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Effect of Parathyroid Hormone on Renin Secretion[1]

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Abstract. The ability of parathyroid hormone (PTH) to increase renin secretion was investigated in pentobarbital-anesthetized dogs. An intravenous infusion of bovine PTH 1-34, at the dose of 0.028 $\mu g\ kg^{-1}\ min^{-1}$ increased renin secretion by 149% (501 ± 105 to 1249 ± 309 ng $hr^{-1}\ min^{-1}$); renin secretion returned to control values during the recovery period. In order to determine whether PTH acted directly on the kidney to increase renin secretion, PTH was infused into the right renal artery at doses of 0.0014 to 0.0028 $\mu g\ kg^{-1}\ min^{-1}$ and renin secretion from the right kidney was compared to that from the left (control) kidney. Renin secretion from the right (PTH-infused) kidney was not greater than control values for that kidney or different from the renin secretory rate of the left (control) kidney. In contrast, the excretion rates of both phosphate and sodium from the right kidney were greater than control values and from the excretion rates of the left kidney. These data suggest that PTH, while acting directly on the kidney to increase phosphate and sodium excretion, does not elevate renin secretion by a direct renal action.

Recent reports have suggested a correlation between elevated levels of parathyroid hormone and high blood pressure. The incidence of hypertension is increased in patients with hyperparathyroidism (1, 2). The serum levels of PTH are elevated in hypertensive patients compared with matched normotensive controls (3). In a deoxycorticosterone acetate–NaCl model of hypertension, parathyroidectomy partially inhibited the development of hypertension (4).

The mechanism underlying the PTH-induced elevation of blood pressure is not known. Brinton *et al.* (5) reported elevated plasma renin activity in hyperparathyroid patients. Recently, it has been demonstrated that an intravenous infusion of PTH elevated plasma renin activity (6, 7); furthermore, in saline-loaded animals, there is a delayed rise in renin secretion during PTH infusion (8). Bolus injections into the renal artery of very large amounts of PTH increase renin secretion from the injected kidney but the relevance of these findings for the low dose effects of PTH is unclear (9). Moreover, a direct renal effect cannot be concluded from these experiments since the response of the control kidney was not evaluated. In order to examine more closely the interaction between PTH and the renin–angiotensin–aldosterone system, the effect of both intravenous and intrarenal infusion of PTH on renin secretion in normovolemic animals was evaluated.

Methods. Mongrel dogs, weighing 15–20 kg, were maintained on a standard laboratory chow (Friskies, Carnation) and were fasted overnight with free access to water. They were anesthetized with sodium pentobarbital (30 $mg\ kg^{-1}$), and supplemental doses were given when required. An endotracheal tube was inserted and both brachial veins and the femoral artery was cannulated. One or both ureters were cannulated through a flank incision. In all experiments, a catheter was inserted through the left femoral vein into the inferior vena cava and manually guided into the right renal vein. In protocol 2 (see below), in which renin secretion was measured from both kidneys, a catheter was inserted, either via the right jugular vein, superior vena cava, and right atrium or via the right femoral vein, into the inferior vena cava and guided into the left renal vein. The positions of the renal vein catheters were visually checked at the conclusion of the experiments. Also, in protocol 2, a 23-gauge needle was inserted into the right renal artery and isotonic saline was infused at

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0.1 ml min^{-1}. In all experiments, a 1- to 2-hr equilibration period was allowed before beginning the actual experimental protocols.

Glomerular filtration rate (GFR) was measured as creatinine clearance. Renal plasma flow (RPF) was determined using *p*-aminohippurate (PAH) and the Fick principle. A PAH concentration in the final renal venous samples less than 30% of the arterial PAH concentration was used as the second required criterion that the renal venous catheters were in place during the experiment. During the last 30–60 min of the equilibration period, each animal received a prime of creatinine and PAH (9.6 g creatinine and 250 mg PAH dissolved in 20 ml saline) followed by a constant infusion of creatinine (30 mg ml^{-1}) and PAH (27 mg ml^{-1}) in saline at 0.2 ml min^{-1}. Arterial blood samples for clearances and electrolytes were collected in heparinized tubes; arterial and renal venous blood for renin analysis was collected in iced tubes to which 30 μl NH_4EDTA (0.67 mg ml^{-1}) had been added.

