Biochemical Pharmacology, Vol. 32, No. 17, pp. 2637–2638, 1983.
Printed in Great Britain.

0006-2952/83 $3.00 + 0.00

PHARMACOLOGICAL PROPERTIES OF T-KININ (ISOLEUCYL-SERYL-BRADYKININ) FROM RAT PLASMA

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(Received 18 April 1983; accepted 7 June 1983)

It is well known that trypsin liberates bradykinin from plasma. Recently we reported that, in addition to bradykinin, trypsin liberated from rat plasma isoleucyl-seryl-bradykinin which we termed "T-kinin" (1-3). T-kinin is a unique natural homolog of bradykinin because it does not contain the lysyl-bradykinin sequence which the known homologs from bovine (4), human (5), and horse (6) plasmas contain. In this communication we describe for the first time the pharmacological actions of T-kinin on the isolated guinea pig ileum, estrus rat uterus, and on the blood pressure of the rat.

MATERIALS AND METHODS

T-kinin was purified to homogeneity from trypsin-treated rat plasma by previously described procedures (3). Synthetic bradykinin and Met-Lys-bradykinin were from Peninsula Laboratories (San Carlos, CA).

For bioassay, the rat uterus and guinea pig ileum were suspended in a 5 ml tissue bath and bathed in de Jalon's (rat uterus) or Tyrode's (guinea pig ileum) solution containing 1 μg/ml of atropine sulfate and 1 μg/ml of diphenhydramine-HCl. The bathing solution was bubbled continuously with 95% oxygen and 5% carbon dioxide. The temperatures of the solutions were kept at 24° for the rat uterus and at 35° for the guinea pig ileum. The rat uterus in estrus was prepared by injecting virgin rats weighing 200-250 g with 100 μg diethylstilbestrol 18 hr before sacrifice. Each muscle was placed under 1 g of tension until a stable baseline was obtained. Increase in tension was recorded by a Grass model 7 polygraph using a Grass force-displacement transducer with no spring load (7).

Blood pressure was recorded from the carotid artery of male Sprague-Dawley rats (300-350 g) anesthetized with ketamine-HCl (150 mg/kg, i.p.) by means of a Statham pressure transducer and a Beckman model R 612 polygraph. Kinins were dissolved in saline and injected into the jugular vein in a volume of 0.3 ml. Baseline blood pressure ranged between 125 and 140 mm Hg.

RESULTS AND DISCUSSION

As seen in Table 1, T-kinin contracted the rat uterus and the guinea pig ileum but was 1.3 and 2.5 times, respectively, less active than bradykinin. In terms of depression of rat blood pressure, the dose-response curves seen in Fig. 1 demonstrate that T-kinin was more potent than bradykinin but less potent than Met-Lys-bradykinin. For example, to decrease the blood pressure 30 mm Hg, doses of 0.48, 0.69, and 1.7 nmoles of Met-Lys-bradykinin, T-kinin and bradykinin, respectively, were required.

Homologs of bradykinin such as Met-Lys-bradykinin are known to be more resistant to converting enzyme degradation during pulmonary passage (8). The enhanced potency of T-kinin in blood pressure depression may be due to similar resistance to converting enzyme.

The confirmation of the pharmacological activity of T-kinin along with the possibility that it is released by trypsin-like proteases and circulates in the blood of the rat and/or other species makes T-kinin a potential endogenous vasoactive mediator. Studies are continuing to determine its role in this regard in the rat and other species.

Table 1. Contracting activity of T-kinin on rat uterus and guinea pig ileum as compared to bradykinin *

	Bradykinin	T-kinin
Rat uterus	0.15 ± 0.03	0.19 ± 0.04
Guinea pig ileum	17 ± 2	46 ± 3

*Values (the mean ± S.E.M., N = 5) represent picomoles of peptides which caused a change in tension of 1 g in a 5 ml bath.

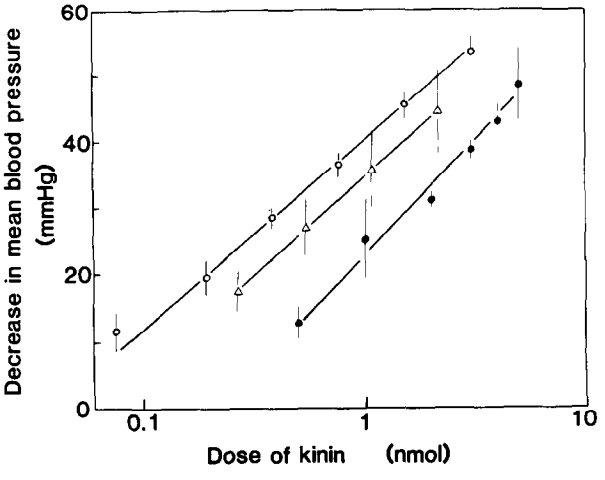

Fig.1. Dose response curves of T-kinin in decreasing the mean blood pressure of rats. Values are the mean ± S.E.M. Bradykinin (N = 5) (—●—), Met-Lys-bradykinin (N = 5) (—○—) and T-kinin (N = 4) (—△—) were injected into jugular veins of rats anesthetized with ketamine-HCl (150 mg/kg, i.p.). The mean blood pressure was recorded from the carotid artery.

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