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Control and Regulation of Blood Pressure: Physiological Basis of Preventive and Therapeutic Interventions

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Abstract

The paper presents a review of recent theories involving the physiological control and regulation of blood pressure (BP). Specifically, the role of sympathetic efferents of autonomic nervous system, their central and peripheral control; renin-angiotensin-aldosterone system, vascular smooth muscle voltage-gated calcium channels, endothelialy-derived vasoregulatory substances like nitric oxide, bradykinin and endothelin; neurohumoral mechanisms exerted by vasopressin, adrenaline, noradrenaline, atrial natriuretic peptides; and locally derived homeostatic autoregulary molecules are discussed in the short-term and long-term regulation of BP. Based on the physiological regulation of BP, the pathophysiology of development of primary and secondary hypertension is discussed specially to provide rational basis for the use of various nonpharmacological preventive and pharmacological therapeutic interventions.

Key Words : Hypertension, blood pressure, autonomic control of BP, renin-angiotensin-aldosterone system, endothelialy-derived vasoregulatory substances, preventive interventions for BP, therapeutic interventions for BP

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Introduction

Hypertension is a common disease that is defined simply as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be necessary for adequate perfusion of essential organs during the early and middle 1900s, it is now identified as one of the most significant risk factors for cardiovascular morbidity and mortality worldwide (1). The risk of cardiovascular complication is as increased as BP is high and as reduced as BP is low; the risk is a continuing function of BP. Hypertension was the first quantifiable condition, identified in surveys on mortality by an American insurance company, that showed a statistical relation between the initial BP and the subsequent risk of cerebral stroke, cardiac failure, and myocardial infarction. In the 40- to 69-year old age group, a 20 mm Hg increase in systolic BP or a 10 mm Hg increase in diastolic BP is associated with more than double the risk of mortality from stroke and double the risk of mortality from myocardial infarction or other cardiovascular complications (e.g. cardiac failure, aneurysms) (2). A development of great importance to world health has been the demonstration that many of the major complications associated with hypertension are preventable by life-style modification and antihypertensive drug treatment (3). Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical public health initiatives to reduce cardiovascular morbidity and mortality.

Physiological Control and Regulation Of Blood Pressure

Arterial BP is generated hemodynamically by the interplay between blood flow and the resistance to blood flow. As per Poiseuille's law related to hydraulic equation, it is defined mathematically as the product of cardiac output (CO) and total peripheral vascular resistance (TPVR): BP = CO x TPVR. CO is the major determinant of systolic BP (SBP), whereas TPVR largely determines diastolic BP (DBP). In turn, CO is a function of stroke volume, heart rate, and venous capacitance. Both CO and TPVR are controlled by the autonomic nervous system (ANS). BP fluctuates substantially with behaviour, but 24-h average BP is tightly regulated. Physiologically, in both normal and

hypertensive individuals, BP is maintained by moment-to-moment regulation of CO and TPVR exerted at three anatomic sites: arterioles, postcapillar venules (capacitance vessels), and heart. A fourth anatomic control site, the kidney, also contributes to mainte-nance of BP by regulating the volume of intravascular fluid. The CO is dependent on three regulated variables: end-diastolic volume, myocardial contractility, and heart rate. End-diastolic volume is the volume reached by the ventricular chamber before contraction and is determined by venous pressure, which is related to blood volume and venous smooth muscle tone, both of which are under sympathetic control (4). Myocardial contractility and heart rate are regulated by both the sympathetic and parasympathetic divisions of the ANS. In contrast, because blood vessels are not innervated by parasympathetic fibres, the para-sympathetic nervous system has little influence on vascular tone.

The neural control of BP operates via parasympathetic neurons that innervate the heart and via three main classes of sympathetic cardiovascular efferents – barosensitive, thermosen-sitive and glucosensitive that inner-vate blood vessels, the heart, the kidneys and the adrenal medulla. The barosensitive sympathetic efferents are under the control of arterial baroreceptors. This large group of efferents plays a dominant role in both short-term and long-term BP regulation. Their level of activity at rest is presumed to be the most crucial parameter for long-term BP control. This background activity is set by a core network of neurons that reside in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus and the nucleus of the tractus solitarius (NTS) (5, 6). Limbic, cortical and midbrain structures are responsible for rapid changes in sympathetic tone that relate to behaviour. It is generally assumed that these changes are not pertinent to the long-term regulation of BP, except in the context of stress-related hyper-tension. The BP is maintained within fairly narrows limits by a series of physiological reflexes that respond to both acute and chronic changes in BP. The two most important regulatory systems which control BP are:

1. The sympathetic nervous system
2. The renin-angiotensin-aldoste-rone system

Role of Sympathetic Nervous System in Regulation of BP

Cardiovascular sympathetic efferents can be broadly classified into three groups according to their dominant characteristics, the thermosensitivity; glucosensitivity; or barosensitivity (7-9). The thermosensitive group of cardiovascular efferents consists primarily of cutaneous vasdoconstrictors that are activated by hypothermia, emotional stimuli and hyperventilation (8, 10). The glucosensitive group controls adrenaline release from the adrenal medulla and is activated by hypoglycemia and physical exercise (11). These two types of cardiovascular efferent are only weakly, if at all, regulated by arterial baroreceptors, and presumably have a secondary role in short- and long-term BP stability. The third class, the barosensitive group of cardiovascular sympathetic efferents, irrespective of organ or tissue that they innervate, show ongoing activity at rest (sympathetic tone). They discharge bursts that are highly synchronized with the arterial pulse and respiration (10, 12, 13). Barosensitive sympathetic efferents control the heart and the kidneys, the release of noradrenaline from a subset of adrenal chromaffin cells, and constrict resistance arterioles, with the exception of those in the skin (8). Barosensitive efferents are responsible for short-term BP fluctuations (8, 14). They are also likely to be a key determinant of the long-term neural control of BP, in part because renin secretion, renal tubular sodium reabsorption and renal blood flow are apparently all under the control of this type of sympathetic efferent (12).

