Aging and Renal Responsiveness to Parathyroid Hormone in Healthy Men*

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ABSTRACT

To determine whether aging impairs renal responsiveness to PTH, we studied the ability of the kidney to respond to infusion of human PTH-(1-34) for 24 h in 16 healthy men, 9 young (39 ± 1 yr) and 7 elderly (70 ± 1 yr), free of any conditions known to influence mineral metabolism and in whom the glomerular filtration rate was greater than 1.17 mL/s·1.73 m². Basal concentrations of blood ionized calcium, serum 1,25-dihydroxyvitamin D [1,25-(OH)₂D], and urinary calcium and phosphorus were similar in both age groups, but basal serum PTH (+148%), plasma cAMP (+44%), nephrogenous cAMP (+56%), and fractional excretion of phosphorus (+44%) were higher in the elderly. PTH infusion increased serum 1,25-(OH)₂D to the same maximum level in the young (113 ± 10 pmol/L) and the elderly (100 ± 11 pmol/L) men, but the response in the elderly was delayed. Urinary cAMP, nephrogenous cAMP, and fractional excretion of phosphorus increased, and neither the time course nor the increment was significantly different between age groups. The phosphate threshold concentration decreased in response to PTH to the same extent in both age groups. The results demonstrate that although the increment in serum 1,25-(OH)₂D in the elderly may be delayed relative to that in the young, renal responsiveness to a 24-h PTH infusion is similar in healthy young and elderly men in whom glomerular filtration rate is normal or near normal. (J Clin Endocrinol Metab 81: 2192-2197, 1996)

THE SERUM concentration of PTH increases progressively with advancing age in men and women (1-10). In healthy men, serum PTH begins to increase as early as the fifth decade (9), and by age 70 yr, it is 2- to 3-fold higher than that in young men (30-40 yr old) (7, 9). PTH normally stimulates the activity of renal 25-hydroxyvitamin D-1α-hydroxylase (1-hydroxylase), the enzyme responsible for the synthesis of 1,25-dihydroxyvitamin D [1,25-(OH)₂D] (11, 12). Despite the age-related increase in the serum concentration of PTH, the serum concentration of 1,25-(OH)₂D tends to remain unchanged (4-8, 13-15) or to decrease (3, 16-18) in the elderly. These findings led to the suggestion that the ability of the kidney to respond to PTH decreases with advancing age (19, 20). Consistent with this idea, Slovik et al. (19) found that iv infusion of human PTH-(1-34) induced an increase in serum 1,25-(OH)₂D in healthy young subjects, but not in elderly patients with osteoporosis. Further, Tsai et al. (20) reported that the increase in serum 1,25-(OH)₂D induced by infusion of bovine PTH-(1-34) was blunted in elderly postmenopausal women with mild to moderate renal insufficiency compared to that in healthy young women. These studies, however, involved elderly patients with osteoporosis or mild to moderate renal insufficiency. Thus, they do not permit separation of the effects of aging from those of other conditions that may impair the ability of the kidney to respond to PTH.

To determine whether aging per se influences the ability of the kidney to respond to PTH, we studied healthy young adult and elderly men free of conditions known to influence mineral metabolism and in whom the glomerular filtration rate (GFR) was greater than 1.17 mL/s·1.73 m² (70 mL/min·1.73 m²). The results demonstrate that although the increase is delayed relative to that in young men, the increment in serum 1,25-(OH)₂D ultimately induced by PTH is not reduced by aging. Furthermore, the urinary cAMP and phosphaturic responses to PTH infusion are virtually identical in healthy young and elderly men in whom GFR is normal or near normal.

