



REVIEW

Recent advances in central cardiovascular control: sex, ROS, gas and inflammation [version 1; referees: 2 approved]

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Abstract

The central nervous system (CNS) in concert with the heart and vasculature is essential to maintaining cardiovascular (CV) homeostasis. In recent years, our understanding of CNS control of blood pressure regulation (and dysregulation leading to hypertension) has evolved substantially to include (i) the actions of signaling molecules that are not classically viewed as CV signaling molecules, some of which exert effects at CNS targets in a non-traditional manner, and (ii) CNS locations not traditionally viewed as central autonomic cardiovascular centers. This review summarizes recent work implicating immune signals and reproductive hormones, as well as gasotransmitters and reactive oxygen species in the pathogenesis of hypertension at traditional CV control centers. Additionally, recent work implicating non-conventional CNS structures in CV regulation is discussed.



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Introduction

According to the World Health Organization (WHO), cardiovascular (CV) disease accounts for approximately 17 million deaths a year worldwide¹, of which more than half (9.4 million) are attributable to complications of hypertension². In 2008, a staggering 40% of adults over the age of 25 had been diagnosed with hypertension³.

The central nervous system (CNS) is essential to maintaining CV homeostasis. Traditional central autonomic CV control centers include the nucleus tractus solitarius (NTS), the rostral ventral lateral medulla (RVLM), and the caudal ventral lateral medulla in the brainstem; the parabrachial nucleus in the pons; and the paraventricular nucleus (PVN) in the hypothalamus. In addition, the area postrema (AP) in the hindbrain, and the organum vasculosum of the lamina terminalis (OVLT) and subformal organ (SFO) in the forebrain, are sensory circumventricular organs (CVOs) characterized by the presence of a wide variety of receptors and the lack of the normal blood-brain barrier, which have also been implicated in central CV regulation. The renin-angiotensin aldosterone system (RAAS) has also been extensively implicated as a critical signaling system, components of which play central roles both as circulating hormones and as CNS neurotransmitters in the regulation of blood pressure (BP). There is growing evidence that the development and progression of hypertension involves dysregulation of the sympathetic nervous system (SNS) (SNS over-activity) (for review, see 4–6) and activation of the RAAS^{7,8}.

Over the past 20 years, our understanding of CNS control of BP regulation (and dysregulation leading to hypertension) has evolved substantially. This review will summarize some of these paradigm shifts, focussing primarily on signaling molecules that either (i) are not classically viewed as CV signaling molecules (i.e. immune signals and reproductive hormones) or (ii) exert effects at CNS targets in a non-traditional manner, acting via membrane receptor-independent signaling mechanisms (i.e. gasotransmitters and reactive oxygen species [ROS]), all of which have been shown to have profound effects on the central control of BP. CNS structures, not conventionally thought of as CV control centers but that more recently have been shown to influence CV regulation, are also discussed.

Inflammation and immune regulators as modulators of cardiovascular regulation and contributors to hypertension

Although it had been speculated decades ago that there was a relationship between the immune system and hypertension⁹, the demonstration of systemic markers of inflammation in patients with essential hypertension in the early 2000s^{10,11} was a catalyst for renewed interest in the relationship between hypertension and the immune system. Emerging evidence suggests that both the innate and acquired immune systems are activated in hypertension, as inflammations in the kidney, vasculature (arteries), and CNS have all been shown to be involved in the pathogenesis of hypertension.

As an immediate first-line defence mechanism to infections or tissue injury, the innate immune system initiates a generalized inflammatory response involving dendritic cells, macrophages, natural killer (NK) T cells, and Toll-like receptors (TLRs), all of which have been shown to be activated in hypertension.

Dendritic cell activation has been shown to promote hypertension by stimulating T-cell proliferation which infiltrates both the kidney and arterial walls^{12,13}. Similarly, macrophage infiltration of the kidney and arteries has been documented in experimental models of hypertension, and a decrease in macrophage infiltration is associated with an improvement of hypertension in these models of hypertension^{14–17}. Recently, NK T-cell activation and TLRs (TLR4, in particular) have been suggested to play a role in hypertension-related inflammation^{18,19}.

