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

LONG-TERM REGULATION OF ARTERIAL BLOOD PRESSURE BY HYPOTHALAMIC NUCLEI: SOME CRITICAL QUESTIONS

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SUMMARY

1. The long-term level of arterial pressure is dependent on the relationship between arterial pressure and the urinary output of salt and water, which, in turn, is affected by a number of factors, including renal sympathetic nerve activity (RSNA). In the present brief review, we consider the mechanisms within the brain that can influence RSNA, focusing particularly on hypothalamic mechanisms.

2. The paraventricular nucleus (PVN) in the hypothalamus has major direct and indirect connections with the sympathetic outflow and there is now considerable evidence that tonic activation of the PVN sympathetic pathway contributes to the sustained increased level of RSNA that occurs in conditions such as heart failure and neurogenic hypertension. The tonic activity of PVN sympathetic neurons, in turn, depends upon the balance of excitatory and inhibitory inputs. A number of neurotransmitters and neuromodulators are involved in these tonic excitatory and inhibitory effects, including glutamate, GABA, angiotensin II and nitric oxide.

3. The dorsomedial hypothalamic nucleus (DMH) also exerts a powerful influence over sympathetic activity, including RSNA, via synapses with sympathetic nuclei in the medulla and, possibly, also other brainstem regions. The DMH sympathetic pathway is an important component of the phasic sympathoexcitatory responses associated with acute stress, but there is no evidence that it is an important component of the central pathways that produce long-term changes in arterial pressure. Nevertheless, it is possible that repeated episodic activation of this pathway could lead to vascular hypertrophy and, thus, sustained changes in vascular resistance and arterial pressure.

4. Recent studies have reactivated the old debate concerning the possible role of the baroreceptor reflex in the long-term regulation of sympathetic activity. Therefore, central resetting of the baroreceptor–sympathetic reflex may be an important component of the mechanisms causing sustained changes in RSNA. However, little is known about the cellular mechanisms that could cause such resetting.

Key words: angiotensin II, baroreceptor reflex, blood pressure regulation, dorsomedial hypothalamic nucleus, hypertension, hypothalamic paraventricular nucleus, nitric oxide, renal sympathetic nerve activity.

INTRODUCTION

The long-term level of arterial blood pressure depends on the relationship between arterial pressure and the urinary output of salt and water. Therefore, if the brain plays a role in determining the long-term level of blood pressure, it can only do so by altering renal sympathetic nerve activity (RSNA) and/or the rate of release of hormones that affect renal function, such as vasopressin. In primary hypertension, the spillover studies of Esler and Kaye indicate that the RSNA is substantially increased, consistent with the view that central neural mechanisms contribute to the maintenance of hypertension in such cases. In the present brief review, we shall consider particularly the central neural regulation of RSNA and the possible mechanisms that could lead to a sustained long-term increase in RSNA, with particular reference to the possible role of hypothalamic nuclei.

The role of the baroreceptor reflex in the long-term regulation of blood pressure has recently become a subject of considerable debate. Several recent studies have challenged the traditional view that the baroreceptor reflex regulates sympathetic activity only in the short term and, instead, have produced evidence indicating that the reflex can regulate sympathetic activity over much longer periods (for reviews, see Thrasher and Malpas). In fact, the original study by Jones and Thoren demonstrated that baroreceptors innervated by unmyelinated afferents show relatively little adaptation to sustained increases in arterial pressure and are therefore capable of signalling long-term changes in pressure. Thus, the fact that in human primary hypertension the baroreceptor reflex control of sympathetic activity is reset to higher levels of arterial pressure is not necessarily due simply to adaptation of the baroreceptors themselves; it could be due, at least in part, to a central modulation of the baroreceptor reflex pathway. This issue...
The role of hypothalamic nuclei in the longer-term control of RSNA will be considered in more detail below, in relation to the possible role of hypothalamic nuclei in the longer-term control of RSNA.

