Plasma Insulin Disturbances in Primary Hyperparathyroidism

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ABSTRACT Plasma insulin dynamics were evaluated in 10 patients with primary hyperparathyroidism before and after parathyroidectomy and correction of hypercalcemia. Before surgery fasting plasma insulin concentrations and insulin responses to administered glucose, tolbutamide, and glucagon were significantly greater than postoperative values. Hyperinsulinemia was not associated with altered glucose curves during glucose or glucagon tolerance tests, but a relatively greater insulin response to tolbutamide resulted in an increased hypoglycemic effect following its administration. The glucose-lowering action of intravenous insulin was slightly impaired before treatment. Intramuscular injections of parathormone to six normal men for 8 days induced mild hypercalcemia and hypophosphatemia and reproduced augmented plasma insulin responses to oral glucose and intravenous tolbutamide. 4-hr intravenous infusions of calcium to another group of six normal men raised serum calcium concentrations above 11 mg/100 ml. This did not alter glucose or insulin curves during oral glucose tolerance but markedly accentuated insulin responses to tolbutamide and potentiated its hypoglycemic effect. When highly purified parathormone was incubated with isolated pancreatic islets of male rats, glucose-stimulated insulin secretion was unaffected.

These findings suggest that chronic hypercalcemia of hyperparathyroidism sustains a form of endogenous insulin resistance that necessitates augmented insulin secretion to maintain plasma glucose homeostasis. This state is insufficient to oppose tolbutamide-induced hypoglycemia because of an additional direct, selective enhancement of hypercalcemia on pancreatic beta cell responsiveness to the sulfonylurea. The possible direct role of parathormone in these events has not been established.

INTRODUCTION

In the syndrome of multiple endocrine adenomatosis two of the most commonly encountered abnormalities are hyperparathyroidism and pancreatic islet adenomas (1). During the course of screening several patients with suspected hyperparathyroidism for evidence of associated endocrine neoplasms and organic hyperinsulinism, the diagnosis of this syndrome could not be established. However, it became apparent that subjects with uncomplicated primary hyperparathyroidism do manifest significant disturbances in plasma concentrations of immunoreactive insulin. Factors that may be responsible for the development of this abnormality were assessed in the present study.

METHODS

Studies of hyperparathyroid subjects. Seven men and three women were referred to the metabolic service for evaluation of persistent hypercalcemia and hypophosphatemia which were discovered during routine multiphasic screening procedures. Each subject had a normal physical examination and gave no history of recent significant illness or marked changes in body weight. Routine blood counts, urinalyses, and concentrations of serum sodium, potassium, chloride, and CO_2 combining power, blood urea nitrogen, and serum creatinine were normal, as were thyroid and liver function studies. Roentgenograms of the chest, gastrointestinal tract, kidneys, and skeleton were unremarkable. All patients were hospitalized in the Clinical Research Center and placed on diets containing 35 cal/kg body weight and 300 g of carbohydrate. After 3 days of dietary preparation, glucose, tolbutamide, glucagon, and insulin tolerance tests were performed. Subsequently, each patient underwent a surgical neck exploration at which time one

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enlarged parathyroid gland was removed from eight subjects and two enlarged glands from two patients. The diagnosis of parathyroid adenoma was confirmed by microscopic examination of permanent histological sections of the tumors in the Department of Pathology of this hospital. There were no unusual postoperative complications, and 6–12 wk later the patients were rehospitalized, placed on the same diets, and, after the 3rd day, all routine laboratory studies and tolerance tests were repeated. Vitamin D or calcium supplements were not administered to any patients during convalescence. All felt well and exhibited a good surgical result.

Studies of volunteer subjects. 12 healthy men participated in two separate investigations in the Clinical Research Center. All were prepared with the same high carbohydrate diet described previously for at least 3 days. Oral glucose and intravenous tolbutamide tolerance tests were performed on successive days in one group of six men. Thereafter, they received intramuscular parathormone, 150–180 USP units every 8 hr, for 8 days. Daily fasting blood specimens were obtained throughout this period for calcium and inorganic phosphorus determinations. On days 7 and 8, the two tolerance tests were repeated.

