Stress and disorders of the stress system

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Abstract | All organisms must maintain a complex dynamic equilibrium, or homeostasis, which is constantly challenged by internal or external adverse forces termed stressors. Stress occurs when homeostasis is threatened or perceived to be so; homeostasis is re-established by various physiological and behavioral adaptive responses. Neuroendocrine hormones have major roles in the regulation of both basal homeostasis and responses to threats, and are involved in the pathogenesis of diseases characterized by dyshomeostasis or cacostasis. The stress response is mediated by the stress system, partly located in the central nervous system and partly in peripheral organs. The central, greatly interconnected effectors of this system include the hypothalamic hormones arginine vasopressin, corticotropin-releasing hormone and pro-opiomelanocortin-derived peptides, and the locus ceruleus and autonomic norepinephrine centers in the brainstem. Targets of these effectors include the executive and/or cognitive, reward and fear systems, the wake–sleep centers of the brain, the growth, reproductive and thyroid hormone axes, and the gastrointestinal, cardiorespiratory, metabolic, and immune systems. Optimal basal activity and responsiveness of the stress system is essential for a sense of well-being, successful performance of tasks, and appropriate social interactions. By contrast, excessive or inadequate basal activity and responsiveness of this system might impair development, growth and body composition, and lead to a host of behavioral and somatic pathological conditions.

Introduction

"Hypothalamic hypophysiotropic factors" were originally proposed by G. W. Harris in the 1940s; since then, a substantial body of evidence has confirmed that these factors do indeed exist.[1–3] The survival of complex organisms—at both the individual and species levels—relies on these factors, which include mediators that regulate homeostasis and influence behavior, energy metabolism, growth, reproduction and immunity. This Review provides a brief, albeit comprehensive, synthesis of information on the conceptual evolution, technological advances and current understanding of homeostasis and stress, and describes the salutogenic changes or pathogenic disturbances that are associated with eustress or distress, respectively. This article is divided into three parts: the first discusses the concepts related to homeostasis and stress, the second details the mediators and mechanisms of the stress response, and the third describes the effects of stress on an organism.

Concepts of homeostasis and stress

All living organisms maintain a complex dynamic equilibrium, or homeostasis, which is constantly challenged by internal or external adverse effects, termed stressors.[4,5] Thus, stress is defined as a state in which homeostasis is actually threatened or perceived to be so; homeostasis is re-established by a complex repertoire of behavioral and physiological adaptive responses of the organism. The development of concepts of homeostasis and stress is summarized in Box 1.

Stressors comprise a long list of potentially adverse forces, which can be emotional or physical. Both the magnitude and chronicity of stressors are important. When any stressor exceeds a certain severity or temporal threshold, the adaptive homeostatic systems of the organism activate compensatory responses that functionally correspond to the stressor. The stress system has a major role in coordination of this process (Box 2).[2,3] The stress syndrome is a relatively stereotypic, innate response that has evolved to co-ordinate homeostasis and protect the organism during acute stress. Changes take place in the central nervous system (CNS) and in various peripheral organs and tissues. In the CNS, the stress response includes facilitation of neural pathways that subserve acute, time-limited adaptive functions, such as arousal, vigilance and focused attention, and inhibition of neural pathways that subserve acutely nonadaptive functions, such as eating, growth and reproduction. In addition, stress-related changes lead to increased oxygenation and nutrition of the brain, heart and skeletal muscles, which are all organs crucial to the central coordination of the stress response and the 'fight or flight' reaction.

Homeostatic mechanisms, including the stress system, exert their effects in an inverted U-shaped dose–response curve (Figure 1). Basal, healthy homeostasis (or eustasis) is achieved in the central, optimal range of the curve. Suboptimal effects may occur on either side of the curve and can lead to insufficient adaptation, a state that has been called allostasis (different homeostasis) or, more correctly, cacostasis (defective homeostasis, dyshomeostasis, distress), which might be harmful for the organism in

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the short term and/or long term.[2,3] Both hypofunction and hyperfunction of the homeostatic systems of the organism have multiple adverse effects. For instance, both defective and excessive reactions to fear entail a decreased ability to survive of the individual and the species. Thus, both fearless, uninhibited individuals and fearful, excessively inhibited individuals have increased risks of morbidity and mortality, the former as a result of underestimating danger, the latter as a result of decreased social integration.

