

# Is There a Major Stress System at the Periphery Other than the Adrenals?

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## ABSTRACT

This manuscript proposes that stress responses, which encompass complex behavioral and physiological adjustments, may be interpreted from a phylogenetic perspective. It is emphasized that the adrenals are not the sole stress response organs in the periphery. As the autonomic nervous system changed through the process of evolution, so did the interplay between the autonomic nervous system and the other physiological systems that respond to stress, including the hypothalamic-pituitary-adrenal (HPA) axis, the neuropeptides oxytocin and vasopressin, and the immune system. From this phylogenetic orientation, a model will be presented that emphasizes the integration among several systems that respond in the periphery during stress.

## INTRODUCTION

Embedded in the mammalian nervous system are neuroanatomical structures related to the expression and experience of stress. Several of these structures are shared with other vertebrates and represent the product of phylogenetic development. Comparative research across vertebrate classes provides evidence that mammalian stress and coping response strategies are hierarchically ordered according to a phylogenetic stage (Porges 1997, 1998). Although research has demonstrated the relevance of neuroanatomical structures to stress and coping strategies, contemporary theories have not incorporated an "evolution" perspective into models of stress.

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## EVOLUTION AS AN ORGANIZING PRINCIPLE

Evolutionary forces have molded both contemporary physiology and behavior. The mammalian nervous system is a product of evolution. Via evolutionary processes the mammalian nervous system has emerged with specific features that react to challenge to maintain visceral homeostasis. These reactions change physiological state and, in mammals, limit sensory awareness, motor behaviors, and cognitive potentials. We can intuitively grasp the motor limitations of behavior in terms such as speed of movement and strength. However, we tend to neglect an important component of behavior that has been both product and contributor to our evolutionary adaptive success. This component is a functional unit that encompasses the regulation of neurobehavioral state to deal with the challenges that we collectively define as stress. Stress 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 to 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 upon 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. Unless we appreciate these design features (i.e., vulnerabilities) of the mammalian nervous system, we will be creating stressful living environments that are not only inefficient, but may be harmful to both mental and physical health.

## NEUROPHYSIOLOGY OF STRESS: LIMITATIONS OF AROUSAL THEORY

For over a century, researchers have measured autonomic variables (e.g., heart rate, palmar sweat gland activity) as indicators of emotional state related to perceived stress (e.g., fear, mental effort, workload, anxiety). Interest in measuring heart rate and sweat gland activity was theoretically supported by the acceptance of the "arousal" theory. Arousal theory made the assumption that 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, heart) were assumed to be accurate indicators of how the brain was processing emotional stimuli. Usually, the emotional states were associated with fight-flight behaviors and the sympathetic-adrenal system (e.g., increases in heart rate, sweat gland activity, and circulating catecholamines) as described by Cannon (1928). The current emphasis on cortisol as a dependent variable in stress research is consistent with historic views of stress-related arousal involving the adrenals.

Measures due, in part, to their availability and their neuroanatomical association with the target organs of the sympathetic nervous system (i.e., sweat, heart rate) and with secretions from the adrenal medulla (i.e., epinephrine, norepinephrine) and the adrenal cortex (i.e., cortisol), have become the primary physiological variables used to assess stress. Not by plan, but by default, an arousal theory emphasis 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 coevolution of stress and coping strategies with the increasing complexity of the autonomic nervous system.

### **POLYVAGAL THEORY: THREE PHYLOGENETIC SYSTEMS RELATED TO STRESS REACTIVITY**

The "polyvagal theory" (Porges 1995, 1997, 1998) 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 the emotional experiences and affective processes that are major components of social behavior. The theory proposes that physiological state limits the range of behavior and psychological experience. In this context, the evolution of the nervous system determines the range of emotional expression, quality of communication, and the ability to regulate bodily and behavioral state. The polyvagal theory links the evolution of the autonomic nervous system to affective experience, emotional expression, facial gestures, vocal communication, and contingent social behavior. Thus, the theory provides a plausible explanation of social, emotional, and communication behaviors and disorders. The theory also provides an explanation of stress-related responses. Relevant to adaptive stress responses, the theory makes the following assumptions:

- Evolution has modified the structures of the autonomic nervous system.
- The mammalian autonomic nervous system retains vestiges of phylogenetically older autonomic nervous systems.
- Emotional regulation and social behavior are functional derivatives of structural changes in the autonomic nervous system due to evolutionary processes.
- 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.
- The phylogenetic stage of the autonomic nervous system determines the behavioral, physiological, and affective features of stress reactivity.

