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The action of ranatensin, a new polypeptide from amphibian skin, on the blood pressure of experimental animals

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Summary

1. The blood pressure response to ranatensin, an undecapeptide from the skin of the frog, *Rana pipiens*, has been studied in various experimental animals.

2. Ranatensin raised blood pressure in the dog and rabbit. The response was not altered by atropine, phentolamine, propranolol or hexamethonium, suggesting a direct peripheral vasoconstrictor action. In both animals ranatensin was about one-tenth as potent as angiotensin. Tachyphylaxis to ranatensin did occur, but there was no cross-tachyphylaxis with angiotensin, bradykinin, or noradrenaline.

3. The peptide lowered blood pressure in the monkey, being as potent as eledoisin. The response was not altered by atropine, phentolamine, propranolol, tripelennamine, tetraethylammonium, bretylium, or methysergide. This again suggests a direct peripheral action on vascular smooth muscle. There was no tachyphylaxis to the depressor action, nor was there cross-tachyphylaxis with angiotensin, eledoisin, bradykinin, or noradrenaline.

4. Ranatensin did not alter the blood pressure in cats and had a variable action in the guinea-pig with a rapid onset of tachyphylaxis.

5. Ranatensin has a variable effect on the blood pressure in the rat that is related to the basal level of blood pressure. When the blood pressure is high, the response to the peptide is hypotension. Ranatensin raises blood pressure in the rat when the basal blood pressure is low. The pressor response to ranatensin appears to be due, in part, to the release of noradrenaline from peripheral sympathetic nerve endings.

6. The composite action of ranatensin on blood pressure of various experimental animals is unlike that of any other peptide. Its hypertensive action in the dog or rabbit, together with a potent hypotensive action in the monkey, readily distinguishes it from all other vasoactive peptides.

Introduction

Amphibian skin is an extremely rich source of hypotensive peptides including bradykinin (Rocha e Silva, Beraldo, & Rosenfeld, 1949 ; Sturmer & Cerletti, 1961 ; Schröder & Hempel, 1964 ; Anastasi, Erspamer & Bertaccini, 1965), phyllokinin (Anastasi, Bertaccini & Erspamer, 1966), caerulein (De Caro, Endean, Erspamer &

Roseghini, 1968; Bertaccini, De Caro, Endean, Erspamer & Impicciatore, 1968), phyllocaerulein (Anastasi, Bertaccini, Cei, De Caro, Erspamer & Impicciatore, 1969), and physalaemin (Bertaccini, Cei & Erspamer, 1965a, 1965b). Eledoisin, another hypotensive peptide, structurally related to physalaemin, has been isolated from the posterior salivary glands of the *Eledone* (Erspamer & Anastasi, 1962; Anastasi & Erspamer, 1962; Erspamer & Glaesser, 1963; De Caro, Farruggia, Minardi & Novarini, 1966).

Recently, another peptide was isolated from the skin of the frog, *Rana pipiens* (Nakajima, Tanimura & Pisano, 1970). This new peptide, ranatensin, is an undecapeptide with the amino-acid sequence Pyr-Val-Pro-Gln-Trp-Ala-Val-Gly-His-Phe-Met.NH_2 (molecular weight=1280). It bears some structural similarity to eledoisin and physalaemin, having the same total number of amino-acids and the same terminal groups. However, the remainder of the structure is unlike that of any other known peptide.

The actions of ranatensin on various isolated smooth muscle preparations were described previously (Geller, Govier, Louis & Clineschmidt, 1970; Clineschmidt, Geller, Govier, Pisano & Tanimura, 1971). In the present study we report the actions of ranatensin on the blood pressure and heart rate of various laboratory animals.

Methods

Mongrel dogs (15–22 kg) and New Zealand white rabbits (1–3 kg) were anaesthetized with sodium pentobarbital, 30 mg/kg, intravenously; cats (2·5 kg) and Hartley guinea-pigs with 30 mg/kg intraperitoneally; Sprague-Dawley rats with 30–45 mg/kg, intraperitoneally, or with chloralose, 100 mg/kg, intravenously; and rhesus monkeys (3–5 kg) with sodium pentobarbital (30 mg/kg, intravenously) or phencyclidine hydrochloride, 1·5 mg/kg, intravenously.

