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BRIEF REVIEW

CENTRAL MECHANISMS UNDERLYING SHORT- AND LONG-TERM REGULATION OF THE CARDIOVASCULAR SYSTEM

RAL Dampney, MJ Coleman, MAP Fontes, Y Hirooka, J Horiuchi, Y-W Li, JW Polson, PD Potts and T Tagawa

Department of Physiology and Institute for Biomedical Research, University of Sydney, Sydney, New South Wales, Australia

SUMMARY

1. Sympathetic vasomotor nerves play a major role in determining the level of arterial blood pressure and the distribution of cardiac output. The present review will discuss briefly the central regulatory mechanisms that control the sympathetic outflow to the cardiovascular system in the short and long term.

2. In the short term, the sympathetic vasomotor outflow is regulated by: (i) homeostatic feedback mechanisms, such as the baroreceptor or chemoreceptor reflexes; or (ii) feed-forward mechanisms that evoke cardiovascular changes as part of more complex behavioural responses.

3. The essential central pathways that subserve the baroreceptor reflex and, to a lesser extent, other cardiovascular reflexes, have been identified by studies in both anaesthetized and conscious animals. A critical component of these pathways is a group of neurons in the rostral ventrolateral medulla that project directly to the spinal sympathetic outflow and that receive inputs from both peripheral receptors and higher centres in the brain.

4. Much less is known about the central pathways subserving feed-forward or 'central command' responses, such as the cardiovascular changes that occur during exercise or that are evoked by a threatening or alerting stimulus. However, recent evidence indicates that the dorsomedial hypothalamic nucleus is a critical component of the pathways mediating the cardiovascular response to an acute alerting stimulus.

5. Long-term sustained changes in sympathetic vasomotor activity occur under both physiological conditions (e.g. a change in salt intake) and pathophysiological conditions (e.g. heart failure). There is evidence that the paraventricular nucleus in the hypothalamus is a critical component of the pathways mediating these changes.

6. Understanding the central mechanisms involved in the long-term regulation of sympathetic activity and blood pressure is a major challenge for the future. As a working hypothesis, a model is presented of the postulated central mechanisms that result in sustained changes in sympathetic vasomotor activity that are evoked by different types of chronic stimulation.

Key words: alerting response, baroreceptor reflex, blood pressure regulation, central cardiovascular pathways, central command, heart failure, hypothalamus, medulla oblongata.

INTRODUCTION

The blood flow to any region in the body depends on the perfusion pressure (which is essentially the arterial pressure) and the resistance to flow in that region. The arterial pressure is regulated by feedback control systems, operating in both the short and long term, which rely on autonomic nerves and circulating hormones as their effector mechanisms. The vascular resistance in any particular region is influenced, to varying degrees depending on the region, by the activity of sympathetic vasomotor nerves, the level of circulating vasoactive hormones and also by local factors, including metabolites and endothelial factors.

Fundamentally, homeostasis depends on the blood flow to all regions of the body being appropriate for the metabolic demands of each region. The metabolic activity may vary greatly, particularly in skeletal muscle or the heart, and, under some circumstances (e.g. strenuous exercise), a large increase in cardiac output is required if the metabolic demands of skeletal muscles and the heart are to be met by appropriate increases in blood flow to those regions. An increase in metabolic activity in these regions results in local vasodilation and, thus, increased blood flow, which depends on the direct effect of metabolites and endothelial factors on vascular smooth muscle.[1] This is a highly efficient means of matching local blood flow to local metabolic demands, provided that the perfusion pressure (arterial pressure) is maintained at an appropriate level.

The optimal level of arterial pressure is presumably determined by a balance between the need to ensure an adequate perfusion pressure and the fact that, as the arterial pressure increases, the cardiac work and risk of structural damage to the heart and blood vessels also increases. The level around which arterial pressure is regulated, the 'set point', varies under different conditions. For example, during dynamic exercise, arterial pressure is increased by

Correspondence: Roger AL Dampney, Department of Physiology and Institute for Biomedical Research, University of Sydney, Sydney, NSW 2006, Australia. Email: rogerd@physiol.usyd.edu.au

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approximately 15–20%[1] and this increase in pressure has been shown to confer the benefit of an increased blood flow to exercising skeletal muscles and consequent reduction in muscle fatigue.[2] Thus, natural selection appears to favour a control system that regulates the arterial pressure around a set point that varies according to the animal's behaviour. Therefore, it is not surprising that continuous measurements of arterial pressure in humans and other animals show large variations in arterial pressure over a 24 h period that are related to changes in the level of activity or arousal.[3]

Apart from being the principal mechanism for regulating arterial pressure in the short term, the sympathetic nervous system also controls the distribution of cardiac output to different vascular beds. The distribution pattern also varies according to the external stimuli or stresses imposed upon an animal. For example, hypoxia (signalled by peripheral chemoreceptors) elicits a pattern of changes in the activity of sympathetic nerves innervating various vascular beds that is different to that evoked by hypotension (signalled by arterial baroreceptors).[4] Thus, central mechanisms can produce differentiated patterns of sympathetic activity according to the particular stimulus.

