Distribution of circulating immunoreactive components of parathyroid hormone in normal subjects and in patients with primary and secondary hyperparathyroidism: the role of the kidney and of the serum calcium concentration

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Summary

1. The distribution of intact parathyroid hormone-(1-84) [PTH-(1-84)] and of its COOH-terminal fragments was determined in human serum by column chromatography. In addition to PTH-(1-84) (peak I), COOH-terminal fragments having molecular weights of approximately 4000–7000 (peak II) and immunoreactive components co-eluting with human PTH-(1-12) (peak III) were observed.

2. Mean concentrations of intact PTH-(1-84) and of its COOH-terminal fragments were significantly raised in chronic renal failure as compared with those of normal subjects. Mean amounts of peak II were higher in patients with chronic renal insufficiency than in nutritional vitamin D deficiency, in pseudohypoparathyroidism and in primary hyperparathyroidism, despite comparable amounts of PTH-(1-84).

3. In chronic renal failure as well as in a group of patients with vitamin D deficiency, pseudohypoparathyroidism and primary hyperparathyroidism and in controls, significant linear relations were found between the serum concentrations of calcium and log (peak II/peak I). Our findings suggest that the conversion of intact PTH-(1-84) into COOH-terminal fragments by the parathyroid glands (resulting in a raised secretion of fragments) and/or in peripheral organs may be directly related to the serum concentration of calcium. However, the degradation of the fragments may also be suppressed in a calcium-dependent manner.

Key words: calcium, hyperparathyroidism, parathyroid hormone fragments, pseudohypoparathyroidism, renal failure, vitamin D deficiency.

Abbreviations: PTH, parathyroid hormone; 25-(OH)D, 25-hydroxycholecalciferol.

Introduction

The immunological heterogeneity of parathyroid hormone (PTH) in plasma of patients with hyperparathyroidism was first described by Berson & Yalow (1968). The presence of several molecular-weight species of PTH in peripheral blood was subsequently confirmed (Habener, Powell, Murray, Mayer & Potts, 1971; Canterbury & Reiss, 1972). PTH fragments were shown to be secreted by the parathyroid glands in vivo and in vitro (Flueck, Di Bella, Edis, Kehrwald & Arnaud, 1977; Mayer, Keaton, Hurst & Habener, 1977; Hanley, Takatsuki, Sultan, Schneider & Sherwood, 1978), as well as to be generated by peripheral organs such as the liver and the kidney (Canterbury, Bricker, Levey,
Kozlovskis, Ruiz, Zull & Reiss, 1975; Hruska, Martin, Mennes, Greenwalt, Anderson, Klahr & Slatopolsky, 1977). The present examination of the distribution of circulating PTH forms in primary and secondary hyperparathyroidism and in normal subjects was prompted by a preliminary observation of Weinstein, Canterbury & Reiss (1974), who reported that a fragment of molecular weight 7000–7500 was absent in pseudohypoparathyroidism. We have also attempted to relate the proportion of COOH-terminal fragments to intact human PTH-(1-84) to renal function and to concentrations of serum calcium. This last factor appears noteworthy in view of the inverse relationship between calcium and PTH metabolism in the parathyroid glands (Sherwood, Mayer, Ramberg, Kronfeld, Aurbach & Potts, 1968), as well as of possible connections between calcium and PTH metabolism in the parathyroid glands and in peripheral organs (Fischer, Oldham, Sizemore & Arnaud, 1972; Chu, MacGregor, Anast, Hamilton & Cohn, 1973; Habener, Kemper & Potts, 1975; Canterbury et al., 1975; Hruska et al., 1977; Oldham, Finck & Singer, 1978).

