Central Neural Components of the Autonomic Nervous System

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The visceral nervous system comprises sensory and motor fibers innervating visceral organs. In addition, there are visceral centers within the brain and spinal cord which integrate the afferent input and modulate efferent activity. The motor functions of the visceral nervous system often are grouped under the separate heading "autonomic nervous system." This motor system is so named because its activities are regulated automatically and not under conscious, willed control; they become manifested primarily through activity within reflex arcs and structures within the brain. Smooth musculature of the organs within the head, thorax, abdomen and pelvis and the blood vessels and glands throughout the body are under the direct control of the autonomic nervous system; by definition it is described as a two-motor-neuron system comprising preganglionic and postganglionic nerve cells. Structurally and functionally, the autonomic nervous system is further divided into sympathetic and parasympathetic systems. The sympathetic preganglionic cells are located in the lateral gray column of the spinal cord between the first thoracic and second lumbar segments, while the postganglionic sympathetic neurons lie within the sympathetic ganglionated chains parallel to the spinal column and within other outlying collateral ganglia. Preganglionic parasympathetic cells are found within the brainstem nuclei of cranial nerves III, VII, IX and X and in the second, third and fourth sacral spinal segments. From these craniosacral sites, the preganglionic elements emerge to synapse with postganglionic parasympathetic neurons located within ganglia close to or within the walls of the viscera. Almost all visceral structures are dually innervated, receiving fibers from each of the divisions of the autonomic nervous system. Exceptions, such as the smooth musculature of blood vessels, sweat glands and hair follicles, do exist.

Sympathetic discharge promotes activity in those visceral systems which are essential during periods of stress and adversity. Flight, fright, fear and certain aspects of mating behavior are accompanied by increased cardiac and respiratory rates and an increased blood pressure. Conversely, periods of rest and tranquility are accompanied by increased parasympathetic activity. Slowing of the heart, lowered blood pressure, and other visceral functions conducive to digestion, growth and repair are promoted by the parasympathetic nervous system.

The parasympathetic and sympathetic systems act reciprocally in assuring an appropriate balance of visceral activity dependent upon the specific needs of the organism. The optimal state of visceral activity is embodied in the concept of homeostasis. Expressed by Cannon in 1928, this concept proposes that coordinated physiologic reactions maintain most of the steady states in the body, an idea which amplified the views of Claude Bernard, whose research emphasized the importance of "le milieu intérieur." 5

Homeostasis is maintained in large measure by reflexes initiated in visceral organs. Sensory information from these organs is conveyed over visceral afferent fibers. It is known that visceral afferent fibers significantly influence central neural activity and account for a significant percentage of autonomic nerves, i.e., of the 30,000 fibers in the vagus nerve, more than 24,000 are sensory in function. 6 Within the thoracic and abdominal cavities more than 15 different receptor types initiate visceral afferent impulses. This information results in the initiation of numerous visceral reflexes and central nervous system correlates. The brain, through a complicated series of suprasegmental centers and pathways functionally interrelated at different cerebral levels, interprets and reacts to visceral afferent activity. Further, the central nervous system receives important cor-

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ollary information from many other types of receptors and can adjust activity in the viscera through both neural and humoral mechanisms.

Respiration

The primary neural centers which control respiration are located within the pons and medulla. Legallois in 1812, and later Flourens were the first to demarcate the respiratory center anatomically as a small area in the medulla at the level of the calamus scriptorius. In the last hundred years many observations have confirmed the existence of intrinsic regulatory centers in the medulla. These bulbar sites contain the minimum central mechanisms necessary for the maintenance of respiration. A major problem yet to be resolved is the relationship between the medullary centers which maintain respiration and centers in the pons which some feel to be essential for the initiation and maintenance of eupneic respiration. Although pontomedullary centers alone are capable of maintaining eupneic respiration, their activity, in turn, is modulated by secondary centers within the cerebellum, midbrain, diencephalon and cerebral cortex. Further, it has been recognized that sensory and chemical factors also influence respiratory patterns.