Short-term (i.e. seconds to minutes) changes in sympathetic activity are triggered either reflexly from peripheral receptors or as part of a centrally generated response (e.g. sympathetic changes that occur at the onset of exercise). Furthermore, long-term changes (i.e. over hours or days or even longer periods) can also be evoked by various stimuli. Long-term changes also accompany certain disease states, such as heart failure. Whatever the source of the stimulus evoking changes in sympathetic activity, the neural substrates generating these changes include nuclei in the hypothalamus and/or medulla (Fig. 1). The present article will briefly consider the different types of central regulatory mechanisms that control the sympathetic outflow to the cardiovascular system in the short and long-term.

SHORT-TERM FEEDBACK REGULATION

Various external disturbances, if not compensated for, may threaten cardiovascular homeostasis. Common examples of such disturbances include a postural change that reduces venous return or increased skeletal muscle activity, which induces vasodilation. These effects result, in turn, in a fall in arterial pressure, which, if not compensated for, may result in an inadequate perfusion pressure (and, thus, oxygen delivery) for vital organs such as the brain and heart, which have little capacity for anaerobic metabolism. The major compensatory reflex mechanism that responds to such changes in arterial pressure is the baroreceptor reflex.

The arterial baroreceptors are located in the walls of the carotid sinus and aortic arch and are the terminals of afferent fibres that run in the glossopharyngeal and vagal nerves. Their adequate stimulus is stretch and they signal changes in arterial pressure over a wide range, from approximately 50 to 150 mmHg.[5]

Studies using a variety of experimental approaches have investigated the central pathways and neurotransmitters that subserve the baroreceptor reflex (for reviews see Guyenet[6] and Dampney[7]). These studies have included electrophysiological and pharmacological studies in anaesthetized animals (for a review see Guyenet[6]), as well as studies in conscious animals using the method of immediate early gene expression in combination with neuroanatomical tracing and immunohistochemistry.[8–11] Collectively, these studies have resulted in a model of the essential pathways subserving the baroreceptor

