominent in relatively young patients, consistent with a contribution to pathogenesis (Goldstein et al., 1983). Many studies have addressed brain sites and mechanisms underlying increased SNS outflows. The sites are within the CAN, such as the rostral ventrolateral medulla (RVLM) (Guyenet et al., 2018) and PVN (Dampney et al., 2018).

The hypertensive response to pressor stimuli can become sensitized to particular stimuli. This seems to be a form of classical conditioning. Hypertensive response sensitization is mediated by neuroplasticity (Johnson et al., 2018). The brain circuitry involved, in the CAN, controls SNS outflows. Central regions thought to be anatomic loci for hypertensive response sensitization include the PVN and the lamina terminalis (Xue et al., 2019). The latter includes the OVLT, a circumventricular hypothalamic area that lacks an efficient blood-brain barrier. Hypertensive response sensitization involves interplays among the sympathetic noradrenergic system, RAS, and brain and peripheral immune systems (Xiao et al., 2020; Xue et al., 2020) and probably other sites in the CAN.

Baroreflex sensitivity, and therefore the ability to keep blood pressure within bounds, declines with age in a manner associated with hypertension (Bristow et al., 1969). The rate of pulse-synchronous bursts of skeletal muscle sympathetic nerve traffic increases with aging (Sundlof et al., 1978); however, arterial baroreflex control of muscle sympathetic nerve traffic (Matsukawa et al., 1998) and of cardiovagal outflow are decreased in the elderly (Bristow et al., 1969).

All forms of distress increase blood pressure and inhibit baroreflex functions (Goldstein, 1983). In baboons trained by operant conditioning to raise their diastolic blood pressure, baroreflex-cardiovagal gain decreases when the blood pressure increases (Goldstein et al., 1977). When psychological factors are attenuated by treatment with a benzodiazepine,

the baroreflex function is less decreased. For instance, in the hyperdynamic circulatory state syndrome, sedation with intravenous diazepam acutely decreases plasma NE levels, increases baroreflex-cardiovagal gain, and mitigates yohimbine-evoked systolic hypertension (Goldstein et al., 1985a). A major source of descending inhibition of baroreflex function seems to be the PVN, since PVN stimulation interferes with phenylephrine-induced increased neuronal firing in the NTS (Duan et al., 1999).

Decreased baroreflexive function is generally associated with poor outcome. This is well documented for myocardial infarction and the risk of sudden death from ventricular fibrillation (La Rovere et al., 1998). Conversely, baroreflex activation therapy improves survival in advanced heart failure (Borisenko et al., 2018).

TREATMENT

The multiple reciprocal inter-relationships among components of the EAS provide a conceptual framework for inducing therapeutic options that transcend unidirectional cause-effect relationships. One can classify such options in terms of education, non-drug treatments, and drug treatments.

The first line in management of a clinical autonomic disorder is education. Given the efficacy of allostatic adjustments in anticipation of a stressor, mutual information exchange between patient and clinician should improve quality of life in dealing with a chronic dysautonomia. A patient can learn about situations that exacerbate or alleviate symptoms, drug interactions, diurnal patterns, dietary constituents, herbal remedies, and danger signs that could mitigate threats to homeostasis by anticipating them. Meanwhile, the clinician learns from the experience gained from what in essence are N=1 experiments.

A variety of non-drug treatments may be considered that exploit the EAS concept. For instance, a patient with orthostatic hypotension or orthostatic intolerance might benefit from swimming or supine bicycle exercise training focusing on anti-gravity muscles (Fu et al., 2018) or, applying the allostasis idea, from drinking 16 ounces of water before the exercise session (Lu et al., 2003; Savard et al., 1995).

Regarding drug treatments, in a patient with post-traumatic stress disorder, electrical carotid sinus stimulation might exert a calming influence (Dworkin et al., 1979). A patient with hypertension and elevated sympathetic noradrenergic outflows might benefit from a central sympatholytic agent like clonidine (Goldstein et al., 1985b), while in a patient with a tendency to faint related to sympathoadrenal imbalance a benzodiazepine and a non-selective beta-adrenoceptor blocker might decrease the frequency of presyncope (Breier et al., 1992; Dendi et al., 2002).

