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LABORATORY INVESTIGATION

Potential role of IGF-1 in parathyroid hormone-related renal growth induced by high protein diet in uninephrectomized rats

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Potential role of IGF-1 in parathyroid hormone-related renal growth induced by high protein diet in uninephrectomized rats. Recent studies indicate that parathyroidectomy (PTX) prevents the progression of kidney damage due to high protein diet in the subtotal nephrectomized rat model of chronic renal failure. Associated with this protection, the difference in the renal "compensatory" growth induced by high (HPr) as compared to normal protein diet (NPr) is completely abolished by PTX. To understand the physiological mechanism responsible for this protection, the changes in both circulating level and kidney content of IGF-1, a growth factor capable of influencing renal "compensatory" growth, was analyzed after unilateral nephrectomy (UNX). In UNX rats, HPr as compared to NPr diet given for five days significantly increased the kidney/body weight ratio ($0.48 \pm 0.01\%$, $N = 11$ vs. $0.44 \pm 0.01\%$, $N = 11$, $P < 0.005$) and the plasma level of IGF-1 (365 ± 10 ng/ml vs. 306 ± 10 ng/ml, $P < 0.001$). In UNX rats fed HPr, PTX completely abolished the renal "compensatory" growth ($0.38 \pm 0.02\%$, $N = 7$, $P < 0.001$) and the increased plasma level of IGF-1 (246 ± 14 ng/ml, $N = 7$, $P < 0.001$). In PTX-UNX rats treated with physiological doses of 1,25-dihydroxyvitamin D_3 which nearly normalized the calcemia, the renal growth and the increased plasma level of IGF-1 induced by HPr were restored towards those recorded in SHAM-UNX rats fed the HPr diet. Similar effects were observed in PTX-UNX rats in which the plasma calcium concentration was increased by the chronic administration of a retinoid derivative, used as an agent where the calcemic effect is essentially mediated by a stimulation of bone resorption. There was a positive significant correlation between the change in kidney growth in response to UNX and the plasma level of IGF-1 ($r = 0.685$, $P < 0.001$). The kidney IGF-1 content was affected neither by the protein intake nor by the PTH status. In rats with an intact renal mass and fed NPr diet, chronic administration of bovine PTH did not alter the plasma IGF-1 concentration. In these animals, both the increase of the plasma IGF-1 level under HPr diet and the blunting effect of PTX thereon were similar to the response observed in UNX animals. There was, however, no significant change in the kidney/body weight ratios in response to HPr diet. In conclusion, the results of the present study provide evidence that calciotropic hormones such as PTH and 1,25-dihydroxyvitamin D_3 and/or the associated change in extracellular calcium concentration modulate the effect of protein intake on hepatic production of IGF-1. In rats with a reduced renal mass, the elevation in the circulating level of IGF-1 is likely responsible for the increased "compensatory" growth of remaining nephrons, which is associated with an acceleration of renal function deterioration induced by high protein diet.

Experimental and clinical evidence indicate that high protein diet accelerates the progression of kidney lesions and functional deterioration in chronic renal failure (CRF) [1–4]. The pathophysiological components involved in the deleterious influence of the protein intake on renal function have not been clearly identified. Recent studies indicate that removal of the parathyroid glands (PTX) conferred remarkable protection against the accelerated deterioration of renal function induced by high protein intake in a model of chronic renal failure [5]. In addition to delay the fall in the glomerular filtration rate (GFR), PTX prevented the high protein diet-induced increment in both the so-called "compensatory" growth and calcium content of the kidney remnants and abrogated the rise in plasma cholesterol. However, in subtotally nephrectomized rats with intact parathyroid glands, high protein intake did not alter the circulating level of parathyroid hormone (PTH) [5]. This finding suggested that PTH, directly and/or through its calcemic activity, may play a permissive role for the expression of the detrimental effects of high protein intake on kidney function in chronic renal failure. A significant role of calciotropic factors was suggested by the observation that substitutive doses of 1,25-dihydroxycholecalciferol partially abolished the protective effect of PTX on the high protein diet-induced "compensatory" renal growth and progression of renal failure [5].