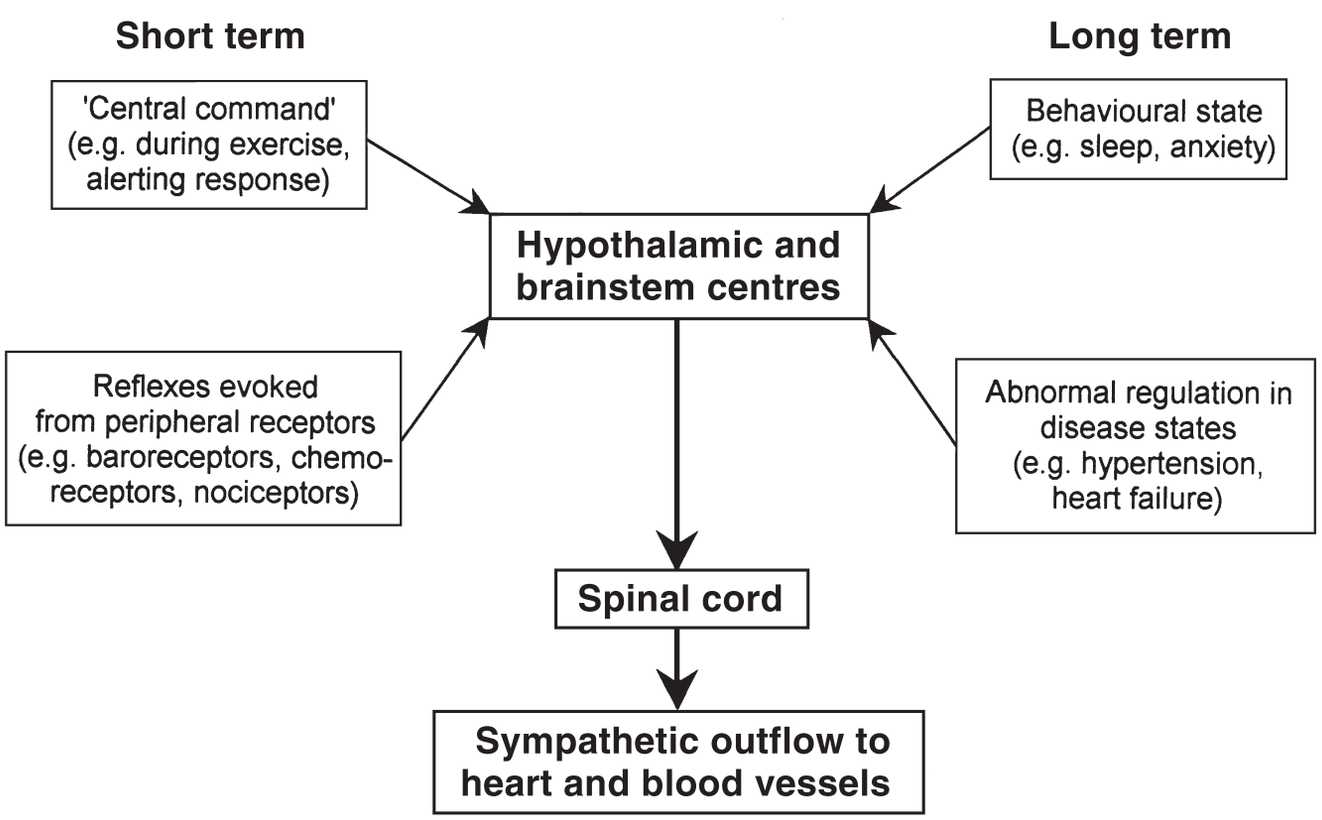

Fig. 1 Schematic diagram indicating short- and long-term mechanisms that influence sympathetic outflow to the heart and blood vessels.

reflex, as illustrated in Fig. 2. In brief, baroreceptor afferent fibres terminate within the nucleus tractus solitarius (NTS) and excite second-order neurons via a glutamatergic synapse. The NTS neurons conveying baroreceptor signals then project to and excite (again via a glutamatergic synapse) neurons within the caudal and intermediate parts of the ventrolateral medulla (VLM). The latter neurons project to and inhibit (via a GABAergic synapse) sympathoexcitatory neurons in the rostral VLM (RVLM). Blockade of this inhibitory synapse in the RVLM completely abolishes the baroreflex,[6] demonstrating the pivotal role that this group of neurons plays in the baroreceptor reflex.

The pathways depicted in Fig. 2 represent the essential central circuitry for the baroreceptor reflex, but baroreceptor signals are also transmitted to supramedullary regions, including the forebrain. These ascending signals regulate, in part, the release of vasopressin in response to a sustained fall in arterial pressure[7,12] and may also play a role in the long-term control of sympathetic vasomotor activity, as discussed later. It is also important to note that the NTS, as well as other key medullary nuclei subserving the baroreceptor reflex, receives inputs from higher centres of the brain, including the hypothalamus and other forebrain regions. Such descending inputs could modulate the operation of the baroreceptor reflex under particular conditions, as will also be discussed later with respect to the cardiovascular response to exercise or alerting stimuli.

The properties of the sympathoexcitatory neurons in the RVLM, which, as mentioned above, are powerfully influenced by baroreceptor signals, have been extensively investigated since a series of studies by Feldberg and Guertzenstein and colleagues in the early 1970s (for a review see Dampney[7]) that showed that the RVLM contained a group of tonically active neurons that play an essential role in the maintenance of tonic sympathetic vasomotor activity and, thus, resting arterial pressure (for a review see Dampney[7]). Many physiological, pharmacological and anatomical studies have shown that the sympathoexcitatory neurons in the RVLM project directly to cardiac and vasomotor sympathetic preganglionic neurons in the thoracic and lumbar spinal cord and, therefore, can be regarded as presympathetic neurons. Furthermore, they are a site of convergence of central pathways mediating cardiovascular responses evoked by stimulation of peripheral receptors as well as higher centres of the brain. The synaptic inputs to RVLM neurons are excitatory or inhibitory and are generally mediated via glutamate or GABA receptors, respectively. In addition, however, the RVLM presympathetic neurons have receptors for other putative neurotransmitters or neuromodulators, such as angiotensin (Ang) II, enkephalin, or ATP.[7,13] The AngII receptors, which are principally of the AT_1 subtype, are particularly interesting because, in the VLM, they appear to be specifically associated with cardiovascular neurons.[14,15]