Within the medulla two bilaterally paired centers initiate inspiration and expiration. The inspiratory center is located within the ventromedial portion of the reticular formation immediately overlying the rostral extent of the inferior olive. The expiratory center also lies within the reticular formation, somewhat dorsal, rostral and lateral to the inspiratory center. The caudal extent of the expiratory center is adjacent to the rostral portion of the inspiratory center. These two centers are related reciprocally in the maintenance of the auto-rhythmicity of inspiration and expiration. The activity of these centers is controlled primarily by vagal afferent impulses and by influences descending from bilaterally paired, pontine respiratory structures; the apneustic and pneumotaxic centers. The apneustic center, found in the middle and caudal pons in the area corresponding to the nuclei reticularis pontis caudalis, magnocellularis and gigantocellularis, is thought to maintain a tonic inspiratory drive and probably acts through the medullary inspiratory center. Hyperactivity of this center results in inspiratory spasm. The pneumotaxic center is found in the dorsolateral portion of the pontine isthmus, appears to have no intrinsic rhythmicity, and is presumed to be driven by other respiratory areas. Electrical stimulation of the pneumotaxic center accelerates respiration, while its ablation decreases the rate of respiration.

The normal respiratory cycle appears to be patterned in the following manner: (1) At some point during inspiration, stretch receptors in the lung set into action the Hering-Breuer reflexes, via afferents in the vagus nerves. (2) These afferent impulses tend to inhibit inspiration by influencing the activity of the medullary and pontine respiratory centers. (3) Thus, the medullary inspiratory center becomes inhibited while the expiratory center becomes activated and the most prominent action of these afferents is to decrease the tonic inspiratory outflow from the pontine apneustic center. (4) Additionally, during inspiration, ascending impulses from inspiratory neurons in the medulla and pons act to initiate activity in the pneumotaxic center located in the rostral pons. (5) The subsequent descending activity from the pneumotaxic center acts upon the inspiratory centers in the pons and medulla to inhibit inspiration in a fashion analogous to that described for vagal afferents. (6) These inhibitions result in a shifting of the respiratory cycle to expiration. (7) During expiration there is an increasing discharge from the expiratory center, which in turn activates the inspiratory center. (8) This heightened activity within the medullary inspiratory center, and outflow from the pontine apneustic center, lead once again to active inspiration.

It is clear that these pontomedullary centers are the key structures which regulate normal eupneic respiration. Other brain areas, however, can influence respiratory activity. The cerebellum appears capable of influencing respiratory functions by inhibiting inspiration via its connections with the inspiratory centers in the medulla and pons. Cerebellar inhibition of inspiration is best observed following stimulation of the anterior lobe, but also can be obtained from posterior lobe stimulation.
There is general consensus that the primary effects on respiration due to midbrain stimulation are: an increase in respiratory rate; an increase in ventilatory volume; and a decrease in the duration of expiration.\textsuperscript{11, 15, 16, 17} Such responses may be elicited from the dorsal midbrain region at the lateral edge of the central gray matter or from various points within the reticular system of the mesencephalon. Although it is possible that integrative respiratory mechanisms may be present within the midbrain, as inferred from some transection experiments,\textsuperscript{17} it appears most probable that the induced respiratory activity is due either to stimulation of the midbrain neurons of the reticular activating system,\textsuperscript{16} or to stimulation of descending fiber tracts (probably the dorsal longitudinal fasciculus \textsuperscript{20}) from rostral respiratory centers. Certain studies, however, report a decreased respiratory rate from midbrain stimulation,\textsuperscript{14} especially from the anterior ventromedial region.

Electrical stimulation of the neuraxis above the midbrain also has been reported capable of influencing respiration. Respiratory changes have been observed following stimulation of certain diencephalic structures.\textsuperscript{11, 14, 18, 19, 20} Thus, excitation in the region of the posterior commissure leads to an increase in respiratory frequency and amplitude. Other sites in the lateral hypothalamus, supraoptic nucleus, perifornical area, and subfornical component of the medial forebrain bundle yield similar effects. Stimulation in the region of the intrahalamic commissure, the lateral thalamus in the vicinity of the fornix, and the genu of the internal capsule results in decreased respiratory activity.