Barosensitive efferents are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to upright posture. Central sympathetic neurons arising from the vasomotor area of the medulla are tonically active. Carotid baroreceptors are stimulated by the stretch of the vessel walls brought about by the internal pressure (arterial BP). A sudden change in systemic BP is detected by baroreceptors in the aorta and carotid arteries. Afferent impulses from baroreceptors are integrated in the vasomotor centres of the sympathetic nervous system (Fig. 1). A rise in BP increases the input of impulses from the baroreceptors to the

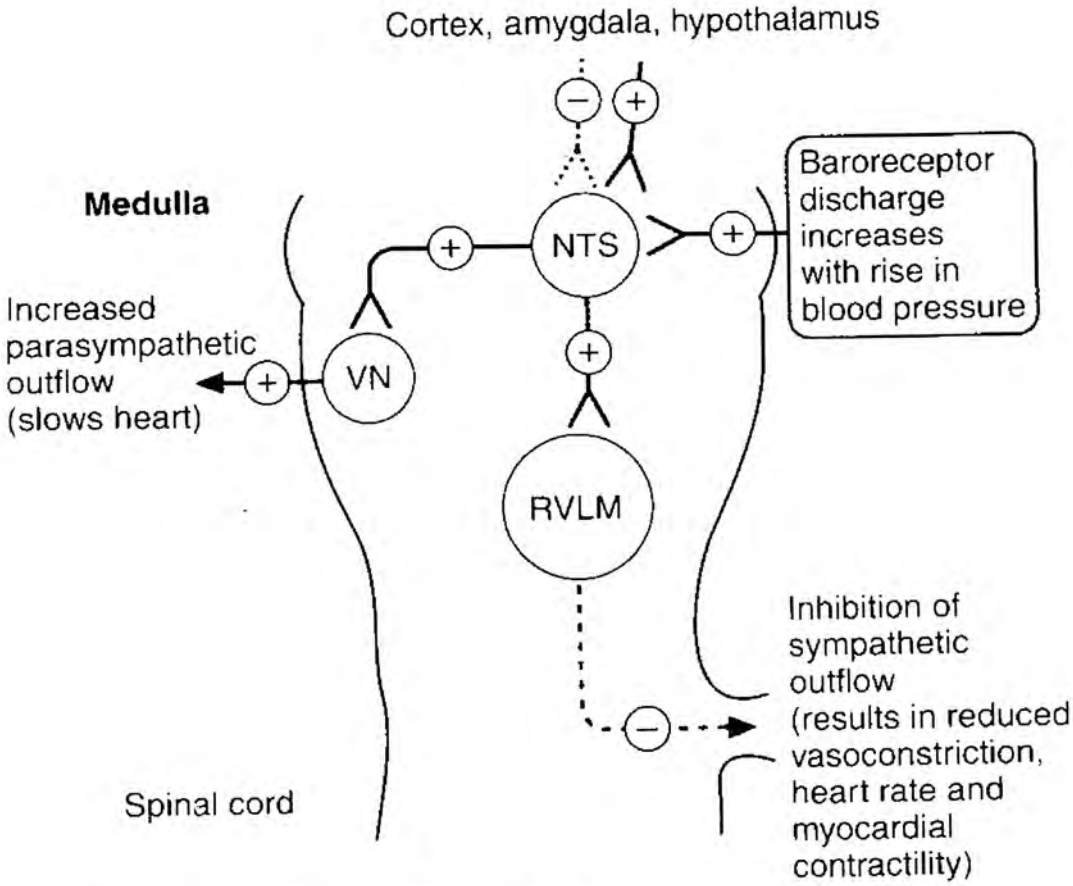

Figure 1. Physiological Control and Regulation of Blood Pressure
NTS, nucleus of the tractus solitarius; VN, vagal nucleus (cardioinhibitory centre); RVLM, rostral ventrolateral medulla, +, stimulation; –, inhibition.

vasomotor centres, resulting in decreased output from the centre and compensatory decrease in the efferent response of sympathetic nervous stimulation. Conversely, a reduction in stretch due to fall in BP results in a reduction in baroreceptors activity. Thus, in the case of a transition to upright posture, baroreceptors sense the reduction in arterial pressure that results from pooling of the blood in the veins below the level of the heart as reduced wall stretch, and sympathetic discharge is disinhibited. The reflex increase in sympathetic outflow acts through nerve endings to

increase peripheral vascular resistance (constriction of arterioles) and cardiac output (direct stimulation of the heart and constriction of capacitance vessels, which increases venous return to the heart), thereby restoring normal BP. The same baroreflex acts in response to any event that lowers arterial pressure, including a primary reduction in peripheral vascular resistance (e.g., caused by vasodilating agent) or a reduction in intravascular volume (e.g., due to hemorrhage or to loss of salt and water via the kidney).

Sympathetic efferents to the heart act mainly through beta-1 adrenoceptors to increase myocardial contractility and heart rate, generating a greater cardiac output. Efferents to arterial resistance vessels stimulate postsynaptic alpha-1 adrenoceptors, producing arteriolar vasoconstriction. This raises blood pressure and redistributes blood flow to specific vascular beds to maintain perfusion of vital organs (15). This redistribution is helped by beta-2 adrenoceptor-mediated vasodilation in selected vascular beds, such as skeletal muscle. Arterial vasoconstriction produces an increase in afterload on the heart but cardiac output is maintained by an increase in cardiac contractility. Stimulation of postsynaptic venous alpha-1 adrenoceptors constricts venous capacitance vessels. This increases venous return to the heart preload) improves cardiac output. If ventricular function is impaired cardiac output may fall (15).

2. Role of Renin-angiotensin-Aldosterone System in Regulation of BP

The sympathetic baroreflex mechanism is a feedback loop, the afferent limb of which involves mechanoreceptors that are activated by distention of the arterial wall (14). An increase in BP activates baroreceptors, thereby causing inhibition of cardiac, renal and vasomotor sympathetic efferents, which, in turn, leads to restoration of BP. The best known function of this reflex, together with its cardiovagal counterpart, is to dampen short-term BP fluctuations (14, 16, 17). However this reflex is also actively reset to allow BP to rise appropriately during certain behaviours such that the operating range is increased to higher BP levels without reduction in reflex sensitivity. Baroreflex resetting involves both neural and humoral mechanisms.