OVERVIEW OF THE ORGANIZATION OF CENTRAL PATHWAYS CONTROLLING RSNA

Renal sympathetic post-ganglionic nerves innervate vascular smooth muscle, the distal tubule and the juxtaglomerular apparatus and, thus, regulate renal vascular resistance, sodium reabsorption and renin release, all of which can alter the renal function curve. The preganglionic neurons that synapse with these renal sympathetic post-ganglionic nerves are located in the lower thoracic and upper lumbar segments of the spinal cord and, in turn, receive descending inputs from sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM), medullary raphe, A5 area in the pons and hypothalamic paraventricular nucleus (PVN). Studies using the method of retrograde transynaptic viral tracing have demonstrated that neurons in other regions that are not labelled by a retrogradely transported virus, such as the midbrain periaqueductal grey, may also exert powerful effects on RSNA. There is very good evidence, at least in the cat, that there is a subgroup of RVLM neurons that specifically regulates the renal sympathetic outflow, but not the sympathetic outflow to other target organs, such as the heart or the cutaneous or skeletal muscle beds. Such a specificity of function is not surprising, given the fact that the sympathetic outflow to these different target organs can be differentially regulated by different reflexes. It is also possible that neurons in higher centres that project to the RVLM, such as the midbrain periaqueductal grey, may also preferentially or exclusively regulate the renal sympathetic outflow. Neurons within the parvocellular portion of the PVN play an important role in regulating sympathetic activity. Apart from direct projections from the PVN to the spinal sympathetic outflow and the RVLM, PVN neurons may also regulate sympathetic activity via projections to other central nuclei, such as the nucleus tractus solitarius (NTS) and pontine parabrachial nucleus. As illustrated in Fig. 1, the PVN receives inputs from a wide variety of sources, including peripheral receptors, higher centres in the brain, and the PVN itself.

Role of the RVLM

With regard to the sympathetic premotor nuclei, the critical role of the RVLM in the tonic and phasic control of RSNA has been clearly demonstrated in several species. For example, bilateral inhibition of RVLM neurons causes virtually complete abolition of RSNA. Similarly, the increase in RSNA reflexly evoked by activation of somatic nociceptive afferent fibres or peripheral chemoreceptors is abolished by pharmacological inactivation of the RVLM. In contrast, although there is evidence that sympathetic premotor neurons in the medullary raphe nuclei exert some control over RSNA, this is much less than that of RVLM neurons. Activation of neurons in the PVN can also produce large increases in RSNA, but this appears to be mediated, in part, by an indirect pathway that includes a synapse in the RVLM, as well as by a direct descending pathway to spinal sympathetic preganglionic neurons.

The tonic activity of the RVLM sympathetic premotor neurons depends upon the balance between both tonic excitatory and inhibitory inputs. In three animal models of hypertension (Golblatt hypertensive rat, spontaneously hypertensive rat (SHR) and the Dahl salt-sensitive hypertensive rat) there appears to be an increase in tonic excitatory synaptic inputs mediated by glutamate and/or AT1 receptors that leads to increased activity of these neurons. The source(s) of this increased excitatory input is not fully known. Nevertheless, there is evidence that the hypothalamic PVN is one source of the increased excitatory input to RVLM sympathetic premotor neurons.

ROLE OF THE PVN IN LONG-TERM REGULATION

Neurons within the parvocellular portion of the PVN play an important role in regulating sympathetic activity. Apart from direct projections from the PVN to the spinal sympathetic outflow and the RVLM, PVN neurons may also regulate sympathetic activity via projections to other central nuclei, such as the nucleus tractus solitarius (NTS) and pontine parabrachial nucleus. As illustrated in Fig. 1, the PVN receives inputs from a wide variety of sources, including peripheral receptors, higher centres in the brain, and the PVN itself.

Fig. 1 Schematic diagram showing the major groups of inputs to hypothalamic paraventricular (PVN) neurons that regulate sympathetic activity and the stimuli that may result in chronic activation of PVN sympathetic neurons via these inputs. As discussed in the text, such inputs could lead to reduced GABAergic inhibition, which may depend, at least in part, on downregulation of neuronal nitric oxide synthase (nNOS) within the PVN. In addition, a sustained increase in sympathetic activity may also be associated with a resetting of the baroreceptor–sympathetic reflex, via central mechanisms.
such as the cortex and amygdala, and circumventricular organs that relay signals related to the levels of circulating factors and blood osmolality. The inputs from peripheral receptors are relayed via brainstem nuclei, such as the NTS or ventrolateral medulla.

