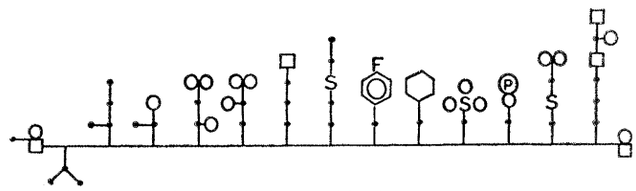

Fig. 3. Symbols for several amino acids not commonly found in proteins: *N*-acetyl-D-valine, and the L-isomers of alloisoleucine, allothreonine, erythro-β-hydroxyglutamic acid, threo-γ-hydroxyglutamic acid, ornithine, ethionine, *p*-fluorophenylalanine, cyclohexylalanine, cysteic acid, phosphoserine, *S*-carboxymethyl-cysteine, citrulline amide.

bols for amino acid residues meaningful in chemical terms, they are immediately and universally understandable, and it becomes easier to think of proteins represented in this manner in terms of the interactions between the side chains of the molecule. The proposed system can be readily adapted to the description of new amino acids as they are discovered, and to new amino acid modifications as further progress is made in the field of protein chemistry.

Note added in proof: The potential usefulness of this system has become apparent in discussions with various investigators who have already used shorthand symbols for amino acid residues in informal research conferences and as an aid in teaching [see, for example, G. H. Haggis, Ed., *Introduction to Molecular Biology* (Wiley, New York, 1964), p. 38].

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1 December 1965

Bradykinin: Effect on Ureteral Peristalsis

Abstract. *Bradykinin, a known smooth-muscle stimulant, affects ureteral peristalsis in the dog; the changes were judged by cinefluorography, peristaltic pressures, and ureteral perfusions. No effect on urine flow was detected. Experiments with rats also demonstrated the effect of the drug on the ureter.*

There are few drugs that have ureteral action. Histamine, the antihistamines, serotonin, and now, bradykinin are effective (*1, 2*). Reserpine is not effective even though significant amounts of catecholamine are found in dog and human ureters (*3*).

Bradykinin, a polypeptide, is formed from the α-globulin of plasma by the enzyme kallikrein and can be formed by proteolytic enzymes of snake venom (*4, 5*). Bradykinin has several effects: stimulation of smooth muscle, vasodilation, increasing capillary permeability, stimulation of leucocyte migration, and production of pain (*6, 7*). It has been suggested to be an active agent in inflammation, allergy, pruritus, dermatitis, the pain of migraine and intermittent claudication, and other disorders (*4*). The substance has been synthesized successfully (*8*); we used synthetic bradykinin.

Experiments were performed in dogs to determine the effect of bradykinin on ureteral pressures, each consisting of a control experiment followed by the administration of several doses of bradykinin at suitable intervals. In two of the experiments, seven different graded doses were given, while in one a continuous infusion was given for 10 minutes. Peristalsis was allowed to return to the frequency, amplitude, and wave form of the control before a subsequent dose was administered. Five experiments were performed under simultaneous cinefluorographic observation. The intravenous dosage ranged between 0.25 μg and 10.5 μg per kilogram of body weight. The threshold intravenous dose was 0.25 to 0.50 μg/kg. In one experiment, a continuous intravenous infusion of 2.8 μg/kg per minute for 10 minutes produced a continuous effect.

In general, there was an increased frequency of peristalsis within 15 seconds after administration. When the doses were higher, the onset was noted within 10 to 12 seconds (see Fig. 1).

The base line of intraluminal resting pressure tended to rise with the larger doses. Frequencies of 11 to 16 peristaltic contractions per minute were recorded; the frequencies in controls had ranged between 3 and 8 per minute. The duration of effect varied from 30 seconds to 2 minutes. Subsequently, there was a period of inactivity lasting 1 to 3 minutes during which occasional, slightly irregular peristalsis was noted. Complete recovery occurred between the 10th and 20th minutes.

Whatever doubt may have arisen about the real nature of an effect of bradykinin on the ureter during the studies of peristaltic pressure was removed by the changes in peristalsis observed cinefluorographically. Four intact unoperated animals were observed in five experiments, and four animals with bladder explants were observed in five experiments under cinefluorography in the course of our study of their peristaltic pressures. Two dogs with bladder explants were observed in the absence of catheters, and two dogs with ureteral stenoses and three with transureteroureterostomy were also observed.

The dosage varied between 2.6 and 30 μg/kg. Peristaltic frequency generally increased for a period of 30 to 60 seconds during which time the bolus diminished in size and the ureter emptied itself more or less completely. The intensity and duration of this effect were dose dependent. There was then a gradual lessening of peristaltic hyperactivity with dilatation of the system and with the ureter filled so as to outline the calyces and the renal pelvis. The effect sometimes lasted into the 5th minute, though often it was over in the 2nd minute. Occasionally a peristaltic block, retrograde waves, ineffective peristalsis, or complete inactivity were noted in the ureters that were abnormal or operated upon. In the recovery period, occasional dyskinetic peristalsis was noted as late as 10 to 35 minutes. During some experiments, filling seemed to be temporarily greater than it had been during the control period. In one experiment in which bradykinin and histamine were administered one after the other, the effect was greater than that seen after each drug was used singly.

