Long-term blood pressure control: is there a set-point in the brain?

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Abstract Mean arterial pressure fluctuates depending on physical or psychological activity, but should be stable at rest at around 100 mmHg throughout an entire life in human. The causes of hypertension and the blood pressure regulation mechanisms have been discussed for a long time, and many aspects have recently become more clear. Circulatory shock or short-term hypotension can be treated based on what is now known, but chronic hypertension is still difficult to treat thoroughly. The exact mechanisms for long-term blood pressure regulation have yet not been elucidated. Neuro–humoral interaction has been suggested as one of the mechanisms. Then, from the 1990s, paracrine hormones like nitric oxide or endothelins have been extensively researched in order to develop endothelial local control mechanisms for blood pressure, which have some relationships to long-term control. Although these new ideas and mechanisms are newly developed, no clear explanation for long-term control has yet been discussed, except for renal abnormality. Recently, a central set-point theory has begun to be discussed. This review will discuss the mechanisms for long-term blood pressure control, based on putative biological missions of circulatory function for life support.

Keywords Neurohumoral · Sympathetic · Open-system · Hemodynamic · Endothelial regulation · Central nNOS neuron · Hypertension · Salt-sensitive

Introduction

The damage caused by high blood pressure is coming to be understood even by the general population. It is also widely understood that reducing salt intake is a means to prevent lifestyle-related disease. In cases where a person does develop hypertension, a range of various kinds of therapeutic agents and antihypertensive drugs is available. Studies on blood pressure regulation appear in some ways to have reached a natural conclusion. However, while the treatment of hypertension may appear simple, it is actually surprisingly difficult, and often results in a multi-drug regimen. It is frequently found that any type of drug used to treat hypertension deteriorates in its effectiveness. On the other hand, having a lifestyle-related disease may force patients into a constant battle with their natural appetite or salt preference, which can be a constant frustration to them. Doctors also face difficulties in diagnosing and treating hypertension and giving lifestyle advice. For example, it cannot be determined from just a single measurement whether or not a person has hypertension. Even more fundamentally, while symptomatic treatment of hypertension can be accomplished, curative treatment cannot. The mechanisms of short-term blood pressure regulation have become quite clear, but much remains unknown about the mechanisms of long-term regulation.

This review focuses on the mechanisms of long-term blood pressure regulation. Based on the mechanisms of blood pressure regulation that have been understood to date, consideration is given first to what the goals of regulating blood pressure should be, and then to the meaning and methods of blood pressure regulation based on physiological significance, in view of biological implications including maintenance of life. The goal of this review is that readers also sense the dilemma involved in the regulation system of long-term blood pressure control.
Basics for the blood pressure control system

There are many papers, textbooks, and reviews [1–3] on the fundamentals of blood pressure regulation mechanisms. However, here we would like to briefly go back over those matters that are relatively certain and unlikely to change in the future, those which are necessary for the following discussion, and look at factors related to blood pressure regulation that have been discussed to date.

Blood pressure regulation, regardless of whether it is long-term or short-term, is determined by three factors: contractile force of the heart (H), blood volume (VOL), and total peripheral resistance (TPR). There are aspects of cardiac contractile force and blood volume that are difficult to separate via venous return, but today they are simply treated as independent factors. A full discussion of this would become an unnecessary digression, and so we will not go into details about this issue. These three factors are controlled by the central nervous system through the media of nerves and hormones to manage blood pressure. The central nervous system receives blood pressure information from baroreceptors, and controls blood pressure to keep fluctuations small. Meanwhile, the kidneys contribute greatly to blood pressure regulation from the aspect of regulating body fluid volume through their diuretic function. At the same time, hormones secreted from the kidneys and afferent nerves originating in the kidneys are also involved in blood pressure control. The short-term blood pressure regulation mechanism is currently explained by the above, and theoretically this is adequate for the treatment of acute hypotension, such as circulatory shock. However, this information by itself does not enable curative treatment of the long-term blood pressure regulation mechanism, such as in hypertension.

