Central neural control of the cardiovascular system: current perspectives

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Dampney RA. Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ 40: 283–296, 2016; doi:10.1152/advan.00027.2016.—This brief review, which is based on a lecture presented at the American Physiological Society Teaching Refresher Course on the Brain and Systems Control as part of the Experimental Biology meeting in 2015, aims to summarize current concepts of the principal mechanisms in the brain that regulate the autonomic outflow to the cardiovascular system. Such cardiovascular regulatory mechanisms do not operate in isolation but are closely coordinated with respiratory and other regulatory mechanisms to maintain homeostasis. The brain regulates the cardiovascular system by two general means: 1) feedforward regulation, often referred to as “central command,” and 2) feedback or reflex regulation. In most situations (e.g., during exercise, defensive behavior, sleep, etc.), both of these general mechanisms contribute to overall cardiovascular homeostasis. The review first describes the mechanisms and central circuitry subserving the baroreceptor, chemoreceptor, and other reflexes that work together to regulate an appropriate level of blood pressure and blood oxygenation and then considers the brain mechanisms that defend the body against more complex environmental challenges, using dehydration and cold and heat stress as examples. The last section of the review considers the central mechanisms regulating cardiovascular function associated with different behaviors, with a specific focus on defensive behavior and exercise.

HOMEOSTASIS can be defined as the maintenance of the physical and chemical properties of the extracellular fluid in all body tissues. It is dependent, among other things, on effective cardiovascular and respiratory regulatory mechanisms that ensure that the delivery of O₂ to all regions of the body is sufficient to match the metabolic demands of each region. This is particularly critical in the case of the heart and skeletal muscles, whose metabolic activity can vary greatly in different circumstances. For example, during maximal exercise in humans, O₂ demand can increase to a level up to 50-fold greater than resting levels (49). This is achieved by an enormous increase in blood flow (up to 20-fold) together with a 2- to 3-fold increase in O₂ extraction from the blood (49). These effects are produced by a combination of local and neural mechanisms, as shown in Fig. 1. Local mechanisms, which include metabolic, endothelial, and myogenic components (49), result in vasodilation in metabolically active skeletal muscle vascular beds, leading to large increases in local blood flow provided the perfusion pressure (arterial pressure) is maintained or increased. Similarly, the increase in O₂ extraction from the blood also depends on both local factors (e.g., local acidosis, which shifts the hemoglobin-oxygen saturation curve to the right) (49) as well as central regulatory mechanisms that maintain the arterial blood PₐO₂ (PaO₂) despite large changes in metabolic activity (1).

Apart from physical exercise, coordinated cardiovascular and respiratory mechanisms regulate the O₂ supply to all tissue during other behaviors, such as defensive behavior or sleep. In addition, such regulatory mechanisms are also required to maintain homeostasis in the face of challenges such as hypoxia, dehydration, or changes in ambient temperature. In this review, I shall focus primarily on the central neural mechanisms that regulate cardiovascular function, although I shall also discuss, where relevant, how these mechanisms are coordinated with respiratory regulatory mechanisms.

As shown in Fig. 1, arterial blood pressure is regulated by autonomic nerves, consisting of sympathetic nerves that innervate the heart and blood vessels, and vagal parasympathetic nerves, which innervate the heart. Sympathetic outflow, in turn, is regulated by sympathetic premotor neurons located in the lower brain stem and hypothalamus, whereas vagal cardiac outflow originates primarily from the nucleus ambiguus in the medulla oblongata. The activity of the sympathetic premotor neurons and cardiac vagal neurons is controlled by two general mechanisms: 1) reflex effects arising from stimulation of a wide variety of peripheral receptors and 2) feedforward control, or “central command,” from descending inputs arising from higher centers in the brain (Fig. 1). One of the most important cardiovascular reflexes is the baroreceptor reflex, and an example of its operation is shown in Fig. 2A. In this example, recordings were made of mean arterial pressure, heart rate, and renal sympathetic nerve activity in a conscious rat during treadmill exercise (35). Changes in arterial pressure were induced by systemic injection of a vasoconstrictor (phenylephrine) and a vasodilator (sodium nitroprusside), resulting in reflex changes in heart rate and renal sympathetic nerve activity.

In contrast to reflex or feedback control, feedforward control (central command) does not require inputs from peripheral receptors. A classic example of such control is shown in Fig. 2B. Recordings of arterial pressure and heart rate were made in a paralyzed, mechanically ventilated, but conscious, human subject, who was asked to attempt to contract leg muscles (18). The numbers indicate the effort as a percentage of the maximum. Note that there were graded increases in arterial pressure and heart rate according to the degree of effort, despite the lack of any afferent feedback from the paralyzed muscles.

These two general mechanisms of feedback and feedforward control are not, however, entirely independent. In particular, as shall be described in more detail below, cardiovascular reflexes such as the baroreceptor reflex can be powerfully modulated by central command signals arising from the forebrain or midbrain.
THE BRAIN AND THE CARDIOVASCULAR SYSTEM

Central Mechanisms Subserving Homeostatic Reflexes

To maintain cardiovascular homeostasis, several key physiological variables must be regulated: arterial blood pressure, the O$_2$ content of the blood, blood volume, and body temperature. The following sections will briefly describe the reflex mechanisms that regulate these variables.