In the second group of six men, 4-hr intravenous infusions of 480 ml of 0.85% saline, 2 ml/min, were done on two different mornings. Flow was regulated by an infusion pump. At the 2nd hour either the oral glucose or intravenous tolbutamide tolerance test was begun. After a 2 day rest period the two infusions were repeated on successive days in the same manner except that the infused solution contained ionized calcium, 16 mg/kg body weight. The infusate was prepared by bringing a concentrated calcium chloride solution to 480 ml with 0.85% saline. During each infusion the patient's pulse, blood pressure, and electrocardiogram were monitored carefully.

Testing procedures and analytical methods. All tolerance tests were performed after an overnight fast. Oral tests employed 100 g of glucose. For the intravenous glucose challenge, 50 ml of 50% glucose in water was infused within 2 min. 1 g of tolbutamide and 1 mg of glucagon were administered intravenously over 1 min periods. Regular U-40 insulin, 0.1 U/kg body weight, was injected rapidly intravenously. Forearm venous blood samples were withdrawn through an indwelling 19-gauge needle attached to a sterile plastic catheter on a syringe. Between sampling the needle was kept patent with a dilute heparin-saline solution. Blood was collected in tubes placed in ice. Tubes were centrifuged at 4°C. Plasma was frozen until glucose, immunoreactive insulin, and growth hormone concentrations were measured (2–4). Samples from each subject were analyzed together on the same assay. Total plasma insulin responses were calculated from the area circumscribed by the plasma insulin response curve above fasting levels. Each curve was drawn to the same scale, measured with a planimeter, and expressed in arbitrary units. Serum calcium and inorganic phosphorus concentrations were determined on a Technicon AutoAnalyzer. The normal range for calcium is 9.0–10.5 mg/100 ml and, for phosphorus is 3.0–5.0 mg/100 ml utilizing this automated method.

In vitro studies of isolated pancreatic islet insulin secretion. Male Sprague-Dawley rats weighing 350–375 g were housed in a room maintained at 72°F with 12 hr lighting from 6 a.m. to 6 p.m. Water and food pellets containing 58% carbohydrate, 11% fat, and 31% protein were fed ad lib. After an overnight 12 hr fast the animals were decapitated and the abdomen was opened. Methods for ***in situ*** retrograde perfusion of the pancreas with cold Hanks' solution, separation of pancreatic islets in collagenase incubations, and washing procedures are those of Lacy and Kostianovsky (5), and modifications for this laboratory have been described in detail elsewhere (6). Final suspensions of islets in Hanks' solution were placed in a Petri dish within a larger Petri dish containing ice and were viewed under a stereomicroscope. Four groups of 10 islets of uniform size and shape were quickly transferred with a 500 μl micropipette to incubation media contained in 5-ml Erlenmeyer flasks. Two sets of islets were utilized for control experiments. The remaining two sets were incubated with parathormone. Incubation media contained 2% albumin-Krebs-Hensleit bicarbonate buffer, pH 7.4 (7), with 5.5 mM sodium salts of fumarate, glutamate, and pyruvate, 1000 kallikrein inactivator units of Trasylol, and varying concentrations of glucose. Final volume was adjusted to 2.0 ml, and incubations were carried out at 37°C under constant gassing with 95% O_2–5% CO_2.

In direct single-phase incubation studies the experimental flasks contained 5, 10, or 25 μg/ml of highly purified parathormone. Control flasks contained no hormone. Two 25-μl samples were removed at 0 time and at 90 min for determinations of immunoreactive insulin.

In each two-phase incubation experiment the four groups of 10 islets were incubated for 120 min in a medium containing 0.5 mg glucose per ml. Two of the four groups of islets were exposed to purified parathormone, 50 μg/ml. Two 25-μl samples were removed from the flasks at 0 and 120 min for insulin determinations. At 120 min the medium was carefully aspirated, and the islets were repeatedly washed with fresh buffer. Volume again was adjusted to 2.0 ml with the same media containing 3.0 mg of glucose per ml, but without parathormone. The four flasks were incubated for 60 min, and samples were removed at the beginning and end of this time period for measurements of insulin as before. All samples of media were diluted in appropriate volumes of cold 5% albumin–0.075 M Veronal buffer, pH 8.6, in preparation for insulin immunoassays.

In all in vitro procedures the differences between total insulin content of media at the beginning and end of an incubation procedure were recorded as total insulin secretion per 10 islets during that specific time interval.