The interaction between homeostasis-disturbing stressors and stressor-activated adaptive responses of the organism can have three potential outcomes. First, the match may be perfect and the organism returns to its basal homeostasis or eustasis; second, the adaptive response may be inappropriate (for example, inadequate, excessive and/or prolonged) and the organism falls into cacostasis; and, third, the match may be perfect and the organism gains from the experience and a new, improved homeostatic capacity is attained, for which I propose the term 'hyperstasis'.

Mediators of homeostasis and stress

Stress mediators, which include the classic neuro-endocrine hormones of the stress system, but also several other neurotransmitters, cytokines and growth factors, regulate both basal and threatened homeostasis and might mediate the pathogenesis of dyshomeostasis-related diseases.[2,6–8] Pivotal to our understanding of these mediators and their effects on the human organism in health and disease has been the above-mentioned concept of hypothalamic hypophysiotropic factors.

Central and peripheral effectors

The principal, greatly interconnected CNS effectors of the stress system, include the hypothalamic hormones arginine vasopressin (AVP), corticotropin-releasing hormone (CRH), the pro-opiomelanocortin-derived peptides α-melanocyte-stimulating hormone and β-endorphin, and norepinephrine produced in the A1/A2 centers of the brainstem's locus ceruleus and in the central, autonomic nervous system.[2,3] Of note, other ascending aminergic pathways, such as the serotonergic pathways that originate from the midbrain (nuclei raphe) and the posterior hypothalamic histaminergic systems, accompany the locus ceruleus-derived norepinephrine central stress response through secretion of 5-hydroxytryptamine and histamine, respectively.

The principal peripheral effectors are glucocorticoids, which are regulated by the hypothalamic–pituitary–adrenal axis, and the catecholamines norepinephrine and epinephrine, which are regulated by the systemic and adrenomedullary sympathetic nervous systems. Interestingly, postganglionic sympathetic nerve fibers also secrete CRH, among other substances, whereas both catecholamines stimulate interleukin (IL-) 6 release by immune cells and other peripheral cells via β-adrenergic receptors.[8–10] The targets of all these stress mediators

include the executive and/or cognitive, the fear/anger and reward systems, the wake–sleep centers of the brain, the growth, reproductive and thyroid-hormone axes, as well as the gastrointestinal, cardiorespiratory, metabolic, and immune systems.

The roles of corticotropin-releasing hormone

Shortly after isolation and sequencing of the 41 amino acid CRH in the mid-1980s,[11] researchers showed that when this neuropeptide, which does not cross the blood–brain barrier, was injected into the cerebral ventricles of experimental animals, it could reproduce the stress response summarized in Box 2.[2,7,12] A series of subsequent

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Key points

- Stress occurs when homeostasis is threatened or perceived to be so
- The stress response is mediated by the stress system, which is located in both the central nervous system and peripheral organs
- The main central effectors of the stress system are highly interconnected, and include hypothalamic corticotropin-releasing hormone and brainstem-derived norepinephrine
- Malfunction of the stress system is associated with behavioral and somatic disorders
- Stress is a major contributor to psychosocial and physical pathological conditions in humans

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Box 1 | History of stress

The term stress originates from the Indo–European root 'str', which has been historically associated with exertion of pressure. Thus, both the Greek 'strangalizein' and its English derivative and synonym 'to strangle', as well as the Latin 'strigere' (to tighten), have their origins in the very distant past. The concept of homeostasis as the general principle of balance or equilibrium of life was first enunciated clearly by the ancient Greek natural philosophers, who called it 'harmony' (Pythagoras) or 'isonomia' (Alkmaeon).[4,75] The modern synonym 'homeostasis', which means steady state, was coined by the American physiologist Walter Cannon in the beginning of the 20th century, whereas the word 'stress' was first used with its current meaning and popularized by the Hungarian Canadian experimentalist Hans Selye a few decades later. Both Cannon and Selye employed Hooke's law of elasticity to heuristically and creatively extrapolate physical concepts into biology.[76–81]

Box 2 | Central and peripheral functions of the stress response[2]

