

Stress and Parasympathetic Control

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Traditionally, the autonomic nervous system is conceptualized as the paired antagonism between the sympathetic and the parasympathetic nervous system. These components of the autonomic nervous system, based on the region of the brain and spinal cord in which the autonomic nerves (i.e., preganglionic fibers) have their origin, compete functionally by either increasing or decreasing activity of specific target organs. The sympathetic system is defined by the autonomic fibers that exit thoracic and lumbar segments of the spinal cord. The parasympathetic system is defined by the autonomic fibers that exit either the brain stem via the cranial nerves (primarily via the vagus) or the sacral segments of the spinal cord. Since most organs in the viscera receive both sympathetic and vagal input, the regulation of the autonomic nervous system has been modeled as a balance system.

Central nervous system regulation of visceral organs is the focus of several historic publications. For example, in *The Expression of Emotions in Man and Animals*, Darwin described the dynamic neural relationship between the heart and the brain. He stated that

when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumogastric [vagus] nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body.

From Darwin's perspective, the vagus as a cranial nerve was a direct portal to and from the brain. Although Darwin acknowledged the bidirectional communication between the viscera and the brain, the subsequent formal description of the autonomic nervous system minimized the importance of central regulatory structures and afferents. A focus on the peripheral motor nerves with an emphasis on the paired antagonism between sympathetic and parasympathetic efferent pathways on the target visceral organs resulted in a lack of interest in afferent influences to the brain stem areas regulating specific efferent pathways. This early conceptualization of the vagus focused on an undifferentiated efferent pathway that was assumed to modulate 'tone' concurrently to several target organs. Thus, neural circuits regulating the supradiaphragmatic

(e.g., myelinated vagal pathways originating in the nucleus ambiguus and terminating primarily above the diaphragm) were not functionally distinguished from the subdiaphragmatic (e.g., unmyelinated vagal pathways originating in the dorsal motor nucleus of the vagus and terminating primarily below the diaphragm). Without this distinction, research and theory focused on the paired antagonism between the parasympathetic and sympathetic innervation to target organs. The consequence of an emphasis on paired antagonism in physiology was an acceptance and use of global constructs focusing on peripheral physiology such as autonomic balance, sympathetic tone, and vagal tone. Ironically, the origin of modern research on stress physiology is often linked to the classical conditioning of autonomic activity, which, as Pavlov demonstrated, requires the involvement of higher brain structures in the modulation of visceral responses.

In the mid-1950s, W Hess proposed that the 'autonomic' nervous system was not solely 'vegetative' and automatic but, rather, was an integrated system with both peripheral and central neurons. In 1949, Hess was awarded the Nobel Prize in Physiology or Medicine. His Nobel lecture was titled 'The central control of activity of internal organs.' In the lecture, Hess acknowledged the importance of the prevailing model of the autonomic nervous system, which emphasized the paired antagonistic innervations of the internal organs and the definition of sympathetic and parasympathetic functions. However, he went well beyond this conceptualization to emphasize the importance of central structures in the regulation of visceral state by describing his studies that demonstrated the influence of the hypothalamus on the autonomic nervous system. By emphasizing the central mechanisms that mediate the dynamic regulation of peripheral organs, Hess anticipated the need for methodologies and technologies to continuously monitor the neural circuits involving both defined brain structures and peripheral nerves in the regulation of visceral function and state and to move from the prevailing conceptualization of autonomic nervous system as a peripheral system. The lecture provides a succinct statement: (1) to emphasize the importance of feedback circuits linking peripheral organs to brain structures and the bidirectionality of these feedback circuits and (2) to acknowledge that, although much can be learned about neural structures and functions via traditional experimental paradigms (e.g., neural blockade, surgery, and electrical stimulation), the dynamic feedback circuits cannot be adequately studied through these paradigms.

Arousal Theory and Stress Responses

For more than a century, researchers have measured autonomic variables (e.g., heart rate and palmar sweat gland activity) as indicators of emotional state related to perceived stress (e.g., fear, mental effort, workload, and anxiety). Historically, arousal theories provided scientists who studied brain–behavior relations with a model that assumed that activation of peripheral physiological measures regulated by the sympathetic branch of the autonomic nervous system provided ‘sensitive’ indicators of brain ‘arousal’ or ‘activation.’ This view was based on a rudimentary understanding of the autonomic nervous system in which changes in easily measured peripheral organs (e.g., sweat glands and heart) were assumed to be accurate indicators of how the brain was processing emotional stimuli. Usually, the emotional states were associated with fight-or-flight behaviors and the sympathetic–adrenal system (e.g., increases in heart rate, sweat gland activity, and circulating catecholamines) initially described by Cannon as well as the increased activity of the hypothalamic–pituitary–adrenal (HPA) axis with an emphasis on cortisol as a dependent variable in stress research as initially described by Selye.