**Blood pressure.** The baroreceptor reflex is the principal mechanism regulating arterial pressure, at least in the short term. For example, a decrease in arterial pressure is sensed by baroreceptors located in the walls of the carotid sinus and aortic arch (Fig. 3A). The baroreceptors are stretch receptors located on the terminal arborizations of afferent fibers, so a decrease in arterial pressure results in a decreased firing rate of baroreceptor afferent fibers. Inputs from baroreceptor afferent fibers reflexly inhibit the sympathetic outflow to the heart and blood vessels and reflexly excite the cardiac vagal outflow via central pathways in the brain stem and spinal cord (described in more detail below). Therefore, a decrease in baroreceptor firing rate results in a reflex increase in sympathetic vasomotor activity, which increases total vascular resistance, and an increase in sympathetic cardiac activity together with a reflex decrease in cardiac vagal activity, which together results in an increase in heart rate and cardiac contractility, and thus cardiac output (Fig. 3A). The reflex increases in total peripheral resistance and cardiac output together help to restore arterial pressure (Fig. 3A). The most important component of the reflex response is the reflex change in total peripheral resistance, which accounts for ~80% of the reflex change in arterial pressure at rest and virtually 100% during exercise (Fig. 3B) (44).

The functional properties of the baroreceptor reflex in any particular situation can be represented by a sigmoidal curve that shows the input-output relationship for the reflex, where the input is the mean arterial pressure and the output is the reflexly controlled variable, e.g., renal sympathetic activity or heart rate (Fig. 4). To determine this curve, changes in mean arterial pressure are induced (e.g., by infusing a vasodilator or vasoconstrictor drug, as shown in Fig. 2A), and reflex changes in the output (e.g., renal sympathetic activity or heart rate) are then measured. The sigmoidal curve that best fits the relationship between the input and output is then determined (e.g., Fig. 4B).

The precise characteristics of the sigmoid baroreflex function curve are defined by 1) the maximum and minimum values of the reflexly controlled output; 2) the maximum gain or sensitivity of the reflex, i.e., where the slope of the curve is maximal; and 3) the operating range of the reflex, which is defined as the range of mean arterial pressure over which changes in pressure can produce significant reflex changes in the output (Fig. 4A) (30).

The baroreceptor reflex is operational at all times, although the functional properties of the reflex can vary under different behavioral conditions. For example, the maximum gain of the baroreceptor-sympathetic reflex is increased both during exer-

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Fig. 1. Flow diagram illustrating how feedforward (central command) and feedback (reflex) mechanisms operate together to regulate the O$_2$ supply to particular regions (skeletal muscle in this example) to match the metabolic demands of that region and thus maintain homeostasis.

Fig. 2. A: example of baroreflex control of the cardiovascular system. Changes in mean arterial pressure (MAP) were induced in a conscious exercising rat by systemic injection of the vasoconstrictor phenylephrine (PE) or the vasodilator sodium nitroprusside (SNP), resulting in reflex changes in heart rate (HR) and renal sympathetic nerve activity (RSNA). [Modified from Miki et al. (35) with permission.] B: example of central command. Recordings of arterial pressure and HR [in beats/min (bpm)] were made in a paralyzed, mechanically ventilated, but conscious human subject, who was asked to attempt to contract leg muscles. The numbers indicate the effort as a percentage of the maximum. Note that there were graded increases in arterial pressure and HR according to the degree of effort, despite the lack of any afferent feedback from the paralyzed muscle. [Modified from Gandevia et al. (18) with permission.]

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**Table 1**

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<td>Symp outflow to skeletal muscle vascular bed</td>
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<td>Symp outflow to other vascular beds &amp; heart</td>
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**Table 3**

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**Fig. 2.** A: example of baroreflex control of the cardiovascular system. Changes in mean arterial pressure (MAP) were induced in a conscious exercising rat by systemic injection of the vasoconstrictor phenylephrine (PE) or the vasodilator sodium nitroprusside (SNP), resulting in reflex changes in heart rate (HR) and renal sympathetic nerve activity (RSNA). [Modified from Miki et al. (35) with permission.] B: example of central command. Recordings of arterial pressure and HR [in beats/min (bpm)] were made in a paralyzed, mechanically ventilated, but conscious human subject, who was asked to attempt to contract leg muscles. The numbers indicate the effort as a percentage of the maximum. Note that there were graded increases in arterial pressure and HR according to the degree of effort, despite the lack of any afferent feedback from the paralyzed muscle. [Modified from Gandevia et al. (18) with permission.]
cise (Fig. 5A) and psychological stress (Fig. 5B). Furthermore, the reflex is reset so that it operates over a higher range of mean arterial pressure and sympathetic activity during exercise and stress (Fig. 5, A and B) (25, 35). Similarly, the baroreceptor-heart rate reflex is reset to a higher operating range of both mean arterial pressure and heart rate during exercise (Fig. 5C), with little change in gain (41). The effect of such baroreflex resetting is that during behaviors where an increase in arterial pressure is physiologically advantageous (e.g., exercise or defensive behavior), the baroreflex continues to be highly effective in regulating arterial pressure at this increased level.