Humoral regulation versus neural regulation

Circulating hormones have a relatively long-acting blood pressure regulation action. However, essential hypertension cannot be explained by the hormonal abnormalities known to date. Since the discovery of atrial natriuretic peptide (ANP) in 1980 [4], new circulatory hormones have been added to what are called the classical circulating hormones, including catecholamines, the renin–angiotensin system, and vasopressin. ANP is also viewed as a new hormone, including among substances such as adrenomedullin [5] and the endogenous digitalis-like factor (EDLF) [6]. Even so, essential hypertension cannot be explained by these newly discovered hormones. Moreover, the resting blood pressure “value” that is supported by these circulating hormones is not that large. Table 1 shows the resting level range of blood pressure with gene knockout of each hormone or its receptor, as determined by several investigators [7–20]. The data vary, some being for systolic blood pressure and others for mean blood pressure, but resting blood pressure with systolic pressure of 35 mmHg/min at most is maintained. As for mean blood pressure, this seems to be around 10–15 mmHg. There are also data suggesting that vasopressin actually acts to lower blood pressure. There may be criticism that this is not a hormone, but EDLF is also thought to be unrelated to the maintenance of resting blood pressure. Circulating hormones do not contribute very much to the formation of the “value” of resting blood pressure.

On the other hand, when hexamethonium was administered to unanesthetized unrestrained rats and sympathetic nerves were completely blocked, arterial pressure decreases largely. The rats moved about and the data were somewhat noisy, but renal sympathetic nerve activity was seen to completely disappear. Mean resting blood pressure at this time was half the normal level (Fig. 1). Vascular constriction from sympathetic nerve activity makes a large contribution to resting blood pressure, supporting about 50% of it. However, as many people know, before long, habituation to

| Table 1 Resting levels of MAP after gene-knockout of each hormone or receptor |
|-----------------|-----------------|-----------------|
|                 | MAP (mmHg)      | References      |
| Angiotensin     |                 |                 |
| Renin           | ~35 s ‡         | Yanai et al. [7]|
| Angiotensinogen | ~33 s ‡         | Ishida et al. [8]|
| Angiotensinogen | ~34 ↓           | Tsuchida et al. [9]|
| AT1a receptor   | ~24 s ↓         | Ito et al. [10]|
| AT1a + AT1b     | ~34 ↓           | Tsuchida et al. [9]|
| AT2 receptor    | ~0              | Hein et al. [11]|
| ACE 0-copy      | ~32 ↓           | Carlson et al. [12]|
| ACE 1-copy      | ~14 ↓           | Carlson et al. [12]|
| Vasopressin     |                 |                 |
| Brattleboro rat | ~7 ↑            | Gardiner et al. [13]|
| Bradykinin      | ~8 s↑           | Madeddu et al. [14]|
| B2 receptor     |                 |                 |
| ANP             |                 |                 |
| Molecule        | (~14 †)         | Carlson et al. [15]|
| Whole-body GC-A receptor | ~10 † | Lopez et al. [16]|
| Vascular GC-A receptor | ~0  | Holtwick et al. [17]|
| Adrenomedullin  |                 |                 |
| Molecule +/-    | ~11 †           | Shindo et al. [18]|
| Uroguanylin      |                 |                 |
| GC-C receptor   | ~0              | Potthast et al. [19]|
| EDLF            |                 |                 |
| ‘Digibind’      | (~0)            | Kaide et al. [20]|

MAP mean arterial pressure, s systolic pressure, ( ) measured under anesthesia, ANP atrial natriuretic peptide, EDLF endogenous digitalis-like factor.
nerve signals occurs or receptors are down-regulated, and the effect is not long-lasting. On this point, hormonal action is known to have a relatively long-lasting action.

**Neuro–humoral interaction**

Therefore, while their acting strength is weak, if long-acting hormones are believed to influence the activity of sympathetic nerves, which have a strong action (Fig. 2), it seems that long-term blood pressure regulation may be possible. This would be convincing if it could be demonstrated that hormones control the sympathetic centers.