The adaptive immune system responds to specific antigens and involves antigen presentation, lymphocyte activation, and antibody production. T cells have been shown to play a role in angiotensin II (ANG II)-induced hypertension²⁰ whereas endogenously produced ANG II increases T-cell activation²¹. Pro-inflammatory T-cell activation and the subsequent release of pro-inflammatory cytokines are associated with hypertension^{22–24} whereas inhibition or genetic ablation of the B7/CD28 T cell costimulatory pathway has been shown to prevent experimental hypertension¹². RAG-1^{-/-} mice and SCID mice, which lack both T and B cells, exhibited a blunted hypertensive response to ANG II infusion^{20,25}, a response that returned when T cells were transferred into RAG-1^{-/-} mice²⁰. T cell-produced cytokines (such as tumor necrosis factor alpha, or TNF α) and many of the interleukins (such as IL-6) have been shown to play a role in hypertension. TNF α antagonism^{20,26} or genetic knockout of IL-6²⁷ has been shown to blunt ANG II-induced hypertension. The presence of agonist antibodies to ANG II receptors has been identified in a number of conditions that are characterized by elevated BP, such as preeclampsia^{28,29}, refractory hypertension^{30,31}, and malignant hypertension³².

Many studies have suggested that arterial inflammation within specific CNS locations is involved in the pathogenesis of hypertension. A role for inflammation in the NTS, a pivotal region for regulating arterial pressure baroreceptor reflex sensitivity, has been suggested in the development of hypertension, as studies have shown not only leukocyte accumulation within the NTS microvasculature³³ but also changes in gene expression of a variety of inflammatory molecules^{34,35} and neurotrophic factors³⁶ in the NTS of spontaneously hypertensive rats (SHRs).

In addition, many of the cytokines, released as a consequence of immune system activation, have been shown to directly influence cardiovascular control centers in the CNS. Microinjection of IL-6 into the NTS attenuates baroreceptor function³⁷ and leads to speculation that abnormal gene expression of IL-6 in the NTS may be associated with hypertension. Augmentation of IL-1 β , IL-6, or TNF- α expression and increased ROS observed in the RVLM following chronic intraperitoneal lipopolysaccharide administration have been suggested to be contributing factors to neurogenic hypertension induced by systemic inflammation³⁸.

Early studies identified the anteroventral third ventricle (AV3V), a broad-based region located along the wall of the third ventricle which includes the OVLT, as a critical CNS structure in the pathogenesis of hypertension³⁹. A more recent study not only confirmed that lesions of the AV3V region attenuate ANG II-induced hypertension but also implicated immune system involvement as AV3V lesions eliminated circulating T-cell activation and

vascular infiltration normally observed in response to ANG II administration⁴⁰. IL-1 β has been shown to influence the excitability of SFO neurons⁴¹, and recent studies have demonstrated that microinjection of IL-1 β (and of TNF α) into SFO increases BP and renal sympathetic nerve activity (SNA)⁴².

The PVN, a hypothalamic autonomic control center with well-documented roles in CV regulation, has been implicated as a CNS structure in which immune signals may act to cause hypertension. Chronic ANG II infusion causes the expression of pro-inflammatory cytokines and markers of oxidative stress in the PVN, effects blocked by central administration of TNF α blocker²⁶. Angiotensin-converting enzyme 2 (ACE2) overexpression in the PVN has also been shown to attenuate both ANG II-induced hypertension and expression of the pro-inflammatory cytokines TNF α , IL-1 β , and IL-6 in the PVN⁴³. Blockade of nuclear factor-kappa-B (NF κ B), a prominent transcription factor that governs inflammatory responses, in the PVN of rats resulted in decreased BP, pro-inflammatory cytokines, and ROS, as well as upregulation of key protective anti-hypertensive RAAS components, suggesting an important role for NF κ B in PVN in the hypertensive response⁴⁴. Finally, rats fed a high-salt diet demonstrated increased expression of IL-1 β and decreased expression of the anti-inflammatory cytokine IL-10, in the PVN. These expression levels were augmented by stimulation of ROS production within the PVN⁴⁵.