Methods

Subjects

Patients with surgically verified primary hyperparathyroidism, secondary hyperparathyroidism due to nutritional vitamin D deficiency, pseudohypoparathyroidism, chronic renal failure or postsurgical hypoparathyroidism, and normal subjects, were examined. Serum concentrations of calcium were decreased or normal in secondary, and raised in primary, hyperparathyroidism; serum calcium was also decreased in the untreated (four of five) hypoparathyroid patients. Serum magnesium was normal or close to the normal range, with the exception of decreased concentrations in two patients with primary hyperparathyroidism (0.47 mmol/l) and with hypoparathyroidism (0.37 mmol/l), respectively, and raised in two patients on haemodialysis (1.27 and 1-6 mmol/l). Serum concentrations of calcium and magnesium were decreased or normal in secondary, and raised in two patients with primary hyperparathyroidism (0.47 mmol/l) and with hypoparathyroidism (0.37 mmol/l), respectively, and raised in two patients on haemodialysis (1.27 and 1.6 mmol/l). Serum creatinine was normal except for slightly raised concentrations in two patients with primary hyperparathyroidism (124 and 133 μmol/l); it was, of course, increased in all the haemodialysed patients (530–1503 μmol/l). Serum concentrations of PTH were raised in all the hyperparathyroid patients and undetectable in the hypoparathyroid patients.

In the patients with secondary hyperparathyroidism the diagnosis of nutritional vitamin D deficiency was established by rachitic bone lesions and decreased serum 25-hydroxycholecalciferol [25-(OH)D] (range: 11.7–31.5 nmol/l). The clinical data of five patients with pseudohypoparathyroidism have been described elsewhere (Werder, Fischer, Illig, Kind, Bernasconi, Fanconi & Prader, 1978). Four additional patients showed brachymetacarpia and calcification of the basal ganglia, and they had raised serum inorganic phosphorus (1.35–2.20 mmol/l). In two of these patients intravenous infusions of 300 U.S.P. units of parathyroid extract (Lilly, Indianapolis, Ind., U.S.A.)/m2 body surface caused a maximal increase in the urinary cyclic adenosine 3',5'-monophosphate excretion from 0.9 and 1.1 to 12.1 and 3.1 nmol min-1 m-2 respectively (normal range from 0.3–5.9 to 16.8–268.1 nmol min-1 m-2), and in the two other patients the tubular re-absorption of phosphate decreased from 93–91%, or remained unchanged at 95% for up to 4 h after the administration of the hormone. Patients with chronic renal failure with one exception required haemodialysis, and the blood samples for analysis were drawn before dialysis. The dialysate concentrations of calcium and magnesium were 1.75 and 0.62 mmol/l respectively. The patients were not nephrectomized.

Blood samples were allowed to clot at room temperature for 30–60 min and then centrifuged at 4°C for 15 min, and serum was removed and kept at −20°C until analysed.

Analytical methods

**Gel filtration.** Columns of Bio-Gel P-150 (100–200 mesh; Bio-Rad Laboratories, Richmond, Calif., U.S.A.), 2.5 cm × 100 cm, were used in the method of Flueck et al. (1977) for the gel filtration of 7–8 ml serum samples by ascending flow (flow rate 8–12 ml/h) at 4°C in ammonium acetate (0.2 mol/l, pH 4.7) containing 0.5 mg of bovine serum albumin/ml (Sigma Company, St Louis, Miss., U.S.A.), and fractions were collected in 4–6 ml volumes. The void volume ($V_0$) was determined with blue dextran (Pharmacia, Uppsala, Sweden) and the salt volume ($V_s$) with Na125I. $K_a$ in column effluents was calculated as the ratio between the elution volume of the components examined minus $V_0$ and the difference between $V_s$ and $V_0$. Tracer amounts of radio-iodinated bovine PTH-(1-84) and synthetic human calcitonin-(1-32), and Na125I, were added to each serum sample as calibrating substances. Radioactivity was determined in an
Circulating forms of parathyroid hormone

437

automatic gamma-well spectrometer (Searle Analytic Inc., Des Plaines, Ill., U.S.A.). The amount of each labelled peptide marker was kept low enough (<10 pg/fraction or up to 1000 $^{131}$I c.p.m.) not to interfere with radioimmunological determinations. Measurements of absorbance were performed spectrophotometrically at 280 nm in 2 ml samples diluted 1:100 (model 240, Gilford Instrument Inc., Oberlin, Ohio, U.S.A.). Column fractions were freeze-dried and analysed radioimmunologically. Overall recoveries of immunoreactive PTH ranged from 33 to 139% (mean ± SD: 89 ± 26%).