Statistical analysis. Statistical comparisons of mean values within groups of patients before and after parathyroidectomy or before and during calcium infusion or parathormone administration were done by applying the Student's t test to paired data. The t test for unpaired data analysis was employed to compare total insulin secretion of islets incubated with and without parathormone (8).

Chemicals and reagents. Collagenase was purchased from Worthington Biochemical Corp., Freehold, N. J. Hanks' balanced salt solution was obtained from Grand Island Biological Co., Grand Island, N. Y. Trasylol was supplied by FBA Pharmaceuticals Co., New York. Purified human growth hormone and human crystalline insulin, which were used as standards in immunoassays, were gifts of the National Pituitary Agency, Baltimore, Md., and The Eli Lilly Research Laboratories, Indianapolis, Ind., respectively. Highly purified parathormone, containing at least 1000 USP units/mg, was purchased from The Wilson Laboratories, Chicago, Ill. Eli Lilly and Co. supplied Parathyroid Injection, 100 USP units/cc, glucagon, and regular U-40 insulin (Iletin). Tolbutamide (Orinase) for injection was purchased from Upjohn Co., Kalamazoo, Mich.

TABLE I
Age, Body Weight, and Changes in Measured

Group	Age	Weight	% > IBW*	Serum calcium‡	Serum phosphorus‡
	yr	*lbs.*		*mg/100 ml*	*mg/100 ml*
Hyperparathyroid (10)‖					
Before surgery	41 ±2	167 ±10	6 ±5	11.9 ±0.2¶	2.7 ±0.2¶
After surgery	—	169 ±9	6 ±4	9.7 ±0.1	3.4 ±0.2
Calcium infusion (6)					
Saline infusion	33 ±5	162 ±9	3 ±2	9.9 ±0.2	4.3 ±0.2
Calcium infusion	—	—	—	See Fig. 6	See Fig. 6
Parathormone administration (6)					
Control period	35 ±3	159 ±6	−2 ±3	9.6 ±0.1	4.0 ±0.3
During administration	—	—	—	See Fig. 4	See Fig. 4

* IBW: ideal body weight (Metropolitan Life Insurance Tables, 1959).
‡ Values for each subject in the hyperparathyroid group are the average of four determinations on 4 separate days. In the other groups they are the average of two determinations on 2 separate days.
§ GTT and TTT refer to oral glucose and intravenous tolbutamide tolerance tests, respectively.
‖ Numbers in parentheses indicate number of subjects. All columns indicate mean values ±SEM.
¶ Significance of the difference between mean values before and after treatment within the same group, $P < 0.05$.

RESULTS

Hyperparathyroid patients. The 10 subjects were nonobese as a group before surgery. At the time of postoperative studies mean body weight had not changed significantly. Serum calcium and phosphorus concentrations were restored to normal values and were significantly different from preoperative levels (Table I).

Plasma glucose curves during oral and intravenous glucose tolerance and glucagon tolerance tests were not altered by surgical treatment, but preoperative plasma insulin concentrations were significantly higher than corresponding posttreatment concentrations at many time intervals (Figs. 1 and 2). A greater hypoglycemic response to tolbutamide administration oc-

