Effect of the Synthetic Peptide, SQ 20,881, on Distribution of Blood Flow in the Rat[1] (37330)

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Angiotensin II is a potent vasoconstrictor agent which will produce changes in renal blood flow. Since the renin–angiotensin system has been implicated in the control of renal hemodynamics (1, 2), it is important to determine if angiotensin II has a preferential action on the kidney. Recently, several peptides which inhibit the conversion of angiotensin I to angiotensin II have become available (3). Reports indicate that these peptides are active *in vivo,* and effectively block the pressor response following injection of angiotensin I. We have utilized one of these peptides (SQ 20,881)[3] to study the redistribution of blood flow to several organs in the rat.

Materials and Methods. At least 4 days prior to the actual experiments, a polyethylene catheter was implanted into the left ventricle or ascending aorta via the right carotid artery in 250–300 g female rats. On the day of the experiment, the animals were anesthetized with pentobarbital sodium (60 mg/kg) and the ventricular catheter was exposed and flushed with saline. A femoral vein was cannulated for injection of SQ 20,881, and a femoral artery was cannulated to measure mean systemic blood pressure using a strain gauge pressure transducer (Statham P23Dd) and Grass polygraph or Beckman dynograph.

Blood flow redistribution was determined in the intestine, liver, kidneys, spleen, adrenals, stomach and skeletal muscle. The uterus was also originally examined, but the variation in blood flow in this organ from animal to animal was found to be too great to yield valid results. In addition, similar studies were performed on three pregnant rats in order to observe the possible effects of the peptide in this situation.

Radioactive microspheres (3M Co.) with a diameter of 15 μm and labeled with either ^{169}Yb or ^{85}Sr were used. The microspheres were diluted in a glucose solution with a density of 1.3 g/cm^3 which is the same as the density of the spheres. After injection of the microspheres, the animals were killed and the organs or pieces of organs were counted in a two-channel well-type scintillation counter.

In control experiments, microspheres were injected in random order and the distribution was calculated for the first and second injection. In experimental animals, SQ 20,881, in doses of 4 or 40 mg/kg, was given between the two injections of microspheres. The injection of microspheres was again randomized and distribution was calculated before and after administration of the peptide.

Percentage distribution of microspheres in various organs was calculated as the counts per minute of either Yb or Sr in a given organ divided by the total counts to all of the organs. The data were analyzed using the Student's *t* test with a .05 probability level of significance.

In order to test the effectiveness of the peptide in inhibiting angiotensin I converting enzyme activity, various doses of angiotensin I and angiotensin II were administered intravenously to 250–300 g rats. The changes in blood pressure were recorded and SQ 20, 881 administered. The animals were then injected with identical doses of angiotensin I and angiotensin II and blood pressure changes again recorded.

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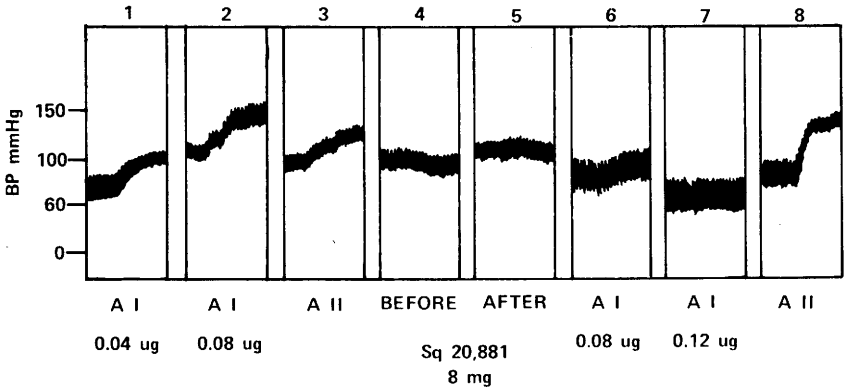

FIG. 1. Effect of SQ 20,881 on the blood pressure response to angiotensin I in the rat.

Results. Figure 1 shows the response to intravenously administered angiotensin I and angiotensin II before and after administration of SQ 20,881. Comparison of panels 1 and 2 with 6 and 7 demonstrates the inhibitory effect of the peptide. The response to angiotensin II is not suppressed and may be slightly enhanced. In addition, panels 4 and 5 indicate that systemic blood pressure is not reduced by SQ 20,881. In all experiments, changes in systemic blood pressure following administration of this peptide were inconsistent, increasing in four experiments, falling in eight and remaining unchanged in eight.

Statistical evaluation of the control experiments yielded no significant differences in distribution of microspheres from the first and second injections in any of the organs studied (Fig. 2). Upon administration of SQ 20,881 in a dose of 4 mg/kg, distribution of micro-