Radioimmunoassay. As described previously (Fischer, Binswanger & Dietrich, 1974), bovine $^{131}$I-labelled PTH-(1-84) was used as ligand and a 5% pure human PTH-(1-84)G-100 as standard. Quantification of hormonal fragments is difficult, since the molecular weights of the circulating forms are not known. In the present study PTH fragments were measured against the human PTH-(1-84)G-100 standard expressed in ng-equivalents [ng-equiv. of human PTH-(1-84)G-100]. Whenever human PTH-(1-84)G-100 is used in the present context, the actual amount of human PTH-(1-84) is calculated. Antibodies to a 0.5% pure urea/trichloroacetic acid extract of human parathyroid tumours were obtained in goat 3, 306 days after primary immunization, and diluted 1:1500. Synthetic human PTH-(1-34) based on structures elucidated by Brewer, Fairwell, Ronan, Sizemore & Arnaud (1972), and donated by Dr W. Rittel, Basle, Switzerland, and by Niall, Sauer, Jacobs, Keuttman, Segre, O'Riordan, Aurbach & Potts (1974), and donated by Dr J. T. Potts, Jr, Boston, Mass., U.S.A., had minimal inhibitory effects in quantities as high as 5 µg, whereas synthetic human PTH-(44-68) (Rosenblatt, Keuttman, Tregear & Potts, 1977), donated by Dr H. Keuttman, Boston, Mass., U.S.A., had inhibitory properties comparable to those of human PTH-(1-84)G-100 (Fig. 1). The antibodies were assumed to be predominantly directed to the COOH-terminal region of human PTH-(1-84).

Serum samples and column effluent fractions were analysed in at least two dilutions. PTH is detectable in more than 90% of control subjects (normal range up to 0.35 ng/ml; Fischer et al., 1974). Inhibition curves of serum and of peak fractions of the gel filtrations of these, and of

![Graph](Fig. 1. Qualitative properties of antibodies to extracted human PTH and immunological characterization of PTH from peak fractions after gel filtration. Inhibition of specific binding of $^{131}$I-labelled bovine PTH-(1-84) to anti-[human PTH-(TCA)] (goat 3, day 306) by $\triangledown$, human PTH-(1-84)G-100, $\triangle$, human PTH-(1-34) (Brewer et al., 1972), $\blacksquare$, human PTH-(1-34) (Niall et al., 1974), $\triangle$, human PTH-(44-68) and peak fractions I ($\blacktriangle$), II ($\bullet$) and III ($\circ$) after gel filtration (for details see Fig. 2). The ordinate shows percentages of initial bound/free $^{131}$I-labelled bovine PTH-(1-84) (without inhibitor added).)
human PTH-(1-84)G-100, were superimposable, indicating immunological similarity (Fig. 1). Intra- and inter-assay coefficients of variation amounted to 7 and 12% respectively.

Additional methods of analysis. Serum calcium was determined as previously described by automatic ethanedioxybis(ethylamine)tetra-acetate (EGTA) titration (normal range 2.08-2.43 mmol/l; Fischer et al., 1974), serum magnesium by absorption flame spectrophotometry (model 305; Perkin-Elmer Corp., Norwalk, Conn., U.S.A.; coefficient of variation 1.3%; normal range in 40 control subjects 0.70-1.07 mmol/l), and serum creatinine by a photometric method (Clark & Thompson, 1949) (coefficient of variation 2.0%; normal range in 40 control subjects 53-115 μmol/l).

Serum 25-(OH)D was determined by the slightly modified radioligand assay reported by Haddad & Chyu (1971). Modifications included the precipitation of serum lipoproteins by the method of Burstein, Scholnick & Mortin (1970) concurrent with the ether extraction, and chromatography of the extracts on hydroxyalkoxypropyl Sephadex columns (0.6 cm x 5 cm). Extracts dissolved in 1 ml of n-hexane were applied to the columns, which were then eluted sequentially with n-hexane (7 ml), 5% diethyl ether in n-hexane (2 ml) and with 20% diethyl ether in n-hexane (7 ml). 25-(OH)D eluted in the last-named. The normal range based on samples collected from November to March in 21 healthy subjects varied between 33.0 and 135.0 nmol/l and the intra- and inter-assay coefficients of variation were 5 and 8% respectively.