It is well known that mean arterial pressure and heart rate show parallel diurnal variations, such that, in humans, both of these variables tend to be minimal during the early hours of the morning (i.e., during the sleep phase) and maximal after waking during the morning period (54). These variations in arterial pressure and heart rate can be explained as a continuous modulation or resetting of the baroreflex, which thus serves to regulate arterial pressure at a level that is optimal for each phase of the sleep-wake or activity cycle.

Studies over the last 35 yr have identified the essential central pathways that mediate the baroreceptor reflex (13, 19), and these are shown in Fig. 6. Primary afferent fibers from arterial baroreceptors located in the carotid sinus and aortic arch, which run in the glossopharyngeal nerve (cranial nerve IX) and vagus nerve (cranial nerve X), terminate in the nucleus tractus solitarius (NTS) in the dorsomedial medulla. From the NTS, second-order neurons project directly to cardiac vagal motoneurons in the nucleus ambiguus or to interneurons in the caudal ventrolateral medulla (CVLM). The

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**Fig. 3.** A: flow diagram showing the sequence of events after a decrease in arterial pressure, leading to a reflex compensatory restoration of arterial pressure. B: histogram showing that the reflex increase in total peripheral resistance (TPR) is the major factor contributing to the reflex response both at rest and during exercise. CO, cardiac output. [Modified from Raven et al. (44) with permission.]

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**Fig. 4.** A: the standard sigmoidal curve that is used to represent the input-output relationship for the baroreceptor reflex. The curve represents the following function: \( Y = \frac{A_1}{1 + \exp\left[A_2(X - A_3)\right]} + A_4 \), where \( X \) is the input (typically MAP) and \( Y \) is the output (e.g., sympathetic activity or HR) and \( A_1, A_2, A_3, \) and \( A_4 \) are the parameters that define the specific curve in any particular situation. The gain or sensitivity of the reflex at any value of \( X \) is represented by the slope of the curve and is maximal at the midpoint of the \( Y \) range (i.e., between the maximum and minimum values of \( Y \)). The threshold (Thr) value of \( X \) is the point at which the value of \( Y \) is 5% of the \( Y \) range below the maximum value of \( Y \), and the saturation (Sat) value of \( X \) is the point at which the value of \( Y \) is 5% of the \( Y \) range above the minimum value of \( Y \). The operating range of \( X \) lies between the Thr and Sat values and is thus the range of \( X \) over which changes in \( X \) evoke significant reflex changes in \( Y \). [Modified from McDowall et al. (30).] B: example of a baroreflex sigmoidal function curve that best fits the reflex relationship between MAP and RSNA. In this experiment, changes in MAP were induced by injections of vasoconstrictor and vasodilator drugs, and the corresponding reflex changes in RSNA were measured (solid circles). [Modified from McDowall et al. (31).]
latter group are GABAergic neurons, which project to and inhibit sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM). RVLM sympathetic premotor neurons are tonically active, and their tonic activity is critical in maintaining sympathetic vasomotor tone and resting arterial pressure (13, 19). Furthermore, the tonic activity of RVLM sympathetic premotor neurons under resting conditions also permits both reflex decreases and increases in sympathetic activity in response to altered input from the arterial baroreceptors.

Some of the neurons within the baroreflex circuitry shown in Fig. 6 receive inputs from nuclei at higher levels of the brain, including the midbrain periaqueductal gray (PAG), dorsomedial and paraventricular nuclei in the hypothalamus, central nucleus of the amygdala, medial prefrontal cortex, and insular cortex (13, 53). Although the precise functions of these inputs has not been determined, it is likely that they include inputs that reset the baroreceptor reflex during different behaviors.

Blood O2 level. Nearly all O2 in the blood is attached to hemoglobin. In arterial blood, >95% of hemoglobin molecules are bound to O2, forming oxyhemoglobin, provided the PaO2 is >90 mmHg. The principal mechanism that helps to maintain PaO2 under hypoxic conditions (e.g., when atmospheric Po2 is reduced at high altitudes or when normal breathing is prevented, such as during submersion in diving animals) is the arterial chemoreceptor reflex. Chemoreceptors located in the carotid and aortic bodies are activated primarily by a decrease in PaO2 (Fig. 7A) (4). The main reflex effects of chemoreceptor activation are 1) an increase in respiratory rate and depth that increases alveolar ventilation and 2) cardiovascular effects that reduce blood flow to peripheral tissues and that also decrease heart rate and thus cardiac work, thus conserving the available O2 (Fig. 7B).

