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Role of Calcium and Beta-Adrenergic System in Control of Parathyroid Hormone Secretion (39202)

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Calcium ion concentration is the well known regulator of parathyroid hormone (PTH) secretion (1). Recent *in vitro* (2) and *in vivo* (3-5) studies have suggested that the β-adrenergic system may also play an important role in the secretion of PTH. *In vivo* studies (3, 4) have shown that β-adrenergic stimulators such as epinephrine and isoproterenol increase PTH secretion whereas β-adrenergic inhibitors such as propanolol decrease PTH secretion (4). *In vitro* studies have shown that the effect of these agents is directly on the parathyroid cells (2). There is evidence from the *in vitro* (2, 6) and *in vivo* (5) studies that cyclic AMP may be the mediator of both low calcium-induced and β-adrenergic-induced PTH secretion.

The present studies were conducted in the rat to evaluate the interrelationship between the Ca ion and the β-adrenergic system in the control of PTH secretion.

Materials and methods. Polyethylene catheters were placed in the jugular vein and the aorta of male Sprague-Dawley rats weighing 275-325 g by the method of Weeks *et al.* (7, 8). Five to 7 days after surgery when the rats had regained their preoperative weight, continuous infusions of various test substances were given by Harvard infusion pump through the jugular vein catheter, and blood samples were drawn from the aortic catheter.

The infusion schemes are shown in Fig. 1. All animals initially received normal saline for 30 min during which time two baseline blood samples were obtained (−30 min and 0 time). The test substances were then infused during the following 2 hr, with blood samples being obtained at 60 and 120 min. Each group consisted of six to eight animals.

One group of control animals received normal saline during the 2-hr test period. In other groups of animals, normal saline was infused during the first hour with isoproterenol 5 μg/kg, or EDTA 100 mg/kg being infused during the second hour. In other rats propranolol 160 μg/kg/hr or calcium (as calcium gluconate) 10 mg/kg/hr was infused during the entire 2-hr period. To determine whether isoproterenol could overcome the inhibition induced by calcium, calcium 10 mg/kg/hr was infused for 2 hr, and isoproterenol 5 μg/kg was added to the infusion during the second hour. In another experiment, to determine whether low calcium induced by EDTA could overcome the inhibi-

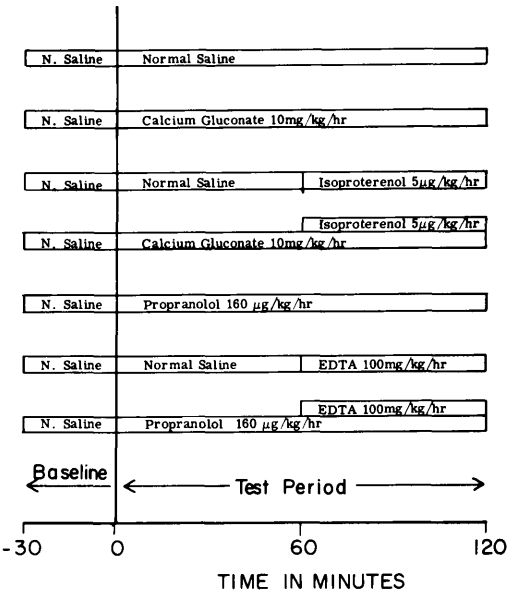

FIG. 1. Infusion schemes of various substances. Normal saline was infused during the first 30 min in all animals. The dose and duration of infusion for each substance is shown in that bar.

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tion in PTH secretion induced by propranolol, propranolol 160 μg/kg/hr was infused during the 2-hr period and EDTA 100 mg/kg/hr was added to the infusion during the second hour. Note that the doses and durations of infusions in the combination infusions were the same as those when the agents were given individually.

All blood samples were allowed to clot at room temperature for 1 hr and then at 4° for 1 hr at which time the serum was separated and frozen for subsequent analysis for PTH.

Serum PTH was determined by a sensitive radioimmunoassay developed in our laboratory (9) using an antibody developed in a chicken against bovine PTH.

All values were expressed as percentage of baseline value (mean of −30 min and 0 time). The results were expressed as mean ± SE. Statistical analysis were performed by Student's *t* test.

Results. Figure 2 shows the serum PTH concentration changes when normal saline was infused during the test period. There was no significant change from baseline in the PTH concentration at either 1 or 2 hr.

Figure 3 shows PTH concentration changes from baseline at 2 hr when calcium gluconate or isoproterenol was infused alone and the PTH change when the two substances were infused together. Calcium gluconate alone significantly inhibited the serum PTH concentration by 24 ± 9% ($P < 0.05$). Isoproterenol alone increased the serum PTH concentration by 43 ± 10% ($P < 0.01$). The observed effect when the two agents were infused together was 21 ± 7%, which is not different from the algebraic sum of 19% of the two mean individual effects.

