

Neural, Hormonal and Renal Interactions in Long-Term Blood Pressure Control

HYPOTHESIS: SET-POINTS AND LONG-TERM CONTROL OF ARTERIAL PRESSURE. A THEORETICAL ARGUMENT FOR A LONG-TERM ARTERIAL PRESSURE CONTROL SYSTEM IN THE BRAIN RATHER THAN THE KIDNEY

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SUMMARY

1. It has been hypothesised that the ‘set-point’ for the long-term control of mean arterial (MAP) resides within the kidney. In this model, the set-point of the ‘chronic renal function curve’ establishes the steady state relationship between renal perfusion pressure and urinary excretion of sodium and water, which, in turn, affects blood volume and cardiac output. The ‘renal–MAP set-point’ theory predicts that the kidney controls MAP to maintain its own excretory function and that long-term regulation of blood volume and cardiac output are paramount to the regulation of arterial pressure.

2. An alternative hypothesis is proposed in which the ‘set-point’ for the long-term control of MAP resides within the central nervous system (CNS) rather than the kidney. In contrast with the ‘renal–MAP set-point’ model, the ‘CNS–MAP set-point’ model dictates that the brain controls MAP to maintain cerebral blood flow and CNS function.

3. The ‘CNS–MAP set-point hypothesis’ predicts that long-term regulation of MAP is paramount to the regulation of blood volume and cardiac output. It is proposed that the ‘CNS–MAP set-point’ system operates independently of the arterial baroreceptor reflex, which is a short-term controller of MAP.

4. The precise mechanisms by which the CNS ‘senses’ MAP are complex and remain to be discovered. The MAP ‘sensor’ likely involves integration of hormone levels linked to body fluid homeostasis and osmoreceptor and baroreceptor inputs. It is also proposed that an as yet undiscovered ‘central baroreceptor’ exists within the brain itself.

5. The ‘CNS–MAP set-point hypothesis’ predicts that many forms of experimental and essential hypertension are due to a primary shift in the CNS–MAP set-point.

Key words: hypertension, renal function curve, set-point, sympathetic nervous system.

INTRODUCTION

Understanding the mechanisms for the long-term control of arterial pressure has important clinical significance, particularly in regard to human essential hypertension, one of the major risk factors for cardiovascular disease. Because the regulation of arterial pressure involves complex, time-dependent interactions among multiple neural, hormonal and intrinsic regulatory systems, theoretical models of the long-term control of arterial pressure are essential for the development of testable hypotheses. Central to these models has been the concept that a ‘long-term arterial pressure set-point’ exists and that hypertension is caused by a primary shift of this set-point to a higher operating pressure.

Does a set-point exist within the body for the long-term control of mean arterial pressure (MAP)? Although the set-point concept provides a logical format to construct physiological control models, it can be argued that the long-term level of arterial pressure is established independent of a set-point-based control system. The reader is referred to the companion paper by Fink in this journal for this viewpoint.¹

In the present paper, I will defend the position that a set-point for the long-term control of arterial pressure does exist. The term ‘set-point’ will be used to designate a true control system for arterial pressure in contrast with a system that modulates pressure irrespective of a ‘reference point’. If such a system does, indeed, exist, then where is it in the body? The most well-established model is that developed by Guyton and colleagues in the 1970s, in which the ‘chronic renal function curve’ determines the relationship between renal perfusion pressure and urinary sodium and water excretion and, therefore, body fluid balance and blood volume.² In what will be referred to in this paper as the ‘renal–MAP set-point model’, the kidney essentially regulates its own perfusion pressure to maintain normal renal excretory function.

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I will present an alternative teleological argument for the existence of a long-term MAP set-point that exists within the central nervous system (CNS) rather than the kidney. Analogous to the renal-MAP set-point model, the 'CNS-MAP set-point model' predicts that the brain regulates its own perfusion pressure to maintain normal central nervous system function, which is vital to long-term survival and homeostasis. The CNS-MAP set-point model differs from the renal-MAP set-point model in two fundamental ways. First, the CNS-MAP set point model is a true pressure control system in that long-term regulation of arterial pressure supersedes the control of cardiac output. Second, the main focus of the CNS-MAP set-point model is maintenance of cerebral and coronary metabolism, in contrast with the 'whole-body autoregulation' theory of the renal-MAP set-point model. This paper will conclude with a discussion of the role of the CNS-MAP set-point model in the pathogenesis of experimental and human essential hypertension.

THE RENAL-MAP SET-POINT MODEL

The details of the renal-MAP set-point theory have been presented in several reviews²⁻⁵ and a monograph⁶ by Guyton. These serve as the basis for presentation of the renal-MAP set-point in this paper.

The teleological argument

This model is based on the argument that long-term control of arterial pressure is required to maintain normal renal excretory function, which is essential to the maintenance of body fluid homeostasis and regulation of blood volume and cardiac output. The primary goal of this system is to ensure that nutrient delivery to the tissues (i.e. cardiac output) is tightly matched to the meet metabolic demand of the tissues. In this model, the regulation of

blood volume and cardiac output is paramount to the control of arterial pressure.

Fundamental pillars of the renal-MAP set-point model: The chronic renal function curve and whole-body autoregulation

Figure 1 illustrates the basic features of the renal-MAP set-point model and the role of the 'chronic renal function curve' and 'whole-body autoregulation' as the central pillars of this hypothesis. The first pillar of this model, the chronic renal function curve, contains the long-term set-point for arterial pressure and establishes the steady state relationship between renal perfusion pressure and renal excretion of sodium and water. In this model, extracellular fluid volume and, therefore, blood volume, is determined primarily by two factors: (i) the intake of salt and water; and (ii) the renal function curve. More importantly, as explained below, the only way in which arterial pressure can change over long periods of time is by changing the relationship between sodium and water intake and renal excretion of sodium and water, which is determined by the position of the renal function curve along the pressure axis.

Whole-body autoregulation is the second pillar of the renal-MAP set-point model. This theory predicts that long-term regulation of blood flow within individual vascular beds is determined by intrinsic controllers linked to metabolic signals within the tissues. These intrinsic signals, which remain to be elucidated, exert dominant control of arteriolar tone over neural and hormonal control systems such that blood flow is regulated to meet the metabolic requirements of the tissues. Because systemic haemodynamic pressure-flow relationships are determined by the sum of individual organ arteriolar resistances and blood flows, whole-body autoregulation ultimately establishes the long-term steady state relationships

