Central Neuronal Histamine Contributes to Cardiovascular Regulation

Steven L. Bealer

Evidence suggests that central histaminergic neurons make important contributions to cardiovascular regulation. For example, histamine-containing neurons project to brain regions important for cardiovascular regulation. Furthermore, stimulation of central histamine receptors changes blood pressure and heart rate and alters activity of major vasoconstrictor systems. Finally, histamine metabolism is changed in hypertension.

Histamine (HA) in the mammalian central nervous system (CNS) is contained in mast cells and in neurons (14), which utilize HA as a classic neurotransmitter. CNS HA has been implicated in control of a number of physiological systems (see Ref. 14 for review). This review will focus on the role of central histaminergic neurons in cardiovascular regulation.

CNS histaminergic neurons

The cell bodies of all HA-containing neurons in the CNS are localized to a region of the posterior hypothalamus known as the tuberomamillary nucleus (TMN) (14). Three distinct receptor subtypes, designated H₁, H₂, and H₃, have been identified that mediate the actions of HA in the CNS.

Axons of HA-containing neurons project from the TMN to many areas of the brain, including most major loci contributing to autonomic regulation of the cardiovascular system (8). Figure 1 is a schematic representation of the rat brain showing the major cardiovascular centers receiving fibers from HA neurons in the TMN. As shown, several forebrain areas that make significant contributions to cardiovascular responses receive projections from the TMN. There are dense HA projections to the diagonal band of Broca (DBB), the paraventricular nucleus of the hypothalamus (PVN), the supraoptic nucleus (SON), and the bed nucleus of the stria terminals (BST). In addition, there is moderate innervation of the central nucleus of the amygdala (CNA). These forebrain sites contribute to autonomic control of the circulation through neural mechanisms and/or release of vasopressin. Furthermore, there are moderate histaminergic projections to the organum vasculosum of the lamina terminalis (OV), a sensory circumventricular organ important for mediating cardiovascular responses to blood-borne substances.

There are also caudal HA projections to autonomic centers of the brain stem, with moderately dense HA innervation of the parabrachial nucleus (PBN) and projections to the locus ceruleus (LC). Finally, in the medulla, the nucleus of the solitary tract (NTS) is heavily innervated, whereas the dorsal motor nucleus of the vagus (DVN) receives some histaminergic projections.

Therefore, it is evident that the CNS HA system has the anatomic connectivity with autonomic control centers to make significant contributions

---

S. L. Bealer is in the Department of Physiology at the University of Tennessee, 894 Union Avenue, Memphis, TN 38163, USA.

"... there are moderate histaminergic projections to the organum vasculosum..."
to cardiovascular regulation through control of major pressor systems.

CNS HA and cardiovascular responses

A potential role for CNS HA in cardiovascular regulation was suggested by the early observations that injections of HA into the cerebral ventricles produce a profound pressor effect (15). This response appears to be mediated predominantly by stimulation of H₁ receptors, because it is produced by central administration of either HA or selective H₁-receptor agonists and abolished by prior administration of H₂-receptor antagonists. However, a role for H₂-receptor stimulation in the pressor response to HA has also been suggested (13). Stimulation of central H₁ receptors causes a biphasic blood pressure response, with an initial increase, because of H₁-receptor stimulation, followed by a sustained depressor response. The hypotension may be caused by the autoinhibition of HA release produced by H₁-receptor stimulation.

Other experiments that manipulated endogenous HA metabolism support a role for CNS neuronal HA in control of blood pressure (14). For example, experimentally induced pressor or depressor responses increase HA release in the hypothalamus, and inhibition of HA degradation in the brain causes an increase in blood pressure similar to that observed after central injections of exogenous HA. Finally, either depletion of neuronal HA or pharmacological blockade of H₁ receptors in the CNS prevents the pressor response associated with peripheral hyperosmolality (1).

Taken together, these studies support the proposition that CNS neuronal HA contributes to blood pressure control by mediating pressor systems primarily through activation of H₁ receptors.

In contrast with increases in blood pressure after central administration of HA that are independent of the state of anesthesia, heart rate responses are qualitatively different in awake and anesthetized preparations. Cerebroventricular injections of HA in anesthetized animals result in tachycardia, whereas central HA injection or inhibition of HA catabolism decreases heart rate in conscious preparations. Furthermore, heart rate responses appear to be species dependent, because rats exhibit the above-described changes, whereas central HA has little effect on heart rate in conscious cats and produces variable responses in goats.