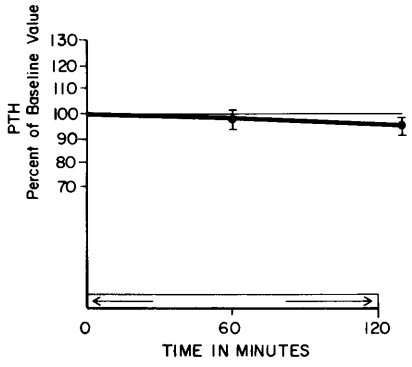

FIG. 2. Effect of normal saline infusion on serum PTH. Note there is no significant change in the serum PTH concentration for the 2 hr. Each point represents the mean ± SE.

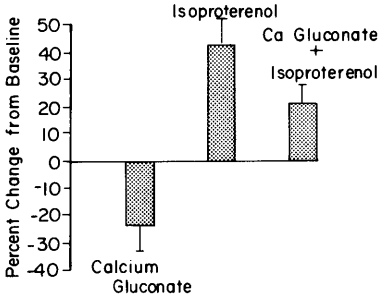

FIG. 3. Comparison of the effects of isoproterenol or of calcium gluconate alone with the effect of the combined infusion of the two substances on serum PTH (see Fig. 1 for schemes of infusions). The 2-hr serum PTH values are shown. Each bar represents the mean percentage change from baseline ± SE.

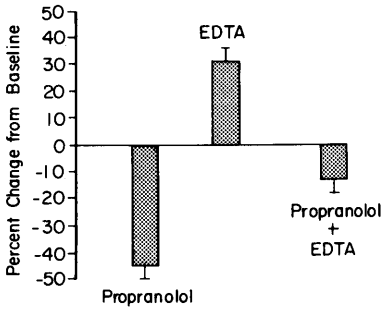

FIG. 4. Comparison of the effects of EDTA or propranolol alone with the effect of the combined infusion of the two substances on serum PTH (see Fig. 1 for schemes of infusions). The 2-hr serum PTH values are shown. Each bar represents the mean percentage change from baseline ± SE.

Figure 4 shows the serum PTH concentration changes from baseline at 2 hr when propranolol or EDTA was infused alone and the PTH change when the two substances were infused together. Propranolol alone significantly inhibited the PTH concentration by 45 ± 5% ($P < 0.001$), and EDTA alone increased the serum PTH by 31 ± 5% ($P < 0.001$). The observed effect when the two agents were infused together was −13 ± 5%, which is not different from the algebraic sum of −14% of the two mean individual effects.

Discussion. Previous *in vitro* studies (2) have shown that epinephrine and proprano-

lol can cause changes in PTH secretion by direct action on parathyroid cells. Recent unpublished *in vitro* studies with isoproterenol in our laboratory have also shown similar results. Therefore, it is likely that the observed changes in serum PTH with isoproterenol and propranolol in this study were also the result of direct effect of these agents on the parathyroid cells. Serum calcium was not determined in the present study; however, there was no significant change in serum calcium during a comparable short term administration of isoproterenol or propranolol in man (4). Normal saline infusion alone did not cause any significant changes in the serial PTH concentrations, ruling out any nonspecific effects of time, infusion procedures, etc., on PTH secretion.

The present studies show that in the rat, the β-adrenergic system plays a role in the control of PTH secretion, similar to the findings in cow (3) and man (4). The stimulatory effect of hypocalcemia was still evident in the presence of β-adrenergic block induced by propranolol. Similarly the stimulatory effect of isoproterenol was still evident in the presence of inhibition of PTH secretion induced by high calcium. Furthermore, the low calcium-induced increment in serum PTH above the control baseline and that above the propranolol-inhibited baseline were equal. Similarly, the isoproterenol-induced increment in serum PTH above the control baseline and that above the calcium-inhibited baseline were equal.

These findings indicate that both calcium and the β-adrenergic system affect PTH secretion, and each can act in the presence of the opposing action of the other. The observation that the degree of stimulation by isoproterenol or low calcium on PTH secretion is unaltered by the presence of block induced by high calcium or propranolol, respectively, would suggest that the two influences affect PTH secretion by separate initial pathways. The final pathway may be common, such as via cyclic AMP, as has been suggested from the previous studies (2, 5, 6), or they may be separate. The studies further suggest that calcium ion and β-adrenergic influences may act in concert in control of PTH secretion.

Summary. In the rat, EDTA and isoproterenol stimulated PTH secretion, whereas high calcium and propranolol inhibited it. The stimulatory effects of EDTA and isoproterenol were still evident and unaltered in the presence of blocks induced by propranolol and high calcium, respectively. The findings suggest that: (i) both calcium and β-adrenergic stimuli affect PTH secretion; and (ii) the two influences affect the PTH secretion by separate initial pathways.

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