Among the factors possibly involved in the mechanism by which PTX affects the renal growth induced by high protein diet, IGF-1 may be a potential candidate. Indeed, in uninephrectomized rats, elevation in the dietary protein supply induced an increase in the renal content of IGF-1 [6]. The plasma concentration of IGF-1 is also influenced by the protein intake [7–9], which affects both the synthesis and secretion of IGF-1 by the liver possibly through transcriptional and translational control mechanisms [10]. Furthermore, in calves PTH and PTHrP have the capacity to enhance hepatic IGF-1 production [11, 12]. Therefore, in the present study, we investigated the role of IGF-1 in the PTH-related changes in renal "compensatory" growth induced by high protein diet in uninephrectomized rats.

Methods

Animal preparation

Male Wistar rats were fed an ordinary chow and allowed to drink distilled water *ad libitum*. Sham operation (SHAM), parathyroidectomy (PTX) or thyroparathyroidectomy (TPTX) were performed under light anesthesia (Ketamin 10 mg/100 g body wt). The adequacy of parathyroid gland removal was verified by determining fasting plasma calcium concentration ($[Ca]_{PL}$) 48 hours after the operation. Only PTX or TPTX rats with $[Ca]_{PL}$ lower than 1.88 mmol/liter were kept in the study. In one series of

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experiments, a group of PTX rats were given 26 pmol/day (s.c.) of chemically synthesized 1,25-dihydroxyvitamin D_3 (1,25 D_3; Hoffmann-La Roche & Co, Basel, Switzerland) to normalize their calcemia. One week after SHAM operation or PTX without or with 1,25 D_3 supplementation, animals were anesthetized and the left kidney was removed and weighed.

Effect of PTX with or without 1,25 D_3 supplementation on kidney growth and plasma level of IGF-1 in response to protein diet in uninephrectomized rats

On day 7 following uninephrectomy (UNX), some animals of SHAM, PTX and PTX+1,25 D_3 experimental groups were anesthetized, exsanguinated and the right kidney removed and weighed. The remaining animals were switched to a semi-synthetic diet containing either 20% or 40% casein and a precise amount of calcium (1.2 g/100 g), phosphorus (0.8 g/100 g) and sodium (0.3 g/100 g) (Kliba, Klingentalmuehle AG, Switzerland). Both diets were made isocaloric with starch and soya oil and contained an equal amount of vitamin supplements. During five days, UNX-SHAM-operated animals were pair-fed with either the 20% (normal) or the 40% casein diet (high), while the UNX-PTX and UNX-PTX+1,25 D_3 were pair-fed with the 40% casein diet. At the end of the experiment, animals were anesthetized, exsanguinated by aortic puncture and the right kidney harvested and weighed.

Effect of protein diet on kidney growth and plasma level of IGF-1 in SHAM and PTX rats with an intact renal mass

On day 7 following PTX or SHAM operation, half of animals in each experimental group were anesthetized, exsanguinated and the right kidney removed and weighed. As described above for UNX rats experimental protocol, the remaining animals were switched to a semi-synthetic diet containing either 20% or 40% casein for five days. At the end of the experiment, anesthetized animals were exsanguinated and the right kidney removed and weighed.

Effect of retinoid administration in PTX rats on kidney growth and plasma level of IGF-1 in response to high protein diet in uninephrectomized rats

As described above, male rats underwent PTX and one week later, the left kidney was removed under anesthesia and weighed. On day 7 following UNX, animals were fed a semi-synthetic diet containing either 20% or 40% casein for five days. In each dietary protein condition, half of the animals were injected s.c. with either 25 μg/rat of a retinoid derivative dissolved in 50 μl ethanol (RO 13–6298, Hoffmann-La Roche & Co, Basel, Switzerland) or the vehicle. At the end of the experiment, animals were anesthetized, exsanguinated, and the right kidney removed and weighed.

