Epinephrine is a Hypophosphatemic Hormone in Man

PHYSIOLOGICAL EFFECTS OF CIRCULATING EPINEPHRINE ON PLASMA CALCIUM, MAGNESIUM, PHOSPHORUS, PARATHYROID HORMONE, AND CALCITONIN

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ABSTRACT The physiologic effects of epinephrine on mineral metabolism are not known. In six healthy men, insulin-induced hypoglycemia, a potent stimulus to endogenous epinephrine secretion, resulted in a decrement of 0.9 ± 0.1 mg/dl (mean$\pm$SE, $P < 0.001$) in serum inorganic phosphorus and smaller increments in magnesium and total and ionized calcium. Plasma immunoreactive parathyroid hormone (iPTH) decreased and plasma immunoreactive calcitonin (iCT) increased appropriately with the increments in calcium and magnesium. We wished to determine to what extent these changes in mineral metabolism might be attributable to epinephrine. Therefore, in the same protocol, we infused the hormone over 60 min in these six men, in doses that resulted in steady-state plasma epinephrine concentrations ranging from 52 to 945 pg/ml (levels that span the physiologic range), for a total of 25 studies. Serum ionized calcium, iPTH, and iCT concentrations were unaltered by these physiologic elevations of plasma epinephrine. However, epinephrine resulted in dose-dependent decrements in serum inorganic phosphorus of 0.6 ± 0.1 mg/dl ($P < 0.005$) for the highest epinephrine infusion rate. The plasma epinephrine concentration threshold for this hypophosphatemic effect was ~50–100 pg/ml. Thus, the sensitivity of the hypophosphatemic re-

sponse to epinephrine is comparable to that of the cardiac chronotropic, systolic pressor, and lipolytic responses to epinephrine, and considerably greater than that of the diastolic depressor, glycogenolytic, glycolytic, and ketogenic responses to the hormone in human beings. In view of its rapidity, the hypophosphatemic effect of epinephrine is probably the result of a net shift of phosphate from the extracellular compartment to intracellular compartments. We suggest that it is a direct effect of epinephrine, in that it is not mediated by changes in availability of the primary regulatory hormones PTH and CT, although indirect effects mediated by changes in other hormones, such as insulin, cannot be excluded. The hypophosphatemic response is also not attributable to increments in plasma calcium. These data indicate that epinephrine in physiologic concentrations is a hypophosphatemic hormone in man.

INTRODUCTION

Sensitive isotope derivative methods for measurement of catecholamines in plasma have stimulated renewed interest in study of the sympathoadrenal system in man, and made possible definition of the endogenous plasma catecholamine concentrations achieved in a variety of physiologic and pathophysiologic states (1). This information permits distinction between pharmacologic and physiologic effects of the catecholamines. For example, it has been shown that physiologic increments in plasma epinephrine affect carbohydrate and lipid metabolism, as well as hemodynamic variables in normal human beings (2).

The physiologic effects of epinephrine on mineral metabolism are not known. Large doses of epinephrine have been reported to decrease serum calcium (3, 4) and inorganic phosphorus (5, 6) concentrations; reported effects of epinephrine on serum magnesium are contradictory (7, 8). A rather large body of evidence (3, 9–14, reviewed in 15) indicates that adrenergic agonists can increase parathyroid hormone (PTH)[1] and calcitonin (CT) secretion. These studies have given rise to the concept of noncalcium, epinephrine-mediated regulation of PTH and CT secretion, which has been proposed to have physiologic significance in man (14). However, none of the cited studies document that plasma epinephrine concentrations comparable to those achieved under physiologic conditions in man can alter PTH or CT secretion or, for that matter, any aspect of mineral metabolism.

In the present studies, we examined the effects of insulin-induced hypoglycemia, a potent stimulus to epinephrine secretion (1), on serum total and ionized calcium, inorganic phosphorus and magnesium, and plasma immunoreactive PTH (iPTH) and immunoreactive CT (iCT) in normal men. In the same protocol, to determine the extent to which the observed changes might be attributable to epinephrine, the hormone was infused in the same subjects in doses that resulted in steady-state plasma epinephrine concentrations spanning the physiologic range. The data do not support the concept that epinephrine plays a physiologic role in the regulation of PTH or CT secretion, but indicate that epinephrine in physiologic concentrations is a hypophosphatemic hormone in man.

METHODS

Experimental design. This study was approved by the Human Studies Committee of the Mayo Clinic and Foundation. Each subject gave written, informed consent to the studies.

