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Effects of Epinephrine and Norepinephrine on Serum Parathyroid Hormone and Calcium in Normal Subjects

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With 4 Figures

Summary. Infusions with stepwise increasing concentrations of epinephrine (from 2.5 to 10 μg/min) and norepinephrine (0.5–2.0 μg/min) were given to normal subjects. During infusion of epinephrine there was a clear rise of the serum parathyroid hormone (PTH) levels already at the lowest concentration. Concomitantly there was a fall in the serum concentrations of calcium. The PTH levels returned to baseline promptly after termination of infusion whereas hypocalcaemia persisted up to 30 minutes, indicating a primary response of PTH to epinephrine.

When propranolol was given prior to and during the epinephrine infusion no significant changes occurred for either PTH or calcium. During infusion of norephinephrine no consistent significant changes were noted for either PTH or serum calcium.

Thus, our data do not support any concept of a basal adrenergic tone which normally modulates the secretion of PTH. However, during conditions of stress the beta-adrenergic stimulation night be of importance.

Key words: Calcium, parathyroid hormone, epinephrine, norepinephrine, propranolol

Introduction

The synthesis and secretion of parathyroid hormone (PTH) is primarily regulated by the extracellular calcium concentration. Several in-vitro (Brown et al., 1977) and in-vivo (Kukreja et al., 1975; Fisher and Blum, 1980) studies have also delineated a role for the beta-adrenergic nervous system in the modulation of PTH release.

There is, however, considerable uncertainty if the effects of catecholamines are of any physiological importance (Epstein et al., 1983) and also if the demonstrated stimulation of PTH secretion in vivo is modified by concurrent changes of the serum calcium levels (McCarron et al., 1982).

In order to further characterize the in-vivo effect of the adrenergic control of PTH secretion we evaluated the response of immunoreactive PTH and serum calcium in normal subjects during infusions of epinephrine (with or without propranolol) and norepinephrine.

Material and Methods

Healthy subjects, medical students and members of the medical staff, took part in the experiments. There were 14 males and 8 females, with ages from 23 to 40 years. They had given informed consent to the study which was approved by the Ethical Committee of the Faculty.

All subjects were studied in the morning after fasting overnight and were recumbent during the procedures.

One vein needle was placed in each antecubital vein. One of them was used for infusions of saline, epinephrine, norepinephrine and propranolol in the different experiments. Through the other were serial blood samples drawn. In some subjects urine was collected before, during and after the infusions in portions of 30 minutes.

During the first 30 minutes normal saline alone was infused and during the last 5—10 minutes of this period basal values were obtained. In four subjects only saline was given during the entire time (controls). Fourteen individuals received a continuous infusion of epinephrine. In this study 5 mg epinephrine was added to 1000 ml of saline and infusion was given with stepwise increasing rate so that a plateau value for pulse and blood pressure was achieved at each concentration. Four different concentrations of epinephrine were used: 2.5, 5.0, 7.5, and 10.0 μg/min, respectively. The plasma levels of epinephrine ranged from 0.3 ng/ml at the lowest rate of infusion to 2.5 ng/ml at the highest rate. After termination of the infusion of active substance the subjects received saline only for the following 30 minutes at the end of which new baseline values were obtained. Baseline plasma levels of epinephrine were reached 10—15 minutes after termination of the epinephrine infusion.

Norepinephrine was given to 8 individuals in stepwise increasing concentrations of 0.5, 1.0, 1.5 and 2.0 μg/min, respectively. At the highest infusion rate the plasma levels ranged from 3 to 5 ng/ml. Measurements of plasma concentrations of epinephrine and norepinephrine were performed by cation exchange HPLC with electrochemical detection.

In five subjects the infusion of epinephrine was repeated after betablockade with propranolol. In this study propranolol was given as a bolus injection of 1 mg followed by an infusion of 1 μg/kg/min. The epinephrine infusion was started 30 minutes after the start of propranolol infusion and both infusions were continued for further 60 minutes.

PTH was analyzed by a radioimmunoassay method employing ^{125}I-labelled bovine PTH (Inolex) and sheep antiserum (S 478) against porcine and bovine PTH. This assay measures intact PTH and the carboxyterminal 2/3 of the hormone. The antiserum reacts predominantly with a midportion (44—68) of PTH but not with a strict N-terminal (1—34) or a small C-terminal (53-84) fragment. In healthy subjects the range of reference is 0.40—1.20 arbitrary units/liter (Ljunghall et al., 1982).

Total serum calcium concentrations were determined by atomic absorption, and serum albumin with a bromcresolbinding technique. All calcium values were adjusted for variations of the serum albumin concentrations according to a formula derived in our laboratory where a deviation of albumin from the normal mean value of 42 g/liter causes a change of the corresponding calcium value of 0.019 mmol/l. Ca^{2+} was measured with an automated method (Microlyte, Kone Instruments. Espoo, Finland).