Effect of chronic PTH infusion on plasma level of IGF-1 in TPTX rats

Successfully thyroparathyroidectomized rats were substituted with thyroxine (4 μg s.c., three times a week). A synthetic fragment of bovine parathyroid hormone (1–34) [bPTH-(1–34), 6800 IU/mg, from Sigma, St. Louis, MO, USA] was dissolved in isotonic saline with 2% cystein-HCl (pH 1.5). The peptide or its vehicle was chronically infused by osmotic minipumps (Alzet, model 2001) implanted in the peritoneal cavity and delivering approximately 1 μl/hr beginning at postoperative day 11 for seven days. At the end of the experiment, animals were anesthetized and blood collected by aortic punction.

Analytical methods

Renal IGF-1 was extracted from powder of kidneys frozen in liquid nitrogen as described by D'Ercole, Stiles and Underwood [13]. Plasma IGF-1 was dissociated from serum binding proteins with 0.5 N HCl and applied to a SEP-PAC C18 cartridge (Waters Associates, Milford, MI, USA). After washing the cartridge with 4% acetic acid, IGF-1 was eluted with methanol. IGF-1 was determined by radioimmunoassay with a rabbit antiserum raised against recombinant human IGF-1 and cross-reacted with rat IGF-1 as described [14]. Calcium (Ca) was measured by atomic absorption spectrophotometry. Inorganic phosphate (Pi) was determined spectrophotometrically as phosphomolybdate after reduction with a 10% ascorbic acid solution [15]. Plasma urea was determined colorimetrically using the urease method modified by Berthelot (Urea Test Kit, Hoffman La Roche & Co.).

Statistical analysis

All results are expressed as means ± SEM. A two sided, unpaired Student's t-test or a one-way analysis of variance for multiple comparisons were used for statistical analysis. A difference between experimental groups was considered as significant when the probability value was less than 5.0%.

Results

Effect of PTX+1,25 D_3 on compensatory renal growth (CRG) in rats fed normal lab chow

Following uninephrectomy (UNX) in rats fed normal lab chow, the fractional kidney growth recorded after seven days was slightly but significantly lower in PTX (kidney/body wt ratio: 0.44 ± 0.01%, $N = 9$, vs. 0.46 ± 0.01%, $N = 10$, $P < 0.05$) as compared to SHAM-operated animals. Administration of 1,25 D_3 in PTX rats restored the slightly lower renal growth effect observed in PTX rats (0.46 ± 0.02%, $N = 9$, not significantly different from SHAM). At that time, the mean body weight plasma creatinine and plasma urea were identical in the three experimental groups (Table 1). Associated with these differences in renal growth, plasma calcium concentration was significantly lower and plasma Pi slightly higher in UNX-PTX compared with that in UNX-SHAM rats. Plasma calcium was normal whereas plasma Pi remained slightly elevated in UNX-PTX rats receiving 1,25 D_3 administration (Table 1).

Effect of PTX ± 1,25 D_3 on CRG induced by HPr diet

UNX rats were switched from the normal rat chow to the semi-synthetic diets containing either 20% (NPr) or 40% casein (HPr) for five days. HPr diet induced a significantly greater renal growth (Fig. 1). In UNX-PTX rats, the renal growth induced by the HPr diet was completely blunted and the mean kidney/body weight ratio was even lower than that observed in UNX-SHAM fed NPr diet (Fig. 1). Administration of 1,25 D_3 to UNX-PTX rats completely restored the renal growth to the level observed in UNX-SHAM animals fed HPr diet. The mean body weight, which was similar in UNX-SHAM fed NPr, UNX-SHAM fed HPr and UNX-PTX fed HPr, was slightly higher in UNX-PTX receiving 1,25 D_3 despite strict "pair-feeding" of these animals (Table 1).