There is conflicting evidence with regard to whether the PVN contributes significantly to sympathetic vasomotor tone in normotensive animals. However, bilateral inhibition of the PVN in SHR and Dahl salt-sensitive hypertensive rats has been shown to cause a large decrease in arterial pressure. Although the RSNA was not measured in these studies, in SHR the hypotension was accompanied by a virtual inhibition of lumbar sympathetic nerve activity, indicating that the baseline sympathetic vasomotor activity in these animals was highly dependent upon the tonic activity of PVN neurons.

There is also clear evidence that the PVN contributes to the maintenance of sympathetic vasomotor tone in other situations. In particular, in heart failure the firing rate of PVN neurons is higher than in normal rats and this increased activity leads to increased levels of RSNA in this condition. Furthermore, intravenous infusion of cytokines increases the activity of neurons in the PVN and RVLM, consistent with the hypothesis that the activation of the PVN–RVLM pathway causes the increased level of RSNA that occurs in this condition. Similarly, in water-deprived rats (but not normal rats), inhibition of the PVN causes a decrease in RSNA and arterial pressure. Because a fall in arterial pressure is also observed following blockade of glutamate receptors in the RVLM, these results suggest that the descending pathway from the PVN that mediates increased tonic levels of RSNA in water deprivation may include a synapse in the RVLM.

Given that tonic activity of PVN sympathoexcitatory neurons appears to be a common factor contributing to the tonic activation of sympathetic vasomotor nerves in a variety of conditions where sympathetic activity, including RSNA, is increased, a critical question is what are the mechanisms that drive PVN sympathoexcitatory neurons, both under normal and abnormal conditions? These neurons receive both a tonic inhibitory input, mediated by GABA receptors, and tonic excitatory synaptic inputs that appear to be mediated by excitatory amino acid and AT₁ receptors. In rats with heart failure, as well as rats made hypertensive by renal wrap or by chronic infusion of angiotensin II, the degree of tonic GABAergic inhibition of PVN sympathoexcitatory neurons is reduced compared with normal rats. Thus, it is suggested that, in such cases, the increase in RSNA is due to increased tonic activity of PVN sympathoexcitatory neurons, as a consequence of reduced GABAergic inhibition, although increased excitation mediated by N-methyl-D-aspartate (NMDA) receptors or AT₁ receptors may also contribute.

There is good evidence that nitric oxide (NO) derived from neuronal nitric oxide synthase (nNOS) plays an important role in neurotransmission in the PVN. For example, an electrophysiological study has shown that NO inhibits the firing rate of PVN neurons that innervate the medulla and that this effect is due to an enhancement of GABAergic neurotransmission. In heart failure, it has been shown that there is reduced expression of nNOS in the PVN and it has been proposed that this, in turn, leads to reduced NO production and, thus, GABAergic disinhibition.

The source(s) of the GABAergic inputs to PVN sympathoexcitatory neurons is unknown, although it is known that there are many GABAergic neurons within other surrounding hypothalamic nuclei that project to the PVN. Similarly, the sources of the tonic excitatory inputs to PVN sympathoexcitatory neurons are also largely unknown, although in the case of inputs mediated by AT₁ receptors, there is good evidence that these originate, at least in part, from neurons in the hypothalamic circumventricular organs. In addition, the inputs to the PVN from higher centres, such as the cortex and amygdala, or brainstem nuclei, such as the NTS or ventrolateral medulla, may also be tonically active, at least under certain physiological or pathophysiological conditions.

Thus, although the data are still very incomplete, the evidence so far suggests that PVN sympathoexcitatory neurons contribute to the tonic activation of sympathetic vasomotor nerves, including those innervating the kidney, in conditions such as water deprivation, heart failure and at least certain types of neurogenic hypertension. It is also conceivable, as shown in Fig. 1, that psychological conditions, such as anxiety, may also lead to sustained long-term activation of PVN sympathoexcitatory neurons via inputs from the cortex and amygdala.