Functions of the central nervous system

- Facilitation of arousal, alertness, vigilance, cognition, attention and aggression
- Inhibition of vegetative functions (e.g. reproduction, feeding, growth)
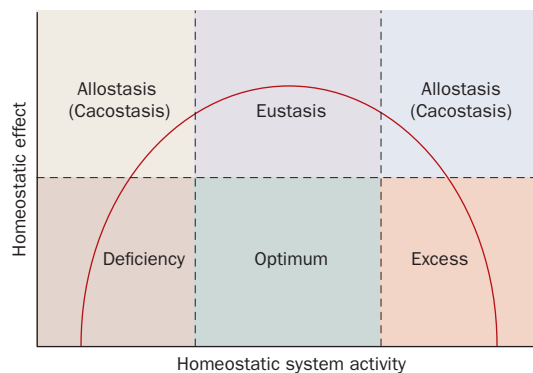- Activation of counter-regulatory feedback loops

Peripheral functions

- Increase of oxygenation
- Nutrition of brain, heart and skeletal muscles
- Increase of cardiovascular tone and respiration
- Increase of metabolism (catabolism, inhibition of reproduction and growth)
- Increase of detoxification of metabolic products and foreign substances
- Activation of counter-regulatory feedback loops (includes immunosuppression)

Figure 1 | Homeostatic systems exert their effects in an inverse, U-type dose response.[2] Eustasis is in the middle, optimal range of the curve. Suboptimal effects may be on either side of the curve and can lead to suboptimal adaptation, termed allostasis or, more correctly, cacostasis, which may be harmful for the organism in the short term or long term.

studies showed that the hypothalamic CRH–AVP and brainstem norepinephrine centers of the stress system mutually innervate and stimulate each other.[2,7,12] This mutually reinforcing positive-feedback system could, therefore, be activated by CRH, norepinephrine or any other stimulus that could set into motion either side of this highly complex, but integrated, brain loop.

The stress system interacts with, influences and is influenced by several systems in the brain that serve cognitive and/or executive, fear and anger and reward functions; these systems form a complex, integrated, positive and negative feedback-system loop.[2,7,12–20] Furthermore, the stress system acutely and in a temporally limited fashion activates the central nucleus of the amygdala, which has its own CRH system involved in the generation of fear and/or anger; in return, the central nucleus of the amygdala stimulates the stress system and forms a mutually reinforcing positive-feedback loop.[13,14] This system also activates (acutely and transiently) the mesolimbic, dopaminergic reward system (which links the ventral tegmental area to the nucleus accumbens) and the mesocortical, dopaminergic system (which links the ventral tegmentum to the frontal–prefrontal lobe), whereas it receives inhibitory input from the latter.[16–19] Finally, the stress system acutely activates the hippocampus—an organ that has a major role in intermediate-term memory—whereas it receives negative input, partly as negative feedback from the circulating glucocorticoids of the hypothalamic–pituitary–adrenal axis to its hypothalamic center, the paraventricular nucleus, and partly as tonic, hippocampal inhibitory input upon the stress system.[20]

Arousal and sleep

Activation of the stress system stimulates arousal and suppresses sleep;[12] conversely, loss of sleep is associated with inhibition of the stress system. Interestingly, sleep loss is also associated with elevated level of circulating IL-6 in spite of the reduced stimulatory effect of catecholamines on IL-6 secretion; this change possibly results from the concurrently decreased cortisol-mediated inhibition.[21–26]

Metabolism

During acute stress, the heart rate and arterial blood pressure are increased, while gluconeogenesis, glycogenolysis, lipolysis and hepatic glucose secretion are stimulated, owing to elevated levels of catecholamines and cortisol (Box 2).

Growth, reproduction and thyroid function

The growth, reproductive and thyroid-hormone axes are inhibited at several levels by stress mediators, whereas estradiol and thyroid hormones stimulate the stress system.[2,7,12,27]

Gastrointestinal function

During stress, the gastrointestinal system is inhibited at the level of the stomach via the vagus nerve, while being stimulated at the level of the large bowel via the sacral parasympathetic system, which is activated by brainstem-derived norepinephrine.[12,28]

The immune system

Stress has complex effects on the immune system and influences both innate and acquired immunity.[6,8,9,29–31] Glucocorticoids and catecholamines influence trafficking and/or function of leukocytes and accessory immune cells and suppress the secretion of proinflammatory cytokines (tumor necrosis factor [TNF], IL-1, IL-6, IL-8 and IL-12), whereas both hormone families induce a systemic switch from a T_H1 response (that is, cellular immunity) to a T_H2 response (humoral immunity). Conversely, proinflammatory cytokines stimulate the stress system, also at multiple levels, in both the CNS and peripheral nervous system, including the hypothalamus, central noradrenergic system, pituitary and adrenal glands, which increases glucocorticoid levels and consequently suppresses the inflammatory reaction. These actions form another important negative-feedback loop that protects the organism from overshoot of the inflammatory response.