It is difficult to assess the direct influence which the cerebral cortex exerts on respiration. So often the direction of change in respiratory activity induced by cortical stimulation may be reversed by small changes in the parameters of stimulation or by varying anesthetic conditions. It is well known that respiration can vary with changes in visceral and somatic motor activity as well as with variations in the organism’s “emotional set.” While certain cortical areas consistently appear capable of influencing respiration, these changes invariably are accompanied by other visceral and somatomotor responses.\textsuperscript{11, 14, 19} Suppression of respiration, characterized by decreased respiratory amplitude and elongation of expiration, has been elicited in the monkey by stimulation of the anterior forebrain. The more specific effective sites include the genu of the corpus callosum, the cingulate gyrus, the olfactory tuberele, the posterior orbital gyrus, and parts of the insula and temporal pole. Homologous areas can induce apneic respiratory apnea in man and in carnivores. Accelerated respiratory activity can be produced by electrical stimulation of the motor cortex and from sites on the cingulate gyrus immediately posterior to the anterior inhibitory area. No consensus exists regarding the direction of respiratory changes induced by stimulation of the pyriform cortex, amygdala or hippocampus.\textsuperscript{11, 15, 21}

The neural pathways connecting higher cerebral centers with brain-stem respiratory areas are largely unknown. One reason for this is the great functional overlap in areas recognized to be effective in the neurophysiology of respiration. For example, stimulation of the orbital cortex leads to activity in the caudal pontine reticular nucleus and in the nucleus reticularis gigantocellularis of the medulla.\textsuperscript{22} Although these brain-stem areas are known to be important respiratory centers, they also are involved in a number of other autonomic and somatic functions, ranging from sleep to the central regulation of somatic reflexes. It is reasonably clear that below the medulla the descending respiratory tracts within the cervical cord lie in the most anterior part of the lateral columns and predominantly innervate ipsilateral phrenic motoneurons.

**Cardiovascular System**

Bilateral neural systems extending from the cerebral cortex to the medulla exist for the homeostatic maintenance of the cardiovascular system.\textsuperscript{25–26} Dual sites within the medulla are thought to be responsible for the maintenance of cardiovascular tone. These are a medullary “depressor” center in the medial reticular formation at the level of the obex and a “pressor” center in the more lateral reticular substance and the adjacent periventricular gray.\textsuperscript{25, 26}

The “depressor” site is thought to act as a relay center for baroreceptor influences and can initiate vasodepressor and bradycardiac re-
sponses which, in turn, appear to be mediated by enhancement of parasympathetic tone and the suppression of sympathetic activity. It is presumed that the decrease in vasomotor tone is accomplished by an inhibition of spinal vasoconstrictor neurons, rather than through the activation of a vasodilator system.

The bulbar "pressor" centers initiate both vasomotor constrictor activity and cardiovascular acceleration. Although bilaterally represented in the medulla, the right medullary site, upon stimulation, yields a greater increase in heart rate and a lesser increase in pulse pressure than the left side, whereas the converse is true upon excitation of the left "pressor" center.

Cerebellar influences on cardiovascular functions are poorly understood. Depressor responses have been described following stimulation of the posterior lobe, whereas pressor responses result from anterior-lobe stimulation. Moruzzi found that both pressor and depressor responses and spontaneous vasomotor activity could be inhibited by stimulation of the cerebellar vermis. The mechanisms by which the cerebellum causes changes in the cardiovascular system are open to question. However, it appears probable that they are mediated through the pontobulbar centers rather than by a direct path to spinal neurons, since the brain stem receives strong projections from the cerebellar nuclei.

The role of intrinsic mesencephalic centers in the control of cardiovascular functions is somewhat unclear also. Since chronic animal preparations with high mesencephalic transections exhibit integrated autonomic responses, such as elicited rage reactions, one would assume that the appropriate cardiovascular adjustments which normally accompany this state are present in these animals. Many vasomotor and cardiac fiber systems originating at more rostral levels traverse the midbrain, making it difficult to differentiate clearly those influences on cardiovascular functions intrinsic to mesencephalic neurons and those due to these through-going paths from higher cerebral areas.