Under resting conditions, carotid body chemoreceptor activity and the reflex ventilatory response do not start to increase markedly until PaO2 decreases to ~60 mmHg (Fig. 7, A and C). This corresponds to the point at which the percentage of hemoglobin binding O2 also starts to decrease rapidly (23), so the result is that the chemoreflex ventilatory response reflects

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**Fig. 5.** A: baroreflex function curves showing the relationship between MAP and RSNA in conscious rats at rest and during exercise. Note that the maximum gain is increased and the operating range is shifted to higher values of MAP during exercise. [Modified from Miki et al. (35) with permission.] B: baroreflex function curves showing the relationship between MAP and RSNA in conscious rats at rest and during psychological stress (air jet stress). Note that the maximum gain is increased and the operating range is shifted to higher values of MAP during psychological stress, similar to the changes observed in exercise. [Modified from Kanbar et al. (25).] C: baroreflex function curves showing the relationship between MAP and HR in human subjects at rest and during exercise. Note that the operating range of the reflex is shifted to higher values of MAP during exercise but with little change in the maximum gain of the reflex. [Modified from Ogoh et al. (41) with permission.]
the degree of hypoxia of arterial blood. The reflex ventilatory response to chemoreceptor stimulation is not constant but is enhanced during exercise (Fig. 7C), as a consequence of increased peripheral chemosensitivity (56). This is a further example of reflex operating properties being altered according to the behavioral state.

The essential central pathways mediating the chemoreceptor reflex are shown in Fig. 8. Chemoreceptor primary afferent fibers arising from the carotid and aortic bodies, which run in cranial nerves IX and X, respectively, terminate on secondary interneurons in the NTS (13, 19, 20). The secondary interneurons, in turn, project to a number of targets, including respiratory neurons that drive the ventilatory response as well as sympathetic premotor neurons in the RVLM that drive the sympathetic component of the reflex (13, 19, 20). In regard to the latter, there is now strong evidence that chemoreflex sympathoexcitation is mediated by both a direct input from the NTS to sympathetic premotor neurons in the RVLM as well as by indirect inputs via neurons within the central respiratory network, including respiratory neurons in the preBötzinger complex and dorsolateral pons (Fig. 8) [for a detailed review, see Guyenet (20)].

Apart from the chemoreceptor reflex, all air-breathing vertebrates have a diving reflex (also called nasopharyngeal reflex), which is another reflex that acts to conserve the available O2 (42). This reflex is particularly powerful in diving animals (Fig. 9A). The reflex is triggered by activation of nasopharyngeal receptors, which leads to a reflex apnea, intense widespread peripheral vasoconstriction (except in the brain and heart), and a profound bradycardia (Fig. 9B). The cardiovascular reflex effects conserve the available O2, which is thus preferentially provided to the brain and heart, two critical regions that cannot sustain an O2 debt. The same pattern of reflex respiratory and cardiovascular effects is also evoked in nondiving animals, in response to stimulation of nasopharyngeal receptors by a noxious substance, such as smoke (57). Under those circumstances, cessation of ventilation combined with O2 conservation will also increase the probability of survival.

**Interactions between reflexes.** In most situations, more than one reflex is activated in response to a particular challenge, and hypoxia is a good example of this. For example, in diving animals, the first effect of submersion is the activation of...
nasopharyngeal receptors that then trigger the diving reflex, including apnea as well as the cardiovascular effects described above. The resultant hypoxia, in turn, triggers the chemoreceptor reflex (Fig. 10). The interaction between the two reflexes reinforces the vasoconstriction and bradycardia, but the normal ventilatory response to chemoreceptor stimulation is suppressed by inputs from nasopharyngeal receptors (Fig. 10).

In contrast, under conditions where hypoxia occurs without activation of nasopharyngeal receptors, (e.g., high altitude), chemoreceptor activation does reflexly increase ventilation, which then activates another reflex arising from pulmonary stretch receptors, innervated by afferent vagal fibers. The pulmonary stretch receptor reflex tends to increase heart rate and decrease vascular resistance, opposing the primary effects of chemoreceptor stimulation (Fig. 10). Thus, the net effect on cardiovascular and respiratory function depends on interactions between a number of reflexes, which ensures that the pattern of reflex cardiovascular and respiratory responses is optimal for the particular environmental challenge faced by the animal.

As shown in Fig. 11, the NTS and RVLM are key components of the central pathways mediating the nasopharyngeal reflex as well as baroreceptor and chemoreceptor reflexes (see above) (42). Furthermore, inputs from a wide range of receptors that reflexly affect cardiovascular function also project to the NTS, either directly or indirectly via other relay nuclei (Fig. 11). These receptors include cardiopulmonary receptors (that respond primarily to changes in blood volume), vestibular receptors that are critical for othostatic reflexes, receptors in skeletal muscle that are activated during exercise (sometimes called “ergoreceptors”), and skin nociceptors (11, 13). In addition, inputs from some of these receptors also project to the RVLM via other pathways that bypass the RVLM (Fig. 11) (38, 42, 59). Ultimately, however, all of the inputs from the receptors shown in Fig. 11 converge on sympathetic premotor neurons in the RVLM. Thus, the RVLM is a major site at which interactions between different inputs regulating sympathetic activity occurs. In addition, it is a likely site, together with the NTS, at which inputs from higher centers modulate baroreceptor, chemoreceptor, and other cardiovascular reflexes (Fig. 11) (13, 19).

The reflex effects of activation of these various inputs on the sympathetic outflow are not uniform (Fig. 12). For example, baroreceptor stimulation results in reflex vasodilation in skeletal muscle vascular beds and a modest vasodilator effect on the skin blood vessels, whereas chemoreceptor stimulation has a similar effect on skin blood vessels, but evokes a powerful vasoconstrictor effect on skeletal muscle vascular beds (24).