The data were treated by stepwise discriminant analysis, one-way analysis of variance among all the means followed by t-tests (the corresponding mean square error being used), and multiple linear regression (programs BMDP7M, BMDP1V and BMDPIR; Dixon, 1976). P > 0.05 was considered as not significant. Coefficients of variation were calculated according to Diem & Lentner (1968).

Results

Gel filtration of sera on Bio-Gel P-150 columns

The results are summarized in Fig. 2 and Table 1.

We have consistently recognized three immunoreactive PTH components, designated peaks I, II and III, on gel filtration of sera from normal subjects and from patients with hyperparathyroidism. In patients with hypoparathyroidism peak III only was observed. Peak I co-eluted with human PTH-(1-84) and it reacted equally well with antibodies directed to the NH₂- and the COOH-terminal parts of human PTH-(1-84) (Hunziker & Fischer, 1977). Peak II was not recognized with antibodies directed to the NH₂-terminal part of human PTH-(1-84) (Fischer et al., 1974; Hunziker & Fischer, 1977). Peak III co-eluted and eluted beyond synthetic radiolabelled human PTH-(1-12) and human calcitonin-(1-32).

Mean amounts of peaks I and III were significantly higher in patients with pseudohypoparathyroidism and with chronic renal failure than in normal subjects (P < 0.05). Mean amounts of peak II were higher in chronic renal insufficiency than in all the other groups of subjects examined (P < 0.01-< 0.0005).

As the patients have been classified according to serum calcium and PTH concentrations as well as other diagnostic criteria (see the Methods section), stepwise discriminant analysis was used to test whether other variables obtained on gel filtration of serum of control subjects and of patients with hyperparathyroidism, but excluding patients with hypoparathyroidism and undetectable peaks I and II, would yield a similar grouping of subjects. The F ratio with 4 and 33 degrees of freedom from the

| Table 1. Amounts of different forms of PTH in serum of normal subjects and of various patient groups |
| --- | --- | --- | --- |
| Subjects | n | Concentration [ng-equiv. of human PTH-(1-84)G-100/ml] |
| --- | --- | --- | --- | --- |
| Peak I | Peak II | Peak III | log(Peak II/peak I) |
| Normal | 5 | 0.014 ± 0.002 | 0.075 ± 0.012 | 0.103 ± 0.013 | 0.745 ± 0.068 |
| Vitamin D deficiency | 6 | 0.133 ± 0.035 | 0.285 ± 0.069 | 0.183 ± 0.026 | 0.350 ± 0.143 |
| Pseudohypoparathyroidism | 9 | 0.143 ± 0.022** | 0.418 ± 0.050 | 0.200 ± 0.037** | 0.493 ± 0.066 |
| Primary hyperparathyroidism | 8 | 0.121 ± 0.052 | 1.951 ± 0.752 | 0.134 ± 0.028 | 1.264 ± 0.075** |
| Chronic renal insufficiency | 10 | 0.145 ± 0.044** | 5.219 ± 1.327* | 0.212 ± 0.031** | 1.728 ± 0.173* |
| Hypoparathyroidism | 5 | <0.005 | <0.005 | 0.111 ± 0.018 | --- |
Circulating forms of parathyroid hormone

Ilr. 2. Characterization of PTH from a normal subject, from hypocalcaemic patients with secondary hyperparathyroidism and hypoparathyroidism, and from a hypercalcaemic patient with primary hyperparathyroidism by chromatography on Bio-Gel P-150. $^{131}$I-labelled bovine PTH-(1-84) (X), $^{131}$I-labelled human calcitonin-(1-32) (Y) and Na$^{22}$ were added as calibration substances to 7-8 ml samples of serum: 2.5 cm x 100 cm column, 0.2 mol/l ammonium acetate, pH 4-6, and serum albumin (0.5 mg/ml) as eluent, reversed flow (flow rate 8-12 ml/h, 4-6 ml fractions) (for details see under 'Analytical methods'). Column fractions were analysed for PTH (○) with an immunoassay (goat 3, day 306) recognizing predominantly COOH-terminal parts of human PTH-(1-84) (see the text). Absorbance readings are of 2 ml effluent fractions diluted 1:100 (●). Subjects: A, normal; B, nutritional vitamin D deficiency; C, pseudohypoparathyroidism; D, hypoparathyroidism; E, chronic renal insufficiency; F, primary hyperparathyroidism. Serum concentrations of calcium in subjects A, B, C, D, E and F were 2.35, 1.40, 1.15, 1.28, 1.65 and 2.55 mmol/l respectively.

