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Allostasis, Homeostats, and the Nature of Stress

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This essay continues discussion of a new formulation of homeostasis that uses the concepts of allostasis and homeostats. The new formulation moves beyond Cannon's concept of "homeostasis," which posits an ideal set of conditions for maintenance of the internal environment. The notion of allostasis recognizes that there is no single ideal set of steady-state conditions in life, and different stressors elicit different patterns of activation of the sympathetic nervous and adrenomedullary hormonal systems. Allostasis reflects active, adaptive processes that maintain apparent steady states, via multiple, interacting effectors regulated by homeostatic comparators—"homeostats." "Allostatic load" refers to the consequences of sustained or repeated activation of mediators of allostasis. From the analogy of a home temperature control system, the temperature can be maintained at any of a variety of levels (allostatic states) by multiple means (effectors), regulated by the thermostat (homeostat). Allostatic load and risks of system breakdown increase when, for example, the front door is left open in the winter. Applying these notions can aid in understanding how acute and chronic stress can exert adverse health consequences via allostatic load.

Keywords: Stress; Distress; Allostasis; Homeostasis; Homeostat

CANNON AND "HOMEOSTASIS"

Walter B. Cannon, extending Claude Bernard's concept of the internal environment, introduced the term, "homeostasis," to describe the product of the "coordinated physiological processes which maintain most of the steady states in the organism" (Cannon, 1929a,b; 1939). According to Cannon, rapid activation of homeostatic systems—especially of what he called the "sympathico-adrenal system"—preserves the internal environment, by producing compensatory and anticipatory adjustments that enhance the likelihood of survival.

Cannon rarely used the term "stress" and never defined it. One may infer that he viewed stress as a noxious aspect of the environment:

> Perhaps a comparative study would show that every complex organism must have more or less effective self-right adjustments in order to prevent a check on its functions or a rapid disintegration of its parts when it is subjected to stress... (Cannon, 1939, pp. 23–25).

According to Cannon, coordinated body processes would work toward the goal of an ideal set of steady-states—"homeostasis." In emergencies and in anticipation of emergencies, activation of the sympathico-adrenal system would enhance survival. It is by now clear that the sympathico-adrenal system is active tonically and contributes to "basal" levels of key internal variables such as blood pressure and glucose. Moreover, activities of daily life, such as meal ingestion, speaking, changing posture, and movement—i.e., not only emergencies—are associated with continual alterations in sympathetic nervous system outflows, maintaining appropriate body temperature, delivery of metabolic fuel to body organs, and so forth.

Each of these activities is associated with a somewhat different set of "normal" apparent steady-states, directed by the brain and determined by coordinated actions of a variety of effector systems. This principle leads directly to the concept of "allostasis," as will be discussed below. It is also by now clear the different everyday challenges, as well as rarer emergencies, can alter sympathetic nervous and adrenomedullary hormonal activities relatively differentially. Thus, sympathetic nervous system activation is especially prominent during exposure to cold, orthostasis, and mild exercise, whereas adrenomedullary hormonal system activation is especially prominent during

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acute glucoprivation and emotional distress (Goldstein, 2001).

THE HOME HEATING ANALOGY

One can assimilate many of the concepts presented here from the analogy of a home temperature control system. In such a system, the thermostat plays a central role, by sensing discrepancy between the setpoint, determined by a regulator, and the temperature, which produces differential bending of metal bands in the thermostat. This type of system is a classical example of regulation by *negative feedback*. Analogously, as discussed below, the body has many comparators—including an actual thermostat.

Home temperature control systems usually include *multiple effectors*. The redundancy comes at relatively little cost, compared with the economies afforded. The availability of multiple effectors for heating, ventilation, and air conditioning has three advantages. First, the multiplicity extends the *range* of external temperatures where the internal temperature can be maintained. Second, when a single effector fails to function, the other are activated compensatorily, and the *compensatory activation* can help to maintain the temperature at about the set level. Third, the use of the effectors can be *patterned* as appropriate to maximize economy and efficiency.

"HOMEOSTATS"

Stress occurs when the organism senses a disruption or a threat of disruption of homeostasis, leading to a compensatory reaction. The sensation requires a comparative process, where the brain compares available information with setpoints for responding. Central to the present theory is that the body possesses numerous homeostatic comparators. We call them "homeostats." Each homeostat compares a specific category of information with a setpoint for responding, determined by a regulator. Homeostatic systems typically use multiple effectors to change values for the controlled variable. The loop is closed by monitoring changes in the levels of the controlled variable, via one or more monitored variables.