When blood vasopressin levels in rabbits was gradually increased, sympathetic activity became suppressed (Fig. 3) [21]. This suppression did not result from arterial baroreceptor reflex, because nerve activity decreases even with the same blood pressure value. The vasopressin-induced sympathetic suppression action is reportedly due to action on baroreceptors [22–25]. It is also reported that since vasopressin acts directly on the heart, the heart rate response is inhibited [26–28]. There is also a report suggesting that vasopressin acts directly on nerve ganglia [29]. These findings are based on the respective experimental results, but even if the receptors and target organs are maintained intact, the vasopressin–sympathetic nerve blocking action...
disappears completely when the area postrema is abolished [30]. If vasopressin V1 receptors in the area postrema are blocked, the vasopressin-induced sympathetic suppression disappears [31]. In other words, despite acting on baroreceptors and target organs, the level of this action is small, and then the major cause of the sympathoinhibition is a central action of AVP on the area postrema. In addition, this suppression depends on the input volume from baroreceptors (Fig. 4), discussed in a previous report [32]. From the above, it is thought that the mechanism is as shown in Fig. 5 [33]. These results show the neuro–humoral interaction present.

An investigation was conducted on whether or not angiotensin II also has this neuro–humoral interaction. Figure 6 shows that the heart rate–blood pressure arterial baroreceptor reflex curve shifts to the right as the dose of angiotensin II is increased. Angiotensin is administered to a vertebral artery, and so the direct action on peripheral vessels or peripheral organs such as the heart is thought to be small, and central nerve action to be strong. In addition, since the simultaneously recorded sympathetic nerve activity is inhibited (Fig. 7) [34], the effect of the shift cannot be explained by sympathetic nerve action and is conjectured to be due to vagal activity inhibition (Fig. 8) [21]. It has also been found that angiotensin II shows a neuro–humoral interaction via circumventricular organs [35]. It is generally thought that angiotensin enhances sympathetic activity [36]. However, the central endogenous angiotensin action and the angiotensin action originating from the blood flow do not necessarily agree.

Recognition of neuro-humoral interaction has given rise to the possibility of long-term blood pressure regulation from these interactions (Fig. 9). The area postrema, which is the “site” of these interactions, was therefore abolished, and the effect on resting blood pressure of a state in which such an interaction is unlikely to occur was investigated. Although angiotensin II would also have been good in this test, it has many strong effects on various targets in the cardiovascular system. Vasopressin, which has relatively few effects, was therefore selected, and very small doses were administered intravenously for five consecutive days. The results showed that the effect of eliminating interactions

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**Fig. 3** Effects of intravenous infusion of arginine vasopressin (AVP) on the baroreflex curve and the reflex gain curve of renal sympathetic nerve activity (RSNA) in a rabbit, modified from Ref. [21]. MAP mean arterial pressure

**Fig. 4** Responses of the baroreflex curve of RSNA to the AVP infusions in intact rabbits, 1CSN + 1AoN rabbits, and 1CSN rabbits, modified from Ref. [32]. 1CSN + 1AoN rabbits the rabbits with one carotid sinus nerve intact and one aortic nerve intact but the others severed. 1CSN rabbits the rabbits with just one carotid sinus nerve intact but the other carotid sinus nerve and two aortic nerves severed. RSNA renal sympathetic nerve activity, AVP arginine vasopressin, MAP mean arterial pressure
in the area postrema was expressed in body fluid balance and heart rate, but not in blood pressure [37] (Fig. 10). In other words, long-term blood pressure regulation action due to neuro–humoral interaction has not been demonstrated. Although it cannot be concluded from this research alone that there is no long-term blood pressure regulation action due to neuro–humoral interactions, the result was disappointing. However, future studies will need to be conducted before any conclusion is reached.

