

Bradykinin and Vasoconstriction in the Perfused Rat Liver* (34069)

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Bradykinin, an endogenously generated nonapeptide, has attracted a great deal of interest as a systemic vasodilator and a potent hypotensive agent. Indeed, in the cerebral (1), coronary (2), and renal circulations (3), bradykinin is a vasodilator; in contrast, vasoconstriction occurs in the pulmonary circulation (4), umbilical artery and vein (5), and in forearm arteries and veins (6). This report presents evidence that bradykinin constricts the hepatic vasculature of the isolated perfused rat liver.

Methods. Male rats (250–300 g) of the Holtzman strain were used both as liver and blood donors. Liver perfusion was conducted using a modified Miller-Brauer system as described in detail previously (7). The perfusate was either 75 ml of heparinized, oxygenated rat blood diluted to a hematocrit of 30–35 % or a balanced salt solution (Table I). The perfusion pressure was adjusted for individual preparations between 13–18 cm of water to yield stable flow rates of 26–30

ml/min. Flow measurements were performed through the use of a graduated overflow tube in the caval efflux. Bradykinin triacetate (Sigma Chemical Company, St. Louis, Missouri) was prepared fresh daily in balanced salt solution at a concentration of 50 $\mu\text{g}/\text{ml}$ and diluted as needed. Dilute solutions were markedly unstable. All injections were made directly into the portal vein cannula.

Results and Discussion. As indicated in Fig. 1, bradykinin introduced into livers perfused with homologous rat blood caused up to a 48% decrease in flow. The effect was transient—lasting only 1–2 min—and maximal at 25 μg per liver. Since blood contains a kininase which inactivates bradykinin, further studies were performed in livers perfused with a balanced salt solution. Contrary to expectation, less vascular responsiveness was observed. This diminished effect may reflect the relative hypoxia resulting from perfusion with an erythrocyte-free salt solution; however, bile production, flow stability, histological examination, and liver weights indicated that no deteriorative hepatic changes occurred during 60-min perfusions with oxygenated salt solution.

Tachyphylaxis to the vasoconstrictor response was demonstrated by introducing a test dose of 50 μg bradykinin at 5, 10, 15, and 30 min after an initial vasoconstricting dose of 50 μg . As indicated in Fig. 2, no diminution of flow occurred until 15 min, and maximal constriction reactivity did not return until 30 min. The tachyphylactic behavior of the liver preparation corroborates similar effects in other systems responsive to kinins (4). In all the perfusions, no visible lobular swelling of the liver occurred, which is suggestive of a presinusoidal site of bradykinin action. Since the liver is a site of bra-

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TABLE I. Composition of Balanced Salt Perfusate Media.

Substance	Concentration
NaCl	137.0 mM
KCl	2.68 mM
CaCl ₂	1.80 mM
MgCl ₂ · 6H ₂ O	0.49 mM
NaHCO ₃	11.9 mM
NaH ₂ PO ₄ · 1H ₂ O	0.67 mM
D-glucose	5.45 mM
Penicillin	20 U/ml
Streptomycin	25 $\mu\text{g}/\text{ml}$
pH	7.4