In all species, systemic arterial pressure was measured from a cannulated femoral artery using a Statham P23Db transducer and recorded on a Hewlett-Packard oscillograph. (1 mmHg≡1·333 mbar.) The electrocardiograph was recorded using lead II in all animals. Heart rate was recorded simultaneously using a Waters Corporation cardiotachometer. In some animals, central venous pressure was measured by inserting a polyethylene catheter into the right jugular vein and positioning it near the heart. Surgically prepared rats (adrenalectomized or adrenaldemedullated) were obtained from Zivic-Miller, Philadelphia, Pa.

Drugs

In each species, it was found that synthetic ranatensin, prepared by this laboratory, had the same qualitative and quantitative activity as the naturally occurring peptide. Because of the limited amount of the natural peptide, the synthetic peptide was used in most studies. Ranatensin was dissolved in 0·9% saline to concentrations of 10–50 μg/ml. All injections of the peptide were made into a cannulated femoral vein in volumes of 0·005–0·1 ml in rats and guinea-pigs and 0·1–1 ml in the other animals. A small volume of saline was used to flush the peptide through the catheter and into the animal. Other peptides used in this study were: eledoisin (synthetic eledoisin was kindly provided by Dr. E. Schröder and Dr. K. Lubke), bradykinin (Sandoz), and angiotensin II-amide (Hypertensin—Ciba).

The following drugs and their respective doses (calculated as the salt) were also used: phentolamine hydrochloride (Regitine), 1–10 mg/kg; phenoxybenzamine hydrochloride (Dibenzyline), 1–10 mg/kg; atropine sulphate, 0·2–1 mg/kg; propranolol hydrochloride (Inderal), 1–5 mg/kg; tetraethylammonium chloride (Etamon), 5–10 mg/kg; hexamethonium bromide, 5–10 mg/kg; lidocaine (Xylocaine), 1–5 mg/kg; bretylium tosylate (Darenthin), 5 mg/kg; tripelennamine hydrochloride (Pyribenzamine), 5–7·5 mg/kg; methysergide maleate (Sansert), 2 mg/kg; reserpine (Serpasil), 5–7·5 mg/kg; guanethidine sulphate (Ismelin), 5 mg/kg; noradrenaline (L-arterenol bitartrate), 0·1–1 μg/kg; and tyramine hydrochloride, 0·5 mg/kg. All drugs were given intravenously unless otherwise indicated.

In preliminary experiments in both dogs and rabbits, it was found that some degree of tachyphylaxis to ranatensin always developed. Therefore, in each dog and rabbit, only the first blood pressure response to ranatensin was used to construct the dose response curves presented in the **Results** section. The curves to both ranatensin and angiotensin were constructed from responses obtained in the same group of animals. Each point on the ranatensin curve represents the average of two or three responses, each being the initial response to ranatensin obtained from a different animal. Several different doses of angiotensin could be given to the same animal with no tachyphylaxis occurring. Points on the angiotensin curve also represent the average of two or three responses from several different animals. In addition to determining dose-response curves to ranatensin and angiotensin, their relative potencies were also compared in every experiment by ascertaining the dose of angiotensin required to produce a change in blood pressure equal to that produced by the first response to ranatensin. In some cases the sequence of drug administration was reversed using the dose relationships established in earlier experiments.

The statistical significance of results described below was analysed by the Student's *t* test.

Results

Dog

Ranatensin, like angiotensin, raises the blood pressure in dogs with the threshold dose for both peptides being about 0·05 μg/kg. The blood pressure response to ranatensin, however, is of longer duration than to angiotensin. Typical blood pressure responses to two doses of ranatensin (in two different animals) and doses of angiotensin to produce an approximately equivalent rise in blood pressure are shown in Fig. 1. Blocking agents such as atropine, phentolamine, phenoxybenzamine, propranolol, or guanethidine did not alter the pressor response to ranatensin. Average dose-response curves to both peptides are presented in Fig. 2. Some degree of tachyphylaxis to ranatensin was noted. For this reason, the dose-response curve to ranatensin was, as previously noted in the **Methods** section, constructed using only the first response to the peptide in each animal. The degree of tachyphylaxis to ranatensin varied from animal to animal. The onset occurred as early as the second dose of ranatensin, 15 min after the first response, or as late as 2 h, after five responses had been obtained. There was no cross-tachyphylaxis with single injections of angiotensin or bradykinin regardless of the sequence of drug administration. Even when there was no longer any response to ranatensin, the responses to several doses of the other peptides were still the same as at the

beginning of the experiment. The pressor response to noradrenaline (0·5 and 1 μg/kg, intravenously) was not affected by previous administration of ranatensin or by the onset of ranatensin tachyphylaxis.

