Review Article

Neuro-endocrine regulation of blood pressure

Sandeep Chopra, Chris Baby, Jubbin Jagan Jacob[1]

Departments of Cardiology and [1]Medicine, Endocrine and Diabetes Unit, Christian Medical College, Ludhiana, India

ABSTRACT

As our understanding of the underlying aetiology of hypertension is far from adequate, over 90% of patients with hypertension receive a diagnosis of essential hypertension. This non-specific diagnosis leads to suboptimal therapeutics and a major problem with non-compliance. Understanding the normal control of blood pressure (BP) is, hence, important for a better understanding of the disease. This review attempts to unravel the present understanding of BP control. The local mechanisms of BP control, the neural mechanisms, renal-endocrine mechanisms, and a variety of other hormones that have a bearing in normal BP control are discussed and the possible role in the pathophysiology is alluded to.

Key words: Blood pressure, neural control, renin-angiotensin-aldosterone system

Introduction

Even with our present understanding of the pathophysiology of hypertension, in about 90% of cases the etiology is unclear and the patients are classified as having essential hypertension. This results in most patients being treated for hypertension nonspecifically resulting in a large number of minor side effects because of inappropriate choice of therapy and over 50% noncompliance rates. Moreover, essential or primary hypertension is a major public health issue, with approximately one fourth of the adult population being affected in industrialized countries. However, the cardiovascular disease epidemic has now moved to the developing countries, with the projected increase in the proportion of cardiovascular mortality expected to increase from around 25% in 1990 to more than 40% in 2020.[1]

With this background, it becomes important to understand the neuro-endocrine regulation of blood pressure (BP) control which is the subject of this review. The regulation of BP is a very complex physiologic function, dependent on a continuum of actions of cardiovascular, neural, renal, and endocrine systems. Investigating the pathophysiology of hypertension thus needs a good understanding of the factors responsible for normal BP control and looking for subclinical abnormalities that precede the increase of BP to abnormally high levels. Improvements in the understanding of the mechanisms that underlie hypertension and especially of those that regulate BP throughout its range should facilitate advances in the prevention and treatment of hypertension.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.86860

An Overview

The control of BP is essentially the sum of the control of blood flow to a given tissue in proportion to its metabolic need. The local mechanisms that control blood flow include vasoconstriction and dilatation acutely, and chronically, change in the number and caliber of the blood vessels supplying a tissue. The endothelial autocrine secretions play an important role in vasoconstriction and vasodilation and will be briefly considered in the review.

In addition to the local control of blood flow, global control of blood flow including changes in cardiac output and control of arterial BP is mediated by the autonomic nervous system. Global neural control of arterial hypertension is essentially through the sympathetic nervous system (SNS).

Corresponding Author: Dr. Jubbin Jagan Jacob, Department of Medicine, Endocrine and Diabetes Unit, Christian Medical College, Ludhiana - 141 008, India. E-mail: jubbin.jacob@gmail.com

The parasympathetic nervous system contributes primarily to regulation of cardiac functions. The first part of the review looks at the role of SNS in the control of systemic hypertension.

The most powerful chronic mechanism that controls BP over weeks and months however is the integrated renal-endocrine systems that balance the body fluid and salt homeostasis with control of arterial hypertension. This is the second part of the review.

The overview of the mechanisms is given in Figure 1.

Neural Mechanisms

There is a wide spectrum of responses of the sympathetic nervous system (SNS) that range from mild to massive and from acute to chronic. The SNS is the only system of the body capable of both momentary and sustained regulation of BP.[2,3] Young adults with hypertension have associated tachycardia, increased cardiac output, and also a rise in plasma norepinephrine levels with an increased vasoconstrictor tone in the peripheral circulation. A rise in sympathetic activity is also noted in patients with hypertension associated with obstructive sleep apnea, obesity, chronic kidney disease, prediabetes, and heart failure.