Role of Renin-Angiotensin-Aldesterone System (RAAS) in the Regulation of BP

A slower compensatory mechanism to overcome reduction in blood pressure is initiated by the release of renin from the juxtaglomerular apparatus of the kidney (Fig. 2). The major stimuli leading to renin release are reduced renal blood flow (often as a result of a decrease in blood pressure), decreased luminal Na^+ delivery or excess Na^+ in the distal renal tubule and direct sympathetic stimulation via beta-1 adrenoceptors at the juxtaglomerular apparatus.

Renin is a protease that acts on circulating renin substrate, the circularing 14-amino acid hepatic prohormone angiotensinogen to release the decapeptide angiotensin I. This in turn is cleaved by the carboxypeptidase, angiotensin-converting enzyme (ACE) located on the endothelial cell surface to release the octapeptide, angiotensin II. Angiotensin II has at least four physiological actions: (i) Stimulation of

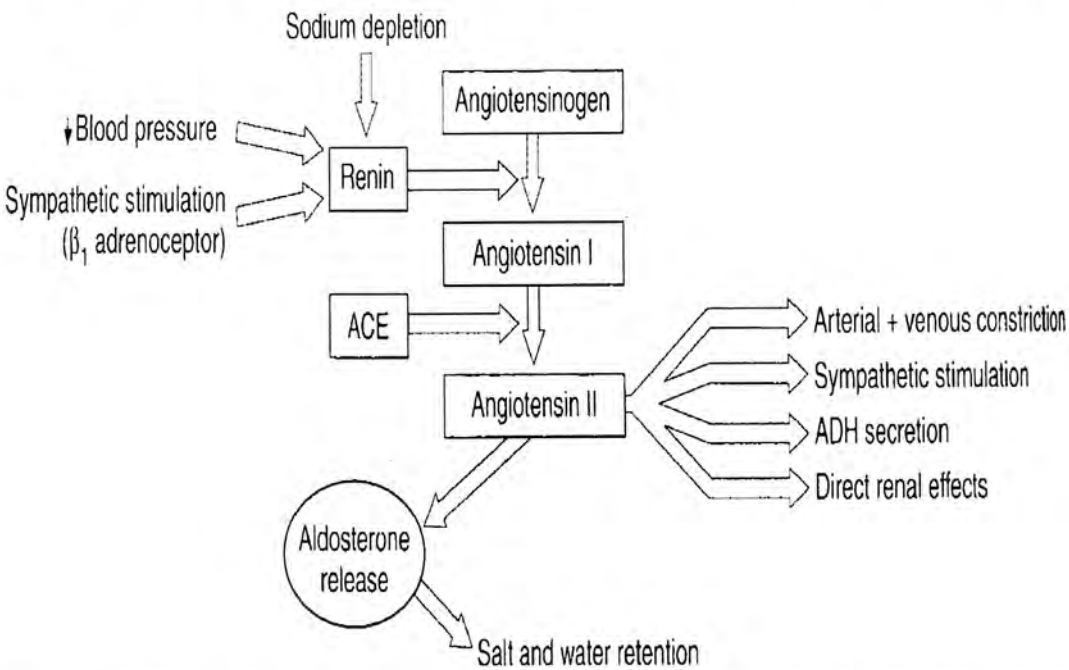

Figure 2. Role of rennin-angiotensin-aldosterone system in regulation of BP
ADH, antidiuretic hormone; ACE, angiotensin-converting enzyme.

aldosterone secretion by zona glomerulosa cells of the adrenal glands; (ii) increased reabsorption of NaCl at the proximal tubule and other nephron segments; (iii) Stimulation of thirst and ADH secretion; and (iv) arteriolar vasoconstriction, as a result of direct potent vasoconstriction and enhanced sympathetic nervous tone by an effect on presynaptic neurons. All of these effects are mediated by its action on type 1 Angiotensin II receptors (AT_1 receptors). By promoting the release of aldosterone, it acts on distal renal tubule to conserve salt and water at the expense of K^+ loss. Thus angiotensin II and aldosterone raise blood pressure by vasoconstriction and by increasing circulating blood volume (18, 19).

The integration of the sympathetic nervous system and renin-angiotensin-aldosterone responses to a fall in blood pressure is shown in Fig. 3. These mechanisms prevent hypotension due to peripheral pooling of blood on standing and during exercise.

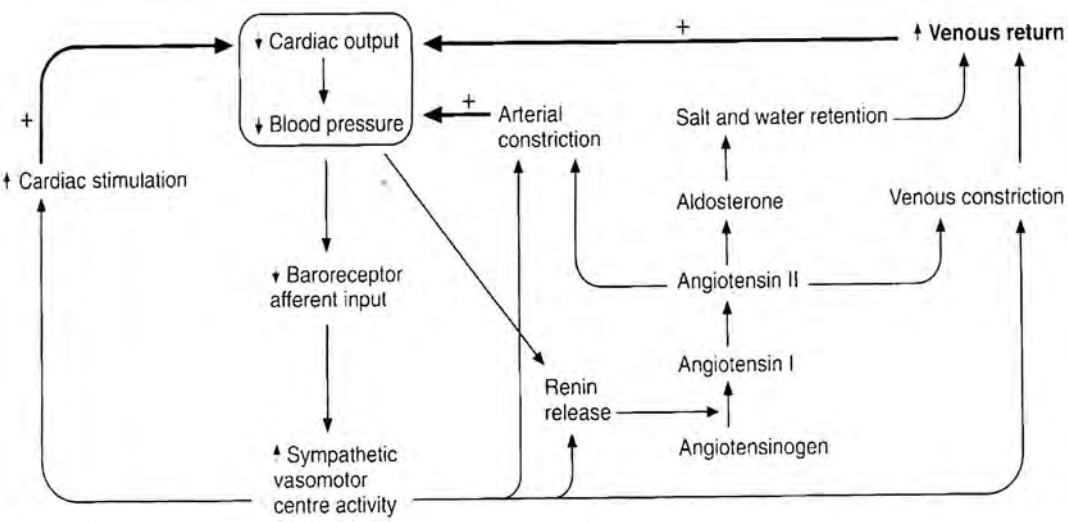

Figure 3. The control of blood pressure via the integration of sympathetic and renion-angiotensin-aldosteron system (RAAS). The sympathetic mediated responses on the left of the Fig. are rapidly responding events, whereas the RAAS events are more slowly responding. The final outcome are increased venous return, increased arterial constriction and increased cardiac output.