Measures due, in part, to their availability and their neuroanatomical association with the target organs of the sympathetic nervous system (i.e., sweat and heart rate) and with secretions from the adrenal medulla (i.e., epinephrine and norepinephrine) and the adrenal cortex (i.e., cortisol) have become the primary physiological variables used to assess stress. An acceptance of a unitary arousal system created a research environment that neglected several important factors, including an understanding of the brain structures that regulate autonomic function; how these structures evolved from the most primitive vertebrates to mammals; how the autonomic nervous system interacts with the immune system, the HPA axis, and the neuropeptides, oxytocin, and vasopressin; and the co-evolution of stress and coping strategies with the increasing complexity of the autonomic nervous system. Missing from the dialog on stress is the role of the parasympathetic nervous system and especially the vagus with its bidirectional portal between the brain and specific visceral organs.

The Mammalian Nervous System Is a Product of Evolution

Embedded in the mammalian nervous system are neuroanatomical structures related to the expression and experience of stress. Via evolutionary processes, the mammalian nervous system has emerged with specific features that react to the challenge to maintain

visceral homeostasis. Stress, simply defined, is the product of demands on the nervous system that result in a deviation from homeostasis. In general, the domains of homeostasis, which have been monitored, have focused on the visceral systems involved in cardiovascular, digestive, reproductive, and immune functions. Adaptive and successful coping to stress results in minimizing the magnitude and duration of this deviation. To survive, mammals must determine friend from foe, when an environment is safe, and communicate with their social unit. These survival-related behaviors limit the extent to which a mammal can be physically approached, whether vocalizations will be understood, and whether coalitions can be established. Moreover, these behavioral strategies, which are used to navigate through the ‘stress of life,’ form the bedrock on which social behaviors and higher cognitive processes can be developed and expressed. Thus, learning and other expansive mental processes must be structured, manipulated, and studied within the context of how the environment fosters or ameliorates stress-related physiological states.

Table 1 illustrates the phylogenetic differences in the structures that regulate the heart in vertebrates. The heart is selected because the regulation of the heart determines the availability of the metabolic resources required for mobilization as well as for growth and restoration. For example, cardiac output must be regulated to remain calm in safe environments, to mobilize for fight-or-flight behaviors, or to immobilize for death feigning or avoidance behaviors. To regulate cardiac output, several efferent structures have evolved. These structures represent two global and often opposing systems: (1) a sympathetic–catecholamine system including catecholamine-secreting chromaffin tissue and spinal sympathetic nerves and (2) a vagal system (a component of the parasympathetic nervous system)

Table 1 Phylogenetic shifts in vertebrate cardiac control

Group	CHM	DVC	SNS	AD/m	VVC
Jawless fish	X ⁺	(X ⁺)			
Cartilaginous fish	X ⁺	X ⁻			
Bony fish	X ⁺	X ⁻	X ⁺		
Amphibians	X ⁺	X ⁻	X ⁺		
Reptiles	X ⁺	X ⁻	X ⁺	X ⁺	
Mammals	X ⁺	X ⁻	X ⁺	X ⁺	X ⁻

CHM, chromaffin tissue; DVC, dorsal vagal complex with vagal efferent pathways originating in the dorsal motor nucleus of the vagus and vagal afferents terminating in the nucleus tractus solitarius; SNS, spinal sympathetic nervous system; AD/m, adrenal medulla; VVC, ventral vagal complex with efferent pathways originating in the nucleus ambiguus that regulate visceral structures (heart, bronchi, and thymus) and striated muscles via special visceral efferents and afferents via the tractus solitarius, trigeminal, and facial nerve.

with branches originating in the medullary source nuclei (i.e., dorsal motor nucleus of the vagus and nucleus ambiguus).