The tubular reabsorption of calcium (%) was calculated as:

$$100\left(1 - \frac{\text{clearance of calcium}}{\text{clearance of creatinine}}\right)$$

assuming a constant ultrafiltrable fraction of 50% in the individual patient.

Conventional statistical methods were used.

Results

Infusion of epinephrine caused an increase in pulse rate in all the subjects, the average being a rise from 63 beats/min to 85 beats/min. In a similar way the stepwise increase of epinephrine gave a concomitant rise of systolic blood pressure from 116 to 144 mm and a decrease of the diastolic pressure from 79 to 61 mm.

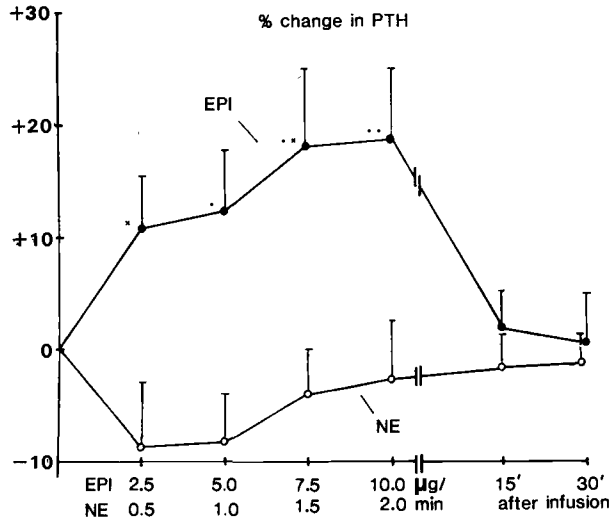

Fig. 1 Effects of infusions of epinephrine (EPI) and norepinephrine (NE) on serum parathyroid hormone (PTH). Symbols denote mean values ± SEM. *p < 0.05; **p < 0.01 (paired t-test) compared to pre-infusion values

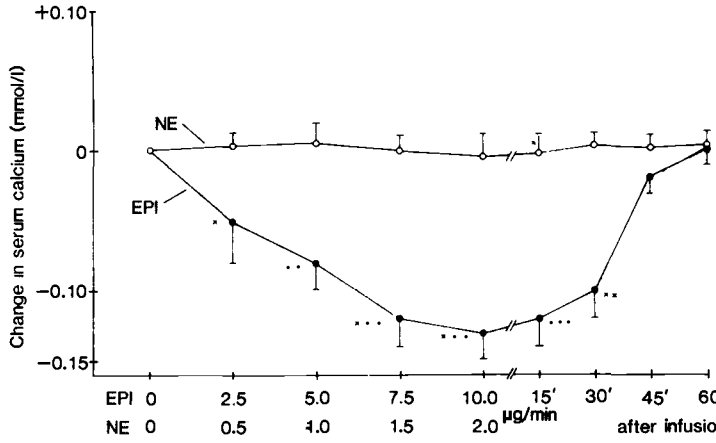

Fig. 2 Effects of infusions of epinephrine (EPI) and norepinephrine (NE) on serum calcium

All subjects had, before the experiment, values for serum calcium and PTH that were within the normal ranges. During infusion of epinephrine (Fig. 1) there was, already at the lowest concentration, 2.5 µg/min, a significant rise of the serum PTH levels of approximately 11%. Thereafter increasing doses of epinephrine caused a slight further increase in PTH. After termination of the epinephrine infusion PTH levels returned to baseline levels within 15 minutes.

The total serum calcium levels decreased significantly during infusion of epinephrine. This decrease also appeared to be related to the given dose and was most pronounced at the highest rate of infusion 10.0 µg/min (Fig. 2). The return to basal levels was slower than for PTH and not complete until 60 minutes after epinephrine infusion was terminated. The plasma ionized calcium values closely followed the same pattern as the

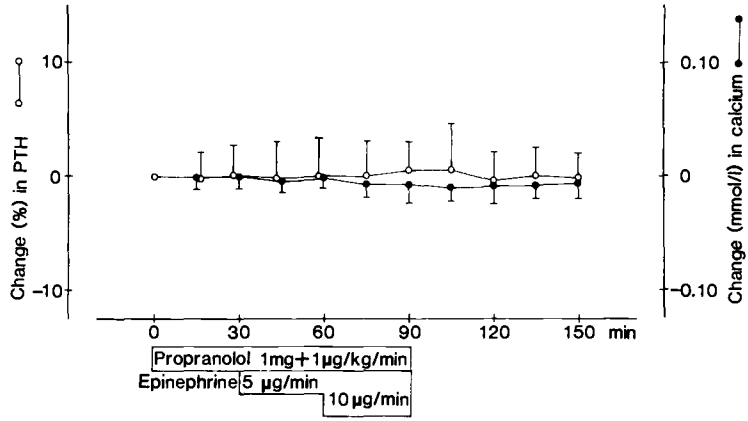

Fig. 3 Effects of the simultaneous infusion of propranolol and epinephrine on serum parathyroid hormone (PTH) and calcium

