Vasoactive Peptides
State-of-the-Art Review

SAMI I. SAID, M.D.

SUMMARY At least 16 naturally occurring peptides either constrict or dilate blood vessels. Many of these peptides are present in nerve cells and nerve terminals supplying systemic and pulmonary blood vessels and the heart. Such neuropeptides are released locally as neurotransmitters, and can influence vascular tone, local and regional blood flow, arterial blood pressure, and cardiac function. There is evidence for the participation of at least some vasoactive peptides in the regulation of these functions and in the mediation or modulation of systemic shock and arterial hypertension. The investigation of vasoactive peptides in relation to cardiovascular function and dysfunction is at a promising threshold. (Hypertension 5 (supp I): M7-I-26, 1983)

KEY WORDS • vasopressor • vasodepressor • hypotension • vasoconstriction • vasodilation • shock • hypertension

A large number of biologically active peptides have been isolated and characterized in recent years. There is a growing conviction that these peptides participate in the regulation of many organ functions. Neuroscientists, endocrinologists, and gastroenterologists have led other groups in recognizing the likely physiological and clinical significance of these peptides, most of which are found in the brain and gut.

Since many biologically active peptides are capable of influencing vascular smooth muscle, and thus blood flow and blood pressure, peptides with these vasoactive properties are reviewed here. Emphasis is placed on the cardiovascular effects of the more recently identified peptides, with special reference to their possible roles in the regulation of blood pressure in normal and abnormal states. Bradykinin and angiotensins, which are extensively reviewed elsewhere, are only briefly mentioned here.

Biological Activity of Peptides
Which Peptides are Vasoactive?

Peptides with vasoactive properties are given in the accompanying list (see box), which is not meant to be complete. For some of these peptides (e.g., angiotensin II, bradykinin), vasoactivity is a dominant feature of their biological actions; for others (e.g., prolactin, parathyroid hormone), the pressor or vasodepressor activity has generally been overshadowed by other actions of the peptide.

As will become apparent in the following paragraphs, the ability to induce either vasodilation or vasoconstriction is shared by a variety of apparently unrelated peptides. It is possible in some instances, however, to recognize certain structural features among these peptides that correlate with their vasodilator or vasoconstrictor activity. Such features will be noted.

Angiotensins

Angiotensin II (table 1) is one of the most potent systemic vasopressors known. Its formation from angiotensin I through the action of angiotensin-converting enzyme, the localization and properties of this enzyme, and the physiology, pathophysiology, and pharmacology of the renin-angiotensin systems in the body are topics of recent comprehensive reviews.

Bombesin

A 14-residue peptide (table 1) isolated from the skin of the frog Bombina bombina, bombesin has spasmodenic activity on a variety of vascular and non-vascular smooth muscle structures. It induces vasoconstriction and systemic hypertension in most animal species, hypotension in monkeys, but neither in humans, A mammalian counterpart of the amphibian peptide is the 27-residue gastrin-releasing peptide, which has been found in the brain and gastrointestinal tract. Bombesin itself may also occur in human oat-cell cancer of the lung.

Bradykinin

A potent systemic vasodilator and vasodepressor, bradykinin (table 1) also increases systemic, but not
Vasoactive Peptides

1. Angiotensin I and II
2. Bombesin
3. Bradykinin
4. Cholecystokinin-pancreozymin
5. Neurotensin
6. Opioid peptides
7. Oxytocin
8. Parathyroid hormone
9. Prolactin
10. Sauvagine
11. Somatostatin
12. Substance P
13. Thyrrotropin-releasing hormone
14. Urotensin
15. Vasactive intestinal peptide
16. Vasopressin

Pulmonary, microvascular permeability. The generation, inactivation, and biological role of bradykinin have been intensely investigated in recent years.6

Cholecystokinin-Pancreozymin (CCK)

Originally thought to be limited to endocrine cells in the gastrointestinal tract, CCK has also been found in the brain, especially the cerebral cortex, and in peripheral nerves. In addition to stimulating gallbladder contraction and pancreatic enzyme secretion, it has distinct, though limited, vasoactive properties. The peptide and its C-terminal octapeptide fragment induce splanchnic vasodilation and mild hypotension in anesthetized dogs.16,17 CCK is naturally present in several molecular forms, including 4-, 8-, 33- and 39-residue peptides.