There are also many other questions regarding the central mechanisms that cause activation of PVN sympathoexcitatory neurons. As mentioned above, reduced tonic GABAergic inhibition of the neurons, which, in turn, may be due to reduced NO production, has been shown to be an important factor that leads to the activation of these neurons in heart failure and in angiotensin-induced hypertension. This raises the following question: is such disinhibition a common feature of all conditions in which the activity of PVN sympathoexcitatory neurons is increased? If so, is the disinhibition a consequence of reduced levels of nNOS expression? Similarly, is overexpression of AT₁ receptors in the PVN, which occurs in heart failure, also a common feature of these conditions? These questions, in turn, raise further questions; for example, what are the mechanisms that can lead to alterations of nNOS or AT₁ receptor gene expression? Clearly, much remains to be learnt about the cellular mechanisms that cause increased tonic activity of PVN sympathoexcitatory neurons and the factors that trigger these mechanisms.

**ROLE OF THE DMH IN LONG-TERM REGULATION**

As reviewed recently, neurons in the DMH appear to be an essential component of the central pathways that subserve increases in arterial pressure and heart rate associated with an acute psychological stress. Activation of neurons in the DMH, by microinjection of bicuculline, results in widespread sympathetic activation, including increases in the activity of sympathetic nerves innervating the heart, brown adipose tissue and renal vascular beds. The descending pathways subserving these cardiac and vasomotor effects include synapses in the midline raphe nuclei in the medulla and in the rostral ventrolateral medulla. The organization of the descending pathways from the DMH to these medullary nuclei is not yet fully elucidated, although there is evidence for both direct pathways and an indirect pathway that includes a synapse in the lateral periaqueductal grey in the midbrain.

Unlike the PVN, there is no experimental evidence that the DMH plays a role in the long-term regulation of blood pressure. However, it was proposed many years ago by Folkow that repeated episodic activation of acute cardiovascular stress...
responses could lead to vascular hypertrophy and, thus, sustained hypertension. Thus, the fact that neurons within the DMH appear to be a crucial component of the pathways subserving the sympathoexcitatory response to acute stress raises the possibility that the DMH may play an important role in the genesis of hypertension in cases where repeated acute psychological stress is an initiating factor. At present, however, many questions remain concerning the role of the DMH in acute stress responses, quite apart from its potential role in long-term arterial pressure regulation. For example, it is not known whether the co-ordinated behavioural, cardiovascular, respiratory and hormonal responses triggered by acute stress are activated by a common population of ‘command neurons’ within the DMH. Second, the precise origins of afferent inputs to the DMH that trigger these responses are not yet fully elucidated, although there is good evidence that the amygdala is one important source of afferent inputs. Third, although the functional evidence indicates that DMH neurons are an important component of the pathways mediating stress-induced sympathoexcitatory responses, the extent to which neurons in other hypothalamic nuclei (e.g. the PVN or perifornical area) also contribute to these responses is unknown.

**HYPOTHALAMIC NUCLEI AND BAROREFLEX SETTING**

It is well established that, in humans with primary hypertension, the baroreceptor reflex control of heart rate is attenuated. In contrast, however, a study by Grassi et al. in such patients showed that the sensitivity of the baroreceptor reflex control of sympathetic vaso-motor activity is not attenuated, although it is reset to higher levels of arterial pressure. It is often assumed that this reflects complete adaptation of the baroreceptors to long-term sustained changes in arterial pressure, but recent studies, as well as a re-evaluation of earlier studies, have stimulated renewed debate on this very important question.

In any case, there is little doubt that modulation of the baroreceptor reflex does occur as part of the overall physiological changes associated with different behavioural states. For example, during exercise, the baroreceptor reflex control of RSNA is shifted to higher levels of both arterial pressure and RSNA, as shown very...
clearly in the conscious rat by Miki et al.\textsuperscript{53} (Fig. 2). Because these changes occur so rapidly (within seconds or minutes), it seems likely that they are due, at least in part, to central modulation of the reflex. If so, it follows that changes in the level of arterial pressure that occur in association with changes in activity or arousal are associated with centrally induced alterations in the baroreflex set-point. Thus, the marked changes in arterial pressure that are observed over 24 h recordings in humans and animals\textsuperscript{54,55} (Fig. 3) reflect changes in the set-point associated with changes in behavioural state, such that the arterial pressure is, at all times, regulated around a level that is appropriate for the particular behavioural state of the animal.