Unlike other vertebrates with a cardioinhibitory vagus, the mammalian vagus contains two branches. One branch originates in the dorsal motor nucleus of the vagus and provides the primary neural regulation of subdiaphragmatic organs such as the digestive tract. However, at the level of the heart and unlike more primitive vertebrates, the efferent vagal pathways that originate in the dorsal motor nucleus of the vagus do not play a major role in the normal dynamic regulation of cardiac output. Rather, during embryological development in mammals, cells from the dorsal motor nucleus of the vagus migrate ventrally and laterally to the nucleus ambiguus. There, they form the cell bodies for the visceromotor myelinated axons that provide potent inhibition of the sinoatrial node, the pacemaker for the heart.

Three principles can be extracted by investigating the phylogeny of the regulation of the vertebrate heart. First, there is a phylogenetic shift in the regulation of the heart from endocrine communication to unmyelinated nerves and, finally, myelinated nerves. Second, there is a development of opposing neural mechanisms of excitation and inhibition to provide rapid regulation of graded metabolic output. Third, with increased cortical development, the cortex exhibits greater control over the brain stem via direct (e.g., corticobulbar) and indirect (e.g., corticoreticular) neural pathways originating in motor cortex and terminating in the source nuclei of the myelinated motor nerves emerging from the brain stem (e.g., specific neural pathways embedded within cranial nerves V, VII, IX, X, and XI), controlling visceromotor structures (i.e., heart, bronchi, and thymus) and somatomotor structures (muscles of the face and head) that results in a neural circuit that functions to facilitate social behavior and to maintain calm behavioral states.

These phylogenetic principles provide a basis for investigating the parasympathetic contribution to stress reactions and recovery. In general, phylogenetic development results in increased neural control of the heart via the myelinated mammalian vagal system, which can promote transitory mobilization and the expression of sympathetic tone without requiring sympathetic or adrenal activation. With this new vagal system, transitory incursions into the environment or withdrawals from a potential predator can be initiated without the severe biological cost of the metabolic excitation associated with sympathetic-adrenal activation. Paralleling this change in neural control of the heart is an enhanced neural control of the face, larynx, and pharynx that enables complex

facial gestures and vocalizations associated with social communication. This phylogenetic course results in greater central nervous system regulation of behavior, especially that needed to engage and disengage with environmental challenges.

Polyvagal Theory: Three Phylogenetic Systems Related to Stress Reactivity

The polyvagal theory emphasizes the phylogenetic origins of brain structures that regulate social and defensive behaviors. The polyvagal theory proposes that the evolution of the mammalian autonomic nervous system provides the neurophysiological substrates for emotional experiences, affective processes, and stress responses. The theory proposes that physiological state limits the range of adaptive behaviors and psychological experiences. In this context, the evolution of the nervous system determines the range of emotional expression, the quality of communication, and the ability to regulate bodily and behavioral state including the expression and recovery of stress-related responses. Relevant to adaptive stress responses, the theory makes the following assumptions:

1. Evolution has modified the structures of the autonomic nervous system.
2. The mammalian autonomic nervous system retains vestiges of phylogenetically older autonomic nervous systems.
3. Emotional regulation and social behavior are functional derivatives of structural changes in the autonomic nervous system due to evolutionary processes.
4. In mammals, the autonomic nervous system response strategy to challenge follows a phylogenetic hierarchy, starting with the newest structures and, when all else fails, reverting to the most primitive structural system.
5. The phylogenetic stage of the autonomic nervous system determines the behavioral, physiological, and affective features of stress reactivity.

The polyvagal theory emphasizes and documents the neurophysiological and neuroanatomical distinction between the two branches of the vagus (i.e., the tenth cranial nerve) and proposes that each vagal branch is associated with a different adaptive behavioral and physiological response strategy to stressful events. The theory describes three phylogenetic stages of the development of the mammalian autonomic nervous system (Table 2). These stages reflect the emergence of three distinct subsystems, which are phylogenetically ordered and behaviorally linked to communication (e.g., facial expression, vocalization, and listening), mobilization

Table 2 Phylogenetic stages of the neural control of the heart proposed by the polyvagal theory

Stage	Autonomic nervous system component	Behavioral function	Lower motor neurons
III	Myelinated vagus (ventral vagal complex)	Social communication, self-soothing and calming, inhibit 'arousal'	Nucleus ambiguus
II	Sympathetic-adrenal system	Mobilization (active avoidance)	Spinal cord
I	Unmyelinated vagus (dorsal vagal complex)	Immobilization (death feigning, passive avoidance)	Dorsal motor nucleus of the vagus

(e.g., fight-or-flight behaviors), and immobilization (e.g., death feigning, behavioral 'shutdown,' and syncope). The mobilization system is dependent on the functioning of the sympathetic nervous system. The most phylogenetically primitive component, the immobilization system, is dependent on the unmyelinated or 'vegetative' vagus, which is shared with most vertebrates. With increased neural complexity due to phylogenetic development, the organism's behavioral and affective repertoire is enriched. These subsystems provide a framework to study the vagal contribution to the regulation of stress responses.