In the Mayo Clinical Study Unit, each of six healthy male volunteers (24–33 yr of age, 66–92 kg) underwent six studies, separated by at least 1 wk, in random sequences unknown to the subjects. The six studies were: insulin-induced hypoglycemia; four 60-min (−)epinephrine infusions; and calcium and EDTA infusions. One subject underwent a fifth epinephrine infusion.[2]

Studies were begun at 0700–0800 h after an overnight fast. The subjects remained supine throughout. Antecubital veins in each arm were cannulated, one for sampling and one for infusions, 90 min before infusions began. Constant drug in-

fusion rates were assured by use of infusion pumps (Travenol Laboratories, Deerfield, IL). The electrocardiogram, heart rate, and blood pressure were monitored every 10 min. No adverse effects occurred during the infusions, although palpitations were commonly noted during 5.0-μg/min epinephrine infusions. Blood was drawn at 5-min intervals for measurement of plasma iPTH and iCT, and serum total calcium, inorganic phosphorus and magnesium, at 10-min intervals for plasma epinephrine and norepinephrine, and at 20-min intervals for serum ionized calcium. Plasma glucose was measured at 5–10-min intervals. Blood loss did not exceed 120 ml per study.

Hypoglycemia was produced by rapid intravenous injection of regular insulin (Regular Iletin II, Eli Lilly & Co., Indianapolis, IN), 0.1 U/kg body wt. For the epinephrine infusions, (−)epinephrine (Bristol Laboratories, Syracuse, NY) was diluted in 0.9% sodium chloride containing 0.25 mg/ml ascorbic acid and infused at nominal rates of 0.5, 1.0, 2.5, and 5.0 μg/min for 60 min. Calcium and EDTA infusions were performed to verify the sensitivity of the hormone assays to small changes in hormone concentrations resulting from increments and decrements in serum calcium. On one day, we administered in sequence: 60 ml of 0.9% sodium chloride over 30 min, 1.5 mg/kg of elemental calcium (as the gluconate salt), over 5 min, 120 ml of 0.9% sodium chloride over 60 min, 10 mg/kg of disodium ethylenediaminetetraacetic acid (EDTA, Endrate, Abbott Laboratories, North Chicago, IL) in 60 ml of 0.9% sodium chloride over 30 min, and 60 ml of 0.9% sodium chloride over the last 30 min.

Note that throughout all of the studies, the intravenous infusion rate (saline or saline plus drug) was held constant at 60 ml/30 min.

Analytical methods. We estimated iPTH by the method of Arnaud et al. (16) using antiserum GP-1M, which has major immunochemical specificity for an amino acid sequence within the 44 to 68 region of human and bovine PTH (17). The ability of this assay to detect small short- and long-term changes in iPTH has been documented (18–22). iCT was measured with antiserum G-1701 by our previously published method (23). Earlier studies established the capacity of this assay to detect small changes in iCT concentrations (23–26). We used our "microassay" modification for both assays to permit triplicate determinations with controls for nonspecific binding using only 200 μl of plasma for each hormone (27). All samples from a given study were analyzed together to exclude the effect of interassay variation. For the PTH and CT assays, the average intraassay coefficients of variation for appropriate internal reference standards were 12.1±1.6% and 10.7±1.3%, respectively.

Plasma epinephrine and norepinephrine were measured with a single isotope derivative assay (28) using 50-μl samples. All samples from a given study were included in a single assay. Intraassay coefficients of variation are <10%.

We measured serum total calcium and magnesium by atomic absorption spectrophotometry (Perkin-Elmer model 2380, Perkin-Elmer Corp., Norwalk, CT), serum ionized calcium with the AMT Electrion (29), serum inorganic phosphorus by the standard colorimetric method of Fiske and Subbarow (30), and plasma glucose by a standard glucose oxidase method. We measured insulin by a conventional radioimmunoassay (31).

Statistical methods. Data were analyzed by two-tailed, paired *t* tests. We made comparisons with the mean of the base-line values (−10, −5, and 0 min) for each individual time value and for the entire epinephrine infusion period (5 to 60 min). Steady-state plasma epinephrine concentra-

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tions (p[E]ss) and threshold values associated with particular parameters were estimated as previously described (1, 2). The data are presented as the mean±1 SE.

RESULTS

Calcium and EDTA infusions (Table I). Increments and decrements from base line in serum ionized calcium were associated with significant decrements and increments, respectively, in iPTH levels. Increases in serum ionized calcium were associated with significant increases in iCT and epinephrine levels, although the latter were trivial.

Insulin-induced hypoglycemia (Fig. 1). After insulin injection the plasma glucose concentration fell from 93±1 to a nadir of 34±2 mg/dl ($P < 0.0001$). Plasma epinephrine rose from 36±12 to 860±49 pg/ml ($P < 0.0001$), and plasma norepinephrine increased from 288±63 to 474±90 pg/ml ($P < 0.005$).