Fig. 9. A: example of the extreme bradycardia evoked during voluntary diving in a rat. Note that despite the extreme bradycardia (decrease in HR of ~80%), the arterial pressure is maintained, due to intense vasoconstriction. [Modified from Panneton et al. (42).] B: flow diagram showing the reflex effects of nasopharyngeal stimulation submersion, leading to cardiovascular reflex changes that conserve the available O2.

Fig. 10. Flow diagram illustrating the interaction between reflexes arising from inputs from arterial chemoreceptors, pulmonary stretch receptors, and nasopharyngeal receptors. When hypoxia occurs under conditions where respiratory activity can increase (e.g., exposure to a high altitude), the reflex decrease in HR and the reflex increase in vascular resistance (in skeletal muscle and visceral beds) is opposed by the secondary reflex effects arising from the activation of pulmonary stretch receptors, which tends to increase O2 uptake. In contrast, when hypoxia occurs under conditions when respiratory activity cannot increase (e.g., during submersion), the primary reflex response to chemoreceptor stimulation is not opposed by these secondary effects. Furthermore, under such conditions, nasopharyngeal receptors may be stimulated, triggering reflex effects that reinforce the primary effects of chemoreceptor stimulation, leading to greater reflex bradycardia and peripheral vasoconstriction and thus a greater degree of O2 conservation. [From Dampney (11).]
Such differentiated effects on the sympathetic outflows to different vascular beds reflect the fact that there are subgroups of sympathetic premotor neurons in the RVLM that preferentially or exclusively control different sympathetic outflows (Fig. 11) (13, 29).

**Blood volume.** The essential central pathways subserving the reflexes described above are contained within the lower brain stem, although they can be powerfully modulated by descending inputs from higher brain regions. In contrast, the central regulatory mechanisms defending the body against a decrease in blood volume (e.g., as a result of hemorrhage or dehydration) are located in the forebrain as well as the lower brain stem and include neural, hormonal, and behavioral components. The signals that activate compensatory responses to a decrease in blood volume are also complex, including those that are an immediate consequence of the hypovolemia as well as secondary effects that result from the hypovolemia (15).

For example, hypovolemia caused by dehydration results in increased blood osmolarity as well as reduced atrial and arterial pressures (as a consequence of the reduced blood volume and venous return) (Fig. 13). Apart from the reflex changes in sympathetic activity resulting from unloading of cardiopulmonary and arterial baroreceptors (11, 13), the reduced arterial pressure also activates the renin-angiotensin system (Fig. 13). The increased levels of osmolarity and ANG II in the blood act on receptors on neurons in the circumventricular organs in the anterior wall of the third ventricle [especially the organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO)] (21, 32, 33, 50, 52). These neurons in the OVLT and SFO have direct and indirect (via the median preoptic nucleus) connections to the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN), and thus activation of these neurons leads to increased sympathetic activity and vasopressin release from the pituitary (Fig. 13) (10, 15, 32, 33, 50, 52). In addition, these signals also trigger an increase in drinking (32, 33) (Fig. 13). The combined effect of all these compensatory responses is to minimize fluid loss and increase fluid intake, thus restoring fluid homeostasis.

Apart from ANG II and Na⁺, other circulating substances (e.g., relaxin, leptin, and cytokines) can also activate OVLT and/or SFO neurons, and there is now strong evidence that both these circumventricular organs, together with the median preoptic nucleus, are critical sites at which these circulating substances can affect cardiovascular function. For example, circulating relaxin acts on receptors in the OVLT and SFO to stimulate vasopressin release (32). Second, infusion of leptin, a hormone derived from adipose tissue, induces an increase in renal sympathetic nerve activity, whereas blockade of leptin receptors in the SFO prevents this effect (60). Third, circulating proinflammatory cytokines act on the brain to increase blood pressure, heart rate, and sympathetic activity, and these effects are blocked by lesions of the SFO (55). It should be noted, however, that these results do not necessarily imply that circulating leptin or cytokines exert their effects exclusively via the SFO. For example, blockade of leptin receptors in the hypothalamic arcuate nucleus also prevents the increase in renal sympathetic nerve activity evoked by circulating leptin (22), whereas Yu et al. (61) found that circulating proinflammatory cytokines can also increase sympathetic activity via increases in prostaglandin production in perivascular macrophages located in hypothalamic regions outside the circumventricular organs.

Taken together, however, the results of many studies over many years have led to the conclusion that the OVLT, SFO, and median preoptic nucleus, which collectively is referred to as the lamina terminalis, have a pivotal role in cardiovascular regulation (for reviews, see Refs. 32, 33, and 50). This region also plays an important role in maintaining increased sympathetic activity in at least some forms of experimental hypertension, as first shown by the pioneering work of Buggy et al. (7).

**Body temperature.** Maintenance of body core temperature within narrow limits is critical for survival in mammals (37). Ambient temperature is sensed by receptors in the skin, whereas body core temperature is sensed by receptors in the hypothalamic preoptic area, spinal cord, and abdomen (33, 37, 39). The afferent signals from all these receptors contribute to thermoregulation, although it has been proposed that signals from body core thermoreceptors are important mainly in more extreme situations where the responses to inputs from periph-

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**Table:**

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Fig. 12. Examples of the different patterns of reflex activation of the sympathetic outflow to different vascular beds in response to stimulation of arterial baroreceptors and chemoreceptors.
eral thermoreceptors are not adequate to maintain body core temperature (39).