A tremendous array of homeostatic systems detect perturbations of monitored variables. In particular, in line with the home heating analogy, afferent information to the brain about cutaneous and blood temperature determines activities of cholinergic and noradrenergic nerve fibers in the skin that regulate sweating and vasomotor tone.

According to the current concept, even a simple homeostatic reflex reflects "stress" when a perceived discrepancy between a setpoint for a monitored variable and information about the actual level of that variable elicits compensatory responses to decrease the discrepancy. Thus, one way of looking at "stress" is as a condition where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and this discrepancy between what is observed or sensed and what is expected or programmed elicits patterned, compensatory responses.

"ALLOSTASIS" AND "ALLOSTATIC LOAD"

Levels of physiological activity that are required to re-establish or maintain homeostasis differ, depending on continually changing conditions in which the organism finds itself—e.g., running vs. standing vs. lying down. "Allostasis" refers to levels of activity required for the individual to "maintain stability through change"—i.e., to adapt (Sterling and Eyer, 1988; McEwen and Stellar, 1993; McEwen, 1998; 2000; Schulkin *et al.*, 1998). In terms of the homeostatic definition of stress, "allostasis" refers to the set of apparent steady-states maintained by multiple effectors. In the home temperature control system, one can regulate temperature at different levels, by appropriate use of effectors. Analogously, among individuals, levels of glucose, blood pressure, body temperature, metabolism, and so forth are normally held stable at different levels, with different patterns of effector activation.

"Allostatic load" refers to effects of prolonged continuous or intermittent activation of effectors involved in allostasis. In the analogy of the home temperature control system, allostatic load would increase if a window or door were left open. In this situation, one or more effectors might be activated frequently or even continuously. An even more extreme example would be having the air conditioner and the furnace on at the same time, as is often the case in an overheated apartment in the spring when there is a warm day before the boilers have been shut down. Continued use of the furnace and air conditioner in opposition to one another, an example of an inefficient "allostatic state," consumes fuel and contributes to wear-and-tear on both pieces of equipment. Long-term allostatic load—the wear and tear cost of adaptation—provides a conceptual basis for studying long-term health consequences of stress.

PRINCIPLES OF HOMEOSTAT OPERATION

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

Homeostatic systems always include regulation by negative feedback. Increases in values of the monitored variable result in changes in effector activity that oppose and thereby "buffer" changes in that variable. This feedback regulation can be modulated at several levels and therefore can be quite complex. Physiological positive feedback loops can occur, such as in the "growth spurt" of adolescence, but these also incorporate negative feedback,

so that a new apparent steady-state is attained, and the system does not "explode."

Homeostatic systems generally use more than one effector. Natural selection would have favored the evolution of systems including multiple effectors. The redundancy comes at relatively little cost, yet increases the range of control, enables a degree of control of regulated variables by compensatory activation when one effector malfunctions, and enables patterned activation of effectors to maximize adaptiveness. Because of effector redundancy in homeostatic systems, disabling an effector compensatorily activates the others, assuming no change in homeostat settings. This enables partial or even complete maintenance of the monitored variable at the previous setting. Examples of compensatory activation include augmentation of sympathoneural responsiveness by adrenalectomy, hypophysectomy, or thyroidectomy (Udelsman *et al.*, 1987; Goldstein *et al.*, 1993; Fukuhara *et al.*, 1996). Another consequence of multiple effectors is the potential for patterned effector responses. Patterning of neuroendocrine, physiological, and behavioral effectors increases the likelihood of adaptiveness to the particular challenge to homeostasis, providing another basis for natural selection to favor the evolution of systems with multiple effectors.

Different homeostats can regulate the activity of the same effector system. For instance, the vasopressin effector is shared by the osmostat and putative "volustat" (Stricker and Verbalis, 1986; Verbalis *et al.*, 1986).

Blockade of afferent information to or interference with the function of a homeostat increases the variability of levels of the monitored variable. Thus, baroreceptor deafferentiation increases the variability of blood pressure, as does bilateral destruction of the nucleus of the solitary tract, the likely brainstem site of the arterial barostat (Nathan and Reis, 1977).