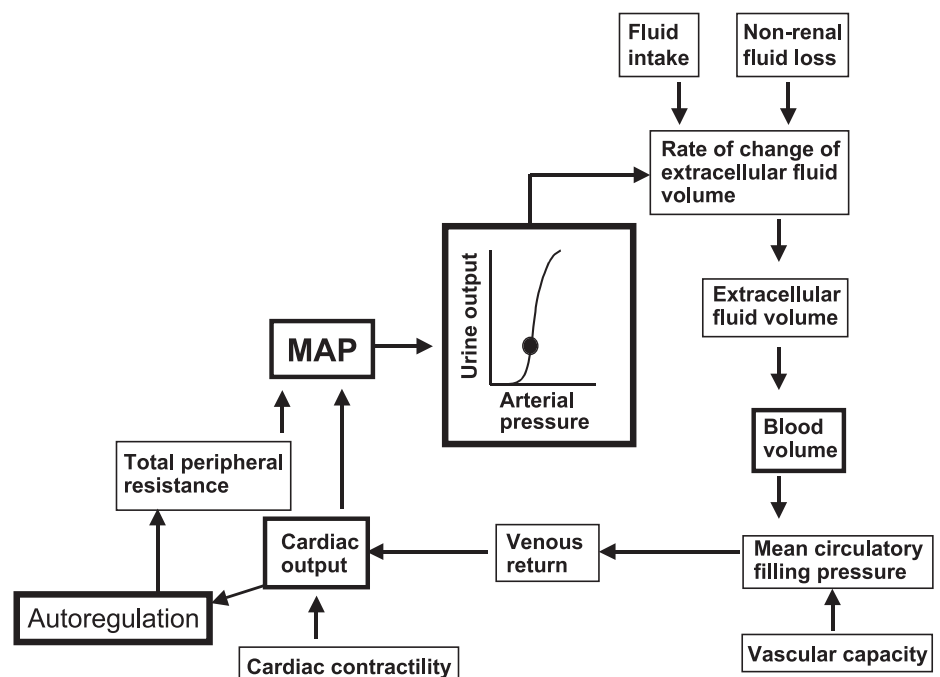


Fig. 1 Schematic of the renal-mean arterial pressure (MAP) set-point model as proposed by Guyton *et al.*² The main tenets of the model are the chronic renal function curve and whole-body autoregulation, which serve ultimately to regulate blood volume and cardiac output. Figure adapted from figs 6-4 in Guyton.⁶ See text for details.

between venous return, cardiac output and total peripheral resistance.

Hypertension caused by a primary shift in the renal–MAP set-point: The whole-body autoregulation haemodynamic profile

The reader is referred to Guyton's excellent monograph *Arterial Pressure and Hypertension*⁶ for a detailed description of the application of control theory to understanding the role of the kidney in the long-term control of arterial pressure. As stated in this monograph:

'... the equilibrium point in the pressure-analysis diagram is the 'set-point' of the kidney–blood volume–pressure feedback control system. And, as has been discussed in the previous few chapters, once this equilibrium point (set-point) is changed to a new pressure level, the arterial pressure soon follows.'

Because the renal function curve determines the long-term set-point of arterial pressure, the renal–MAP set-point model predicts that the only way in which arterial pressure can change over long-periods of time is by a primary shift in the set-point of the chronic renal function curve. Based on this model, Guyton predicts that:

'It is impossible for the long-term arterial pressure to stabilize at any other pressure level besides the set-point level, for at no other level can intake and output be in balance.'³

Finally, because whole-body autoregulation establishes the long-term levels of cardiac output, the only way cardiac output will change over long periods of time is if metabolic activity changes over the long-term.

Assuming a constant metabolic rate, the renal–MAP set-point model predicts that all forms of hypertension, regardless of the specific underlying cause, are initiated by a specific sequence of events that result in the temporal haemodynamic profile illustrated in Fig. 2. First, a shift of the renal function curve to a higher operating pressure results in a decrease in renal excretion of sodium and water because renal perfusion pressure is no longer high enough to maintain urine output at this new set-point. Second,

assuming sodium and water intake remain constant, the decrease in urine output leads to expansion of extracellular fluid volume, increased blood volume and an elevation of cardiac output. This results in an 'acute' phase in which arterial pressure is elevated due to increased blood volume and cardiac output. At this point, total peripheral resistance may be decreased due to baroreceptor reflex-mediated vasodilatation. Because cardiac output is now elevated and metabolic rate has not changed, overperfusion of tissues evokes a whole-body autoregulation response and total peripheral resistance gradually increases over time. At steady state, arterial pressure reaches the new 'set-point' and urinary excretion of sodium and water returns to normal. The normalization of renal function, coupled with the rise in total peripheral resistance and resistance to venous return, results in a return of blood volume and cardiac output towards normal levels. As a result, the steady state haemodynamic profile is one in which hypertension is sustained by a marked increase in total peripheral resistance and small immeasurable changes in blood volume or cardiac output. In other words, cardiac output is chronically regulated at the expense of an elevated arterial pressure.

Cracks in the pillars of the renal–MAP set-point model

The renal–MAP set-point model put forth by Guyton and colleagues is elegant in its simplicity and logic. At the present time, it is the most comprehensive model for the long-term control of arterial pressure and has provided a strong theoretical framework for the role of the kidney in the pathogenesis of human essential hypertension. However, the renal–MAP set-point model contains three 'absolutes' that, upon careful examination of the literature, suggest the model is incorrect. The first absolute is that the renal function curve always determines the level of arterial pressure and hypertension cannot occur without a primary shift in the curve. The second absolute is that hypertension is always initiated by blood volume expansion and increased cardiac output. Finally, the last absolute is that chronic blood volume expansion always leads to hypertension as a result of whole-body autoregulation. The inconsistencies of these absolutes with the literature are discussed below.

The most difficult component of the renal–MAP set-point model to validate experimentally has been the chronic renal function curve. Although it is clear that there is an acute relationship between renal arterial pressure and urine output,⁷ to date it has been essentially impossible to establish *in vivo* the long-term relationship between these variables and the link of that relationship to regulation of arterial pressure. In order to circumvent this problem, the shape of the chronic renal function curve is established by first plotting the steady state relationships between sodium and water intake, as the independent variable, and arterial pressure as the dependent variable.² It is then reasoned that, because renal excretion and intake of sodium and water are equivalent at steady state, the axes can be flipped such that arterial pressure is now plotted on the *x*-axis and sodium and water excretion, rather than intake, is plotted on the *y*-axis. This approach clearly does not establish any long-term 'cause and effect' relationship between renal perfusion pressure and sodium and water excretion. Moreover, similar to resetting of arterial baroreceptors, the acute renal function curve may reset to changes in arterial pressure. If this is true, then the cause-and-effect relationship of the chronic renal function curve is invalid.

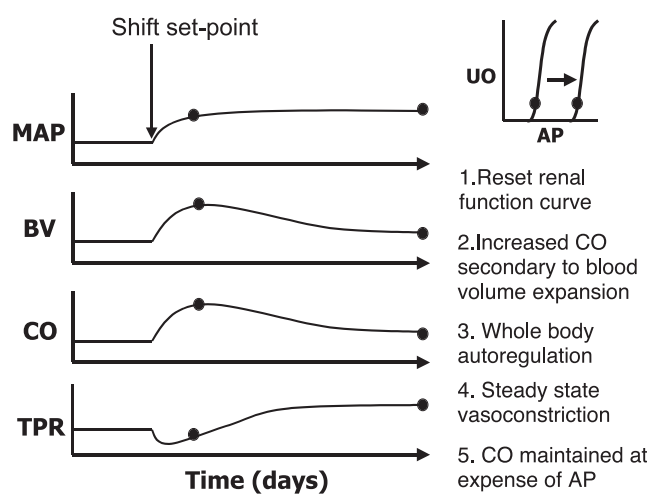


Fig. 2 The 'whole-body autoregulation haemodynamic profile' as proposed by Guyton.³ The sequence of events is described in detail in the text and steps 1–5 are described in the figure. MAP, mean arterial pressure; BV, blood volume; CO, cardiac output; TPR, total peripheral resistance; UO, urine output; AP, arterial pressure.

