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Baroreflex control of long-term arterial pressure

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ABSTRACT

The sympathetic nervous system and the kidneys exert considerable influence on the long-term control of blood pressure. The ability of the baroreflex to influence both these systems of arterial pressure regulation via the central nervous system suggests that the baroreflex may contribute to the chronic regulation of mean arterial pressure. The ability of the baroreflex to powerfully buffer acute changes in arterial pressure is well established. Baroreflex -mediated changes in sympathetic nerve activity to the heart and peripheral vasculature counter short-term fluctuations in arterial pressure. While baroreflex -mediated changes in sympathetic nerve activity to the kidney may influence the renin-angiontensin-aldosterone system and therefore may mediate more long-term changes in mean arterial pressure. However, it has been suggested that resetting of the baroreflex in the direction of acute and chronic pressure changes, and the observed effect of sinoaortic denervation on baroreflex indicates that the baroreflex may not be critical for setting the long-term "set point" of arterial pressure.

KEY WORDS

Baroreflex sympathetic nervous system, renin-angiotensin-aldosterone system, hypertension.

INTRODUCTION

Understanding autonomic and reflex control of the cardiovascular system is critical. Neural control of the cardiovascular system is accomplished through the autonomic nervous system, which integrates chemical and mechanical input and regulates efferent sympathetic and parasympathetic tone to target-organs (Figure 1). Blood pressure is affected by baroreflex (BR)-mediated changes in efferent autonomic nerve activity to the heart, kidneys, and other vascular beds. Mechanosensitive baroreceptor neurons constitute the afferent signal of the "BR arc" which consists primarily of arterial, cardiopulmonary, and carotid sinus baroreceptors. Patients with impaired BR function suffer an increase in cardiovascular morbidity and mortality[1]. While BR control of the cardiovascular system is necessary to regulate blood pressure (BP), heart rate (HR), and sympathetic nerve activity (SNA), BR resetting may contribute to the maintenance of hypertensive states. Inappropriate regulation of blood pressure and sympathetic nerve activity is associated with structural and hormonal changes that contribute to the development and progression of cardiovascular disease. In diseases such as hypertension, decreased arterial compliance due to arterial stiffening attenuates baroreceptor stimulation and leads to further dysregulation of BP and SNA.

The afferent signal, central nervous system (CNS) and efferent components of the BR arc will be discussed in this review in the context of resetting and long-term blood regulation. A brief discussion of the mechanisms of baroreceptor modulation and mechanosensation will also be included as it pertains to afferent signaling mechanisms.

Baroreflex arc and resetting

The BR arc consists of an afferent arm, composed of baroreceptors in the heart, lungs, aortic arch, and carotid sinus that sense changes in arterial pressure, which are transduced into a neural signal. The afferent signal is processed and integrated in the

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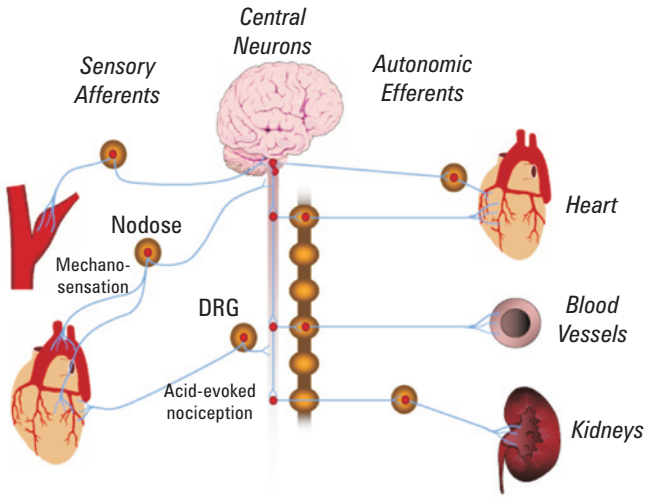
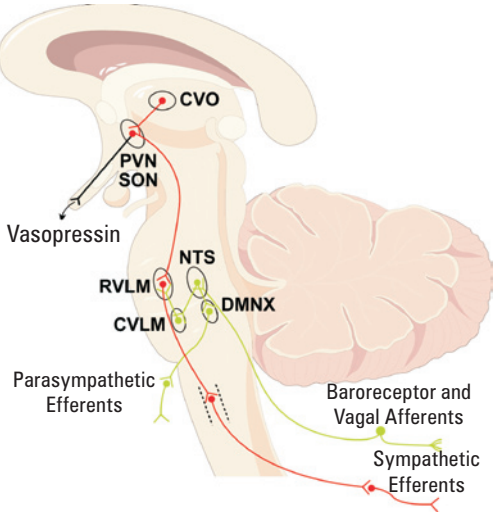


Afferent input from baro- and chemoreceptors contribute to neural control of blood pressure through the regulation of parasympathetic and sympathetic nerve activity. Heart rate, contractility, vasomotor tone, and activation of the renin-angiotensin-aldosterone are regulated by autonomic efferents to target organs.

Figure 1. Neural control of the circulation.

nucleus of the solitary tract (NTS), which influences sympathetic and parasympathetic outflow from the rostral ventrolateral medulla (RVLM) and the dorsal motor nucleus of the vagus (DMNX)[2] (Figure 2). Humoral factors, such as angiontensin II (ANGII), are able to act in circumventricular organs (CVO) and influence the RVLM through the paraventricular nucleus (PVN) and supraoptic nucleus (SON).



Key CNS nuclei: Nucleus tractus solitarius (NTS), caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM), and the dorsal motor nucleus of the vagus (DMNX). Peripheral stimuli can influence BP through interactions with circumventricular organs (CVO), paraventricular nucleus (PVN), and supraoptic nucleus (SON).

Figure 2. Autonomic regulation of BP.

Humans with essential hypertension exhibit impaired baroreceptor reflex control of heart rate[3]. However, the sensitivity of BR control of sympathetic vasomotor tone is not attenuated in individuals with essential hypertension, although it is reset to higher levels of arterial pressure[4]. The permanency, extent, and components of baroreflex resetting are matters of significant debate and recent studies have revitalized discussion on this important question[5,6,7].

It has been postulated that any component (e.g., afferent, central, or efferent) of the BR is able to reset and influence reflex control of BP[5,8,9]. In other words, the afferent signal may become modified in the face sustained of increases or decreases in arterial pressure, the CNS may "re-wire" its connections that regulate sympathethic nerve activity, and/or the amount of SNA to different vascular beds may reset to varying degrees. The degree to which target-organs, especially the kidney, respond to reset reflex control of SNA also helps determine the long-term level of blood pressure and development of hypertension.

The neural contribution to the development of hypertension has been elucidated from early studies using the renal artery clamp-model of hypertension[10]. McCubbin *et al.* concluded that the ability of reflex mechanisms to control sympathetic outflow was impaired. Resetting of the BR operating range was thought to be one of the mechanisms underlying this reflex dysfunction[10]. In discussing the function and dysfunction of the BR it is useful to define its operating parameters and alterations that occur in response to BP changes.