Regulation of Blood Pressure and Sympathetic Nervous System

While short-term changes in BP are regulated by SNS and renin–angiotensin-aldosterone system (RAAS), long-term BP control is controlled by the kidney.[4] High pressure baroreceptors in the carotid sinus and aortic arch respond to acute elevations in systemic BP by causing a reflex vagal bradycardia that is mediated through the parasympathetic systems and inhibition of sympathetic output from the CNS. Low pressure cardio pulmonary receptors in the atria and ventricles likewise respond to increases in atrial filling by causing tachycardia through inhibition of cardiac SNS, increasing atrial natriuretic peptide (ANP) release and inhibiting vasopressin release.[5-7]

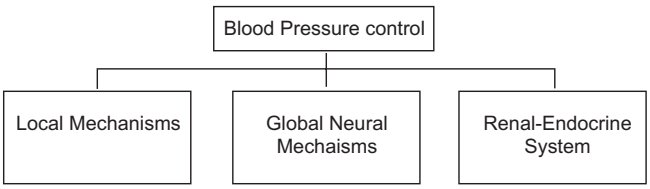

Figure 1: Outline of blood pressure regulation

Sympathetic regulation also plays a role in long-term BP regulation, as the most important stimulus to renin release in the juxtaglomerular apparatus is through renal sympathetic nerves.

Some of the strongest clinical evidence of sustained neurogenic hypertension comes from studies done in patients with obstructive sleep apnea. Activation of the carotid body chemoreceptors occurs during the apneic spells with arterial desaturation. This causes high BP episodes and a long-term resetting of the chemoreceptor reflex.

The normal control of the arterial BP by SNS is summarized in Figure 2**.**

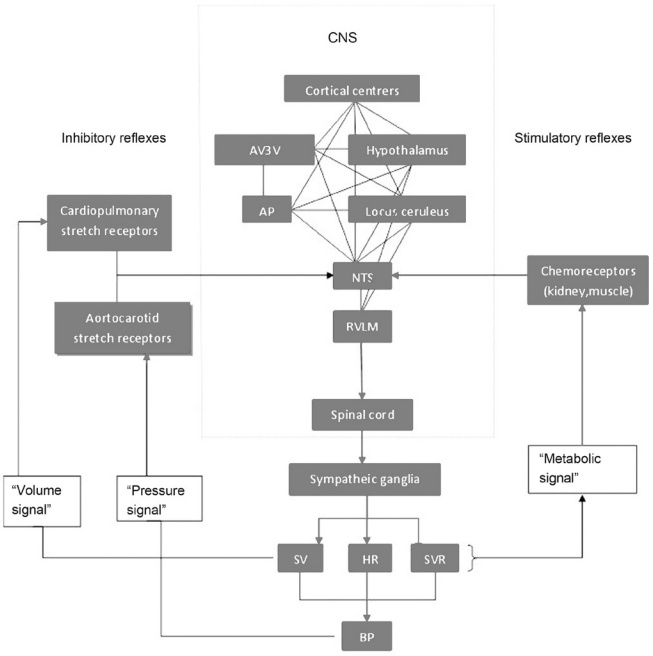

Figure 2: CNS control of sympathetic outflow. Efferent SNS output is the result of integrated actions of several CNS centers, including many areas of the cortex as well as lower centers in hypothalamaus, basal ganglia(especially the locus ceruleus), and circumventricular regions, including the area postrema (AP) and the AV3V region. The critical integrator region is the nucleus tractussolitaries (NTS), which lies in the medulla oblongata. The NTS receives inhibitory afferent signals from the baroreflexes (volume and pressure signals) and stimulatory afferent signals from renal and muscular chemoreceptors (metabolic signals). SNS outflow is ultimately dependent on stimulation of the rostral ventrolateral (the RVLM or vasomotor control center), which is tonically inhibited by the adjacent NTS. Circumventricular regions such as the AP are of particular interest because they have no blood-brain barrier; stimulation of the AP by circulating angiotensin II (Ang II) blunts the inhibitory effects of the NTS. Ultimately, RVLM stimulation sends signals via the spinal cord and sympathetic ganglia to regulate heart rate, cardiac stroke volume(SV), and systemic vascular resistance(SVR), which together determine momentary and chronic blood pressure (BP) levels.[71]

Renal Endocrine-Hormonal Mechanisms

Renin-angiotensin-aldosterone system

Activation of the RAAS is a very important mechanism responsible for regulation of BP.[8]

Renin – Renin is an aspartyl protease that is first synthesized as an enzymatically inactive precursor, prorenin. The vast majority of renin in the circulation originates in the juxtaglomerular (JG) cells surrounding the renal afferent arterioles. Lab measurements for renin are most commonly expressed as the capacity of plasma to generate angiotensin I. Thus plasma renin activity (PRA) reflects not only the amount of renin in circulation but also the amount of substrate angiotensinogen and is therefore the best measure of RAS activity *in vivo*.