Central set point

It has long been known that high blood pressure occurs temporarily when baroreceptors are denervated, but after several weeks blood pressure returns to the original resting
pressure [38]. Normal systolic blood pressure is thought to be about 130 mmHg or less throughout life [39], although in the case of aged people, opinions are divided. This appears to be just like a “set point” for blood pressure that extends over the long term. In addition, it has been reported that long-term hypertension results when a high-salt diet load is applied after baroreceptors are denervated [40]. Even with baroreceptors intact, it is reported that when the renal nerve is denervated long-term hypotension occurs regardless of the amount of salt intake [41]. These findings suggest that there is probably a central blood pressure set point even in long-term blood pressure regulation [3, 42]. However, is there really a central set point?

Biological significances or missions of circulation

The essential purpose of circulation is to rapidly transport oxygen and other substances to a level that would be impossible with simple diffusion, and to mix the entire body fluid concentration of an individual so that it is as uniform as possible. This links the organs and tissues, which are the parent bodies of various types of specially differentiated functions so that a single, indivisible being is formed. To fulfill this purpose, circulation needs to transport substances and link and integrate all parts of the body in a wide range of states. If this is not done adequately the organism cannot be sustained. Blood pressure is the driving force of circulation, and circulation needs to be able to deal as necessary with various circumstances that occur in the body to fulfill its mission. For example, if oxygen consumption increases as a result of exercise, it is necessary to raise the driving force and increase blood flow. If respiratory function declines, it is necessary to quickly raise the driving force and increase the rate of circulation. Or, when eating, blood flow is concentrated in the gastrointestinal tract. Or when body temperature increases, it is probably necessary to change the driving force so that blood flow is routed to the skin (Fig. 11). While it is certain that the arterial baroreceptor reflex acts to minimize blood pressure fluctuations, it has been found that during exercise even this reflex is suppressed [43]. Thus, even though the arterial baroreceptor reflex system is set mechanically, the reflex can be suppressed by the center when it becomes an interference. These may indicate that the cardiovascular system can achieve its essential function by changing the

**Fig. 9** Putative concept for long-term control of sympathetic activity by a neuro–humoral interaction mechanism via the area postrema

**Fig. 10** Effects of the 5-day infusion of vasopressin on arterial pressure and heart rate in intact and area postrema-lesioned rabbits, modified from Ref. [37]. **INT** intact rabbits, **APX** rabbits with the area postrema lesioned, **MAP** mean arterial pressure, **HR** heart rate, **AVP** arginine vasopressin.

*"p < 0.05 compared with control, †"p < 0.05 between INT and APX"
driving force and acting as needed so that the function of each organ and tissue can be fulfilled in each condition. The meaning here is central drive regulation. If there was a set point in the central nervous system, the blood pressure control system could become a completely closed, self-contained type system so that blood pressure always returns to the set level whatever may happen. Then, the functions of the organs and tissues would not be protected even if the circulatory system itself is. The individual would not even be able to sustain life, so that such a system would be putting the cart before the horse. In this sense, the cardiovascular system should be an open system, and the characteristic of being able to change as circumstances demand is probably essential (Fig. 11).

**Phasic control by the neural and hormonal axes**

Reconsidering the blood pressure regulation mechanism from this perspective, the nervous and hormonal regulation mechanisms are most likely media that act as regulatory and phasic control systems that transiently regulate blood pressure in time units of seconds and minutes to deal with whatever circumstances arise (Fig. 12a). The results described below might suggest this putative concept.

Rabbit baroreceptors were denervated, and 24-h blood pressure and cardiac output were measured in one study with the time periods divided into when the rabbits were sitting still and when the rabbits were standing and moving in some way. The total peripheral vascular resistance was calculated by blood pressure and cardiac output. Histograms for them were compared with those of rabbits having normal baroreceptors (Figs. 13 and 14). With body movement, blood pressure shifted toward hypertension in the intact baroreceptor animals. There was no shift in blood pressure in the baroreceptor-denervated animals [44].

While no progress has been made in elucidating the detailed mechanism, in animals with normal intact nervous systems, an exercise pressor response occurs when it is necessary for the body. In other words, the neural blood pressure regulation mechanism seems to be a phasic control to the circulatory status demanded for life. It is also generally well known that in times of acute circulatory shock it is not only the sympathetic nerves but also “classic” circulatory hormones, such as sympathetic catecholamine, renin, angiotensin, and aldosterone, that act strongly.