Definitions

- Resetting: refers to the phenomenon whereby the baroreflex operating range and pressure threshold shifts in the direction of the arterial pressure change (Figure 3a).
- Central resetting: refers to functional and/or anatomic changes in the CNS that occur in BR resetting associated with sustained changes in BP; may be quantified using the ratio of baroreceptor input to the amount of efferent SNA
- Efferent resetting: refers to the relative amount of change in efferent SNA as mediated by the CNS in response to reset BR signaling
- Pressure threshold: the arterial pressure at which baroreceptors begin to fire (Figure 3a).
- Resting point: the mean arterial pressure at which the baroreflex maintains its buffering capacity, pressures above this result in reflex inhibition of heart rate and sympathetic nerve activity, pressures below this level result in disinhibition (Figure 3a).

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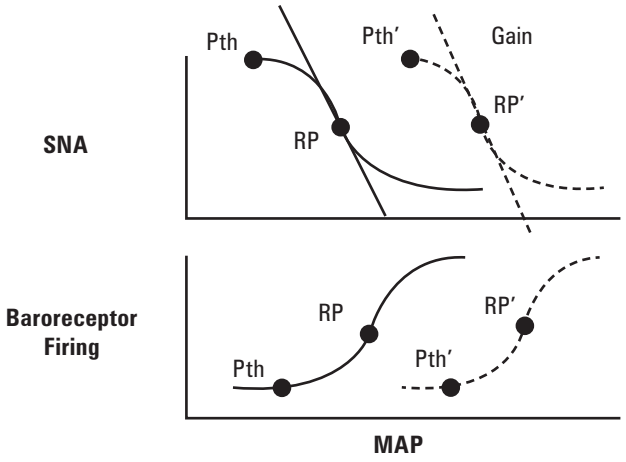
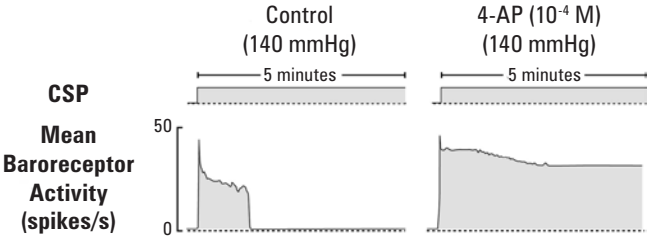


Figure 3a. BR sensitivity or gain is represented by the straight line parallel to the steepest part of the BR curve. Pressure threshold (Pth), reset pressure threshold (Pth'), resting point (RP), and reset resting point (RP') are shown.

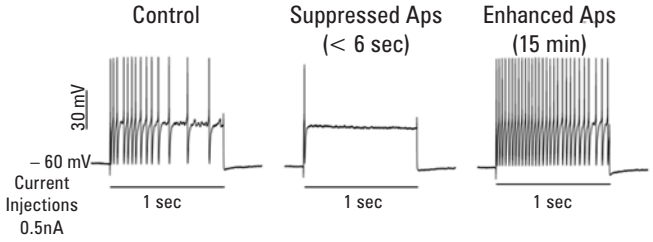
- Baroreflex Gain or Sensitivity: refers to the capacity of the baroreflex to buffer changes in arterial pressure; often depicted graphically as the slope of the relationship between mean arterial pressure and heart rate, sympathetic nerve activity, R-R interval or baroreceptor firing (Figure 3a).
- Adaptation: refers to the phenomenon whereby baroreceptors activity initially increases with a sustained increase in blood pressure but declines (or adapts) over time as the elevated pressure is maintained (Figure 3b).



Decreased responsiveness of a single baroreceptor nerve fiber in response to a sustained increase in arterial pressure. The K+ channel blocker, 4-aminopyridine (4-AP), markedly reduces adaptation[2]

Figure 3b. Adaptation.

- Postexcitatory depression: the suppression, or refractory period, of baroreceptor activity following a period of acute hypertension (Figure 3c).
- Adaptation: refers to the phenomenon whereby baroreceptors activity initially increases with a sustained increase in blood pressure but declines (or adapts) over time as the elevated pressure is maintained (Figure 3b).



The response of isolated baroreceptor neurons (BRNs) to current injection following neuronal activation (NA), which consisted of a current of 1 nA delivered at 20 Hz for 1 minute. Recordings from BRNs reveal generation of action potentials (APs) before NA (control), suppression of APs immediately after NA (middle panel), and recovery with enhancement of APs after 15 minutes in response to the same current injection[11].

Figure 3c. Postexcitatory depression.

- Postexcitatory depression: the suppression, or refractory period, of baroreceptor activity following a period of acute hypertension (Figure 3c).

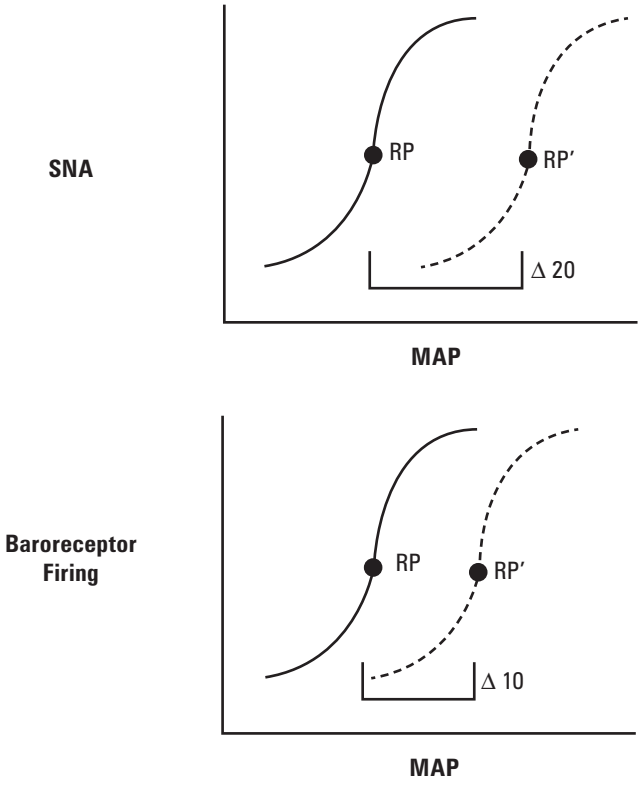
CNS AND EFFERENT RESETTING

Integration and processing of afferent information from pressure-sensing regions of the circulatory system is accomplished in the central nervous system. The NTS is the key brainstem nucleus that responds to afferent baroreceptors signaling. The RVLM and CVLM mediate sympathetic outflow from the CNS mediated by the NTS, humoral factors, and higher cortical regions. Prolonged stimulation of the CNS via baroreceptor afferents, or a sustained absence of baroreceptor input (ie, baroreceptor unloading), may result in remodeling of the neural networks responsible for processing BR input. CNS "rewiring" likely contributes to the resetting, adaptation, and postexcitatory depression of the BR. Given the neural plasticity of the CNS, these changes are likely to be reversible or incomplete, and remain sensitive to changes in afferent signaling.