Neurotensin

A 13-residue peptide (table 1), neurotensin is present in the central and peripheral nervous systems and gastrointestinal organs. It causes vasodilation, hypotension, peripheral cyanosis, and increased vascular permeability in anesthetized rats. In dogs, however, neurotensin is a systemic vasoconstrictor.18 The chemically related amphibian peptide, xenopsin, is also vasoactive.

Opioid Peptides

The endogenous opioid peptides, including endorphins and enkephalins, have important effects on cardiovascular function. The specific effects in experimental animals depend on the individual peptide and the method of its administration. Like morphine, opioid peptides generally cause peripheral vasodilation and a fall in arterial blood pressure, when given intravenously.19,20 Administered intracisternally in anesthetized dogs and rats, morphine, β-endorphin, D-alal-met enkephalin and D-alal-met-enkephalaminamide induce hypotension and bradycardia, while α-endorphin induces hypertension.21,22 Centrally administered, met-enkephalin is vasopressor in rats but ineffective in dogs.

Oxytocin

One of the two “neurohypophyseal peptides” (though actually secreted in the hypothalamic magnocellular nuclei), oxytocin has vasodepressor activity, at least in birds. The ability of oxytocin to lower chicken blood pressure is the basis for a bioassay method for this peptide.23

Parathyroid Hormone (PTH)

Bovine parathyroid hormone (1–34 fragment) produces dose-related arterial hypotension in dogs, rats and other species. This action is not mediated by adrenergic, cholinergic, or histamine receptors.24,25 PTH exerts a direct vasodilator action in perfused rabbit hindlimbs and in dog renal, hepatic, pancreatic and coronary vascular beds; it also relaxes isolated strips of rabbit aorta.26,27 The vasodilator effect of PTH in dogs is evident at doses that are too small (0.01 U/kg) to cause hypercalcemia. Chemical manipulations of the

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Amino-acid sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin I</td>
<td>H - Asp - Arg - Val - Tyr - Ile - His - Pro - Phe - His - Leu - OH</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>H - Asp - Arg - Val - Tyr - Ile - His - Pro - Phe - OH</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>H - Arg - Pro - Pro - Gly - Phe - Ser - Pro - Phe - Arg - OH</td>
</tr>
<tr>
<td>Substance P</td>
<td>H - Arg - Pro - Lys - Pro - Gln - Gln - Phe - Phe - Gly - Leu - Met - NH₂</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>pyroGlu - Leu - Tyr - Glu - Asn - Lys - Pro - Arg - Arg - Pro - Tyr - Ile - Leu - OH</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>H - Ala - Gly - Cys - Lys - Asn - Phe - Phe - Trp - Lys - Thr - Phe - Thr - Ser - Cys - OH</td>
</tr>
<tr>
<td>Bombesin</td>
<td>pyroGlu - Arg - Leu - Gly - Asn - Glu - Trp - Ala - Val - Gly - His - Leu - Met - NH₂</td>
</tr>
<tr>
<td>Thyrrotropin-releasing hormone</td>
<td>pyroGlu - His - Pro - NH₂</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>H - Cys - Tyr - Ile - Gln - Asn - Cys - Pro - Leu - Gly - NH₂</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>H - Cys - Tyr - Phe - Gln - Asn - Cys - Pro - Arg - Gly - NH₂</td>
</tr>
</tbody>
</table>
PHT molecule show that distinct and different parts of the sequence are responsible for the hypercalcemic and vasoactive properties. The occurrence of basic amino acids in adjacent positions may be important to the vasodilator activity of PHT. Other vasodilator peptides, including VIP and neurotensin, also possess adjacent basic residues.