Homeostat resetting redefines the conditions required to maintain homeostasis. Regulation around an altered apparent steady state is the essence of allostasis. Resetting alters activities of multiple effector systems required to maintain allostasis, at least for short durations. During stress, short-term changes in homeostatic settings generally enhance the long-term well being and survival of the organism. Responses during exercise provide an obvious example. When superimposed on a substrate of pathology, however, homeostatic resetting can cause harm. For instance, in the setting of ischemic heart disease, global or patterned increases in sympathetic outflows from homeostat resetting would increase cardiac work, the resulting imbalance between oxygen supply and demand precipitating angina pectoris, myocardial infarction, or sudden death.

MEDICAL AND PSYCHOLOGICAL CONSEQUENCES OF STRESS AND ALLOSTASIS

The homeostatic theory of stress and the concepts of allostasis, allostatic states, and allostatic load can help to understand chronic as well as acute medical consequences of stress. Chronic activation of allostatic effectors in allostatic states promotes wear and tear, or allostatic load. For instance, chronic elevations in sympathetic neuronal and hypothalamic-pituitary–adrenocortical outflows might worsen insulin resistance or accelerate cardiovascular hypertrophy. Chronic activation of hypothalamic-pituitary–adrenocortical activation and release of endogenous excitatory amino acids in the brain lead to remodeling of neurons in the hippocampus and impairment of cognitive function, processes that may participate in psychiatric illnesses such as major depression (McEwen, 2000).

One way to conceptualize the application of the homeostatic idea to medical consequences of stress is in terms of the perceived ability to cope. An organism experiences "distress," a form of stress when an aversive experience follows recognition that allostasis is or will not be sufficient to restore or maintain homeostasis. In contrast with distress, stress does not imply a conscious experience. For instance, even heavily sedated humans have substantial adrenomedullary stimulation in response to acute glucoprivation. Indeed, the greater extent of the adrenomedullary response to the same stressor in alert than in sedated humans might provide a measure of the distress.

Distress elicits instinctive, observable signs and pituitary–adrenocortical and adrenomedullary activation (Goldstein, 1995; 2001). Via these neuroendocrine changes, distress could worsen pathophysiologic processes. Because of adrenomedullary activation in a patient with coronary artery stenosis, distress could elicit cardiovascular stimulation and produce an excess of myocardial oxygen consumption over supply, precipitating myocardial infarction or lethal ventricular arrhythmias.

Long-term physical or mental consequences of stress would depend on long-term effects of allostatic load. Prolonged, intensive activation of effector systems could exaggerate effects of intrinsic defects in any of them, just as increased air pressure in a pneumatic tyre could expand and eventually "blow out" a weakened area. It is not difficult to imagine that repeated or long-term stress or distress could lead to a medical or psychiatric "blowout," via a positive feedback loop.

Maintenance of allostatic states requires energy. This requirement is perhaps clearest in allostasis of core temperature. In mammals, maintenance of a constant core temperature accounts for a substantial proportion of total body energy expenditure at rest. One may hypothesize that reducing allostatic load exerts beneficial health effects, just as one may hypothesize that excessive allostatic load exerts deleterious health effects.

Atrophy of brain structures such as the hippocampus and amygdala in major depression impairs cognitive function and processing of emotional information and contributes to the disease psychopathology (McEwen, 1998; 2000). Whether long-term distress itself causes

physical disease remains an issue for research and should not be assumed. Chronic effector system activation might alter the efficiency of the homeostatic system itself. For instance, chronic sympathetic nervous stimulation of the cardiovascular system could promote cardiovascular hypertrophy, "splinting" arterial baroreceptors in stiff blood vessel walls, in turn contributing to systolic hypertension and the risk of heart failure, kidney failure, and stroke. Moreover, an inappropriately large adrenomedullary response to a stressor might exaggerate the experience of emotional distress (Schachter and Singer, 1962). Exaggerated distress responses might increase the risk of worsening an independent pathologic process, such as in panic-induced angina pectoris (Mansour *et al.*, 1998; Wilkinson *et al.*, 1998).

In summary, this essay reflects a merging of the homeostat theory of stress with the concept of allostatic load. Until this conceptual merging, the homeostat theory did not lead easily to testable predictions about long-term effects of stress and distress; and the concept of allostatic load did not incorporate determinants of that load as sensed discrepancies between afferent information and setpoints for responding, leading to patterned alterations in activities of multiple effectors. Merging of the homeostat theory of stress with the notions of allostasis and allostatic load can provide a basis for explaining and predicting physical and psychiatric effects of acute and chronic stress.

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