Protocol 1a. Effect of systemic infusion of PTH on renin secretion (BSA infused only during experimental period). (n = 5). The experiment was divided into control, experimental, and recovery periods, each 1 hr long. Two 15-min clearances were performed during the last half hour of each period. Saline was infused at 0.4 ml min^{-1} during the control and recovery periods. Synthetic bovine PTH 1-34 (Beckman, 3820 IU mg^{-1}) and bovine serum albumin (BSA, 1 mg ml^{-1}) were both added to the saline infusion during the experimental period. The dose of PTH infused was 0.028 μg kg^{-1} min^{-1}. Arterial and renal venous blood samples (4 ml each) were collected in the middle of the two clearances of each period. The volume of blood removed from the animal was immediately replaced with an equivalent amount of Dextran (6%) in isotonic saline.

Protocol 1b. Effect of systemic infusion of PTH on renin secretion (BSA infused throughout). (n = 7). This series of experiments was identical to protocol 1a, except that the saline infusion during both the control and recovery periods also contained BSA (1 mg min^{-1}).

Protocol 2. Infusion of PTH directly into the right renal artery. (n = 6). After a 2-hr equilibration period during which saline was infused at 0.1 ml min^{-1}, two 15-min control clearances were collected. The subsequent experimental period was divided into two half-hour segments, with two 10-min clearances collected during the last 20 min of each experimental period. PTH was added to the saline and infused at two concentrations (0.0014 and 0.0028 μg kg^{-1} min^{-1}) during consecutive half-hour periods. The stepwise increase in PTH concentration was achieved by increasing the rate of intrarenal saline infusion from 0.1 ml min^{-1} to 0.2 ml min^{-1}. Blood samples were collected from the right and left renal veins and the femoral artery at 5, 10, 15, and 25 min of each 30-min experimental period. The total volume of blood (6 ml at 5 and 10 min; 12 ml at 15 and 25 min) collected from the animal was replaced with an equivalent volume of 6% Dextran in isotonic saline.

Analytical methods. Plasma renin activity (PRA) was determined by a modification of the method of Haber *et al.* (10) as has been described previously (6). Given a constant substrate concentration, there is a linear relationship between plasma renin concentration and plasma renin activity (11). It has been previously shown that the concentration of plasma substrate does not change during PTH infusion (6). Therefore, PRA was used as an index of change in renin concentration and renin secretion was calculated as the renal venous–arterial difference in PRA multiplied by the renal plasma flow.

Blood pressure and heart rate were measured continuously from the femoral artery catheter with a Statham pressure transducer recording on a Grass polygraph; for statistical purposes, values were read from the graph paper at the midpoint of each clearance period. Sodium and potassium concentrations in plasma and urine were measured by flame photometry, phosphate by the method of Hurst (12), creatinine by the method of Bonsnes and Taussky (13), and PAH by the method of Smith *et al.* (14).

Data from two consecutive 10- or 15-min clearances were averaged and expressed as a single value for statistical analysis. Unless otherwise noted, the other data from the blood samples at the midpoints of the two clearances were also averaged for statistical analysis. All values are expressed as means ± SEM. For protocols 1a and 1b, Student's t test was

used to compare group means using paired-samples analysis. In protocol 2, the data were first analyzed with analysis of variance and secondly with Student's t test using paired-samples analysis when indicated. Interrenal comparisons were made using paired-samples analysis.