The tonic activity of RVLM presympathetic neurons appears to be the major factor driving tonic activity in sympathetic preganglionic vasomotor neurons, at least in anaesthetized animals (for reviews see Dampney *et al*.[16] and Guyenet[6]). Such tonic activity obviously also permits sympathetic vasomotor activity to be decreased as well as increased via inhibition and excitation, respectively, of the RVLM presympathetic neurons. The mechanisms generating tonic activity in these neurons have been a controversial subject for a long time. There is, however, clear evidence that these neurons receive tonic GABAergic inputs that are, at least in part, independent of peripheral baroreceptors,[17] as well as phasic GABAergic inputs that are activated only under certain circumstances.[18] There is also some evidence that the RVLM presympathetic neurons receive tonic excitatory inputs.[16] However, the source of these tonic inputs is unknown.

A second example of short-term feedback regulation of the cardiovascular system is the chemoreceptor reflex. The chemoreceptors are highly specialized receptors that are stimulated primarily by a decrease in the oxygen partial pressure of arterial blood. They are located in the carotid and aortic bodies and their afferent fibres, like baroreceptor afferent fibres, run in the glossopharyngeal and vagus nerves. Chemoreceptor stimulation reflexly evokes both an increase in ventilation and sympathetically mediated vasoconstriction in most vascular beds (excluding the brain and heart). The increase in ventilation will tend to increase oxygen uptake into the blood,

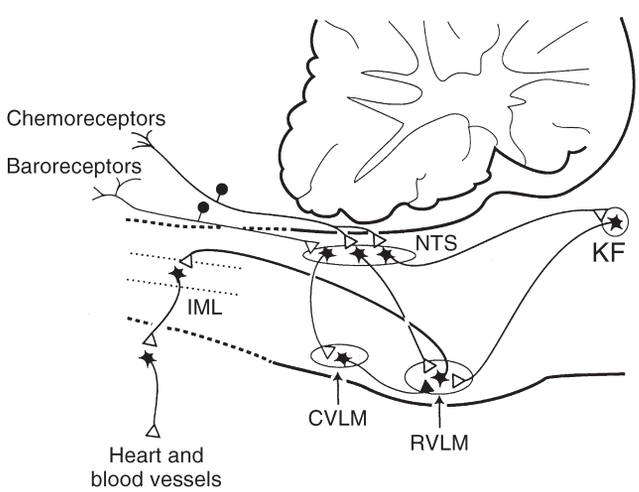

Fig. 2 Pathways within the lower brainstem and spinal cord that subserve the baroreceptor and chemoreceptor reflex control of sympathetic outflow to the heart and blood vessels. (△), excitatory synaptic inputs; (▲), inhibitory synaptic inputs. CVLM, caudal ventrolateral medulla; IML, intermediolateral cell column in the spinal cord; KF, Kölliker-Fuse nucleus in pons; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla.

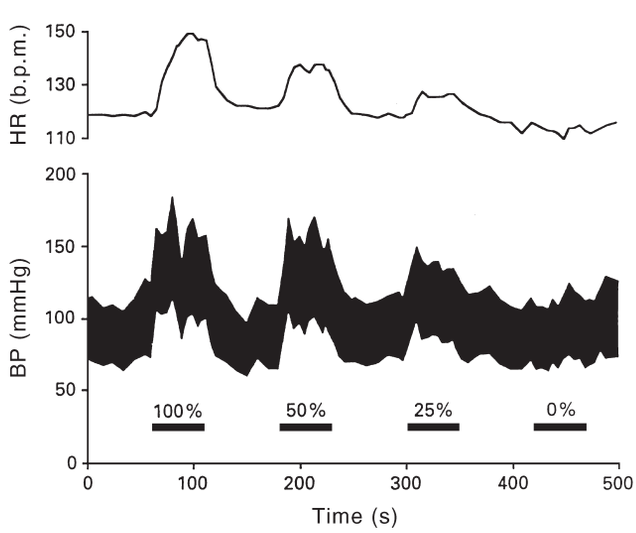

Fig. 3 Changes in heart rate (HR) and arterial blood pressure (BP) during attempted voluntary movements in a paralysed, mechanically ventilated, but conscious, human subject. Numbers indicate the percentage of maximum effort. Reproduced with permission from Gandevia *et al*.[24]

whereas the sympathetic vasoconstriction will tend to reduce oxygen consumption by the tissues and, thus, conserve the available oxygen. Like the baroreceptor reflex, studies in both anaesthetized and conscious animals have helped to define the essential pathways that mediate the chemoreceptor reflex[19,20] and these are shown in Fig. 2.