Additional Control Mechanism Involved In the Regulation of Vascular Volume And BP

A number of recent studies have shown that besides ANS and RAAS, there are some other control mechanism involved in the regulation of vascular tone and circulating blood volume, which include circulating or local hormones and metabolites such as atrial natriuretic peptide, prostaglandins, kinins, nitric oxide, endothelin, adenosine, etc. Their relative importance may differ in health and disease states. In addition, the vascular tone is also maintained by actin-myosin contractile apparatus of vascular smooth muscle cells which can be influenced not only by the circulating and local hormones as mentioned above but also by voltage-gated Ca^{2+} channels in the sarcolemma (20, 21).

Vascular Smooth Muscle Voltage-gated Calcium Channels

Like any other muscle, various regulators of vascular tone act by influencing actin-myosin contractile apparatus of vascular smooth muscle cells. This actin-myosin interaction leads to contraction and is regulated by the intracellular calcium (Ca^{2+}) concentration. A steep transmembrane gradient of Ca^{2+} concentration is maintained by the relative impermeability of the plasma membrane to Ca^{2+} ions and by membrane pumps that actively remove Ca^{2+} from the cytoplasm. Stimulation of vascular smooth muscle cells can increase the cytoplasmic Ca^{2+} concentration by two mechanisms. Firstly, Ca^{2+} can enter the cells by way of voltage-gated L-type calcium channels (VGCC) in the sarcolemma (22). Secondly, an increase in cytopalasmic Ca^{2+} can be released by intracellular Ca^{2+} from the sarcoplasmic reticulum. Constriction in the vascular smooth muscles is commonly initiated by the opening of VGCC in the sarcolemma during plasma membrane depolarization. The open Ca^{2+} channels mediate Ca^{2+} fluxes into the cytoplasm and activation of cytoplasmic protein, calmodulin (CaM) leading to the formation of Ca^{2+}-CaM complex which binds and activates myosin light chain kinase, which phospholyrates myosin-II light chains. When the light chain is phosphorylated the myosin head can slide over the active filament leading to smooth muscular contraction.

In contrast, relaxation of vascular smooth muscles occurs upon dephos-

phorylation of the myosin like chain. The process of dephosphorylation is potentiated with glutylyl cyclase is activated inside the smooth muscle cells. Activated guanylyl cyclase increases the production of cyclic guanosine 3',5'-monophosphate (cGMP). In turn the cGMP stimulates cGMP-dependent protein kinase, which then activates myosin light chain phosphatase. Dephosphorylation of the myosin light chain inhibits the sliding interaction of myosin head with actin, leading to smooth muscle relaxation (23).

Substances Elaborated in the Vascular Endothelium

Research in the past two decades has revealed several signaling molecules in the vascular endothelium to control vascular tone. Endothelial cells elaborate many signaling mediators and alter the expression of many genes in response to diverse stimuli (Fig. 4). Two of the most pharmacologically important signaling molecules which have been well defined in the recent past are nitric oxide and endothelin (24, 25).

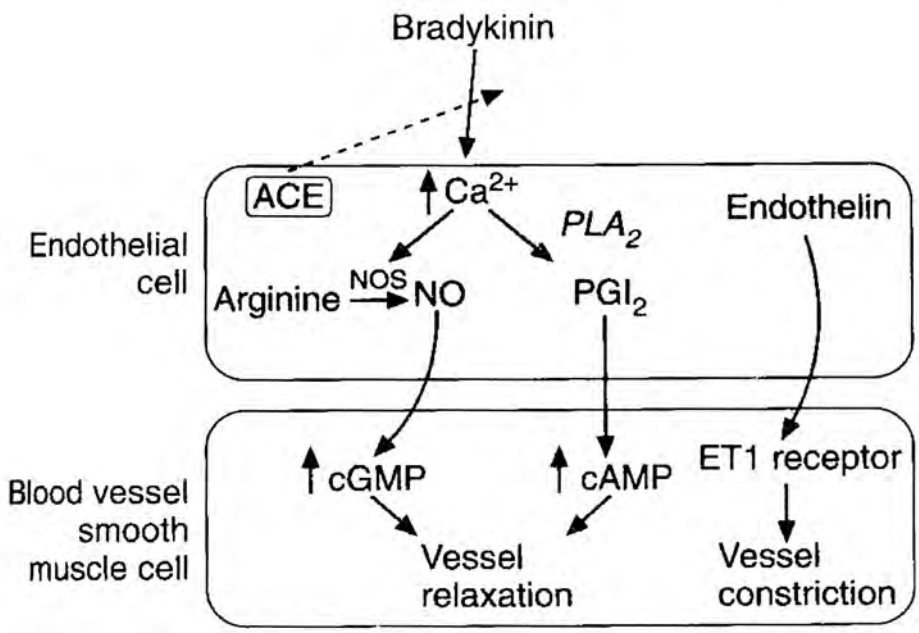

Figure 4. The endothelialy derived vasoactive substances involved in regulation of BP

Nitric oxide

The permissive role of endothelial cells in regulating vascular tone was first recognized with the observation that acetylcholine causes vasoconstriction when applied directly to de-endothelialized blood vessels, but causes vasodilatation when applied to normally endothelialized vessels (24). It was postulated that muscarinic cholinergic stimulation of the endothelium produces a relaxant molecule in the endothelial cell which diffuses to subjacent vascular smooth muscle cells to activate gunylyl cyclase. This vasodilatory compound was termed endothelial-derived relaxing factor (EDRF). Later EDRF was identified as nitric oxide (NO). Although acetylcholine was the first ligand to be identified that promotes NO synthesis in endothelial-cells, later on a number of other mediators which could do so were described. Shear stress, histamine, bradykinin, serotonin, substance P, ATP and sphingosine 1-phosphate can all produce increased NO synthesis by vascular endothelial cells. NO is synthesized by a family of Ca^{2+}-CaM-activated NO synthases (NOS). Endothelial NOS (eNOS) is responsible for endothelial-cell NO synthesis. This enzyme plays a critical role in controlling vascular tone and platelet aggregation. The importance of No in regulating vascular tone is underscored by the observation that eNOS-deficient mice are hypertensive.