A slight decrease in heart rate (10–20 beats/min) was usually associated with the blood pressure response to ranatensin. This effect was blocked by atropine or vagotomy. There was no change in any component of the electrocardiograph (lead II) following the administration of ranatensin. Central venous pressure was recorded in three dogs. The venous pressure level (0–1 mmHg) was unchanged by any dose of ranatensin.

Rabbit

Ranatensin also raises the blood pressure in rabbits and, as in the dog, is less potent than angiotensin in this respect. The threshold dose of ranatensin was about

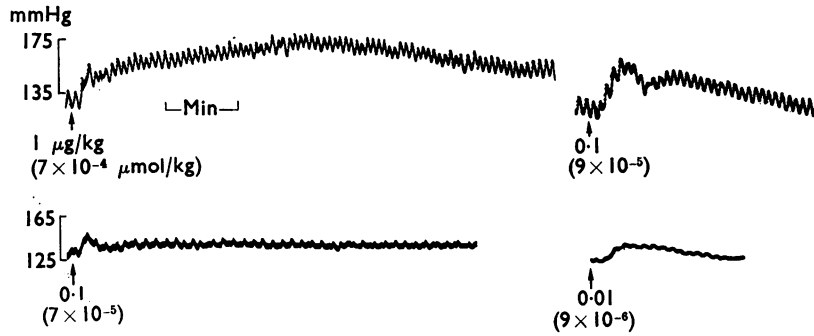

FIG. 1. Changes in mean blood pressure to ranatensin and angiotensin in two dogs anaesthetized with sodium pentobarbital. Upper panel: Responses to 1 μg/kg ranatensin (left) and 0·1 μg/kg angiotensin (right) in one dog. Lower panel: Responses to 0·1 μg/kg ranatensin (left) and 0·01 μg/kg angiotensin (right) in another dog. Dose expressed as μmol/kg is indicated in parentheses.

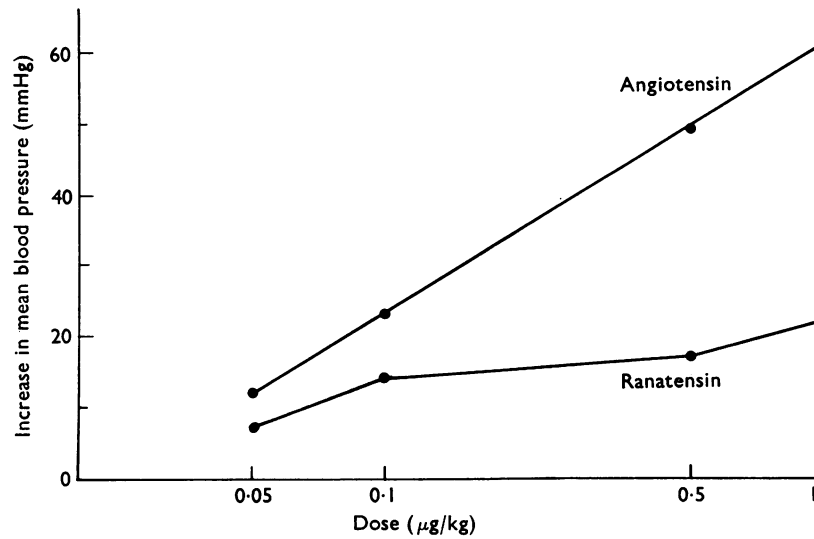

FIG. 2. Log dose response curves to ranatensin and angiotensin in dogs. Each point represents the average of two or three responses.