Like baroreceptor primary afferent fibres, chemoreceptor primary afferent fibres terminate in the NTS. However, in contrast with the baroreflex pathways, chemoreceptor signals are transmitted to the RVLM presympathetic neurons via a direct excitatory glutamatergic synapse.[19] Blockade of this glutamatergic synapse abolishes the sympathetic component of the chemoreceptor reflex,[19] again illustrating the pivotal role of RVLM neurons in subserving fundamental cardiovascular reflexes. In addition, there is also evidence that a group of neurons in the pons (A5 cells) is also a component of central chemoreflex pathways.[21]

SHORT-TERM FEED-FORWARD REGULATION

Neurally mediated cardiovascular responses are also evoked as part of more complex behavioural responses. For example, there is an immediate increase in heart rate and ventilation at the onset of exercise, accompanied by an increase in skeletal muscle blood flow and increase in the activity of sympathetic nerves innervating other vascular beds, such as the kidney.[22] The cardiovascular and respiratory changes that occur at the onset of exercise have been shown to be a consequence of 'central command', initiated from the cortex at the same time as the somatomotor activity is increased (e.g. Goodwin *et al.*[23]). A dramatic demonstration of 'central command', or feed-forward regulation, is shown in Fig. 3, which is from a study by Gandevia *et al.*[24] in which a paralysed, artificially ventilated human subject attempted to perform isometric contractions. Although these attempts did not result in any movement of the muscle, thus eliminating the contribution of afferent feedback from the muscle, they did result in marked increases in arterial pressure and heart rate, which were graded according to the degree of attempted force.

Therefore, it is clear that signals arising from cortical regions can result in a patterned activation of sympathetic outflows to the heart and blood vessels. The descending pathways that subserve these effects are unknown, although there is some evidence that a region in the caudal hypothalamus may be involved.[25] Thus, it is possible that neurons in this region of the hypothalamus may generate the somatomotor and autonomic changes that occur during exercise. However, even if this is correct, key questions remain, such as the origin of the inputs to the region and the organization of the descending pathways from this region to the spinal sympathetic outflow. A further question is whether there is a common set of 'command neurons' within this region of the hypothalamus that trigger both the somatomotor and autonomic changes.

It is well known that acute emotional or threatening stimuli can also elicit a marked cardiovascular response. For example, the classic 'defence' or 'alerting' response is characterized by an increase in arterial pressure, heart rate and skeletal muscle blood flow, accompanied by vasoconstriction in the splanchnic, renal and cutaneous vascular beds.[26] Such a response has been observed in conscious animals or humans subjected to an acute alerting stimulus, such as air-jet stress or a loud noise.[27–29] This patterned response has the effect of increasing cardiac output and redistributing it preferentially towards the skeletal muscle beds and is thus appropriate for an animal that may need to fight or flee from a threatening situation. Such a response is not part of a feedback regulatory mechanism[26] and, therefore, can be regarded as a feed-forward response.

It was first shown many years ago that electrical stimulation of a region in the hypothalamus, referred to as the 'defence area', elicits a cardiovascular response very similar to that described above.[26] It is not clear, however, whether this response is due to activation of neuronal cell bodies within this hypothalamic region or to fibres of passage that originate from higher centres, such as the amygdala.

More recently, evidence has accumulated to suggest that the dorsomedial hypothalamic nucleus (DMH) plays a key role in integrating the cardiovascular response to acute stress. It is possible that this nucleus corresponds with the hypothalamic 'defence area', although the boundaries of the latter region are not clearly defined. In any case, it is very interesting to note that activation of DMH neurons, by microinjection of either excitatory amino acids or GABA receptor antagonists, results in a cardiovascular response that is very similar to the defence or alerting reaction, as well as neuroendocrine, gastrointestinal and behavioural changes very similar to those evoked by an acute emotional stress.[30] Even more importantly, inhibition of neurons in the DMH greatly reduces the pressor and tachycardic response evoked by air stress in the conscious rat.[31]