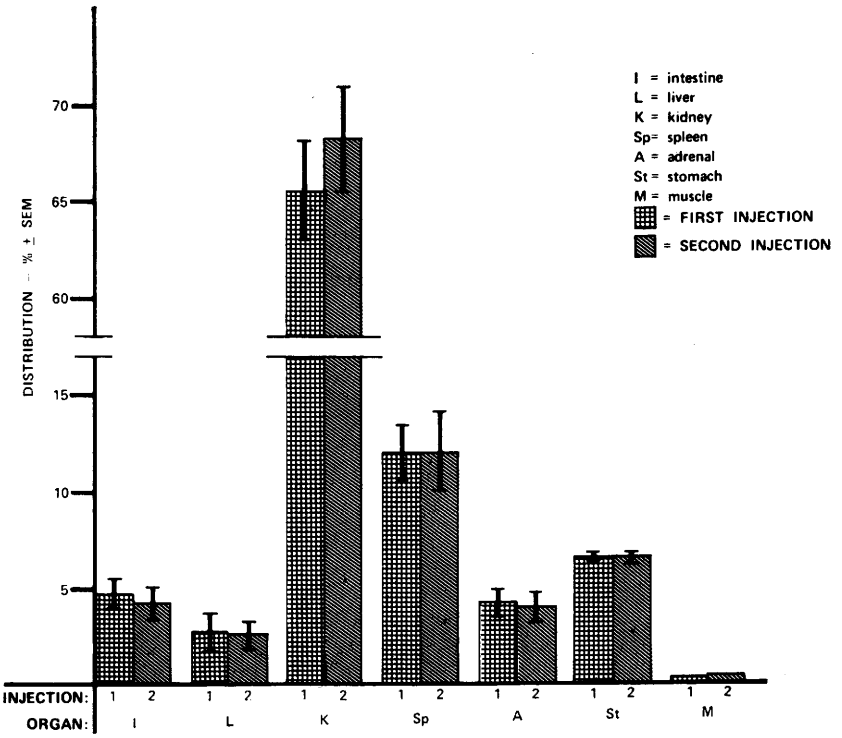

FIG. 2. Changes in microsphere distribution to several organs in the rat in control experiments. No significant changes were seen in any of the organs in the control animals. $N = 13$.

spheres to the kidneys increased significantly while there was a significant fall in distribution to the spleen and other organs showed small but insignificant changes (Table I). When the peptide was injected in a higher dose (40 mg/kg), similar results were achieved (Table II): redistribution of microspheres to the kidneys was again significantly increased while that to the stomach fell. The intestine, adrenals, spleen, and muscle also received a smaller proportion of microspheres after injection of the peptide, although this decrease was not significant ($.2 > p > .1$).

SQ 20,881 was also administered in a dose of 40 mg/kg to three pregnant rats. Two of the animals were in Day 17 of pregnancy and one was in Day 19 of pregnancy. The results from these animals were similar to those obtained from the nonpregnant animals given the same dose of SQ 20,881. The fraction of microspheres to the kidneys was increased while small nonsignificant decreases were seen in other organs including the uterus.

Discussion. Inhibition of angiotensin I converting enzyme activity was first reported using venom from *Bothrops jararaca* (4). This material also contained bradykinin potentiating activity. Synthetic peptides also have been shown to have effects on both converting enzyme activity and bradykinin potentiation (3). In the present experiments one of these synthetic peptides, SQ 20,881, was studied. Its structure is as follows: Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro.

TABLE I. Effect of SQ 20,881 (4 mg/kg) on Redistribution of Microspheres on the Rat.[a]

Organ	Injection	Distribution (% ± SEM)
Intestine	C	3.7 ± 0.4
	E	3.8 ± 0.7
Liver	C	1.8 ± 0.5
	E	2.6 ± 1.3
Kidney	C	68.4 ± 2.2[b]
	E	74.0 ± 2.3
Spleen	C	15.5 ± 2.2[b]
	E	10.8 ± 1.4
Adrenal	C	3.6 ± 0.7
	E	3.5 ± 0.6
Stomach	C	5.0 ± 0.7
	E	4.2 ± 0.6
Muscle	C	0.17 ± 0.03
	E	0.16 ± 0.03

[a] C = control injection; E = experimental injection (after SQ 20,881); $n = 8$.
[b] $p < 0.05$.

TABLE II. Effect of SQ 20,881 (40 mg/kg) on Redistribution of Microspheres in the Rat.[a]

Organ	Injection	Distribution (% ± SEM)
Intestine	C	5.2 ± 0.8
	E	3.9 ± 0.6
Liver	C	3.00 ± 0.7
	E	3.10 ± 0.4
Kidney	C	62.4 ± 2.7[b]
	E	71.6 ± 3.7
Spleen	C	15.5 ± 2.4
	E	12.3 ± 2.3
Adrenal	C	5.4 ± 0.5
	E	4.7 ± 0.7
Stomach	C	6.7 ± 1.6[b]
	E	3.4 ± 0.6
Muscle	C	0.20 ± 0.05
	E	0.16 ± 0.03

[a] C = control injection; E = experimental injection (after SQ 20,881); $n = 10$.
[b] $p < 0.05$.

Administration of this synthetic peptide to the rat results in redistribution of radioactive microspheres toward the kidney. This experiment does not allow separation of possible effects of the peptide on bradykinin potentiation and angiotensin I converting enzyme inhibition, which might result in similar hemodynamic effects. While there was no consistent redistribution away from any specific organ to the kidney, small changes from several organs were observed.

Since blood pressure changes were inconsistent following administration of SQ 20,881, it is likely that at least part of the observed effect of the peptide was due to renal vasodilitation. We have also noted an increase in total renal blood flow to the dog kidney following intrarenal arterial infusion of SQ 20,881.[4]

Since both angiotensin II and bradykinin

[4] Unpublished observations.

have opposing effects on renal hemodynamics (5, 6), it is of interest that the kidney appears to be the organ most effected by SQ 20, 881. This suggests that angiotensin and/or bradykinin may be involved in some aspects of regulation of renal function.

Summary. Changes in blood flow distribution were studied in the rat following administration of the peptide SQ 20,881, a known inhibitor of angiotensin I converting enzyme and a potentiator of bradykinin activity. Administration of the inhibitor resulted in redistribution of blood flow toward the kidney. The possible relation to effects of angiotensin II and bradykinin on renal function are discussed.

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