Reproductive hormones and cardiovascular regulation

The interest in the role of sex hormones in hypertension has been driven by a number of observations regarding sexual dimorphism in BP regulation in humans and animals. Epidemiological findings that prior to menopause the prevalence of essential hypertension is lower in women than in men of the same age⁴⁶ and that young women have lower resting SNA than men⁴⁷, differences that disappear after menopause, suggest that estradiol is important in BP regulation and, in fact, may protect against hypertension. Findings that estradiol administration attenuates increases in BP normally exhibited by intact males and ovariectomized females, and prevents development of hypertension in experimental models of hypertension^{48,49}, suggest a role for estradiol in the regulation of BP.

Studies in humans and animals suggest that exogenous testosterone may also play a crucial role in BP regulation. In humans, low testosterone levels have been correlated with higher BP^{50,51} whereas testosterone replacement has been shown to cause significant reductions in BP^{52,53}, suggesting a role for testosterone in BP regulation. Moreover, in experimental models of hypertension high BP develops more rapidly and becomes more severe in the male than in the female, effects which were shown to be androgen-dependent^{48,54,55}. Further support for a role of testosterone in the etiology of hypertension is derived from studies showing that castration prevents the development of hypertension in SHR rats⁵⁶.

Evidence for a role for central actions of estradiol on BP regulation is derived from a variety of sources. Firstly, many of the CNS sites with well-documented roles in CV regulation have been shown

to possess estrogen receptors (ER α and ER β)⁵⁷⁻⁶¹. Moreover, intracerebroventricular (icv) administration of estradiol in ovariectomized mice and in male mice attenuated the increase in BP normally elicited by ANG II⁶². In rats, aldosterone/salt-induced hypertension is exhibited by intact males and ovariectomized females, effects attenuated by activation of central ER receptors. Central ER blockade⁶³ or icv injections of small interfering RNA-ER α (siRNA-ER α) or siRNA-ER β ⁶⁴, on the other hand, augmented aldosterone-induced hypertension in intact females.

Further to these findings, estradiol has been shown to act via ER α or ER β (or both) at specific brain regions in both males and females to influence sympathetic outflow and baroreflex function. The AP and SFO predominantly express ER α ⁵⁷⁻⁶², and estradiol has been shown to decrease the activity of AP⁶⁵ and SFO neurons⁶⁶, and inhibits ANG II activation of AP⁶⁷ and SFO neurons⁶⁶, whereas genetic knockdown of ER α in the SFO enhances ANG II-induced hypertension in female mice⁶⁸.

Estrogen actions at ER β in PVN inhibit hypertensive effects of glutamate activation⁶⁹. In the RVLM, estradiol actions at ER β receptors have been shown to cause decreases in BP in normotensive rats⁷⁰ and to attenuate aldosterone-induced increases in SNA and BP⁶⁴ whereas ER β knockdown in RVLM or PVN results in the augmentation of aldosterone-induced increases in SNA and BP⁶⁴, effects that are not seen in intact females⁶⁴.

Relaxin, a member of the insulin family best known for its role in pregnancy, has also been shown to influence BP. Early studies revealed that chronic intravenous (iv) administration of relaxin elicited a decrease in BP in SHRs⁷¹. Relaxin binding sites and relaxin receptors have been shown to be widely distributed throughout the brain, including the SFO, NTS, and PVN⁷², suggesting that relaxin may be involved in the central control of BP. Hypertensive effects of central administration of relaxin into the dorsal third ventricle are totally abolished by lesions of the SFO⁷³, identifying this CVO as one central target mediating these cardiovascular effects. A recent study demonstrating that acute microinjection of relaxin-2 into the PVN increased sympathetic outflow and BP in SHR, whereas chronic PVN administration caused a profound increase in BP in normotensive rats⁷⁴, supports the conclusion that there are multiple central targets for this reproductive hormone/neurotransmitter. Moreover, this same study revealed that neutralization of endogenous relaxin reduced BP in SHR but had no significant effect in WKY⁷⁴, suggesting a role for relaxin in the pathogenesis of hypertension.