The mammalian vagus functions as an active vagal brake in which rapid inhibition and disinhibition of vagal tone to the heart can support behavioral mobilization or self-soothe and calm an individual. When the vagal tone to the pacemaker is high, the vagus acts as a restraint or brake limiting heart rate. When vagal tone to the pacemaker is low, there is little or no inhibition of the pacemaker. Due to vagal influences to the sinoatrial node (i.e., the heart's pacemaker), resting heart rate is substantially lower than the intrinsic rate of the pacemaker. In mammals, the primary vagal inhibitory pathways occur through the myelinated vagus originating in the nucleus ambiguus. Consistent with assumptions of the polyvagal theory, the vagal brake contributes to the modulation of cardiac output by decreasing or increasing the inhibitory vagal control of the heart to influence rate and thereby adjust metabolic resources to support either mobilization or social engagement behaviors.

By transitory downregulation of the cardioinhibitory vagal tone to the heart (i.e., removing the vagal brake), the mammal is capable of rapid increases in cardiac output without activating the sympathetic-adrenal system. By engaging this system, rather than the sympathetic-adrenal system, mammals have an opportunity to rapidly increase metabolic output for immediate mobilization. Under prolonged challenge, the sympathetic system may also be activated. By rapidly re-engaging the vagal system, the sympathetic input to the heart is inhibited, resulting in a decrease in metabolic output and a calm behavioral state.

The Vagal Brake: Parasympathetic Regulation of the 'Stress' Response

Due to the tonic vagal influences to the sinoatrial node, resting heart rate is substantially lower than the intrinsic rate of the pacemaker. When the vagal tone to the pacemaker is high, the vagus acts as a brake on the rate at which the heart is beating. When vagal tone to the pacemaker is low, there is little or no inhibition of the pacemaker. Thus, the vagal brake may be used as a construct to describe the functional modulation of heart rate by the myelinated vagal efferent pathways. Neurophysiologically, the vagal brake provides a mechanism to support the metabolic requirements for mobilization and communication behaviors. Functionally, the vagal brake, by modulating visceral state, enables the individual to rapidly engage and disengage with objects and other individuals and to promote self-soothing behaviors and calm behavioral states. Thus, withdrawal of the vagal brake is associated with an adaptive stress response and a reinstatement of the vagal brake with recovery.

Withdrawal of the vagal brake will facilitate the recruitment of other neural mechanisms (e.g., excitation of sympathetic or the unmyelinated vagal pathways) and neural chemical mechanisms (e.g., stimulation of the HPA axis) to regulate physiological state. Thus, consistent with the polyvagal theory, if the vagal brake is not functioning or will not serve the survival needs of the organism, then the phylogenetically 'older' systems (e.g., the sympathetic-adrenal system or unmyelinated vagus originating in the dorsal motor nucleus of the vagus) will be recruited to regulate metabolic output to deal with environmental challenges. For example, if the vagal brake is not functioning, there is the potential for greater dependence on the sympathetic excitation of the cardiovascular system.

The Social Engagement System

Mammals have evolved to have a well-defined neurally mediated social engagement system. Embryologically, components of several cranial nerves develop

together (i.e., myelinated vagal pathways from the nucleus ambiguus and special visceral efferent pathways from cranial nerves V, VII, IX, X, and XI) to form the neural substrate of a social engagement system. This system provides the neural gatekeepers for social–emotional interactions. The social engagement system has a control component in the cortex (i.e., upper motor neurons) that regulates brain stem nuclei (i.e., lower motor neurons) to control eyelid opening (e.g., looking), facial muscles (e.g., emotional expression), middle ear muscles (e.g., extracting human voice from background noise), muscles of mastication (e.g., ingestion), laryngeal and pharyngeal muscles (e.g., vocalization and language), and head-turning muscles (e.g., social gesture and orientation). Collectively, these muscles function as filters and control social engagement with the environment. The neural control of these muscles determines social experiences. In addition, the source nuclei (i.e., lower motor neurons) of these nerves, which are located in the brain stem, communicate directly with an inhibitory neural circuit that slows heart rate, lowers blood pressure, and actively reduces arousal to promote calm states consistent with the metabolic demands of growth and restoration of neurophysiological systems. Direct corticobulbar pathways reflect the influence of frontal areas of the cortex (i.e., upper motor neurons) on the regulation of this system. Thus, the social nervous system is intimately related to stress reactivity. In addition, the anatomical structures involved in the social engagement system have neurophysiological interactions with the HPA axis, the neuropeptides of oxytocin and vasopressin, and the immune system. Thus, the social engagement system, as illustrated in **Figure 1**, provides a theoretical model to explain the interactive and stress-related functions of several physiological systems that have central regulatory components but are expressed in the periphery.