Materials and Methods

We studied 16 healthy Caucasian men, 7 elderly (age, 70 ± 1 yr) and 9 young (age, 39 ± 1 yr), in whom the GFR was greater than 1.17 mL/s·1.73 m². Only men were studied to avoid the potentially confounding effects of estrogen deficiency on mineral metabolism observed in elderly women. The men were selected from a pool of healthy volunteers from the local community. All were normally active and free of active renal, gastrointestinal, or cardiopulmonary disease. Subjects were excluded if they were obese or receiving drugs that could affect mineral metabolism: corticosteroids, anticonvulsants, diuretics, or ß-blockers. All studies were performed at the General Clinical Research Center under a protocol approved for use by the committee on human research, University of California-San Francisco. Informed consent was obtained from each subject.

Throughout the 12-day study, each subject received a constant whole food diet that provided, by calculation, 5 mmol calcium, 16 mmol phosphorus (P), 4 mmol magnesium, and 70 mmol sodium/day·70 kg ideal BW (IBW). Oral supplements of calcium carbonate and solutions of neutral sodium and potassium phosphate as well as magnesium sulfate were administered, so that each subject received a total (diet plus supplement) of 21.2 mmol calcium, 48.4 mmol P, 14.4 mmol magnesium, and 140 mmol sodium/day·70 kg IBW. The basic diet provided, by calculation, 2600 Cal/day·70 kg IBW, 9% as protein, 34% as fat, and 57% as carbohydrate. Meals were offered each day at 0900, 1230, and 1715 h. IBW was estimated from the Metropolitan Life Insurance Co. height-weight tables for 1983.

The first 7 days of the study served as an equilibration period. We
have previously shown that after 7 days of a constant diet, the serum concentrations of calcium, P, 1,25-(OH)2D, and PTH, and the urinary excretion rates of calcium and P are constant (21). On days 7–12 of the study, arterialized venous blood was drawn without stasis before breakfast at 0830 h for measurement of whole blood ionized calcium and serum concentrations of creatinine, total calcium, inorganic P, CAMP, creatinine clearance was measured daily to provide an estimate of GFR. Because creatinine clearance may underestimate GFR in some patient populations, we also measured iothalamate clearance in the elderly subjects, as previously described (7).

On day 9 of the study, human synthetic PTH-(1–34) (Pararath, Rorer Pharmaceuticals, Fort Washington, PA) was infused iv beginning at 0900 h at a constant rate of (0.5 U/kg/h) for 24 h. This protocol has been shown to cause a rapid increase in the serum concentration of PTH-(1–34) and to maintain a constant serum level of PTH-(1–34) of approximately 14.5 pmol/L throughout a 24-h infusion (22). Blood samples were collected at 2- to 4-h intervals for measurement of whole blood ionized calcium, P, PTH-(1–84), and 1,25-(OH)2D. Urine samples were collected periodically throughout the infusion for measurement of creatinine, calcium, P, and CAMP.

**Laboratory methods**

Serum concentrations of 1,25-(OH)2D were measured in duplicate using a competitive protein binding assay employing 1,25-(OH)2D receptor from calf thymus, as previously described (23). All determinations for each subject were made in a single assay. Minimum detection limits are less than 5 nmol/L tube; overall recovery ranged from 60–70%. Inter- and intraassay coefficients of variation of 1,25-(OH)2D in serum were 13.4% and 12.6%, respectively, at a concentration of 75 pmol/L. Serum concentrations of intact PTH were measured in duplicate by immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). Whole blood ionized calcium was measured in triplicate using the Nova 8 ionized calcium/pH analyzer (Nova Biomedical, Newton, MA). Serum and urinary concentrations of calcium were measured by atomic absorption spectrophotometry, serum and urinary P were determined by a modification of the Fiske-Subbarow method, urinary creatinine was measured by autoanalyzer, and plasma and urinary CAMP were determined in duplicate by RIA (ImmunoNuclear Corp., Stillwater, MN). The phosphate threshold concentration (TmP/GFR) was calculated using the method of Walton and Bijvoet (24).