Angiotensinogen – Circulating angiotensinogen (a large protein with over 450 amino acids and 13% carbohydrate content) can be found in the alpha – 2 – globulin fraction of the plasma globulins. It is synthesized in the liver with 32 amino acid signal sequence that is removed in the endoplasmic reticulum. Renin acts enzymatically on angiotensinogen (renin substrate) to release a small 10-amino acid peptide, angiotensin I.

Angiotensin I – has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function.

Angiotensin II - also called angiotonin previously, produces arteriolar constriction and a rise in systolic and diastolic BP.

Angiotensin Converting Enzyme – Angiotensin Converting Enzyme (ACE) is a dipeptidylcarboxypeptidase enzyme that is located in the endothelial cells. It splits off the histidyl – leucine complex from the physiologically inactive angiotensin I, to form the octapeptide angiotensin II. The same enzyme is responsible for inactivating bradykinin. Much of this conversion occurs as the blood carrying angiotensin I passes through the lungs, but this can also occur in many other parts of the body. In mammals, ACE occurs as two iso-forms that are produced from a single gene with alternate spacing.

a. A somatic form (sACE) which is a type I integral membrane glycoprotein and which is widely distributed in many endothelial cells in variety of tissues, including the heart[9] and kidney.
b. A testicular form (germinal ACE or gACE) that is smaller and found solely in post meiotic spermatogenic cells and spermatozoa.

Both ACEs have a single transmembrane domain and a short cytoplasmic tail. However, somatic ACE is a 170 kDa protein with two homologous extracellular domains, each containing an active site. Germinal ACE is a 90 kDa protein that has only one extracellular domain with an active site. Both enzymes are formed from a single gene.[10,11]

The renin angiotensin system cascade is summarized in Figure 3.

The Angiotensin receptors: AT_1 and AT_2

The effects of angiotensin II, the principal effector hormone of the RAS, are mediated through its interaction with the above cell membrane receptors.[12-14] The development of highly selective angiotensin II receptor antagonists has allowed the characterization of at least two distinct angiotensin II receptor subtypes, AT_1, and AT_2.[15] Both receptors belong to the super family of seven transmembrane- spanning G protein coupled receptors.[16,17] The expression of these receptors is not static and certain hormones, and pharmacologic agents, and pathologic conditions can enhance or suppress their expression.[18,19]

The opposing post-receptor effects of the two subtypes are highlighted in Table 1 and Figures 4 and 5.

Aldosterone

Aldosterone is a steroid hormone produced mainly though not exclusively in the adrenal cortex Aldosterone's mineralocorticoid activity is 3000 times greater than that of cortisol, but the plasma concentration of cortisol is 2000

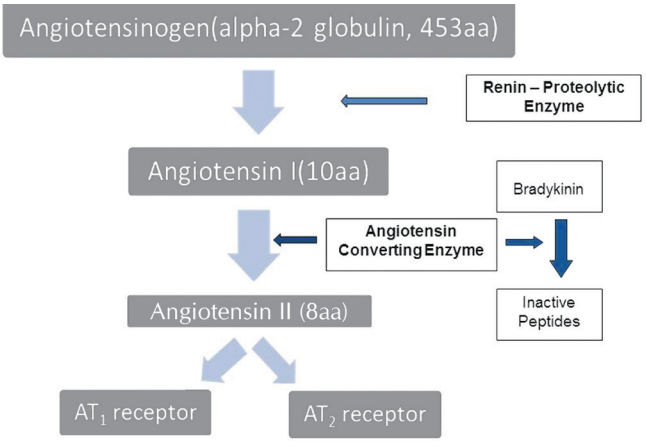

Figure 3: Renin angiotensin system

Table 1: Actions at receptors[19]

Opposing actions of angiotensin II at AT_1 and AT_2 receptors	
AT_1	**AT_2**
Vasoconstriction	Vasodilation
Anti diuresis/antinatriuresis	Diuresis/natriuresis
Cell growth and proliferation	Anti proliferation

Effects of Angiotensin II via AT_1 receptor									
Vasoconstriction	Activate SNS	Aldosterone, vasopressin and endothelin secretion	PAI-1 synthesis	Platelet aggregation	Thrombosis	Cardiac contractility	Superoxide production Vascular smooth muscle growth	Myocyte growth	Collagen formation

Figure 4: AT_1 receptor actions

Effects of Angiotensin II via AT_2 receptor						
Tissue bradykinin produciton	Tissue NO production	Tissue cGMP production	Anti Proliferation	Apoptosis	Cell differentiation	Tissue regeneration

Figure 5: AT_2 receptor actions

times that of aldosterone. Aldosterone increases absorption of sodium and increases secretion of K^+ by the renal tubular epithelial cells mainly in the collecting tubules, but also in the distal tubules and collecting ducts, though to a lesser degree. Aldosterone thus causes conservation of extra cellular Na^+ and increases urinary excretion of K^+.

