1- Vasoactive Peptides

2- ■ **INTRODUCTION**

1- angiotensin II

2- **vasopressin,**

3- **Endothelin**

4- **neuropeptide Y**

5- **Urotensin**

6- **calcitonin gene-related peptide**,

7- **adrenomedullin**).

1- ANGIOTENSIN

Within the kidney, renin is synthesized and stored in the juxtaglomerular apparatus of the nephron.

. Active renin secretion is controlled by a variety of factors, including a renal vascular receptor, the macula densa, the sympathetic nervous system, and angiotensin II.

ACTIONS OF ANGIOTENSIN II

Blood Pressure

Angiotensin II also interacts with the autonomic nervous system. It stimulates autonomic ganglia, increases the release of epinephrine and norepinephrine from the adrenal medulla, and—what is most important—facilitates sympathetic transmission by an action at adrenergic nerve terminals. The latter effect involves both increased release and reduced reuptake of norepinephrine.

INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM

Drugs That Block Renin Secretion

Renin Inhibitors

Aliskiren is the most advanced of these. In healthy subjects, aliskiren produces a dose-dependent reduction in plasma renin activity and angiotensin I and II and aldosterone concentrations. In patients with essential hypertension, **aliskiren** suppresses plasma renin activity and causes dose-related reductions in blood pressure similar to those produced by angiotensin II receptor antagonists.

Angiotensin-Converting Enzyme Inhibitors

Kallikreins

Kallikreins are present in plasma and in several tissues, including the kidneys, pancreas, intestine, sweat glands, and salivary glands.

Plasma prekallikrein can be activated to kallikrein by trypsin,

Hageman factor, and possibly kallikrein itself.

Kininogens

Kininogens—the precursors of kinins and substrates of kallikreins—are present in plasma whereas HMW kininogen is confined to the bloodstream and serves as the substrate for plasma kallikrein.

VASOPRESSIN

INTRODUCTION

Vasopressin (**antidiuretic hormone, ADH**

increase water reabsorption.

Vasopressin also plays an important role in the short-term regulation of arterial pressure by its vasoconstrictor action

VASOPRESSIN RECEPTORS & ANTAGONISTS

NATRIURETIC PEPTIDES

The atria and other tissues of mammals contain a family of peptides with natriuretic, diuretic,

Vasorelaxant

synthesized primarily in cardiac atrial cells, but small amounts are synthesized in ventricular cells.

most important one appears to be atrial stretch via mechanosensitive ion channels. (Atrial natriutec peptide)ANP release is also increased by volume expansion,

ANP release can also be increased by sympathetic stimulation via α_{1A}-adrenoceptors, , glucocorticoids, and vasopressin.

Finally, plasma ANP concentration increases in various pathologic states, including heart failure, primary aldosteronism, chronic renal failure, and inappropriate ADH secretion syndrome.

Administration of ANP produces prompt and marked increases in sodium excretion and urine flow. Glomerular filtration rate increases, with little or no change in renal blood flow, so that the filtration fraction increases.

he ANP-induced natriuresis is apparently due to both the increase in glomerular filtration rate and a decrease in proximal tubular sodium reabsorption.

ANP also inhibits the secretion of renin, aldosterone, and vasopressin; these changes may also increase sodium and water excretion.

Finally, ANP decreases arterial blood pressure. This hypotensive action is due to vasodilation,

Administration of BNP as **nesiritide**

ENDOTHELINS

Actions

Endothelins cause dose-dependent vasoconstriction in most vascular beds. Intravenous administration of ET-1 causes a rapid and transient decrease in arterial blood pressure followed by a prolonged increase.

The depressor response results from release of prostacyclin and nitric oxide from the vascular endothelium,

whereas the pressor response is due to direct contraction of vascular smooth muscle.

Endothelins also exert direct positive inotropic and chronotropic actions on the heart and are potent coronary vasoconstrictors.

They act on the kidneys to cause vasoconstriction and decrease glomerular filtration rate and sodium and water excretion. In the respiratory system, they cause potent contraction of tracheal and bronchial smooth muscle.

INHIBITORS OF ENDOTHELIN SYNTHESIS & ACTION

The endothelin system can be blocked with receptor antagonists and drugs that block endothelin-converting enzyme. Endothelin ET_A or ET_B receptors can be blocked selectively, or both can be blocked with nonselective ET_A-ET_B antagonists.

Bosentan is a nonselective antagonist. This drug is active intravenously and orally, and blocks both the initial transient depressor (ET_B) and the prolonged pressor (ET_A) responses to intravenous endothelin.

SUBSTANCE P

Substance P is present in the central nervous system, where it is a neurotransmitter and in the gastrointestinal tract, where it may play a role as a transmitter in the enteric nervous system and as a local hormone

Substance P exerts a variety of incompletely understood central actions that implicate the peptide in behavior, anxiety, depression, nausea, and emesis.

It is a potent arteriolar vasodilator, producing marked hypotension in humans and several animal species.

The vasodilation is mediated by release of nitric oxide from the endothelium.

NEUROTENSIN

Neurotensin is a tridecapeptide that was first isolated from the central nervous system but subsequently was found to be present in the gastrointestinal tract and in the circulation.

secreted into the circulation after ingestion of food.

neurotensin exerts potent effects including hypothermia, antinociception, and modulation of dopamine neurotransmission.

When administered into the peripheral circulation, it causes vasodilation, hypotension, increased vascular permeability,

increased secretion of several anterior pituitary hormones, hyperglycemia, inhibition of gastric acid and pepsin secretion, and inhibition of gastric motility.

In the central nervous system, there are close associations between neurotensin and dopamine s**ystems,**

neurotensin may be involved in clinical disorders involving dopamine pathways **such as schizophrenia, Parkinson's disease, and drug abuse**.
Consistent with this, it has been shown that central administration of neurotensin produces effects in rodents similar to those produced by antipsychotic drugs.

Three subtypes of neurotensin receptors, designated **NT_1**, **NT_2**, and **NT_3**, have been cloned. NT_1 and NT_2 receptors belong to the G protein-coupled superfamily with seven transmembrane domains; the NT_3 receptor is a single transmembrane domain protein that belongs to a family of sorting proteins.

Neurotensin agonists that cross the blood-brain barrier have been developed and may have potential as therapeutic agents for diseases such as schizophrenia and Parkinson's disease.

CALCITONIN GENE-RELATED PEPTIDE

Evidence is accumulating that release of CGRP from trigeminal nerves plays a central role in the pathophysiology of migraine.

The peptide is released during migraine attacks,

successful treatment of migraine with a selective serotonin agonist normalizes cranial CGRP levels.

BIBN4096BS has recently been shown to be an effective, well-tolerated treatment for migraine.