Bioelectronic medicine

The myriad neurotransmission pathways to, from, and within the brain offer fertile ground for treatment via “bioelectronic medicine.” (Cracchiolo et al., 2021) Bioelectronic medicine is an emerging approach for neuromodulation therapies in disorders that until recently were treated medicinally.

This concept has attracted media attention that so far is beyond what the data justify (Blase et al., 2021). The use of vagus nerve stimulation has been advocated for myocardial reperfusion injury (Statz et al., 2020) and stress-related psychiatric disorders (Bremner et al., 2020; Noble et al., 2019). Appropriately controlled studies designed to address placebo effects and observer bias are needed.

Left cardiac sympathetic denervation is well established for decreasing the risk of ventricular fibrillation after myocardial infarction (La Rovere et al., 2020).

Bioelectronic approaches such as cardiac sympathetic denervation, renal denervation, vagal stimulation, and ganglionated plexi ablation are expanding in treating arrhythmias in clinical cardiology (Manolis et al., 2020).

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Abbreviations:

ACTH	adrenocorticotropin (corticotropin)
ADH	anti-diuretic hormone
AII	angiotensin II
ANS	autonomic nervous system
APUD	amine precursor uptake and decarboxylation
AVP	arginine vasopressin
CRH	corticotropin-releasing hormone
DA	dopamine
DOPA	3,4-dihydroxyphenylalanine
DRD1	type 1 dopamine receptor
ENS	enteric nervous system
EPI	epinephrine (synonymous with adrenaline)
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
HPA	hypothalamic-pituitary-adrenocortical
IL-6	interleukin-6
LC	locus ceruleus
MnPO	median preoptic nucleus
NE	norepinephrine

OVLT	organum vasculosum of the lamina terminalis
PNS	parasympathetic nervous system
PVN	paraventricular nucleus of the hypothalamus
RAS	renin-angiotensin-aldosterone system
SAS	sympathetic adrenergic system
SCN	suprachiasmatic nucleus
SNS	sympathetic noradrenergic system (SNS is also used as an abbreviation for Langley's sympathetic nervous system)
SFO	Subfornical organ
TNFα	tumor necrosis factor alpha
VTA	ventral tegmental area

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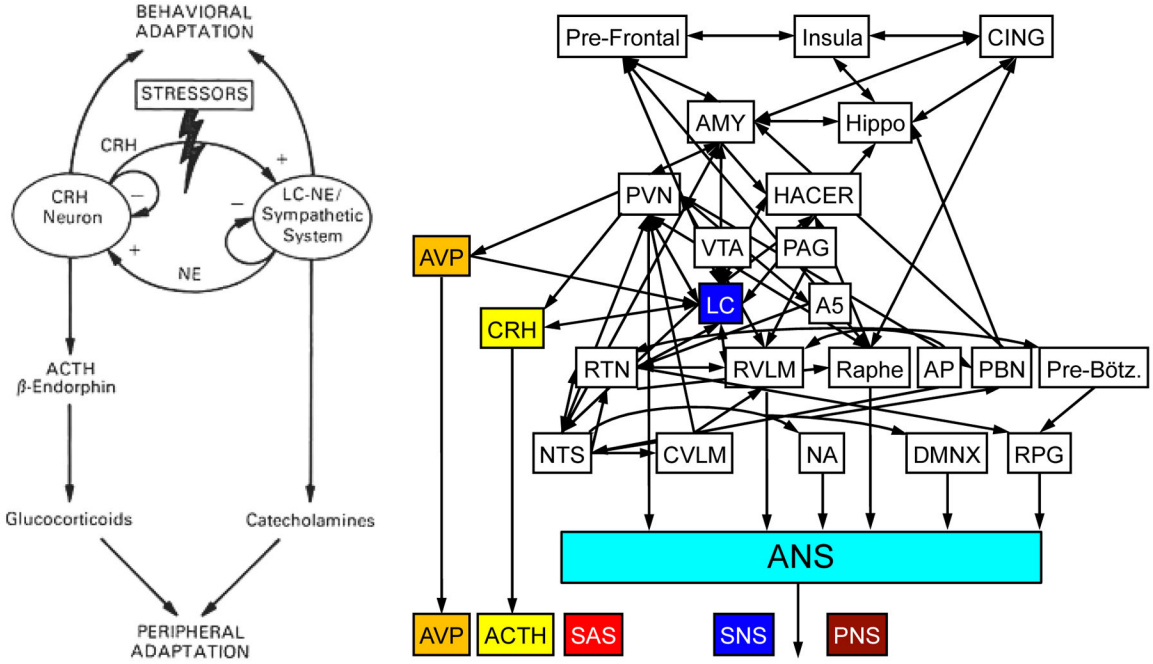