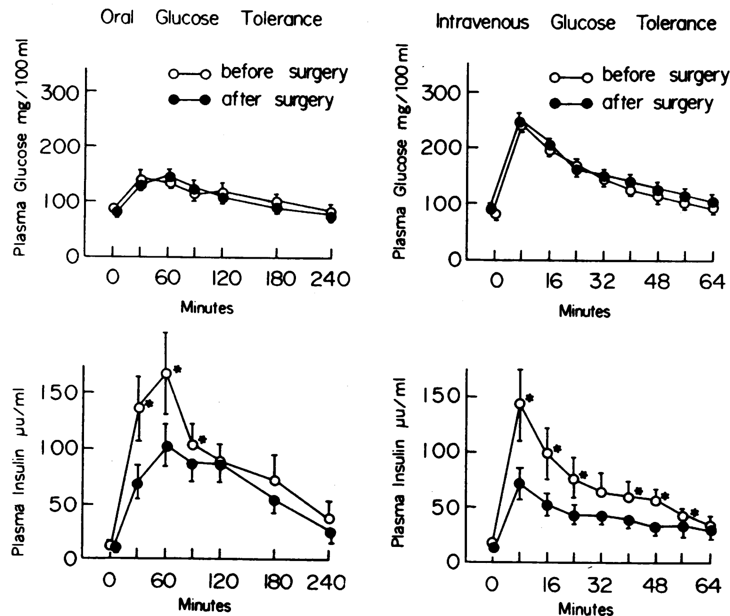

FIGURE 1 Plasma glucose and insulin responses during oral glucose and intravenous glucose tolerance tests in 10 hyperparathyroid subjects. Values are mean ±SEM. Asterisks denote significance of the difference between corresponding means before and after surgery, $P < 0.05$.

Parameters before and after Treatment

Fasting plasma glucose‡	Fasting plasma insulin‡	GTT total plasma insulin response§	Per cent change	TTT total plasma insulin response§	Per cent change
mg/100 ml	*μU/ml*	*Planimetry units*	*%*	*Planimetry units*	*%*
87 ±1	20 ±2¶	2595 ±284¶	+41%	387 ±89¶	+72%
87 ±1	14 ±1	1772 ±208		225 ±49	
87 ±3	18 ±2	1882 ±344		278 ±75	
84 ±2	18 ±3	1720 ±194	−9%	625 ±179¶	+125%
86 ±2	12 ±2	1362 ±179		164 ±40	
86 ±1	12 ±2	1999 ±311¶	+47%	310 ±77¶	+89%

curred before surgery in association with increased plasma insulin concentrations (Fig. 2).

When basal insulin concentrations for the four tolerance tests were averaged, preoperative mean values were significantly higher than postoperative concentrations (Table I). Total plasma insulin responses during glucose and tolbutamide tolerance tests before treatment also exceeded posttreatment responses significantly (Table I).

Plasma glucose nadirs during insulin tolerance tests were slightly, though significantly higher before treatment of hyperparathyroidism. Peak growth hormone

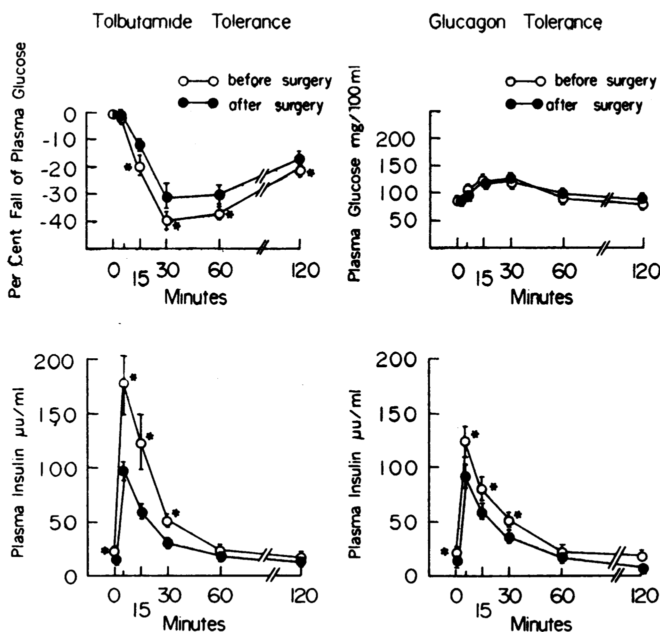

FIGURE 2 Plasma glucose and insulin responses during tolbutamide and glucagon tolerance tests in 10 hyperparathyroid subjects. Values are mean ±SEM. Asterisks denote significance of the difference between corresponding means before and after surgery, $P < 0.05$.

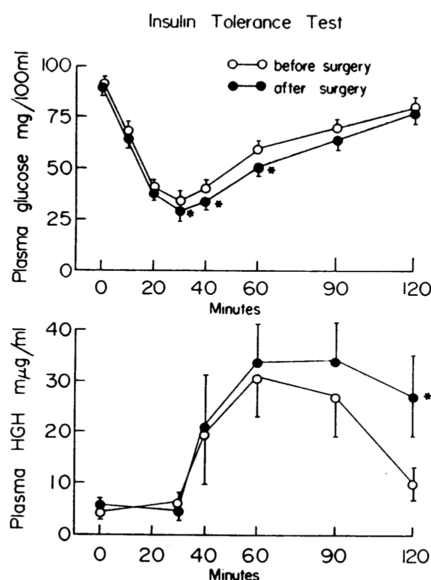

FIGURE 3 Plasma glucose and growth hormone responses during intravenous insulin tolerance tests in 10 hyperparathyroid subjects. Values are mean ±SEM. Asterisks denote significance of the difference between corresponding means before and after surgery, $P < 0.05$.

responses to induced hypoglycemia were similar before and after treatment with the exception of the 120 min value (Fig. 3).