**Tonic control by the renal function**

In contrast, the long-term stabilization mechanism for resting blood pressure may not be regulated solely by signals that can be easily fluctuated, such as nerves and hormones. It might also be circumscribed by factors like structural alternatives that cannot be directly fluctuated, such as vascular structure. It may probably be the case that “stubborn” tonic control systems are adopted as a life support mechanism (Fig. 12b). The pressure diuresis function of the kidneys may be one such system. Although the mechanism is not completely understood, one aspect of diuresis and blood pressure regulation occurs as a result of a relatively simple pressure-related physical force [45], which is powerful as a long-term blood pressure regulation mechanism in an open system [46]. However, when hypertension has developed, the renal function curve shifts to high blood pressure [47, 48], with the result that the high blood pressure cannot return to the normal level. Another aspect separate from the kidneys may be related to local regulation in the vessels and long-term regulation of that network. This is discussed in the following paragraphs.
Fig. 13 Histograms of 24-h MAP in an intact rabbit and in a SAD rabbit, modified from Ref. [44]. MAP mean arterial pressure, SAD sinoaortic denervated, All all MAP data (8,474 points for intact, 8,398 points for SAD) during 24 h, Rest MAP data (4,059 points for intact, 4,258 points for SAD) during rabbits sitting without movement, Move MAP data (2,507 points for intact, 2,140 points for SAD) during rabbits standing or moving, Other the other data (1,908 points for intact, 2,000 points for SAD) which are recorded during neutral phases.

Fig. 14 Histograms of 24-h heart rate (HR), aortic blood flow (AoBF) and total peripheral resistance (TPR) in an intact rabbit and a SAD rabbit, modified from Ref. [44]. AoBF equals (cardiac output − coronary flow). TPR is calculated from ([arterial pressure − central venous pressure]/AoBF). Abbreviations and sampling points are as in Fig. 13.
Local control theory

Local regulation mechanisms have come to be included in research efforts in recent years. As shown in Table 2, regulation of vascular smooth muscle contraction by vascular endothelial cells has been shown by a number of investigators [49–62] since about 1956. However, as stated by Swales [55] in 1987, there were questions about the “competence” of such a mechanism. Regulation of vascular smooth muscle contraction by vascular endothelial cells attracted much attention with the discovery of nitric oxide (NO) in 1980. The discoveries of endothelin [61] and the C-type natriuretic peptide (CNP) [62] further advanced this concept, which has come to be established as a local regulation mechanism.

The commander for the local regulation mechanism is the local cell population, consisting mainly of vascular endothelial cells; it is not located in the central nerves. Signals generated in local endothelial cells (cytokines in the sense of physiologically active substances secreted by cells) act as paracrine signals in nearby smooth muscle cells, characterized by control. Of course, they also respond to circulating hormones and sympathetic nerves, but the main actors are locally generated signals. A typical example is coronary circulation, which, although affected by autonomic nerves and hormones, is mainly controlled by locally produced adenosine and NO. The vasodilatory action from these signals considerably exceeds the constriction effect from nerves and hormones [63]. Based on this mechanism, the heart itself can set the blood flow volume to the heart according to its own workload [63]. No matter what the “central authority” says, the “outlying regions” have their own circumstances and cannot do what they cannot do. Unless the entrusted “regional” mission is fulfilled with “regional” power, the overall life of the individual will not exist.

Reconstruction of concept of regulation system

With the addition of such local regulation mechanisms, there are understood to be three main mechanisms that contribute to the regulation of blood pressure: (1) feedback regulation based on information from baroreceptors, (2) central drive regulation from central nerves in the limbic system and hypothalamus of the brain and elsewhere, as well as central nerves that regulate functions other than circulation, and (3) local regulation based on local circumstances and features (Fig. 15).

Can the local control system regulate systemic blood pressure?