0·5 μg/kg and for angiotensin 0·025–0·05 μg/kg in the same animals. Doses of ranatensin and angiotensin that produced the same change in blood pressure also had the same duration of action. A dose of between 0·2–0·5 μg/kg angiotensin usually produced a response comparable to 5 μg/kg ranatensin, tested in the same animals. Average dose response curves are shown in Fig. 3.

Blocking agents such as atropine, phentolamine, hexamethonium, propranolol and lidocaine did not alter the blood pressure response to ranatensin. The rise in blood pressure to ranatensin was again associated with a slight decrease in heart rate which was blocked by atropine. There was no change in the pattern of the Lead II e.c.g. during any blood pressure response to ranatensin.

As in the dog, some degree of tachyphylaxis to ranatensin did develop after repeated doses of the peptide. The onset was variable from animal to animal, but eventually occurred in all rabbits. After the development of tachyphylaxis to ranatensin, single injections of angiotensin or bradykinin produced their normal response.

Monkey

Ranatensin lowers the blood pressure in monkeys being as potent as eledoisin in this regard. The threshold dose for both ranatensin and eledoisin ranged between 0·0025–0·009 μg/kg. Representative responses to both peptides in the same monkey are shown in Fig. 4. Both the magnitude and the duration of the responses are comparable. The blood pressure response to ranatensin was not altered by propranolol, atropine, tripelennamine, phentolamine, phenoxybenzamine, tetraethyl-

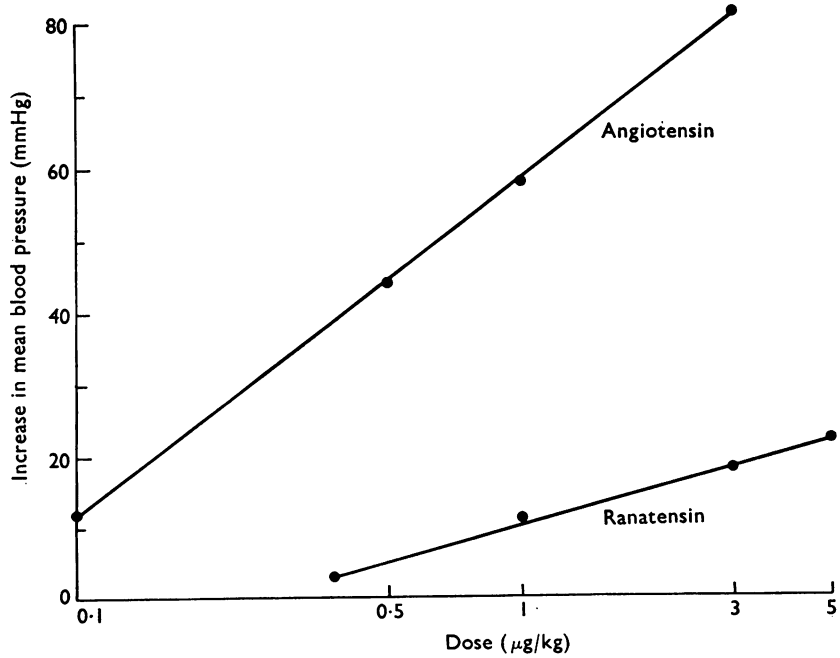

FIG. 3. Log dose response curves to ranatensin and angiotensin in rabbits. Each point represents the average of two or three responses.

ammonium, bretylium or methysergide. Propranolol blocked the increase in heart rate that always accompanied the hypotensive action of ranatensin.

There was no tachyphylaxis to the response to various doses of ranatensin (0·025–0.25 μg/kg) over a 4 h period, nor to a single dose (0·1 μg/kg) given at 5 min intervals during a 20 min period. Prior administration of ranatensin did not alter the responses to eledoisin, angiotensin, bradykinin, or noradrenaline. Similarly, the response to ranatensin was not altered by prior administration of these drugs. Ranatensin was able to exert a hypotensive action even when the blood pressure was as low as 50 mmHg.