Insulin-induced hypoglycemia was associated with a sharp decrease in serum inorganic phosphorus from 2.9±0.1 to 2.0±0.2 mg/dl ($P < 0.0001$ throughout 20 to 60 min), and with small increases in serum total calcium (9.2±0.2 to 9.6±0.2 mg/dl, $P < 0.005$ during 20 to 40 min), ionized calcium (4.29±0.09 to 4.60±0.08 mg/dl, $P < 0.01$ at 40 min), and magnesium (2.1±0.1 to 2.3±0.1 mg/dl, $P < 0.005$ throughout 10 to 55 min). Mean iPTH levels decreased (16±3 to 12±2 μleq/ml, $P < 0.05$ during 45 to 70 min) and iCT levels increased (44±7 to 53±6 pg/ml, $P < 0.01$ throughout 30 to 50 min).

Epinephrine infusions (Figs. 2 and 3). Steady-state plasma epinephrine concentrations were usually achieved by 10 min of infusion and ranged from 52 to 945 pg/ml, values in good agreement with those observed by Clutter et al. (2) at the same nominal infusion rates. Plasma norepinephrine concentrations did not change (data not shown).

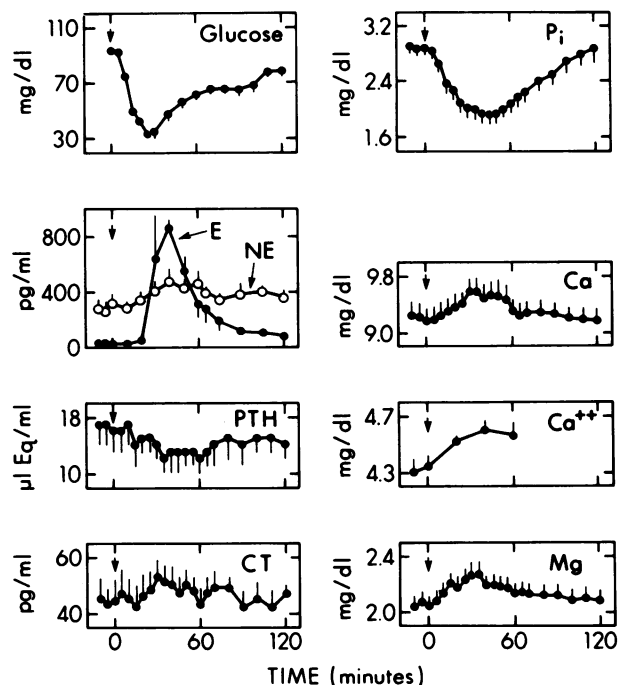Epinephrine accelerated heart rate (Fig. 2), as expected, with threshold steady-state plasma epineph-

FIGURE 1 Plasma glucose, epinephrine (E), norepinephrine (NE), PTH, CT, and serum inorganic phosphorus (P_i), total calcium (Ca), ionized calcium (Ca^{++}), and Mg concentrations before and after the rapid intravenous injection of 0.1 U of regular insulin/kg (arrows) in six normal human subjects. Data are mean±SE.

rine concentrations approximating 50–100 pg/ml, again in good agreement with the data of Clutter et al. (2). Despite this documentation of the biological effectiveness of the measured increments in plasma epinephrine, iPTH and iCT concentrations (Fig. 2) and serum ionized calcium levels (Fig. 3) were unaltered. An initial increment in serum magnesium concentrations (Fig. 3) at steady-state plasma epinephrine

TABLE I
Effects of Low-dose Calcium Infusion (5 Min) and EDTA Infusion (30 Min)

Measured variable	Calcium infusion		EDTA Infusion	
	0	5 min	0	30 min
Total calcium, mg/dl	9.2±0.2	10.1±0.3*	9.6±0.1	9.5±0.1
Ionized calcium, mg/dl	4.27±0.08	4.69±0.12*	4.49±0.07	4.24±0.07*
Parathyroid hormone, μl eq/ml	16±2	12±2*	12±2	19±2*
Calcitonin, pg/ml	43±5	63±7‡	48±5	46±6
Epinephrine, pg/ml	19±3	36±4§	28±4	30±4
Norepinephrine, pg/ml	267±49	283±40	332±45	309±72