The polyvagal construct was introduced to emphasize and document the neurophysiological and neuroanatomical distinction between two branches of the tenth cranial nerve (i.e., vagus) and to propose that each vagal branch was associated with a different adaptive behavioral strategy. The vagus nerve, a primary component of the autonomic nervous system, exits the brain stem and has branches that regulate the striated muscles of the head and face (e.g., facial muscles, eyelids, middle ear muscles, larynx, pharynx, muscles of mastication) and in several

**Table 10.1** The three phylogenetic stages of the neural control of the heart proposed by the polyvagal theory.

Phylogenetic stage	Autonomic nervous system component	Behavioral function	Lower motor neurons
III	Myelinated vagus	Social communication, self-soothing and calming, inhibit sympathetic-adrenal influences	Nucleus ambiguus
II	Sympathetic-adrenal	Mobilization (active avoidance)	Spinal cord
I	Unmyelinated vagus	Immobilization (death feigning, passive avoidance)	Dorsal motor nucleus of the vagus

visceral organs (e.g., heart, gut). The theory proposes that the different branches are related to unique adaptive behavioral strategies and articulates three phylogenetic stages of the development of the mammalian autonomic nervous system (see Table 10.1). These stages reflect the emergence of three distinct subsystems, which are phylogenetically ordered and behaviorally linked to communication (e.g., facial expression, vocalization, listening), mobilization (e.g., fight-flight behaviors), and immobilization (e.g., death feigning, behavioral "shutdown," and syncope). The mobilization system is dependent upon the functioning of the sympathetic nervous system (SNS). The most phylogenetically primitive component, the immobilization system, is dependent upon 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. In this chapter, I expand the polyvagal theory to include response systems that interact with the autonomic nervous system (i.e., neuropeptides, HPA axis, immune) to mediate physiological state in response to stress.

Table 10.2 illustrates the phylogenetic differences in the structures that regulate the heart in vertebrates (Morris and Nilsson 1994; Santer 1994; Taylor 1992). 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: (a) a sympathetic-catecholamine system including catecholamine secreting chromaffin tissue and spinal sympathetic nerves, and (b) a vagal system (a component of the parasympathetic nervous system) with branches originating in medullary source nuclei (i.e., dorsal motor nucleus of the vagus and nucleus ambiguus).

In the jawless fish, the neural control of the heart is very primitive. Some jawless fish, such as hagfish, rely on circulating catecholamines from diffuse chromaffin tissue to provide excitatory influences on the heart. Other jawless fish, such as lampreys, have a cardiac vagus. However, in contrast to all other vertebrates, which have a cardio-inhibitory vagus that acts via muscarinic cholinergic receptors, the lamprey vagus is cardioexcitatory and acts via nicotinic receptors.

**Table 10.2** Neural regulation of the heart as a function of vertebrate phylogeny.

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, thymus) and striated muscles via special visceral efferents and afferents via the tractus solitarius, trigeminal, and facial nerve.

Cartilaginous fish, such as the sharks, rays, and skates, have an unmyelinated cardio-inhibitory vagus. Similar to the more recent vertebrates, the vagus has cells of origin in the dorsal motor nucleus of the vagus located in the medulla. The vagus in these fish is inhibitory and the cholinceptors on the heart are muscarinic as they are in other vertebrates. The cardio-inhibitory vagus is functional in the cartilaginous fish. During conditions of hypoxia, the metabolic output is adjusted by lowering heart rate. This modification of neural regulation may provide a mechanism to enable the cartilaginous fish to increase their territorial range, by providing a neural mechanism that adjusts metabolic output to deal with changes in water temperature and oxygen availability. However, unlike the phylogenetically more recent bony fish and tetrapods, the cartilaginous fish do not have direct sympathetic input to the heart. Instead, cardiac acceleration and increases in contractility are mediated via  $\beta$ -adrenergic receptors stimulated by circulating catecholamines released from chromaffin tissue. Thus, since activation of metabolic output is driven by circulating catecholamines and not by direct neural innervation, once the excitatory system is triggered, the ability to self-soothe or calm is limited.