Although the pressor response to cerebroventricular administration of HA is caused predominantly by stimulation of H₁ receptors, it appears that H₂ receptors mediate the effects of central HA on heart rate. Although central blockade of H₁ receptors can prevent the bradycardia associated with central administration of HA, this effect is probably caused by a reduction of the HA-induced pressor response and, consequently, the baroreflex-mediated fall in heart rate. However, experiments with specific H₂-receptor antagonists found that HA effects on heart rate are mediated directly by H₂-receptor stimulation (13). In support of this proposition, selective central H₂-receptor blockade prevents the fall in heart rate during intravenous administration of hypertonic saline without altering the pressor response (9). Finally, stimulation of central H₁ receptors also evokes bradycardia.

These data suggest that the effects of HA on heart rate are dependent on the state of anes-
the effects of cerebroventricular administration of HA on heart rate are caused by stimulation of \( \text{H}_2 \) receptors.

**CNS sites of HA effects on cardiovascular responses**

A number of studies employing more discrete injections of HA and HA agonists and antagonists into individual brain sites have revealed site-specific responses in blood pressure and heart rate. Localized injections in a number of forebrain sites result in pressor responses. For example, microinjections of HA into the posterior hypothalamic region or the anterior hypothalamic area produce cardiovascular responses similar to those observed after cerebroventricular administration of HA, i.e., a pressor response and bradycardia. Another hypothalamic nucleus receiving dense HA innervation that is an important CNS site for autonomic regulation of the cardiovascular system is the PVN. As reported for other brain areas, local administration of HA to the PVN increases blood pressure. However, unlike cerebroventricular administration, or microinjections of HA into the posterior or anterior hypothalamic areas in conscious rats, local PVN application of HA increases heart rate (2).

In addition to forebrain loci, microinjections of HA have been administered into the rostral ventrolateral medulla (RVLM), a medullary site critical in regulation of the cardiovascular system. In contrast with HA treatments in forebrain areas, bilateral microinjections of HA into the RVLM in anesthetized rats produce dose-dependent hypotension and bradycardia. Furthermore, prior treatment with an \( \text{H}_2 \) antagonist prevents the fall in both blood pressure and heart rate, whereas \( \text{H}_1 \) receptor blockade does not alter the responses (7).

These data show that central histaminergic control of the cardiovascular system is complex. The precise qualitative nature of HA actions and the HA receptor subtypes mediating blood pressure and heart rate responses are dependent on the specific brain site stimulated.

**Mechanisms of HA control of cardiovascular responses**

A large number of studies have investigated the specific peripheral mechanisms activated and/or inhibited after stimulation of central HA receptors that contribute to changes in blood pressure and heart rate. Figure 2 is a schematic representation of cardiovascular regulatory systems affected by CNS HA neuron stimulation. The vasoconstrictor activity of the sympathetic nervous system as well as the vasoconstrictor hormones vasopressin and angiotensin II are implicated in contributing to cardiovascular responses mediated by CNS HA systems.

The role of central HA in activation of the sympathetic nervous system has been evaluated by measuring plasma concentrations of catecholamines after CNS administration of exogenous HA and after stimulation of endogenous

---

*FIGURE 2. Schematic drawing of cardiovascular autonomic systems controlled by central histamine (HA). ANG II, angiotensin II; AVP, arginine vasopressin; RVLM, rostral ventrolateral medulla; DVN, dorsal motor nucleus of the vagus; NTS, nucleus of the solitary tract; HR, heart rate; PP, posterior pituitary; SNS, sympathetic nervous system.*
HA systems. Infusion of HA into the lateral cerebral ventricles as well as stimulation of the HA cell bodies in the TMN increase plasma concentrations of norepinephrine. In addition, cardiac responses evoked by central HA are attenuated by propranolol but not altered by bilateral vagotomy, indicating that the changes in heart rate after cerebroventricular HA are mediated by cardiac sympathetic activation. These results indicate that stimulation of central HA receptors can increase activity of peripheral sympathetic nerves and/or catecholamine secretion from the adrenal medulla. Furthermore, direct measurements of sympathetic nerve activity have been made during HA administration into the RVLM (7). The hypotension and bradycardia produced by HA injections in this brain region are associated with decreased renal sympathetic nerve activity. These results suggest that the fall in heart rate and blood pressure evoked by HA stimulation in the RVLM is mediated by withdrawal of sympathetic nervous system activity. Taken together, these data support a role for HA in control of peripheral sympathetic nerves and catecholamine release from the adrenal medulla.