Glucose and tolbutamide tolerance after parathormone administration. After 24–48 hr of parathormone injections, significant changes in serum calcium and phosphorus began to occur. On days 7 and 8 mean calcium levels approached 11 mg/100 ml and hypophosphatemia was observed (Fig. 4).

On day 7 oral glucose tolerance was unaffected. Mean plasma insulin concentrations were higher than during the control period, but individual variations in hormonal response at specific intervals in this small group of patients prevented the demonstration of a statistically significant change (Fig. 5). Nevertheless, the total plasma insulin response to oral glucose was increased significantly as it was during tolbutamide tolerance on day 8 (Table I). In the latter test 5- and 15-min plasma insulin concentrations were higher after parathormone treatment. The plasma glucose nadir at 30 min also tended to be lower than the corresponding control value, but the difference was not significant (Fig. 5).

Glucose and tolbutamide tolerance during intravenous calcium infusions. When calcium was infused into six normal men, serum calcium concentrations rose to levels in excess of 11 mg/100 ml by the 2nd hour with little change in serum phosphorus concentrations. After terminating the infusion at hour 4, serum calcium fell slightly but remained in the hypercalcemic range (Fig. 6). Similar control infusions of saline did not change serum calcium or phosphorus concentrations from base line values significantly. Plasma glucose and insulin concentrations during oral glucose tolerance were not altered by calcium infusion. However, the induction of hypercalcemia produced an increased plasma insulin response to intravenous tolbutamide that was attended by a greater glucose-lowering effect similar to that observed in hyperparathyroid patients before surgery (Fig. 7).

Fasting plasma glucose and insulin concentrations were unaffected by hypercalcemia. Total plasma insulin responses were significantly increased during tolbutamide tolerance, but not during glucose tolerance (Table I).

Pancreatic islet studies. In single-phase studies incubation of isolated rat pancreatic islets with different concentrations of parathormone had no effect on glucose-stimulated insulin secretion (Table II). Two phase incubation studies utilized 24 sets of 10 islets obtained from pancreatic tissue of six rats. When 12 sets were preincubated with parathormone (50 μg/ml) in a low glucose medium (0.5 mg/ml) for 2 hr, total insulin secretion was 446±51 μU. This did not differ from the response of 12 control sets incubated without parathormone (357±48 μU, $P > 0.05$). Subsequent incubation of experimental group of islets in a high glucose medium (3.0 mg/ml) for 1 hr in the absence of parathormone induced a total insulin secretion (741±36 μU) that was higher, but not significantly different

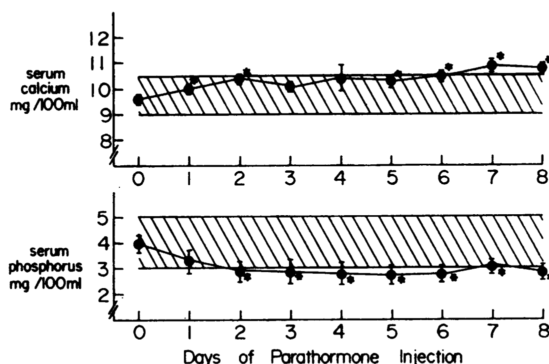

FIGURE 4 Serum calcium and inorganic phosphorus concentrations in six normal adult men during an 8 day period of intramuscular parathormone administration. Values are mean ±SEM. Asterisks indicate significance of the difference between serum calcium and phosphorus concentrations on day 0 and subsequent days, $P < 0.05$. Hatched areas represent normal ranges.