During exercise, emotional stimuli, and "fight-or-flight" situations the BR reversibly resets[8]. The resetting that occurs in these situations occurs in the CNS and could be due to decreased responsiveness of the autonomic regulation centers (i.e., NTS, CVLM, RVLM) to baroreceptor signaling. Another possibility is that the relative amount of efferent SNA to the peripheral vasculature, heart, and other vascular beds is modulated according to the nature of the stimulus. The transient nature of BR resetting in these settings indicates that alterations in the central components of the BR arc are not related to neuroanatomic changes in the acute settings. Whereas in hypertension and sinoaortic denervation (SAD), as discussed below, resetting may be due to the changing mileu of humoral factors and remodeling of autonomic neural circuitry.

Resetting of CNS components of the BR arc may be deleterious. For example, the shift in magnitude of the arterial

pressure-SNA relation after acute changes in arterial pressure may be greater than the shift in the arterial pressure-baroreceptor activity relation[8] (Figure 4). A central mechanism is presumably responsible for overriding the relatively preserved afferent baroreceptor input, thereby permitting sympathetic activity to "escape" BR-mediated inhibition[8,12]. CNS resetting results in impaired regulation of SNA and likely contributes to chronic elevations in mean arterial pressure (MAP) in the setting of BR dysfunction; however, resetting preserves buffering of SNA in response to acute pressure changes. The regulation of efferent SNA by the CNS may be influenced by not only baroreceptor afferent signaling, but also by other effectors of centrally-mediated SNA. Circulating hormones and other central stimuli may serve as pathophysiologic signals to the CNS that, in combination with remodeling of central neural circuitry, may generate changes in the BR control of sympathetic and parasympathetic responses.



Baroreceptor firing is near saturated at the resting point of the reset MAP-SNA curve. CNS resetting permits SNA to remain elevated in the setting of relatively preserved BR afferent signaling.

Figure 4. Central resetting and sympathetic escape.

In addition to alterations in the processing of the afferent signal, central resetting may also influence the relative amount of efferent SNA. CNS-mediated changes in efferent SNA, as regulated by the BR, appears capable of differential resetting with respect to the target-organ of SNA. For example, in the animal model of angiotensin II-mediated hypertension, BR control of SNA to the heart may reset while BR control of SNA to the kidneys may resist resetting[5]. Decreased SNA to the kidneys results in decreased activation of the renin-angiotensin-aldosterone (RAA) system, and subsequently decreased fluid retention, cardiovascular remodeling, and activation of peripheral sympathetic efferents. As opposed to the harmful effect of sympathetic "escape" mentioned above, CNS changes that result in restraint of RAA system activation serve to attenuate the development of hypertension and limit cardiovascular remodeling. In the study by Barrett *et al.* described below, changes in BR control of SNA to the kidney and heart may represent an attempt by the autonomic nervous system to decrease activation of the renin-angiotensin system yet maintain acute buffering of BP with changes in HR.

In lean and obese hypertensive patients, SNA is elevated to the heart, muscle and kidneys; obese individuals without hypertension, on the other hand, have elevated SNA to skeletal muscle and kidneys but suppressed levels of cardiac SNA[13,14]. The differing amount and type of SNA in these populations likely reflects central and efferent changes in the BR arc and its CNS neural circuitry. Long-term blood pressure control and target-organ damage is critically influenced by the relative amount of SNA to these efferent sites.

Evidence of CNS resetting of sympathetic and parasympathetic responses has been elucidated from a variety of experimental techniques. Electrical stimulation and pressure-induced stimulation of baroreceptor afferents in animal models allow for the study of not only peripheral but also central resetting, particularly in the case of direct electrical stimulation[8]. The experimental preservation of the afferent signal demonstrates that the CNS is capable of resetting the degree of efferent SNA outflow partly independent of afferent input.

Electrical modulation of the baroreflex

Using chronic baroreceptor electrical activation in dogs, Lohmeier *et al.* demonstrated that central or efferent components of the BR resist resetting[15]. Lohmeier *et al.* utilized bilateral carotid sinus stimulation to maintain a quantifiable afferent stimulus to the CNS. While direct stimulation of the carotid sinus bypasses the pressure-encoding step of the BR, this technique permits indirect examination of the central and efferent components of the BR arc.

In Lohmeier's study, 7 days of carotid stimulation resulted in significant reductions in MAP and HR for the duration of electrical stimulation indicating that the BR did not reset[15]. Plasma NE concentration was also reduced consistent with inhibition of the sympathetic nervous system. Furthermore, urinary sodium excretion remained at control levels suggesting that renal excretory

function was enhanced. Maintaining a constant level of sodium excretion during the hypotension produced by carotid stimulation, requires a shift in pressure natriuresis to a lower pressure. In addition, plasma renin activity (PRA) did not increase throughout the duration of stimulation. Enhanced renal excretion of sodium and a constant level of PRA suggest a decrease in Renal SNA (RSNA) and associated activation of the RAA system[6].

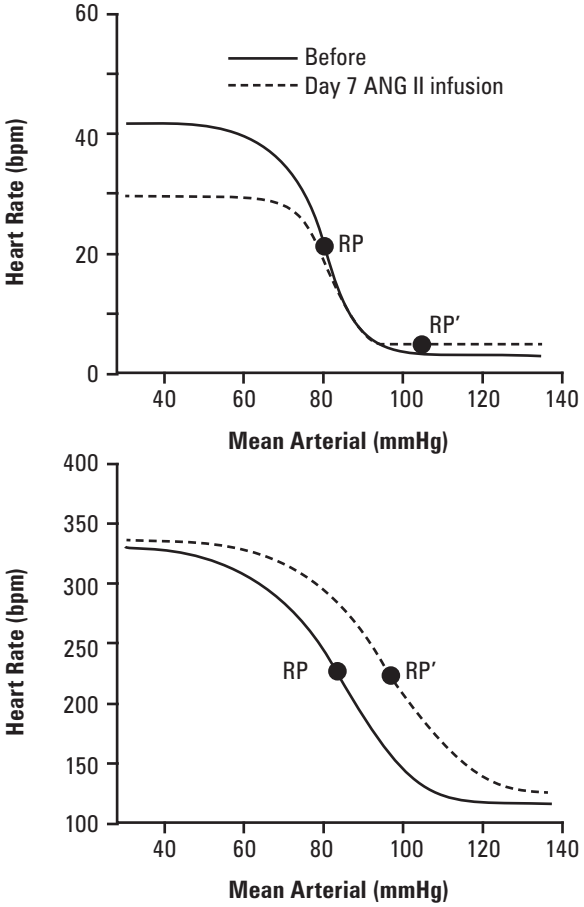
Because Lohmeier *et al*. did not directly record efferent SNA (i.e. RSNA) it is not possible to precisely determine what component of the BR did or did not reset. However, the experiment provides important clues as to contribution of the BR in the long-term control of BP, in particular the CNS components of the BR arc that may resist resetting. Of particular relevance to this review, is the observation that BR control of MAP did not reset during the period of carotid sinus stimulation, and presumably decreased activation of the RAA system via BR-mediated inhibition of RSNA contributed to the sustained reduction in BP.