Peripheral secretion of 'authentic' CRH (originally described as 'immune' CRH because of its inflammatory actions) by postganglionic sympathetic neurons and norepinephrine-activated release of IL-6 by peripheral immune cells and other cells, respectively, lead to degranulation of mast cells (that is, the release of inflammatory and vasoactive molecules from their secretory vesicles) in several tissues and activates the sickness syndrome.[6,8,9,31–33] The former action represents an important component of the neurogenic inflammatory response, whereas the sickness syndrome results from innate processes of the organism that are triggered and sustained by a systemic, inflammatory reaction. The syndrome includes somnolence, fatigue, nausea and depressive mood; these symptoms occur concurrently with activation of the acute-phase reaction by the liver

and stimulation of the sensory-afferent nervous system, which manifests as hyperalgesia and fatigue.

Cortisol is a greatly pleiotropic hormone that influences up to 20% of the expressed human genes and affects all major homeostatic systems of the body, including innate and acquired immunity.[34–36] Of great interest are the mutual interactions of the multiple isoforms of the activated glucocorticoid receptor with several transcription factors, such as AP-1, COUP-TF1, NFκB, and the STATs, through which various brain functions, growth, immunity and metabolism are regulated in a coordinated and highly stochastic fashion.[34–36]

Stress-system disorders

The stress system has a basal circadian activity and also responds to stressors on demand.[2–5] Appropriate basal activity, as well as quantitatively and temporally tailored responsiveness of the stress system to stressors, is essential for a sense of well-being, adequate performance of tasks and positive social interactions. On the other hand, inappropriate basal activity and/or responsiveness of the stress system, in terms of both magnitude and duration, might impair growth, development and body composition, and might account for many behavioral, endocrine, metabolic, cardiovascular, autoimmune, and allergic disorders. The development and severity of these conditions depend on the genetic, epigenetic and constitutional vulnerability or resilience of the individual to stress, their exposure to stressors during 'critical periods' of development, the presence of concurrent adverse or protective environmental factors, and the timing, magnitude and duration of stress.

Prenatal development, infancy, childhood and adolescence are times of increased vulnerability to stressors. The presence of stressors during these critical periods can have prolonged effects, such as sustained cacostasis that can last the entire lifetime of an individual. These effects are determined constitutionally and/or epigenetically and are (to a large extent) mediated by stress hormones, such as CRH and cortisol, that have profound effects on the brain's stress response (Figure 2).[2,37–40] Naturally, during these same critical periods, individuals are similarly sensitive to propitious environments, which induce hyperstasis and lead to the development of resistance to stressors in adulthood.