Cellular mechanisms of aldosterone action

- Aldosterone is lipid soluble and diffuses into the tubular epithelial cells
- It combines with a receptor protein and diffuses into the nucleus to form different types of messenger RNA
- The mRNA diffuses out of the nucleus and forms enzymes and membrane transport proteins like sodium – potassium adenosine triphosphatase which are required for Na/K^+ transport across the cells.

Local Endothelium-Derived Factors

Nitric oxide

Nitric oxide (NO) also called endothelium-derived relaxing factor (EDRF) is a free radical gas with a very short half-life. It is released from endothelial cells in response to blood flow-induced shear stress and by activation of a number of receptors.[20-22] NO is synthesized from arginine by NO synthase (NOS).[23] In addition to vasodilatation NO also has anti-proliferative, anti-thrombotic, leukocyte adhesion inhibition effects, and influences myocardial contractility.[24-27] The primary hemodynamic effect of pharmacologic NO inhibition includes an increase in systemic and pulmonary arterial BP, and a parallel decrease in cardiac output. The vasoconstrictor effect of Ang II is enhanced in the absence of NO.[28]

Endothelin

Endothelial cells produce endothelin 1 (ET-1), which is one of the most potent vasoconstrictor ever isolated. The evidence suggesting the existence of ET was shown by studies by Hickey *et al*.[29] It was named endothelin by Yanagisawa *et al*.,[30] due to its origin from vascular endothelium. ET-1, ET-2, and ET-3 are members of a family of similar polypeptides but each is encoded by different genes. There are two different types of ET receptors which have been cloned, ET_A and ET_B. ET_B receptor activation leads to decreased arterial pressure and natriuresis through effects on adrenal gland, heart (negative inotropy), decreasing sympathetic activity and systemic vasodilatation. ET_A receptor activation leads to increased arterial pressure and sodium retention via increased sympathetic activity, positive inotropy of the heart, increased catecholamine release and, systemic vasoconstriction.[31] Stimulators of ET-1 secretion include angiotensin II, catecholamines, growth factors, hypoxia, insulin, oxidized LDL, HDL, sheer stress and thrombin. Inhibitors of ET-1 secretion include NO, ANP, PGE-2, and prostacyclin. Several reports show that ET levels maybe high in hypertensive patients,[32,33] while there are other studies which have reported no difference in ET levels in patients with or without hypertension.[34,35] ET receptor antagonists have been investigated for their use as anti-hypertensive agents.[36,37] ET antagonists are available now for the treatment of pulmonary hypertension.

Other Hormones Involved in BP Control

Natriuretic peptides

These are a group of hormones which include ANP, brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP was the first NP to be discovered.[38] It is synthesized mainly in the atrial myocardium. BNP is synthesized mainly in the ventricles, while CNP is secreted by the vascular endothelium. NPs exert their functions by binding to the guanylyl cyclase-linked NP receptors: type A (NPR-A) and type B (NPR-B).[39] The biological effects of ANP and BNP are mediated through NPR-A and those of CNP are mediated through NPR-B. NPs inhibit the RAAS and regulate water and electrolyte balance. They inhibit the sympathetic nervous system causing bradycardia and a decrease in BP. In this context of sympathetic outflow control ANP plays a major role.[40] NPs play an active role in cardiac remodeling and have been used as markers of left and right ventricular hypertrophy.[41,42] ANP has been accepted to behave as a friendly mechanism toward hypertrophic cardiac responses,[43] and an inadequate response of this system favors cardiac hypertrophy and long-term development of cardiac failure. ANP also induces endothelium-independent vasodilatation in both small and large arteries. NPs have anti-inflammatory and anti-fibrotic effects and also affect cardiac fibroblasts by reducing collagen synthesis. High levels of NPs have been associated with acute cardiac failure especially with BNP. BNP levels have been studied to reflect severity of LV dysfunction in heart failure and help to provide prognostic information about future outcomes in patients with congestive cardiac failure.[44]