Preliminary studies in humans indicate that prolonged BR activation using carotid sinus stimulation shows promise for the treatment of refractory hypertension. The use of internally implanted carotid sinus stimulation devices has been shown to be technically feasible, and a reliable means of lowering BP in patients with drug-resistant forms of hypertension. The Rheos Feasibility Trial examined ten patients implanted with carotid sinus stimulation devices and resistant hypertension on a mean of 6 $\pm$ 1 antihypertensive medications. BR activation resulted in a drop in BP from 188 $\pm$ 31/105 $\pm$ 19 to 140 $\pm$ 40/77 $\pm$ 28 mmHg with a fall in HR from 83 $\pm$ 11 to 73 $\pm$ 13 without symptomatic hypotension, prolonged bradycardia, or heart block during activation. While these studies are still in their early phases, the prospect of utilizing prolonged BR activation in clinical practice is extremely encouraging[15,16].

Mechanical modulation of the baroreflex

The efferent components (sympathetic and parasympathetic nerve activity) of the BR arc have been observed to exhibit differential resetting in the setting of experimental models of hypertension. In the renal artery clamp rabbit model of hypertension, BR control of RSNA was reset at 3 wk after clamping but not 6 wk. BR control of HR, however, was observed to have reset at both time points[17]. Using L-NAME, a nitric oxide synthase antagonist, or volume expansion, to increase arterial pressure results in greater reductions of RSNA than Lumbar SNA (LSNA) in rabbits presumably through a BR-mediated mechanism[18]. The difference in the time and extent of BR resetting likely reflects the central modulation of afferent signal processing and efferent SNA trafficking.

ANGII infusion-induced hypertension is another modality of examining the pressure-induced stimulation of the BR and central resetting. Barrett *et al.* provide further evidence of differential and incomplete resetting using ANGII infusion for a period of 1 wk[19]. As arterial pressure increased with ANGII infusion, equivalent resetting of all BR efferent components was not observed. BR control of HR was reset, however BR control of RSNA did not appear to reset (Figure 5). Barrett *et al.* concluded that ANGII-induced hypertension resulted in baroreflex-dependent sympathoinhibition of RSNA in agreement with a previous study by Carroll *et al*.[20] who measured renal NE spillover. Central remodeling of neural networks in the BR arc may have preserved BR buffering of HR by maintaining the BR resting point on the steepest part of the curve, while sacrificing the ability of BR to acutely buffer RSNA. By resisting resetting to a higher pressure, the BR is able to suppress the more powerful regulator of long-term blood pressure, the RAA system, via BR-mediated sympathoinhibition.



Solid line: before ANG II infusion. Dashed line: after 7 days of ANG II.
Adapted from Barrett *et al.*[19]

Figure 5. BR control of RSNA does not exhibit classic resetting. The resting point of the MAP-RSNA relationship is moved along the curve to a higher pressure but the curve is not shifted in the direction of the pressure change (*top*). BR control of HR is reset as demonstrated by a shift in the resting point of the MAP-heart rate relationship (*bottom*).

Thus, central and efferent components of the BR arc may reset differently and be more or less responsive to various stimuli. With respect to the clinical significance of differential resetting, baroreflex control of sympathetic activity may be preserved despite a significant decrease in baroreceptor afferent sensitivity in hypertension and heart failure[21, 22, 23, 24]. The discrepancy in sympathoinhibition between the varying pathophysiologic stimuli may be due to the effect of humoral factors. ANGII and aldosterone, for example, may alter responsiveness of central neural circuitry in the BR arc. The CNS is capable of tremendous adaptations in response to changes in afferent signaling and circulating humoral factors. Altered responsiveness of central components of the BR arc may compensate for decreased BR sensitivity as observed with reflex control of RSNA, or alternatively contribute to reflex dysfunction as observed with reflex control of HR[21,22,24,25].

Humoral modulation of the baroreflex

A number of humoral factors may act centrally to influence the CNS response to baroreceptor input as well as directly influence the behavior of the baroreceptors themselves. Arginine vasopressin (AVP), aldosterone, and ANGII are hormones that act in the CNS in the area postrema (AP) and peripherally on baroreceptors to influence arterial pressure regulation and SNA. While AVP has beneficial effects on BR function, ANGII attenuates BR control of heart rate and causes sympathoexcitation[26]. Interestingly, it has been observed in the renal artery clamp model of hypertension that inhibition of ANGII synthesis with captopril returned BR control of LSNA to lower arterial pressure. In addition, lifetime treatment of spontaneously hypertensive rats (SHR) with captopril increased BR sensitivity with respect to HR and LSNA[27,28]. Furthermore, selective inhibition of type 1 ANG II receptors in the NTS increased the sensitivities for BR control of RSNA and HR in SHR and control (WKY) rats[29].

Individuals with congestive heart failure (CHF) exhibit BR dysfunction as well as excess circulating ANGII and aldosterone as well as increased production of reactive oxygen species (ROS). Aldosterone administration has been shown to impair BR control SNA and HR in humans[30] and animals[31,32]. Increased production of reactive oxygen species in heart failure, such as superoxide, may combine with nitric oxide (NO) reducing the NO-mediated production of prostacyclin[33]. The effect of prostacyclin on the baroreflex has been demonstrated in isolated carotid sinus preparations and in isolated baroreceptor neurons[11,34]. It has been hypothesized that reduced synthesis of neuronal prostacyclin contributes to the resetting phenomenon and the suppressed activity of arterial baroreceptors in hypertension[11].

Bradykinin is also able to exert an effect on the baroreflex. Bradykinin B2-receptor (B2R) knockout mice had higher BP and HR and lower baroreflex sensitivity under basal conditions when compared to the wild-type mice[35]. Furthermore, human polymorphisms in the B2R gene has been shown to be associated with decreased baroreflex sensitivity due to a presumed reduction in bradykinin effect[36].

Serotonin released from activated platelets in the carotid sinus has also been shown to affect baroreceptor function. Activated platelets in the carotid sinus rapidly increase the activity of type II baroreceptors (containing primarily C fibers) through the release of serotonin. This results in reflexive abolishment of SNA and profound hypotension[37,38].