Another reproductive peptide that warrants further investigation into its potential contribution to the pathogenesis of hypertension is prolactin, a hormone best known for its involvement in lactation and reproduction. Very few studies have investigated the role of prolactin in the central control of CV regulation despite epidemiological evidence suggesting correlations between circulating prolactin levels and increased BP. Plasma prolactin has been shown to be elevated in patients with essential hypertension⁷⁵ and preeclampsia^{76,77}. Furthermore, higher plasma prolactin levels have been shown to be associated with increased risk of hypertension in menopausal⁷⁸ and post-menopausal⁷⁹ women and in preeclampsia⁵⁴. Prolactin receptors are widely distributed throughout the body⁸⁰

and brain⁸¹. mRNA for the prolactin receptor has been reported in the PVN^{81,82}, and we have identified the presence of the prolactin receptor at levels similar to the AT1 receptor in the SFO⁸³. However, to our knowledge, studies investigating the CV consequences of central administration of prolactin (icv or microinjection into discrete brain nuclei) on BP, or the effects of prolactin on neuronal excitability in central CV control centers, are lacking.

Gasotransmitters and cardiovascular regulation: hydrogen sulfide

Gasotransmitters are endogenously produced membrane permeable gas molecules which act at specific, targeted cells via membrane receptor-independent signaling mechanisms to exert well-defined physiological effects. The action(s) of nitric oxide (NO) and carbon monoxide (CO) at peripheral tissues and in the CNS to influence cardiovascular regulation are well documented^{84,85}. More recently, a third gasotransmitter, hydrogen sulfide (H₂S), an environmental air pollutant with well-known deleterious health effects, has been identified and suggested to play a role in the pathogenesis of hypertension. H₂S is endogenously produced from catalysis of L-cysteine by using four enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), or 3-mercaptopyruvate sulfur transferase (3MST) in tandem with cysteine aminotransferase (CAT). CBS is highly expressed in the CNS where it produces H₂S from L-cysteine⁸⁶, whereas CSE is the predominant enzyme expressed in the myocardium and vasculature smooth muscle cells⁸⁷. Though predominantly found in the mitochondria where they work in tandem to produce H₂S, 3MST and CAT are also expressed in the brain and vascular endothelium⁸⁸. In addition, H₂S can be produced in red blood cells by the conversion of polysulfides which are obtained from dietary sources⁸⁹.

Evidence for a role of H₂S in the pathogenesis of hypertension is suggested by the observation that plasma H₂S concentrations are lower in patients with grade 2 or grade 3 hypertension, portal hypertension, and pulmonary hypertension⁹⁰⁻⁹² and in preeclampsia where plasma H₂S levels and placental CBS mRNA expression are decreased^{93,94}.

H₂S has been shown to be endogenously produced in peripheral vascular tissues and has been demonstrated to be a potent vasodilator, causing vasorelaxation in mesenteric arteries⁹⁵, aortic rings^{96,97}, the ductus arteriosus⁹⁶, and pulmonary arteries⁹⁸ via actions on vascular smooth muscle cells. Unlike its gasotransmitter counterparts, NO and CO, vascular smooth muscle relaxation occurs independently of cGMP pathway activation. Activations of Ca²⁺-activated potassium channels (BKCa)⁹⁹, ATP-sensitive potassium channels (K_{ATP})¹⁰⁰, Kv7 voltage-gated potassium channels⁹⁷, and cytochrome P-450 2C (Cyp2C)⁹⁹ have all been implicated as mechanisms of the H₂S vasorelaxation.

A bolus iv injection of H₂S elicited an immediate depressor response in normotensive rats¹⁰⁰ whereas chronic intraperitoneal administration of H₂S decreases BP in hypertensive rats¹⁰¹⁻¹⁰⁴. These findings, along with the fact that mice lacking CSE exhibit hypertension and reduced endothelium-dependent vasorelaxation¹⁰⁵, provide evidence of a direct role for H₂S in BP regulation.