The vasopressin system

Vasopressin, also known as anti-diuretic hormone (ADH) is synthesized in the hypothalamus. The human hormone is called arginine vasopressin (AVP) as it contains arginine. There are three kinds of vasopressin receptors: V_{1A},V_{1B}, and V_2 all of which are G-protein coupled. ADH increases the permeability of the collecting ducts of the kidney so as to concentrate the urine leading to its primary physiological effect of retention of water and decreasing the effective osmotic pressure of the body fluids. Vasopressin secretion is stimulated by increased effective osmotic plasma pressure, decreased ECF volume, pain, emotion, nausea, vomiting and inhibited by decreased effective osmotic plasma pressure, increased ECF volume and alcohol ingestion. Vasopressin receptor antagonists decrease vascular smooth muscle contraction (V_1 antagonists) and have diuretic effects (V_2 antagonists). Both drugs are under clinical evaluation.[45-48]

Vasodilator peptides: Adrenomedulin, Substance P, and calcitonin gene related peptide

Adrenomedulin (ADM) is a 52 amino acid peptide whose name comes from its abundance in normal adrenal medulla as well as pheochromocytoma tissue arising from adrenal medulla.[49] Plasma ADM levels are increased in hypertensive patients and the rise in ADM is proportionate to the severity of hypertension and the target organ damage.[50,51] This suggests that ADM is released to compensate for the elevated BP.[52]

Substance P is an 11 amino acid peptide that is found in the intestine, peripheral nerves and many parts of the CNS. It is probably the mediator at the first synapse in the pathways for pain transmission in the dorsal horn of the spinal cord. It is also found in high concentration in the nigrostriatal system and in the hypothalamus where it may play a role in neuro-endocrine regulation. It is also a potent vasodilator with little effect on heart rate and cardiac contractility.[53]

Calcitonin gene related peptide (CGRP) is a 37 amino acid neuro-peptide which is widely distributed in the nervous and cardiovascular systems.[54,55] It is a very potent vasodilator and has positive chronotropic and inotropic effects.[56,57]

The levels of circulating immunoreactive CGRP in hypertensive patients reported in different studies have been inconsistent,[55,58] and its role in human hypertension is unclear.

The tissue Kallikrein-Kinin system

The KKS comprises kallikreins (kinin forming enzymes), kininogens (substrates), kinins (vasoactive peptides), kinin-degrading enzymes and kinin receptors. The KKS plays a major role in controlling systemic and local hemodynamics. The actions of kinins include contraction of visceral smooth muscles and relaxation of vascular smooth muscle via NO, lowering BP. Angiotensin converting enzyme inhibitors partially exert their beneficial cardiovascular effects by potentiating endogenous kinins.[59]

Phosducin

PDC is a 33-kDa cytosolic regulator of G-protein mediated signaling and is found in the retina, CNS, pineal gland, and sympathetic ganglia. Recent research has revealed the potential role of the PDC gene in modulating the adrenergic and BP response to stress and hence its significance as a mediator in stress-dependent hypertension.[60]

Adipose tissue and adipokines

Adipose tissue is not just a passive reservoir for energy storage but is an endocrine organ which secretes bioactive peptides like adipokines.[61] Adipokines include hormones, inflammatory cytokines, and other proteins like angiotensinogen which act at both local (autocrine/paracrine) and systemic (endocrine) levels. Adipokines influence vascular tone under normal conditions but this regulation of vascular tones is compromised with patients with obesity. leptin and tumor necrosing factor alpha (TNF- α) have vasorelaxing and vasoconstricting physiologic effects.[62,63] Adiponectin is released by both brown and white adipocytes and has cardio-protective properties.[64] It is a vasorelaxing adipokine which increases NO and inhibits TNF-α production. A decrease in adiponectin levels, which are found in obesity related disorders, leads to endothelial dysfunction and are an independent predictor of premature atherosclerosis.[65] Other adipokines which have vasorelaxing properties omentin, visfatin and adipocyte-derived relaxing factor.