The relevance of these humoral factors in the discussion of baroreflex resetting can be understood in the context of pathologic conditions such as hypertension and heart failure. In hypertension, the use of ACE inhibitors decreases the production of ANGII and is associated with improved HR variability and BR sensitivity[38,39,40]. In patients with heart failure, the use of ACE inhibitors and aldosterone antagonists improve HR variability, and is associated with improved survival[41,42]. Thus, pharmacologic manipulation of these humoral factors not only contributes to reversal of BR dysfunction but may also improve survival.

AFFERENT RESETTING

McCubbin *et al*. first demonstrated that the afferent signal produced by the BR resets in response to prolonged changes in arterial pressure[10]. Direct recordings from the carotid sinus nerve and aortic depressor nerve revealed that hypertensive dogs have a higher threshold (Pth) to produce baroreceptor firing 1-3 days after clamping the renal artery. It was hypothesized that BR suppression of SNA was insufficient to completely eliminate sympathetically mediated vasoconstriction. McCubbin *et al*. concluded that resetting of the BR operating range occurred resulting in impaired buffering (loss of BR gain or sensitivity) and a shift in the set point (resetting) of MAP in chronic renal hypertension. Resetting of the BR results in impaired regulation of BP and SNA, however it has been noted that resetting of the afferent signal may be incomplete. The shift in threshold pressure (Pth) for baroreceptor activation has been observed to be less than the change in MAP indicating a relative preservation of BR opposition to increases in SNA and BP[43] (Figure 6). Although resetting may not be incomplete with respect to Pth, complete resetting of the RP contributes to the maintenance of the hypertensive state. Increases in MAP above the RP quickly leads to saturation of BR firing and decreases the ability of the BR to inhibit SNA and attenuate further elevations in MAP. In addition, McCubbin *et al*. reported that the response to carotid occlusion, or baroreceptor unloading, in animals with renal hypertension was preserved suggesting that any resetting that occurred is not likely to be complete.

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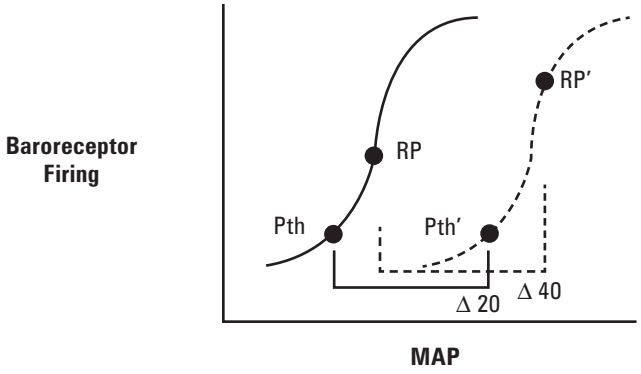

The extent of resetting may differ with respect to the pressure threshold (Pth) of BR activation and resting point (RP). While afferent BR signaling may be relatively preserved due to incomplete resetting of Pth, complete resetting of the RP contributes to the maintenance of the hypertensive state.

Figure 6. Incomplete resetting.

Baroreceptor unloading

Occluding the internal carotid artery causes baroreceptor "unloading" resulting in a perceived drop in pressure by the BR. In a novel study design by Thrasher, dogs underwent unilateral carotid occlusion by ligating the common carotid artery and denervating the contralateral carotid sinus and aortic arch resulting in the development of neurogenic hypertension[44]. The increase in systemic MAP observed by Thrasher did not depend on chemoreceptor stimulation, because there was no difference between dogs with denervated chemoreceptors and dogs with functional chemoreceptors on the innervated side. With respect to resetting, this model permits examination of the BR response to prolonged decreases in arterial pressure, and provides insight into the incomplete and reversible nature of afferent resetting.

Thrasher *et al*. observed that MAP returned to basal levels relatively rapidly after removal of carotid ligation, suggesting that the afferent signal did not completely reset[44]. During carotid ligation, the resultant sustained elevation in MAP indicates that the BR is capable of influencing the long-term regulation of MAP. It is noteworthy to point out that in contrast to the work by Lohmeier *et al*. described below, Thrasher's work did not bypass the afferent pressure-encoding step of the BR arc. This aspect of Thrasher's experimental model provides the opportunity to indirectly study the afferent signal. However, one cannot exclude the possibility that the efferent and CNS components of the BR arc may have also resisted complete resetting in the chronic unloading model.

Thrasher's experiments demonstrate that baroreceptor unloading can generate an increase in MAP (20-30 mmHg rise) that is reversed when the ligation is removed. Therefore, when the pressure sensing regions of the carotid sinus sense a chronic (7 days) drop in pressure, resetting may not occur and may be reversible as evidenced by the post-ligation response. Extending the period of ligation to 5 weeks revealed that the increase in MAP observed during the first 7 days was not sustained[45]. After the first week of ligation, MAP gradually declined to and stabilized at about 10 mmHg above control during the final 2 weeks. This reduction in MAP is likely due to either resetting of the BR and/or vascular adaptations that permit adequate delivery of the cardiac impulse to the carotid sinus with subsequent BR activation[45].

Pulsatile pressure

In Thrasher's study, carotid sinus pressure (CSP) was not different from controls and thus the afferent stimulus was presumably not different. However, animals with carotid ligation exhibited a 50% reduction in pulsatile pressure in the carotid[44]. The reduction in pulsatile pressure delivery to the carotid sinus may account for the partial resetting and subsequent decrease in MAP over the 5-week period. Chapleau *et al*. previously demonstrated that the maintenance of elevated pulsatile pressure stimuli results in attenuation of BR resetting when compared to an elevated static pressure stimulus[46]. A study by Chan *et al*. utilized nocturnal hemodialysis in end-stage renal disease patients to increase arterial compliance and therefore the pulsatile pressure stimulus sensed by baroreceptors. The restoration of the pulsatile stimulus translated into increased BR sensitivity and reversal of BR resetting to the prevailing pressure established by the nocturnal hemodialysis[47]. While BR resetting was observed in Thrasher's study, the persistence of a pulsatile stimulus, albeit reduced, may have prevented complete BR resetting. It is interesting to consider the possibility that the BR may have not reset had pulsatile pressures not been reduced[44,45].

The varied nature of BR resetting in response to static vs. pulsatile stimuli is reflected in the different fiber types that compose baroreceptor afferents, A- and C-fibers. The A-fibers fire more frequently and have a lower pressure threshold than C-fibers[48]. At normal resting pressures, the majority of A-fibers are firing while most C-fibers are inactive[49]. Seagard *et al*. observed that A-fibers are more likely to reset in response to initial change in pressure, since they appear to respond to the acute pressure changes. Conversely, C-fibers will not reset in response to acute changes in pressure, presumably because their primary role is to maintain consistent information on the level of existing pressure[50]. Further, many of the baroreceptor afferents communicate with the CNS via the unmyelinated C fibers[50]. The activity of these unmyelinated fibers may therefore be more critical in effecting prolonged changes in SNA and arterial pressures[51].