**Prolactin**

Among the least widely known actions of prolactin is its ability to influence vascular smooth muscle. In low concentrations (0.6 μg/hr), acute or chronic administration of ovine prolactin raises blood pressure in rabbits and rats and potentiates pressor responses of rat mesenteric vessels to norepinephrine and angiotensin II. Infusions of higher concentrations (8.9 μg/hr) of prolactin decrease blood pressure in rats.

**Sauvagine**

Recently isolated from the skin of the frog *Phylomedusa sauvagei*, sauvagine is a 40-residue peptide with a long-lasting hypotensive activity in many species, including humans. Sauvagine, structurally related to corticotropin-releasing factor, also has potent endocrine effects, provoking the release of ACTH and β-endorphin from the pituitary.

**Somatostatin**

This hypothalamic tetradecapeptide (table 1), which is also present in peripheral tissues, can influence vascular smooth muscle. Intravenous infusion of somatostatin (1 μg/kg) in anesthetized human subjects reduced splanchic blood flow (by up to 56%), augmented external iliac blood flow (by 43%), and raised mean arterial blood pressure (by 20%).

**Substance P**

Widely distributed in the brain and in nerves supplying many organs, Substance P is an 11-residue peptide with some structural similarities to bradykinin (table 1) and major actions on the circulation. These actions include peripheral vasodilation and transient systemic hypotension. A related peptide, physalaemin, originally discovered in amphibian skin, has also been found in mammalian tissues.

**Thyrotropin-Releasing Hormone (TRH)**

Injections of TRH (2 mg/kg) in awake rats cause an increase in mean arterial blood pressure that persists for 30 minutes. TRH (table 1) appears to antagonize the cardiovascular effects of endogenous opiate peptides, which have overall vasodepressor activity.

**Urotensin I**

A 41-residue peptide recently isolated from the urophysis of a teleost fish, *Catostomus commersoni*, urotensin I is a selective dilator of mesenteric vessels in mammals. It also induces hypotension and increases cardiac output in anesthetized dogs. These effects are not influenced by adrenergic, histaminergic, or muscarinic cholinergic blockade. Urotensin I shows a striking sequence homology with ovine corticotropin-releasing factor and with sauvagine.

**Vasoactive Intestinal Peptide (VIP)**

Originally isolated from porcine intestine, VIP has subsequently been found in the brain and peripheral nerves of all mammalian species and lower forms. The 28-residue peptide has potent vasodilator activity in coronary, splanchic, extremity, extracranial, and other vascular beds. As a consequence of this generalized vasodilation, VIP induces systemic hypotension (fig. 1). The vascular effects of VIP are independent of adrenergic or cholinergic receptors and, with the exception of the vasodilation of pial vessels, are not mediated by prostaglandin release. The related peptides, secretin and glucagon, have considerably weaker activity on vascular and nonvascular smooth muscle.

**Vasopressin**

The second of the neurohypophyseal peptides, vasopressin has pressor activity that was the basis for its recognition and its given name. On a molar basis, vasopressin is as potent as angiotensin II or norepinephrine in raising mean arterial blood pressure of rats. Arginine-vasopressin (table 1) has equal pressor and antidiuretic activities. Structural changes in the molecule (e.g., deamination at Position 1, substitution of a more lipophilic amino acid for Gln at Position 4, and of D-for L-Arg at Position 8) have led to the synthesis of peptides with enhanced antidiuretic, relative to pressor, activity. Thus, 1-deamino-4 valine-8-D arginine vasopressin has no detectable vasopressor activity, but has four times the antidiuretic activity of arginine-vasopressin. The latter compound also antagonizes the pressor response of arginine vasopressin. Other substitutions have resulted in enhancement of the pressor/antidiuretic activity. For example, 8-ornithine vasopressin has a pressor/antidiuretic activity ratio of 4, and 2-phenylalanine-8-ornithine vasotocin is the most highly selective pressor/antidiuretic agent known to date, with a pressor/antidiuretic activity ratio of 255. As noted earlier, the closely related peptide oxytocin is actually vasodepressor, at least in birds.