Recent evidence suggest that NO may effect vasodilatation not only by activating guanylyl cyclase, but also by activating Ca^{2+}-dependent K^+ channels in vascular smooth muscle cells. NO appears to activate these K^+ channels directly via a guanylyl cyclase-independent mechanism leading to hyperpolarization of the cells and subsequently, to vasodilatation.

Endothelin

Endothelin, a 21-amino acid vasoconstrictor peptide is a potent endothelium-derived vasoconstrictor (25). This peptide is considered a functional 'mirror-image' of NO as the latter is a potent endothelium-derived vasodilator. Besides its effect on vasculature, endothelin has positive inotropic and chronotropic actions on the heart and also contributes to remodeling within the cardiovascular system. Proposed mechanisms of endothelin-induced remodeling include neointimal proliferation and increased collagen deposition leading to fibrosis. Three isoforms of endothelin ET-1, ET-2 and ET-3 have been identified. The ET-1 produced by endothelial cells

(and vascular smooth muscle cells under inflammatory conditions) is mainly involved in cardiovascular actions – acting locally in a paracrine or autocrine fashion. Local ET-1 concentration within the vascular wall is more than 100 times greater than that in the circulation, because it is secreted mainly on the basal side of endothelial cells. Endothelins are known to act through to endothelin receptor subtypes, ET_A and ET_B. Both receptors are G protein-coupled receptors, whose effectors likely involve phospholipase C-mediated pathways. ET_A receptors on vascular smooth muscle cells mediate vasoconstriction, whereas ET_B receptors are located predominantly on vascular endothelial cells, where they mediate vasodilatation via the release of prostacyclin and NO. ET_B receptors are also found on vascular smooth muscle cells, where they mediate vasoconstriction. Thus, endothelins produce vasoconstriction by acting through both ET_A and ET_B receptors in the vascular smooth muscles and vasodilatation by acting through ET_B receptor in the endothelium.

Neurohormonal Mechanisms

Besides the angiotensin II as described above, circulating catecholamines from the adrenal gland (adrenaline and noradrinaline) can influence vascular tone via alpha-1 and beta-2 adrenergic receptors on vascular smooth muscle cells. In addition vasopressin or antidiuretic hormone (ADH) secreted in response to angiotensin II affects the vascular tone by acting on its 3V types of receptors. V_{1a} receptors mediate the vasoconstrictor action of ADH; V_{1b} potentiate the release of ACTH by pituitary corticotropic cells; and V_2 receptors mediate the further release of ADH to increase intravascular volume. All these actions of ADH play a minor role regulating the BP in certain situations (26).

Homeostatic Autoregulatory Mechanisms

A number of locally controlled mechanisms also modulate vascular tone. These homeostatic autoregulatory mechanisms in vascular smooth muscle respond to increases or decreases in perfusion pressure by vasoconstriction or vasodilation, respectively to preserve blood flow at a constant level. (Blood Flow = Perfusion Pressure/Resistance). Vascular tone, and thus blood flow, is governed by metabolites – such as H^+, CO_2, O_2, adenosine, lactate and K^+ – produced in surrounding tissue. Local mechanisms of vascular tone regula-

tion predominate in the vascular beds of essential organs (e.g. heart, brain, lung, and kidney), so that blood flow, and thus O_2 supply, can be adjusted quickly to meet the demand of local metabolism in these organs (27).

Role of Natriuretic Peptides in Regulating Blood Pressure

Tho atria and other tissues of mammals contain a family of peptides with natriuretic, diuretic, vasorelaxant and other properties (28). This family of peptides consist of atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptide (CNP). ANP, a 28-amino acid peptide is synthesized primarily in cardiac atrial cells, but small amounts are also synthesized in ventricular cells. It is also synthesized by neurons in the central and peripheral nervous systems and in the lungs. Several factors which increase the release of ANP from the heart are - atrial stretch via mechanosensitive ion channels, blood volume expansion, head-out water emersion, changing from standing to supine position and exercise (28). ANP release can also be increased by sympathetic stimulation via alpha-1a adrenergic receptors, endothelins via ET_A receptor subtype, glucorticoids, and vasopressin. A rise in plasma ANP is also seen in various pathological states, like heart failure, primary aldosteronism, chronic renal failure and inappropriate ADH secretion syndrome. As described above ANP produces marked increases in sodium excretion and urine flow. The ANP-induced natriuresis is apparently due to both the increase in the glomerular filtration and decrease in proximal tubular sodium reabsorption. Several effects of ANP also decreases arterial BP. Besides its action on kidney, a number of other effects which contribute to its hypotensive actions are: (i) inhibition of the secretion of renin, aldosterone and vasopressin (which all increase sodium and water excretion), (ii) decrease in sympathetic tone to the peripheral vasculature and antagonism of vasoconstrictor action of angiotensin II and other vasoconstrictors, and (iii) a direct vasodilatory action resulting from stimulation of guanylyl cyclase activity leading to increased cGMP and decrease cytosolic Ca^{2+}concentration. There is considerable evidence that ANP participates in the physiological regulation of sodium excretion and blood pressure, e.g. suppression of ANP production or blockade of its action impairs the natriuretic response to volume expansion, and increases blood pressure (28).

Patho-Physiological Mechanisms in the Development of Hypertension

Hypertension is a heterogeneous medical condition. In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). Some of the suggested mechanisms for the development of essential hypertension have been elaborated in Table 1. While this form of hypertension cannot be cured, it can be controlled.