Comparison with 0 time value: * $P < 0.0005$, ‡ $P < 0.01$, § $P < 0.05$. These results verify that appropriate changes in plasma iPTH and iCT are detectable with small increments and decrements of serum calcium.
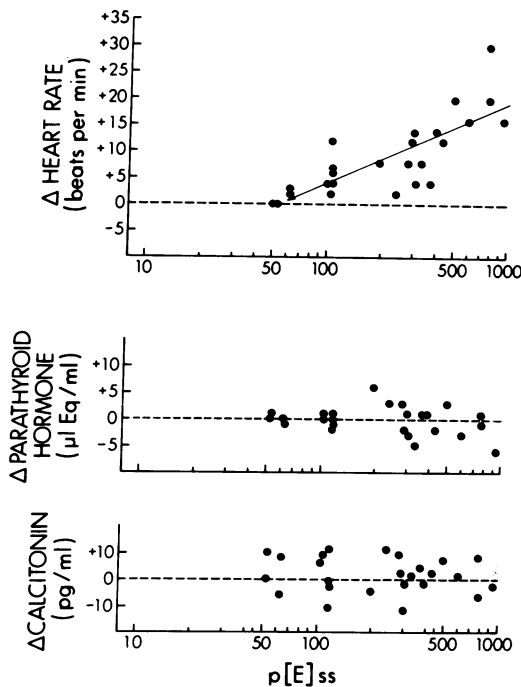
FIGURE 2 Change (Δ) from basal at 60 min in heart rate, plasma iPTH, and plasma iCT plotted against steady-state plasma epinephrine concentrations (p[E]ss, in picograms per milliliter) during 25 epinephrine infusions at nominal rates of 0.5, 1.0, 2.5, and 5.0 μg/min over 60 min in six normal human subjects. Note the log scale.

FIGURE 3 Change (Δ) from basal at 60 min in serum inorganic phosphorus, total and ionized calcium and magnesium plotted against steady-state plasma epinephrine concentrations (p[E]ss, in picograms per milliliter) during 25 epinephrine infusions at nominal rates of 0.5, 1.0, 2.5, and 5.0 μg/min over 60 min in six normal human subjects. Note the log scale. For magnesium, data between 0 and 15 min of infusion are also shown.

concentrations of >300 pg/ml was of questionable significance ($P < 0.05$ at 15 min).

Epinephrine infusions resulted in dose-dependent decrements in serum inorganic phosphorus that reached a plateau by 20–30 min. Phosphorus levels returned toward base-line levels after discontinuation of epinephrine infusions. The decrements in phosphorus were significant at all four nominal epinephrine infusion rates (infusion interval vs. basal: 0.5 μg per min, $P < 0.01$; 1.0 μg/min, $P < 0.05$; 2.5 μg/min, $P < 0.001$; and 5.0 μg/min, $P < 0.005$). The dose-response relationship between increased steady state plasma epinephrine concentrations and decrements in serum inorganic phosphorus is illustrated in Fig. 3. Clearly, progressively higher plasma epinephrine levels were associated with progressively greater decrements in phosphorus. These data, grouped on the basis of steady-state plasma epinephrine concentrations and compared with data obtained during 30-min saline infusions (prior to calcium and EDTA infusions), are summarized in Table II. From the data in Fig. 3 and Table II, one can estimate the steady-state plasma epinephrine concentration threshold for the hypophosphatemic effect to be between 50 and 100 pg/ml.
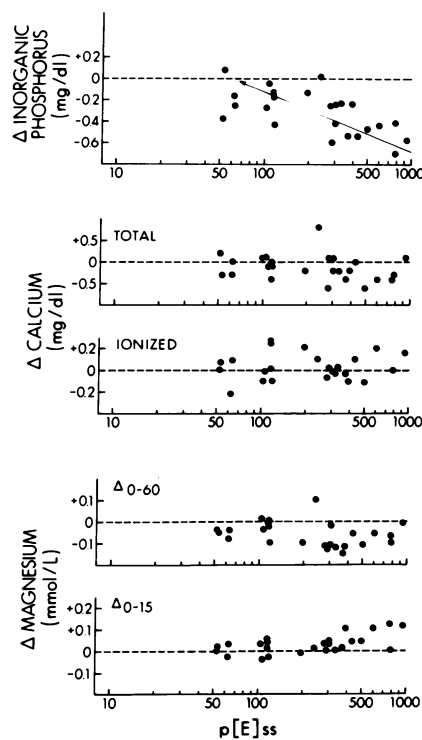
Plasma glucose concentrations (Fig. 4) were similar to those reported by Clutter et al. (2) with dose-dependent increments first apparent at steady-state plasma epinephrine concentrations of 100–200 pg/ml. Dose-dependent changes in plasma insulin were not detected, perhaps because samples were not obtained prior to 10 min of infusion (2).