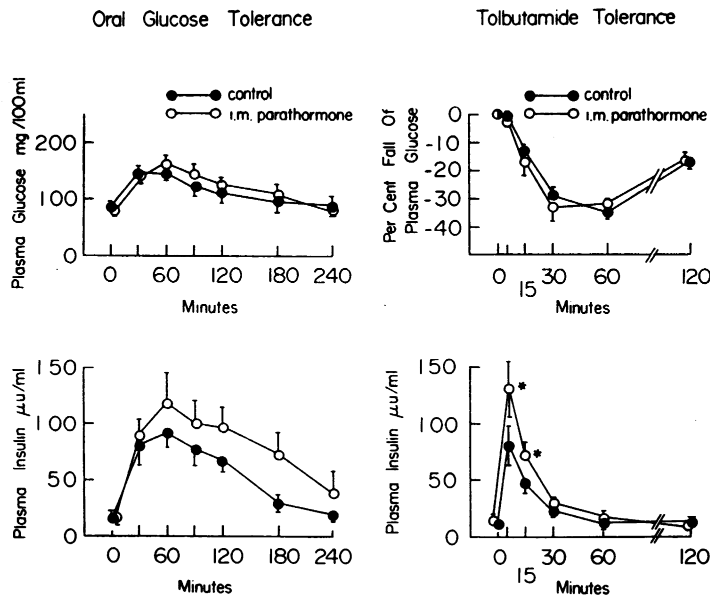

FIGURE 5 Plasma glucose and insulin responses in six normal adult men during oral glucose and tolbutamide tolerance tests before and on days 7 and 8 of parathormone administration (see Fig. 4). Values are mean ±SE. Asterisks indicate significance of the difference between corresponding means before and during parathormone treatment, $P < 0.05$.

from total hormonal output of the control islet group (670 ±48 μU, $P > 0.05$).[1]

DISCUSSION

Correction of plasma insulin disturbances after surgical treatment of patients with primary hyperparathyroidism suggests that either excessive blood parathormone levels or hypercalcemia or combined effects of both enhance pancreatic islet responsiveness to known stimuli.

Actions of parathormone on bone and kidney have been linked to adenyl cyclase stimulation and generation of cyclic 3′-5′ adenosine monophosphate (10–12). A similar system is present in the beta cell. Its activation promotes insulin secretion (13, 14) although the relative importance of cyclic nucleotide in glucose-stimulated insulin output remains controversial (15–17). The possibility that parathormone may play upon beta cell adenyl cyclase or a related mechanism and facilitate insulin release in response to glucose is not supported by acute in vitro studies of isolated pancreatic islets in this laboratory. In preliminary investigations of two normal men, the intravenous infusion of parathormone, 1000 USP units in saline over a 3 hr period, also did not alter basal plasma glucose or insulin concentrations measured every 30 min. The administration of oral glucose or intravenous tolbutamide at the completion of infusions was not attended by an increased plasma insulin response. However, none of these studies excludes possible long-term effects the hormone ultimately may have on islet function.

In contrast to parathormone, calcium is known to exert significant positive action on secretory processes of nonendocrine and endocrine tissues including those of nerve endings, salivary glands, exocrine pancreas, the pituitary, adrenal, and thyroid (18). The ion is an absolute requirement for physiologic release of stored insulin from the pancreas, but there is no evidence that it influences *de novo* synthesis of the hormone (19–21). Others have demonstrated that glucose entry into pancreatic islets is accompanied by increased penetration of calcium ion (22–24). Lacy has summarized electron microscopic evidence which suggests that calcium ion influx promotes emiocytosis by stimulating contraction of microtubular structures and deliverance of insulin granules attached in tandem to the surface membrane of the beta cell for extrusion (25). One might speculate that chronic hypercalcemia of hyperparathyroidism may accentuate this process, perhaps by inducing a greater inward movement of the ion in response to

[1] In these experiments 5–50 μg of parathormone per ml are not physiologic concentrations. Estimates of parathormone content in normal human plasma may range from 0.0005 to 0.006 μg/ml. This calculation is based on a reference serum from a patient with primary hyperparathyroidism that was believed to contain at least 0.06 μg/ml of parathormone (9).