Within the hypothalamus there are both pressor and depressor centers capable of exerting cardiovascular reactions in chronic decorticate animals. Corticohypothalamic fiber systems probably modulate hypothalamic output, but are not required for the initiation of hypothalamic cardiovascular reactions. Vasocostrictor neurons are located throughout the ventrolateral hypothalamus, passing in the ventral gray to the tegmentum of the midbrain. There is presumed to be a greater density of vasoconstrictor and cardioaccelerator neurons in the posterior hypothalamus, while depressor and bradycardic sites are found more in the rostral areas, especially the septal and preoptic regions. Generally speaking, autonomic reactions from the caudal hypothalamus have been described as sympathetic. This region was referred to by Hess as the "ergotropic zone." From the anterior hypothalamus systemic responses are more parasympathetic; Hess called this area of the diencephalon the "trophotropic zone."

It has been recognized for a long time that information received at a cortical level could, under the appropriate circumstances, induce changes in blood pressure and heart rate; yet it is difficult to pinpoint with certainty specific pressor and depressor forebrain sites. Animal experiments have resulted in certain inconsistencies; however, it is clear that effective cardiovascular foci exist in the motor and premotor gyri, the orbital area, insula, cingulate gyrus and temporal lobe. Each of these areas can elicit both pressor and depressor responses. Several explanations offered to elucidate these curious findings include: pressor and depressor neurons are in anatomical juxtaposition; groups of neurons have certain unique response characteristics, e.g., the phenomenon of "surround inhibition" in which excitation of a focus of nerve cells simultaneously invokes inhibition of surrounding nerve cells; the cortical effects may be accompanied by compensatory adjustments in subcortical cardiovascular centers.

The lowering of systemic blood pressure by the central nervous system is thought to be accomplished by two mechanisms: through a diminution of vasoconstrictor tone, neurophysiologically envisioned as a suppression or inhibition of sympathetic activity; and through the excitation of systems which act directly on blood vessels, causing vasodilatation. The former mechanism (decrease in vasoconstrictor tone) appears resistant to atropine, but the latter (active vasodilatation, probably mediated through cholinergic sympathetic neurons) is
affected by atropine and further potentiated by physostigmine. Thus, active vasodilatation does not appear to be tonically active and seems not to be a mechanism which participates in vasomotor reflexes initiated by baro- or chemoreceptors. It is believed that cortical vasodilator neurons descend through the ventromedial hypothalamus to relays in the midbrain tegmentum. On their course they are joined by other vasodilator nerve cells of diencephalic origin. Below the level of the superior colliculi, the descending vasodilator paths are found in the ventrolateral medulla, passing uninteruptedly to the lateral horns of the cervical spinal cord through the lateral fasciculi.

Gastric Secretion

Ample evidence supports the belief that the vagus nerves are the sole effenter neural pathways mediating gastric secretory responses. Peripheral vagal stimulation leads to an increase in flow of gastric juices. The latency of this response varies for the different gastric secretions and, while pepsin output may increase quickly following stimulation, the secretion of HCl and water may require a latent period of five to ten minutes. Thus, the final common pathway of this response involves the visceral motor neurons in the medulla, whose axons course through the vagi to reach the mucous membranes and the exocrine glands responsible for the secretion of gastric juice. The suprabulbar connections to these visceral motor neurons are largely unknown, although it is common knowledge that psychic and emotional factors can influence gastric secretions significantly. Thus, cortical, limbic, hypothalamic and lower brain-stem centers must be considered in any discussion of the central regulation of alimentary secretory processes.