Rat

Ranatensin had a variable effect on the blood pressure in the rat anaesthetized with chloralose or pentobarbital, which is related to the basal level of blood pressure. An initial hypotensive response to ranatensin was seen in two groups of animals, having average mean blood pressures of 135 and 126 mmHg (Table 1, groups 1 and 2). Ranatensin (1 μg/kg) lowered the blood pressure an average of 25 and 18 mmHg respectively in these two groups of animals. However, ranatensin raised blood pressure an average of 36 mmHg in another group of rats having an average mean pressure of 85 mmHg (group 3). A clear hypo- or hypertensive action of ranatensin occurred evenly in about 90% of the animals. A biphasic response, consisting of an initial depressor, followed by a pressor component, was seen in the others. Although the initial response to ranatensin is, in most cases, related to the basal level of blood pressure, some hypertensive responses have occurred when the pressure was high and some hypotensive responses have occurred when the pressure was low. The threshold dose for any blood pressure response was between 0·1 0·5 μg/kg. No clear dose-response relationship could be determined for either the hypertensive or hypotensive action of the peptide. As indicated

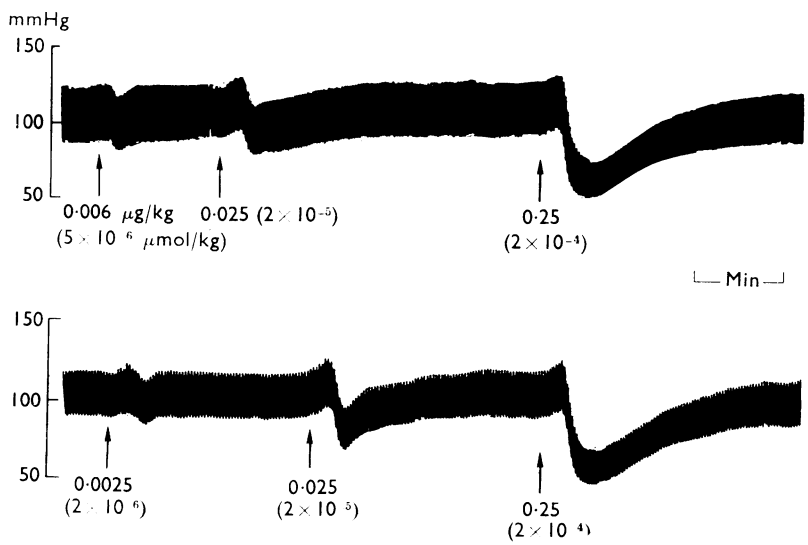

FIG. 4. Continuous recording of blood pressure responses to several doses of ranatensin (upper panel) and eledoisin (lower panel) in one monkey (2·5 kg) anaesthetized with sodium pentobarbital. Dose expressed as μmol/kg is indicated in parentheses.

in Table 1, 1 μg/kg of ranatensin could lower pressure by 5–50 mmHg (groups 1 and 2, control) or raise pressure 5 to 65 mmHg (group 3, control). Because of this variability of the action of ranatensin, comparisons of potencies relative to other peptides could not be made.

The initial hypotensive response to ranatensin in rats having a higher basal blood pressure could be converted to a hypertensive response by lowering the blood pressure. This was observed after the administration of the beta-receptor blocker propranolol (Table 1 and Fig. 5) or after hexamethonium, a ganglionic blocking agent (Table 1). A pressor response to ranatensin could also be seen after the blood pressure was lowered using pronethalol, pentolinium bitartrate, tetraethylammonium chloride, or lidocaine.

In untreated rats having an initial low blood pressure, ranatensin raised blood pressure. The pressor response, seen initially or after chemically lowering the blood pressure, was significantly ($P<0.01$) reduced or converted to a depressor response by administering the alpha-blocking agent, phentolamine. This effect of phentolamine is shown in Figs. 5 and 6, and the results are summarized in Table 1. Phenoxybenzamine was also able to reduce or eliminate ranatensin induced pressor responses. Atropine, tripelennamine, diphenhydramine or methysergide, did not affect either the hypo- or hypertensive actions of ranatensin.