Table 1. Plasma levels of calcium (Ca), inorganic phosphate (Pi) and urea in uninephrectomized SHAM and PTX rats fed lab chow for 7 days and a semisynthetic diet with either a normal (20%) or a high (40%) protein content for 5 additional days

	Day 7			Day 12			
	Sham (10)	PTX (9)	PTX+1,25 D_3 (9)	SHAM-20% (11)	SHAM-40% (11)	PTX-40% (7)	PTX-40% +1,25 D_3 (9)
Plasma Ca *mmol/liter*	2.48 ± 0.05	2.07 ± 0.07[a]	2.42 ± 0.05	2.44 ± 0.03	2.46 ± 0.03	1.21 ± 0.05[c]	2.16 ± 0.02
Plasma Pi *mmol/liter*	2.44 ± 0.06	2.63 ± 0.07	2.70 ± 0.06	2.68 ± 0.06	2.63 ± 0.04	4.26 ± 0.16[d]	3.07 ± 0.06[d]
Plasma urea *mmol/liter*	5.86 ± 0.38	5.84 ± 0.42	5.36 ± 0.19	3.16 ± 0.33	7.45 ± 0.73	8.63 ± 1.52	8.07 ± 1.13
Plasma creatinine *μmol/liter*	64.2 ± 1.4	62.8 ± 1.9	61.3 ± 0.7	67.3 ± 1.7	60.5 ± 2.7	74.8 ± 2.7[b]	62.3 ± 1.1
Body weight *g*	212.7 ± 1.5	217.4 ± 2.2	212.4 ± 1.5	263.2 ± 1.9	267.2 ± 1.3	264.3 ± 3.6	277.7 ± 3.2

The results are means ± SEM with animal number indicated in parenthesis. ANOVA followed by Scheffe's test was used for statistical analysis.
[a] $P < 0.001$ as compared to SHAM or PTX+1,25 D_3
[b] $P < 0.01$ as compared to SHAM-40% or PTX-40%+1,25 D_3
[c] $P < 0.001$ as compared to SHAM-(20 or 40%) or PTX 40%+1,25 D_3
[d] $P < 0.001$ as compared to SHAM-(20 or 40%)

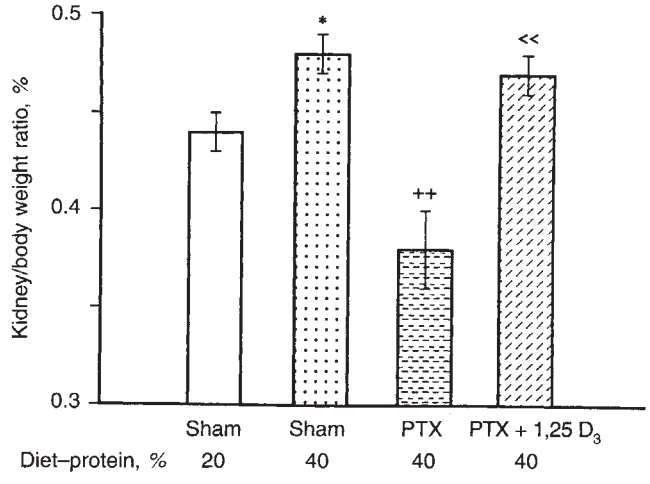

Fig. 1. *Influence of parathyroidectomy (PTX) and 1,25 dihydroxyvitamin D_3 (1,25 D_3) supplementation in PTX animals on kidney growth induced by high protein diet in uninephrectomized rats.* *$P < 0.05$ as compared to SHAM 20% (ANOVA followed by Scheffer's test). ++, >> $P < 0.001$ as compared to SHAM 40% and PTX 40%, respectively (ANOVA followed by Scheffer's test).