The second absolute of the renal–MAP set-point model predicts that all forms of hypertension are initiated by blood volume expansion in response to a primary shift in the renal function curve and that, in the steady state, only a 5% expansion of blood volume is required to maintain the increase in vascular resistance driven by whole-body autoregulation. Establishing the validity of this component of the model is hampered by the fact that most techniques for determination of blood volume have a substantial degree of error, approximately 10–20%. Nonetheless, there are studies in which experimental renovascular hypertension^{8,9} and human essential hypertension¹⁰ appear to occur without a transient increase in blood volume. Conversely, there are also reports in which an elevation in sodium and water intake increases blood volume, but not arterial pressure, chronically,^{11–13} which further calls into question the link between blood volume and arterial pressure. Indeed, this is perhaps the weakest link in the renal–MAP set-point model: the assumption that increased blood volume always leads to hypertension.

The fact that chronic blood volume expansion does not always lead to hypertension is inconsistent with the whole-body autoregulation hypothesis. The clearest examples of this are studies in normal rats,¹¹ dogs¹² and humans,¹⁴ in which a chronic increase in sodium and water intake results in a sustained increase in blood volume and cardiac output, but no change in arterial pressure. These studies are inconsistent with the two pillars of the renal–MAP set-point model in that volume expansion occurred in the presence of normal renal function and this volume expansion did not trigger a whole-body autoregulation haemodynamic profile.

THE CNS-MAP SET-POINT HYPOTHESIS

In the 30 years since it was first proposed, the renal–MAP set-point model of Guyton and colleagues has provided valuable insight into mechanisms for the long-term control of arterial pressure and the pathogenesis of hypertension. However, it has become increasingly evident over time that the main tenets of the model are inconsistent with many studies. In addition, there has been a significant amount of new knowledge generated since the model was introduced regarding neural pathways that maintain fluid and metabolic homeostasis. The remainder of this paper will present a theoretical

argument for an alternative model in which a long-term MAP set-point exists within the CNS rather than the kidney. The basic components of the model will be introduced, including proposed sensory mechanisms of the model. The role of this model in experimental hypertension will be discussed briefly.

The teleological argument for a CNS-MAP set-point for the long-term control of arterial pressure

Why would a long-term set-point for arterial pressure exist within the CNS? Similar to the logic of the renal–MAP set-point model in which arterial pressure is regulated to maintain normal renal function, it is proposed that a CNS-MAP set-point exists for the maintenance of normal cerebral function. Clearly, homeostasis and survival of the organism is dependent on maintenance of cerebral blood flow. In addition, because of the anatomical proximity of the coronary circulation within the vascular tree, maintenance of cerebral perfusion would insure maintenance of coronary perfusion as well. As a result, this system ensures perfusion of the vital organs of the body: the brain and the heart.

Dismissing the arterial baroreceptor reflex does not rule out the nervous system in the long-term control of arterial pressure

The renal–MAP set-point model largely dismissed the nervous system in the long-term control of arterial pressure on the basis that the arterial baroreceptor reflex is strictly a short-term control system. This idea is based on the fact that arterial baroreceptors reset^{15,16} and that sinoaortic denervation does not affect the basal level of arterial pressure or the steady state levels of pressure in experimental models of hypertension.^{17–20}

The problem with this argument is it assumes the arterial baroreceptor reflex is the primary neural controller of arterial pressure. This is understandable because much of the research on the neural control of arterial pressure was centred on the arterial baroreceptor reflex at the time the renal–MAP set-point model was first introduced. However, since that time, it has become increasingly evident that long-term levels of sympathetic nerve activity are regulated independent of arterial baroreceptor input.²¹ For example, although

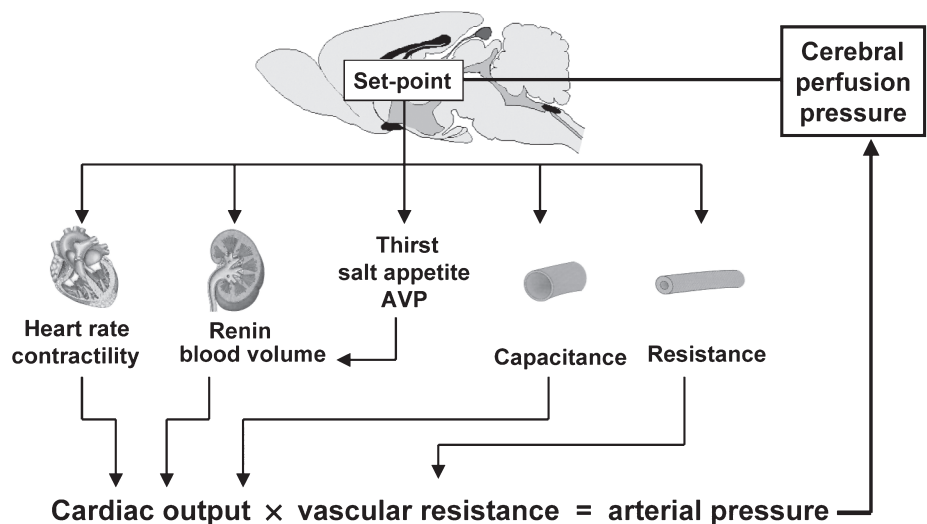


Fig. 3 Schematic of the numerous parallel pathways used by the brain to regulate cerebral perfusion pressure as described in the central nervous system (CNS)–mean arterial pressure (MAP) set-point hypothesis. See text for details. AVP, arginine vasopressin.

sinoaortic denervation does result in an acute increase in sympathetic nerve activity and hypertension, the normalization of arterial pressure over time appears to result from a return of sympathetic activity to control levels,^{22–24} rather than pressure natriuresis as originally proposed by Guyton and colleagues.³ In other words, the reason that sinoaortic denervation does not alter basal levels of arterial pressure chronically is not because the kidneys are dominant in the long-term control of arterial pressure but, rather, because sympathetic activity is controlled by ‘baroreceptor-independent’ pathways. These findings redirect our search for the neural site of the long-term MAP set-point away from the baroreceptor reflex, which is most likely a short-term controller of arterial pressure, to ‘non-baroreceptor reflex’ pathways in the brain.

The brain has many ‘tools’ it can use to control its own perfusion pressure

In the renal–MAP set-point model, arterial pressure is controlled by regulation of a single variable, blood volume, which, in turn, affects haemodynamics via whole-body autoregulation. Although several variables are involved in this control system, they are essentially linked in a series fashion, with blood volume being the single determinant of arterial pressure. This is clearly a weak aspect of this model because the control of arterial pressure is entirely dependent on regulation of one variable.

A more powerful control system is one that incorporates redundant parallel pathways that converge on the regulated variable, arterial pressure. Indeed, the brain has several ‘tools’ it can use to control its own perfusion pressure and these tools are arranged in parallel pathways that ultimately influence arterial pressure (Fig. 3). As in the renal–MAP set-point model, regulation of blood volume is an important component of this model, but it is not solely responsible for the regulation of arterial pressure. Blood volume is regulated in several ways, such as direct control of tubular sodium reabsorption, control of tubular water reabsorption via vasopressin, control of thirst and salt appetite and regulation of the renin–angiotensin–aldosterone system. However, in addition to controlling cardiac output via regulation of blood volume, the CNS–MAP set-point model also controls heart rate and cardiac contractility and indirectly controls cardiac filling pressure via regulation of venous capacitance. All these variables (blood volume, cardiac pumping ability and venous capacitance) ultimately establish cardiac output, which, in turn, affects arterial pressure. Finally, the brain regulates arteriolar resistance of several vascular beds, which also will determine the final level of arterial pressure.