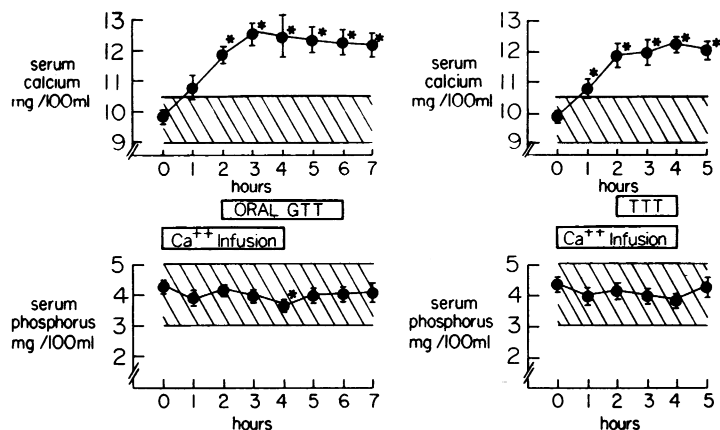

FIGURE 6 Serum calcium and inorganic phosphorus concentrations during intravenous calcium infusions to six normal adult men on 2 separate days. Infusion periods were from hour 0 to hour 4. Oral glucose tolerance (GTT, left panel) was performed between hours 2 and 6. Tolbutamide tolerance (TTT, right panel) was done between hours 2 and 4. Values are mean ±SE. Asterisks indicate significance of the difference between mean serum calcium and phosphorus concentrations at 0 time and values during or after infusions, $P < 0.05$. Hatched areas represent normal ranges.

substrate entry or by conditioning the secretory mechanism within the beta cell to overreact to an appropriate signal.

This conclusion is untenable in the acute situation, because calcium infusions did not alter the plasma insulin response curve to oral glucose in six normal men in contradistinction to marked increases in hormonal response to tolbutamide. These data confirm previous observations that demonstrate a differential effect of increased calcium concentrations on insulin output by the isolated perfused pancreas and pancreatic slices when glucose and tolbutamide stimulation are compared (19–21).[2]

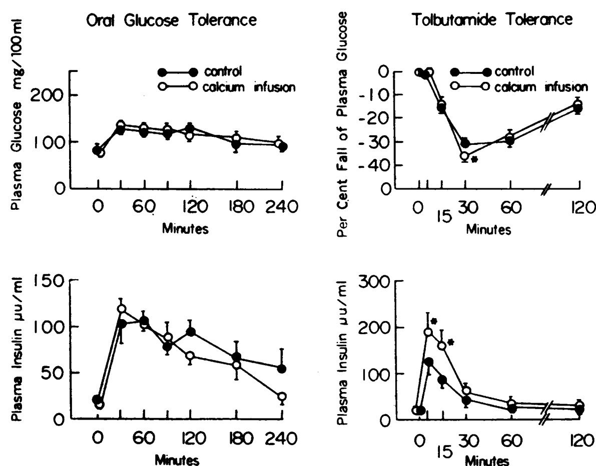

FIGURE 7 Plasma glucose and insulin concentrations during oral glucose and tolbutamide tolerance tests in six normal adult men. Time relationships between periods of calcium infusion and performance of tolerance tests are illustrated in Fig. 6. Values are mean ±SE. Asterisks indicate significance of the difference between corresponding means during control saline infusions and calcium infusions, $P < 0.05$.

If both acute and chronic hypercalcemia do not directly enhance islet responsiveness to glucose, it is possible that the ion may influence endocrine pancreas indirectly by modifying membrane properties and metabolism of peripheral tissues. The induction of hypercalcemia is associated with tissue accumulation of the ion (30), which, in several in vitro experiments, has been shown to inhibit glycolysis by suppressing the activity of key glycolytic enzymes including pyruvate kinase and phosphofructokinase (31).

Inhibitory effects on glycolysis may be compounded by the additional suppressive action calcium–adenosine triphosphate complexes might have on Na^+-K^+–activated adenosine triphosphatases whose maintenance of an inward sodium gradient promotes glucose cotransport into cells in some instances (31–33). This inhibition of glucose cotransport does not apply to all tissues,

[2] This is additional evidence that the two substances promote insulin secretion by different mechanisms. Unlike glucose, tolbutamide also evokes insulin release that is not inhibited by diazoxide or mannoheptulose (26, 27) and appears to be due, in part, to cyclic adenosine monophosphate phosphodiesterase inhibition (28). Physical changes in beta cells viewed by electron microscopy also suggest a distinction between effects of glucose and the sulfonylurea (29).