The central mechanisms that have evolved to maintain body core temperature are complex and include autonomic (both cardiovascular and noncardiovascular) and somatomotor components. For example, a decrease in ambient temperature is detected by skin cold receptors, leading to reflex increases in the activity of sympathetic nerves innervating skin blood vessels and skin piloerector muscle, causing skin vasoconstriction and an increase in skin insulation, both of which reduce heat loss and thus conserve heat (Fig. 14). In addition, it is now known that, like many other species, both newborn and adult humans have a significant amount of brown adipose tissue (BAT), which is innervated by sympathetic nerves (48). An increase in BAT sympathetic activity increases BAT metabolic activity and thus heat production (Fig. 14). The somatomotor component of the reflex response to ambient cold temperature is an increase in the activity of nerves supplying skeletal muscle, resulting in increased metabolic activity, which, together with increased BAT metabolic activity, also aids heat production (Fig. 13) (37).

An increase in ambient temperature is detected by warmth receptors in the skin and leads to autonomic and somatomotor effects that are opposite to those described above (i.e., cutaneous vasodilation due to inhibition of sympathetic vasoconstrictor activity and excitation of sympathetic vasodilator activity, together with inhibition of BAT thermogenesis and shivering) (27, 37, 39, 46). In addition, in humans and other mammals with sweat glands, sympathetic sudomotor activity is reflexly increased, causing increased sweat production and consequently increased evaporative heat loss from the skin. In mammals that lack sweat glands, panting is the most common means of evaporative cooling (33, 39).

Fig. 13. A: flow diagram showing the sequence of events following dehydration, which leads ultimately to compensatory cardiovascular, hormonal, and behavioral responses that restore fluid balance. The subformical organ (SFO) and organum vasculosum laminae terminalis (OVLT) are key components of these central mechanisms via their projections to the paraventricular nucleus (PVN), median preoptic nucleus (MnPO), and supraoptic nucleus (SON) in the hypothalamus. B: sagittal section of the rat brain indicating the locations of the nuclei referred to in A. C: examples of increased neural activity, indicated by c-Fos expression, within the SON and PVN induced in a rat after dehydration compared with a control rat. [Modified from Ho et al. (21).]
Figure 15A shows the neural pathways that mediate the physiological responses to cold stress. Afferent fibers conveying signals from cold receptors terminate in the dorsal column of the spinal cord, from which an ascending pathway conveys cold signals to the median preoptic nucleus (MnPO) in the hypothalamus via a relay in the external subnucleus of the lateral parabrachial nucleus (eLPB) (33, 37). From the MnPO, there are direct and indirect descending projections to the raphe pallidus in the midline medulla, synapsing with sympathetic premotor neurons that produce skin vasoconstriction and BAT thermogenesis, as well as premotor neurons that control shivering thermogenesis (33, 37). The indirect descending pathways include synapses in the preoptic area and dorsomedial hypothalamus (DMH), which are also thus important components of central thermoregulatory mechanisms (33, 37). In response to a heat stress, the signals arising from warm receptors in the skin are also conveyed to the MnPO, but via a separate ascending pathway that includes a relay in the dorso-lateral subnucleus of the lateral parabrachial nucleus (dLPB) (Fig. 15B). The neurons in the MnPO that receive these inputs project to and excite neurons in the preoptic area that inhibit the sympathetic premotor neurons that produce skin vasoconstriction and BAT thermogenesis, both directly and via the DMH (Fig. 15B) (33).

The MnPO thus plays a central role in thermoregulation as well as in the regulation of blood volume, as discussed above. Furthermore, it has become clear that the MnPO is also a critical region for other homeostatic functions, including the regulation of salt balance and sleep (33).

Central Mechanisms Coordinating Cardiovascular Responses With Different Behaviors: Central Command

The above examples of central cardiovascular mechanisms all involve reflexes with feedback from peripheral receptors. As stated in the Introduction, the other general mechanism of central cardiovascular control is central command, or feedforward control. Such cardiovascular responses are components of more complex and highly coordinated responses, which typically include appropriate respiratory and behavioral components.

Defensive behavior. The ability to respond rapidly and appropriately to a threat in the external environment is critical for survival, and so it is not surprising that highly complex brain systems have evolved that subserve such defensive responses. Such responses may be triggered by a wide variety of stimuli, which may be either unconditioned salient stimuli (e.g., sight, sound, or odor of a predator or prey) or else conditioned stimuli (e.g., stimuli that are normally innocuous but which an animal has
learned is indicative of a threat or other stimulus that requires immediate action).