The power of a control system of this design, in which several parallel pathways can be used to control arterial pressure, is that loss of one pathway does not necessarily impair the ability of the system to control arterial pressure. The impact of this control strategy in regulating arterial pressure around the ‘set-point’ is discussed below.

Arterial pressure is more tightly controlled than cardiac output

Unlike the renal–MAP set-point model, in which cardiac output is regulated at the expense of arterial pressure, the CNS–MAP

set-point prioritizes the control of arterial pressure over cardiac output. This is based on the concept that most peripheral vascular beds are overperfused at rest and increases or decreases of flow are not deleterious because oxygen extraction can be regulated at the tissue level independent of modest changes in oxygen delivery. In contrast, the cerebral and coronary circulations are more susceptible to reductions of oxygen delivery, so the driving force for flow for these vascular beds (arterial pressure) must be tightly regulated. This design permits a larger degree of error in the regulation of cardiac output than arterial pressure.

This concept is consistent with numerous studies in animals^{11,12} and humans²⁵ in which blood volume and cardiac output are poorly regulated chronically but arterial pressure is tightly controlled. It also explains experimental models of hypertension in which the haemodynamic profile is inconsistent with regard to the relative contributions of cardiac output versus peripheral vascular resistance over time. For example, hypertension produced by administration of deoxycorticosterone acetate (DOCA) and salt, a model that is neurogenically driven,^{26–29} has been shown to occur as a result of either increased cardiac output, total peripheral resistance or a combination of the two.^{30–32} These studies are inconsistent with the renal–MAP set-point model in which a single haemodynamic pattern, the whole-body autoregulation haemodynamic profile, is proposed to underlie all forms of hypertension. In contrast, the CNS–MAP set-point model predicts that arterial pressure is the regulated variable and does not impose any single haemodynamic profile to the pathogenesis of hypertension. Rather, when arterial pressure deviates from the ‘set-point’, any combination of efferent pathways may be used to return arterial pressure to normal and this could result in more than one haemodynamic profile to achieve this goal.

The concept of multiple parallel pathways converging to regulate arterial pressure is further supported by studies of DOCA-salt hypertension. A study in DOCA-salt dogs showed that, under control conditions, the haemodynamic profile was one in which the hypertension was driven by an increase in cardiac output. Although administration of a β_1 -adrenoceptor antagonist prevented the increase in cardiac output, it did not affect the magnitude of hypertension, which then resulted from an increase in peripheral vascular resistance.³² These observations support the idea that DOCA-salt shifts the CNS–MAP set-point and activates the multiple parallel pathways shown in Fig. 3 until arterial pressure reaches the new set-point. The effect of blocking a single pathway on arterial pressure will depend on the ‘relative power’ of that pathway in affecting arterial pressure. For example, the above study suggests that, in dogs, DOCA-salt increases arterial pressure by increasing cardiac sympathetic activity and cardiac output, but this pathway does not carry much ‘power’ because blocking it does not prevent the system from reaching the new set-point via other pathways. In contrast, it has been shown that renal denervation attenuates, but does not abolish, the development of hypertension in the DOCA-salt model in the rat,³³ which is consistent with the concept that the renal nerves carry more ‘power’ in this control system.

It is important to note that this concept has been proposed in the past. Over 20 years ago, Bohr hypothesised that DOCA-salt hypertension is due to mineralocorticoid actions that result in ‘...resetting of a pressure regulating centre in the hypothalamus’.³⁴ This conclusion resonates with the idea that arterial

pressure is, indeed, the regulated variable and that hypertension is due to shifting an MAP set-point in the brain. Although these ideas remain speculative at this time, they do fit within the framework of the CNS-MAP set-point model.

Afferent inputs modulating the CNS-MAP set-point: The search for the ‘sensor’

The viability of the CNS-MAP set-point hypothesis is dependent on the complete elucidation of sensory inputs that determine the ultimate level of sympathetic nerve activity and arterial pressure. As discussed previously, the majority of studies suggest that surgical interruption of arterial baroreceptor inputs to the brain have no long-term effect on arterial pressure.^{17–20} Recent reports also suggest that sympathetic nerve activity appears to be chronically regulated independent of arterial baroreceptor input.^{22–24} This leads to the question if arterial baroreceptors do not modulate the CNS-MAP set-point, then what does? At the present time, the answer to this question is unknown.

Two possibilities for sensory modulation of the CNS-MAP set-point are presented in Fig. 4. The first predicts that pathways originating in the hypothalamus that play a critical role in the maintenance of body fluid homeostasis are, in fact, the site of the CNS-MAP set-point. The second possibility is that an as yet undiscovered ‘central baroreceptor’ exists within the brain that plays a major long-term role in establishing basal levels of sympathetic activity.

Forebrain modulation of the CNS-MAP set-point

Because body fluid homeostasis is linked to the control of arterial pressure, it is logical to predict that central pathways involved in the control of extracellular fluid volume and osmolality modulate the CNS-MAP set-point. In the 1970s, Brody *et al.* proposed that the tissue surrounding the anteroventral region of the third ventricle of the hypothalamus, the AV3V, played a crucial role in the regulation of body fluid composition and sympathetic activity

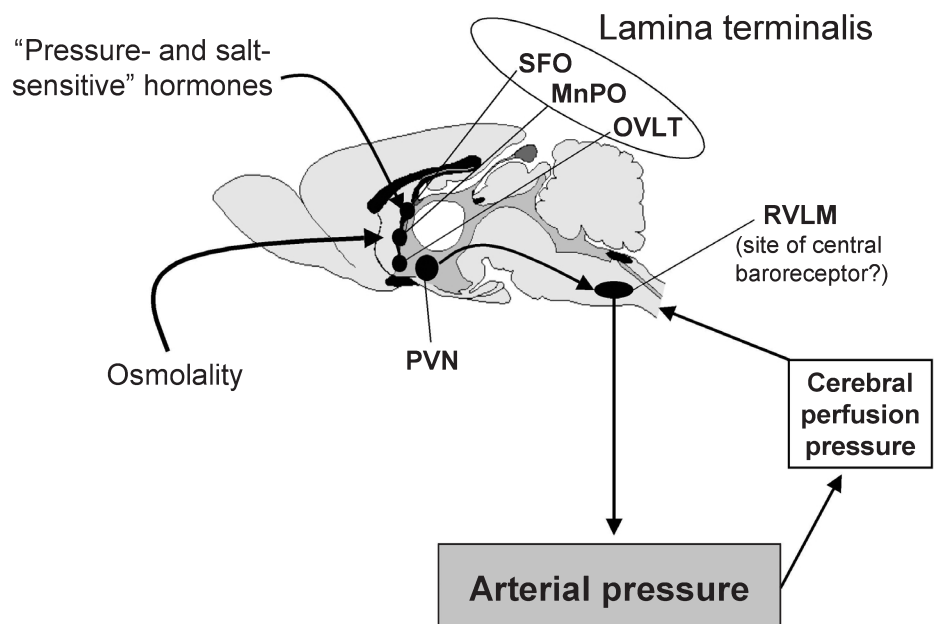
and the pathogenesis of hypertension.^{35,36} Indeed, lesion of the AV3V prevents several forms of experimental hypertension, including the DOCA-salt model.³⁷ This is consistent with the idea proposed by Bohr that that DOCA-salt results in ‘. . . resetting of a pressure regulating centre in the hypothalamus’³⁴ and the AV3V is a site at which DOCA-salt acts.