Acute and chronic stress-related diseases

Through its mediators, stress can lead to acute or chronic pathological, physical and mental conditions in individuals with a vulnerable genetic, constitutional and/or epigenetic background.[3–10,20,36] Acute stress may trigger allergic manifestations, such as asthma, eczema or urticaria, angiokinetic phenomena, such as migraines, hypertensive or hypotensive attacks, different types of pain (such as headaches, abdominal, pelvic and low-back pain), gastrointestinal symptoms (pain, indigestion, diarrhea, constipation), as well as panic attacks and psychotic episodes. Chronic stress may cause physical, behavioral
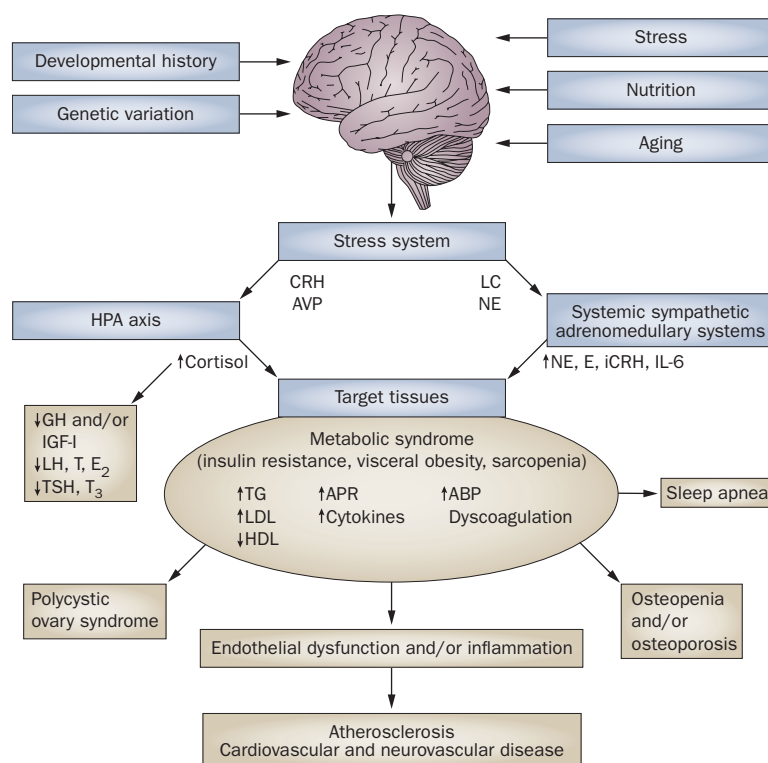
Figure 2 | Chronic stress can lead to development of the metabolic syndrome.[35] Abbreviations: ABP, arterial blood pressure; ACTH, adrenocorticotropic hormone; APR, acute-phase reactants; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; iCRH, immune CRH; E, epinephrine; E_2, estradiol; GH, growth hormone; HPA, hypothalamic–pituitary–adrenal; IGF-I, insulin-like growth factor I; IL-6, interleukin 6; LC, locus ceruleus; LH, luteinizing hormone; NE, norepinephrine; T, testosterone; TG, triglycerides.

and/or neuropsychiatric manifestations: anxiety, depression, executive and/or cognitive dysfunction; cardiovascular phenomena, such as hypertension; metabolic disorders, such as obesity, the metabolic syndrome, and type 2 diabetes mellitus; atherosclerotic cardiovascular disease; neurovascular degenerative disease; osteopenia and osteoporosis; and sleep disorders, such as insomnia or excessive daytime sleepiness.

The pathogenesis of acute-stress-induced disorders can be attributed to increased secretion and effects of the major stress mediators in the context of a vulnerable background.[2,3,9,30–33] Thus, acute allergic attacks may be activated by immune-CRH-induced degranulation of mast cells in the vulnerable organ (for example the lungs or skin). These reactions cause asthma or eczema, respectively. Similarly, migraine headaches could be caused by immune-CRH-induced degranulation of mast cells in meningeal blood vessels, which causes local vasodilatation and increased permeability of the blood–brain barrier; panic or psychotic attacks could be triggered by CRH bursts in the central amygdala that activate a fear response; hypertensive or hypotensive attacks could be caused by stress-induced, excessive sympathetic or parasympathetic system outflow, respectively.

Box 3 | Conditions with altered HPA axis activity[2]

Increased activity of the HPA axis
- Cushing syndrome
- Chronic stress
- Melancholic depression
- Anorexia nervosa
- Obsessive–compulsive disorder
- Panic disorder
- Excessive exercise (obligate athleticism)
- Chronic, active alcoholism
- Alcohol and narcotic withdrawal
- Diabetes mellitus
- Central obesity (metabolic syndrome)
- Post-traumatic stress disorder in children
- Hyperthyroidism
- Pregnancy

Decreased activity of HPA axis
- Adrenal insufficiency
- Atypical/seasonal depression
- Chronic fatigue syndrome
- Fibromyalgia
- Premenstrual tension syndrome
- Climacteric depression
- Nicotine withdrawal
- Following cessation of glucocorticoid therapy
- Following Cushing syndrome cure
- Following chronic stress
- Postpartum period
- Adult post-traumatic stress disorder
- Hypothyroidism
- Rheumatoid arthritis
- Asthma, eczema

Abbreviation: HPA, hypothalamic–pituitary–adrenal.

The pathogenesis of chronic-stress-related disorders can also be explained by sustained, excessive secretion and effects of the major mediators of stress and sickness syndromes, which influence the activities of multiple homeostatic systems.[2,3,9,30–36] These disorders thus represent chronic, maladaptive effects of two physiological processes whose mediators are meant to be secreted in a quantity-limited and time-limited fashion but have gone awry. The negative consequences of these effects are both behavioral and somatic.