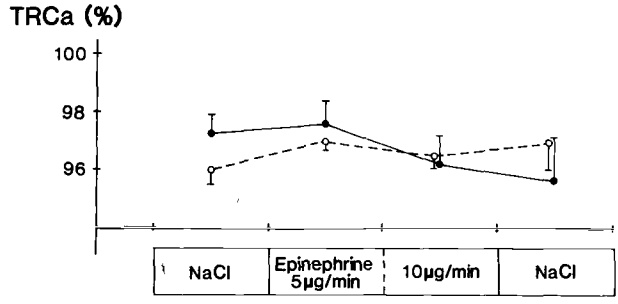

Fig. 4 Changes in tubular reabsorption of calcium (TRCa) during infusion with epinephrine (solid line) and NaCl alone (interrupted line)

total calcium values (data not shown). When propranolol was given prior to and during the infusion of epinephrine both the rise in PTH and the decline in serum calcium were abolished (Fig. 3).

The infusion of epinephrine did not affect the tubular reabsorption of calcium compared to a control infusion of NaCl alone (Fig. 4).

During infusion with norepinephrine there was, in all subjects, an increase of both systolic (mean value from 125 to 135 mm) and diastolic (mean value from 80 to 85 mm) blood pressure and a concomitant stepwise reduction of the pulse rate from a baseline value of 81 beats/min to a lowest value at the highest rate of infusion of 69 beats/min. During infusion of norepinephrine there was initially a lowering of the serum PTH levels. During continuous infusion, at increasing rates, no further changes of either the serum PTH or calcium values appeared (Figs. 1, 2).

Discussion

Epinephrine caused a dose-related release of PTH and a decrease of the serum calcium levels. This response was abolished by propranolol and was not found with norepinephrine. Thus, within the dose ranges of epinephrine that was used in this study there appeared to be specific beta-adrenergic influences on PTH and serum calcium that could be of physiological importance.

A reduction of serum calcium concentrations by a beta-adrenergic agonist has also been described by McCarron et al. (1982). These authors studied the responses of a single subcutaneous injection of isoproterenol. Since serum ionized calcium was lowered and PTH (not significantly) increased, the authors concluded that hypocalcaemia might be one contributing factor to the release of PTH.

In our study, it appeared that the stimulation of PTH occurred concomitantly with the lowering of serum calcium and, furthermore, that when infusion of epinephrine was terminated PTH returned to baseline values more rapidly than did serum calcium. Thus, it seems that these changes were independent of one another.

The precise mechanism by which serum calcium was lowered is not established. Since the tubular reabsorption of calcium was not affected it seems obvious that some prerenal mechanism must operate. It has been shown that stimulation of beta-adrenergic receptors causes an influx of potassium and sodium into muscle cells (Clausen, 1983). Our findings may suggest that calcium is involved in the same or a similar transport.

There seems to be unanimity that in-vitro beta-adrenergic agonists stimulate the release of PTH (Fischer and Blum, 1880). However, if this applies also to the in-vivo situation is under debate. Kukreja et al. (1975, 1980) have in several reports described an increase of PTH levels after administration of isoproterenol or epinephrine to normal subjects. On the other hand, Epstein et al. (1983) using an identical experimental design were unable to detect any significant changes of PTH after injections with isoproterenol or dopamine. The reason for this controversy is not clear but such factors as the uses of different radioimmunoassay systems are clearly of importance.

In the present study, although we found a significant increase in PTH during infusion with epinephrine, there was no reduction of basal PTH or calcium levels during propranolol administration. These findings agree with our earlier observations (Ljunghall et al., 1982) and also with those of Epstein et al. (1983) and indicate that there is no basal beta-adrenergic "tone" which normally affects the secretion of PTH.

Alpha-adrenergic catecholamines inhibit the release of PTH stimulated by beta-adrenergic agents in vitro independent of changes of extracellular calcium (Brown et al., 1978). However, in the present study we could not detect any significant effects of norepinephrine on PTH or serum calcium levels. This further supports the view (Epstein et al., 1983) that during basal conditions the adrenergic system does not play any major role in regulating the secretion of PTH. However, the responses to increments in epinephrine concentrations, apparently within a physiological range, suggest that during stress conditions a modulating role could be of physiologic importance.

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