Table 1. Patho-physiological Mechanisms in the Development of Hypertension

Blood pressure is the mathematical product of cardiac output and peripheral resistance. Increased BP can result form increased cardiac output and/or increased total peripheral resistance.	
Increased cardiac output	Increased cardiac preload: • Increased fluid volume for excess sodium intake or renal sodium retention (from reduced number of nephrons or decreased glomerular filtration) Venous constriction: • Excess stimulation of the RAAS • Sympathetic nervous system over activity
Increased peripheral resistance	Functional vascular constriction: • Excess stimulation of the RAAS • Sympathetic nervous system over activity • Genetic alterations of cell membranes • Endothelial-derived factors Structural vascular hypertrophy: • Excess stimulation of the RAAS • Sympathetic nervous system over activity • Genetic alterations of cell membranes Endothelial-derived factors Hyperinsulinemia resulting from obesity or the metabolic syndrome

Essential Hypertension

Over 90% of individuals with hypertension have essential hypertension (primary hypertension) (29). Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. Hypertension often runs in families, indicating that genetic factors may play an important role in the development of essential hypertension (30). Data suggest that there are monogenic and polygenic forms of BP dysregulation that may be responsible for essential hypertension. (31, 32). Many of these genetic traits feature genes that affect sodium balance (32), but genetic mutations altering urinary kallikrein excretion, nitric oxide release, aldosterone excretion, other adrenal steroids, and angiotensinogen are also documented (31). In the future, identifying individuals with these genetic traits could lead to alternative approaches to preventing or treating hypertension.

Insulin resistance and hyperinsulinaemia as a cause of primary hypertension

In some patients evidence has linked insulin resistance and hyperinsulinaemia with the development of essential hypertension, sometimes referred to as the metabolic syndrome (33). Hypothetically, increased insulin concentrations may lead to hypertension because of increased renal sodium retention and enhanced sympathetic nervous system activity. Moreover, insulin has growth hormone-like actions that can induce hypertrophy of vascular smooth muscle cells. Insulin also may elevate BP by increasing intracellular calcium, which leads to increased vascular resistance. The exact mechanism by which insulin resistance and hyperinsulineamia occur in hypertension is unknown. It has been suggested that insulin resistance may be the consequence of chronic sympathetic activation. Sympathetic activation generates vasoconstriction an, secondarily, a thickening of arterioles, which lead to less smooth muscle perfusion. Consequently, muscle use of glucose is reduced because fast-contracting fibres become less sensitive to insulin due to beta-adrenergic hyperactivity. The pancreas responds by acute secretion of insulin. Sympathetic activation observed in the obese patient could, in certain cases result from a cerebral action of leptin, secreted in excess by adipocytes (34).

Secondary Hypertension

Fewer than 10% of patients have a specific cause of their hypertension, termed as secondary hypertension where either a comorbid disease or a drug is responsible for elevating BP (Table 2). In most cases renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause (35). Table 2 describes some of the prescription drugs and potential secondary causes that are either

Table 2. Secondary Causes of Hypertension

Disease	Drugs and food substances associated with hypertension in humans
Chronic kidney disease Cushing's syndrome Coarctation of the aorta Obstructive sleep apnea Parathyroid disease Pheochromocytoma Primary aldosteronism Renovascular disease Thyroid disease	**Prescription drugs** Corticosteroids; Estrogens (oral contraceptives with high estrogenic activity); NSAIDs, COX-2 inhibitors; Phenylpropanolamine and analogues; Cyclosporine and tacrolimus; Erythropoetin; Sibutramine; Antidepressants (especially fluoxetine, venlafaxine); bromocriptine; buspirone; carbamazepine; clozapine; desfulrane; ketamine, metoclopramide; Clonidine/beta-blocker combination, Pheochromocytoma: beta-blocker with alpha-blocker first **Street drugs and other natural products** Cocaine and cocaine withdrawal; Ma huang (herbal ecstasy); Nicotine and withdrawal; Anabolic steroids, Narcotic withdrawal, Methylphenidate, Phencyclidine, Ketamine, Ergotamine and other ergot-containing herbal products, St. John's wort. **Food substances** Sodium, Ethanol, Tyramine-containing foods if taken with a monoamine oxidase inhibitor, Licorice **Chemical elements and other industrial chemcials** Cadmium, Lead, Lithium, Mercury, Thallium

concurrent medical conditions or are endogenously induced diseases. If the cause of the secondary hypertension can be identified, hypertension in these patients potentially can be cured.

Antihypertensive Drugs

Principal classes of antihypertensive drugs and their sites of action is given in Table 3 and Figure 4.

Table 3. Principal classes of antihypertensive drugs and their sites of action

Site of action	Drug class	Drugs
Sympathetic nervous system	β-Adrenoceptor antagonists (β-blockers)	Atenolol, Propranolol, Pindolol
	α_1-adrenoceptor antagonists (α_1-blockers)	Prazosin, Doxazosin
	Selective imidazoline receptor agonists	Moxonidine
	Centrally acting α_2-adrenoceptor agonists	Methyldopa, Clonidine
Blockers of Rennin-Angiotensin-Aldosterone System (RAAS)	Antiotensin-converting enzyme (ACE) inhibitors	Captopril, Enalapril, Rampril, Lisinopril, Perindopril
	Angiotensin II receptor antagonists	Losartan, Candesartan
Vasodilatation by other mechanisms	Diuretics	Hydrochlorothiazides, Chlorthalidone, Bendrofluazide, Indepamide, Furosemide, Bumetinide
	Calcium channel antagonists	Amlodepine, Nifedipine, Diltiazem, Verapamil
	Potassium channel activators	Minoxidil, Cromakalim, Penacidil, Nicorandil
	Nitrovasodilators	Nitroprusside
	Endothelin antagonists	Bosantan, Sitaxentan, Ambrisentan, Tezosentan, Phosphoramidon (ECE-I)

