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Inhibition by Salmon Calcitonin (SCT) of Desoxycorticosterone Acetate (DOCA) Induced Hypertension in the Rat (39439)

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We have previously reported the capability of SCT to produce an acute diuresis and natriuresis in the saline loaded rat (1), as well as its ability to reduce the paw edema or inflammatory phase associated with the chronic disease state known as rat adjuvant arthritis (12). In addition, we have noted a significant decrease in the heart weight of normal rats given high doses of salmon calcitonin for 7 days (unpublished). We thus became interested in determining what effects SCT might have in a chronic hypertensive state such as that produced in rats by administration of DOCA in combination with a high salt intake.

Methods. Two separate experiments were performed in which female Sprague-Dawley rats with initial weights of 50-70 g were treated sc for 5 weeks with 5 or 25 mg/kg/dose of DOCA given b.i.d. with 1% NaCl in the drinking water. Synthetic salmon calcitonin (4000 MRC u/mg), purified porcine calcitonin (100 MRC u/mg), or synthetic human calcitonin (80 MRC u/mg) was administered sc at a dosage of 5 MRC u/kg/dose b.i.d. in a 16% gelatin vehicle concomitantly with DOCA but at a different injection site.[1] At the end of the treatment period direct measurements of aortic blood pressure were recorded in the unanesthetized state over at least a 5-min period following cannula insertion and pressure stabilization. Systolic, diastolic, mean blood pressure, and heart rate were recorded. The animals were then sacrificed and measurements made of heart and kidney weights. Appropriate control groups receiving distilled water or 1% NaCl to drink and injected with vehicle were included. Levels of statistical significance for group differences were determined using Student's t test.

[1] Calculated on a weight basis, the doses given were: SCT 1.25 μg/kg b.i.d.; porcine calcitonin 50.0 μg/kg b.i.d.; and human calcitonin 62.5 μg/kg b.i.d. All were manufactured by Armour Pharm. Co.

Results. In Table I are shown the results of the blood pressure measurements in the two experiments after 5 weeks of treatment. Since systolic and diastolic pressures varied proportionally, only data on mean pressure are presented. Substitution of 1% NaCl for distilled drinking water had no effect on mean blood pressure. As may be observed in experiment 1, 5 mg/kg b.i.d. of DOCA given for 5 weeks had no effect on mean pressure, and SCT had no modifying effect on this dose of DOCA. However, 25 mg/kg b.i.d. of DOCA produced a highly significant increase in mean blood pressure in both experiments ($P < .001$) and the addition of 5 MRC u/kg b.i.d. of SCT to this dose of DOCA significantly reduced ($P < .001$) the hypertension in each experiment. It should be noted that although SCT produced a significant lessening of DOCA-induced hypertension, these animals were still significantly hypertensive compared to control animals receiving no DOCA. In experiment 2, groups of DOCA-treated rats were given purified porcine calcitonin or synthetic human calcitonin at equivalent hypocalcemic dosages as SCT with no significant reduction in the markedly elevated levels of blood pressure.

Measurements of heart rate (data not presented) show a statistically significant increase with 25 mg/kg b.i.d. of DOCA compared to the distilled water control in experiment 2 only. As this effect was not observed in both experiments, we do not consider this finding to be of major importance.

The effects on heart weight are shown in Table II. DOCA, at a dosage of 5 mg/kg b.i.d. had no effect on heart weight, while 25 mg/kg b.i.d. produced a highly significant increase in this parameter in both experiments. SCT decreased DOCA-induced cardiac hypertrophy in both experiments but this effect achieved statistical significance ($P < .02$) only in experiment 1. Por-

TABLE I. Effect of SCT on Mean Blood Pressure in DOCA Treated Rats.[a]