Effect of PTX with or without 1,25 D_3 on kidney IGF-1 content and plasma IGF-1 in response to HPr

The kidney IGF-1 content measured five days after feeding rats with the semi-synthetic diets was affected neither by dietary protein content nor by parathyroidectomy (Fig. 2A). In UNX-PTX rats receiving 1,25 D_3, the renal IGF-1 content was slightly but significantly lower compared with UNX-SHAM control animals fed NPr diet. In contrast to the absence of any change in renal IGF-1 content, the plasma level of IGF-1 was significantly increased in UNX-SHAM fed HPr compared to NPr diet. Of particular interest, this elevation in plasma IGF-1 concentration induced by HPr diet was completely blunted in UNX-PTX rats. In fact, in these animals the IGF-1 plasma level was even lower than that measured in UNX-SHAM fed NPr diet (Fig. 2B). Administration of 1,25 D_3 in UNX-PTX rats nearly completely abolished the blunting effect induced by parathyroidectomy on elevation of plasma IGF-1 concentration in response to high protein diet (Fig. 2B). Associated with the lower plasma level of IGF-1 in UNX-PTX animals, plasma calcium concentration was lower and plasma Pi concentration higher than in UNX-SHAM animals fed either NPr or HPr diet. In these animals, 1,25 D_3 administration nearly normalized plasma calcium and plasma Pi towards levels recorded in the UNX-SHAM experimental group (Table 1).

Relation between plasma IGF-1 and kidney growth

As shown in Figure 3, there was a positive and significant correlation between kidney/body weight ratio and plasma level of IGF-1 ($r = 0.630$, $P < 0.001$) measured in the various experimental groups (UNX-SHAM fed either NPr or HPr diet, UNX-PTX and UNX-PTX+1,25 D_3 fed the HPr diet).

Effect of a retinoid derivative on plasma calcium and changes in kidney growth and plasma IGF-1 in response to HPr diet

To investigate the potential role of extracellular calcium in mediating the change in the plasma level of IGF-1 and renal growth in response to HPr diet, UNX-PTX rats were fed either NPr or a HPr diet, and were treated with a retinoid derivative which increases plasma calcium by essentially acting on bone resorption. As shown in Figure 4, treatment of UNX-PTX rats with the retinoid derivative, which has no effect on plasma levels of calciotropic hormones [16], induced a similar elevation in plasma calcium in rats fed NPr and HPr diets. Associated with this elevation of plasma calcium, both kidney growth and plasma IGF-1 level were significantly increased in response to HPr diet. In animals not treated with the bone resorbing agent, plasma calcium remained low and was not influenced by the protein intake. In these animals, neither plasma IGF-1 concentration nor kidney growth was affected by changing the protein intake.

Effect of HPr diet on plasma IGF-1 and kidney growth in rats with intact renal mass

As previously described [8], the changes in the plasma level of IGF-1 in response to HPr diet was also observed in rats with intact renal mass (Table 2). Renal growth, however, was not significantly

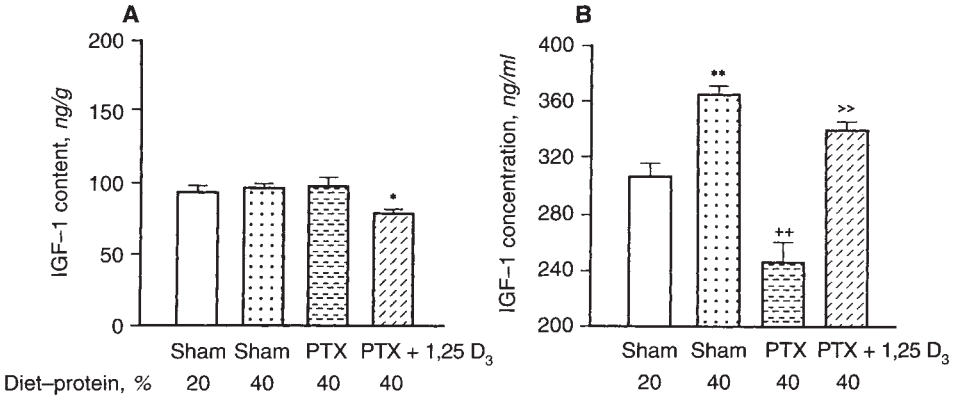

Fig. 2. *Influences of parathyroidectomy (PTX) and 1,25 dihydroxyvitamin D_3 (1,25 D_3) supplementation in PTX animals on changes in kidney IGF-1 content* **(A)** *and plasma IGF-1 concentration* **(B)** *in response to high protein diet in uninephrectomized rats.* $^*P < 0.01$, $^*P < 0.001$ as compared to SHAM 20% (ANOVA followed by Scheffer's test). ++, >> $P < 0.001$ as compared to SHAM 40% and PTX 40%, respectively (ANOVA followed by Scheffer's test).