A general scheme illustrating the brain regions that are involved in generating these coordinated responses is shown in

Fig. 16. Signals relating to the stimulus (e.g., sight, sound, or touch) reach the cortex, amygdala, and hippocampus via thalamic relay nuclei. The amygdala also receives inputs from the cortex and hippocampus. The amygdala, which consists of

Fig. 17. Flow diagram showing the major pathways that subserve the cardiovascular and respiratory responses to an acute psychological stressor. Note that the DMH and perifornical area (PeF) are key components of these pathways, and they receive inputs from the cortex, amygdala, and brain stem that signal the real or perceived threatening stimulus. Note also that the sympathetically mediated vasoconstriction is dependent on two mechanisms: 1) central command subserved by sympathetic premotor neurons located outside the RVLM, possibly in the rostral ventromedial medulla (RVMM), and 2) baroreflex resetting, mediated by descending inputs from the DMH/PeF. The solid lines indicate direct connections that have been clearly identified, whereas the dashed lines may be direct or indirect. Amy, amygdala; mPFC, medial prefrontal cortex; PAG, periaqueductal gray. For other abbreviations, see previous figures.

Fig. 18. Schematic diagram showing the longitudinal columns within the midbrain PAG that mediate different types of defensive responses. Neurons in the lateral (l) and dorsolateral (dl) columns generate active coping responses, characterized by flight or freezing and increases in blood pressure (BP) and HR, whereas neurons in the ventrolateral (vl) column generate passive coping responses, characterized by quiescence and decreases in BP and HR. [Modified from Bandler et al. (2) with permission.]
several interconnected nuclei (43), plays a critical role in generating cardiovascular and respiratory responses to unconditioned and conditioned alerting stimuli (6, 36). The input to the amygdala from the hippocampus (Fig. 16) is essential for the expression of physiological responses to conditioned stimuli but not unconditioned stimuli (43). Inputs arising from unconditioned salient stimuli that project to the thalamus then project to the amygdala directly or indirectly via the cortex (Fig. 16). The direct input from the thalamus is believed to generate rapid responses to simple external stimuli (e.g., a sudden loud noise), whereas more complex stimuli require cortical processing (43).

The output pathways from the amygdala to cardiovascular, respiratory, and somatomotor nuclei in the lower brainstem responses include synapses in hypothalamic and midbrain regions (Fig. 16) (12). One of these regions is the DMH and adjacent perifornical area (PeF), which, like the amygdala, have a critical role in generating cardiovascular and respiratory responses to alerting or stressful stimuli (5, 12, 16, 51). Apart from the amygdala, there are also inputs to the DMH/PeF from the cortex and brainstem (Fig. 17) that also may signal alerting or stressful stimuli. The output pathways from the DMH/PeF have not been completely identified but include direct descending projections to sympathetic premotor neurons in the medullary raphe pallidus that regulate the sympathetic outflows to the heart, skin blood vessels, and BAT. These sympathetic outflows are activated in response to alerting or stressful stimuli (12) as well as in response to a cold stress, as discussed above. In addition, there are output pathways from the DMH/PeF to other sympathetic premotor neurons that regulate the sympathetic outflow to renal, splanchnic, and other visceral blood vessels. These premotor neurons are not within the RVLM, but there is evidence that they are located more medially, within the rostral ventromedial medulla (RVMM) (12). Thus, in summary, the sympathetic premotor neurons that drive the sympathetic outflow during arousal or defensive behavior appear to be distinct from the sympathetic premotor neurons within the RVLM that mediate the baroreceptor, chemoreceptor, and other homeostatic cardiovascular reflexes, as described above (see Central Mechanisms Subserving Homeostatic Reflexes).

As also discussed above, however, the baroreceptor reflex is reset during defensive behaviors, such that the sympathetic outflow continues to be regulated but within a higher operating range of arterial blood pressure and sympathetic activity. The DMH/PeF contains neurons that, when activated, reset the baroreceptor-sympathetic reflex in this way (31), probably via descending pathways to the NTS (Fig. 17) (12, 34).

It is well established that the PAG in the midbrain is another brain region that can coordinate a wide variety of behavioral responses associated with appropriate cardiovascular and respiratory changes (2, 8, 26). The PAG is organized into longitudinal columns, including dorsolateral, lateral, and ventrolateral columns. The dorsolateral PAG and lateral PAG columns regulate what has been termed an active coping strategy (26), consisting of freezing and/or flight, associated with increases in blood pressure and heart rate, visceral vasocnstriction, skeletal muscle vasodilation, and increased ventilation (Fig. 18) (2, 8, 26). Conversely, the ventrolateral PAG column regulates what has been termed a passive coping strategy (2, 26), consisting of behavioral quiescence, associated with decreases in blood pressure and heart rate as well as sympathoinhibition (2, 8, 26) (Fig. 18).

The precise pattern of responses generated by the PAG naturally depends on the pattern of inputs to the PAG. For example, inputs from visceral nociceptors trigger passive coping responses, whereas inputs from somatic nociceptors (e.g., a painful stimulus to the skin) trigger active coping responses (2, 26). It is also important to note that active coping responses triggered by physical stimuli (such as the above example of a painful stimulus to the skin) are generated by activation of neurons within the lateral PAG, whereas those triggered by emotional or psychological stressors (e.g., sight, sound, or odor of a predator or a perceived emotional stressor) generate a similar pattern of behavioral, cardiovascular, and respiratory responses via activation of the dorsolateral PAG (Fig. 19) (14).