The AV3V includes the median preoptic nucleus and organum vasculosum of the lamina terminalis (OVLT). These structures, in combination with the subfornical organ (SFO), are referred to as the lamina terminalis. Since the discovery of the role of this region in fluid balance regulation, the neuroanatomical and neurochemical substrates of the lamina terminalis, as well as its afferent and efferent connections, have been studied intensively in several laboratories. The reader is referred to several excellent reviews for a detailed discussion of this work.^{38–41}

The possible role of the lamina terminalis in modulation of the CNS-MAP set-point is summarized in Fig. 4. The SFO and OVLT, like other circumventricular organs in the brain, have a poor blood–brain barrier and are able to ‘sense’ plasma concentrations of several hormones involved in the maintenance of body fluid volume and osmolality.³⁹ The SFO and OVLT are also osmosensitive, with some suggesting that the OVLT is the ‘central osmoreceptor’.³⁹ Moreover, there are prominent efferent projections from these structures to the paraventricular nucleus (PVN), which sends excitatory projections to the sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM).^{42–44} Studies indicate that these efferent projections, from the lamina terminalis to the PVN to the RVLM, may mediate the sympathetic excitatory responses to both increased cerebral fluid osmolality and plasma angiotensin II.^{45,46}

Clearly, these forebrain structures are critical to the maintenance of body fluid homeostasis by regulating thirst, salt appetite, vasopressin secretion and sympathetic activity.^{39,41} However, the question that needs to be answered is this: do these pathways simply modulate arterial pressure or do they in fact control it? It remains to be shown whether the lamina terminalis and downstream neural pathways do, in fact, comprise a true CNS-MAP

Fig. 4 Schematic of proposed sensory inputs modulating the central nervous system (CNS)–mean arterial pressure (MAP) set-point. Forebrain structures within the lamina terminalis are responsive to blood-borne signals (hormones and osmolality) related to arterial pressure and body fluid composition. These structures include the subfornical organ (SFO), median preoptic nucleus (MnPO) and organum vasculosum of the lamina terminalis (OVLT). These signals are integrated and this information is transmitted via efferent projections of the paraventricular nucleus (PVN), which sends excitatory projections to sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM). It is also proposed that a ‘central baroreceptor’ exists within the brainstem, perhaps within the RVLM itself.



set-point system. In other words, can all the sensory inputs to these structures be integrated in such way as to ultimately regulate arterial pressure around a predetermined 'set-point'? One argument against this idea is that that we still do not understand how these sensory inputs are integrated to reflect the absolute level of arterial pressure. This leads us to question whether there is another input to the brain related to the arterial pressure that we have yet to discover.

Could a 'central baroreceptor' exist and modulate the CNS-MAP set-point?

Surgical removal of arterial baroreceptors does not chronically affect arterial pressure or the pathogenesis of experimental hypertension. It is now becoming apparent that this is because the long-term basal level of sympathetic activity is regulated independent of arterial baroreceptor input.²¹ One possible mechanism responsible for the chronic regulation of sympathetic activity is the existence of a 'central baroreceptor' within the brain itself. Such a possibility has not been discussed in the literature or explored experimentally.

Similar to peripheral and central chemoreceptors that serve different roles in the regulation of ventilation, it is hypothesised that both peripheral and central baroreceptors exist and serve different roles in the regulation of sympathetic activity and arterial pressure. Peripheral chemoreceptors located in the carotid sinuses and aortic arch sense oxygen tension in the blood and send afferent nerve activity via the 9th and 10th cranial nerves, respectively, to the ventral lateral medulla to modulate respiratory activity.⁴⁷ In contrast, central chemoreceptors are located in the ventral medulla itself and sense pH primarily to influence ventilation.⁴⁸ Denervation of peripheral chemoreceptors can alter ventilatory patterns, but it is clear that regulation of ventilation still occurs and blood gases are regulated long term in the absence of peripheral chemoreceptor input.^{47,48}

Is it not possible that a similar strategy exists for arterial baroreceptors? Similar to the peripheral chemoreceptors, arterial baroreceptors located in the carotid sinuses and aortic arch send afferent projections to the ventral medulla via the 9th and 10th cranial nerves, respectively. It is suggested that a central baroreceptor exists within the ventral medulla that exerts predominant control over the long-term control of sympathetic nerve activity and arterial pressure. It is logical to predict that this baroreceptor is located in close proximity to, or within, the RVLM itself. It remains to be established whether sympathetic activity is generated by pacemaker neurons within the RVLM or if this region is one component of a network within the brainstem that regulates sympathetic preganglionic neurons. Regardless, it is still an ideal location for a central baroreceptor because this site is clearly integral to the regulation of sympathetic activity.⁴⁹ It is suggested that the 'central baroreceptor' may play a predominant role in establishing the basal level of sympathetic activity, whereas the peripheral baroreceptors are involved primarily with the short-term regulation of sympathetic activity and arterial pressure.

The central baroreceptor hypothesis is compatible with two lines of investigation. First, both animal^{50,51} and clinical studies^{52,53} suggest that neurovascular compression in the RVLM region increases sympathetic activity and arterial pressure. These studies are consistent with the idea that mechanical compression of RVLM neurons can alter sympathetic nerve discharge independent of the arterial baroreceptor reflex and may be linked to hypertension.^{52,53}

Second, there is a well-established relationship between cerebral perfusion pressure and sympathetic activity, the so-called 'Cushing response', in which decreases in pressure below approximately 60 mmHg result in large increases in sympathetic activity in anaesthetized animals. In a recent commentary to a review by Thrasher by Dickinson,⁵⁴ the possibility is raised that, in unanaesthetized animals and humans, this relationship may be responsible for sustained increases in arterial pressure and sympathetic activity secondary to occlusion of cerebral arteries.⁵⁴ It is argued that this '...putative hypertensive effect should be powerful and sustained enough to overcome the automatic resetting such as is seen in all peripheral baroreceptor systems'.⁵⁴

This concept of perfusion pressure modulating pacemaker activity is not without precedent in cardiovascular control systems. It has been proposed that the pacemaker potential of sinoatrial node cells in the heart is directly influenced by a mechanotransduction mechanism in which changes in vascular pressure within the sinoatrial node alter the membrane properties of cardiac pacemaker cells.⁵⁵⁻⁵⁷ This has been proposed to be one mechanism underlying the direct relationship between coronary perfusion pressure and heart rate in the isolated heart⁵⁸ and respiratory sinus arrhythmia in cardiac transplant patients.⁵⁹ Although it remains controversial whether RVLM neurons exhibit pacemaker activity,⁶⁰ it is certainly possible that changes in vascular pressures within the RVLM itself alter membrane excitability of sympathetic premotor neurons in this brainstem site.