Figure 1: Early and current conceptualizations of the central stress system.

The diagram on the left depicts the original conception, in which corticotropin-releasing hormone (CRH) in the PVN and norepinephrine (NE) in the locus ceruleus (LC) are the major effector chemicals (reproduced from (Sternberg et al., 1992) with permission of the American College of Physicians). The diagram on the right shows the central system stress embedded in the central autonomic network. Arginine vasopressin (AVP) emanates from the PVN. Adrenocorticotropin (ACTH) is the anterior pituitary hormone released by CRH. Across stressors, SAS responses are closely tied to ACTH and AVP responses.

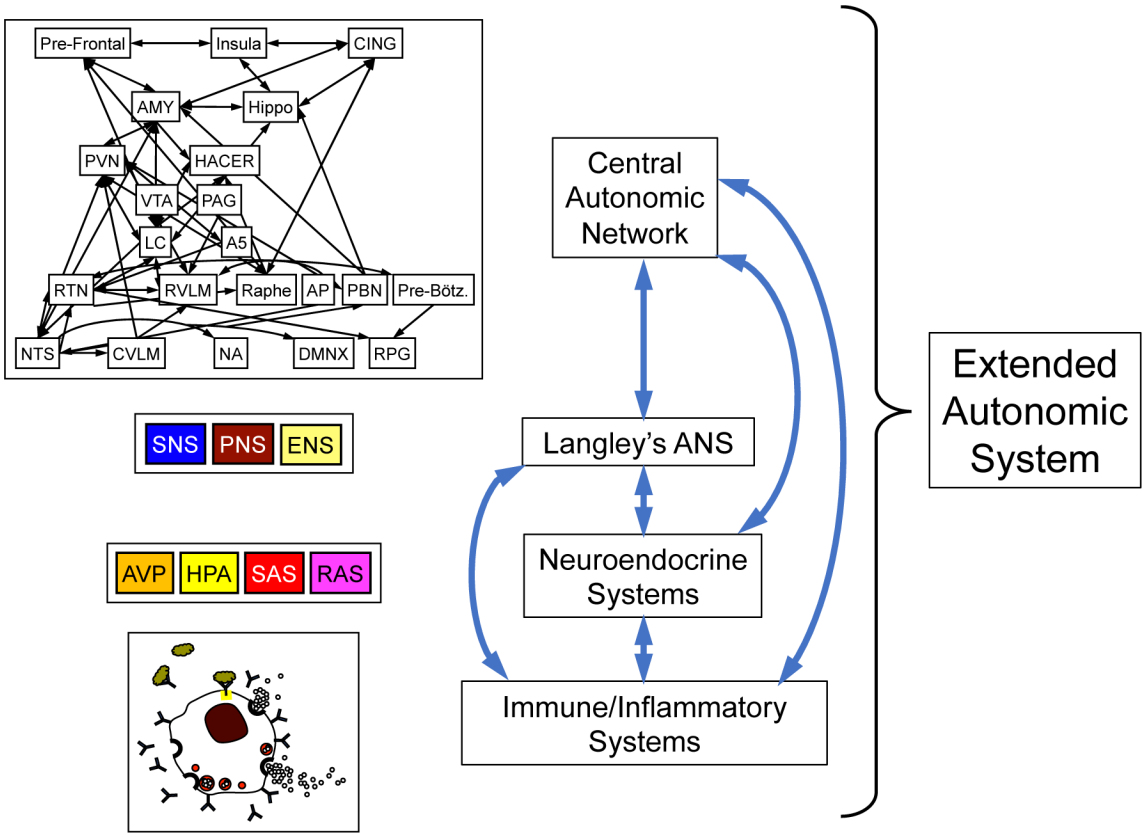

Figure 2: Overview of the Extended Autonomic System (EAS).

The EAS is conceptualized to consist of the central autonomic network (CAN); Langley's autonomic nervous system (ANS), with its three component sub-systems the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous system (ENS); neuroendocrine systems including the arginine vasopressin (AVP) system, hypothalamic-pituitary-adrenocortical (HPA) system, sympathetic adrenergic system (SAS), and renin-angiotensin-aldosterone system (RAS); and immune/inflammatory systems, represented by a stylized mast cell. Not shown here, Langley's SNS involves three chemical messengers, norepinephrine (sympathetic noradrenergic system, abbreviated as SNS in this review), acetylcholine (sympathetic cholinergic system), and epinephrine (SAS). The 4 components of the EAS are complexly inter-related (blue bi-directional arrows).