These observations indicate that the DMH may be a critical region integrating the cardiovascular as well as other autonomic and non-autonomic components of the response to an acute emotional stress or alerting stimulus. Consistent with this, the DMH receives inputs from several forebrain nuclei that are believed to play a role in mediating the response to stress, including the amygdala.[32] In particular, activation of the basolateral nucleus of the amygdala generates a cardiovascular response very similar to that evoked by acute stress[33] and this evoked response is dependent on synaptic transmission in the DMH.[34] Very recently, a study in our laboratory demonstrated that the vasomotor and cardiac responses evoked from the DMH

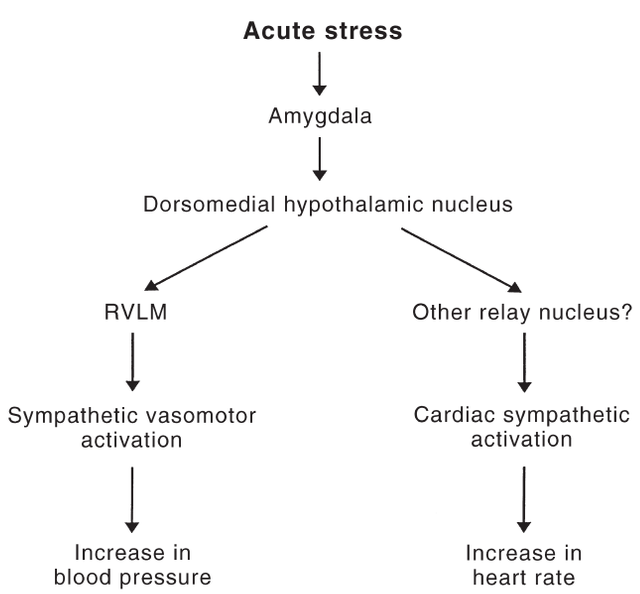

Fig. 4 Schematic diagram showing the postulated central pathways that mediate the cardiovascular response to an acute stress. CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla.

are mediated by descending pathways that are dependent and independent, respectively, of synaptic transmission within the RVLM.[35] Taking all these different observations into account, Fig. 4 is a model of the key central connections mediating the cardiovascular response to an acute emotional stress.

The classic 'defence reaction' is not the only stereotyped response that is evoked by a threatening or alerting stimulus. For example, in the conscious rabbit, a stimulus such as a sound or touching the fur elicits cutaneous vasoconstriction but, unlike the defence reaction, this is not accompanied by hindlimb vasodilation or an increase in heart rate.[36] At the same time, the amygdala appears to play a critical role in mediating this response,[37] as is the case with the stimuli that produce a classic 'defence reaction'. Therefore, it seems clear that different acute stressors can produce quite different patterns of cardiovascular responses and that even though the same key nuclei may be involved in mediating these different responses, the relay neurons involved may be quite specific for the particular stimulus.

The cardiovascular changes that accompany exercise or that occur in response to an acute emotional stimulus are usually associated with an increase in arterial pressure. Therefore, it is not surprising that the role of the baroreceptor reflex in regulating arterial pressure under these conditions has been a subject of intense investigation.[38,39] In general, it appears that the baroreceptor reflex maintains its ability to regulate arterial pressure, but the 'set point' may vary according to the particular situation. There are major inputs to the NTS from many supramedullary nuclei, including those that are believed to play important roles in mediating cardiovascular responses to acute stresses. For example, there are neurons in the DMH that project directly to the NTS and a high proportion of these have collateralized projections also to the RVLM.[35] Furthermore, physiological studies in anaesthetized animals have shown that electrical stimulation of the hypothalamic 'defence area' modulates the baroreceptor reflex (for a review see Spyer[39]). Thus, it has been hypothesized that descending inputs from the hypothalamus and other supramedullary regions are activated as part of the response to an alerting or stressful stimulus and that this results in modulation of the baroreceptor reflex.[39] However, there is not yet any direct evidence that these descending inputs are activated during naturally evoked defensive behaviour.

