Bradykinin and the Cardiovascular System

BRADYKININ is the prototype of a group of related vasoactive polypeptides termed “kinins.” This prototype is composed of nine amino acids whose sequence is critical for the effects of the peptide. Kallidin and methionyl-lysyl bradykinin are N-substituted decapeptide and an undeca-peptide, respectively—whose pharmacologic effects in man resemble those of bradykinin.

In vivo, bradykinin is derived from species-specific alpha-2-globulins (kininogens) found in the plasma and presumably synthesized by the liver. Kallikreins, enzymes that usually exist in inactive form in plasma and a number of tissues, convert the kininogen to kinin. Originally described as a smooth muscle contracting substance, bradykinin has subsequently been recognized as having potent influences on the cardiovascular system. This editorial briefly discusses the current status of recent investigations of the physiologic and pathogenetic roles of bradykinin in the cardiovascular system.

Cardiovascular Pharmacology of Bradykinin

The action of bradykinin in vivo will vary depending upon the species being investigated, the vessels under observation, the dose of peptide, and the interaction of bradykinin with other endogenous vasoactive substances. Bradykinin directly causes arteriolar vasodilation which decreases peripheral vascular resistance and blood pressure. Subsequent events include increased heart rate, increased cardiac output and force of myocardial contraction, and redistribution of regional blood flow. These later events appear to be secondary to reflex activation of the sympatho-adrenal system, and direct release, by the peptide, of catecholamines from the adrenals and other sites.

Bradykinin dilates the majority of systemic arterioles including the coronary, cerebral, splanchnic arterioles in almost all species studied. The peptide produces a net dilation in the resistance vessels of the human forearm. Work in progress in this laboratory indicates that the arteriolar beds of different organs may be variably responsive to bradykinin, resulting in redistribution of blood flow independent of sympathetic activation and preceding major changes in blood pressure or cardiac output during kinin infusion in the primate.

The effects of bradykinin on the postcapillary vascular bed are complex. Bobbin and Guth have demonstrated that the polypeptide produces constriction when applied locally to

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veins in the rabbit ear. This effect is independent of innervation of the vessel and of the release or blockade of other vasoactive substances. The veins of the human forearm also constrict during intravenous infusion of the peptide, but this constriction is a reflex event, secondary to the hypotension and is blocked by anti-adrenergic agents. The primary effect of the peptide on these veins in man is dilation. As bradykinin has not been extensively studied in other venous beds, we cannot yet identify the differences between veins that determine whether they constrict or dilate under the influence of the peptide.

The role of bradykinin in the pulmonary vascular bed is also complex. The peptide clearly causes decreased pulmonary vascular resistance and increased pulmonary blood flow in fetal or newborn lambs. Bradykinin also causes dilation of the pulmonary arterioles in adult dogs but does not dilate canine pulmonary veins. Kinin infusion may actually cause constriction of pulmonary veins, or the changes in pulmonary resistance occurring with bradykinin may be passive, that is, the result of redistribution of blood flow and increased pulmonary vascular blood volume which occurs during kinin infusion.

Bradykinin in vivo has positive inotropic effects on the myocardium. However, it is difficult to separate experimentally the reflex sympathetic activity which follows hypotension in the animal from a possible direct inotropic effect of the peptide. The effects of autonomic ganglionic blockade have been used to try to settle this question, but ganglionic blockade does not prevent the effects of catecholamines which are directly released from chromaffin tissue by bradykinin.

Intravenous injection or infusion of bradykinin into intact animals produces a biphasic blood pressure response. Following an initial but brief fall, the blood pressure rapidly returns toward control levels and often will overshoot the control values producing a secondary pressor phase. Lang and Pearson have demonstrated that this biphasic response is mediated via activation of both central and peripheral sympathetic reflexes. Thus, a functional relationship exists between the kinin-generating and the sympatho-adrenal systems. We have been able to block the secondary rise in peripheral resistance which occurs during bradykinin infusion in the primate by simultaneously infusing trimethaphan. Under these conditions the rise in heart rate is also prevented and cardiac output sharply decreases. These studies suggest that reflex autonomic mechanisms are capable of markedly modifying the primary effects of this vasodilator peptide. The predominant responses to simultaneous bradykinin and ganglionic blockers may be different in different animal species.

