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Insulin-Induced Hypoglycaemia Stimulates Secretion of Parathyroid Hormone

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With 1 Figure

Summary. In-vitro and in-vivo studies have suggested a role for the adrenergic system in the regulation of secretion of parathyroid hormone (PTH). In the present study the effects of insulin induced hypoglycaemia on serum concentrations of PTH, cortisol, calcium and phosphate were evaluated in ten healthy subjects.

Maximum hypoglycaemia occurred 25 to 35 min after administration of insulin at a standard dose of 0.15 U/kg body weight. All this time there was a slight and transient increase of the serum calcium concentrations whereas there was a marked drop in the serum phosphate levels with a nadir 15 min after maximum hypoglycaemia. Cortisol levels were below baseline when blood glucose was as lowest but increased to a maximum level of 200% 60 minutes after maximum hypoglycaemia.

Serum PTH levels increased significantly and reached a maximum of 130% of baseline values concomitant with maximum hypoglycaemia, whereafter they returned to pre-insulin-injection levels within 15 minutes. These findings indicate that during stress endogenous catecholamines affect the secretion of PTH which could be of physiologic importance.

In five patients with primary hyperparathyroidism there was, however, no increase in the PTH levels, although they displayed the same response to hypoglycaemia for cortisol and phosphate. This supports previous suggestions that these patients have an impaired capacity to respond to circulating catecholamines.

Key words: Parathyroid hormone, calcium, phosphate, catecholamines, hypoglycaemia, hyperparathyroidism

Introduction

In-vitro studies have shown that the secretion of parathyroid hormone can be stimulated by beta-adrenergic agonists (Brown et al., 1977; Fischer and Blum, 1980). If this mechanism is of importance in-vivo has been debated. While it has been reported in some studies that isoproterenol could raise the serum PTH levels (Kukreja et al., 1981) this has not been confirmed in other investigations (Epstein et al., 1983).

We have recently described that infusions of epinephrine increased the serum levels of PTH in normal subjects. This increase was prevented by simultaneous infusion of propranolol and could not be seen when norepinephrine was administered. Thus there appeared to be a specific betaadrenergic response of PTH (Ljunghall et al., 1983).

In order to evaluate further if this mechanism was of an any importance during normal conditions we have in the present study investigated the effects of release of endogenous catecholamines, during an insulin-induced hypoglycaemic stress, on the serum levels of PTH, calcium and phosphate.

Material and Methods

Ten subjects, with no evidence of abnormalities of calcium metabolism were studied. The age range was 22—56 years, with an average of 42 years. We also investigated 5 patients with primary hyperparathyroidism (3 females, 2 males) with ages between 28 and 62 years. All these patients had hypercalcaemia (serum calcium between 2.66 and 2.82 mmol/l) and following parathyroid surgery (3 adenomas, 2 hyperplasias) all became normocalcaemic. Each participant gave informed consent to the study, which was approved by the Ethical Committee of the Faculty of Medicine.

The procedures were performed between 8 and 10 a.m. after an overnight fast. A vein needle for sample collection was placed in an antecubital vein. Insulin (0.15 U/kg) was rapidly administered intravenously in the opposite extremity. Venous blood was collected at regular intervals for 90 minutes for the measurements of blood glucose and serum PTH, calcium, albumin, phosphate and cortisol levels.

Serum PTH concentrations were measured by a radioimmunoassay technique as described earlier (Ljunghall et al., 1982). In short, this assay measures preferentially intact PTH and a mid-portion fragment (44—68) of this hormone. The range of values in normal subjects is 0.40—1.20 arbitrary units/liter. The serum calcium concentrations were measured by atomic absorption and phosphate with a molybden-complexing method.

Results

As indicated in Fig. 1a, insulin caused a significant hypoglycaemia in all the normal subjects. The maximum hypoglycaemia occurred between 25 and 35 min following the administration of insulin and was accompanied in each subject by the expected signs and symptoms of hypoglycaemia, such as sweating and mild tachycardia. The plasma glucose returned to near baseline values at 90 min.

The baseline serum calcium values were in all cases within the normal range. At the time of maximum hypoglycaemia there was a slight and transient, but statistically significant, rise in the serum calcium levels (Fig. 1b). The serum phosphate concentrations decreased rapidly to 75 ± 5 (SD) % of baseline value at the time of maximum hypoglycaemia (Fig. 1c). They thereafter decreased further to a nadir of 65 ± 5 % at 15 min later.

The serum cortisol levels were below baseline values at the time of maximum hypoglycaemia but began to rise thereafter and reached a maximum at 60 min after the most pronounced hypoglycaemia (Fig. 1d).

The baseline pre-insulin-injection concentrations of PTH were normal in all subjects with a mean value of 0.76 ± 0.27 (SD) arb U/l. Fig. 1e shows the changes of PTH following insulin administration. A significant increase in serum PTH occurred concomitant with the maximum hypoglycaemia reaching 130 ± 20 % of the baseline value. The PTH levels returned to baseline levels already within 15 minutes thereafter.

The hyperparathyroid patients displayed similar responses for serum calcium, phosphate and cortisol during hypoglycaemia as the normal subjects. However, in these patients there were no changes of the serum PTH values (Table 1).