One-way analysis of variance was 1.40 [not significant (n.s.)] with peak I, 7.03 (P < 0.01) with peak II and 1.89 (n.s.) with peak III. With peak II/peak I we found 6.24 (P < 0.01) and with log (peak II/peak I) 22.6 (P < 0.001). Finally, the log (peak II/peak I) was significantly higher in patients with...
primary hyperparathyroidism and with chronic renal insufficiency than in normal subjects ($P < 0.01$ and $< 0.001$ respectively).

**Ratio between COOH-terminal PTH fragments and intact human PTH-(1-84) as a function of serum calcium, magnesium and creatinine concentrations**

The results are summarized in Fig. 3.

At any serum calcium concentration, the ratio between peak II and peak I was higher in chronic renal failure than in patients with secondary hyperparathyroidism and normal renal function, and in normal subjects. As a consequence, discriminant analysis separated the two groups of subjects. In addition, linear regression analyses with log (peak II/peak I) as dependent variable were performed. In patients with chronic renal insufficiency a significant relationship was observed to the serum concentrations of calcium, but not to concentrations of magnesium and creatinine. In the remaining subjects treated as a single group, the serum concentrations of calcium and of creatinine, but not of magnesium, were significantly related to the log (peak II/peak I); by using multiple linear regression with calcium and creatinine as independent variables, the coefficient for calcium ($P < 0.02$) was more important than that for creatinine ($P < 0.1$). A significant ($P < 0.01$) difference of the slopes of the regression lines relating the serum concentrations of calcium and log (peak II/peak I) in the
patients with chronic renal failure, and in the remaining subjects, indicated that the serum concentration of calcium was more directly related to the log (peak II/peak I) in chronic renal failure than in the subjects with normal or borderline abnormal renal function.

**Discussion**

We have demonstrated different profiles of immunoreactive PTH peaks on gel filtration in patients with primary and secondary hyperparathyroidism with or without renal failure, and in control subjects. As expected, a peak co-eluting with intact human PTH-(1-84) was frequently higher in patients with hyperparathyroidism than in normal subjects and undetectable in hypoparathyroidism. It was interesting that the concentrations of immunoreactive human PTH-(1-84) were comparable in normal subjects, as well as in patients with primary hyperparathyroidism, with the recently reported concentrations of biologically active PTH determined by a highly sensitive cytochemical assay (Chambers, Dunham, Zanelli, Parsons, Bintensky & Chayen, 1978).

The characteristic 4000-7000 molecular-weight COOH-terminal fragments, previously reported by us with the same radioimmunoassay (Fischer et al., 1974; Binswanger, Fischer, Iselin, Oswald, Keusch, Frei & Willimann, 1979) as the predominant immunoreactive PTH forms in the peripheral circulation of patients with primary hyperparathyroidism and with secondary hyperparathyroidism due to chronic renal insufficiency, were found in proportionally lower amounts in relation to intact human PTH-(1-84) in patients with secondary hyperparathyroidism and normal renal function. In fact, the ratio between the 4000-7000 molecular-weight COOH-terminal fragments (peak II) and intact human PTH-(1-84) (peak I) [log (peak II/peak I)] was significantly higher in patients with chronic renal insufficiency than in normal subjects and in patients with vitamin D deficiency, pseudohypoparathyroidism and primary hyperparathyroidism. This is consistent with the finding that exogenously administered PTH and its fragments as well as endogenous PTH are more slowly metabolized in patients with chronic renal disease than in normal subjects (Melick & Martin, 1969; Papapoulos, Hendy, Tomlinson, Lewin & O'Riordan, 1977; Freitag, Martin, Hruska, Anderson, Conrades, Ladenson, Klahr & Slaptopolsky, 1978).