Although there are presently no data to directly support the concept of a 'central baroreceptor', it is a possibility that needs to be explored. It is important to point out that the existence of a baroreceptor in the brain for the CNS-MAP set-point model is similar to the proposed existence of the 'renal baroreceptor' that plays a role in the regulation of renin release and the long-term control of arterial pressure.⁶¹

The CNS-MAP set-point hypothesis and the pathogenesis of arterial hypertension

The concept that a neural control system exists for the long-term control of arterial pressure has been presented. This model is based on the teleological argument that evolutionary strategies have developed to maintain the driving force for cerebral blood flow and arterial pressure. Under conditions in which these are threatened, specifically hypovolaemia as a result of water deprivation or haemorrhage, mechanisms are in place to counteract the effects of these challenges on cerebral blood flow. These strategies evolved such that hormones released during hypovolemic stress (e.g. angiotensin II, aldosterone), in concert with other signals, such as osmolality, act on the brain to stimulate sympathetic outflow to several peripheral targets, including the kidney, the heart and the vasculature to maintain cerebral and coronary perfusion pressure to protect the metabolic needs of these vital tissues.

Could primary dysfunction of the CNS-MAP set-point contribute to the pathogenesis of human essential hypertension? The evidence for increased SNA in humans with essential hypertension is extremely compelling. This is supported by assessment of sympathetic activity using complementary techniques, such as microneurography and noradrenaline spillover rate to plasma, which have yielded remarkably consistent results.^{62,63} More recent studies measuring single fibre activity have provided

unequivocal proof that sympathetic activity is increased in hypertension.^{64,65}

Theoretically, neurogenic hypertension occurs as the result of a primary shift of the CNS-MAP set-point to a higher operating pressure, resulting in increases sympathetic nerve activity. Such a shift may result from either increases in blood-borne signals that act on the CNS-MAP set-point, such as plasma osmolality, angiotensin II or mineralocorticoids, and/or alterations in the cellular signalling pathways within the neural networks responsive to these signals. Studies in patients with chronic angiotensin-dependent renovascular hypertension have generally demonstrated sympathetic activation, the magnitude of which is correlated with circulating angiotensin II concentrations.^{66,67} The centrally acting sympatholytic drug clonidine is effective in lowering blood pressure in humans with renovascular hypertension without suppressing circulating angiotensin II.⁶⁸ Furthermore, angiotensin-converting enzyme inhibitors^{69,70} and angiotensin receptor antagonists⁷¹ tend to suppress sympathetic nerve activity when used to lower arterial pressure in hypertensive humans (although baroreflexes can mask this response). Similar to humans, the literature supports the concept that angiotensin II mediates many forms of neurogenic hypertension in the rat as well.⁷²

CAVEATS

During the peer review of this manuscript, two concerns were raised regarding the validity of an 'MAP set-point' in general that I would like to address here.

The first issue was related to the concept of a set-point in general in cardiovascular control:

'What is really a set-point? Is it a reference value? If so, how do biologists transfer this well defined engineering term to biological settings and hypotheses? It would be very appropriate to define this issue so that we know explicitly what we are dealing with.'

This is a valid point to which I do not have a definite answer. As stated at the beginning of this paper, the term 'set-point' is used to designate a control system that does, in fact, maintain the regulated variable (i.e. arterial pressure) via feedback control pathways in response to deviation from a 'reference value'. Within the framework of the Guyton model, for example, the 'renal function curve' is a two-dimensional plot of renal perfusion pressure on the *x*-axis and urine output on the *y*-axis with the 'equilibrium point' (i.e. set-point) establishing the long-term level of arterial pressure. This is clearly an oversimplification and the precise variables influenced by renal perfusion pressure that result in natriuresis and diuresis are still unknown and the subject of ongoing research. As such, if the 'long-term MAP set-point' is in the kidney, we still have no clear idea what the physical nature of this 'set-point' is. Does that mean that a set-point does not exist within the kidney or that we have yet to discover how the kidney transduces changes in perfusion pressure to changes in sodium and water excretion?

The second issue raised by the reviewer relates to a link between arterial pressure and organ blood flow, specifically renal and cerebral blood flow:

'Furthermore, it is surprising that the author provides an (in many ways adequate and interesting) overview of the potential roles of the kidneys and the brain without mentioning that these organs represent vascular beds which are heavily autoregulated. Powerful

local autoregulation has always been difficult to reconcile with phenomena related to efficient regulation of blood supply.'

There is no question that both the cerebral and renal vascular beds are extremely efficient at autoregulation of blood flow when whole-organ blood flow is measured. However, over the past few years, the concept has emerged that flows within specific regions may not be well autoregulated. For example, the hypothesis has been advanced that renal medullary flow is poorly autoregulated and that the physical link between renal perfusion pressure and sodium excretion is via changes in renal medullary blood flow.⁷³ Is it not possible that a similar situation exists within the brain, where blood flow in a specific region is poorly autoregulated? For example, what if flow in the RVLM is poorly controlled such that a decrease in arterial pressure results in a localized decrease in flow through the RVLM? Could that not serve as the transduction mechanism that established the 'long-term physical link' between cerebral perfusion pressure and sympathetic activity? In essence, such a system would act as a highly sensitive localized 'Cushing response'. I am not aware of any studies that refute such a possibility.

Both of the concerns are valid and in need of further discussion and debate. Most importantly, the idea that a 'set-point' for arterial pressure control can, in fact, be described in physical terms, its location within a specific organ system and the underlying physiological mechanisms defined is the subject of an entire meeting by itself.

CONCLUDING COMMENTS

The long-term control of arterial pressure is extremely complex, involving time-dependent interactions of neural, hormonal and local control systems acting on the heart, kidney and vasculature to control the systemic circulation. Understanding the complexity of these interactions is impossible without applying a computational biology approach to generate testable hypotheses. In 1974, Guyton *et al.* published their classic paper *A Systems Analysis Approach to Understanding Long-Range Arterial Blood Pressure Control and Hypertension*.² This paper was revolutionary in that it was the first to use computer modelling methods to understand the long-term control of arterial pressure. This approach, combined with the emphasis of conducting longitudinal studies in conscious animals, has been extremely powerful in advancing our understanding of the regulation of arterial pressure and hypertension. Thirty years later, this approach is again in vogue in the new age of 'systems biology'.

Although the renal-MAP set-point model has provided valuable insights into our understanding of the long-term control of arterial pressure, it has become outdated in terms of incorporating advancements in our knowledge of central neural networks involved in the maintenance of body fluid homeostasis and sympathetic drive to the cardiovascular system. In the present paper, a model is presented in which the brain, rather than the kidney, establishes the long-term set-point for arterial pressure. A theoretical argument is presented for the existence of a CNS-MAP set-point system.

It remains to be shown whether a CNS-MAP set-point system exists and the relative importance of such a system to the renal-MAP set-point model. Moreover, as proposed by Fink in a companion paper in this journal,¹ the use of 'set-point control theory' to understand long-term control of arterial pressure may not

be the correct approach. It may be that a 'set-point' does not exist and arterial pressure is simply an 'emergent property' of the system. Whether a 'set-point model' or a 'free market system' is what determines the long-term level of arterial pressure remains to be established. What is clear is that we must move forward with the goal of developing an updated model of the long-term control of arterial pressure in order to better understand the underlying mechanisms of hypertension, as well the development of therapeutic strategies to treat this disease.