Results. *Protocols 1a and 1b.* Renin secretion increased during the PTH infusion (Fig. 1) in protocol 1a (662 ± 149 to 1347 ± 394 ng hr^{-1} min^{-1}, solid lines) and protocol 1b (415 ± 146 to 1180 ± 474 ng hr^{-1} min^{-1}, dashed lines). The mean increase in renin secretion for both groups was 725 ± 318 and 765 ± 433 ng hr^{-1} min^{-1} for protocols 1a and 1b, respectively. The mean arterial pressure (MAP), which slightly decreased during protocol 1a (124 ± 5 to 119 ± 3 mm Hg), remained constant during protocol 1b (117 ± 6 to 117 ± 7 mm Hg). Because the changes in renin secretion and measurements of renal function were similar for protocols 1a and 1b, the data from both protocols were subsequently pooled for statistical analysis. For the combined group, renin secretion increased 149% (501 ± 105 to 1249 ± 309 ng hr^{-1} min^{-1}, $P < 0.01$). Plasma renin activity was also elevated during the PTH infusion (9.3 ± 1.3 to 15.6 ± 1.8, ng ml^{-1} hr^{-1}, $P < 0.01$). MAP and GFR did not change during the PTH infusion while RPF (129 ± 8.1 to 157 ± 11.3 ml min^{-1}, $P < 0.01$) and sodium excretion (14.3 ± 3.0 to 51.2 ± 8.5 μeq min^{-1}, $P < 0.01$) were both increased (data not shown).

Protocol 2. The basal renin secretory rates from each kidney (Table I) were similar (753 ± 199 and 737 ± 195 ng hr^{-1} min^{-1} for the right and left kidney, respectively). Compared to basal values, there was no change in renin secretion from the right PTH-infused kidney or the left control kidney during the PTH infusions. Both PRA and MAP were not significantly changed although there was a tendency for the PRA to increase and the MAP to decrease during the PTH infusions. GFR and RPF did not change in either kidney during the PTH infusion (Table I). Total plasma calcium during the PTH infusions was not different from control values (6.01 ± 0.19 meq $liter^{-1}$ in the control period versus 5.86 ± 0.16 and 5.77 ± 0.14 meq $liter^{-1}$ during the infusion of PTH at 0.0014 and 0.0028 μq kg^{-1} min^{-1}, respectively.

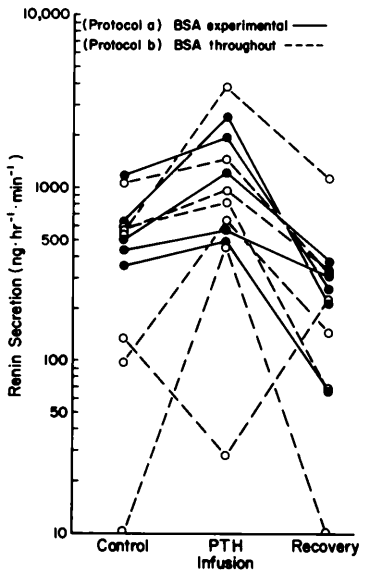

FIG. 1. Protocol 1. Effect of PTH on renin secretion. Experiments in which BSA was infused only during the experimental period (n = 5) are indicated by solid lines. Experiments in which BSA was infused throughout the protocol (n = 7) are indicated by dashed lines. Each point represents the average of two blood samples (at 37 and 52 min) collected at the midpoint of the two clearances taken during the last half hour of the control, PTH-infusion, and recovery periods. In one animal, during the control and recovery periods, there was a negative venous–arterial PRA difference (indicated by half-circles on the X-axis).

Phosphate excretion from the PTH-infused kidney was increased during infusion of each PTH dose (400.9 ± 109.3 to 495.6 ± 89.4, μg min^{-1}, $P < 0.05$ for PTH infused at 0.0014 μg kg^{-1} min^{-1} and 400.9 ± 109.3 to 619.1 ± 101.8 μg min^{-1}, $P < 0.01$ for PTH infused at 0.0028 μg kg^{-1} min^{-1}). Phosphate excretion from the left control kidney increased during the higher PTH dose only (378 ± 105 to 472 ± 89 μg min^{-1}, $P < 0.05$). Phosphate excretion from the infused kidney was greater than that of the control kidney at the PTH dose of 0.0028 μg kg^{-1} min^{-1} (619.1 ± 101.8 vs 472 ± 89 μg min^{-1}, $P < 0.05$ for the infused and control kidney, respectively).