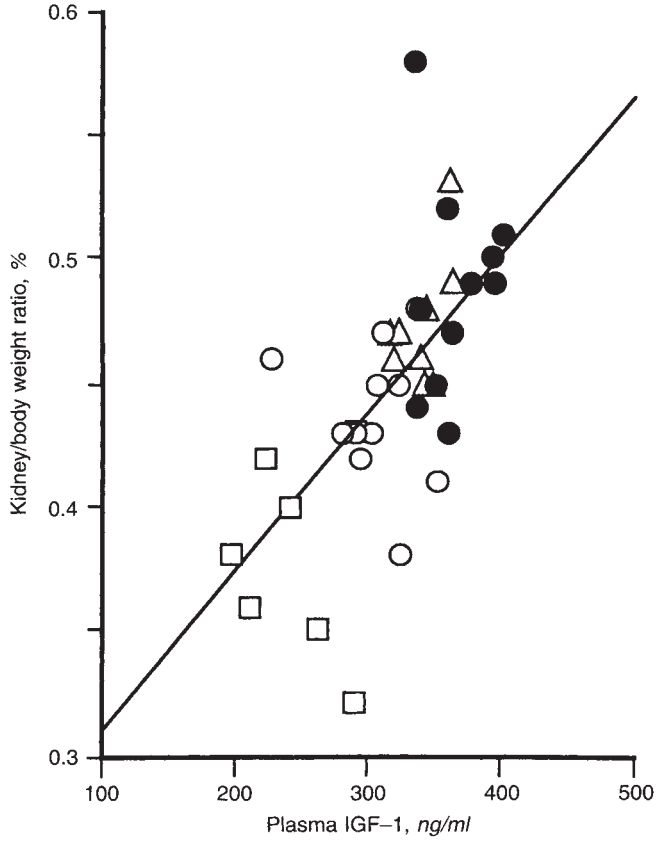

Fig. 3. *Relationship between changes in kidney/body weight ratio and plasma IGF-1 concentration in SHAM 20% (○), SHAM 40% (●), PTX 40% (□) and PTX+1,25 D_3 40% (△) in uninephrectomized rats.* The correlation was significant with linear regression analysis ($r = 0.630$, $P < 0.01$).

increased when compared to animals fed NPr diet (Table 2). As observed in UNX rats, the rise in plasma IGF-1 concentration in response to high protein diet was blunted in PTX rats with intact renal mass, and this effect was associated with a markedly reduced plasma calcium concentration.

Effect of PTH infusion on plasma IGF-1 level in TPTX rats fed NPr diet

Chronic (7 days) infusion of bPTH restoring the calcemia to normal high level in TPTX rats with normal renal mass and fed NPr diet, failed to alter the plasma level of IGF-1 (Table 3). This suggests that the rise in plasma IGF-1, in response to HPr diet, was not directly related to the circulating level of PTH although requires its presence or that of another calcemic factor.

Discussion

The results of the present study provide evidence that the influence of the protein intake on the degree of compensatory renal growth is mediated by variations in the level of circulating IGF-1. This notion is sustained by the positive relationship between the kidney/body weight ratio and plasma IGF-1 concentration found in UNX rats under various investigated conditions. In the experimental setting used in this study, the protein-dependent compensatory growth did not seem to be related to the kidney IGF-1 content. Nevertheless, it cannot be ruled out that such a relation might have been detectable at an earlier time period in the course of renal compensatory growth.