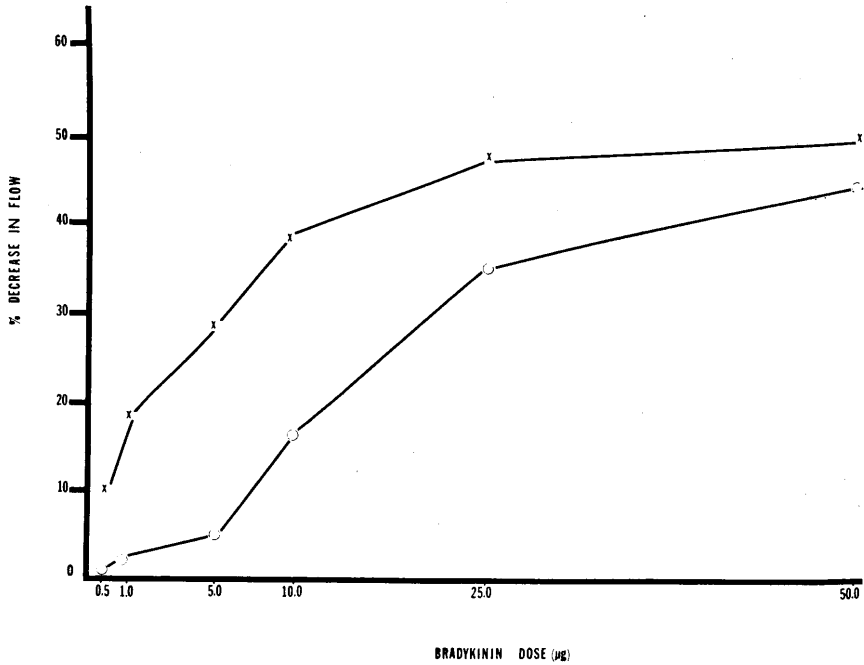


FIG. 1. Effect of bradykinin on flow in the isolated perfused rat liver. Each point represents four separate perfusions. Average standard error was 0.6–1.2 ml/min. Liver perfused with rat blood (X—X); liver perfused with balanced salt solution (O—O).

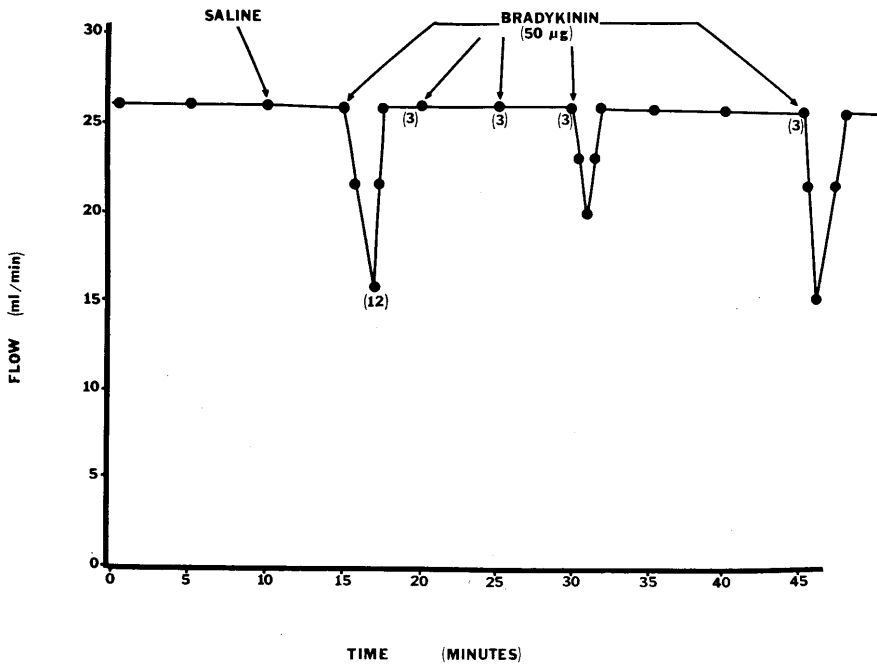


FIG. 2. Tachyphylaxis to bradykinin in the blood-perfused rat liver. Parentheses enclose number of preparations for each point.

dykinin accumulation during infusion (8), it is possible that a hepatic detoxification mechanism exists for the kinin system. Furthermore, since the intestine contains kallikrein, the enzyme which is responsible for kinin generation, perhaps the hepatic vaso-toxic material produced by gut ischemia or shock is a kinin (9).

Summary. Bradykinin administered intraportally produced transient decreases in flow in isolated rat livers perfused at constant pressure with either homologous blood or a balanced salt solution. The minimal effective dose of bradykinin in blood-perfused preparation was 0.5 μg ; maximal effects were achieved with 25.0 μg . Flow decreases induced by bradykinin were greater in blood-perfused livers than in livers perfused with a balanced salt solution. Tachyphylaxis was demonstrated by the inability of a second bradykinin dose to produce prominent effects

until 30 min after an initial vasoconstrictor dose.

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