TABLE II

Effects of Parathormone on Isolated Pancreatic Islet Insulin Secretion

Study	Group	No. of incubations	Glucose concentration	Parathormone concentration	Total insulin secretion*	P value
			mg/ml	*μg/ml*	*μU/10 islets per 90 min*	
1	Control (6)‡	12	0.3	—	237 ±38	
	Parathormone (6)	12	0.3	25	196 ±69	NS§
2	Control (6)	12	1.5	—	456 ±108	
	Parathormone (6)	12	1.5	25	430 ±81	NS
3	Control (6)	12	3.0	—	588 ±74	
	Parathormone (6)	12	3.0	25	645 ±54	NS
4	Control (6)	12	3.0	—	527 ±52	
	Parathormone (6)	12	3.0	10	556 ±51	NS
5	Control (1)	2	3.0	—	558	—
	Parathormone (1)	2	3.0	5	585	

‡ Numbers in parentheses indicate number of animals. Each pancreas provided four sets of 10 islets, two for control incubations and two for parathormone incubations.
* Values are mean ±SE.
§ NS: no significant difference between mean values of control and parathormone incubations, $P > 0.05$.

including insulin-sensitive skeletal muscle (34, 35), but further studies are indicated to define the outcome of unphysiologic calcium concentrations on insulin action generally. In this context it is of interest that calcium imparts greater cohesiveness between cells, has a "tightening" effect on cytoplasmic membranes and reduces their permeability to a variety of substances (36). One or more of these mechanisms may relate hypercalcemia to impaired peripheral tissue glucose utilization which, in turn, may sustain a greater glucose feedback stimulus for the pancreatic islet to synthesize and release more insulin. Acute calcium infusion studies may have been too brief to reproduce this effect.

This hypothesis is strengthened by the findings of basal hyperinsulinemia and slightly impaired hypoglycemic effects of intravenous insulin in hyperparathyroid patients before treatment. The significance of the first observation with respect to endogenous insulin resistance has been reviewed elsewhere (37). These results together with the uniformly increased plasma insulin responses to glucose, tolbutamide, and glucagon share characteristics of other conditions believed to exemplify states of insulin antagonism (38–42).

Although impaired carbohydrate tolerance was not a feature of hyperparathyroidism in this investigation and is similar to the reported experience of both Dent (43) and Halver (44), chemical diabetes was found in 80% of patients with this disorder in another study and was ameliorated in the majority of cases after parathyroidectomy.[3] The paradoxical enhancement of tolbutamide-induced hypoglycemia in hyperparathyroid patients does not necessarily exclude the presence of a contra-insulin effect. It is suggested that the greater sensitivity of the pancreatic islet to tolbutamide in hypercalcemic states results in enough additional insulin secretion to overcome relatively weaker forces opposing this effect.

Compensatory pancreatic islet hypertrophy frequently is demonstrable in acquired forms of endogenous insulin resistance and diabetogenic stress including obesity and pregnancy (46, 47). Similar changes have been reported in 12 of 15 autopsied cases of primary hyperparathyroidism (48). Although the authors attributed this finding to pancreatitis and alpha cell hyperplasia, islet cell types were not identified. The observation could represent beta cell hyperplasia, since this would be in accord with the plasma insulin abnormality that exists in the hyperparathyroid state.

Nevertheless, interest in the role of hyperglucagonemia in the genesis of hyperparathyroidism (48) has been revived recently following the report that glucagon infusions increase parathormone concentrations in human subjects (49). These results point to the influence of the pancreatic alpha cell hormone on parathyroid function while the present study establishes an association between hyperfunctioning parathyroid glands and overactivity of the beta cell. The relevance of

[3] Birge, S. Unpublished data described in a clinicopathological conference (45).

these data to interglandular control mechanisms and to the actual development of polyendocrine syndromes remains to be determined. Another dimension, that of ionic control of intracellular metabolism, deserves further investigation with regard to disposition of glucose in peripheral tissues and possible modifying influence of calcium ion on insulin action. It is not known to what extent parathormone acts independently or in concert with hypercalcemia during the evolution of these metabolic changes.

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