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REFERENCES

- Fink GD. Hypothesis: The systemic circulation as a regulated free-market economy. A new approach for understanding the long-term control of blood pressure. *Clin. Exp. Pharmacol. Physiol.* 2005; **32**: 377–83.
- Guyton AC, Coleman TG, Cowley Jr AW, Manning Jr RD, Norman Jr RA, Ferguson JD. A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. *Circ. Res.* 1974; **35**: 159–69.
- Guyton AC. Dominant role of the kidneys and accessory role of whole-body autoregulation in the pathogenesis of hypertension. *Am. J. Hypertens.* 1989; **2**: 575–85.
- Guyton AC. Renal function curves and control of body fluids and arterial pressure. *Acta Physiol. Scand.* 1990; **139** (Suppl. 591): 107–13.
- Guyton AC, Coleman TG, Cowley Jr AW, Scheel KW, Manning Jr RD, Norman Jr RA. Arterial pressure regulation: Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am. J. Med.* 1972; **52**: 584–94.
- Guyton AC. *Circulatory Physiology III: Arterial Pressure and Hypertension*. WB Saunders, Philadelphia. 1980.
- Roman RJ, Cowley Jr AW. Characterization of a new model for the study of pressure-natriuresis in the rat. *Am. J. Physiol.* 1985; **248**: F190–8.
- Cowley Jr AW, Skelton MM, Papanek PE, Greene AS. Hypertension induced by high salt intake in absence of volume retention in reduced renal mass rats. *Am. J. Physiol. Heart Circ. Physiol.* 1994; **267**: H1707–12.
- Fink GD, Johnson RJ, Galligan JJ. Mechanisms of increased venous smooth muscle tone in deoxycorticosterone acetate-salt hypertension. *Hypertension* 2000; **35**: 464–9.
- Julius S, Nesbitt S. Sympathetic overactivity in hypertension: A moving target. *Am. J. Hypertens.* 1996; **9**: 113s–20s.
- Greene AS, Yu ZY, Roman RJ, Cowley Jr AW. Role of blood volume expansion in Dahl rat model of hypertension. *Am. J. Physiol.* 1990; **258**: H508–14.
- Krieger JE, Liard J-F, Cowley Jr AW. Hemodynamics, fluid volume, and hormonal responses to chronic high-salt intake in dogs. *Am. J. Physiol. Heart Circ. Physiol.* 1990; **259**: H1629–36.
- Sullivan JM, Ratts TE. Hemodynamic mechanisms of adaptation to chronic high sodium intake in humans. *Hypertension* 1983; **5**: 814–20.
- Sullivan JM, Ratts TE. Sodium sensitivity in human subjects: Hemodynamic and hormonal correlates. *Hypertension* 1988; **11**: 717–23.
- Andresen MC, Yang M. Arterial baroreceptor resetting: Contributions of chronic and acute processes. *Clin. Exp. Pharmacol. Physiol.* 1989; **15** (Suppl.): 19–30.
- McCubbin JW, Green JH, Page IH. Baroreceptor function in chronic renal hypertension. *Circ. Res.* 1956; **4**: 205–10.
- Cowley Jr AW, DeClue JW. Quantification of baroreceptor influence on arterial pressure changes seen in primary angiotensin-induced hypertension in dogs. *Circ. Res.* 1976; **39**: 779–87.
- Cowley Jr AW, Liard JF, Guyton AC. Role of the baroreceptor reflex in daily control of arterial blood pressure and other variable in dogs. *Circ. Res.* 1973; **32**: 564–76.
- Cowley Jr AW, Quillen EW, Barber BJ. Further evidence for lack of baroreceptor control of long-term level of arterial pressure. In: Sleight P (ed.). *Arterial Baroreceptors and Hypertension*. Oxford University Press, New York. 1980; 391–9.
- Osborn JW. Pathogenesis of hypertension in the baroreceptor-denervated spontaneously hypertensive rat. *Hypertension* 1991; **18**: 475–82.
- Osborn JW, Jacob F, Guzman P. A neural set point for the long-term control of arterial pressure: Beyond the baroreceptor reflex. *Am. J. Physiol.* 2005; **288** (available online: doi:10.1152/ajpregu.00474.2004).
- Barres C, Lewis SJ, Jacob HJ, Brody MJ. Arterial pressure lability and renal sympathetic nerve activity are dissociated in SAD rats. *Am. J. Physiol.* 1992; **263**: R639–46.
- Iirgoyen MC, Moreira ED, Ida F, Pires M, Cestari IA, Krieger EM. Changes of renal sympathetic activity in acute and chronic conscious sinoaortic denervated rats. *Hypertension* 1995; **26**: 1111–16.
- Osborn JW, England SK. Normalization of arterial pressure after barodenervation: Role of pressure natriuresis. *Am. J. Physiol.* 1990; **259**: R1172–80.
- Sullivan JM, Prewitt RL, Ratts TE, Josephs JA, Connor MJ. Hemodynamic characteristics of sodium sensitive human subjects. *Hypertension* 1987; **9**: 398–406.
- Berecek KH, Murray RD, Gross F. Significance of sodium, sympathetic innervation, and central adrenergic structures on renal vascular responsiveness in DOCA-treated rats. *Circ. Res.* 1980; **47**: 675–83.
- Clarke D, Smookler HH, Barry H. Sympathetic nerve function and DOCA-NaCl induced hypertension. *Life Sci.* 1970; **9**: 1097–108.
- Matsuguchi H, Schmid P. Pressor response to vasopressin and impaired baroreflex-function in DOC-salt hypertension. *Am. J. Physiol.* 1982; **242**: H44–9.
- Takeda K, Bunag RD. Augmented sympathetic nerve activity and pressor responsiveness in DOCA hypertensive rats. *Hypertension* 1980; **2**: 97–101.
- Miller II AW, Bohr DF, Schork AM, Terris JM. Hemodynamic responses to DOCA in young pigs. *Hypertension* 1979; **1**: 591–7.
- Bravo E, Tarazi R, Dustan H. Multifactorial analysis of chronic hypertension induced by electrolyte-active steroids in trained, unanesthetized dogs. *Circ. Res.* 1977; **40** (Suppl. I): I–140 (Abstract).
- Conway J, Hatton J. Development of deoxycorticosterone acetate hypertension in the dog. *Circ. Res.* 1966; **43** (Suppl. 1): I–82.
- Jacob F, LaBine BG, Ariza P, Katz SA, Osborn JW. Renal denervation causes chronic hypotension in rats: Role of β_1 -adrenoceptor activity. *Clin. Exp. Pharmacol. Physiol.* 2005; **32**: 254–61.
- Bohr DF. What makes the pressure go up? A hypothesis. *Hypertension* 1981; **3**: 11 106–65.
- Brody MJ, Fink GD, Buggy J, Haywood JR, Gordon FJ, Johnson AK. The role of the anteroventral third ventricle (AV3V) region in experimental hypertension. *Circ. Res.* 1978; **43** (Suppl. I): I–2–13.
- Buggy J, Fink GD, Johnson AK, Brody MJ. Prevention of the development of renal hypertension by anteroventral third ventricular tissue lesions. *Circ. Res.* 1977; **40** (Suppl. I): I–110–17.
- Songu-Mize E, Bealer SL, Caldwell RW. Effect of AV3V lesions on development of DOCA-salt hypertension and vascular Na^+ -pump activity. *Hypertension* 1982; **4**: 575–80.