Chen and Sanders [64] administered L-arginine orally to Dahl salt-sensitive hypertensive rats and reported that the hypertension improved with a high-salt diet. This effect was not seen with D-arginine. The arteries of the Dahl rats with hypertension induced by high-salt intake were removed, then its vasoconstrictivity was examined by the Magnus method. The results revealed that they had greater constrictive activity [65] (Fig. 16). Further investigation showed that NO production capacity of the vascular endothelial cells had decreased and that the NO responsiveness of vascular smooth muscle had decreased [65]. Lüscher et al. [66] and Hayakawa [67] reported similar findings. Thus, abnormality of the local regulatory function of NO production by vascular endothelial cells leads to the

Table 2  Pioneering process for endothelial regulation of vascular smooth muscle activity, called as Local Control

| Year | Event |
|------|-------|
| 1956 | Renin-like enzyme in vascular wall [49] |
| 1971 | Brain renin–angiotensin system [50, 51] |
| 1976 | Tissue renin–angiotensin system [52] |
| 1984 | Vascular renin–angiotensin system [53, 54] |
| 1987 | “Vascular RAS is still doubtful” [55] |
| 1988 | Local generation of vascular Ang II [56] |
| 1990 | Chymase in human heart [57] |
|      | Overexpression of human chymase in rat vessels produces hypertension [58] |
| 1976 | PGI2, Prostacyclin [59] |
| 1980 | EDRF [60] |
| 1987 | NO, NOS (Ignarro, Palmer, Moncada) |
| 1998 | Nobel Prize Award |
| 1988 | Endothelin [61] |
| 1990 | CNP C-type natriuretic peptide [62] |
long-term blood pressure regulation abnormality of salt-sensitive hypertension, and if the local abnormality is resolved, hypertension can be greatly corrected [64]. A similar disorder of vascular endothelial cell NO production was also indicated in the spontaneously hypertensive rat (SHR) [68]. Not only NO but also endothelin production and secretion disorders have been pointed out in such cases [69–71]. In addition, a novel special vasoconstrictive factor has been discovered in salt-sensitive hypertension [72].

While local regulatory abnormalities are too numerous to list here, they show general arterial pressure abnormalities resulting from local or target tissue abnormalities.

The sympathetic center

What then is happening with control by the central and sympathetic nervous systems at this time? Are abnormalities also occurring on the controller side? When NO synthase (NOS) and 7-nitroindazole were administered intraperitoneally to salt-sensitive hypertensive rats and NO production was blocked, it was found that renal sympathetic nerve activity was increased even though blood pressure had become even higher (Fig. 17). The increase in sympathetic activity was surprisingly large and occurred at a level of the generator site of the rostral ventrolateral medulla, based on the data from the suppressing study of the baroreflex [73]. Thus, in salt-sensitive hypertension, the sympathetic nerve activity inhibiting mechanism was strongly amplified centrally via nNOS neurons. Since then, results have shown that compensatory mechanisms for hypertension are amplified centrally. However, since 7-nitroindazole lacks specificity for neuronal NOS (nNOS) [74, 75], and the action of inhibitors is not limited to central nerves with general administration, a change was made to s-methyl-L-thiocitrulline, which has a high specificity for nNOS. It was administered intra-cerebroventricularly, and, as expected, sympathetic nerve inhibition was seen due to amplification of central nNOS in salt-sensitive hypertensive rats (Fig. 18) [76]. Moreover, it was...
found that nerve nuclei that were strongly related to the inhibition of sympathetic nerve activity showed a rise in nNOS activity (Fig. 19) [77]. It thus appears that in high-salt hypertension the inhibitory limb in the sympathetic center is strongly enhanced. In other words, it has been shown that in salt-sensitive hypertension there are disorders in the local regulation mechanism and not in the regulation center, and rather that the sympathetic nerve centers respond as if compensating (Fig. 20).