The bony fish are phylogenetically the first group of vertebrates in which the heart is regulated by both sympathetic and parasympathetic neural pathways. With opposing neural mechanisms from sympathetic and vagal pathways, rapid transitory changes in metabolic output are possible to support immediate changes in behavior from mobilization to immobilization. In bony fish this is observed as darting and freezing with direct neural components from the spinal cord via the sympathetic chain producing increases in heart rate and contractility, and direct neural pathways from the brain stem via the vagus producing cardio-inhibitory actions. Amphibians, similar to bony fish, have both sympathetic and parasympathetic neural innervation of the heart.

A distinct adrenal medulla, formed of chromaffin tissue, is present only in birds, reptiles and mammals (Santer 1994). The medulla is of ectodermal origin from which the epidermis, nervous tissue, and, in vertebrates, sense organs develop. Neural regulation by sympathetic nerves of the adrenal medulla provides a mechanism for rapid and controlled release of epinephrine and norepinephrine to increase cardiac output to match the metabolic demands of mobilization behaviors. In bony fish, chromaffin tissue is primarily related to parts of the cardiovascular system, but there also is chromaffin tissue associated with the kidney. However, in amphibians chromaffin tissue is primarily associated with the kidney and there are substantial aggregations of chromaffin cells located along the sympathetic chain ganglia. Thus, there is a phylogenetic shift in the location of chromaffin tissue and the concurrent evolution of a distinct adrenal medulla near the kidney.

Birds are conspicuously missing from Table 10.2; it represents mammals and their phylogenetic antecedents. Although mammals and birds are phylogenetic descendants of reptiles, mammals are not "direct" phylogenetic descendants of birds.

Unlike other vertebrates with a cardio-inhibitory 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 (Schwaber 1986). There they form the cell bodies for the visceromotor myelinated axons that provide potent inhibition of the sinoatrial node, the pacemaker for the heart.

By transitory down-regulation of the cardio-inhibitory 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 increase metabolic output rapidly for immediate mobilization. Under prolonged challenge, the sympathetic system also may be activated. However, by rapidly reengaging the vagal system, mammals have the capacity to inhibit sympathetic input on the heart (Vanhoutte and Levy 1979) and rapidly decrease metabolic output to self-soothe and calm.

Three phylogenetic principles can be extracted from Table 10.2. First, there is a phylogenetic shift in the regulation of the heart from endocrine communication, to unmyelinated nerves, and finally to 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., special visceral efferent neural pathways embedded within cranial nerves V, VII, IX, X, XI).

These phylogenetic principles provide a basis for speculations regarding the behavioral and physiological responses associated with mammalian stress and coping strategies. 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 behaviors needed to engage and disengage with environmental challenges.

### **The Vagal Brake**

The myelinated mammalian vagus can inhibit the influence of the SNS at the level of the heart. The mammalian vagus may function as an active vagal brake (see Porges et al. 1996) in which rapid inhibition and disinhibition of the vagal tone to the heart can rapidly mobilize or calm an individual. In addition, since the mammalian vagus has distinct pathways involved in the voluntary regulation of the striated muscles (e.g., corticobulbar pathways, afferents from face and mouth, efferents to larynx and pharynx), the regulation of heart rate is neuroanatomically and neurophysiologically linked to the function of the special visceral efferents.

Due to the tonic 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. When the vagal tone to the pacemaker is high, the vagus acts as a brake on the rate the heart is beating. When vagal tone to the pacemaker is low, there is little or no inhibition of 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. The vagal brake provides a neural mechanism to change visceral state rapidly by slowing or speeding heart rate. Consistent with the assumptions of the polyvagal theory, the vagal brake contributes to the modulation of cardiac output by decreasing the inhibitory vagal control of the heart to speed heart rate and by increasing the inhibitory vagal control of the heart to slow heart rate. Thus, 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 engage and disengage objects and other individuals rapidly and to promote self-soothing behaviors and calm behavioral states.