A role for H₂S in the central control of BP stems from studies demonstrating that icv administration of H₂S has been shown to dose-dependently decrease BP, effects which are followed by potent long-lasting hypertension actions attributed to modulation of H₂S on K_{ATP} channels and α adrenergic stimulation, respectively¹⁰⁶. Furthermore, microinjection of H₂S into discrete brain nuclei known for their involvement in CV regulation has also been shown to affect BP. H₂S administration into the RVLM elicits decreases in BP, effects again mediated by K_{ATP} channels¹⁰⁷, whereas similar microinjections into the PVN¹⁰⁸ and SFO¹⁰⁹ have been shown to dose-dependently increase BP. Moreover, H₂S has been shown to influence the excitability of neurons in the NTS¹¹⁰, PVN¹¹¹, and SFO¹⁰⁹, CNS areas involved in CV regulation.

Reactive oxygen species and cardiovascular control

When produced at appropriate concentrations, ROS have been implicated in the regulation of many critical physiological processes, including cell signaling, maintenance of appropriate vascular tone, inflammation, and immune responses. ROS overproduction, on the other hand, is a feature common to a number of pathological conditions, including hypertension.

A role for ROS in hypertension is suggested in humans as a positive correlation between BP and biomarkers of oxidative stress in patients with essential hypertension has been reported^{112,113}. Furthermore, mice lacking nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, key enzymes in the production of ROS, are protected against experimental hypertension¹¹⁴, whereas overexpression potentiates ANG II-induced hypertension¹¹⁵.

ROS production in specific CNS cardiovascular control centers, including both brain stem (NTS, RVLM) and hypothalamic (PVN) nuclei, and within the CVOs (SFO) has been shown to play a role in neurogenic hypertension¹¹⁶⁻¹¹⁸. Superoxide dismutase (SOD), an enzyme that metabolizes superoxide, overexpression in the brain abolished the hypertensive response normally observed in response to icv ANG II administration¹¹⁹, whereas specific SOD3 deletion in the SFO increased baseline BP and potentiated ANG II-induced increases in BP¹²⁰. Interestingly, this same study showed that ROS in the SFO leads to infiltration by activated lymphocytes in the peripheral vasculature¹²⁰, linking oxidative stress in the CNS with immune activation in the periphery, which in concert would serve to intensify hypertension.

A high-salt diet increases NADPH oxidase (NOX-2 and NOX-4) expression in the PVN, whereas microinjection of amino-triazole (ATZ), a catalase inhibitor which increases ROS, into the PVN augments renovascular hypertension as well as increasing BP in normal rats⁴⁵.

A role for 'other' central nervous system structures in the central control of blood pressure

This review has focussed on actions of non-traditional CV signaling molecules at CNS structures with well-documented roles in CV regulation. Another emerging area that warrants mention is the role of CNS regions not classically viewed as CV control centers that have been suggested to play a role in the pathogenesis of

hypertension, secondarily or as a co-morbidity to other disease states. For example, the explosion of obesity research further to the discovery of leptin in the 1990s¹²¹ has highlighted the involvement of a number of CNS autonomic control centers not typically viewed as CV control centers, such as the arcuate nucleus and the anterior hypothalamus, in the pathogenesis of hypertension as a consequence of direct actions of metabolic signals in these areas (for review, see 122,123). Furthermore, many metabolic signals associated with obesity have been demonstrated to influence BP regulation via actions at the ‘classical’ CNS CV control centers. Further study of the actions of traditional CV signals (such as ANG II) within these non-traditional CV CNS centers may elucidate previously unknown roles of these regions in normal CV regulation.

Conclusions

In this brief review, we have highlighted some emerging new perspectives which over the past 20 years contributed new and important information to the evolution of our understanding of CNS mechanisms involved in central CV control. The areas we

have chosen to discuss are far from an exhaustive list of what is new and interesting, but do emphasize that this is a continually developing area of research with an inherent complexity associated with the requirement for integration of diverse autonomic systems. This points us in the direction of understanding that we perhaps should not expect to consider either single brain areas or single signalling molecules as “cardiovascular” at the expense of also describing their roles in other systems. Such conclusions point us to the broader perspective that all of these brain areas, signalling molecules, and autonomic systems contribute to the complex homeostatic regulation which maintains our “milieu interior” in a state of optimal health.

Competing interests

The authors declare that they have no competing interests.

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Version 1

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