Central disturbances in essential hypertension

However, it is also well known that peripheral sympathetic nerve activity is elevated in patients with essential hypertension [78]. It has been reported that patients with spontaneous and essential hypertension have a genetic overexpression of the inflammation precursor JAM-1 in vascular endothelial cells in solitary tract nuclei of the brainstem, which results in hypertension [79]. It has also
come to be thought that active enzymes produced by inflammatory reactions or immune responses, or oxidative stress, act on central nerves via circumventricular organs, particularly the AV3V region, raising sympathetic nerve activity and producing hypertension [80]. Meanwhile, inflammatory oxidative stress of peripheral vessels has also come to be included as a cause of hypertension [80]. These findings indicate that faulty control of central nerves plays a main role in conditions such as essential hypertension and SHR. If at this time sympathetic nerve activity is again enhanced in a similar manner to the case of salt-sensitive hypertension, a question is whether this will still be overcome, even though sympathetic nerve inhibition due to central nNOS causes peripheral nerve activity to increase. The answer to this will have to await further research. Conversely, another question is whether there are central abnormalities due to oxidative stress in salt-sensitive hypertension, as seen in SHR. This answer will also have to wait for further research.

Conclusion

The mechanisms of long-term blood pressure regulation remain unresolved. The quest for understanding needs to keep moving forward, even in small steps. There are two main types of blood pressure regulation, homeodynamic regulation and homeostatic regulation; it may be that the two missions of circulation are fulfilled by these two types of regulation (Fig. 21). To achieve the purpose of the former of integrating the differentiated functions into one, the systemic media of nerves and hormones based on a central drive with compromise or cooperation is used. The latter

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Perspectives: Tradeoff mission of peripheral resistance vessels

"Maintaining a circulatory driving force for the entire body"

A stronger driving force is obtained with constriction and higher blood pressure

"Autoregulation for peripheral tissue"

Greater blood flow is obtained with relaxation

Does this tradeoff mission normally maintain both at once by chance?

If abnormality in local regulation occurs and tends toward constrictiveness, there will be a move toward slightly higher driving pressure because of compensation for poor tissue circulation.

(cf.) Considering chemoreceptor reflexes, local hormones from local tissues, kidneys, and/or heart. A vicious spiral occurs because of these two missions, and then hypertension develops, which leads to structural changes → wasting breakdown of vascular endothelial function → vascular disorder → organ damage.
also uses the systemic media of nerves or hormones so as not to exceed a certain line, based on short-term feedback regulation. Long-term regulation, however, might be achieved by a local regulation network or harmonization.

**Perspectives**

The peripheral resistance vessels that are the “sites” of local regulation are given the two jobs simultaneously of maintaining the circulatory driving force for the entire body and attracting blood flow to the blood flow region that is governed by that vessel. If a vessel is constricted, the former role can be fulfilled but the latter cannot. If a vessel is dilated, the latter role can be fulfilled but the former cannot. Peripheral resistance vessels are given the mission of balancing this tradeoff (Fig. 22). Of course, the blood flow distribution within tissue is left to the precapillaries by resistance vessels, but if the resistance vessels constrict, no blood flow above that level is produced in precapillary resistance of the control region. In addition to the mission of balancing this tradeoff, a dilemma is also produced by a clash between central control via nerves and hormones and local regulatory control. It is an extremely difficult situation. If the vessels of a given organ thicken and sufficient blood flow is not obtained with normal arterial pressure, the systemic blood pressure must unavoidably be raised in the long term [81]. Once blood pressure increases over a long period, systemic arteriosclerosis progresses and blood pressure is forced to go even higher. It is a vicious spiral. In consideration of this, one starts to think that perhaps the tradeoff mission may be formed by chance. This area may be a huge source of frustration for the “blood pressure regulation” researcher. While striving to solve this problem, if 120/80 mmHg is taken as the value that meets the regulation’ researcher. While striving to solve this problem, this area may be a huge source of frustration for the “blood pressure regulation” researcher. While striving to solve this problem, if 120/80 mmHg is taken as the value that meets the regulation requirement, a novel hypotensive peptide isolated from human pheochromocytoma. Biochem Biophys Res Comm 192:533–560.

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