The hypothesis that the baroreceptor reflex is modified during changes in behaviour, particularly during arousal or alerting responses, was proposed by Hilton over 40 years ago.\textsuperscript{56} It is often suggested that the baroreceptor reflex is suppressed during such behaviours, because the reflex bradycardia and sympathoinhibition normally evoked by baroreceptor afferent stimulation is abolished by electrical stimulation of the ‘hypothalamic defence area’.\textsuperscript{57} However, studies in conscious animals have shown that baroreflex control of heart rate during acute emotional stress is not abolished but, instead, is reset to a higher level.\textsuperscript{58} Similarly, as already mentioned, the baroreflex control of heart rate and RSNA is also reset, rather than inhibited, during exercise.\textsuperscript{59} In fact, the gain of the baroreflex control of RSNA is increased during exercise.\textsuperscript{55} Thus, the available evidence in conscious behaving animals demonstrates powerful modulation, but not inhibition, of the baroreceptor reflex during behaviours associated with increases in arterial pressure. The fact that electrical stimulation of the hypothalamic defence area does not reproduce the modulation of the baroreceptor reflex that is observed during natural behaviours, such as exercise or acute stress, could be interpreted to suggest that the hypothalamus does not play a key role in producing such modulation. An alternative possibility is that the inhibition of the baroreceptor reflex evoked by electrical stimulation of the hypothalamic defence area\textsuperscript{57} is due to activation of fibres of passage, rather than of neurons within hypothalamic nuclei. However, the effects of selective activation of neurons within the hypothalamic defence area (which corresponds most closely to the DMH and the perifornical area) remains unknown.

The central mechanisms that produce modulation of the baroreceptor reflex during exercise or acute stress are still largely unknown. Potts and Mitchell\textsuperscript{59} demonstrated that, during exercise, there is an interaction between inputs from somatic afferents and from arterial baroreceptors, such that the reflex is reset to a higher level of arterial pressure while sensitivity is maintained. More recently, Potts\textsuperscript{60} proposed that this interaction occurs within the NTS and involves a GABAergic mechanism. In addition, inputs originating from the motor cortex may also contribute to baroreflex resetting, as well as sympathoexcitation, during exercise, although direct evidence for this is, so far, lacking. The resetting of the baroreceptor reflex that occurs during psychological stress is best explained as a consequence of inputs from higher brain regions rather than peripheral inputs from somatic receptors, because it occurs even during immobility.\textsuperscript{58}

In theory, the modulation of the baroreceptor reflex that occurs in different states, such as exercise or defensive behaviour (i.e. alteration of the arterial pressure range over which the baroreceptor reflex operates and changes in the gain or sensitivity of the reflex) could result from an interaction between baroreceptor inputs and inputs associated with the behavioural response in any of the key nuclei that subserve the reflex (i.e. NTS, caudal ventrolateral medulla or RVLM). Given that baroreflex modulation is a key component in the regulation of autonomic responses during different behaviours, elucidation of the central sites at which this modulation occurs and the cellular mechanisms that produce these effects is a major goal for future studies. Furthermore, if it is established that central resetting of the baroreceptor reflex is a factor contributing to the long-term level of RSNA, then this information will be of great importance in understanding the long-term regulation of arterial pressure, as well as short-term changes associated with different behaviours. For example, if activation of PVN sympathoexcitatory neurons is a common feature of conditions in which a sustained increase in RSNA and arterial pressure occur, then it is possible that this activation will result in baroreflex resetting as an important component of the changes that lead to the sustained increase in RSNA (Fig. 1).

CONCLUSIONS

In this brief review, we have raised a number of specific questions concerning the possible mechanisms by which hypothalamic nuclei may contribute to generating sustained increases in sympathetic activity, particularly RSNA. We have focused on the PVN and DMH, largely because there have been many studies on the role of these nuclei in cardiovascular regulation. However, there are other hypothalamic regions that are also known to be capable of producing large changes in sympathetic activity, such as the perifornical area and lateral hypothalamus, and that may also have a major role in the long-term regulation of sympathetic activity and arterial pressure.\textsuperscript{61,62} Thus, many questions remain concerning the role of hypothalamic mechanisms in cardiovascular regulation. To answer these questions, many different types of experiments will need to be performed, ranging from studies at the cellular level to studies in behaving conscious animals.

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