Difficulties in regulating the vagal brake result in the recruitment of other neural mechanisms (e.g., sympathetic regulation of the heart) 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) 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.

### *Evolution and Dissolution: A Hierarchical Stress Response Strategy*

The evolution of the autonomic nervous system provides substrates for the emergence of three stress and coping subsystems, each linked to structures that evolved during identifiable phylogenetic stages. The polyvagal theory proposes that during danger or threat, the "older"

less social are recruited. The older systems, although functional in short term, may result in damage to the mammalian nervous system when expressed for prolonged periods. Thus, the stress and coping neurophysiological strategies that are adaptive for reptiles (e.g., apnea, bradycardia, immobilization), may be lethal for mammals.

Although reminiscent of the triune brain proposed by MacLean (1990), the polyvagal theory emphasizes that even the phylogenetically more primitive structures have changed in structure and function. This phylogenetic adjustment of the autonomic nervous system represents an exaptation (i.e., a shift in function) of structures to express emotions and to adapt to the complex environment.

The polyvagal theory proposes a hierarchical response strategy to environmental challenges, with the most recent modifications employed first and the most primitive last. However, the response strategy is not all-or-none and may include transitional blends between the boundaries of the three hierarchical stages. These transitional blends may be determined by both visceral feedback and higher brain structures (including the HPA axis and vasopressinergic and oxytocinergic pathways that communicate between the hypothalamus and the dorsal vagal complex (DVC) consisting of the nucleus tractus solitarius and the dorsal motor nucleus of the vagus). Thus, the neurophysiological substrate of specific behavioral states and coping strategies may incorporate activation of a sequence of response systems representing more than one phylogenetic stage.

This phylogenetically based hierarchical response strategy is consistent with the concept of dissolution proposed by John Hughlings Jackson (1958) to explain disease of the nervous system. Jackson proposed that since the phylogenetically newer or "higher" components of the nervous system regulated or controlled the "lower" components (i.e., phylogenetically older), damage to the newer components would "disinhibit" the activity of the lower. The polyvagal theory (Porges 1995, 1997, 1998) proposes dissolution, not in response to disease or brain trauma, but as a response strategy to differential challenges (i.e., threats to survival) associated with stress. The ventral vagal complex (VVC), with its mechanisms for signaling and communication provides the initial response to the environment. The VVC inhibits, at the level of the heart, the strong mobilization responses of the spinal SNS. Withdrawal of the VVC, consistent with the Jacksonian principle of dissolution, results in a disinhibition of the sympathetic control of the heart. Similarly, withdrawal of sympathetic tone results in a disinhibition of the DVC control of the gastrointestinal tract and a vulnerability of the bronchi (i.e., constriction) and the heart (stopping or significantly slowly heart rate). There are several clinical consequences to unopposed DVC control, including defecation, due to a relaxation of the sphincter muscles and increased motility of the digestive tract; apnea, due to constriction of the bronchi; and bradycardia, due to stimulation of the sinoatrial node. Thus, when all else fails, the nervous system may elect a metabolically conservative course that is adaptive for primitive vertebrates, but lethal for mammals.

### The Social Nervous System

Mammals and especially primates have evolved to have a well-defined social nervous system. Embryologically, components of several cranial nerves develop together to form the neural substrate of a social engagement system (see Porges 1998). 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), muscle 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 system 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 our 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 nervous system 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.