Another important aspect of the present work is the role played by PTH in the plasma IGF-1 elevation in response to the protein intake. The plasma level of IGF-1 is mainly determined by its synthesis and secretion by the liver [16–18]. Therefore the foregoing study strongly suggests that PTH and/or the associated change in plasma calcium concentration plays a permissive role in the expression of the protein effect on hepatic IGF-1 production. The mechanism by which PTH and/or extracellular calcium influences hepatic IGF-1 production in response to high protein diet remains to be elucidated.

The results of the present study also indicate that in a way similar to PTH, another calciotropic hormone, 1,25-dihydroxyvitamin D_3 (1,25 D_3), modulates the hepatic IGF-1 production in response to variations in the protein intake. Indeed, 1,25 D_3 given to PTX rats restores the stimulatory effect of HPr diet on both plasma IGF-1 and compensatory renal growth. This observation suggests that PTH is not directly involved in the regulation of IGF-1 production by the liver. This notion is sustained by results presented in this study showing that after parathyroidectomy, chronic administration of PTH in rats with intact renal mass did

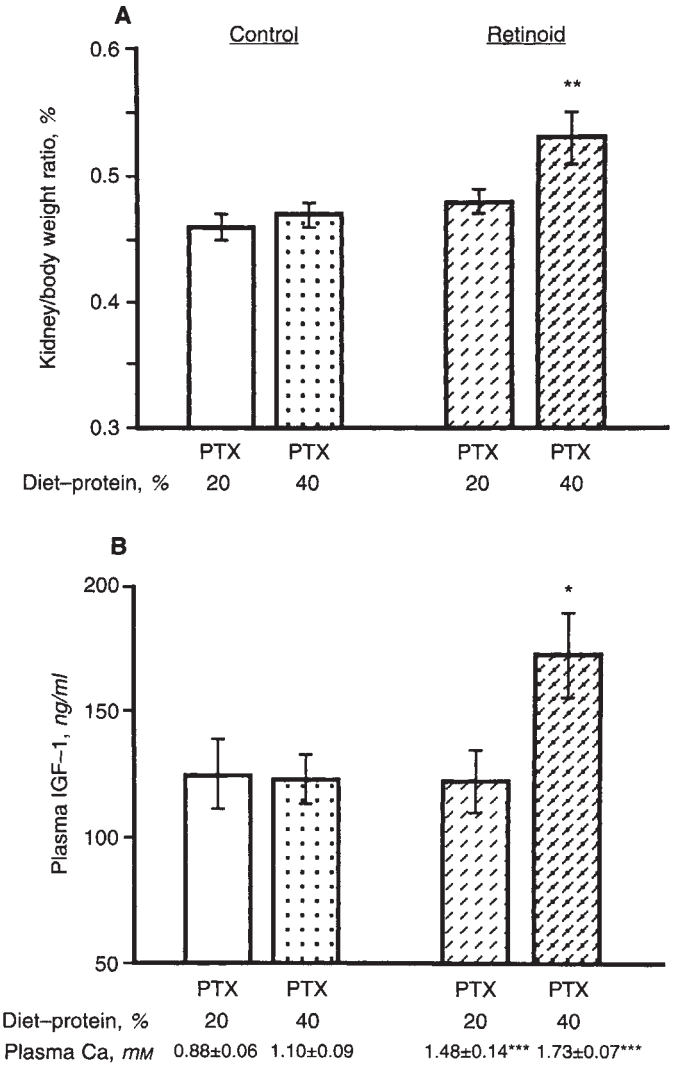

Fig. 4. *Effect of chronic changes in plasma calcium concentration in parathyroidectomized (PTX) rats by a bone resorbing agent (retinoid derivative) on kidney growth and plasma level of IGF-1 in uninephrectomized rats.* $^{*}P < 0.05$, as compared to PTX 20% treated with retinoid (ANOVA followed by Fischer's test); $^{**}P < 0.025$ as compared to PTX 40% control (ANOVA followed by Scheffer's test); $^{***}P < 0.005$ as compared to control group receiving the vehicle (ANOVA*** followed by Scheffer's test).

not enhance the plasma level of IGF-1 (Table 3). This is also consistent with the previous observation indicating that high protein diet did not alter the plasma level of parathyroid hormone [5]. Recent observations in young milk-fed calves indicate, however, that acute administration of PTH in the mesenteric artery can directly modulate IGF-1 production by the liver [11]. Further studies are required to delineate the exact role of PTH, 1,25 D_3 and extracellular calcium on the hepatic production of IGF-1.