Leptin

Leptin is a 16 kDa 167 amino acid polypeptide hormone and plays an important link between obesity and the development of cardiovascular disease.[66] Increased leptin levels are associated with lower arterial distensibility and leptin levels have been positively co related with systolic and diastolic BP in both obese,[67,68] and non-obese individuals.[69,70]

Conclusions

A combination of local endothelial derived factors, sympathetic nervous system, changes in renal hemodynamics and endocrine secretions are responsible for the control of BP in normal human beings. Understanding the systems help us in understanding the pathophysiology behind the elevations in BP seen in primary and secondary hypertension.

References

1. Reddy KS. Cardiovascular disease in non-western countries. N Engl J Med 2004;350:2438–40.
2. Izzo JL Jr. The Sympathoadrenal system in the maintenance of elevated arterial pressure. J Cardiovasc Pharmacol 1984;6 Suppl 3:S514–21.
3. Izzo JL Jr. Sympathoadrenalactivity, catecholamines and the pathogenesis of vasculopathic hypertensive target-organ damage. Am J Hypertens 1989;2:305S-312S.
4. Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 1972;52:584–94.
5. Morimoto S, Sasaki S, Itoh H, Nakata T, Takeda K, Nakagawa M, *et al*. Sympathetic activation and contribution of genetic factors in hypertension with neurovascular compression of the rostral ventrolateral medulla. J Hypertens 1999;17:1577–82.
6. Laitinen T, Hartikainen J, Niskanen L, Geelen G, Länsimies E. Sympathovagal balance is major determinant of short term blood pressure variability in healthy subjects. Am J Physiol 1999;276:H1245-52.
7. Adamopoulos S, Rosano GM, Pomkowski P, Cerquetani E, Piepoli M, Panagiota F, *et al*. Impaired baroreflex sensitivity and sympathovagal balance in syndrome X. Am J Cardiol 1998;82:862-8.
8. Johnston CI. Franz Volhard lecture. Renin Angiotensin system: A dual tissue and hormonal system for cardiovascular control. J Hypertens Suppl 1992;10:S13–26.
9. Paul M, Stoll M, Kreutz R, Fernandez-Alfonso MS. The cellular basis of angiotensin converting enzyme mRNA expression in rat heart. Basic Res Cardiol 1996;91 Suppl 2:57-63.
10. Sarzani R, Salvi F, Dessi-Fulgheri P, Rappelli A. Renin–angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: An integrated view in humans. J Hypertens 2008;26:831-43.
11. Nguyen G. Renin and Prorenin Receptor in Hypertension: What's New? Curr Hypertens Rep 2011;13:79-85.
12. Zitnay C, Siragy HM. Actions of angiotensin receptor subtypes on the renal tubules and vasculature: Implications for volume homeostasis and atherosclerosis. Miner Electrolyte Metab 1998;24:362-70.
13. Siragy HM. AT_1 and AT_2 receptors in the kidney: Role in disease and treatment. Am J Kidney Dis 2000;36 (3 Suppl 1):S4-9.
14. Carson P, Giles T, Higginbotham M, Hollenberg N, Kannel W, Siragy HM. Angiotensin receptor blockers: Evidence for preserving target organs. Clin Cardiol 2001;24:183-90.
15. de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International Union of Pharmacology XXIII. The angiotensin II receptors. Pharmacol Rev 2000;52:415-72.
16. Zou Y, Komuro I, Yamazaki T, Kudoh S, Aikawa R, Zhu W, *et al*. Cell type–specific angiotensin II–evoked signal transduction pathways:

Critical roles of G–beta–gamma subunit, Src family and Ras in cardiac fibroblasts. Circ Res 1998;82:337-45.
17. Kang J, Posner P, Summers C. Angiotensin II type 2 receptor stimulation of neuronal K^+ currents involves an inhibitory GTP binding protein. Am J Physiol 1994;267:C1389-97.
18. Kaschina E, Unger T. Angiotensin AT_1/AT_2 receptors: Regulation, signaling and function. Blood Press 2003;12:70-88.
19. Carey RM, Siragy HM. Newly recognized components of the renin-angiotensin system: Potential roles in cardiovascular and renal regulation. Endocr Rev 2003;24:261-71.
20. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial amooth muscle by acetyl choline. Nature 1980;288:373-6.
21. Rubanyi GM, Romero JC, Vanhoutte PM. Flow–induced release of endothelium-derived relaxing factor. Am J Physiol 1986;250: H1145-9.
22. Anderson EA, Mark AL. Flow – mediated and reflex changes in large peripheral artery tone in humans. Circulation 1989;79:93-100.
23. Palmer RM, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 1988;333:664-6.
24. Luscher TF, Vanhoutte PM. Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. Hypertension 1986;8:344-8.
25. Diederich D, Yang ZH, Buhler FR, Lüscher TF. Impaired endothelium dependent relaxations in hypertensive resistance arteries involve cyclooxygenase pathway. Am J Physiol 1990;258:H445-51.
26. Kelm M, Feelisch M, Krebber T, Motz W, Strauer BE. The role of nitric oxide in the regulation of coronary vascular resistance in arterial hypertension: Comparison of normotensive and spontaneously hypertensive rats. J Cardiovasc Pharmacol 1992;20 Suppl 12:S183-6.
27. Nava E, Noll G, Luscher TF. Increased activity of constitutive nitric oxide synthase in cardiac endothelium in spontaneous hypertension. Circulation 1995;91:2310-3.
28. Dijkhorst-Oei LT, Stroes ES, Koomans HA, Rabelink TJ. Acute simultaneous stimulation of nitric oxide and oxygen radicals by angiotensin II in humans *in vivo*. J Cardiovasc Pharmacol 1999;33:420-4.
29. Hickey KA, Rubanyi G, Paul RJ, Highsmith RF. Characterization of a coronary vasoconstrictor produced by cultured endothelial cells. Am J Physiol 1985;248:C550-6.
30. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, *et al*. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411-5.
31. Emoto N, Yanagisawa M. Endothelin-converting enzyme-2 is a membrane-bound, phosphoramidon-sensitive metalloprotease with acidic pH optimum. J Biol Chem 1995;270:15262-8.
32. Clozel M, Clozel JP. Effects of endothelin on regional blood flows in squirrel monkeys. J Pharmacol Exp Ther 1989;250:1125-31.
33. Januszewicz A, Lapinski M, Symonides B, Dabrowska E, Kuch-Wocial A, Trzepla E, *et al*. Elevated endothelin-1 plasma concentration in patients with essential hypertension. J Cardiovasc Risk 1994;1:81-5.
34. Bragulat E, de la Sierra A, Antonio MT, Jimenez W, Urbano-Marquez A, Coca A. Effect of salt intake on endothelium-derived factors in a group of patients with essential hypertension. Clin Sci (Lond) 2001;101:73-8.
35. Hoffman A, Grossman E, Goldstein DS, Gill JR Jr, Keiser HR. Urinary excretion rate of endothelin-1 in patients with essential hypertension and salt sensitivity. Kidney Int 1994;45:556-60.
36. Dhaun N, Goddard J, Kohan DE, Pollock DM, Schiffrin EL, Webb DJ. Role of endothelin-1 in clinical hypertension: 20 years on. Hypertension 2008;52:452-9.
37. Iglarz M, Schiffrin EL. Role of endothelin-1 in hypertension. Curr Hypertens Rep 2003;5:144-8.
38. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981;28:89-94.
39. Suga S, Nakao K, Hosoda K, Mukoyama M, Ogawa Y, Shirakami G, *et al*. Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. Endocrinology 1992;130:229-39.
40. Luchner A, Schunkert H. Interactions between the sympathetic nervous system and the cardiac natriuretic peptide system. Cardiovasc Res 2004;63:443-9.
41. Nishikim T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, *et al*. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. Hypertension 1996;28:22-30.
42. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, *et al*. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202-8.
43. Molkentin JD. A friend within the heart: Natriuretic peptide receptor signaling. J Clin Invest 2003;111:1275-7.
44. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, *et al*. B type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392-7.
45. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, *et al*. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. JAMA 2004;291:1963-71.
46. Doggrell SA. Conivaptan Yamamouchi. Curr Opin Investig Drugs 2005;6:317-26.
47. Conivaptan: YM 087. Drugs RD 2004;5:94-7.
48. Russel SD, Selaru P, Pyne DA, Ghazzi MM, Massey KD, Pressler M, *et al*. Rationale for use of an exercise end point and design for the ADVANCE(A Dose evaluation of a Vasopressin ANtagonist in CHF patients undergoing Exercise) trial. Am Heart J 2003;145:179-86.
49. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, *et al*. Adrenomedulin: A novel hypotensive peptide isolated from human pheochromocytoma. Biochem Biophys Res Commun 1993;192:553-60.
50. Kitamura K, Ichiki Y, Tanaka M, Kawamoto M, Emura J, Sakakibara S, *et al*. Immunoreactive adrenomedullin in human plasma. FEBS Lett 1994;341:288-90.
51. Cheung B, Leung R. Elevated plasma levels of human adrenomedullin in cardiovascular, respiratory, hepatic and renal disorders. Clin Sci (Lond) 1997;92:59-62.
52. Hinson JP, Kapas S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. Endocr Rev 2000;21:138-67.
53. Maggi CA. The mammalian tachykinin receptors. Gen Pharmacol 1995;26:911-44.
54. Dockray GJ. Physiology of enteric neuropeptides. In: Johnson LR, editors. Physiology of the Gastrointestinal tract. New York: Raven Press; 1994. p. 169.
55. Yaksh TL, Bailey SB, Roddy DR. Peripheral release of substance P from primary afferents. In: Dubner R, Gebhart GF, Bond MR, editors. Proceedings of the Vth World Congress on Pain. Amsterdam: Elsevier; 1988. p. 51.
56. Asimakis GK, DiPette DJ, Conti VR, Holland OB, Zwischenberger JB. Hemodynamic action of calcitonin gene-related peptide in the isolated rat heart. Life Sci 1987;41:597-603.
57. DiPette DJ, Schwarzenberger K, Kerr N, Holland OB. Dose dependent systemic and regional hemodynamic effects of calcitonin gene related peptide. Am J Med Sci 1989;297:65-70.