It is possible that certain physiologic conditions (i.e. preservation of pulsatile stimuli) exist whereby resetting resist resetting,

and therefore are able to restrain SNA and further elevations in MAP. The ability of baroreceptors to return to their pre-reset reflex parameters is also an important factor in the ability of the BR to contribute to long-term BP control. The reversibility of baroreceptor afferent signal resetting may be related to the duration of exposure to changes in blood pressure. Acute resetting of the BR has been observed to occur within minutes of changes in blood pressure[43,49,52-54]. Acute resetting is fully reversible and is characterized by a shift in the Pth that is stable for at least an hour without a change in BR sensitivity[43]. However, chronic resetting is accompanied by a shift in Pth, as in acute resetting, but is not entirely reversible and is characterized by a decreased sensitivity of the BR[54]. It has been suggested that the mechanisms underlying acute and chronic resetting may be different[7], which may reflect underlying cellular and molecular changes in baroreceptor mechanosensation.

Mechanisms of baroreceptor resetting and mechanosensitivity

A number of different mechanisms for BR resetting have been proposed. BR resetting depends on the ability of baroreceptors to detect sustained changes in mechanical stimulation. Baroreceptors possess mechanosensitive molecular complexes that are responsible for sensing changes in blood pressure in the pressure-sensing regions of the vasculature. The arterial compliance of these pressure-sensing regions and the resultant amount of pulsatile pressure is critical in BR as mentioned above. Furthermore, changes in the molecular transduction molecules of baroreceptors are likely to occur during resetting, and thus it is critical to understand the molecular mechanisms of mechanosensation.

The following vascular, mechanical, neural, molecular, and paracrine mechanisms affect the properties of baroreceptor activation, including resetting, adaptation, postexcitatory depression, and mechanosensation[2]:

Mechanical

Vascular compliance

Vessel compliance determines the extent of distention for given increase in pressure. This distention is translated into an electrical signal by activation of baroreceptors through mechanical deformation of their nerve endings and molecular transduction molecules. Baroreceptor activation is therefore impaired with decreased vessel compliance (as occurs in atherosclerosis, hypertension, and aging) due to reduced vessel distention and resultant baroreceptor deformation[55,56].

Viscoelastic relaxation

Vessels progressively distend as elevated arterial pressures are maintained leading to relaxation of elements responsible for transmitting pressure through the vessel wall to baroreceptors. This relaxation reduces the tension transmitted to the nerve ending despite increased vessel diameter[57]; since the baroreceptors "sense" a decreased pressure, their buffering capacity is reduced.

Destruction of baroreceptors

Loss of baroreceptor nerve terminals in pressure-sensing regions (i.e., aortic arch, carotid sinus, etc.) reduces the integrity of the afferent signal[58,59].

Molecular

Na+ Pump Activation

Increased arterial pressure and subsequent baroreceptor depolarization due to Na+ influx activates an electrogenic Na+/K+ pump that causes membrane hyperpolarization of the baroreceptor and postexcitatory depression[60,61,62].

K+ Channel

The K+ channel blocker 4-aminopyridine (4-AP) reduces the magnitude of baroreceptor adaptation when injected into the carotid sinus[60,63]. Polymorphisms in large-conductance, voltage and Ca++-sensitive potassium channels (BK) have been shown to influence heart rate variability and baroreflex function in humans[64]. Mice lacking the beta1 subunit of the BK channel are hypertensive and have a reset baroreflex[64,65].

Intrinsic properties of baroreceptors

Genetically determined variations in the expression of baroreceptors, including Na+/K+ channels and/or the molecular subunits that comprise the pressure-sensing components of the nerve endings affect mechanotransduction and therefore influence resetting. Genetic disruption and polymorphisms of suspected components of the baroreceptor complex have offered insight into the molecular composition of the baroreflex complex and determinants of baroreflex sensitivity[66,67,68]. The DEG/ENaC family of ion channels, which in mammalians includes epithelial sodium channels (ENaC) and acid sensing ion channel (ASIC), has been implicated in the mechano- and chemosensitivity of baro- and chemoreceptors, respectively[68]. Mutations in these channels have been associated with channel dysfunction and hypertension in humans[67,69,70]. ENaC subunits have been localized to the kidney and baroreceptor afferent nerve terminal where they mediate sodium reabsorption and mechanosensation, respectively[58]. Liddle's syndrome is associated with a mutation in the beta subunit of ENaC that results in inappropriate sodium reabsorption and hypertension[59]. It may be speculated that baroreceptor sensitivity and resetting are affected in Liddle's syndrome.

ASIC subunits have been found in DRG neurons of rats, the mechanosensitive regions of the aortic arch, and nodose neurons of mice[68]. Disruption of the ASIC2 subunit in mice produces significant impairment of the baroreflex and mild hypertension[71]. However, baroreceptor responsiveness to the

initial rise in pressure in ASIC2 null mice was not impaired suggesting that baroreflex resetting may be premature or pressure-transduction may be exaggerated in these animals compared to the wild-type[72]. Preliminary data from ASIC1 null, ASIC2 null, and ASIC3 null mice suggests that ASIC2 provides a major role for baroreceptor mechanoelectrical transduction, ASIC1 and ASIC3 contribute to chemoreflex activation, and disruption of ASIC2 may result in augmented expression of ASIC1 and ASCI3 chemosensitive subunits[68]. This augmented chemosensation mirrors the cardiovascular responses in individuals with obstructive sleep apnea (OSA) and heart failure, wherein they exhibit an impaired baroreflex and an enhanced chemoreflex response to hypoxia.

Humoral factors

The effect of ANGII has been indirectly by demonstrating that angiotensin converting enzyme inhibitors (ACEI) lower the pressure threshold of baroreceptor activation. Vasopressin acts in the area postrema to cause a decrease in the threshold (Pth) for baroreceptor activation and sympathoinhibition. Arachidonic acid derivatives, such as prostacyclin, peptides, such as bradykinin, and serotonin have also been shown to play an important role in influencing baroreceptor sensitivity. Further discussion of this matter is provided below[8,26].

There is some evidence to suggest that these mechanisms may differentially influence the characteristics of baroreceptor resetting. For example, it has been proposed that the shift in the Pth, or threshold for baroreceptor activation, is more directly related to the pressure to which the receptors are exposed. Changes in baroreceptor sensitivity, however, are likely to be related to the distensibility of the vessel wall and structural characteristics of the cardiovascular system[7,73-77]. Na+ pump inhibition with oubain or low K+ solutions prevents or attenuates postexcitatory depression and resetting, but not adaptation of baroreceptor firing[60,61,62]. The K+ channel blocker, 4-AP, attenuates adaptation of baroreceptors but not resetting after a period of acute hypertension[63]. Baroreceptor resetting, adaptation, and postexcitatory depression appear to be mediated by different mechanisms. Therefore, the ability of the BR to buffer acute or chronic changes in MAP may depend on which components of afferent signal are changed and whether or not they are reversible, including molecular components and transduction mechanisms.