Studies in adrenalectomized rats

In rats bilaterally adrenalectomized, the initial response to ranatensin was again related to the basal blood pressure level. In five animals having an average pressure of 119 mmHg, ranatensin (1 μg/kg) decreased pressure an average of 15 mmHg

TABLE 1. *Changes in rat mean blood pressure* ±S.E.M. *in response to* 1 μg/kg *ranatensin*

	Treatment	Basal mean blood pressure (mmHg)	Δ Mean blood pressure (mmHg) to 1 μg/kg ranatensin
Group 1 (n=10)*	Control	135±2 (120 to 145)†	−25±4 (−6 to −50)
	Propranolol	94±6 (53 to 130)	+34±5 (+5 to +87)
	Propranolol + Phentolamine	85+6 (45 to 108)	+5±2 (−14 to +13)
Group 2 (n=12)	Control	126±6 (85 to 145)	−18±7 (−5 to −50)
	Hexamethonium	79±4 (50 to 115)	+25±3 (+5 to +40)
	Hexamethonium + Phentolamine	70±5 (40 to 100)	+5±4 (−5 to +10)
Group 3 (n=15)	Control	85±5 (55 to 145)	+36±4 (+5 to +65)
	Phentolamine	73±4 (47 to 117)	+3±3 (−22 to +25)
Group 4 (n=15)	Reserpine pretreatment	74+3 (45 to 97)	24±2 (+10 to +40)
	Phentolamine	78±3 (55 to 105)	−4±4 (−30 to +10)

* Number of animals.
† Range indicated in parentheses.

(range= −8 to −30). In eight animals having a lower average pressure of 85 mmHg, the peptide raised the pressure by about 38 mmHg (range 20–70). Propranolol, hexamethonium, and phentolamine had the same effect on the blood pressure response to ranatensin in the adrenalectomized animals as in the intact animals. Similar effects of ranatensin were also obtained in bilaterally adrenal-demedullated rats. The responses shown in Fig. 6 were obtained in adrenal-ectomized rats.

Studies in reserpine pretreated rats

Fifteen rats were pretreated 24 h earlier with reserpine (5–7·5 mg/kg, intra-peritoneally). The blood pressure and heart rate response to a test dose of tyramine were used as a measure of the effectiveness of reserpine treatment. In three control rats, 0·5 mg/kg tyramine (three responses/animal) raised blood pressure 65 ± 2 mmHg and increased heart rate 81 ± 4 beats/min. In the reserpinized rats, this dose raised pressure by 18 ± 3 mmHg and increased heart rate 14 ± 5 beats/minute.

In reserpinized rats, 1 μg/kg ranatensin raised blood pressure 10 to 40 mmHg (average=24) and phentolamine significantly reduced ($P<0{\cdot}01$) this pressor action (Table 1, group 4). The pressor response in reserpinized rats was significantly smaller ($P<0{\cdot}01$) than the initial pressor response seen in nontreated animals

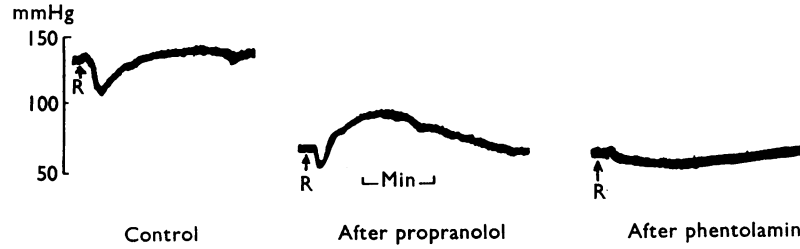

FIG. 5. Changes in mean blood pressure in one rat to 1 μg/kg ranatensin (at R) during a control period, after propranolol (3 mg/kg), and after the propranolol plus phentolamine (10 mg/kg). Responses are separated by 5 min.