Bradykinin did not change the urine flow of the animals with bladder explants. In one experiment, the urine flow in a dehydrated dog was measured

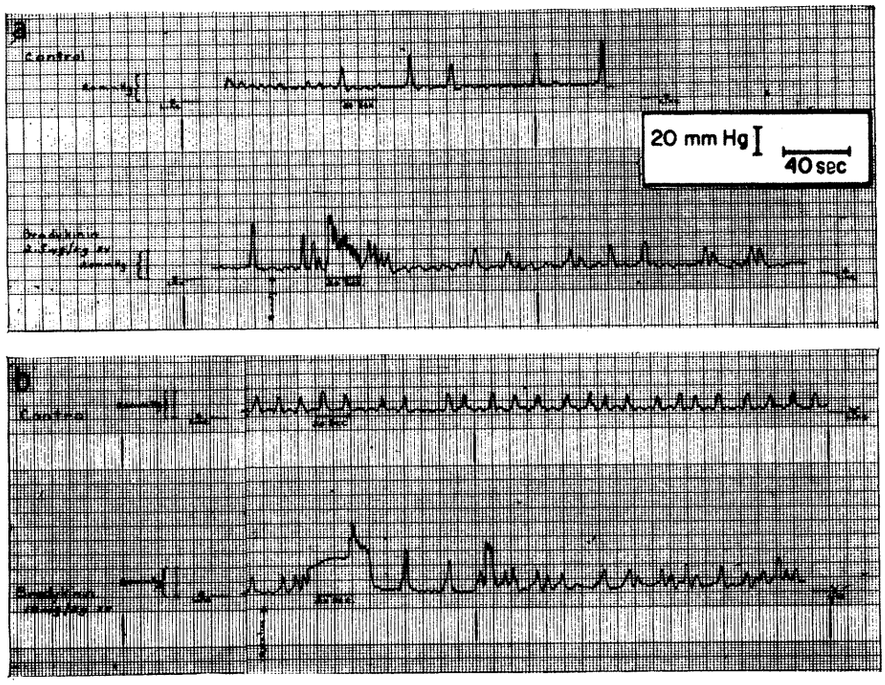

Fig. 1. The effect of bradykinin on ureteral peristaltic pressures in dog with explanted bladder: (*a*) 2.5 μg/kg intravenously; (*b*) 10 μg/kg intravenously.

at intervals of 1 minute for the first 5 minutes and during the 12th and 17th minute after the administration of an estimated 2.5, 5.0, and 10.0 μg/kg. There was significant diuresis or antidiuresis. In all the ureters the urine flow was between 0.05 and 0.30 ml per minute.

The effect of bradykinin upon ureteral perfusion was similar to that of histamine or serotonin. In two experiments on one dog, the rate of flow by ureter from a reservoir 14 and 30 cm above the renal pelvis was depressed from 24 drops per minute to 7 and 8 drops per minute after the administration of 1.4 μg/kg of bradykinin. The effect lasted 2 minutes after the first dose and slightly longer after the second dose.

Two rats (200 g) were anesthetized with ether, and the abdominal cavity was opened. The animals were given 25 or 50 μg of bradykinin per kilogram of body weight. Frequency of ureteral peristalsis increased for 2 to 4 minutes. After the largest dose (100 μg/kg), ureteral contractions occurred that were unaccompanied by a urinary bolus. With larger doses dyskinesias, with to-and-fro peristalsis and irregularities of peristalsis, appeared for a short period.

Bradykinin can be grouped with histamine and serotonin as a ureteral stimulant. Certain antihistamines in large doses act as weak histamine agonists, stimulating the ureter (*2*). Histamine, serotonin, and bradykinin have all been implicated in the cellular response to injury, inflammation, or allergy and all three have potent extracellular antagonists (*6*).

The enzymatic destruction of bradykinin explains its evanescent effect (*9*). Discovery of the ureteral activity by bradykinin sheds light on ureteral contractility by demonstrating that a nonapeptide is active.

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Cyclopentanoid Terpene Biosynthesis in a Phasmid Insect and in Catmint

Abstract. *The stick insect,* Anisomorpha buprestoides, *and the catmint,* Nepeta cataria, *produce closely related cyclopentanoid terpenes, anisomorphal and nepetalactone. Tracer experiments with isotopes indicate that anisomorphal is synthesized by the walking stick from normal terpene precursors (acetate or mevalonate). In the catmint plant, isolated leaf disks synthesized nepetalactone, utilizing the same precursors.*

Cyclopentanoid monoterpenes have been found in both plants and animals (*1*). Although not a very large group of compounds, they are beginning to attract increased attention (*2*). A monocyclic representative of this group, anisomorphal (I) (*3*), has recently been shown to serve a defensive function in the Southern walking stick, *Anisomorpha buprestoides* (*4*). The best studied of these compounds is nepetalactone (II) (*5*), long known for its bizarre effect on feline behavior (*6*), and recently shown to have a possible protective role for the catmint which produces it (*7*). We have been interested in the general question of the origin of repellent compounds in the defensive secretions of arthropods and have recently reported on the biosynthesis of two acyclic terpenes, citronellal (III) and citral (IV), in an ant (*8*). Plausible ionic (*9*) and photochemical (*10*) pathways have been suggested for forming cyclopentanoid terpenes from acyclic precursors such as III and IV; we now report exploratory biosynthetic experiments for the insect terpene I, along with parallel results for nepetalactone, II (*11*).