Vagal Regulation of the HPA Axis

The vagus is involved in the regulation of the HPA axis. Vagal afferents exhibit an inhibitory influence on the HPA axis and reduce cortisol secretion. Studies have demonstrated a covariation between increases in cortisol and decreases in cardiac vagal tone (i.e., measured by the amplitude of respiratory sinus arrhythmia). Thus, there appears to be a coordinated response that functions to promote metabolic activity and mobilization behaviors by withdrawal of vagal tone through the myelinated vagus and increasing both sympathetic activity and activation of the HPA axis. In general, the functioning of the adrenal cortex and the secretion of cortisol appear to be integrated

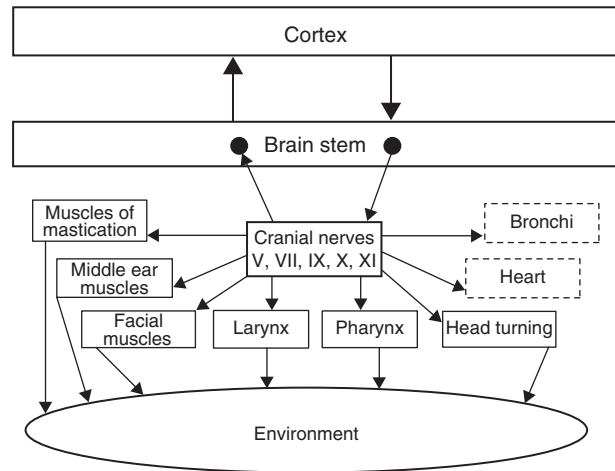


Figure 1 The social engagement system. Social communication is determined by the cortical regulation of medullary nuclei via corticobulbar pathways. The social engagement system consists of a somatomotor component (i.e., special visceral efferent pathways that regulate the striated muscles of the face and head) and a visceromotor component (i.e., the myelinated vagus that regulates the heart and bronchi). Solid rectangles indicate the somatomotor component, and dashed rectangles indicate the visceromotor component.

into the mobilization function of the autonomic nervous system by increasing sympathetic activation and circulating catecholamines. These effects suggest that, consistent with the phylogenetic approach described in the polyvagal theory, cortisol secretion may be related to maintenance of mobilization (i.e., the conversion of norepinephrine into epinephrine) for fight-or-flight behaviors and in the recovery from the lactate buildup that may contribute to a functional oxygen debt (i.e., gluconeogenesis).

In addition, reports of dysregulation of the HPA axis, low cortisol, or low cortisol reactivity in disorders such as schizophrenia and posttraumatic stress disorder and also the consequences of neglect and abuse in children may be explained within the context of a phylogenetically ordered response strategy (i.e., polyvagal theory). For example, if mobilization strategies (i.e., fight-or-flight behaviors) are ineffective in removing the individual from the stressor and in modulating the effect of the stress, then the nervous system may degrade to a phylogenetically earlier level of organization. Thus, low cortisol or a hyporesponsive HPA axis may reflect a neural strategy associated with immobilization (i.e., passive avoidance) that would require a reduction in energy resources.

Immune Function

The vagus has been implicated in the immune system. Studies have demonstrated the important role of subdiaphragmatic vagal afferents in conveying information regarding visceral state to the brain.

The studies conceptualize the afferent vagus as providing a signal alerting the central structures regulating immune function. A few studies have described motor pathways via the vagus to the thymus. The link between the vagal function and the immune system is not clear. However, it might be plausible to speculate that the neural mediation of the myelinated vagus, via direct influence on thymus and direct inhibition of the sympathetic nervous system, may trigger a physiological state that would promote immune function. Likewise, withdrawal of vagal tone to the heart, increased sympathetic tone, and the release of cortisol have been associated with suppressed immune function.