Cardiovascular Physiology of Bradykinin

Despite a reasonably detailed knowledge of the pharmacologic effects of bradykinin on the cardiovascular system, we know little of its physiologic role. Generation of the peptide may play a major role in the adaptation of the neonatal circulatory system to extra-uterine life. The neonate is capable of producing bradykinin, and bradykinin produces responses in vessels of the newborn which allow conversion of fetal to adult circulatory patterns. Both the umbilical artery and veins of man and the ductus arteriosus of several species constrict in the presence of low concentrations of kinin. Concentrations of bradykinin sufficient to constrict umbilical vessels have been detected in human umbilical arterial and venous blood after spontaneous delivery of the child. Kinin is also a potent dilator of the pulmonary artery of the fetus. The production of kinin seems in part dependent on the presence of oxygen, and peptide production is initiated and becomes maximal at oxygen concentrations found in the neonate, but not in the fetus. The strong possibility exists that bradykinin does contribute to neonatal circulatory adaptation because (a) the peptide is capable of exerting the necessary vascular effects, (b) it is present in significant concentration during birth, and (c) physiologic factors present at birth, but not during gestation, favor initiation.
of kinin generation. Whether blockade of bradykinin production or effect or removal of kininogen will prevent the normal completion of these perinatal circulatory adjustments remains to be tested. To our knowledge, the rare newborn who fails to complete neonatal circulatory adaptation has not been tested for his ability to make, destroy, or respond to bradykinin.

Other proposed physiologic roles for this substance are discussed in recent reviews. The authors of these reviews state that there is little evidence that bradykinin subserves other physiologic functions of the cardiovascular system than those just described. One might expect, from the characteristics of bradykinin (its short half-life, the potential for its production in many tissues, and its potent effect in extremely low concentration) that the peptide would play an important part in the regulation of regional blood flow. However, there is no conclusive proof for such a role.

The physiologic significance of the pharmacologic and biochemical interrelationships between kinin peptides and endogenous vasoactive amines remains to be defined. The functional relationships between bradykinin and the catecholamines have been mentioned. Kinins directly release catecholamines from the adrenals and chromaffin tissue and reflexly activate the sympathetic nervous system. Conversely, epinephrine is capable of activating at least one of the inactive tissue kallikreins (in patients with a malignant carcinoid tumor who have the carcinoid syndrome). The full significance of these relationships and others which are certain to be defined requires further investigation.

**Cardiovascular Pathology of Bradykinin**

Our understanding of the importance of bradykinin in pathologic processes involving the cardiovascular system is broadening. A definite pathophysiologic role has been established for kinins in patients who have carcinoid syndrome and cutaneous flushing. In some of these patients, exogenous bradykinin can create flushes identical to spontaneous episodes, and bradykinin is produced during spontaneous flushes that are preceded by release of a kallikrein enzyme from the carcinoid tumor. The enzyme can be released by a variety of stimuli known to produce symptoms of the disease and may be released by injections of subpharmacologic doses of catecholamines. Injections of epinephrine, to provoke kinin production and flushing, are used to diagnose the presence of a functioning carcinoid tumor particularly when the patient is excreting minimally or inconsistently abnormal quantities of indole acids in the urine. Bradykinin seems to contribute both to the cutaneous vasodilation of the carcinoid flush and to the associated hypotension. The kinins also have the pharmacologic potential of contributing to the diarrhea and asthma often seen in patients with this disease, but how significant a role the kinins play in these symptoms is uncertain.

Kinin is generated in the earliest phases of endotoxin shock in the monkey and human. The peptide can produce the decrease in peripheral vascular resistance seen during this disease state but by itself cannot reproduce all the regional vascular changes seen in early endotoxin shock. Simultaneous vasodilation and blockade of sympathetic reflexes seem to be required before the vascular changes mimic those seen with endotoxin infusion.

Considerable information has been gathered on the mechanism of kinin generation by endotoxin. The endotoxin interacts either with plasma kallikrein in the presence of antigen and complement or may release a kallikrein or kallikrein activator from human granulocytes which phagocytize the intact endotoxin molecule in the presence of complement. It seems highly likely that other disease states involved in antigen-antibody reaction may result in kinin generation. Although bradykinin may have a possible role during other states of shock and during myocardial infarction and angina, its actual importance in these conditions awaits extensive investigation.

The discussion of bradykinin has been limited to its effects on the cardiovascular system. Potent as these actions seem to
be, they comprise only one aspect of the pharmacologic spectrum that this substance is capable of producing. Development of new immuno-assays for the peptide and methods which soon will allow us to isolate and purify components of the kinin-generating system will certainly enable more precise definition of the role of the peptide in health and disease.

Critical areas for future investigation include defining which vascular effects are direct and which are reflex, and determining the mechanisms underlying the differences in response of various regional vascular beds to bradykinin. We also must carefully examine the differences between bradykinin-induced responses occurring in the venous and arterial portions of the circulation, as well as resolve the controversy as to whether bradykinin has direct effects on the myocardium.

Undoubtedly we will begin to explore the biochemical and molecular mechanisms of the actions of bradykinin. At present there is almost no knowledge of these mechanisms. If bradykinin is a significant mediator of both normal and abnormal physiology, we must understand its mechanism of action to be able to define rational controls for its production or effects. The foundations of our appreciation of a role for kinins have been set, but the edifice remains to be built.

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