Groups No.	To drink	DOCA (mg/kg b.i.d.)	CT	Mean blood pressure (mm Hg)	
				Expt 1	Expt 2
1	H_2O	–	–	113 ± 8	120 ± 5
2	1% NaCl	–	–	113 ± 11	117 ± 8
3	1% NaCl	5	–	116 ± 11	–
4	1% NaCl	5	SCT	117 ± 8	–
5	1% NaCl	25	–	166 ± 18*	191 ± 21*
6	1% NaCl	25	SCT	131 ± 11**, ***	140 ± 10*, ***
7	1% NaCl	25	PCT	–	171 ± 18*
8	1% NaCl	25	HCT	–	186 ± 15*

[a] Values are mean ± 1 standard deviation; $N = 7$ rats/group.
* $P < .001$ vs groups 1 and 2.
** $P < .01$ vs groups 1 and 2.
*** $P < .001$ vs group 5.

TABLE II. Effect of SCT on Heart Weight in DOCA Treated Rats.[a]

Group No.	To drink	DOCA (mg/Kg b.i.d.)	CT	Heart weight (mg%)	
				Expt 1	Expt 2
1	H_2O	–	–	320 ± 15	316 ± 7
2	1% NaCl	–	–	319 ± 16	314 ± 12
3	1% NaCl	5	–	333 ± 19	–
4	1% NaCl	5	SCT	327 ± 21	–
5	1% NaCl	25	–	450 ± 72[a]*	394 ± 56**
6	1% NaCl	25	SCT	367 ± 29**, ***	359 ± 26**
7	1% NaCl	25	PCT	–	385 ± 28*
8	1% NaCl	25	HCT	–	455 ± 85*

[a] Values are mean ± 1 standard deviation; $N = 7$ rats/group.
* $P < .001$ vs groups 1 and 2.
** $P < .01$ vs groups 1 and 2.
*** $P < .02$ vs group 5.

cine and human calcitonin did not significantly modify DOCA-induced cardiac hypertrophy. Histologic evaluation of cardiac tissue has not yet been performed.

Measurements of kidney weight (data not presented) showed that 25 mg/kg DOCA b.i.d., but not 5 mg/kg DOCA b.i.d., resulted in a highly significant ($P < .001$) increase in kidney weight in both experiments. Treatment with SCT, PCT, or HCT did not significantly ($P > .05$) modify kidney hypertrophy.

Discussion. An antihypertensive effect of SCT in rat hypertension induced by DOCA administration and high salt intake has not, to our knowledge, been previously reported, although a significant lowering of blood pressure by SCT in the spontaneously hypertensive rat has been shown (9). The capability of natriuretic agents such as chlorothiazide and spironolactone to prevent or reduce DOCA-salt hypertension is well documented (3, 4).

In earlier studies we noted a significantly greater diuretic and natriuretic potency of SCT in the rat compared to PCT (1) or HCT (unpublished) using equivalent hypocalcemic doses. Similar observations concerning the relative effects of salmon and human calcitonin on renal electrolyte excretion in the rat have been reported by Williams *et al.* (5). These differences in diuretic and natriuretic activity appear to parallel the antihypertensive potencies now reported for the three hormones. It is tempting to speculate that this parallelism is the result of a cause and effect relationship; however, studies to examine patterns of urine electrolyte excretion in developing DOCA-salt hypertension have not been completed.

Our previously reported observations of the ability of SCT to reduce paw edema in rat adjuvant arthritis (2) and our present data showing antihypertensive activity of SCT in DOCA-salt hypertension in the rat are compatible with the possibility of a common underlying mechanism of action through a diuretic–natriuretic pathway in these two experimental diseases. However, such a mechanism may be independent from any effect of SCT on the kidney since it has been reported that the antihypertensive action of certain diuretics such as the benzothiadiazines persists in patients who are refractory to their diuretic action due to their uninterrupted use (3). As an alternative hypothesis a mechanism of action of SCT can be considered based on the well-established ability of calcitonin to produce compartmental shifts in calcium (6). Such shifts can reduce capillary permeability and thus might modify a potentially edematous state (7, 8). Further studies are obviously required to resolve the means by which calcitonin can modify the progression of these experimental disease states.

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