THE IMPORTANCE of the baroreceptor reflex is to stabilize perfusion pressure in the face of disturbances of circulatory homeostasis. This is achieved by a number of neuronal (8, 29, 37, 48) and humoral (37, 45, 46) regulatory adjustments. These adjustments are initiated by a change in the pressure load at specialized pressure sensors located at the aortic arch and the carotid sinuses. Especially with regard to experiments involving sinoaortic denervation (6, 13, 14, 20, 31), it is important to note that these two pressure-sensitive sites are not equivalent with respect to defending arterial blood pressure during hypotensive challenges, such as hypovolemia. In conscious dogs, blood pressure started to decline at a lower volume of hemorrhage in carotid baroreceptor-denervated animals compared with animals with disrupted aortic baroreceptors (47). Thus, in dogs, the carotid baroreceptors are required to achieve a normal blood pressure response to hemorrhage. In addition, they are able to compensate for the loss of aortic baroreceptor function.

At resting blood pressure levels, the majority of baroreceptor afferents are providing a tonic, excitatory input to neurons in the nucleus of the solitary tract (NTS), where these peripheral afferents make their initial synapses (49). However, the blood pressor increase in response to bilateral common carotid artery occlusion is enhanced in commissural NTS-lesioned rats (41). Thus the termination of baroreceptor afferents is more widespread and other regions than the commissural NTS are also involved. The NTS constitutes the brain stem site for afferent baroreceptor inputs, whereas the rostral ventrolateral medulla (RVLM) is the output site for baroreceptor reflex modulation of efferent sympathetic nerve activity. Beside the RVLM, the activity of other nuclei is also modulated by the baroreceptor reflex. The primary stimulus for vasopressin release from the supraoptic nucleus is osmolality (5, 38). However, the baroreceptor reflex exerts an additional regulatory input to supraoptic vasopressin-releasing neurons (19, 20, 45, 46).

Two parameters are often determined to estimate baroreceptor reflex function. First is the operating point of the reflex, i.e., arterial pressure, at which the reflex responds most effectively to changes in arterial pressure. Second is the sensitivity of the reflex, i.e., the magnitude of the reflex response per unit of arterial blood pressure deviation from the operating point. In addition to these two traditional parameters, a baroreflex effectiveness index has recently been proposed that may provide information on how active the baroreceptor reflex is involved in blood pressure and heart rate regulation (11, 44).

The RVLM receives inputs from a variety of central nervous system areas directly or indirectly linked to baroreceptor reflex function, such as the NTS (10, 30, 34, 43), the medullary lateral tegmental field (3), or the ventrolateral periaqueductal gray (2, 17). The natural discharge pattern of RVLM spinal neurons is synchronized with the cardiac rhythm, and baroreceptor activation decreases the activity of these neurons. Furthermore, suppression of RVLM neurons by local injection of an imidazoline receptor agonist decreased the sensitivity of the baroreceptor-renal sympathetic nerve reflex activity reflex in conscious chronically instrumented rabbits (35). Conversely, excitation of the RVLM via microinjections of glutamate increased the sensitivity of the baroreceptor-renal sympathetic nerve activity and the baroreceptor-heart rate reflex (35). Thus the sensitivity of the baroreceptor reflex appears to be directly related to the neuronal activity within the pressure region of the RVLM.

Recently, the role of 5-hydroxytryptamine 1A [5-HT(1A)] receptors within the RVLM in mediating sympathoinhibition and baroreceptor reflex function was studied in anesthetized rats (2, 9, 36). Microinjection into the RVLM of a selective 5-HT(1A) receptor agonist decreased arterial blood pressure and peripheral sympathetic nerve activity (36), whereas microinjection of a specific 5-HT(1A) receptor antagonist attenuated or even reversed the sympathoinhibitory and hypotensive response to activation of the ventrolateral periaqueductal gray matter of the midbrain (2). Furthermore, the hypotensive and sympathoinhibitory effect of severe hemorrhage, a baroreceptor-independent response, was attenuated by microinjection of a specific

Baroreceptor reflex function

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5-HT(1A) antagonist into the RVLM (9). However, baroreceptor reflex inhibition of renal sympathetic nerve activity in response to a hypertensive challenge evoked by intravenous administration of phenylephrine was not altered by the 5-HT(1A) receptor antagonist (2). Furthermore, the depressor and splanchnic sympathoinhibitory response to supramaximal aortic nerve stimulation was also not altered by the specific 5-HT(1A) receptor agonist (36). Thus 5-HT(1A) receptors do not appear to be involved in baroreceptor reflex modulation within the RVLM, but they are important for the regulation of basal sympathetic outflow to the periphery.

The operating point and the sensitivity of the baroreceptor reflex are altered in physiological and pathophysiological situations, such as development (1, 21), aging (25), pregnancy (23, 24), different sleep states (40), and hypertension (15). Baroreflex function is also altered during thermoregulation. In conscious unrestrained rats, hyperthermia caused a shift in the operating point of the baroreceptor-heart rate and baroreceptor-sympathetic nerve activity reflex to higher blood pressure levels (33). This resetting of the reflex guarantees that the reflex continues to operate at a high gain despite the pressure rise that accompanies hyperthermia. Reflex-mediated changes in sympathetic tone can have a dramatic impact on thermoregulation, as demonstrated in patients undergoing lower abdominal surgery (39). Baroreceptor loading by a leg-up position caused cutaneous vasodilation and subsequent hypothermia. This effect is attenuated by positive expiratory pressure ventilation (39) thought to operate via baroreceptor unloading. Exercise is also accompanied by a modulation of baroreceptor reflex function, as indicated by microencephalography of muscle sympathetic nerve fibers of the tibial nerve during static handgrip exercise (29). In this study, the sensitivity of the baroreceptor-muscle sympathetic nerve activity reflex was increased by more than 300%. Thus an increase in arterial blood pressure during exercise is associated with a three times greater reduction in sympathetic nerve activity compared with resting conditions. This may be seen as a protective mechanism that buffers the degree of sympathoexcitation evoked by the exercise pressor reflex (22). In this regard, a differential baroreflex regulation of vascular conductance in working (iliac) and nonworking (mesenteric) vascular beds has been reported in rats during dynamic treadmill exercise (32). Under these conditions, an increase in arterial blood pressure caused a greater increase in iliac than in mesenteric vascular conductance. The differential regulation of baroreceptor reflex-mediated control of vascular conductance helps to preserve a proper blood supply of the working skeletal muscle.

Hypovolemia frequently leads to orthostatic dysfunc-
tion, which is a common problem after prolonged bed rest or in astronauts after return from spaceflights (4, 7, 12, 26–28). It has been demonstrated that hypovolemia is associated with a reduced baroreceptor-heart rate reflex and an augmented baroreceptor-muscle sympathetic nerve activity reflex (26). The symptoms of hypovolemia-related orthostatic dysfunction, such as hypotension (42) or a decrease in central venous pressure (18), can be reduced by the application of lower body positive pressure. As assessed by microneurography of the tibial nerve, this maneuver also attenuates the sympathoexcitation associated with orthostatic challenges (16). Thus application of lower body positive pressure normalizes the baroreceptor-muscle sympathetic nerve activity reflex that is often enhanced in patients with orthostatic dysfunction (27).

Knowledge about the neuronal pathways and neurotransmitter systems involved in the adjustments of baroreceptor reflex function to physiological and pathophysiological conditions has increased substantially in the last few years but is still far from being completely understood. Further regulatory, integrative, and comparative studies are needed to address these issues.

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