However, despite the positive relationship between stimulation of central HA receptors and indexes of peripheral sympathetic nervous system activity, the role of sympathetic adrenal activation in HA-induced cardiovascular responses is not definitive. Although early studies reported that ganglionic blockade or spinal transection prevented the pressor response to cerebroventricular HA (15), later experiments found no effect of adrenal demedullation, spinal transection, or ganglionic blockade on the increase in blood pressure after central HA injections (6). In addition, the pressor response and tachycardia produced by PVN stimulation with HA were not affected by ganglionic blockade (2). It is clear from these data that additional pressor system(s) are activated by central HA stimulation.

Several studies demonstrate that central HA is a potent stimulus for release of vasopressin (4). However, the contribution of vasopressin to blood pressure responses evoked by central HA depends on the experimental paradigm. Studies directly examining the contribution of vasopressin to the pressor effect of cerebroventricular injections of exogenous HA found that pretreatment with an antagonist of the vasoconstrictor actions of this hormone significantly reduced the pressor response to central HA (6). However, studies evaluating the role of endogenous central HA on the increase in blood pressure evoked by intravenous hypertonic saline found that central H1-receptor blockade or depletion of central neuronal HA with α-fluoromethylhistidine prevents the hypertonic saline-induced pressor response without reducing vasopressin secretion (1). These data suggest a limited role for vasopressin in the increase in blood pressure during activation of endogenous HA systems induced by this experimental treatment. In contrast, the pressor response produced by local administration of exogenous HA to the PVN is prevented by a peripheral vasopressin receptor antagonist and not altered by ganglionic blockade, which indicates that pressor responses produced by stimulation of PVN HA receptors are mediated by circulating vasopressin.

These data suggest that the contributions of sympathetic nervous system activation and vasopressin to increased blood pressure during stimulation of central HA receptors are dependent on the central site of HA stimulation, the method of administration, and the experimental treatments that are tested. However, it is clear that both of these pressor systems have the potential to make significant contributions to cardiovascular responses evoked by central HA-receptor stimulation.

Cerebroventricular injections of HA also increase plasma renin concentration, and consequently, circulating levels of the vasoconstrictor hormone angiotensin II. Increased plasma renin after central HA was prevented by prior treatment with an H2 antagonist (11). These data suggest that angiotensin II could contribute to pressor responses after central HA. However, intravenous injections of a competitive angiotensin II antagonist did not alter the pressor response to central HA (6). Therefore, although central HA increases plasma renin concentration, a role for circulating angiotensin II in the HA-induced pressor response has not been established.

In summary, CNS HA systems can directly effect sympathetic nerve activity, increase plasma concentrations of norepinephrine, vasopressin, and angiotensin II, and modify heart rate. These results suggest that there are redundant mechanisms through which central HA mediates cardiovascular responses, each regulated through discrete neural circuits, receptor subtypes, and peripheral systems. Furthermore, the relative contribution of each of these cardiovascular regulatory systems to blood pressure and heart rate responses during central HA receptor stimulation is dependent on the animal preparation, the central site of stimulation, and the experimental treatment.

Central HA interactions with other central neurotransmitter systems

Many of the cardiovascular effects of CNS HA are mediated through interactions with other central neurotransmitter systems. For example,
studies have shown a functional relationship between HA and adrenergic receptors in the CNS. HA induces release of norepinephrine from both hypothalamic brain slices and isolated synaptosomes, as well as from selected brain sites in vivo. Studies of the physiological significance of this relationship demonstrate that prior central α-adrenergic-receptor blockade or destruction of central noradrenergic nerve terminals can prevent or attenuate pressor responses after cerebroventricular administration of HA (5). Similarly, the increase in blood pressure observed during microdialysis probe perfusion of the PVN with HA is prevented if an α₁-adrenergic-receptor antagonist is administered simultaneously (2). These data suggest that CNS HA interacts with noradrenergic neurons to produce effects on blood pressure after cerebroventricular administration or local application of HA to the PVN. However, in other brain sites the blood pressure responses produced by HA are independent of α-adrenergic receptor stimulation. For example, administration of α-adrenergic antagonists into the posterior hypothalamus or RVLM does not alter the blood pressure responses to local microinjections of HA.