Discussion

The present study demonstrates stimulation of PTH secretion during insulin-induced hypoglycaemia. During this test the catecholamine responses are known to occur at 15—20 min after insulin injection or 10—15 min prior to the time of maximum hypo-

glycaemia (Christensen et al., 1975). Thus the stimulation of secretion of various hormones (e. g. growth hormone, adrenocorticotropic hormone, glucagon) which occurs after the time of maximal hypoglycaemia may be caused by the action of already released catecholamines on other endocrine glands.

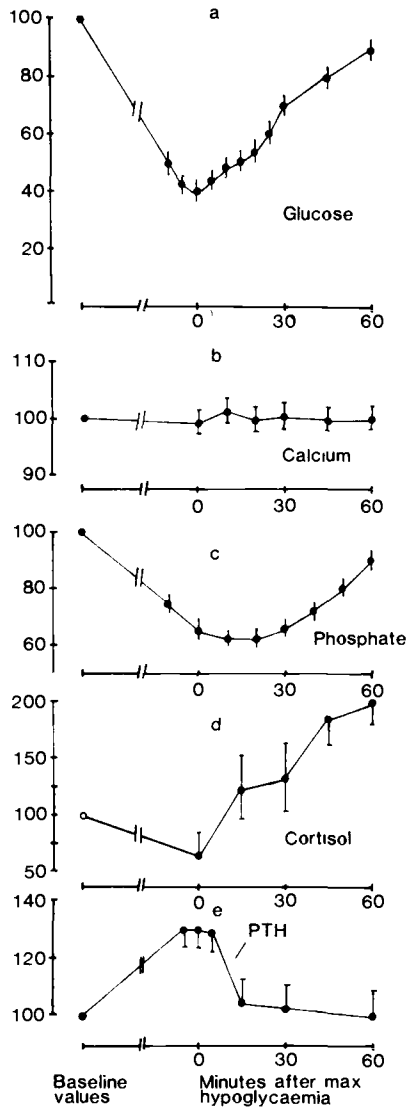

Fig. 1a—d Effects of insulin-induced hypoglycaemia on blood glucose, serum calcium, phosphate cortisol and PTH (from top to bottom) in relation to time after maximum hypoglycaemia (mean values ± SEM). At the time of maximum hypoglycaemia the values for blood glucose, serum phosphate, cortisol and PTH were all significantly ($p < 0.001$) lower than baseline values, while serum calcium was higher ($p < 0.05$) (Student's t-test for paired data)

Table 1 Maximal response (mean ± SD) for serum parathyroid hormone (PTH), calcium, phosphate and cortisol to insulin-induced hypoglycaemia in patients with primary hyperparathyroidism

	PTH (arb U/l)	Calcium (mmol/l)	Phosphate (mmol/l)	Cortisol (μmol/l)
Baseline	1.01 ± 0.16	2.79 ± 0.07	0.70 ± 0.10	470 ± 190
Maximal response	0.98 ± 0.16	2.82 ± 0.03	0.38 ± 0.07*	925 ± 180*

* $p < 0.001$ compared to baseline (paired t-test)

In the present study there was a clear secretory response of PTH, a response that occurred already while the glucose levels were decreasing. The maximum rise appeared approximately concomitant with maximum hypoglycaemia. In a previous study, where we evaluated the effects of exogenous epinephrine it was found that PTH levels increased within 15 minutes after starting an infusion with 2.5 μg/min and PTH levels returned to baseline within 15 minutes after termination of infusion (Ljunghall et al., 1984). This time sequence is closely similar to that found in the present study during insulin-induced hypoglycaemia. Thus it appears likely that endogenous catecholamines caused the secretion of PTH. Similar findings were reported by Shah et al. (1975).

During hypoglycaemia in man the plasma epinephrine levels increase to values ranging between 0.5 and 1.5 ng/ml (Christensen et al., 1975). These concentrations correspond well to those that were obtained in our previous study when we performed infusions of epinephrine at rates between 2.5 and 10 μg/min. During the continuous infusion of epinephrine serum calcium concentrations were reduced already at the lowest rate and decreased even further at the higher rates of epinephrine administration (Ljunghall et al., 1984). In contrast, in the present study serum calcium levels were slightly raised concomitant with hypoglycaemia and marked clinical adrenergic symptoms. In the chick, insulin stimulates the release of calcium from bone (Guthmann et al., 1982) and causes hypercalcaemia. Possibly the multihormonal response to hypoglycaemia also involves counterregulatory factors that oppose the calcium-lowering action of epinephrine. McCarron et al. (1982) suggested that, at least in part, the beta-adrenergic stimulation of PTH secretion may be mediated by antecedent changes in serum calcium. Our observations, in the present study, indicate that a decrease of serum calcium is not a pre-requisite for the stimulation of PTH by endogenous catecholamines.

We were, however, unable to detect any significant changes of the concentrations of PTH during insulin-induced hypoglycaemia in the patients with primary hyperparathyroidism. This occurred although they displayed the same reactions to insulin in blood glucose, serum cortisol and phosphate. Kukreja et al. (1981) have reported that hyperparathyroid patients have an impaired PTH response to exogenous injections of isoproterenol. Our findings could therefore most likely be explained by a reduced sensitivity of the parathyroid gland also to endogenous catecholamines in primary hyperparathyroidism.

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