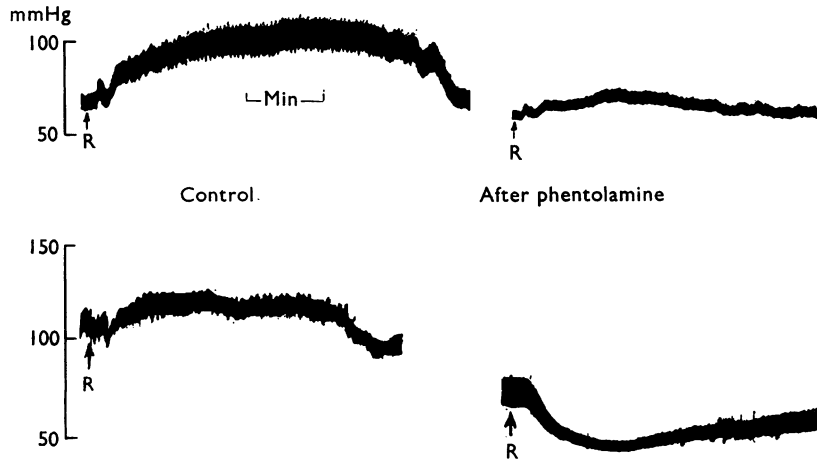

FIG. 6. Changes in mean blood pressure in two rats (upper and lower panels) to 1 μg/kg ranatensin before and after 10 mg/kg phentolamine.

(group 3) having about the same basal blood pressure. It was also smaller than the pressor response seen after propranolol (group 1), but is not different from the pressor response obtained after hexamethonium.

Tachyphylaxis to ranatensin

In general, there was no tachyphylaxis to the hypotensive action of ranatensin. The test dose, 1 μg/kg, could be given at 5–10 min intervals without seeing a progressive decrease in the depressor action. The variability of the depressor response, however, has already been noted. Moderate tachyphylaxis to the pressor action of ranatensin was occasionally observed. It was more frequently seen at the beginning of an experiment than after treatment with propranolol or hexamethonium. In no case, however, could a pressor response be converted to a depressor response with time or by repeated injections of the peptide.

Heart rate

The action of ranatensin on heart rate in treated or nontreated animals was inconsistent and appeared to be unrelated to the change in blood pressure. The initial hypotensive blood pressure response was usually accompanied by a slight decrease or no change in heart rate. The hypertensive response was usually associated with an increase in heart rate which persisted after the blood pressure had returned to the baseline. However, all blood pressure effects of ranatensin could be observed with no change in heart rate.

Cat

Using doses up to 20 μg/kg, ranatensin did not alter the blood pressure or heart rate in two cats having mean pressures of 100 and 120 mmHg. Moreover, there was no response to ranatensin after 5 mg/kg propranolol when the mean pressure had been lowered to 75 mmHg. The cats did respond normally to angiotensin, noradrenaline, and tyramine. The ranatensin stock solution used in these experiments was fully active when tested in rats.

Guinea-pig

Ranatensin moderately raised the blood pressure in guinea-pigs, having a threshold dose of 1–3 μg/kg. A hypotensive phase sometimes followed the pressor response. The magnitude of the response varied from animal to animal and no dose-response relationship could be determined. There was a rapid onset of tachyphylaxis to ranatensin, but no cross-tolerance with angiotensin or eledoisin.

Discussion

The effects of ranatensin on blood pressure differ from one species to another. The peptide raised blood pressure in the dog and rabbit, having about one-tenth the potency of angiotensin. In the rabbit, doses of ranatensin and angiotensin raising pressure to the same magnitude had the same duration. However, in the dog, the duration of the response to ranatensin was longer than that of a comparable dose of angiotensin. In both species the effect of ranatensin appears to be a direct peripheral action since the rise in pressure was not altered by phentolamine,

atropine, hexamethonium or propranolol. Varying degrees of tachyphylaxis occurred in both animals, but there was no cross-tachyphylaxis with single injections of angiotensin, bradykinin, or noradrenaline. However, infusions of large amounts of angiotensin ((5 μg/kg)/min) in dogs reduce the pressor response to 0·5 μg/kg ranatensin, but do not alter the threshold dose (W. J. Louis, personal communication). No change in blood pressure was observed in cats using a dose 400 times the threshold dose in the dog.

Ranatensin lowered blood pressure in the monkey and could not be distinguished from eledoisin either in regard to potency, duration of action, or by the shape of the response curve. This hypotensive response was not blocked by a wide variety of autonomic blocking agents, suggesting a direct peripheral site of action. There was no tachyphylaxis to the depressor action, nor was the response affected by pretreatment with other peptides.