Sinoaortic denervation

Denervation of carotid sinus and aortic arch baroreceptors, or sinoaortic denervation (SAD), results in a transient increase in arterial pressure and SNA in animal models. The arterial pressure and SNA eventually return to normal, or near-normal, levels. However, humans without adequate baroreceptor restraint of SNA may manifest BR failure. This clinical condition is characterized by recurrent bouts of unrestrained sympathetic excitation with severe hypertension, headache, and diaphoresis[78]. Thus, while long-term arterial pressure and SNA may be normalized in the absence of the BR, acute fluctuations in arterial pressure and SNA persist. It would seem that the normalization of MAP seen in chronic SAD argues against a role for the BR in the regulation of long-term BP control, however, inferences made from SAD models may not be entirely applicable to the state of BR dysfunction seen in human pathologic states. The normalization of long-term arterial pressure may not reflect the changes that occur in human disease since there is complete loss of baroreceptors in SAD as compared to the resetting and loss of BR gain in hypertension.

Animal Models

Early animal studies support the notion that removing the inhibitory influence of the BR causes an increase in MAP and SNA[78]. Later it was observed that the increased MAP was mostly the result of marked fluctuations in MAP caused by environmental stimuli. Yet it has been shown that dogs with SAD have a modest increase (10 mmHg) in MAP when compared to control animals[79]. The increased variability that persists following SAD seems to be the characteristic feature of removing BR buffering, whereas the initial increase in MAP and SNA following SAD has generally been regarded as transient or of small magnitude.

The mechanism underlying the normalization of MAP and SNA after SAD is not entirely clear. Cardiopulmonary receptors were thought to be responsible for returning MAP towards basal levels in SAD animal models. However, continuous recordings of MAP in combined SAD and cardiopulmonary receptor denervated (CPD) animals revealed that MAP was not increased compared to control animals[80]. However, the effect of SAD+CPD on SNA was not documented in the Just *et al*. study, raising the possibility that SNA may be elevated with combined SAD+CPD.

Loss of input from baroreceptor afferents may result in central remodeling of neural pathways involved in the BR arc, as discussed above[7]. Producing a lesion in the NTS of SAD rats does not affect MAP whereas in control rats, NTS lesions produce acute hypertension[81]. This observation suggests that CNS remodeling may have permitted BP regulatory systems to exclude the NTS and its afferent BR input in the regulation of MAP. Thus, CNS remodeling may allow control of arterial pressure to occur without input from afferent reflex mechanisms, and therefore without the usual inhibition of SNA via the NTS. This remodeling is thought to involve GABA-mediated inhibition of the NTS based on the observation that bicuculline microinjection into the NTS of SAD rats causes hypotension but only a small decrease in MAP of control animals[82].

SAD in the context of ANGII-induced hypertension has also provided some helpful clues as to the contribution of the BR in the long-term control of arterial pressure. Using sodium excretion as an index of RSNA in a SAD dog split bladder preparation with one denervated kidney, Lohmeier *et al*. demonstrated the critical role of the BR in the inhibition of RSNA[83-86]. Consistent with observations made in a NE infusion model of hypertension, Lohmeier *et al*. found that sodium excretion was greater from the innervated kidney compared to the denervated kidney in dogs with intact baroreceptor afferents[83-85]. This suggests that BR-mediated sympathoinhibition of the renal nerves acted to decrease salt retention and presumably RAA activation in animals with an intact BR.

The studies by Lohmeier *et al*. are supported by the observation that in chronic SAD rats, lumbar SNA (LSNA) and HR were increased during ANGII infusion compared to the decreased LSNA and HR in the baroreceptor intact state[85,86]. While it appears that the BR is capable of attenuating SNA (renal, cardiac, and lumbar), MAP was not statistically different between SAD and intact animals. In the setting of ANGII infusion, the BR may act to suppress RSNA, and therefore promote sodium excretion and influence long-term levels of fluid balance, but the effect on MAP may be negated by the direct vasoconstrictive and sympathoexcitatory effects of ANGII.

Human Studies

The effect of removing carotid baroreceptors in humans has been studied in the context of therapeutic removal of the carotid sinus for asthma, neck/chest irradiation, and surgical removal of tumors associated with the carotid body[77,87-90]. Holton *et al*. observed that individuals with surgically resected carotid bodies had elevated MAP for more than a year after surgery. The subjects also had an absent HR response to passive tilt testing, which was restored 12-30 weeks following surgery. Smit *et al*. found that three out of four subjects with bilateral carotid body resection had elevated daytime MAP and had impaired responses to orthostatic stress and Valsalva maneuver. These subjects also had increased MAP variability for 3 months to 2 years after surgery. Timmers *et al*. also studied normotensive subjects with bilateral carotid body resection 4-20 years earlier who did not show signs of baroreflex failure. The study found decreased HR responses to administration of vasoactive drugs compared to age-matched controls. BR control of muscle SNA in response to baroreceptor unloading (e.g. sodium nitroprusside) was impaired but was not different from control during baroreceptor loading (e.g., phenylephrine). The autonomic control of blood pressure is clearly affected by manipulation of the carotid sinus pressure-sensing regions. The extent and permanence of these changes is unknown, however the pathology associated with perturbations in the carotid sinus baroreceptors underlines the importance of the BR in the long-term control of MAP.

Sharabi *et al*. recorded HR responses to vasoactive drugs in three individuals with baroreflex failure who had undergone neck irradiation. These subjects exhibited chronic orthostatic intolerance and labile hypertension. BR-mediated changes in HR were absent in response to sodium nitroprusside or phenylephrine. In addition, 24-hour ambulatory blood pressure measurements demonstrated elevated systolic pressures and MAP with increased variability. Furthermore, two of the subjects also had an elevated average HR. Intact sympathetic efferent function and parasympathetic control of HR were established using cold stress test and spectral analysis, respectively. It was also demonstrated using ultrasonography that these subjects had significant atherosclerotic narrowing of the carotid artery bifurcation and bilateral intimal thickening in the region of the carotid sinus. Thus, it was not possible to attribute all of the impairment in BR-control of HR and MAP to the absence of carotid sinus baroreceptors due to the reduced vascular compliance.

In the case of carotid body removal or damage in humans, the extent of baroreceptor denervation is likely not complete. Removal of the carotid sinus alone does not remove the influence of aortic arch or cardiopulmonary baroreceptors. Further, resection of carotid body associated tumors may not completely destroy carotid sinus baroreceptors; rather they may only be damaged. Animal studies with SAD demonstrate that the CNS is able to compensate for the absence of baroreceptor input by tonically inhibiting the NTS from higher order structures or by developing entirely new neural circuitry. The reorganization of the CNS seen in SAD animal models, and the questions surrounding human models of baroreceptor denervation, suggest that these studies may not provide the necessary information to understand the consequence of chronic baroreceptor unloading.