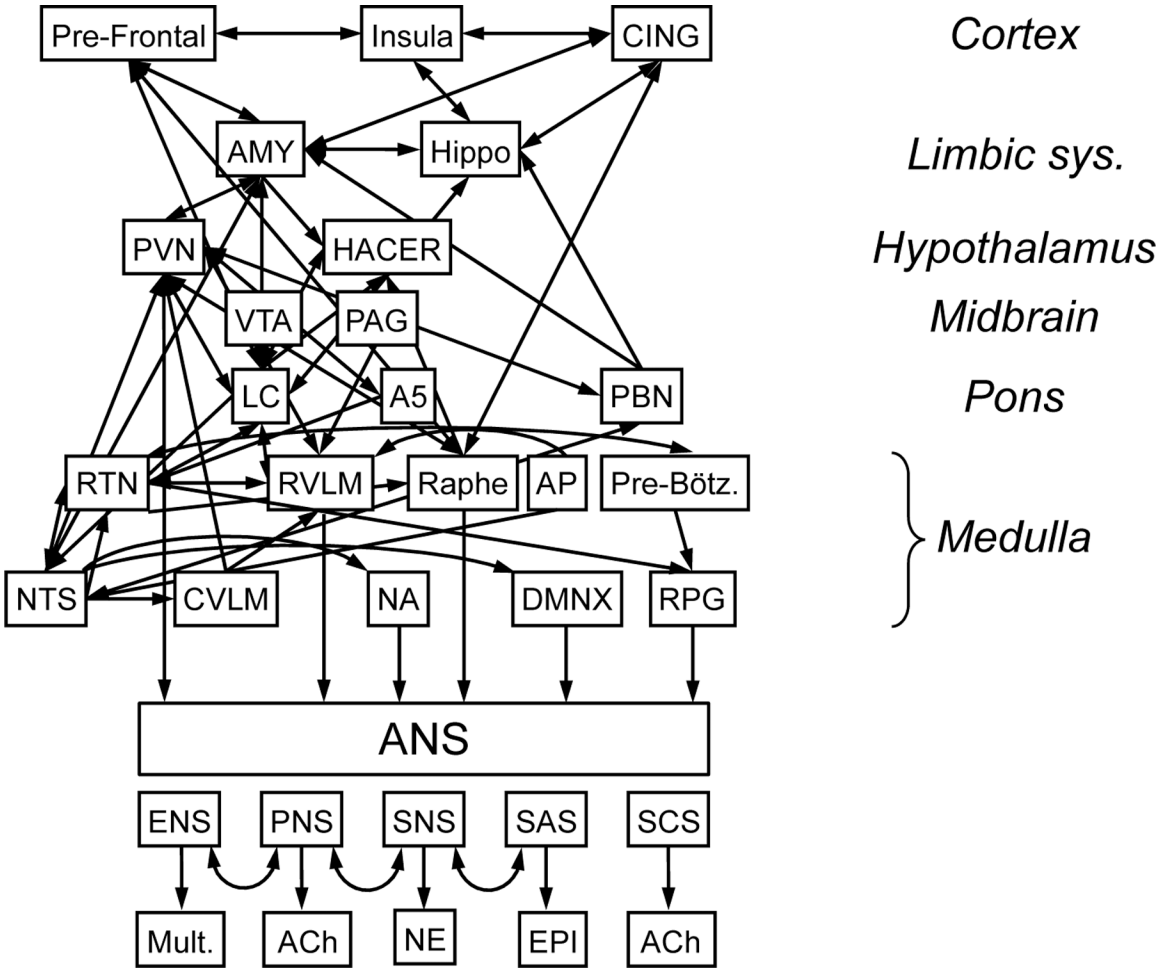

Figure 3: The Central Autonomic Network (CAN).

The CAN involves all levels of the central neuraxis. At the cortical level the CAN includes the medial prefrontal cortex (PFC), anterior cingulate (CING), and insula (INS). Limbic system sites include the amygdala (AMY) and hippocampus (Hippo). Hypothalamic regions include the paraventricular nucleus (PVN) and the hypothalamic area controlling emotional responses (HACER). Midbrain components include the peri-aquaductal gray (PAG) and ventral tegmental area (VTA). Pontine components are the locus ceruleus (LC), parabrachial nucleus (PBN), and A5 noradrenergic cell groups. Among several medullary nuclei in the CAN there are the raphe serotonergic cell groups (Raphe), C1 noradrenergic neurons and respiration-related neurons (respiratory pattern generator (RPG), pre-Bötzinger (Pre-Bötz) complex, retrotrapezoid nucleus (RTN) in the rostral ventrolateral medulla (RVLM), A1 noradrenergic neurons in the caudal ventrolateral medulla (CVLM), the nucleus ambiguus (NA) the dorsal motor nucleus of the vagus nerve (DMNX), and the nucleus of the solitary tract (NTS), which is the main site of initial synapse formation in the baroreceptor and chemoreceptor reflexes. Other regions associated with the CAN include the circumventricular regions with an imperfect blood-brain barrier (e.g., the area postrema (AP) in the dorsal medulla). Five components of the autonomic nervous system are the enteric nervous system (ENS), which involves multiple neurotransmitter (Mult.), the

parasympathetic nervous system (PNS) and sympathetic cholinergic system (SCS), which use acetylcholine (ACh) as the neurotransmitter, the sympathetic noradrenergic system (SNS), with norepinephrine (NE) the neurotransmitter, and the sympathetic adrenergic system (SAS), with epinephrine (EPI) the hormone. Neuronal clusters in regions of the CAN interact complexly, often in a bi-directional manner.