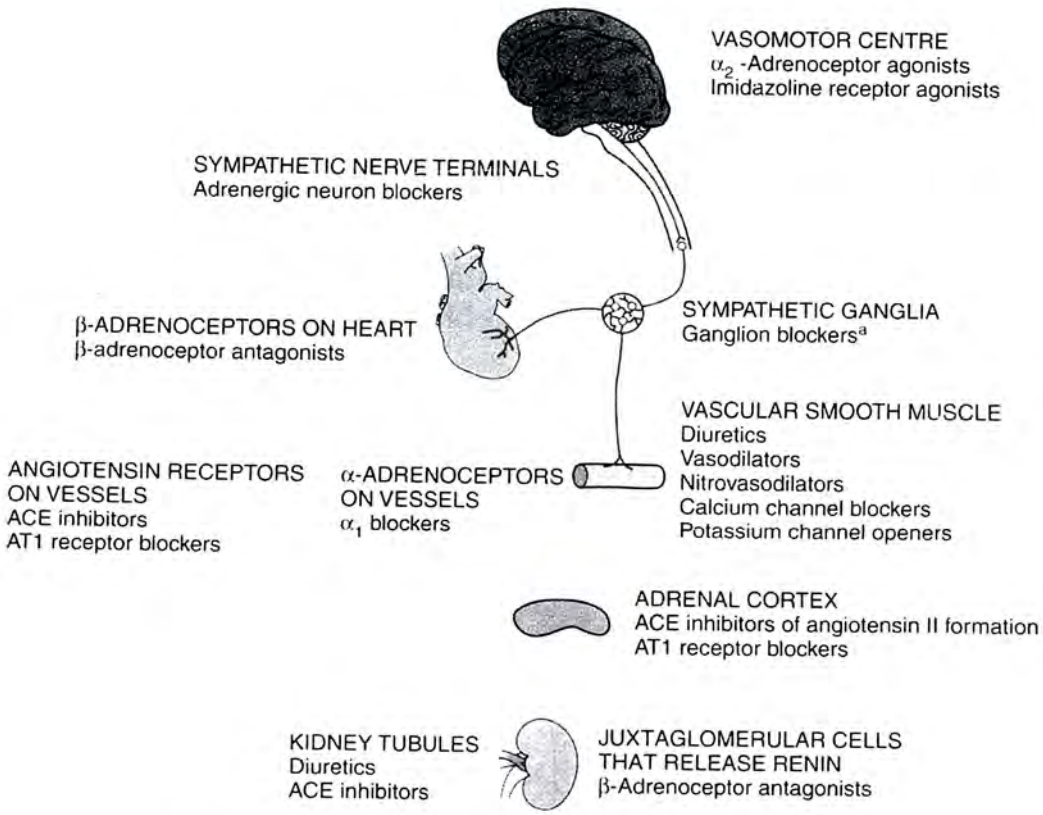

Figure 5. Principal classes of antihypertensive drugs and their sites of action

Drugs Acting on Sympathetic nervous system

β-Adrenoceptor antagonists (β-blockers)

Mechanism of action

- Reduction of heart rate and myocardial contractility, which decrease cardiac output
- Blockade of renal juxtaglomerular beta-1-adrenoceptors, which reduces renin secretion
- Peripheral vasodilatation, produced by compounds with beta-2-adrenoceptor partial agonist activity, e.g. pindolol
- Blockade of presynaptic beta-adrenoceptors in sympathetic nerves supplying arteriolar resistance vessels may reduce the outflow of noradrenaline but the importance of this is clinically uncertain.

- Decrease in central sympathetic flow to periphery by blocking beta-receptors in brain

Alpha-1-adrenoceptor antagonists (α_1-blockers)

Mechanism of action: Blockade of postsynaptic alpha-1-adrenoceptors lowers blood pressure by:

- Reduced tone in arteriolar resistance vessels
- Dilating venous capacitance vessels, which reduces venous return and, therefore, cardiac output
- The fall in BP is detected by arterial baroreceptors, which initiate reflex sympathetic stimulation.
- Selective alpha-1-adrenoceptor antagonists do not block the inhibitory presynaptic alpha-2-adrenoceptors on sympathetic nerve terminals.

Selective imidazoline receptor agonists

Mechanism of action

- Imidazoline I-2 receptors are concentrated in the RVLM, a part of the brain stem for centre are important for sympathetic drive
- Increased neuronal activity in this area, either through baroreceptors stimulation or by direct stimulation of I-1 receptors, will decrease sympathetic outflow and increase vagal tone.
- This results in reduction in BP with no reflex tachycardia

Centrally acting α_2-adrenoceptor agonists

Mechanism of Action:

- The alpha-2-agonists reduce central sympathetic nervous outflow from the medullary vasomotor centre which reduces both arterial and venous tone (TPVR).
- Methyldopa by its conversion to methylnoradrenaline and clonidine directly stimulate central presynpatic alpha-2-adrenoceptor which inhibit neurotransmitter release by negative feedback.
- Clonidine also acts on imidazoline I-1 receptors. In high doses it also has peripheral postsynaptic alpha-1-adrenoceptor agonist activity, which produces direct peripheral vasoconstriction; this initially may offset some of the BP lowering effect.

Blockers of Renin-Angiotensin-Aldosterone System (RAAS)

Antiotensin-converting enzyme (ACE) inhibitors

Mechanism of Action: The ACE inhibitors act by several mechanisms

- Competitive inhibition of ACE reduces generation of angiotensin II and consequently reduces the release of adosterone. Inhibition of tissue ACE in vascular wall (rather than plasma ACE) is most important for the hypotensive effect of these drugs. Reduced tissue concentrations of he angiotensin II leads to arterial and, to a lesser extent, venous dilatation.
- Lack of reflex tachycardia may be because of stimulation of the vagus nerve or because of reduced potentiation of sympathetic nervous activity by angiotensin II
- Angiotensin II is also implicated in the development of arterial and left ventricular hypertrophy in hypertension. The importance of ACE inhibitors compared with other antihypertensives in limiting these effects is uncertain
- ACE also degrades vasodilator kinins. Increased kinins or vasodilator prostaglandins and NO in the vascular wall may contribute to the hypotensive action of ACE inhibitors.