Serum calcium concentrations were signifi-
cantly related to log (peak II/peak I) both in haemodialysed patients as well as in a group of subjects including patients with nutritional vitamin D deficiency, pseudohypoparathyroidism and primary hyperparathyroidism, and in controls. In view of the close relation between the serum concentrations of calcium and of the ratio between COOH-terminal fragments and intact PTH-(1-84) several calcium-mediated mechanisms can be discussed. The secretion of COOH-terminal fragments by the parathyroid glands may be related to the serum concentrations of calcium. Indeed, Mayer et al. (1977) and Hanley et al. (1978) have presented evidence that the amounts of COOH-terminal fragments in the venous effluent as well as in the perfusate of bovine parathyroid slices are proportionally higher at high than at low calcium concentrations, suggesting that the cleavage of human PTH-(1-84) within parathyroid cells is calcium-related. Furthermore, calcium has been shown to affect the degradation of intact PTH in vitro by porcine parathyroid extracts, in rat parathyroid glands and in bovine parathyroid slices (Fischer et al., 1972; Chu et al., 1973; Habener et al., 1975). Moreover a positive correlation between the serum calcium concentration and the arteriovenous difference of human PTH-(1-84) across the kidney is consistent with a calcium-regulated peripheral degradation of the hormone (Oldham et al., 1978). It appears possible that calcium, in addition to its inhibitory effect on PTH secretion (Sherwood et al., 1968), stimulates the conversion of the biologically active intact human PTH-(1-84) into biologically inactive COOH-terminal PTH fragments (Canterbury et al., 1975) in the parathyroid glands and in peripheral organs. An enhanced formation of PTH fragments in the presence of decreased calcium concentrations in vitro by peptidase activity, present in several tissues of the rat including the parathyroid glands, and by rat liver and dog kidney perfusion, is difficult to interpret in the light of the present findings (Fischer et al., 1972; Canterbury et al., 1975; Hruska et al., 1977). Finally, the elimination of PTH fragments from the circulation may also be inversely related to the serum concentration of calcium.

We have, furthermore, consistently observed 'PTH-like' material eluting with and beyond the position of radio-iodinated human calcitonin-(1-32) and human PTH-(1-12). Since peak III was not only observed in normal and hyperparathyroid subjects, but also in hypoparathyroid patients, the question must be raised as to whether peak III is...
artifactually caused by a non-specific inhibition of the immunological reaction by salts eluting close to the position of $^{125I}$, or whether peak II represents low-molecular-weight PTH-like forms not necessarily originating from the parathyroid glands. Extraction and desalting of human serum with dodecylsilyl silica gel (Huwyler, Born, Ohnhaus & Fischer, 1979) and rechromatography on columns of Bio-Gel P-150 yielded comparable immunoreactive human PTH fragments (J. A. Fischer et al., unpublished observations). The presence of similar PTH fragments was verified after selective removal from bovine serum by antibodies against bovine PTH coupled to CNBr-activated Sepharose 4B (Huwyler & Fischer, 1977). Moreover, fragments co-eluting with peak III have been generated during incubation of radiolabelled bovine PTH-(1-84) by porcine parathyroid extracts (Fischer et al., 1972). The mean concentrations of peak III in serum were significantly higher in the group of patients with pseudohypoparathyroidism and chronic renal failure than in patients with post-surgical hypoparathyroidism and in normal subjects, suggesting but not proving that at least a fraction was due to the metabolic breakdown of endogenous PTH.

The present investigation was stimulated by the preliminary observation of Weinstein et al. (1974), who demonstrated that a 7000–7500 molecular-weight PTH fragment was absent in pseudohypoparathyroidism. The proportionally low amounts of this fragment in relation to human PTH-(1-84) as compared with primary hyperparathyroidism are consistent with their findings. However, in view of the similar results obtained in nutritional vitamin D deficiency, an apparent abnormal elution profile both of COOH-terminal fragments, as shown in the present study, and of NH$_2$-terminal fragments (J. A. Fischer et al., unpublished observations) could not be specifically associated with pseudohypoparathyroidism.

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References


Circulating forms of parathyroid hormone