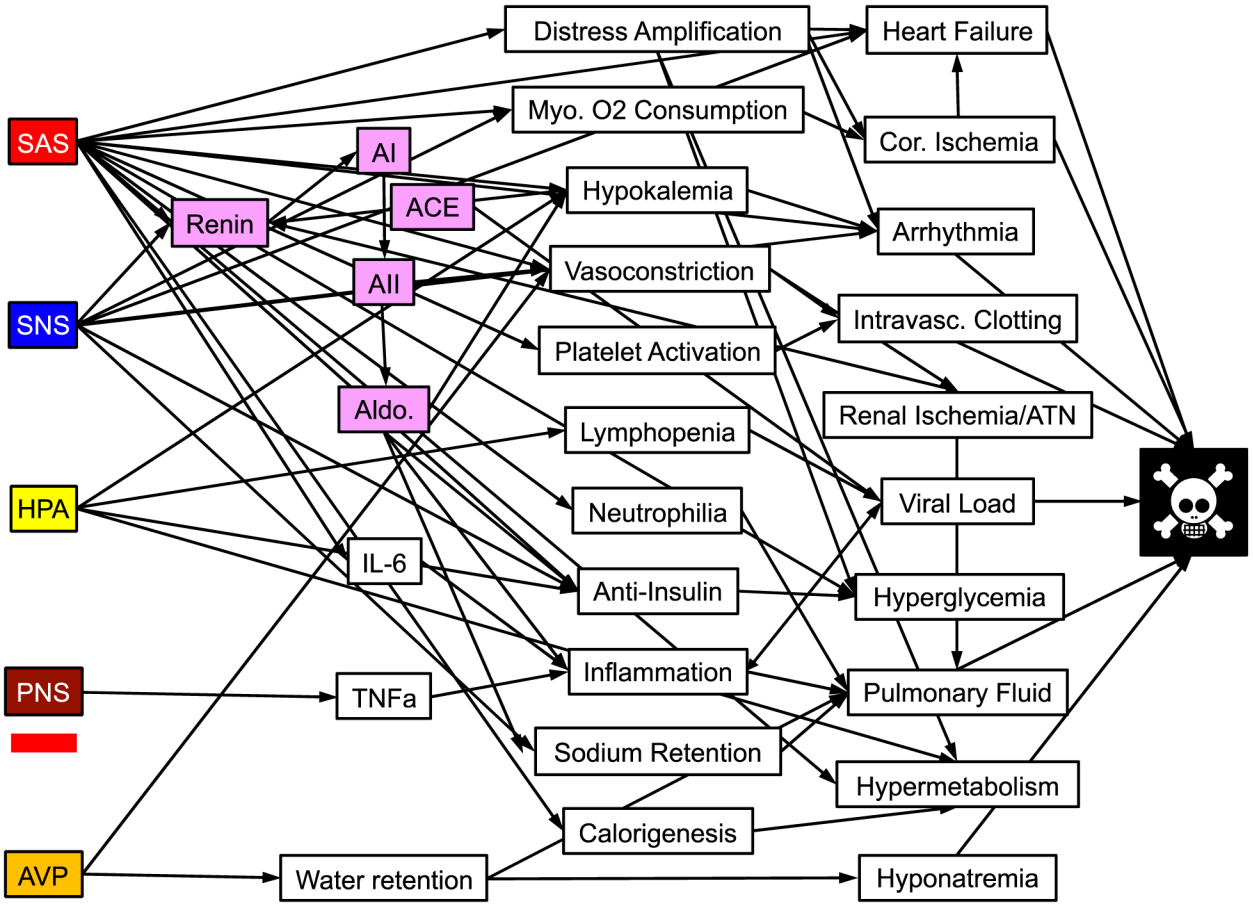

Figure 4: From stress system activation to dyshomeostasis to death due to a viral illness (in particular, COVID-19).

Five effectors of the central stress system are on the left. Intervening variables are in the center. Factors contributing the critical illness or death are on the right. The red bar under PNS indicates PNS inhibition. Other abbreviations besides those defined previously: AI = angiotensin I; ACE = angiotensin-converting enzyme; AII = angiotensin II; Aldo = aldosterone; Myo. = myocardial; Cor. = coronary; IL-6 = interleukein 6; TNFa = tumor necrosis factor alpha; ATN = acute tubular necrosis.