#### **HOW DOES A PHYLOGENETIC ORIENTATION PROVIDE A THEORETICAL PLATFORM TO UNDERSTAND THE ADRENAL "STRESS" SYSTEMS AND THEIR FUNCTIONAL INTERACTIONS WITH THE AUTONOMIC NERVOUS SYSTEM?**

The adrenal exhibits phylogenetic changes in structure and function. Above, because of its complementary function to the SNS, the adrenal medulla was discussed. However, since the adrenal cortex is treated as an endocrine organ and part of the HPA axis, it is traditionally studied and discussed independently of the adrenal medulla and the autonomic nervous system. Unlike the medulla, which is of ectodermal origin, the cortex is of mesodermal origin. The adrenal cortex secretes cortisol or corticosterone, which are frequently used to index stress. All vertebrates produce glucocorticoids and catecholamines. However, the structures that produce these secretions follow a phylogenetic trend that results in two anatomical changes. First, the chromaffin tissue and the adrenocortical cells, which are scattered through the viscera in the primitive vertebrates, cluster together to form functional structures. Second, these structures establish a close anatomical relation (the adrenal) with communication between the secretions of the two components of the adrenal and only in mammals does the adrenal have its own vascular supply and venous drainage.

Only mammals have adrenocortical cells clustered as a cortex of the adrenal. Interestingly, several reptiles (e.g., lizards and some snakes), which have a functioning adrenal medulla, have the adrenocortical cells partially encapsulated by the chromaffin cells. In the more primitive fish (jawless and cartilaginous), the chromaffin and adrenocortical cells are entirely separate. In the bony fish, both the adrenocortical cells and chromaffin tissue are scattered as independent groups within the "head" kidney. In amphibians, the chromaffin and

adrenocortical tissues are scattered over the ventral surfaces of the kidney. In reptiles, the chromaffin and adrenocortical tissues become consolidated into distinct adrenal glands. Reptiles provide a phylogenetic marker in which the interrenals have an independent vascular supply and venous drainage and no longer (as in amphibians and bony fish) rely on the kidney and a renal portal system for the distribution of secretory products.

Several investigators have explored the adaptive function of the close proximity of the adrenocortical-cortisol-secreting adrenocortical cells (that subsequently forms the adrenal cortex) and the catecholamine-secreting chromaffin tissue (that subsequently forms the adrenal medulla) (Norris 1997). The medulla receives large quantities of glucocorticoids through the adrenal vascular system, and these hormones activate the enzyme system for converting norepinephrine into epinephrine. This effect would support sympathetic-adrenal medulla functions associated with mobilization and increased metabolic activity. Epinephrine has a potent effect on the elevation of blood glucose convergent with the influences of some of the adrenal steroids. Additionally, cortisol may directly enhance mobilization by converting lactate to glucose via gluconeogenesis in the liver. This process would contribute to the metabolic demands of mobilization by increasing the availability of glucose and also in reducing oxygen debt due to the accumulation of lactate.

Vagal activity has been implicated in the function of the adrenal cortex. Reports suggest that afferents originating in the subdiaphragmatic vagus (i.e., DVC) exhibit an inhibitory influence on HPA axis and reduce cortisol secretion (e.g., Miao et al. 1997; Bueno et al. 1989). Other research has demonstrated a covariation between increases in cortisol and decreases in cardiac vagal tone (Gunnar et al. 1995), which, consistent with the removal of the vagal brake and the stimulation of the SNS, would promote mobilization. Similarly, psychological stressors reduce cardiac vagal tone and increase cortisol plasma level (e.g., Cacioppo et al. 1995). Thus, in several situations there appears to be a coordinated response that functions to promote metabolic activity and mobilization behaviors by withdrawal of VVC tone and increasing both SNS activity and activation of the HPA axis.

In general, the functioning of the adrenal cortex and the secretion of cortisol appears to be integrated 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-flight behaviors and in the recovery from the lactate build up that may contribute to a functional oxygen debt (i.e., gluconeogenesis).