Angiotensin II type I receptor antagonists

Mechanism of action

- The angiotensin receptor antagonists are selective for the AT_1, receptor subtype, which is found in the heart, blood vessels, kidney, adrenal cortex, lung and brain.
- They have less effect at a second receptor subtype, known as AT_2, which is believed to be involved in regulation of vascular growth in response to angiotensin II.
- Reduced generation of the intracellular second messengers diacylglycerol and inositol triphosphate in target cells is responsible or the actions of these drugs.
- The effects show similarities to those produced by ACE inhibitors, except that kinin degradation is unaffected by angiotensin II antagonists, and inhibition of the effects of angiotensin II on the AT_1 receptor is more complete.

Vasodilatation by other mechanisms

Diuretics

Mechanism of Action

There are several actions involved in lowering blood pressure:

- An initial hypotensive effect is produced by intravascular salt and water depletion. However, compensatory mechanisms such ass activation of the renin-angiotensin-aldosterone system largely restore plasma and extracellular fluid volumes (unless salt and water retention was a major component of the initial hypertension e.g. in advanced renal failure or as a consequence of other antihypertensive treatment).
- Direct arterial dilatation is responsib le for the longer-term reduction in blood pressure. Vasodilatation may result from reduced CA^{2+} entry into the smooth muscle of the arteriolar resistance vessel walls (perhaps as a consequence of Na^{+} depletion) and from synthesis of the vasodilator prostaglandins PGE_2 and PGI_2.

Calcium channel antagonists

Mechanism of Action

- The voltage-gated Ca^{2+} L-channel antagonists lower blood pressure principally by arterial vasodilatation by preventing the Ca^{2+} fluxes into the vascular smooth muscle cells.

Potassium channel activators

Mechanism of Action

- Minoxidil activates cell membrane potassium channels leading to potassium accumulation in the cell and hyperpolarisation of cell membrane.
- Minoxidil is one of the most powerful peripheral arterial dilators

Nitrovasodilators

Mechanism of Action

- Nitroprusside is a nitrovasodilator with a mechanism of action similar to that of organic nitrates
- It produces dilatation of aerterioles and veins, reducing both peripheral resistance and venous return
- Its use is limited to the emergency management of some hypertensive states

Endothelin antagonists

Mechanism of Action

- By blocking the ET_A (vasoconstrictors) and ET_B

(vasodilators), these agents produce a fall in BP and are in the process of development and available for research use.

- These agents are Bosantan, Sitaxentan, Ambrisentan and Tezosentan which act by blocking ET receptors, whereas Phosphoramidon is a **E**ndothelin **C**onerting **E**nzyme-**I**nhibitor (ECE-I), an agent which block the processing of ET from its pre-pro-peptide structures.

Preventive Interventions for Hypertension

Physical inactivity (sedentary state) per se has been suggested to a risk factor for cardiovascular diseases. Subjects with low levels of physical fitness had a relative risk of 1.52 for development of hypertension when compared with subjects with high levels of fitness. A vast epidemiological literature describes an apparent relationship between raised BP and lifestyle choices and habits. Several nonpharmacological interventions are recommended for primary prevention of hypertension and other cardiovascular diseases. Regular moderate physical aerobic exercises, such as walking, jogging, cycling or swimming and dietary modifications such as reduced intake of sodium chloride (salt), reduced alcohol consumption, and possible increased dietary potassium, calcium, magnesium and fish oil, are some of the suggested life style interventions which have been shown to reduce the BP in patient with mild essential hypertension in a number of randomized controlled trials.

Physical aerobic exercise

Regular aerobic exercise of moderate intensity decreases systolic BP by 6-10 mmHg and diastolic BP by 4-8 mmHg in patients with essential hypertension and have been demonstrated to prevent the cardiovascular mortality and morbidity. The WHO/ international Society of Hypertension and seventh report of the JNC of High BP recommend exercise at an intensity of ~50% of maximum oxygen consumption (Vo_{2max}) for 30 min per time, and 5-7 times per week, for patients with mild to moderate essential hypertension. According to these guidelines, the beneficial effects of exercise appear after 10 weeks when patients perform exercise for at least 30 min per time and at least 3 times per week.

Mechanism of action of Physical aerobic exercise in improving the BP and cardiovascular disease status: Some of the beneficial effect of exercise

is improvement in endothelial function through (36, 37 and ref. therein):

- An increase in NO bioavailability (increase in NO production and/ or decrease in NO inactivation) by a number of mechanisms,
- Increase in capillary density and the capillary-to-fibre ratio in skeletal muscle in humans,
- Decrease in reactive free oxygen (RFO)-radicals due to up-regulation of antioxidant system,
- Inactivation of NADH/NADPH oxidase system which may contribute to the improvement in endothelial function.
- Increased synthesis vasodilatory prostaglandins – PGI_2 and PGE_2 and endothelium-derived hyperpolarizing factor (EDHF)
- Reduction in weight, insulin resistance and insulin levels, and increase in HDL cholesterol

Mechanism of action of dietary modifications in improving the BP and cardiovascular disease status: Although a number of dietary modifications have been advised, it is difficult to ascertain which specific choices have clinically important influences on BP as such factors are often inter-related. Further patients may not follow regimens designed to change dietary habits. The available evidence suggests that patients should be encouraged to:

- Follow weight reducing diet which is low in fat and high in fruits and vegetables
- Restrict their dietary sodium intake to under 6 g/day, by avoiding processed foods with high salt content and by adding less salt to food or substituting low-sodium slat
- Overweight patients should be encouraged to lose weight through a low-calorie diet
- A reduction in BP (about 2 mm Hg) was observed to be associated with fish oil supplements and high calcium, magnesium, potassium diet. All these maneouvers have been shown to improve the endothelial function by reducing the vasoconstrictor response to a number of agents. Since fish oil supplements are not cost effective, it may be more appropriate to recommend a fatty fish in healthy diet (38 and ref. therein).

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