58. Wimalawansa SJ. Calcitonin gene related peptide and its receptors: Molecular genetics, physiology, pathophysiology, and therapeutic potentials. Endocr Rev 1996;17:533-85.
59. Landmesser U, Drexier H. Effect of angiotensin II type 1 receptor antagonism on endothelial function: role of bradykinin and nitric oxide. J Hypertens Suppl 2006;24:S39-43.
60. Beetz N, Harrison MD, Brede M, Zong X, Urbanski MJ, Sietmann A, *et al*. Phosducin influences sympathetic activity and prevents stress-induced hypertension in humans and mice. J Clin Invest 2009;119:3597-612.
61. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord 1998;22:1145-58.
62. Frühbeck G. Pivotal role of nitric oxide in the control of blood pressure after leptin administration. Diabetes 1999;48:903-8.
63. Wagner EM. TNF-α induced bronchial vasoconstriction. Am J Physiol Heart Circ Physiol 2000;279:H946-51.
64. Antoniades C, Antonopoulos AS, Tousoulis D, Stefanadis C. Adiponectin: From obesity to cardiovascular disease. Obes Rev 2009;10:269-79.
65. Shargorodsky M, Boaz M, Goldberg Y, Matas Z, Gavish D, Fux A, Wolfson N. Adiponectin and vascular properties in obese patients: Is it a novel biomarker of early atherosclerosis? Int J Obes (Lond) 2009;33:553-8.
66. Flanagan DE, Vaile JC, Petley GW, Phillips DI, Godsland IF, Owens P, *et al*. Gender differences in the relationship between leptin, insulin resistance and the autonomic nervous syste. Regul Pept 2007;140: 37-42.
67. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. Hypertension 1998;31:409-14.
68. Aizawa-Abe M, Ogawa Y, Masuzaki H, Ebihara K, Satoh N, Iwai H, *et al*. Pathophysiological role of leptin in obesity-related hypertension. J Clin Invest 2000;105:1243-52.
69. Kunz I, Schorr U, Klaus S, Sharma AM. Resting metabolic rate and substrate use in obesity hypertension. Hypertension 2000;36:26-32.
70. Golan E, Tal B, Dror Y, Korzets Z, Vered Y, Weiss E, *et al*. Reduction in resting metabolic rate and ratio of plasma leptin to urinary nitric oxide: influence on obesity related hypertension. Isr Med Assoc J 2002;4:426-30.
71. Izzo JL Jr. The Sympathetic Nervous System in Acute and Chronic blood pressure elevation. In: Oparil S and Webber AM, editors. Hypertension: Companion to Brenner and Rector's The Kidney. 2nd ed. Saunders: Elsevier; 2005. p. 60-76.

Cite this article as: Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. Indian J Endocr Metab 2011;15:281-8.

Source of Support: Nil, **Conflict of Interest:** None declared.