Behavioral and somatic consequences

The behavioral consequences of chronic stress result from continuous or intermittent activation of the stress and sickness syndromes, and prolonged secretion of their mediators.[2,7,8,12,41–47] Thus, CRH, norepinephrine, cortisol and other hormones activate the fear system, which produces anxiety, anorexia or hyperphagia; the same mediators cause tachyphylaxis of the reward system, which produces depression and cravings for food, other substances or stress. These mediators also suppress the sleep system, which causes insomnia, loss of sleep and daytime somnolence. On the other hand, IL-6 and other mediators, possibly in synergy with those mentioned above, generate fatigue, nausea, headaches and other pains. Executive and cognitive systems also malfunction as a result of prolonged, chronic activation of stress and sickness syndromes and people may perform and plan suboptimally and make and pursue the wrong decisions. A vicious cycle is initiated and sustained, in which behavioral maladjustment leads to psychosocial problems in the family, peer group, school and/or work, which sustain or cause further mediator changes and exacerbate behavioral maladjustment. The young, developing brain is particularly vulnerable, as it lacks prior useful experiences to which it can resort.

The somatic consequences of continuous or intermittent activation of the stress and sickness syndromes can be equally devastating (or even worse) than their behavioral consequences.[2,3,7,8,27,31,41–47] In developing children, growth may be suppressed as a result of a hypofunctioning growth hormone axis; in adults, stress-induced hypogonadism can manifest as loss of libido and/or hypofertility, and hyperactivity of the sympathetic system can lead to essential hypertension. Chronic hypersecretion of stress mediators, in individuals with a vulnerable background exposed to a permissive environment, may lead to visceral fat accumulation as a result of chronic hypercortisolism, reactive insulin hypersecretion, low growth-hormone secretion and hypogonadism (Figure 2).[2,3,27,47–52] These same hormonal changes lead to sarcopenia, osteopenia and/or osteoporosis. Visceral obesity and sarcopenia are associated with manifestations of the metabolic-syndrome, such as dyslipidemia (elevated levels of total cholesterol, triglycerides and LDL-cholesterol and decreased level of HDL-cholesterol), hypertension and carbohydrate intolerance or type 2 diabetes mellitus. Genetically or constitutionally vulnerable women of reproductive age may develop polycystic ovary syndrome. Stress-related IL-6 hypersecretion plus adipose-tissue-generated inflammatory hypercytokinemia, as well as hypercortisolism, contribute to increased production of acute-phase reactants and blood hypercoagulation.[49–52] Insulin resistance, hypertension, dislipidemia, hypercytokinemia and blood hypercoagulation lead to endothelial dysfunction and consequently atherosclerosis, with its cardiovascular and neurovascular sequelae.

Chronic-stress-induced immune dysfunction, primarily the T_H1 to T_H2 switch, increases the vulnerability of individuals to certain infections and autoimmune disorders (Figure 1).[6–8,29–31,34] For instance, the immune dysfunction observed in individuals who are chronically stressed might contribute to the persistence of infection with *Helicobacter pylori,* granted that this pathogen

Table 1 | Adaptive responses to evolutionary stressors and related diseases in modern human societies[68]

Response to survival threat	Selective advantage	Contemporary disease
Combat starvation	Energy conservation	Obesity Metabolic syndrome
Combat dehydration	Fluid and electrolyte conservation	Hypertension
Combat injurious agents	Potent immune reaction	Autoimmunity Allergy
Anticipate adversaries	Arousal and fear	Anxiety Insomnia
Minimize exposure to danger	Social withdrawal	Depression
Prevent tissue strain and damage	Retain tissue integrity	Pain syndromes Fatigue syndromes

primarily induces and is defended against through activation of a cellular immune response. The same is true for infections with *Mycobacterium tuberculosis* and the common cold viruses. Similarly, this switch increases vulnerability to T_H2-driven autoimmune diseases, such as Graves disease, systemic lupus erythematosus and some allergic conditions. Increased vulnerability to certain neoplasms and their progression might be another effect of chronic stress, but this issue remains controversial.