The blood pressure response to ranatensin in the rat was variable and, in part, related to the basal level of pressure. The predominant response was hypertension when the pressure was low and hypotension when the pressure was high. Artificially lowering the blood pressure from an initially higher level to a lower level, converted a depressor response to ranatensin to pressor. This was accomplished using a wide variety of compounds to lower the basal blood pressure. These included: propranolol, pronethalide, lidocaine, hexamethonium, pentolinium, tetraethylammonium, and guanethidine. Phentolamine reduced or abolished the pressor action of ranatensin, suggesting that the peptide may be acting through the release of catecholamines from the adrenal glands or from sympathetic nerve endings. However, neither bilateral adrenalectomy nor adrenal-demedullation altered the ability of ranatensin to raise blood pressure in the rat. Reserpine pretreatment reduced the pressor response to ranatensin, but never abolished it, even in animals in which there was little or no response to tyramine. These observations suggest that a part of the pressor response to ranatensin in the rat is mediated through an indirect adrenergic component involving the release of noradrenaline from peripheral nerve endings rather than from the adrenal glands. There may also be a second component in the pressor action of ranatensin—that is a direct action of the peptide on α-adrenoceptors or an action on other receptors that are also susceptible to blockade by phentolamine. The residual pressor activity in reserpine treated animals may, however, only reflect incomplete depletion of catecholamines.

TABLE 2. *Effects of peptides on blood pressure of man and laboratory animals**

	Dog	Cat	Rabbit	Man	Monkey†	Guinea-pig	Rat
Ranatensin†	+	0	+		−	+,−	+,−
Eledoisin-like peptides							
Eledoisin	−	−	−	−	−	+,−	+,−
Physaelamin	−	−	−	−			+,−
Caerulein	−	−	−	−			+,−
Kinins							
Bradykinin	−	−	−	−	−	−	−
Phyllokinin	−		−				
Kallidin	−	−	−				−
Other							
Angiotensin†	+	+	+	+	+	+	+

Data presented here were * extracted from the reports cited in the introduction or † obtained in our laboratory.
+=Pressor; −=depressor; 0=no effect; +,−=variable.

Table 2 compares the vasoactive properties of ranatensin to eledoisin, angiotensin and peptides isolated from the skin of various other amphibians. With the exception of angiotensin, which is hypertensive in all species, all other peptides listed are hypotensive agents. Although structually related to the hypotensive eledoisin-like peptides, ranatensin is hypertensive in dog and rabbit, and consistently hypotensive only in the monkey. Ranatensin can similarly be distinguished from the kinins, another group of hypotensive peptides isolated from amphibian skin, by its pressor action in the dog and rabbit. There is no vascular effect of ranatensin in the cat and a variable effect in the guinea-pig. The variable action of ranatensin in the rat is similar to that reported for other peptides. Bradykinin, which normally has hypotensive properties, will raise blood pressure in rats with a low initial blood pressure (Parratt, 1964) or after ganglionic blockade (Croxatto & Belmar, 1962). Eledoisin and physalaemin raise blood pressure in pithed rats and in rats having low blood pressure resulting from the administration of a ganglionic blocking agent (Erspamer & Glaesser, 1963 ; Bertaccini *et al.*, 1965). The hypertensive response to these peptides appears to be mediated through the release of catecholamines either from the adrenal glands or from adrenergic nerve endings (Miele & De Natale, 1967 ; Lang & Pearson, 1968).

The overall spectrum of action of ranatensin on blood pressure of various laboratory animals is unlike that of any other peptide. Ranatensin, therefore, cannot be placed into any of the established groups of vasoactive peptides. Its hypertensive action in the dog or rabbit, together with a potent hypotensive action in the monkey, readily distinguishes ranatensin from other vasoactive peptides. The actions of ranatensin on isolated smooth muscle preparations are also unlike those of any other peptide. Ranatensin relaxes the rat duodenum and contracts the aortic strip of the rabbit but not the rat. The peptide is a potent stimulant of the rat uterus, being four times as active as bradykinin. It also appears to produce bursts of acetylcholine release in the guinea-pig ileum resulting in repeated maximal spike contractions (Geller *et al.*, 1970 ; Govier *et al.*, 1970). The unique actions of ranatensin on the blood pressure of various animals and on various isolated smooth muscle preparations should permit relatively simple pharmacological identification.

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