DISCUSSION

Hypoglycemia produced by rapid intravenous injection of insulin resulted in significant changes in all of the measured variables relating to mineral metabolism in the present study. Most striking was a 35% decrease in serum inorganic phosphorus, but smaller increments in serum total and ionized calcium and total magnesium, and decrements in iPTH and increments in iCT occurred. These changes are all plausibly explained on the basis of the known effects of insulin. The hypophosphatemic effect of insulin, thought to represent net movement of phosphate from the extracellular compartment to intracellular compartments, is well

TABLE II

Relationship between Increasing Steady-state Plasma
Epinephrine Concentrations and Decrements in
Serum Inorganic Phosphorus Concentrations

Condition	Steady-state plasma epinephrine concentration	Number of observations	Change from basal in serum inorganic phosphorus
	pg/ml		mg/dl
Saline infusion	12–28	6	+0.01±0.03
	52–63	4	−0.18±0.10
	102–117	6	−0.20±0.05*
Epinephrine infusions	196–288	4	−0.24±0.13‡
	302–390	5	−0.33±0.06§
	427–945	6	−0.58±0.10§

Comparison with preinfusion value: * $P < 0.01$, ‡ $P < 0.05$, § $P < 0.001$.

recognized. For example, DeFronzo et al. (32) demonstrated decrements in plasma inorganic phosphorus during euglycemic insulin infusions in normal humans. Significant increments in plasma calcium were not observed in that study (32) (perhaps because insulin was infused rather than rapidly injected), but have been reported in animal studies (33–35); there is some evidence that insulin stimulates calcium release from bone (35). Parenthetically, since we used highly purified insulin, it is unlikely that the increments in calcium we saw were the result of contaminants in the injected insulin (33). To our knowledge, insulin-induced rises in serum magnesium have not been re-

FIGURE 4 Change (Δ) from basal at 60 min in plasma glucose (top panel), and at 0–60 min (middle panel) and 0–10 min (bottom panel) in plasma insulin plotted against steady-state plasma epinephrine concentrations (p[E]ss, in picograms per milliliter) during the 25 epinephrine infusions depicted in Figs. 2 and 3. Note the log scale.

ported previously. Lastly, the decrements in iPTH and increments in iCT observed in association with insulin-induced hypoglycemia are reasonably attributed to the observed increments in serum calcium, perhaps in concert with the observed increases in serum magnesium. This idea is supported by our documentation of measurable decrements in iPTH and increments in iCT in response to small increases in serum calcium produced by low-dose calcium infusions (Table I).

Hypoglycemia elicits an array of neuroendocrine responses, including those that play a physiologic role in promoting restoration of euglycemia, specifically, glucagon and epinephrine secretion (36–40). In view of reports, mentioned earlier, that pharmacologic doses of adrenergic agonists including epinephrine can alter serum calcium (3, 4) and phosphorus (5, 6) concentrations, and increase iPTH and iCT levels (3, 9–15), we sought to determine to what extent the changes observed during insulin-induced hypoglycemia might be attributable to epinephrine.

Epinephrine was infused over 60 min in doses resulting in steady-state plasma epinephrine concentrations that ranged from 52 to 945 pg/ml, levels that span the physiologic range (1), in a total of 25 studies. Epinephrine had no effect on the plasma concentrations of PTH or CT or the serum concentrations of ionized calcium. These findings, therefore, do not support the concept that epinephrine plays a physiologic role in the regulation of PTH and CT secretion or in the regulation of serum calcium concentrations in man. Our results contrast with data from several in vitro studies. The ability of epinephrine to increase PTH secretion from parathyroid cells in vitro has been well demonstrated (9, 11). The most likely explanation for this discrepancy lies in the epinephrine concentrations used: an epinephrine concentration in vitro of 10^{-7} M is necessary to raise PTH secretion 50% above control (9), whereas the steady-state epinephrine concentrations achieved during the highest dose infusion were about two orders of magnitude lower, 3.6 × 10^{-9}±0.4 × 10^{-9} M.

The results of our study differ also from some in vivo data. In cows, circulating epinephrine concentrations between 2,000 and 3,000 pg/ml (1.1 × 10^{-8} − 1.6 × 10^{-8} M) can double iPTH levels (13). These concentrations are higher than the ones we achieved, and are clearly supraphysiological for humans (1). Moreover, it is hazardous to relate epinephrine actions in cattle to human physiology, since epinephrine-induced changes in iPTH and free fatty acid levels occur in that species before any increase in heart rate (3), whereas the heart rate is the most sensitive index of epinephrine action in man (2).