Sodium excretion from the infused kidney increased during the PTH infusion of 0.0014 μg kg^{-1} min^{-1} (17.2 ± 2.4 to 28.6 ± 5.4 μeq min^{-1}, $P < 0.01$) and 0.0028 μg kg^{-1} min^{-1} (17.2 ± 2.4 to 40.8 ± 9.9 μeq min^{-1},

TABLE I. EFFECT OF RIGHT INTRARENAL INFUSION OF PTH AT DIFFERENT DOSES ON RENIN SECRETION AND RENAL FUNCTION (PROTOCOL 2)

		PTH dose ($\mu g\ kg^{-1}\ min^{-1}$)	
	Control	0.0014	0.0028
Right kidney renin secretion ng $hr^{-1}\ min^{-1}$	753 ± 199	760 ± 276 NS	670 ± 275 NS
Left kidney renin secretion ng $hr^{-1}\ min^{-1}$	737 ± 195	944 ± 342 NS	968 ± 420 NS
PRA, ng $ml^{-1}\ hr^{-1}$	11.3 ± 2.1	12.8 ± 3.4 NS	14.3 ± 3.3 NS
MAP, mm Hg	134 ± 5	132 ± 6 NS	128 ± 7 NS
Right kidney renal plasma flow ml min^{-1}	129.5 ± 19.3	127.8 ± 15.5 NS	133.8 ± 12.3 NS
Left kidney renal plasma flow ml min^{-1}	108.8 ± 6.2	112.7 ± 5.5 NS	115.6 ± 6.9 NS
Right kidney GFR ml min^{-1}	47.4 ± 5.0	48.0 ± 3.7 NS	46.2 ± 2.5 NS
Left kidney GFR ml min^{-1}	46.5 ± 2.5	46.5 ± 2.4 NS	45.1 ± 1.6 NS
Right kidney U_{PO_4} V $\mu g\ min^{-1}$	400.9 ± 109.3	495.6 ± 89.4 $P < 0.05$	619.1 ± 101.8* $P < 0.01$
Left kidney U_{PO_4} V $\mu g\ min^{-1}$	378.0 ± 105.0	376.0 ± 87.0 NS	472.0 ± 89.0* $P < 0.05$
Right kidney U_{Na} V $\mu eq\ min^{-1}$	17.2 ± 2.4	28.6 ± 5.4* $P < 0.01$	40.8 ± 9.9 $P < 0.01$
Left kidney U_{Na} V $\mu eq\ min^{-1}$	19.7 ± 5.3	23.0 ± 6.9 NS	28.5 ± 11.2 NS

Note. Data for renin secretion, PRA, and MAP are based on average of four consecutive measurements obtained during each period, and values are means ± SEM. For renal function variables, data are based on the average of two clearances obtained during each period, and values represent the means ± SEM. Data were statistically evaluated first using analysis of variance followed by paired-samples analysis when indicated. Interrenal comparisons were made using paired-samples analysis. *P* values refer to difference compared to control levels.

* Significant difference between the right and left kidney at $P < 0.05$.

$P < 0.01$). The sodium excretion from the control kidney did not change. Sodium excretion from the right PTH-infused kidney exceeded that of the left control kidney at the lower PTH dose (28.6 ± 5.4 vs 23 ± 6.9 for right and left kidney, respectively, $P < 0.05$).

Discussion. Infusion of PTH (6, 7) or stimulation of endogenous PTH secretion (6) produced an increase in PRA.[2] Elevation in PRA

[2] At the time of our previous publication (6), we had been unable to measure the PTH concentrations achieved during physiological stimulation (decreased plasma ionized calcium of the parathyroid gland) that were associated with increased PRA. Since then Dr. Arnaud and Dr. Teitelbaum (University of California, San Francisco) graciously consented to make these measurements. During intracarotid citrate infusions, PTH rose from undetectable levels (<4) to 9.2 ± 2.2 ng eq bovine $PTH^{-1}\ ml^{-1}$ (standard urea–TCA purified) in five of the seven animals. In the other two animals, the PTH levels remained undetectable during the intracarotid citrate infusion. Thus, the intracarotid citrate infusions (in contrast to the iv citrate infused during control periods), which were shown (6) to produce natriuresis and elevate PRA, clearly stimulated PTH secretion.

could be due to either a change in metabolic clearance or an increase in renin secretion. Studies by Powell *et al.* (8) in which intravenous PTH infusion into saline-loaded animals produced a dose-related rise in renin secretion, suggest the latter mechanism.