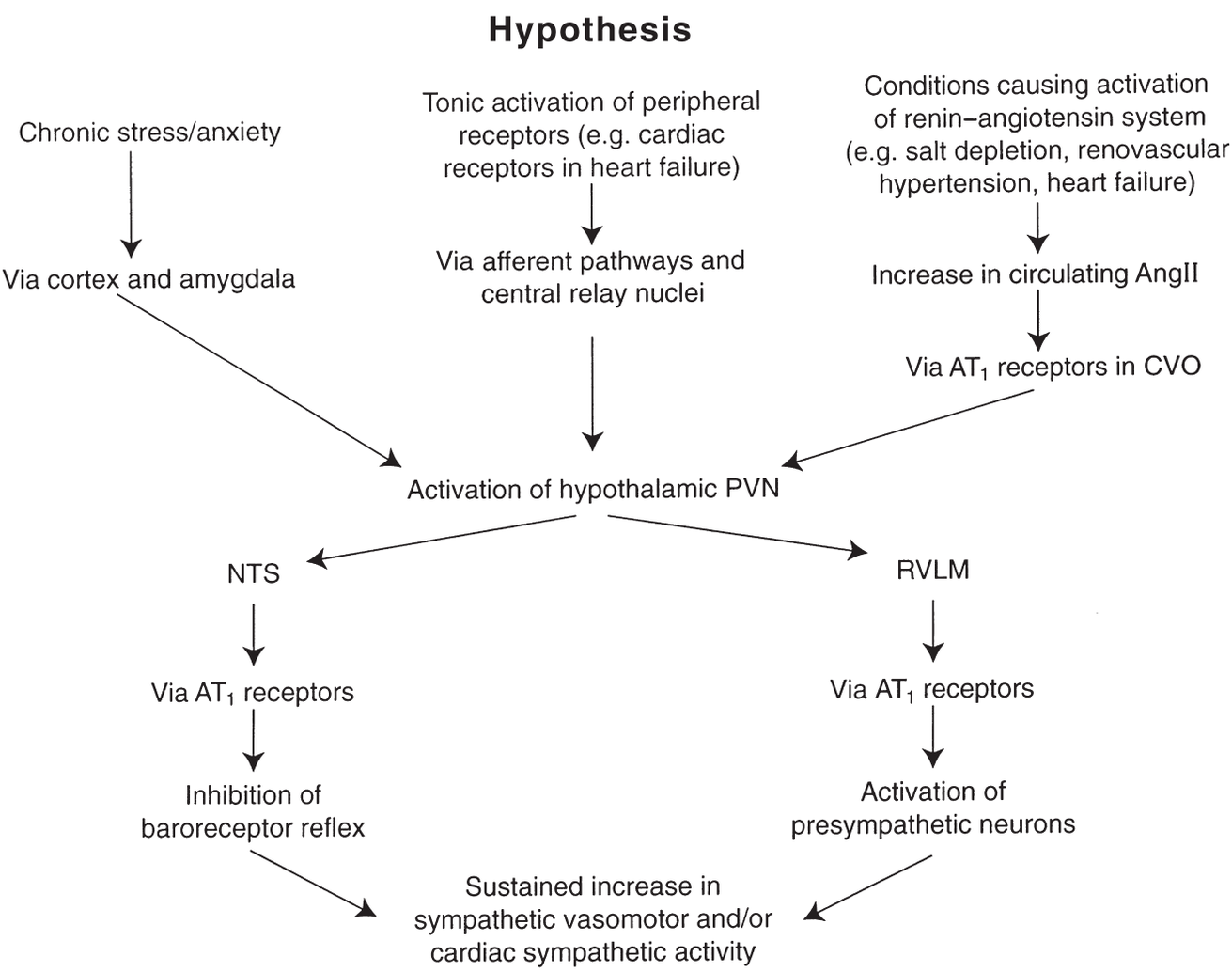

Fig. 5 Schematic diagram showing the postulated central mechanisms that result in a sustained increase in sympathetic vasomotor and sympathetic cardiac activity evoked by different types of chronic stimulation. AngII, angiotensin II; CVO, circumventricular organs; PVN, paraventricular nuclei; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla.

LONG-TERM REGULATION

Cardiovascular homeostasis in the longer term depends on an interaction between hormones and the sympathetic nervous system. For example, a change in salt intake is associated with both changes in renin release and long-term changes in sympathetic activity. Brooks and Osborn[40] have proposed a model to explain the fact that, at least in normal animals, sustained changes in salt intake do not result in sustained changes in arterial blood pressure, despite the fact that a change in salt intake will affect blood volume and, consequently, cardiac output. Key elements in this model are that: (i) a change in salt intake will result in a reciprocal change in the level of circulating AngII; and (ii) a sustained change in the level of circulating AngII will result in a sustained change (in the same direction) in the level of sympathetic nerve activity.[40] For example, salt depletion leads to activation of the renin–angiotensin system and, thus, an increase in sympathetic nerve activity, which helps to maintain arterial pressure despite the reduced salt intake. According to this model, AngII (and probably other hormones as well) have a major influence in determining the long-term level of sympathetic activity. This mechanism could also be a major factor contributing to the increase in sympathetic nerve activity in other conditions where the renin–angiotensin system is activated (such as renovascular hypertension or severe heart failure).[41] Consistent with this, blockade of AT_1 receptors has been shown to reduce sympathetic nerve activity in congestive heart failure.[42]