BAROREFLEX FUNCTION AND ANTIHYPERTENSIVE THERAPY

Antihypertensive therapy is associated with improvements in reflex control of circulation[76,91-96]. Improved baroreflex buffering of HR in essential hypertension appears to occur with long-term treatment, while resetting reversal can occur quickly and independently of the type of antihypertensive agent[4,76]. This suggests that impaired baroreflex buffering results from structural changes that occur with longstanding hypertension, while resetting of the baroreflex occurs due to the nonspecific effect of a relative rapid fall in blood pressure[76].

Impaired baroreflex control of SNA is thought to contribute to increased activation of the RAA system, less effective regulation of blood pressure and volume, and subsequently increased MAP[76]. These changes in cardiovascular reflex control are

associated with the development and progression of left ventricular hypertrophy, vascular remodeling, vascular hypertrophy, and atherogenesis[76,92-96]. Thus it is critical for antihypertensive treatment to not only lower blood pressure but also to reduce SNA via improved BR control[76,92,93].

Different antihypertensive agents are able to regulate both BP and SNA to varying degrees. A recent paper by Grassi *et al*. summarizes the effect of several classes of antihypertensive drugs on muscle SNA in hypertensive patients complicated or uncomplicated by obesity or renal insufficiency: (1) diuretics or long-term calcium

antagonists may have neutral effects on muscle SNA or may even trigger a sympathoexcitation, (2) beta-blockers, central sympatholytic agents, drugs acting on the RAA system, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, may produce inhibition of muscle SNA[76,93]. Questions remain with respect to the sympathoinhibition observed with antihypertensive therapy: (1) is SNA to the kidney and heart also affected?, (2) does the time course of decreased muscle SNA correspond more closely with improved baroreflex buffering or resetting reversal?, and (3) what is the relative contribution of central vs. peripheral sympathoinhibition?

SUMMARY

The character of BR resetting influences the extent to which BR dysfunction affects long-term BP regulation

The reversible and incomplete nature of BR resetting suggests that the BR continues to oppose further elevations in blood pressure even in the setting of established hypertension. Central components of the BR arc are influenced by the nature and duration of the hypertensive stimulus. Electrical and mechanical modulation of the BR has shown that CNS components of the BR arc may be reversibly or incompletely reset. The seminal work of McCubbin, Thrasher, and others has demonstrated that resetting of the BR afferent signal may also be reversible and incomplete. Efferent SNA and HR control may be affected differentially by BR dysfunction depending on the extent of afferent signaling dysfunction and circulating humoral factors. The continued ability of the reset BR to attenuate RAA activation via RSNA inhibition in the setting of BR dysfunction (e.g., hypertension, aging, heart failure) demonstrates the critical role of the BR in regulating long-term BP levels.

Baroreflex-mediated inhibition of renal sympathetic nerve activity

BR-mediated inhibition RSNA is an important determinant of long-term arterial pressure regulation. The baroreflex may contribute to the maintenance of hypertension in that reflex control may reset to a higher operating range and thus does not oppose the chronic elevation of BP. However, BR-mediated inhibition of RSNA appears to represent the contribution of reflex mechanisms in the control of long-term BP. Decreased RSNA is of critical importance in maintaining fluid balance and preventing pathologic activation of the RAA system and further elevation of BP.

The afferent signal and mechanosensation/transduction

The production of the neural signal produced by baroreceptors requires the mobilization and coordination of pressure-sensing and transduction molecules, ion channels, vascular, and cellular structural components. These intrinsic elements of baroreceptors may be altered by molecular (e.g., up- and downregulation of ASIC channels) and circulatory (e.g., vascular remodeling) changes in pathologic states such as hypertension. The influence of the BR on long-term BP regulation may critically depend on the molecular and structural mechanisms responsible for BR signal generation. Further experiments are needed to examine these transduction and signal generating mechanisms to understand the molecular substrates that modify the process of resetting.

The application of the sinoaortic denervation model to pathophysiologic states

Denervation of baroreceptors allows us to understand acute loss of BR input to the CNS. However, a number of issues surrounding the SAD model may limit the utility of these experiments in our understanding of the long-term loss of BR input and BP control. While it has been observed that BP essentially returns to normal after chronic SAD, nonneural (humoral) and neural (CNS remodeling) compensatory changes may occur that contribute to the normalization of arterial pressure in the absence of baroreceptor input. In addition, the information obtained from SAD and CPD models may not be entirely representative of pathologic conditions in which BR dysfunction exists.

The baroreflex, blood pressure variability, and end-organ damage

The role of the BR in long-term BP regulation is clearly still under investigation. In the context of this discussion, it is crucial to note that variability in BP, in addition to a stable elevation in MAP, is also associated with end-organ damage. Increasing evidence suggests that the[97-101]. BP level itself is not the exclusive determinant of hypertensive end-organ damage A number of animal studies suggest that blood pressure variability (BPV) is closely correlated with end-organ damage in aged spontaneously hypertensive rats and pharmacologic reduction of BPV can attenuate organ damage[102,103]. Increased BPV alone without hypertension can also cause organ damage in normotensive Sprague-Dawley rats[102, 104-106]. Furthermore, animal studies have shown that BR sensitivity (i.e., BPV) is an independent variable that can influence organ damage in hypertension[107]. In fact, SAD has been observed to cause arterial remodeling associated

with an increased BPV and activation of the RAA perhaps due to deficient BR control of RSNA[106].

THE BR ARC AND THE NEURAL SET POINT OF LONG-TERM BP REGULATION

A number of arguments have been put forth that suggest the BR does not influence the long-term "set point" of arterial pressure. Osborn *et al*. has suggested that humoral (ANGII, AVP, aldosterone) and osmolar (water and sodium) mediators influence CNS nuclei (NTS, CVLM, and RVLM) by acting through circumventricular organs (CVO) to modulate autonomic activity[108]. The integration of these signals in the CNS ultimately determines the neural set point of arterial pressure in the CNS independent of the BR input. The author would argue that the BR is able to influence chronic levels of SNA to the kidneys, which regulates levels of humoral factors active in autonomic regulation. Furthermore, a number of these humoral factors are known to influence components of the BR arc. In addition, as reviewed by Lohemeier *et al*.[6] the neurons in the central BR arc in both primary and secondary hypertension remain activated. This observation suggests that the BR is able to exert a sustained influence on CNS nuclei that are critical to the neural cardiovascular regulation.

CONCLUSIONS

The precise role of the BR in the long-term control of arterial pressure remains to be elucidated. The potential for normalizing BR sensitivity and restoring the BR pressure threshold is an exciting prospect for individuals with compromised BR function (e.g., hypertension, aging, obstructive sleep apnea, and atherosclerosis). These individuals could potentially improve BP control using novel therapeutics that improve BR function through the alteration of humoral factors and molecular mechanisms responsible for baroreceptor signaling and CNS regulation of efferent SNA.

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