Thus, the present data provide strong evidence against a physiologic role for the adrenomedullary
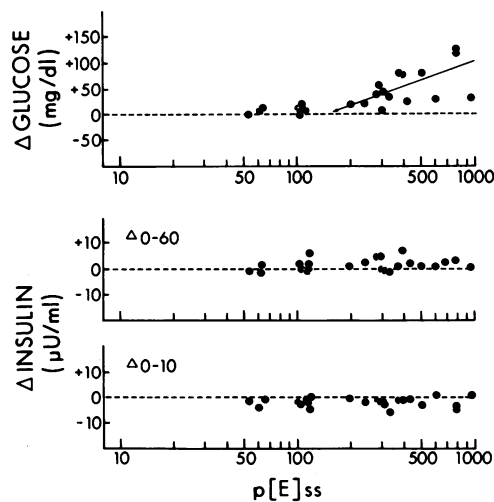
hormone, epinephrine, in the regulation of PTH and CT secretion. They do not, of course, exclude a role for sympathetic neural norepinephrine (15).

Notably, however, physiologic elevations of plasma epinephrine resulted in significant dose-dependent decreases in serum inorganic phosphorus. In the study of Clutter et al. (2), steady-state plasma epinephrine concentration thresholds for the cardiac chronotropic effect of the hormone were estimated to be in the range of 50 to 100 pg/ml; those for the systolic pressor and lipolytic effects in the range of 75 to 125 pg/ml; those for the diastolic depressor, glycogenolytic, glycolytic, and ketogenic effects in the range of 150 to 200 pg/ml; and those for the initial suppression of insulin > 400 pg/ml in the normal human subjects. From the present data, the estimated steady-state plasma epinephrine concentration threshold for the hypophosphatemic effect is 50–100 pg/ml. Thus, the hypophosphatemic effect is among the most sensitive of the known responses to epinephrine in man.

In view of its rapidity, the hypophosphatemic response to epinephrine is probably the result of a net shift of phosphate from the extracellular compartment to intracellular compartments. The mechanisms by which epinephrine causes this shift are not clear. The hypophosphatemic response would appear to be a direct effect of epinephrine, since it is not attributable to increments in serum calcium or to changes in the secretion of PTH or CT, the hormones generally thought to be the primary regulators of rapid changes in mineral metabolism. We have no data regarding whether the phenomenon is mediated by α- or β-receptors. It is conceivable that the hypophosphatemic effect might be secondary to changes in other hormones, particularly insulin. As mentioned earlier, insulin lowers the serum phosphorus concentration, at least when infused in rather high doses (32). Further, although insulin secretion is restrained relative to the hyperglycemia occurring during infusions of epinephrine, small increments in plasma insulin can occur during 60-min epinephrine infusions (2). However, the data of Clutter et al. (2) and the present data argue against the interpretation that insulin alone mediates the hypophosphatemic effect of epinephrine, since steady-state plasma epinephrine concentrations substantially higher than those shown here to cause decrements in serum phosphorus are required to produce meaningful increments in plasma insulin above baseline levels. Lastly, it is unlikely that hyperglycemia alone mediates the hypophosphatemic effect of epinephrine since, again, steady-state plasma epinephrine levels that do not consistently raise plasma glucose (2 and present data) are here shown to lower serum inorganic phosphorus.

Regardless of its mechanisms, these data indicate that epinephrine in physiologic concentrations is a hypophosphatemic hormone in man. In contrast, the data clearly show that circulating epinephrine is not a physiologic regulator of PTH or CT secretion. The hypophosphatemic effect occurs at plasma epinephrine concentrations that are commonly achieved under physiologic conditions. The mechanisms and biologic roles, if any, of this hypophosphatemic action of epinephrine, remain to be established. However, one might speculate that the hypophosphatemia occurring in several clinical states, including sepsis (41), acute myocardial infarction (42), and toxic shock syndrome (43) results in part from epinephrine release.

