PRESENCE OF SPECIFIC BRADYKININ RECEPTORS IN SMOOTH MUSCLE OF ARTERIES AND VEINS

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The contradictory data on the effect of bradykinin on the circulatory system can be explained by the complex effects brought about through liberation of prostaglandins [4]. Cautious views have also been expressed [6] on the role of bradykinin as an endogenous hypotensive agent. In experiments on most isolated blood vessels (except the coronary and cerebral) bradykinin induces a contractile response. However, the sensitivity of vessels in different regions to bradykinin has hitherto virtually not been investigated despite its recognized role as one of the factors concerned in regulation of the circulation [5, 7].

The action of bradykinin on the isolated aorta, pulmonary and renal arteries, and jugular and mesenteric veins of the rabbit has recently been analyzed [2, 3, 8] from the standpoint of receptor theory, and the presence of specific bradykinin-sensitive receptors has been demonstrated in these vessels.

This paper gives the results of a comparative investigation of the action of bradykinin on the rabbit aorta and jugular vein, which have specific receptors for bradykinin, and on the rabbit femoral artery and rat portal vein, now being investigated from this standpoint for the first time. The choice of these vessels was determined by the following considerations: The aorta is a vessel of elastic type, the jugular vein is a large collector of venous blood (these vessels have been shown to contain specific bradykinin-sensitive receptors), the femoral artery closely approximates to a vessel of muscular type (the smooth muscle of these vessels consists of muscles of tonic type), and the portal vein is a vessel with an endogenous mechanism of activation (the presence of pacemakers), whose smooth muscle, which is longitudinally oriented, consists of muscle of phasic type.

EXPERIMENTAL METHOD

Experiments were carried out on isolated rings of the aorta, femoral artery, and jugular vein of the rabbit and longitudinal strips of the rat portal vein. The vessels were placed in an experimental chamber with a capacity of 7.5 ml, perfused with Krebs' solution (in mM): NaCl 118.5, KCl 4.69, NaH_2PO_4 1.18, $NaHCO_3$ 25.88, $MgSO_4$ 1.16 glucose 5.5, saturated with a mixture of 95% O_2 and 5% CO_2; pH 7.4; 37°C. The initial load on the artery was 2 g and on the vein 500 mg. The contractile response was recorded by means of an FT-03 transducer on a polygraph (model 7D, from 'Grass') 2 h (1 h for the portal vein) after the vessels had been placed in the experimental chamber. To determine how the response depended on the bradykinin (Sigma, USA) concentration, the latter was added to the chamber in a volume of 1-10 μl 30-90 min after the previous dose has been rinsed out with Krebs' solution.

EXPERIMENTAL RESULTS

Records of the contractile response of the test vessels to above-threshold and submaximal concentrations of bradykinin are illustrated in Fig. 1. Differences in the action of bradykinin on the veins and arteries will be seen. The action of bradykinin on veins was observed as early as 10-30 sec after application (depending on concentration), whereas the contractile response of the femoral artery and aorta, when a low concentration of bradykinin was used, developed after rather a long time (2-3 min), although with higher concentrations of bradykinin this period was reduced to 1 min. The action of bradykinin on the portal vein, which possesses spontaneous contractile activity, was characterized by initial brief inhibition of spontaneous activity followed

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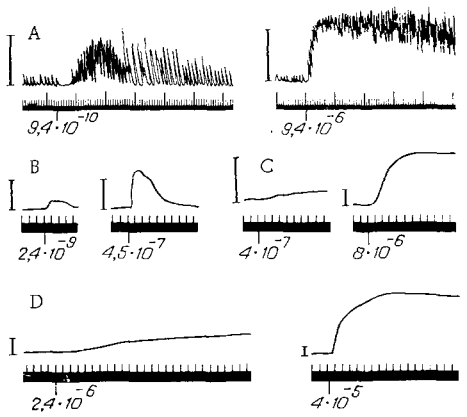

Fig. 1. Effect of bradykinin on rat portal vein (A) and on rabbit jugular vein (B), femoral artery (C), and aorta (D). Calibration 500 mg; time marker 1 min. Numbers near marker of injection (short line running downward) represent bradykinin concentration (in M).