**Data analysis**

Data are presented as the mean ± SEM. To determine whether blood and urine variables differed significantly between age groups, we used one-way repeated measures ANOVA. To determine whether the response to PTH infusion differed significantly between age groups, we used one-way repeated measures ANOVA implemented by multiple linear regression (25, 26), as previously described (27), and two-way (age and time) repeated measures ANOVA. These analyses were performed using Sigma Stat (Jandel Scientific, San Rafael, CA).

**Results**

The clinical and metabolic characteristics of the subjects studied are shown in Table 1. The mean creatinine clearance was near normal in the elderly men, but was significantly lower (−21%) than that in the young men. Iothalamate (1.67 ± 0.10 mL/s/1.73 m2) and creatinine (1.52 ± 0.09 mL/s/m2) clearances were nearly identical in the elderly. Basal whole blood ionized calcium and total serum calcium concentrations did not differ significantly between the groups, but morning fasting serum P was significantly lower (−16%; P < 0.002) in the elderly men. The serum concentration of 1,25-(OH)2D at baseline was normal in the elderly men, but the basal serum PTH level was approximately 2.5-fold higher than that in the younger men (P < 0.001). Plasma CAMP was higher in the elderly men (P < 0.001). Total 24-h urinary excretions of calcium and P were similar in the young and elderly men, fractional excretion of P (FEpi; +44%; P < 0.01) and naphrogenous CAMP (NCAMP; +56%; P < 0.01) were higher, and the TmP/GFR (−14%; P < 0.01) was lower in the elderly men.

Continuous infusion of PTH-(1–34) for 24 h increased the serum concentration of 1,25-(OH)2D in both young (P < 0.001) and elderly (P < 0.001) men (Fig. 1). In the young men, the serum concentration of 1,25-(OH)2D increased to a level significantly above the baseline after 8 h of infusion (+40%; P < 0.05), decreased slightly after 12–16 h, and then increased further, reaching a mean peak concentration of 113 ± 10 pmol/L after 24 h (P < 0.01). In the elderly men, the serum concentration of 1,25-(OH)2D increased progressively but more slowly, reaching a level significantly above baseline after 20 h of PTH infusion. The peak serum concentration of 1,25-(OH)2D reached in the elderly men (106 ± 11 pmol/L) was not significantly different from that in the young men. Multiple linear regression analysis for the time points between 1–12 h indicated that the initial rate of increase in serum 1,25-(OH)2D was significantly lower (P < 0.02) in the older men. With analysis of all time points, however, the rate of increase did not differ significantly between age groups.

PTH infusion induced a rapid and sustained increase in urinary CAMP in both young and elderly men (Fig. 2A). Plasma CAMP after 23 h of PTH infusion was not significantly different from basal levels in either young (7.9 ± 0.7 and 8.0 ± 0.8 nmol/L, respectively) or elderly (11.2 ± 0.9 and 11.5 ± 0.9 nmol/L, respectively) men. The FEpi increased progressively during PTH infusion, reaching a peak between 8–12 h, and then decreased, yet remained significantly above the basal morning fasting level (Fig. 3A). The increments in both urinary CAMP and FEpi induced by PTH infusion were nearly identical in the young and elderly men (Figs. 2B and 3B).