How can an increase in circulating AngII lead to an increase in sympathetic nerve activity? It is possible that AngII may act by enhancing neurotransmitter release at sympathetic nerve terminals or else enhance synaptic transmission through sympathetic ganglia.[43] Alternatively, although circulating AngII does not cross the blood–brain barrier, there are abundant AngII receptors in the circumventricular organs, particularly the subfornical organ and the area postrema. Activation of these receptors as a result of an increase in circulating AngII leads to various brain-mediated effects, including the release of vasopressin from the posterior pituitary and also drinking behaviour.[43,44] In addition, it has long been thought that circulating AngII may also increase blood pressure via a centrally evoked activation of sympathetic nerve activity, although the pathway responsible for this effect has not been defined.

There are several lines of evidence to suggest that the hypothalamic paraventricular nucleus (PVN) could be a key component in the central pathways mediating sustained increases in sympathetic nerve activity in response to a raised level of circulating AngII. First, the PVN receives direct and indirect inputs from Ang-sensitive neurons in the subfornical organ and activation of this pathway has been shown to increase arterial pressure.[44] Second, PVN neurons appear to have a higher tonic activity in renal-wrapped hypertensive rats, in which AngII levels are high.[45] Furthermore, there is also evidence that the PVN may contribute to sustained high levels of sympathetic activity in other models of hypertension, such as the spontaneously hypertensive rat[46] or the Dahl salt-sensitive hypertensive rat,[47] as well as in heart failure.[48] Thus, the PVN could be a central site mediating sustained increases in sympathetic activity in response to inputs from a variety of sources. Consistent with this, the PVN receives inputs originating from higher centres and peripheral receptors, as well as from circumventricular organs.[7] Thus, it may be proposed that PVN sympathoexcitatory neurons are tonically activated by inputs that are activated, in turn, by one or more of a variety of stimuli, such as increases in the level of circulating AngII, chronic stress or anxiety, or peripheral receptors that may be tonically activated under certain conditions (e.g. chemosensitive cardiac receptors during heart failure;[49] Fig. 5).

Sympathoactivation evoked by activation of PVN neurons is partly mediated by a descending pathway that includes a synapse in the RVLM and partly via a pathway that is independent of the RVLM.[50] It is interesting to note that the activation of RVLM presympathetic neurons in response to activation of the PVN is mediated by AT_1 receptors,[50] just as the activation of PVN neurons by inputs from the subfornical organ is also mediated, at least in part, by AT_1 receptors.[44] In addition, the PVN also has a major direct projection to the NTS[7] and it is possible that activation of this pathway causes inhibition of the baroreceptor reflex, as also occurs in conditions in which sympathetic activity is chronically increased, such as heart failure.[51] It is interesting to note that AT_1 receptors in the NTS mediate the inhibitory effect on the baroreceptor reflex that occurs in heart failure.[51] Thus, AngII within the brain, quite apart from circulating AngII, may play a key role in generating sustained high levels of sympathetic activity. Consistent with this view, many studies have indicated that the activity of the brain renin–angiotensin system is upregulated in various models of hypertension (for a review see Steckelings *et al*.[52]). A simplified model of the hypothesized role of the PVN and AT_1 receptors in the long-term regulation of sympathetic activity is shown in Fig. 5.

CONCLUSIONS

Great progress has been made in the past two decades in identifying the central pathways and neurotransmitters that regulate the cardiovascular system, particularly those that subserve the short-term reflex control of sympathetic vasomotor activity. The importance of the hypothalamus and other forebrain regions in circulatory regulation has been recognized for many years, but relatively little is known about the functional organization of forebrain mechanisms that regulate the cardiovascular system, both in the short and long term. Much more attention is now being paid to defining these forebrain mechanisms. In particular, it is now clear that these central mechanisms can be up- or downregulated in response to long-term physiological or pathophysiological stimuli, such as exercise training (e.g. Kramer *et al*.[25]), changes in environmental temperature (e.g. Peng and Phillips[53]) heart failure (e.g. Patel and Zhang[48]) or hypertension (e.g. Kramer *et al*.[25]). The application of new experimental approaches, including molecular techniques, promises to reveal much new information about these mechanisms.

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