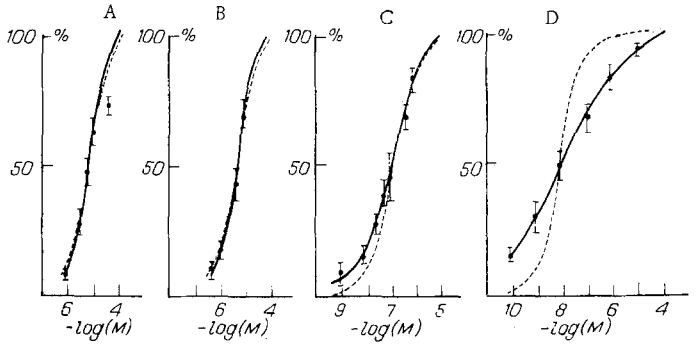

Fig. 2. Dependence of contractile response on bradykinin concentration. A) Rabbit aorta (17 experiments); B) rabbit femoral artery (11 experiments); C) rabbit jugular vein (nine experiments); D) rat portal vein (12 experiments). Theoretical dose–effect curves for bradykinin on test vessels represented by dots. Abscissa, negative logarithm of bradykinin concentration; ordinate, percentage of maximal contractile response.

by a sharp increase in the frequency of spontaneous contractions and by the development of contracture. When contractile activity was reduced the amplitude of phasic contractions was considerably greater than the amplitude of the spontaneous contractions and it gradually recovered irrespective of the presence or absence (after rinsing out) of bradykinin in the solution. By contrast with veins, in which bradykinin caused an unmaintainable tonic contraction, in the arteries a long and maintained contracture was observed.

Graphs showing the action of bradykinin on the test vessels as a function of its concentration are given in Fig. 2. An increase in bradykinin concentration clearly was accompanied by an increase in the contractile response. The dissociation constants of bradykinin for the femoral artery, aorta, jugular vein, and portal vein were $3.98 \cdot 10^{-6}$, $6.3 \cdot 10^{-6}$, $1.26 \cdot 10^{-7}$, and $7.6 \cdot 10^{-9}$ M, respectively, i.e., with respect to their sensitivity to bradykinin the test vessels can be arranged in the following order: rat portal vein > rabbit jugular vein > rabbit femoral artery > rabbit aorta.

For comparison, Figure 2 also shows experimental dose–effect curves and theoretical curves plotted on the basis of the use of experimentally obtained dissociation constants, substituted in Clarke's equation modified by Ariens [8]: $R/R_m = A/(A + K_d)$, where R/R_m is the fraction of the maximal response; A the concentration of the agonist; K_d the dissociation constant. The coincidence of the theoretical and experimental curves, from the standpoint of receptor theory, is proof of monomolecular interaction between agonist and receptor [1, 8].

Complete coincidence of the theoretical and experimental curves for the femoral artery and aorta, slight noncoincidence of these curves within the range of low concentrations for the jugular vein, and considerable divergence of the theoretical curve from the experimental for the portal vein will be clearly seen in Fig. 2.

The results confirm existing data [2, 3, 8] on the presence of specific receptors for bradykinin in the rabbit aorta and jugular vein and they are evidence that bradykinin receptors also are present in blood vessels in other regions, specifically in the rabbit femoral artery and rat portal vein.

Divergence of the experimental and theoretical dose–effect curves for bradykinin obtained for the rat portal vein reflects the complex mechanism of interaction of bradykinin with receptor rather than absence of specificity of the action of bradykinin on the smooth muscle of this vein. The presence of well-marked desensitization of bradykinin-sensitive receptors responsible for pacemaker activation may be a factor leading to noncongruence of the experimental and theoretical curves, for the spike-dependent mechanism of activation of the contractile system of the portal vein is predominant. The phenomenon of desensitization (tachyphylaxis) may also be evidence in support of the existence of receptors for the agonist, for it is evidently based on long-term binding of the substance added with receptors on which bradykinin exerts its action.

The noncongruence of the experimental and theoretical curves, a result of complex interactions between agonist and receptors [1], cannot therefore serve as a basis for rejection of the presence of bradykinin receptors in the portal vein.

The results of this investigation and data in the literature suggest that vessels in different regions have specific receptors for bradykinin. High sensitivity of the smooth muscle of veins to bradykinin, greater than the sensitivity of the smooth muscle of arteries, suggests that the primary pharmacological effects of endogenous bradykinin may develop at the level of the smooth-muscle cells of the veins. Changes in the hemodynamics during liberation of bradykinin may thus be due to its direct action on the smooth-muscle cells of veins and arteries, and also to veno–arterial interrelations.

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