**TABLE 1. Clinical and metabolic characteristics of healthy young and elderly men**

<table>
<thead>
<tr>
<th></th>
<th>Young men</th>
<th>Elderly men</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 ± 1</td>
<td>70 ± 1</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>77 ± 6</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>1.92 ± 0.07</td>
<td>1.52 ± 0.09*</td>
</tr>
<tr>
<td>Whole blood Ca2+</td>
<td>1.22 ± 0.01</td>
<td>1.20 ± 0.01</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>2.57 ± 0.02</td>
<td>2.55 ± 0.02</td>
</tr>
<tr>
<td>Serum P</td>
<td>1.19 ± 0.03</td>
<td>1.00 ± 0.03*</td>
</tr>
<tr>
<td>Serum 1,25-(OH)2D</td>
<td>75 ± 8</td>
<td>77 ± 10</td>
</tr>
<tr>
<td>Serum 250HD</td>
<td>60 ± 2</td>
<td>50 ± 2</td>
</tr>
<tr>
<td>Serum PTH-(1–84)</td>
<td>2.1 ± 0.3</td>
<td>5.2 ± 0.8*</td>
</tr>
<tr>
<td>Plasma CAMP</td>
<td>6.0 ± 0.6</td>
<td>11.5 ± 0.9*</td>
</tr>
<tr>
<td>Urinary Ca (mmol/day · 70 kg)</td>
<td>3.90 ± 0.72</td>
<td>2.82 ± 0.39</td>
</tr>
<tr>
<td>Urinary P (mmol/day · 70 kg)</td>
<td>31 ± 2</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Urinary CAMP (nmol/L GFR)</td>
<td>10 ± 1</td>
<td>28 ± 1*</td>
</tr>
<tr>
<td>Fractional excretion of P (%)</td>
<td>16 ± 1</td>
<td>23 ± 2*</td>
</tr>
<tr>
<td>TmP/GFR (nmol/L GFR)</td>
<td>1.32 ± 0.04</td>
<td>1.13 ± 0.05*</td>
</tr>
<tr>
<td>Nephrogenous CAMP (nmol/L GFR)</td>
<td>9 ± 1</td>
<td>14 ± 2*</td>
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</table>

Values are the mean ± SEM. Significance was determined by Student's t test.

*P < 0.001.

**P < 0.001.

**P < 0.05.
hPTH(1-34) Infusion (35U/70kg/hr)

FIG. 1. Effect of PTH infusion on the serum concentration of 1,25-(OH)₂D in young (solid line) and elderly (broken line) men. Values are given for the 2 days before PTH administration and every 4 h during a 24-h infusion. The asterisks denote significant differences (P < 0.05) from baseline (i.e., days 0, −1, and −2), using two-way repeated measures ANOVA.

Fasting NcAMP measured between 0700–0900 h also increased in response to PTH infusion in both young and elderly men, and the increments between basal and stimulated values were nearly identical (young, 12.7 ± 2.0; elderly, 13.3 ± 2.2 nmol/L GFR; Fig. 4A). Regression analysis showed a strong correlation (r = 0.74; P < 0.001; n = 16) between the PTH-induced change in the serum concentration of 1,25-(OH)₂D and the change in NcAMP. The TmP/GFR measured between 0700–0900 h decreased in response to PTH, and the decrements were similar in both age groups (young, 0.46 ± 0.08; elderly, 0.44 ± 0.06 nmol/L GFR; Fig. 4B).

Twenty-four-hour urinary calcium excretion increased in the young (P < 0.05), but not in the elderly, during PTH infusion (Table 2). During the 24-h period immediately following the infusion, urinary calcium increased from baseline by 2-fold (P < 0.05) in both age groups. Fasting urinary calcium excretion measured between 0700–0900 h was nearly identical in the young and elderly men in the basal state (13 ± 3 and 12 ± 2 µmol/L GFR, respectively), and it increased during PTH infusion in both groups (P < 0.05) by 3.2-fold (young) and 2.9-fold (elderly). Neither the basal value nor the increment in fasting urinary calcium differed with age. The fasting fractional excretion of calcium was also nearly identical in young and elderly men during the basal state and during PTH infusion.