**Distribution of Vasoactive Peptides**

**Peptides Hormones and Neurotransmitters**

Few of the vasoactive peptides (e.g., bombesin, CCK, parathyroid hormone) are localized in endocrine cells. Such peptides may function as hormones, acting on remote target organs, or as locally active paracrine secretions. On the other hand, most other peptides are localized mainly in nerve cell bodies, nerve fibers and nerve endings. These peptides, occurring in neurons of the central and peripheral nervous systems, are known as neuropeptides. Many are already known to exhibit characteristic features of neurotransmitters, such as concentration in nerve terminals and synaptosomes, axonal transport, and release with depolarizing concentrations of K⁺ in the presence of Ca²⁺.
Neuropeptides are being increasingly recognized as forming a third component of the autonomic nervous system, the peptidergic system of nerves. The existence of a nonadrenergic, noncholinergic nervous system has been demonstrated in many tissues and organs, including blood vessels.\(^{41-43}\) The identity (or identities) of the transmitter(s) of this system, sometimes also known as the "purinergic" system, has been in dispute.\(^{44}\) Certain neuropeptides, especially VIP, are now under investigation as the possible responsible transmitters.\(^{44,45}\)

The localization of vasoactive peptides in the central nervous system is of special interest in relation to their possible regulatory role. For example, neurons containing Substance P, VIP, and enkephalins innervate cardiovascular centers in the nucleus tractus solitarius and other nuclei;\(^{46}\) and norepinephrine-containing neurons innervate the large hypothalamic neuroendocrine cells which secrete arginine vasopressin (see below).\(^{47}\)

Co-Existence of Peptides and "Classical" Neurotransmitters

Despite the earlier, widely propagated dictum of "one neuron, one transmitter," recent evidence has documented the frequent occurrence, in the same neurons, of more than one transmitter.\(^{48}\) These are usually a peptide together with a catecholamine, acetylcholine, or serotonin. Examples of this coexistence (and sometimes co-release) of peptides and other neurotransmitters are given in table 2.

Vasoactive Peptides and the Systemic Circulation

Peptides in Systemic Vessels

Immunohistochemical techniques have demonstrated the presence of some vasodilator peptides in nerve fibers and nerve terminals within the walls of systemic blood vessels. This distribution is best exemplified by VIP and Substance P. VIP-containing nerves supply vessels to the digestive organs, upper respiratory passages, tracheo-bronchial tree, skin, skeletal muscle, brain, ocular and extracranial structures, genitourinary system, adrenal gland, and other sites.\(^{49-52}\) (fig. 2). Locally released, VIP is therefore well positioned to influence blood flow to individual organs, regional blood flow, total peripheral vascular resistance, and arterial blood pressure.

Peptides in the Heart

Recently, VIP-, neurotensin-, and Substance P-containing nerves have been localized in cardiac structures,\(^{53}\) including the sinoatrial node,\(^{54}\) specialized conducting tissue, atrial and ventricular myocardium, and the walls of coronary vessels (figs. 3 and 4). Both

\[ \text{TABLE 2. Coexistence of Peptides and Amines in Neurons of the Central and Peripheral Nervous Systems.} \]

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Amine</th>
<th>Site</th>
</tr>
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<tbody>
<tr>
<td>Enkephalins</td>
<td>E, NE</td>
<td>Adrenal medulla, sympathetic ganglia</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>Dopamine</td>
<td>Carotid body</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>NE</td>
<td>Sympathetic ganglia</td>
</tr>
<tr>
<td>VIP</td>
<td>Ach</td>
<td>Nerves to exocrine glands and cerebral vessels</td>
</tr>
<tr>
<td>Substance P</td>
<td>Serotonin</td>
<td>CNS nuclei</td>
</tr>
<tr>
<td>CCK</td>
<td>Dopamine</td>
<td>CNS nuclei</td>
</tr>
</tbody>
</table>

\[ \text{Ach = acetylcholine; E = epinephrine; NE = norepinephrine; VIP = vasoactive-intestinal peptide; CCK = cholecystokinin-pancreozymin.} \]
VIP and Substance P are known to dilate coronary vessels. VIP also has a positive inotropic action on the myocardium, binds to specific membrane receptors, and stimulates adenylate cyclase activity in the heart.