Functional interactions have also been demonstrated between central HA and central cholinergic and neuropeptide Y receptor systems. Although CNS α-adrenergic-receptor blockade did not change heart rate responses to central HA, prior cerebroventricular treatment with atropine significantly reduced the HA-induced tachycardia in anesthetized rats (5). Finally, blockade of H₁ HA receptors in the posterior hypothalamus abolishes the pressor response to local administration of neuropeptide Y (10).

In summary, the results of these studies demonstrate that central HA can interact with other neurotransmitter systems, as well as act directly through stimulation of H₁ and H₂ receptors, to control blood pressure and heart rate. These neurotransmitter interactions and/or direct effects of HA are specific to discrete brain loci and act to selectively alter either blood pressure or heart rate.

CNS HA and experimental hypertension

The consistent findings that administration of exogenous HA and stimulation of endogenous central HA systems have profound effects on blood pressure and cardiac responses suggest that this amine could contribute to development and/or maintenance of hypertension. Several studies have investigated HA content and/or metabolism in the spontaneously hypertensive rat (SHR). Initial studies analyzing HA concentrations in selected brain nuclei reveal that HA content is greater in the median eminence, arcuate, and nucleus premammillaris in SHR than in age-matched, normotensive control rats (3). Other experiments have reported that HA metabolism and/or HA release is altered in hypertensive animals (12). These reports are consistent with the hypothesis that increased CNS HA content and/or altered HA metabolism contributes to the development and maintenance of experimental hypertension. However, the specific brain sites, stages of hypertension, and precise peripheral mechanisms by which central HA contributes to hypertension have not been precisely determined.

Summary

The histaminergic neurons in the CNS project to and innervate many central loci with demonstrated importance in cardiovascular regulation. These include a number of forebrain structures as well as pontine and medullary sites. Furthermore, stimulation of central HA neurons and/or receptors has been implicated in contributing to activity of the sympathoadrenal axis, circulating levels of vasoconstrictor hormones, and cardiac function. Finally, CNS HA content and metabolism are altered in at least some forms of experimental hypertension. These data support the proposal that central HA neurons contribute to cardiovascular homeostasis through regulation of the autonomic nervous system.

The mechanisms by which central HA contributes to cardiovascular regulation are complex. The qualitative nature of the peripheral responses evoked by CNS HA, the receptor subtype stimulated, interactions with other neurotransmitter systems, and the specific peripheral effectors activated or inhibited are dependent on the brain site stimulated, the state of anesthesia, and the experimental treatment. These data suggest that specific physiological conditions can selectively activate separate components of the central HA circuitry to evoke distinct effector responses.

References

4. Dogterom, J., T. B. V. W. Creidanus, and D. DeWeid. Histamine is a potent releaser of vasopressin in the rat. Expe-
hypoxia and inhibition of oxidative phosphorylation. The first gene whose transcription is dually stimulated in response to hypoxia-inducible factor 1, enhances GLUT-1 transcription. GLUT-1 is stimulated by hypoxia or azide. Moreover, hypoxia per se, acting through and GLUT-4 glucose transporter function. GLUT-1 expression is also 8. Inagaki, N., A. Yamatodani, M. Ando-Yamamoto, M. Tohyama, T. Watanabe, and H. Wada. Organisation of paracrine and endocrine factors that promote specific cells, and their products are secreted as conditions. Some of these genes are transcribed in response to hypoxia and glucose uptake by cells and tissues is a fundamental adaptation that is criti- cal to the maintenance of cellular homeostasis. It should be noted that although glucose transport is acutely stimulated by hypoxia through enhanced GLUT-1 expression, the processes such as erythropoiesis and vascularization. Other genes encode products (such as cal inhibitors of oxidative phosphorylation. Inhibition of this process, can be mimicked by exposure to pharmacologi- cal antagonists of central histaminergic neurons. Neuroendocrinology 53: 175–180, 1990.