![Fig. 19. Schematic diagram showing major inputs to the dIPAG and IPAG and the proposed output pathways subserving the coordinated changes in sympathetic vasomotor and respiratory activity regulated by the dIPAG and IPAG. The lines with arrows indicate connections that are either direct (monosynaptic) or indirect (polysynaptic). Neurons in the dIPAG are activated primarily by inputs related to psychological stressors, whereas those in the IPAG are activated primarily by inputs related to physical stressors. Note that the dIPAG projects to the DMH via both direct and indirect [via the superior lateral parabrachial nucleus (PBsl) or cuneiform nucleus (CnF)]. The cardiovascular and respiratory responses generated from the dIPAG are dependent on its connections with the DMH, whereas the responses generated from the IPAG are mediated by direct descending projections to the medulla. [From Dampney (12).]
These differences in inputs to the lateral PAG and dorsolateral PAG are also reflected in differences in outputs (Fig. 19). Whereas neurons in the lateral PAG descend directly to the medulla where they synapse with neurons regulating somatomotor, cardiovascular, and respiratory responses, there are no direct descending projections to the medulla from the dorsolateral PAG (Fig. 19) (14). There are, however, ascending projections from the dorsolateral PAG to the DMH (Fig. 19), and this projection is essential for the expression of cardiovascular and respiratory responses generated from the dorsolateral PAG (12, 14). Thus, the DMH is a site of convergence of inputs related to psychological stressors that are relayed via the dorsolateral PAG as well as those from the cortex and amygdala, as discussed above.

A further component of the brain mechanisms that subserve the cardiovascular and respiratory responses associated with defensive behavior is the basal ganglia/collliculi system (for a more detailed review of this system, see Müller-Ribeiro et al. (40)). The basal ganglia/collliculi system is phylogenetically ancient and independent of the cortex and DMH/PeF and is capable of responding to threats that require immediate stereotype responses (17, 40). In contrast, the defense systems described above that include the DMH/PeF and cortex as important components appear to be better adapted to integrating responses to more sustained threats that require cognitive appraisal.

**Exercise.** The cardiovascular and respiratory changes associated with exercise have been well described, both in animals and humans (9, 16, 34, 45, 47). It is well established that central command plays a major role in generating these responses (Fig. 2A) (58), but reflexes also have an important role (16, 34, 58).

There are many similarities in the pattern of cardiovascular and respiratory changes associated with exercise and psychological stress (e.g., in both cases, there are increases in blood pressure, heart rate, and cardiac output, vasoconstriction in the renal and splanchnic beds, and vasodilation in skeletal muscle beds) (16). In addition, in both exercise and psychological stress, the baroreflex is reset in a similar way, as described above (e.g., Fig. 5). This naturally raises the question as to whether the cardiovascular and respiratory responses to exercise and those to stress are driven, at least in large part, by the same central mechanisms. Relatively little is known about the brain regions responsible for central command during exercise (58), although studies in animals have indicated that the DMH and immediately adjacent regions are activated during exercise (3), as is the case in psychological stress (12). Furthermore, neurons that contain the peptide orexin (also called hypocretin) in the DMH/PeF are activated during both exercise and stress, and it is thought that orexin neurons facilitate cardiorespiratory responses in both exercise and psychological stress (28).

In summary, the studies to date are consistent with the hypothesis that the cardiovascular and respiratory responses associated with exercise and psychological stress are driven by common central mechanisms, at least in part.

**Conclusions and Key Points**

This article has attempted to highlight some of the key pathways and mechanisms in the brain that are responsible for regulating the autonomic outflow to the cardiovascular system. I have emphasized that cardiovascular regulatory mechanisms do not operate in isolation but are closely coordinated with respiratory and other regulatory mechanisms to maintain homeostasis. The key points can be summarized as follows:

- The brain regulates the cardiovascular system by two general means: 1) feedforward regulation (central command) and 2) feedback regulation (reflex control).
- The baroreceptor and chemoreceptor reflexes are the primary homeostatic reflexes.
- The baroreceptor reflex regulates blood pressure not at a constant fixed level but at a level appropriate for each specific behavioral state (e.g., rest, exercise, or sleep).
- The chemoreceptor reflex maintains oxygenation of the arterial blood but in cases of O$_2$ deficiency also conserves O$_2$, often in concert with other reflexes (e.g., pulmonary reflexes or the diving reflex).
- Other critical reflexes maintain body temperature and salt and water balance.
- The brain also can generate patterned changes in autonomic, respiratory, and neuroendocrine activity during different behaviors (e.g., exercise, defense, feeding, sexual activity, or sleep).
- The essential circuitry for baroreceptor and chemoreceptor reflexes is in the lower brain stem but can be modified by inputs from higher centers or other peripheral inputs.
- The lamina terminalis in the forebrain (OVLT, SFO, and median preoptic nucleus) is critical for the regulation of salt and water balance and in the long-term regulation of sympathetic activity and blood pressure.
- The brain mechanisms regulating cardiovascular and respiratory changes during defensive behavior are complex, but the prefrontal cortex, amygdala, hypothalamus, midbrain PAG, and colliculi play key roles.
- During arousal and defensive behavior, orexin (hypocretin) neurons in the hypothalamus are activated, and this has the effect of facilitating the cardiovascular and respiratory responses associated with these behaviors.

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