There is little question that electrical stimulation in certain hypothalamic centers alters the activity of the visceral motor neurons of the vagus nerve, as well as inducing changes in endocrine balance. Results of experiments performed in monkeys suggest that hypothalamic stimulation results in an increased secretion of gastric hydrochloric acid by two distinct, separate routes. The first, entirely neural in nature, originates in the anterior hypothalamus and reaches its destination by way of the vagus nerve. Such stimulation results in a prompt increase in acid secretion which reaches a maximum in one-half to one hour. This response is unaffected by adrenalectomy, but abolished by vagotomy. The second route appears to arise from posterior hypothalamic structures and affects hydrochloric acid secretion through humoral agents mediated by the pituitary-adrenal system. This "humorally" mediated response is unaffected by vagotomy, and the autonomic nervous system does not appear to be directly involved in its transmission.

Not all authors agree completely on the exact role that the hypothalamus assumes in the control of gastric secretions. That this part of the brain is generally considered of pivotal importance with respect to numerous visceral functions makes it reasonable to accept the many reports that anterior hypothalamic stimulation results in an increased gastric acid output.

Until recently, structures included in the limbic system were believed concerned primarily with olfaction. It is now known that these structures are involved in many visceral regulatory functions. Cerebral cortical areas, phylogenetically older and structurally less complex than the six-layered neocortex, are considered limbic structures. These cortical areas include the four- to five-layered juxtalalloecortex (structures such as the cingulum, retrosplenial and hippocampal gyri, portion of the frontotemporal cortex, etc.) and the most primitive three-layered allocortex (structures such as the olfactory bulb, diagonal band of Broca, prepyriform and periamygdaloid complex, etc.). Located within the temporal lobe, the amygdaloid nuclei have efferent connections with other portions of the limbic cortex and, therefore, they too usually are considered to be limbic structures. Anand and his associates reported that in both cats and monkeys electrical stimulation of the amygdaloid nuclei, posterior orbital gyrus and anterior cingulate gyrus resulted in significant increases in gastric acid secretion. Other limbic sites such as the cortex of the pyriform lobe, the temporal tip, and the hippocampus were not as productive upon stimulation.

By their very nature, studies related to gas-
tric physiology using Pavlovian conditioning techniques implicate the cerebral cortex in the secretion of gastric juice. It is widely recognized that psychic factors may influence gastric secretion, although the mechanisms involved remain unexplained. Pavlov himself postulated that the psychic determinants of gastric secretion depend upon the functional integrity of the cerebral cortex. This hypothesis is supported by the observation of an increased gastric secretion following stimulation of the sigmoid gyrus in carnivores and primates, and a decrease in secretion following ablation of this cortical region. Klopper was able to record gastric pH continuously by electrodes placed in the esophagi of cats. Stimulation inferior to the anterior sigmoid gyrus lowered gastric pH significantly, indicating an increased secretion of gastric juices; other cortical sites in cats were not effective. It has not been ascertained whether these or other cortical influences on gastric secretions are due to hormonal or neural mechanisms, although Klopper believes that his results were due to a liberation of some hormone.

Agonistic Behavior

Certain areas in the brain have been recognized to be capable of influencing certain autonomic functions specifically, whereas other regions exhibit more generalized influences on visceral effectors. Certainly one of the most dramatic examples of this latter type of control over visceral phenomena is found in the integrated patterns of autonomic activity accompanying CNS-induced "rage reactions." Rage, as an example of agonistic behavior, may be separated into three categories: defense, attack, and flight. The autonomic functions which predominate during aggressive behavior are almost exclusively sympathetic, i.e., increases in blood pressure and heart rate, dilatation of the pupils, piloerection, etc. It is certainly most probable that parasympathetic activity during such a reaction is inhibited simultaneously.

These integrated patterns of agonistic behavior, or at least fragments thereof, are dependent upon the functional integrity of certain CNS structures. Transection experiments have indicated that while some of the autonomic components of aggressive behavior are retained in the spinal animal, it is not until a transection that spares the midbrain is made that some of the somatic motor components become organized.