ACKNOWLEDGMENTS

REFERENCES

1. Cryer, P. E. 1980. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. *N. Engl. J. Med.* **303:** 436–444.
2. Clutter, W. E., D. M. Bier, S. D. Shah, and P. E. Cryer. 1980. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. *J. Clin. Invest.* **66:** 94–101.
3. Fischer, J. A., J. W. Blum, and U. Binswanger. 1973. Acute parathyroid hormone response to epinephrine in vivo. *J. Clin. Invest.* **52:** 2434–2440.
4. Phillippo, M., J. B. Bruce, and C. B. Lawrence. 1970. The effect of adrenaline on calcitonin secretion in conscious sheep. *J. Endocrinol.* **46:** xii–xiii.
5. Perlzweig, W. A., E. Latham, and C. S. Keefer. 1923. The behavior of inorganic phosphate in the blood and urine of normal and diabetic subjects during carbohydrate metabolism. *Proc. Soc. Exp. Biol.* **21:** 33–34.
6. Pekkarinen, A., and H. Hortling. 1951. The effect of continuous intravenous infusion of adrenaline on the circulation and blood chemistry. *Acta Endocrinol.* **6:** 193–214.
7. Rayssiguier, Y. 1977. Hypomagnesemia resulting from adrenaline infusion in ewes: its relation to lipolysis. *Horm. Metab. Res.* **9:** 309–314.
8. Classen, H.-G., P. Marquardt, M. Spath, and K.-A. Schumacher. 1971. Hypermagnesemia following exposure to acute stress. *Pharmacology.* **5:** 287–294.
9. Brown, E. M., S. H. Hurwitz, and G. D. Aurbach. 1977. Beta-adrenergic stimulation of cyclic AMP content and parathyroid hormone release from isolated bovine parathyroid cells. *Endocrinology.* **100:** 1696–1702.
10. Brown, E. M., S. H. Hurwitz, G. D. Aurbach. 1978. Alpha-adrenergic inhibition of adenosine 3',5'-monophosphate accumulation and parathyroid hormone release from dispersed parathyroid cells. *Endocrinology.* **103:** 893–899.

11. Brown, E. M., D. G. Gardner, R. A. Windeck, S. Hurwitz, M. F. Brennan, and G. D. Aurbach. 1979. Beta-adrenergically stimulated adenosine 3',5'-monophosphate release from dispersed human parathyroid cells. *J. Clin. Endocrinol. Metab.* **48:** 618–626.

12. Metz, S. A., L. J. Deftos, D. J. Baylink, and R. P. Robertson. 1978. Neuroendocrine modulation of calcitonin and parathyroid hormone in man. *J. Clin. Endocrinol. Metab.* **47:** 151–159.

13. Blum, J. W., J. A. Fischer, W. H. Hunziker, U. Binswanger, G. B. Picotti, M. DaPrada, and A. Guillebeau. 1978. Parathyroid hormone responses to catecholamines and to changes of extracellular calcium in cows. *J. Clin. Invest.* **61:** 1113–1122.

14. Kukreja, S. C., G. K. Hargis, E. N. Bowser, W. J. Henderson, E. W. Fisherman, and G. A. Williams. 1975. Role of adrenergic stimuli in parathyroid hormone secretion in man. *J. Clin. Endocrinol. Metab.* **40:** 478–481.

15. Heath, H., III. 1980. Biogenic amines and the secretion of parathyroid hormone and calcitonin. *Endocrine Rev.* **1:** 319–338.

16. Arnaud, C. D., H. S. Tsao, and T. Littledike. 1971. Radioimmunoassay of human parathyroid hormone in serum. *J. Clin. Invest.* **50:** 21–34.

17. Gallagher, J. C., B. L. Riggs, C. M. Jerpbak, and C. D. Arnaud. 1980. The effect of age on serum immunoreactive parathyroid hormone in normal and osteoporotic women. *J. Lab. Clin. Med.* **95:** 373–385.

18. Foley, T. P., H. C. Harrison, C. D. Arnaud, and H. E. Harrison. 1972. Familial benign hypercalcemia. *J. Pediatr.* **81:** 1060–1067.

19. Goldsmith, R. S., J. Furszyfer, W. J. Johnson, A. E. Fournier, G. W. Sizemore, and C. D. Arnaud. 1973. Etiology of hyperparathyroidism and bone disease during chronic hemodialysis. III. Evaluation of parathyroid suppressibility. *J. Clin. Invest.* **52:** 173–184.

20. Heath, H., III, G. W. Sizemore, and J. A. Carney. 1976. Preoperative diagnosis of occult parathyroid hyperplasia by calcium infusion in patients with multiple endocrine neoplasia, type 2a. *J. Clin. Endocrinol. Metab.* **43:** 428–435.

21. Van Den Berg, C. J., L. H. Smith, D. M. Wilson, R. Kumar, and H. Heath III. 1980. Orthophosphate decreases urine calcium excretion and serum 1,25-dihydroxyvitamin D levels in idiopathic hypercalciuria. *J. Clin. Endocrinol. Metab.* **51:** 998–1001.

22. Heath, H., III, and D. C. Purnell. 1980. Urinary cyclic 3',5'-adenosine monophosphate responses to exogenous and endogenous parathyroid hormone in familial benign hypercalcemia and primary hyperparathyroidism. *J. Lab. Clin. Med.* **96:** 974–984.

23. Heath, H., III, and G. W. Sizemore. 1977. Plasma calcitonin in normal man: differences between men and women. *J. Clin. Invest.* **60:** 1135–1140.

