TRANEXAMIC ACID ENHANCES BRADYKININ INDUCED VENOCONSTRICTION

AKIRA SAKUMA AND SACHIKO OH-ISHI
Department of Pharmacology, Institute for Cardiovascular Diseases,
Tokyo Medical & Dental University, Bunkyo-ku, Tokyo

Received for publication August 8, 1966

Tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid, Transamin), an antifibrinolytic agent potentiated the venoconstriction induced by bradykinin in the perfused saphenous vein in rabbits.

A rabbit was anesthetized with pentobarbital sodium, 30 mg/kg, intravenously, and fixed on its back. The saphenous vein was exposed at the distal and proximal portions about 5 cm apart. A polyethylene tube (PE 60) connected to the perfusion apparatus was inserted into the distal portion, and another tube into the proximal portion for outflow recording. Then the animal was killed by intravenous injection of air. Locke solution was placed in a Mariotte bottle and led to the inflow tube via a thermobath of 40°C. The pressure head was about 30 cm to obtain 50 drops/min of outflow. In order to exclude the leakage of perfusate into small branches, 0.5 ml of 1% licopodium suspension was injected into the inflow tubing about 30 minutes previous to the onset of experiment. Drug solution, usually 0.2 ml, was injected into the inflow tubing at a rate of 0.1 ml/5 sec. Dye injection indicated that the dye appeared in the outflow drops in 10 seconds, reached a peak concentration in 30 to 60 seconds, and nearly disappeared in 8 minutes. The effect of drug was recorded with a drop counter. The decreased outflow or venoconstriction increased the height of tracing in an exponential fashion and vice versa.

Bradykinin, 0.01 to 0.2 µg, depending on the preparation, produced a moderate venoconstriction, the outflow being reduced by about 50%. The simultaneous injection of tranexamic acid, 250 to 500 µg, definitely enhanced the venocon-
stricting action of bradykinin as shown in Fig. 1, the outflow being reduced by about 70% or more. A similar potentiation was observed when the perfusate had been changed to that containing tranexamic acid, 100 to 200 μg/ml, 5 minutes before the injection of bradykinin.

Tranexamic acid per se caused no significant changes in the outflow. It lacked obvious effects on the venoconstriction produced by histamine, 0.2 to 2 μg. A mixed preparation containing tranexamic acid and its cis-isomer in 1 : 3 also exhibited a similar potency in enhancing bradykinin effect. This finding is not consistent with an explanation that the potentiation is directly connected with the antifibrinolytic activity, since the cis-isomer had been reported to be a very weak antifibrinolytic agent (1). Detailed analyses are under way in order to specify the action of tranexamic acid.

REFERENCE


INTERACTION BETWEEN KININ RELEASING ENZYMES AND THE SYNTHESIZED Bradykinin DERivATIVES*

KENJI SUZUKI, KENICHI SASAKI AND TSUTOMU KAMEYAMA

Department of Chemical Pharmacology and Department of Biochemistry,
Tohoku College of Pharmacy, Sendai

Received for publication August 16, 1966

Methionyllysyl-, lysyl- and bradykinin are produced from serum bradykininogen by the action of kinin releasing enzymes, i.e. trypsin, certain snake venoms, or kallikreins. Bovine serum bradykininogen have been isolated in pure form and the action of bradykinin releasing enzymes on the bradykininogen have liberated kinins (1, 2). The amino acid sequence being adjacent to the C-terminus arginine of methionyl-lysylbradykinin moiety in bovine bradykininogen have been elucidated as follows: Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-Ser-Val-Glu(NH$_2$), and synthesized bradykininyl-Ser have been shown to be applicable for synthetic bradykininogen (3).

In the present communication, the bradykininogen-like characters of synthesized Gly-Gly-Lys-6-0-acetyl-Ser-bradykinin, 6-0-acetyl-Ser-bradykinin-Gly-Val-Glu(NH$_2$), and bradykininyl-Gly** have been identified by a combination of thin-layer chromatography and biological testing.

Enzymatic digestion of the synthesized bradykinin derivatives was carried out according to the directions given by Suzuki et al. (1). The incubation mixture contained the synthesized bradykinin derivatives (0.1~0.5 μ moles), enzyme solution (0.1 ml), and 0.05 M ammonium formate (pH 8.0) (0.3 ml) in total volume of 0.6 ml. Ten μg of crystalline trypsin*** [EC 3.4.4.4], and 20 μg of hog pancreatic kallikrein [EC 3.4.4.21] (100 units per mg) were used respectively. Hog pancreatic kallikrein solution was heated for 3 minutes in a boiling water bath to inactivate some contaminated kininase just

鈴木 謙次・佐々木 健一・亀山 勉


** Synthesis of these peptides will be reported in separate paper.

*** Trypsin was purchased from Nutritional Biochemicals Co. Lot 4655.