The results of the present study demonstrate that renin secretion is elevated during intravenous infusion of PTH but indicate that this rise in renin secretion is not a direct effect of PTH on the kidney. In protocol 1, PTH was infused intravenously at a rate of 0.1 U kg^{-1} min^{-1} which corresponds to 1.5 to 2.0 U in a 15- to 20-kg dog, respectively. In protocol 1a, infusion of PTH was accompanied by a slight decrease in MAP, 124 ± 5 mm Hg to 119 ± 3 mm Hg. It has been shown that infusion of much larger doses of PTH 1-34 (1 U kg^{-1}) lowered MAP by 10 mm Hg (15) so it was possible that this decrease in MAP was due to PTH itself. However, protocol 1a had a potentially confounding variable in that BSA (1 mg ml^{-1}) was added to the PTH infusion vehicle (to prevent binding of hormone to tubing and syringe). If the decrease in MAP stemmed from BSA rather than PTH, then at least a portion of the increased renin secretion may be related to the BSA-induced drop in MAP. Further, in pilot experiments, intravenous infusion of BSA–saline vehicle alone did lower MAP about 5 mm Hg (data not shown). Therefore, the basic protocol was altered (protocol 1b) so that BSA–saline was infused throughout the experiment and PTH alone added to the infusate during the experimental period. In these latter experiments, the fall in MAP was eliminated during the PTH infusion while renin secretion was elevated in six of the seven animals. These data indicate that the rise in renin secretion during infusion of 1 to 2 U of PTH intravenously is attributable to an effect of PTH rather than due to alterations in MAP.

If PTH acted directly on the kidney to stimulate renin secretion, it was expected that the renin secretion from the right PTH-infused kidney would exceed that of the left control kidney. Partial metabolism of PTH by the kidney and the short half-life of the PTH 1-34 fragment of 4 1/2 min (16) validates comparison of the infused and uninfused kidneys. The doses of PTH infused into the kidney, 0.0014 and 0.0028 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were equivalent to one-twentieth and one-tenth, respectively, the intravenous dose of PTH which had elevated renin secretion from the kidney. Many of the studies evaluating the effect of PTH on the renin–angiotensin system have used pharmacologic doses of PTH. In protocol 2, PTH infusion at 0.0014 and 0.0028 μg kg^{-1} min^{-1} should elevate the plasma PTH concentration in the renal artery to 1.8 and 3.7×10^{-10} g ml^{-1}, respectively. Since the upper limit of endogenous bioactive PTH is believed to be approximately 200 pg ml^{-1} and an *in vivo* effect on phosphate and calcium excretion has been observed at PTH concentrations between 10^{-11} and 10^{-9} g ml^{-1} (17), the low concentrations of PTH employed in protocol 2 should more closely reflect the physiologic effect of PTH on renal function. Although intrarenal infusion of PTH increased phosphate and sodium excretion from the right infused kidney compared to the left control kidney (Table I), there was no increase in renin secretion from the infused kidney compared either to control values or that of the uninfused kidney. These data demonstrate that, in contrast to a direct effect on the kidney to increase phosphate and sodium excretion, PTH does not act on the kidney directly to increase the secretion of renin. Since PTH elevates renin secretion by some indirect mechanism, this may explain the delayed rise in renin secretion observed by Powell *et al.* (8) following both intrarenal and intravenous infusion of PTH.

The indirect mechanism by which PTH infusion does increase renin secretion is not known. Since MAP remained stable during both the intravenous and intrarenal infusion of PTH, a decrease in blood pressure can be ruled out. Total plasma calcium had been measured during a similar intravenous PTH infusion (6) and did not change. Total plasma calcium also did not change during the intrarenal infusions of PTH. These findings suggest that changes in total plasma calcium were not responsible for the elevation in renin secretion. However, this does not exclude a change in ionized calcium (18) which, in turn, may alter renin secretion. An interplay between PTH, renal nerves, and the adrenal hormones should be evaluated.

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