Stimulation at high intensities of the dorsal tegmentum adjacent to the central gray of the mesencephalic reticular formation may lead to various forms of agonistic behavior. Midbrain stimulation at lower intensities can potentiate the effects of hypothalamically-induced rage. These and other studies support the concept that, in addition to serving as a descending relay for somatic and autonomic pathways, the midbrain reticular system can, itself, induce certain aspects of the integrated pattern of agonistic behavior. Midbrain lesions reduce the severity of hypothalamically-induced rage, whereas ablation of hypothalamic sites leaves unaltered the midbrain-induced rage reactions. Although midbrain-induced agonistic behavior may depend primarily on pain sensations, it is reasonable to assume that the midbrain contains, in addition to descending fibers from higher agonistic centers, some capability for integrative aggressive behavior. The descending pathways appear to be diffusely distributed throughout the midbrain, but large tegmental lesions have been shown to be capable of preventing the spontaneous and evoked rage reactions present in the deccorticatized preparation.

It is clear that within the hypothalamus lie the principal foci whose functional integrity is necessary for the elaboration of agonistic activity. The ventromedial hypothalamic area is concerned with defensive and attack behavior. Highly specialized patterns of stalking and prey-killing may be induced by stimulating the lateral boundaries of this ventromedial zone, which, interestingly, is almost coextensive with the "feeding" center.

The specialized autonomic and behavioral components of "flight" behavior may be elicited by stimulating sites dorsal to the ventromedial hypothalamic area. Lesions in these sites, in the main, have substantiated the results of the stimulation studies. One exception to this generalization has been noted. A lesion placed in the ventromedial nucleus may lead to aggressive behavior which one might predict would result in a decrease in agonistic activity. Such a paradoxical finding might be explained with reference to the hypothalamic structures involved in feeding. It is thought that the
ventromedial nucleus of the hypothalamus tonically inhibits the lateral hypothalamic "feeding" center. Electrical stimulation of the ventromedial region leads to aphagia; lesions therein result in hyperphagia. By analogy it can be suggested that a similar mechanism might be operant with regard to agonistic behavior, i.e., that lesions within the ventromedial zone might release some laterally-located center controlling attack behavior.

The extent to which descending forebrain systems influence hypothalamic areas responsible for agonistic activity is demonstrated dramatically in decorticate preparations. These animals respond to almost any stimulus (light touch, for example) with an undifferentiated pattern of aggressive behavior. The directed rage in the decorticate preparation is not as well integrated as in the intact animal, but it is far better organized than that seen in the midbrain animal. On the other hand, decorticate preparations rarely display patterns of flight behavior. The cerebral cortex is thought to exert an inhibitory influence on mechanisms related to defense and attack behavior. The removal of this inhibition is believed responsible for the lowered threshold for rage observed in the decorticate animal. It is possible that flight behavior is more dependent on a "psychic assessment" of the situation, requiring cortical integrity.

Other forebrain structures also have been implicated in agonistic behavior. Thus, bilateral destruction of the septal nuclei results in a heightened aggressive reactivity. Further, stimulation of discrete amygdaloid sites leads to specific patterns of agonistic behavior. Amygdaloid ablation usually has been reported to lead to increased docility.

The functional integrity of the hypothalamus appears necessary for the elaboration of rage reactions induced by amygdaloid stimulation. On the other hand, hypothalamically-induced rage occurs even following bilateral amygdaloid lesions. The efferent pathways mediating the amygdaloid rage reactions have been identified as either the stria terminalis or a ventral system of amygdalofugal fibers.

The need for careful physiologic, neuroanatomic and behavioral approaches to central autonomic functions can be illustrated by the development of our knowledge of the "rage reaction" induced by hypothalamic stimulation. Initially, a "rage" response was observed; subsequently, a distinction was made between sites which yielded "sham" or undirected rage and those which brought about directed rage. This differentiation of effective sites was followed by studies combining carefully controlled and localized stimulation with precise anatomical verification. In turn, this led to clarification of the hypothalamic substrates which originally had been presumed to induce only simple rage behavior. We now believe that there is a specific system which yields flight responses, another for defense, and a third for attack. The excitation of each of these systems is accompanied by appropriate autonomic, somatomotor, and humoral activities.

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