38. Johnson AK, Loewy AD. Circumventricular organs and their role in visceral functions. In: Loewy AD, Spyer KM (eds). *Central Regulation of Autonomic Functions*. Oxford University Press, New York. 1990; 247–67.
39. McKinley MJ, Johnson AK. The physiological regulation of thirst and fluid intake. *News Physiol. Sci.* 2004; **19**: 1–6.
40. McKinley MJ, McAllen RM, Davern P *et al.* *The Sensory Circumventricular Organs of the Mammalian Brain*. Springer, Berlin. 2003.
41. Johnson AK, Gross PM. Sensory circumventricular organs and brain homeostatic pathways. *FASEB J.* 1993; **7**: 678–86.
42. Allen AM. Blockade of angiotensin AT₁-receptors in the rostral ventrolateral medulla of spontaneously hypertensive rats reduces blood pressure and sympathetic nerve discharge. *J. Renin Angiotensin Aldosterone Syst.* 2001; **2** (Suppl. 1): S120–4.
43. Allen AM. Inhibition of the hypothalamic paraventricular nucleus in spontaneously hypertensive rats dramatically reduces sympathetic vasomotor tone. *Hypertension* 2002; **39**: 275–80.
44. Ito S, Komatsu K, Tsukamoto K, Kanmatsuse K, Sved AF. Ventrolateral medulla AT₁ receptors support blood pressure in hypertensive rats. *Hypertension* 2002; **40**: 552–9.
45. Ferguson AV. Paraventricular nucleus neurons projecting to the dorsomedial medulla are influenced by systemic angiotensin II. *Brain Res. Bull.* 1988; **20**: 197–201.
46. Ferguson AV, Bains JS. Angiotensin actions in subfornical organ and area postrema: Implications for long-term control of autonomic output. *Clin. Exp. Pharmacol. Physiol.* 1997; **24**: 96–101.
47. Lahiri S. Physiological responses: Peripheral chemoreceptors and chemoreflexes. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds). *The Lung: Scientific Foundations*. Lippincott-Raven, Philadelphia. 1997; 1747–56.
48. Cherniack NS, Altose MD. Central chemoreceptors. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds). *The Lung: Scientific Foundations*. Lippincott-Raven, Philadelphia. 1997; 1767–76.
49. Sved AF, Ito S, Sved JC. Brainstem mechanisms of hypertension: Role of rostral ventrolateral medulla. *Curr. Hypertens. Rep.* 2003; **5**: 262–8.
50. Morimoto S, Sasaki S, Miki S *et al.* Pressor response to pulsatile compression of the rostral ventrolateral medulla mediated by nitric oxide and c-fos expression. *Br. J. Pharmacol.* 2000; **129**: 859–64.
51. Morimoto S, Sasaki S, Miki S *et al.* Pressor response to compression of the ventrolateral medulla mediated by glutamate receptors. *Hypertension* 1999; **33**: 1207–13.
52. Morimoto S, Sasaki S, Takeda K *et al.* Decreases in blood pressure and sympathetic nerve activity by microvascular decompression of the rostral ventrolateral medulla in essential hypertension. *Stroke* 1999; **30**: 1707–10.
53. Smith PA, Meaney J, Graham L *et al.* Relationship of neurovascular compression to central sympathetic discharge in essential hypertension. *J. Am. Coll. Cardiol.* 2004; **43**: 1453–8.
54. Thrasher TH. Baroreceptors and the long-term control of blood pressure. *Exp. Physiol.* 2004; **89**: 331–41.
55. Hashimoto K, Tanaka S, Hirata M, Chiba S. Response of the sinoatrial node to change in pressure in the sinus node artery. *Circ. Res.* 1967; **XXI**: 297–304.
56. Musgrave GE. Bimodal relationship between sinus node arterial distension and sinus node automaticity. *Am. J. Physiol.* 1981; **241**: H311–16.
57. Loeb JM, deTarnowsky JM, Doerschuk SH, Whitson CC. Autoregulation of cardiac cycle length: Role of catecholamines. *J. Pharmacol. Exp. Ther.* 1984; **231**: 281–5.
58. Slovut D, Wenstrom J, Moeckel R, Salerno C, Park S, Osborn J. Beat-to-beat modulation of heart rate is coupled to coronary perfusion pressure in the isolated heart. *J. Appl. Physiol.* 1999; **86**: 694–700.
59. Slovut DP, Wenstrom IC, Moeckel RB, Wilson RF, Osborn JW, Abrams JH. Respiratory sinus arrhythmia persists in transplanted human hearts following autonomic blockade. *Clin. Exp. Pharmacol. Physiol.* 1998; **25**: 322–30.
60. Guyenet PG. Role of the ventral medulla oblongata in blood pressure regulation. In: Loewy AD, Spyer KM (eds). *Central Regulation of Autonomic Functions*. Oxford University Press, New York. 1990; 145–67.
61. Ehmke H, Persson P, Kircheim H. Pressure-dependent renin release: The kidney factor in long-term control of arterial pressure in conscious dogs. *Clin. Exp. Theory Practice* 1987; **A9** (Suppl. 1): 181–95.
62. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 1998; **31**: 68–72.
63. Esler M. The sympathetic system and hypertension. *Am. J. Hypertens.* 2000; **13**: 995–1055.
64. Greenwood JP, Stoker JB, Mary D. Single unit sympathetic discharge: Quantitative assessment in human hypertensive disease. *Circ. Res.* 1999; **100**: 1305–10.
65. Mary D. The activity of single vasoconstrictor nerve units in hypertension. *Acta Physiol. Scand.* 2003; **177**: 367–76.
66. Johansson M, Elam M, Rundquist B *et al.* Increased sympathetic nerve activity in renovascular hypertension. *Circulation* 1999; **99**: 2537–42.
67. Grassi G, Esler M. The sympathetic nervous system in renovascular hypertension: Lead actor or bit player? *J. Hypertens.* 2002; **20**: 1071–3.
68. Mathias CJ. Role of sympathetic efferent nerves in blood pressure regulation and in hypertension. *Hypertension* 1991; **18** (Suppl. 5): III22–30.
69. Tuncel M, Augustyniak R, Zhang W, Toto RD, Victor RG. Sympathetic nervous system function in renal hypertension. *Curr. Hypertens. Rep.* 2002; **4**: 229–36.
70. Johansson M, Elam M, Rundquist B *et al.* Differentiated response of the sympathetic nervous system to angiotensin-converting enzyme inhibition in hypertension. *Hypertension* 2000; **36**: 543–8.
71. Struck J, Muck P, Trubger D *et al.* Effects of selective angiotensin II receptor blockade on sympathetic nerve activity in primary hypertensive subjects. *J. Hypertens.* 2002; **20**: 1143–9.
72. Fink GD. Long-term sympathoexcitatory effect of angiotensin II: A mechanism of spontaneous and renovascular hypertension. *Clin. Exp. Pharmacol. Physiol.* 1997; **24**: 91–5.
73. Cowley Jr AW, Mattson DL, Lu S, Roman RJ. The renal medulla and hypertension. *Hypertension* 1995; **25**: 663–73.