With infusion of PTH, the serum concentration of endogenous PTH decreased from 2.1 ± 0.3 to 0.5 ± 0.1 pmol/L in the young men and from 5.2 ± 0.8 to 1.2 ± 0.2 pmol/L in the elderly men (Fig. 5). The nadir reached was significantly lower in the young men (P < 0.001). Whole blood concentrations of ionized calcium progressively increased during PTH infusion, but the rate of increase was significantly lower in the elderly men (P < 0.001; Fig. 6). The serum concentration of P in the elderly men was significantly lower throughout the 24-h infusion than that in the young men (data not shown). The morning fasting serum concentration of P after 24 h of PTH infusion was lower than the corresponding values before PTH infusion in both age groups,
Our findings provide evidence that the renal response to PTH in healthy elderly men in whom GFR is normal differs little from that in healthy young men. The serum concentration of 1,25-(OH)_2D increased in response to PTH in both young and elderly men, and although the increase in serum 1,25-(OH)_2D occurred earlier in the young men (P < 0.05 compared to young baseline and elderly PTH, by ANOVA). and the magnitude of reduction was greater in the young men than in the old men (-0.25 ± 0.02 vs. -0.14 ± 0.03 mmol/L; P < 0.001).

**Discussion**

Our findings provide evidence that the renal response to PTH in healthy elderly men in whom GFR is normal or near

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**TABLE 2.** Effect of PTH infusion on urinary calcium in young and elderly men

<table>
<thead>
<tr>
<th></th>
<th>Young men</th>
<th>Elderly men</th>
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<tr>
<td>24-h urinary Ca (mmol/day · 70 kg)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>3.9 ± 0.7</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>PTH</td>
<td>5.2 ± 0.9b</td>
<td>2.8 ± 0.5</td>
</tr>
<tr>
<td>Recovery</td>
<td>10.8 ± 1.4c</td>
<td>5.2 ± 0.6c</td>
</tr>
<tr>
<td>Fasting urinary Ca (μmol/L GFR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13 ± 3</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>PTH</td>
<td>41 ± 5c</td>
<td>33 ± 4c</td>
</tr>
<tr>
<td>Fasting fractional excretion of Ca (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>PTH</td>
<td>2.5 ± 0.4e</td>
<td>2.5 ± 0.3e</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM.

a Urinary Ca was given for the following periods: baseline, 24 h before PTH infusion; PTH, 24 h during PTH infusion; recovery, 24 h after PTH infusion. 

b P < 0.05 compared to young baseline and elderly PTH, by ANOVA.

c P < 0.05 compared to baseline and PTH, by ANOVA.

d To calculate the fasting urinary Ca and fasting fractional excretion of Ca, urine was collected between 0700–0900 h.

"P < 0.01 compared to baseline, by ANOVA."
FIG. 5. Effect of PTH infusion on the serum concentration of endogenous PTH-(1–84) in young (solid line) and elderly (broken line) men. Serum endogenous PTH is significantly \( (P < 0.05) \) lower at all time points in the young men than in the elderly men (by two-way ANOVA).

FIG. 6. Effect of PTH infusion on the whole blood concentration of Ca\(^{2+}\) in young (solid line) and elderly (broken line) men. Both the rate and the concentration of Ca\(^{2+}\) reached at 24 h were significantly \( (P < 0.05) \) higher in the young than in the elderly men.

Urinary cAMP increased rapidly and maintained a constant high level throughout the PTH infusion period. Plasma cAMP after 23 h of PTH-(1–34) infusion was not significantly different from the basal level either in the young or elderly men. Thus, the PTH-induced increase in urinary cAMP appears to reflect an increase in NcAMP. That the increment in urinary cAMP was the same in both young and elderly men suggests that the ability of the kidney to produce cAMP in response to PTH is not impaired by aging. That the change in NcAMP between the basal level and that 22–24 h after beginning the PTH infusion, directly calculated from the plasma and urinary levels of cAMP, is virtually identical in young and elderly men is consistent with this idea. Basal urinary cAMP was higher in the elderly in part because their plasma cAMP levels, and thus the filtered load of cAMP, was higher and in part because NcAMP was higher. That NcAMP is elevated in the elderly men is presumably a consequence of their high serum PTH levels.

The increments in FEPi observed during PTH infusion were also virtually identical in both age groups, suggesting that aging does not impair renal handling of P in response to PTH. As with the increase in baseline NcAMP, the high basal FEPi in the elderly is probably a consequence of their high serum PTH levels.