Vasoactive Peptides and the Pulmonary Circulation

Peptides in the Lung

The search for peptides in the lung is relatively recent. By now, however, this search has led to the discovery and identification of almost all the "brain-gut" peptides in the lung. This finding is not surprising, since the lung develops from the embryonic foregut.

The list of peptides already shown to exist in the lung is rapidly lengthening, and now includes at least 11 (table 3). The sites of localization of these peptides include nerve cells and nerve endings (VIP, Substance P, and possibly bombesin), endocrine cells (calcitonin, bombesin, and enkephalins), endothelium (angiotensin II), and other undetermined sites (table 3).

Effects of Peptides on the Pulmonary Circulation

The possible influence of vasoactive peptides on the lung and the pulmonary circulation have only begun to be investigated. Among the peptides normally present in lung tissue, angiotensin II, spasmonic lung peptide, and, to a lesser extent, Substance P contract isolated segments of pulmonary artery. Bombesin also constricts pulmonary vessels, but the activity of its mammalian counterpart (gastrin-releasing peptide) on pulmonary vasculature has not been tested.

On the other hand, VIP relaxes isolated strips of cat pulmonary artery in which the tone has been increased with prostaglandin endoperoxide analog. In this action, VIP is at least as potent as prostacyclin, on a molar basis. VIP also reduces pulmonary vascular resistance and pulmonary arterial pressure in cats receiving infusions of prostaglandin endoperoxide analog.

None of the pulmonary peptides, administered alone, has been shown to increase pulmonary microvascular permeability. However, combinations of bradykinin with hypoxia or with PGE_2 and activated complement fragments (C5a) with hypoxia or with PGE_2, can result in increased permeability of lung microvessels.

Physiological Role

The physiological role of vasoactive peptides remains at an early stage of investigation. As outlined above, many of these peptides are present in nerves that supply blood vessels and the heart, or innervate nerve centers that influence cardiovascular function. Further, some of these peptides have the capacity to function as neurotransmitters or neuromodulators.

The possibility that certain peptides do indeed serve such a role in the regulation of cardiovascular function seems even more likely in view of the interactions between peptides and "classical" hormonal transmitters. Examples of such interactions in the case of VIP are: VIP stimulates the synthesis or release of prolactin, growth hormone, and LHRH, as well as of renin and steroids. At the same time, VIP release is stimulated by neostigmine and by serotonin.

Certain potential physiological roles of cardiovascular peptides are suggested by the data presented above on their localization and actions. These roles include the regulation of regional blood flow, peripheral vascular resistance, and arterial blood pressure; and the regulation of cardiac function, including coronary blood flow, myocardial contractility, cardiac rhythmicity, and conductivity.