Oxytocin/Vasopressin

Because the peripheral influences of oxytocin and vasopressin function through feedback, primarily via afferent vagal pathways, the peripheral effects of these peptides are less clear and may be level dependent or differ as a function of acute versus chronic exposure. For example, it is possible that peripheral vasopressin, by stimulating vagal afferents, may trigger massive vagal responses via the dorsal motor nucleus of the vagus. In support of this speculation, it is known that in humans, peripheral vasopressin, and not oxytocin, is related to the nausea experienced during motion sickness. In addition, systemic vasopressin may induce a baroreceptor-mediated bradycardia and a decrease in plasma concentration of norepinephrine.

Based on the polyvagal theory, the mammalian vagus, with myelinated motor fibers originating in the nucleus ambiguus, provides a system for voluntary engagement with the environment, with special features associated with the prosocial behaviors of communication. Paralleling this evolutionary shift in the vagus is a mammalian modification of the hypothalamic regulation of the dorsal vagal complex (i.e., source nucleus of the afferent and efferent pathways of the unmyelinated vagus originating in the dorsal motor nucleus of the vagus and the nucleus of the solitary tract) via both oxytocin and vasopressin. The advent of specific receptors for oxytocin and vasopressin has increased the range of adaptive functions involving the unmyelinated vagus. In mammals, the dorsal motor nucleus of the vagus, the motor component of the dorsal vagal complex, is sensitive to oxytocin and insensitive to vasopressin. In contrast, the sensory components of the vagus, the nucleus of the solitary tract and area postrema, are most sensitive to vasopressin. Although the nucleus of the solitary tract has receptors for oxytocin, area postrema may not be directly influenced by oxytocin. The differential sensitivity of specific components of

the dorsal vagal complex to these two neuropeptides (the differential effects of central and systemic release on visceral function and a potential level dependency) results in a wider range of response options, including maximizing mobilization behaviors and the co-opting of the primitive vagal system associated with immobilization to support 'antistress' functions such as social engagement and growth and restoration.

Phylogenetic Approach to the Study of Stress

The phylogenetic orientation focuses our interest on the parasympathetic neural structures and neurobehavioral systems that we share with or have adapted from our phylogenetic ancestry. First, the three response systems proposed in the polyvagal theory (i.e., cranial nerves to regulate the face, sympathetic-adrenal system to increase metabolic output, and an inhibitory vagal system to decrease metabolic output and promote freezing and defecation) are the products of distinct neurophysiological systems. Second, these distinct neurophysiological systems represent a phylogenetically dependent hierarchy, with the use of cranial nerves to regulate facial expression emerging in mammals (well developed in primates); the sympathetic-adrenal system shared with other vertebrates including reptiles; and the inhibitory vagal system shared with more primitive vertebrates, including amphibians, bony fish, and cartilaginous fish. The three systems represent different phylogenetic stages of neural development. This phylogenetic development starts with a primitive behavioral inhibition system, progresses to a fight-or-flight system, and, in humans (and other primates), culminates in a complex facial gesture and vocalization system. Thus, from a phylogenetic perspective, the nervous system of vertebrates evolved to support a greater range of behaviors and physiological states, including states that are often associated with stress.

The physiological responses associated with stress in mammals do not concisely fit into a single neurophysiological system. Although cortisol has often been labeled as the stress hormone, other systems clearly respond to stress. Moreover, there are situations of severe stress in which cortisol is neither responsive nor at a high level. By expanding the phylogenetic model proposed in the polyvagal theory to emphasize the interactions between parasympathetic mechanisms and the HPA axis, the hyporesponsive HPA can be interpreted as reflecting a primitive passive avoidance system. Thus, several systems with target organs at the periphery contribute to the organism's adaptation to challenge and stress. These neurobiological systems are not solely stress systems. Rather, they are intimately

involved in the dynamic regulation of homeostasis, growth and restoration, metabolism, and mobilization. These systems form a complex set of mutually interacting neurophysiological pathways that communicate via nerves and neurally active chemicals (e.g., neurotransmitters, neuropeptides, and hormones) to cope with survival challenges.

See also: Autonomic Nervous System; Parasympathetic Nervous System; Stress Response and Self-Esteem; Stress Response: Neural and Feedback Regulation of the HPA Axis; Stress Response: Sex Differences; Stress: Definition and History; Stress: Homeostasis, Rheostasis, Allostasis and Allostatic Load.

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