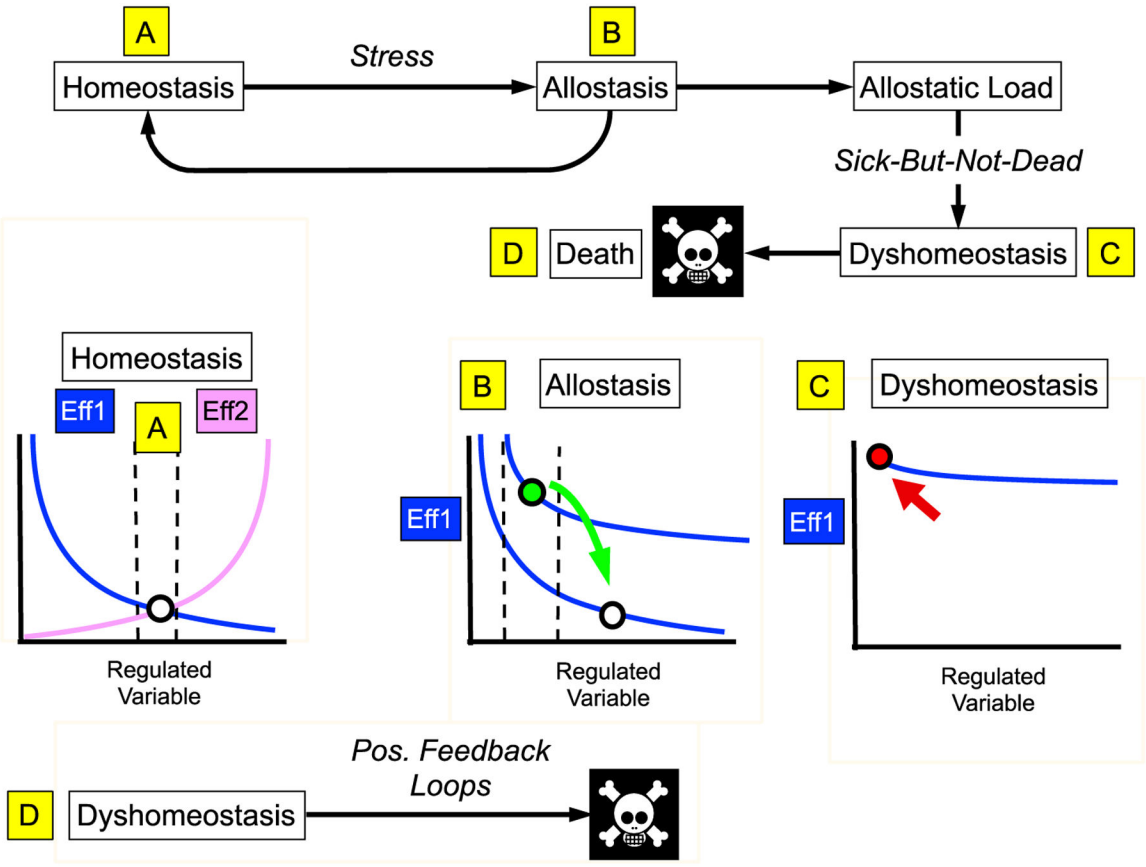

Figure 5: Homeostasis, stress, allostasis, allostatic load, dyshomeostasis, and death.

(A) In homeostasis effectors (Eff1, Eff2) with opposite effects on a Regulated Variable keep the level of the variable (circle) within bounds (vertical dashed lines). This panel is adapted from that drawn by Cannon (Cannon, 1929), where the Regulated Variable was blood glucose and the effectors the sympathico-adrenal system (activated when blood glucose falls) and the vago-insular system (activated when blood glucose is increased). (B) Allostatic processes result in a shift in the input-output curve relating the level of the Regulated Variable to the extent of activation of the effector (here only one effector is depicted). The level of the Regulated Variable is kept within bounds, but the acceptable bounds are different. The low grade fever attending a viral infection is an example of allostasis. Temporary allostatic adjustments are beneficial, and afterward the level of the Regulated Variable reverts to baseline (green arrow). (C) Prolonged, exaggerated, or inappropriate allostatic changes result in wear-and-tear (allostatic load), which decreases efficiencies of allostatic processes and the ability of the organism to adapt (dyshomeostasis). Dysfunctions may be sufficient to produce symptoms or signs of illness, without overt loss of the effectors (“sick-but-not-dead” phenomenon). (D) Dyshomeostatic states decrease thresholds for induction of destabilizing positive feedback loops that can be lethal.