24. Owyang, C., H. Heath III, G. W. Sizemore, and V. L. W. Go. 1978. Comparison of the effects of pentagastrin and meal-stimulated gastrin on plasma calcitonin in normal man. *Am. J. Dig. Dis.* **23:** 1084–1088.

25. Lambert, P. W., H. Heath III, G. W. Sizemore. 1979. Pre- and post-operative studies of plasma calcitonin in primary hyperparathyroidism. *J. Clin. Invest.* **63:** 602–608.

26. Austin, L. A., H. Heath III, V. L. W. Go. 1979. Regulation of calcitonin secretion in normal man by changes of serum calcium within the physiologic range. *J. Clin. Invest.* **64:** 1721–1724.

27. Heath, H., III, and F. P. DiBella. 1978. Reduced-volume radioimmunoassays for parathyrin and calcitonin in serum for use in pediatric and small animal studies. *Clin. Chem.* **24:** 1833–1835.

28. Cryer, P. E., J. V. Santiago, and S. D. Shah. 1974. Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright posture. *J. Clin. Endocrinol. Metab.* **39:** 1025–1029.

29. Burritt, M. F., A. M. Pierides, and K. P. Offord. 1980. Comparative studies of total and ionized serum calcium values in normal subjects and patients with renal disorders. *Mayo Clin. Proc.* **55:** 606–613.

30. Fiske C. H., and Y. Subbarow. 1925. The colorimetric determination of phosphorus. *J. Biol. Chem.* **66:** 375–400.

31. Herbert, V., K.-S. Lau, C. W. Gottlieb, and S. J. Bleicher. 1965. Coated charcoal immunoassay of insulin. *J. Clin. Endocrinol. Metab.* **25:** 1375–1381.

32. DeFronzo, R. A., C. R. Cooke, R. Andres, G. R. Faloona, and P. J. Davis. 1975. The effect of insulin on the renal handling of sodium, potassium, calcium, and phosphate in man. *J. Clin. Invest.* **55:** 845–855.

33. Taylor, J., H. S. Tager, and E. L. Kaplan. 1976. A hypercalcemic factor in commercially prepared insulin. *J. Surg. Res.* **20:** 361–364.

34. Palmieri, G. M. A., J. Hawrylko, A. Hinton. 1979. Hypercalcemic effect of insulin in the chick. *Endocrinology.* **104:** 1774–1777.

35. Guthmann, H. M. II, G. M. A. Palmieri, A. B. Hinton, and A. L. Guthmann. 1982. The mechanism of insulin-induced hypercalcemia in the chick. *Endocrinology.* **110:** 571–574.

36. Garber, A. J., P. E. Cryer, J. V. Santiago, M. W. Haymond, A. S. Pagliara, and D. M. Kipnis. 1976. The role of adrenergic mechanisms in the substrate and hormonal response to insulin-induced hypoglycemia in man. *J. Clin. Invest.* **58:** 7–15.

37. Clarke, W. L., J. V. Santiago, L. Thomas, E. Ben-Galim, M. W. Haymond, and P. E. Cryer. 1979. The role of adrenergic mechanisms in recovery from hypoglycemia in man: Studies with adrenergic blockade. *Am. J. Physiol.* **236:** E147–E152.

38. Gerich, J., J. Davis, M. Lorenzi, R. Rizza, N. Bohannon, J. Karam, S. Lewis, S. Kaplan, T. Schultz, and P. Cryer. 1979. Hormonal mechanisms of recovery from insulin-induced hypoglycemia in man. *Am. J. Physiol.* **236:** E380–E385.

39. Rizza, R. A., P. E. Cryer, and J. E. Gerich. 1979. Role of glucagon, epinephrine and growth hormone in human glucose counterregulation. Effects of somatostatin and adrenergic blockade on plasma glucose recovery and glucose flux rates following insulin-induced hypoglycemia. *J. Clin. Invest.* **64:** 62–71.

40. Cryer, P. E. 1981. Glucose counterregulation in man. *Diabetes.* **30:** 261–264.

41. Riedler, G. F., and W. A. Scheitlin. 1969. Hypophosphatemia in septicemia: higher incidence in gram-negative than in gram-positive infections. *Br. Med. J.* **1:** 753–756.

42. Betro, M. G., and R. W. Pain. 1972. Hypophosphatemia and hyperphosphatemia in a hospital population. *Br. Med. J.* **1:** 273–276.

43. Tofte, R. W., and D. N. Williams. 1981. Toxic shock syndrome: clinical and laboratory features in 15 patients. *Ann. Intern. Med.* **94:** 149–156.