In the young men, total 24-h urinary calcium was slightly, but not significantly, higher before PTH infusion, and it increased significantly during PTH administration, whereas in the elderly no changes in 24-h urinary calcium were observed. During recovery from PTH infusion, 24-h urinary calcium increased in both groups, but the increment in the young men was twice that in the elderly men. By contrast, fasting urinary calcium and fractional calcium excretion, both basally and during PTH infusion, were not significantly different between age groups. The slightly, but not significantly, lower basal 24-h urinary calcium in the elderly men may be a consequence in part of their higher basal serum concentration of PTH and lower gastrointestinal absorption of calcium. That PTH induced an increase in 24-h urinary calcium in the young, but not the elderly, men could reflect the higher blood ionized calcium and, thus, the higher filtered load and perhaps differences in the efficiency of 1,25-(OH)\(_2\)D-stimulated intestinal calcium absorption between young and elderly individuals (29–31). The slightly, but not significantly, higher fasting urinary calcium in young men during PTH infusion can be accounted for by their increased infusion correlated positively with GFR. When GFR was held constant in a multiple linear regression analysis, there was no correlation with age. Thus, age per se did not appear to be an important determinant of renal sensitivity to PTH. Our studies extend these observations and demonstrate that in healthy elderly men in whom GFR is normal or near normal, the response of serum 1,25-(OH)\(_2\)D to continuous infusion of PTH for 24 h is little changed by aging.

The reason for the apparent delay in the response of serum 1,25-(OH)\(_2\)D to PTH we observed in elderly men is not clear. Down-regulation and subsequent desensitization of the renal PTH receptor resulting from the higher basal serum level of PTH in the elderly (28) may play a role. Whether the delayed response we observed is of physiological significance is not clear.
filtered load of calcium. Collectively, we found no evidence that renal handling of calcium is impaired by aging.

During PTH infusion, endogenous serum PTH (1-84) decreased; the level reached at 24 h was significantly higher in the elderly than in young men. Whether this is a consequence of the enlargement of the parathyroid gland associated with aging (higher nonsuppressible component of PTH secretion), a shift in the calcium set-point for PTH release (32), or both is not clear. Although blood ionized calcium increased to a higher level in the young men, (young, 1.49 ± 0.02; elderly, 1.39 ± 0.02 mmol/L; P < 0.001), the concentration reached in each group would be expected to maximally suppress PTH release.

That whole blood ionized calcium increased more rapidly in the young men than in the elderly men suggests that bone sensitivity to PTH may be impaired in the elderly (33). This could occur as a consequence of down-regulation of the PTH receptor in bone or be related to senescent changes within the bone. Fasting serum P decreased, presumably as a result of the increase in fractional excretion.

Collectively, our data suggest that renal responsiveness to PTH administration in healthy elderly men in whom GFR is normal or near normal is similar to that in young men. The high basal levels of urinary cAMP and NcAMP, the high FEiP, and the low basal level of fasting serum P in the elderly are presumably consequences of the mild hyperparathyroidism found in this population. That the serum concentration of 1,25-(OH)2D is not elevated in the elderly despite their higher serum concentrations of PTH may reflect other age-related changes in mineral metabolism. Synthesis of 1,25-(OH)2D is influenced by calcium, P, GH, insulin-like growth factor I, glucocorticoids, and sex hormones, as well as PTH. The serum concentrations of most of these factors change with age. It is possible, therefore, that the altered relationship between the serum concentrations of 1,25-(OH)2D and PTH in the elderly is the result not of resistance to PTH, but, rather, of a decrement in other trophic factors (e.g. GH and insulin-like growth factor I) and/or resistance to these factors. That serum 1,25-(OH)2D is normal in healthy elderly men may be a consequence of the increase in the serum concentration of PTH. Reported blunting of renal responsiveness to exogenous PTH in the elderly is probably a consequence of renal insufficiency and/or other age-related pathologies.

Acknowledgments

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References