Increased levels of CRH and/or stress-system abnormalities have been reported in behavioral and neuropsychiatric disorders, such as hypothalamic oligomenorrhea and amenorrhea, reduced fertility, obligate athleticism, anxiety, depression, post-traumatic stress disorder in children, eating disorders and chronic, active alcoholism (Box 3).[2,3,27,53–55] On the other hand, overproduction of CRH in the brain and in peripheral tissues, as well as disruption of the hypothalamic–pituitary–adrenal axis and the functions of the arousal and sympathetic systems, have been reported in obesity, metabolic syndrome and essential hypertension. Furthermore, dysregulation of the stress-system and autonomic nervous system is a distinctive feature of common gastrointestinal disorders, such as irritable bowel syndrome and peptic ulcer disease.[56]

Consistent with the observation that central or peripheral hypersecretion of CRH seems to be involved in a large number of behavioral and somatic disorders, preclinical and clinical evidence suggests therapeutic potential for CRH type 1 receptor antagonists, such as antalarmin, in the treatment of all or some of these diseases and other neuropsychiatric and somatic entities.[57–62]

Abnormal neuroendocrine, autonomic and immune functions are also present in chronic inflammatory and/or autoimmune and allergic diseases, in fibromyalgia and chronic fatigue syndromes; substantial evidence demonstrates that these abnormalities are related to low CRH activity (Box 3).[2,6–8,29–31,34,63] Similarly, low CRH activity has been implicated in atypical, seasonal depression, postpartum 'baby blues' and depression, premenstrual dysphoric disorder and climacteric depression.[2,3,27,64–67] In all these disorders, the problem seems to be cacostasis secondary to inadequate stress-system activity and responsiveness, which influence the functions of the homeostatic systems.

Stress in modern societies

We might wonder why modern societies are plagued by clusters of the so-called multifactorial polygenic disorders: obesity, the metabolic syndrome and type 2 diabetes mellitus; hypertension; autoimmunity and allergy; anxiety, insomnia, and depression; and pain and fatigue syndromes. All these disorders are associated with dysfunction of the stress system (Table 1). Such dysfunction, in fact, has a lot to do with the development of these common and frequently comorbid pathologies.[68] In its evolutionary path, the human species experienced environmental stressors, which applied selective pressure upon its genome. Such selection favored ancestors who were efficient at conserving energy, combating dehydration, fighting injurious agents, anticipating adversaries, minimizing exposure to danger and preventing tissue strain and damage. In modern societies, lifestyle has changed dramatically from that of our past. The modern environment and extension of our life expectancy seem to permit the expression of these affluence-related ills.

Stress is ubiquitous and universally pervasive; however, its objective quantification has not been easy. In modern life, statistics show powerful effects of stress early in life, concurrent chronic stress, and socioeconomic status on both the morbidity and mortality of chronic disease.[69–74] Similarly, comparisons between non-Hispanic white people in the US and those in the UK show that the sociopolitical system has a potent effect on the burden of chronic disease—an influence well above and beyond that predicted by socioeconomic status, which can only be interpreted as an individual, chronic, stress-driven cacostasis with a deleterious effect on health.[73]

Finally, analyses of data obtained in the National Health and Nutrition Examination Surveys show that, despite increasing obesity rates, mortality has been decreasing in the US. This decrease probably reflects public health improvements and, most likely, chronic use of pharmacological agents, such as β-blockers, angiotensin-converting-enzyme inhibitors and statins,

which interrupt the pathogenic effects of disturbed homeostatic mechanisms.[74]

Conclusions

The stress response, which occurs when homeostasis is threatened or perceived to be threatened, is mediated by the stress system. Central effectors (including hypothalamic hormones, such as AVP, CRH and pro-opiomelanocortin-derived peptides and brainstem-derived norepinephrine) and peripheral effectors (including glucocorticoids, norepinephrine and epinephrine) of this system regulate the brain's cognitive, reward and fear systems and wake–sleep centers as well as the growth, reproductive and thyroid hormone axes, and influence the gastrointestinal, cardiorespiratory, metabolic, and immune systems. Malfunction of the stress system might impair growth, development, behavior and metabolism, which potentially lead to various acute and chronic disorders. Our lifestyles and environment in modern societies seem to be particularly permissive for such stress-related disorders.

Review criteria

The author has been working in the general area of stress for over 30 years. Multiple book sources and articles in MEDLINE and PubMed were employed. All papers selected were English-language, full-text papers. We also searched the reference lists of identified articles for further primary information. The terms "homeostasis", "stress", "glucocorticoids" and "catecholamines" were crossreferenced with terms pertaining to homeostatic functions influenced by stress, such as "arousal", "sleep", "growth", "reproduction", "metabolism" and "immunity", or to pathological conditions related to stress, such as "anxiety", "depression", "obesity" and "metabolic syndrome".

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