In addition, the reports of dysregulation of the HPA axis, low cortisol, or low cortisol reactivity in disorders such as schizophrenia (Jansen et al. 2000), posttraumatic stress disorder (Yehuda et al. 1996), and the consequences of neglect and abuse in children (De Bellis et al. 1994) may be explained within the context of the polyvagal theory. According to the theory, when mobilization strategies (i.e., fight-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 (e.g., Watkins et al. 1995). Recent 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 (e.g., Bulloch and Pomerantz 1984). The link between the vagal function related to the stages of the polyvagal theory and the immune system is not clear. However, it might be plausible to speculate that the neural mediation of the myelinated vagus may, via direct influence on thymus and direct inhibition of the SNS, 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 and Vasopressin**

Phylogenetically, although all vertebrates have peptides similar in structure to both oxytocin and vasopressin, only mammals have the specific receptors for both peptides. Oxytocin and vasopressin are synthesized primarily in the paraventricular and supraoptic nuclei of the hypothalamus and released centrally via parvocellular neurons and systemically via magnocellular neurons (Swanson and Sawchenko 1977). The central and systemic effects of these neuropeptides are different. Central release of oxytocin regulates the output of the dorsal motor nucleus of the vagus, usually maintaining output within levels optimal to support homeostasis. Thus, providing a proposed "antistress" function (see Carter 1998). Peripheral release of oxytocin is related to milk ejection, uterine contractions, and ejaculation. Central release of vasopressin appears to modulate afferent feedback from the viscera and to shift set points, independent of sensitivity, for vagal reflexes such as the baroreceptor reflex (Michelini 1994). The raising of the baroreceptor set point would, by increasing cardiac output, potentiate fight-flight behaviors and allow sympathetic excitation of the heart to be unopposed by homeostatic vagal reflexes. Thus, central levels of oxytocin have been assumed to be associated with vagal processes and central levels of vasopressin have been assumed to be associated with sympathetic processes (Uvnas-Moberg 1997).

Because the peripheral influences of oxytocin and vasopressin function through feedback, primarily via the sensory component of the DVC, 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 may, by stimulating vagal afferents, 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 (Koch et al. 1990). In addition, systemic vasopressin may induce a baroreceptor-mediated bradycardia and a fall in plasma concentration of norepinephrine (Buwalda et al. 1992; Michelini 1994).

Oxytocin may be part of a complex response profile related to the perception of the environment as safe. Consistent with this view, Uvnas-Moberg (1997) and Carter and Altemus (1997) propose that oxytocin promotes states resistant to stress (i.e., anti-stress). In contrast, vasopressin may be part of a complex response profile related to the perception that the

environment is challenging or dangerous (i.e., stress). In fact, central vasopressin could potentiate mobilization responses via sympathetic excitation, while high levels of systemic vasopressin may potentiate a physiological shutdown associated with fear (e.g., bradycardia) via feedback to the dorsal motor nucleus and inhibition of sympathetic outflow (Ferguson and Lowes 1994). In addition, lesions of vagal afferents, which functionally block the visceral input to the sensory component of the DVC (areas sensitive to vasopressin), attenuate or abolish specific conditioned taste aversions (Andrews and Lawes 1992).

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 DVC via both oxytocin and vasopressin. The advent of specific receptors for oxytocin and vasopressin increases the range of adaptive functions involving the DVC. In mammals, the dorsal motor nucleus of the vagus, the motor component of the DVC, is sensitive to oxytocin and insensitive to vasopressin. In contrast, the sensory components of the DVC, 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 (Landgraf et al. 1990), the area postrema may not be directly influenced by oxytocin (Carpenter 1990). The differential sensitivity of specific components of the DVC to these two neuropeptides, i.e., 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 "anti-stress" functions such as social engagement and growth and restoration (see Porges 1998).

## A PHYLOGENETIC APPROACH TO THE STUDY OF STRESS

The phylogenetic orientation focuses our interest on the 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, as a system 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 (see Porges 1997, 1998). The three systems, which have been frequently studied in emotion research, represent different phylogenetic stages of neural development. This phylogenetic development starts with a primitive behavioral inhibition system, progresses to a fight-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 we often associate 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 include the HPA axis, the hyporesponsive HPA can be interpreted as reflecting a primitive passive avoidance system. Thus, in response to the question proposed in the title of this paper, several systems with target organs at the periphery contribute to the organism's adaptation to challenge and stress. These neurobiological systems are not stress systems solely. 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, hormones) to cope with survival challenges. This chapter has attempted to employ phylogeny as an organizing principle to illustrate the interactive and adaptive nature of several physiological systems that respond to stress.

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