<table>
<thead>
<tr>
<th>Table 3. Lung Peptides and their Localization</th>
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<tbody>
<tr>
<td><strong>Peptide</strong></td>
</tr>
<tr>
<td>1. Vasoactive-intestinal peptide</td>
</tr>
<tr>
<td>2. Substance P</td>
</tr>
<tr>
<td>3. Bombesinlike peptide</td>
</tr>
<tr>
<td>4. Calcitonin</td>
</tr>
<tr>
<td>5. Enkephalins</td>
</tr>
<tr>
<td>6. Angiotensin II</td>
</tr>
<tr>
<td>7. Eosinophil-chemotactic peptides</td>
</tr>
<tr>
<td>8. Bradykinin</td>
</tr>
<tr>
<td>9. Complement fragments</td>
</tr>
<tr>
<td>10. Cholecystokinin</td>
</tr>
<tr>
<td>11. &quot;Spasmogenic lung peptide&quot;</td>
</tr>
</tbody>
</table>
FIGURE 3. VIP-immunoreactive (IR) nerve fibers in dog heart. Upper panel: Nerve fibers within the sinoatrial node. (× 640). Lower panel: around the coronary artery and between myocardial cells of the right atrium. (× 960). Peroxidase-antiperoxidase technique; courtesy of Prof. W.G. Forssmann, Heidelberg, W. Germany, from unpublished work by E. Weihe, M. Reinecke and W.G. Forssmann.
Peptides with vasoconstrictor or pressor activity include: angiotensin I and II, vasopressin, and prolactin. Those with vasodilator or vasodepressor activity include: bradykinin, VIP, sauvagine, Substance P, enkephalins/endorphins, urotensin I, and parathyroid hormone. Evidence for the possible physiological participation of some of these peptides in the maintenance of normal blood pressure has recently become available. For example, a role for prolactin is suggested by experiments in which newborn rats, 2–5 days old, received antiserum to prolactin. At 14 weeks, these rats had lower blood pressure levels than did rats given saline or normal rabbit serum. The possibility that opioid peptides contribute to the reduction of blood pressure during fasting is suggested by the observations that fasting lowers systolic blood pressure to a greater extent in spontaneously hypertensive rats than in normotensive rats, and that this lowering of blood pressure is attenuated by naltrexone (2 mg/kg), an opiate receptor antagonist.

Role of Vasoactive Peptides in Cardiovascular Disease

Vasoactive peptides have considerable potential significance in the pathogenesis or pathologic physiology of cardiovascular disease. Evidence for such significance has already been provided for several peptides.

Hypertension

Peptides that have been implicated in the pathogenesis of hypertension are angiotensin II, opioid peptides, VIP, and arginine vasopressin.

1. The significance of the renin-angiotensin system in the pathogenesis of hypertension is well established, and is reviewed elsewhere.5

2. A possible relationship between enkephalins (predominantly hypotensive peptides) and hypertension is suggested by the report that enkephalin-like immunoreactivity is lower in tissues from spontaneously hypertensive rats than in normal control rats.76

3. Similarly, it has been found that VIP-sensitive adenylate cyclase activity in cardiac tissue from spontaneously hypertensive rats (10 weeks and older) is greatly and selectively reduced, relative to the responses to isoproterenol, glucagon, and fluoride. In the same animals, adenylate cyclase stimulation by VIP is normal in all other tissues examined (pancreatic acini, liver, and brain).77

4. Selective destruction of A1 noradrenergic neurons in the caudal ventrolateral medulla oblongata of...
rabbits produces a striking syndrome of accelerated hypertension and "neurogenic" pulmonary edema. The terminals of these neurons are concentrated around the supraoptic and paraventricular (magnocellular) nuclei, which secrete arginine vasopressin. This experimental lesion is associated with a marked increase in plasma vasopressin concentrations, which probably accounts for the acute hypertension; an antagonist of vasopressin largely prevents this hypertension.47

Shock
Peptides that have been implicated in shock states include bradykinin, opioid peptides, vasopressin, and VIP.

Opioid Peptides
The following findings suggest that opioid peptides may participate in mediating endotoxin shock and other forms of shock.
1. An opiate receptor antagonist, naloxone reduces the morbidity and mortality of systemic shock from a variety of causes, including endotoxemia, hemorrhage, anesthesia, spinal cord injury, and acid aspiration.78-83
2. Studies show that endotoxin evokes opioid peptide secretion into the blood and cerebrospinal fluid in sheep.84

Vasopressin
The pressor effect of circulating vasopressin may be essential for the recovery of blood pressure following hemorrhagic shock:
1. Hemodynamic recovery from hemorrhagic shock is subnormal in Brattleboro rats (which have a genetic hypothalamic lesion causing total inability to synthesize vasopressin and, as a consequence, have diabetes insipidus).38
2. An antipressor vasopressin analog impairs recovery of blood pressure levels in normal rats bled to hypotensive levels.38

Vasoactive Intestinal Peptide (VIP)
It has been shown that VIP is released into the circulation during hemorraghic and endotoxin shock in dogs.85 The released peptide may serve to promote blood flow to vital organs, including the heart, brain, and splanchnic bed.

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