Both PTH and 1,25-dihydroxyvitamin D_3 markedly influence extracellular calcium concentration in PTX animals. Therefore, both hormones could modulate the hepatic IGF-1 production indirectly by affecting the extracellular concentration of calcium. As shown in Figure 4, chronic elevation of plasma calcium concentration, induced by a retinoid derivative of which the

Table 2. Changes in the weight of the right kidney and plasma level of IGF-1 in response to high protein diet for 5 days in either SHAM or PTX rats with intact renal mass

	SHAM-20% (6)	SHAM-40% (7)	PTX-20% (7)	PTX-40% (7)
Kidney weight *g*	0.85 ± 0.02	0.97 ± 0.02[b]	0.56 ± 0.02	0.70 ± 0.03[b]
Body weight *g*	204.8 ± 3.0	222.0 ± 2.3[b]	149.3 ± 6.7	169.1 ± 6.7[a]
Kidney wt/ body wt %	0.42 ± 0.02	0.44 ± 0.01	0.38 ± 0.02	0.41 ± 0.03
Plasma IGF-1 *ng/ml*	108.0 ± 10.7	152.5 ± 10.5[a]	101.2 ± 9.2	104.0 ± 10.9
Plasma Ca *mmol/liter*	2.60 ± 0.02	2.53 ± 0.04	1.13 ± 0.02	1.07 ± 0.01

The results are means ± SEM with animal number indicated in parenthesis. The data shown for SHAM and PTX are from two separate experiments.
[a] $P < 0.05$, [b] $P < 0.005$, as compared to 20% protein diet (Student's *t*-test).

Table 3. Effect of chronic PTH infusion on plasma IGF-1 level in TPTX rats fed a normal protein diet

	Control ($N = 5$)	bPTH-(1-34) ($N = 5$)
Plasma Ca *mmol/liter*	1.54 ± 0.12	2.96 ± 0.09[a]
Plasma IGF-1 *ng/ml*	118.0 ± 7.1	110.8 ± 3.1

The results are means ± SEM with animal number indicated in parenthesis.
[a] $P < 0.001$ as compared to control (Student's *t*-test)

calcemic effect is mainly due to stimulation of bone resorption [19], mimicked the effect of the two calciotropic hormones on plasma level of IGF-1 and kidney growth in response to high protein diet. This suggests that extracellular calcium plays the key role in protein-dependent CRG. Nevertheless, one cannot rule out that retinoid derivative, like the other two calciotropic hormones, could play a permissive role in the protein-induced stimulation of hepatic IGF-1 production.

The physiological and pathophysiological importance of the modulatory role of calciotropic hormones on hepatic IGF-1 production has not been considered so far. In subjects with normal renal function, the positive action of calciotropic hormones on plasma level of IGF-1 might be beneficial for bone anabolism, especially in young individuals during rapid growth of the skeleton. However, in presence of a reduced renal function, an increased plasma level of IGF-1, resulting from high protein diet, could contribute to the so-called "compensatory renal growth." This response will not be necessarily beneficial for the remaining functional nephrons, since, as suggested from a recent report, renal "compensatory" hypertrophy induced by a high protein diet was associated with an acceleration in the progression of renal failure [5].

The data presented in this study and previous observations [5, 20, 21] suggest that calciotropic factors influence compensatory renal growth by at least two different mechanisms. As schematically depicted in Figure 5, calciotropic factors appear to affect, at the hepatic level, the production of IGF-1 in response to variations in the protein intake. In addition, PTH and 1,25 D_3 either directly or indirectly, via their calcemic activity, can also modulate

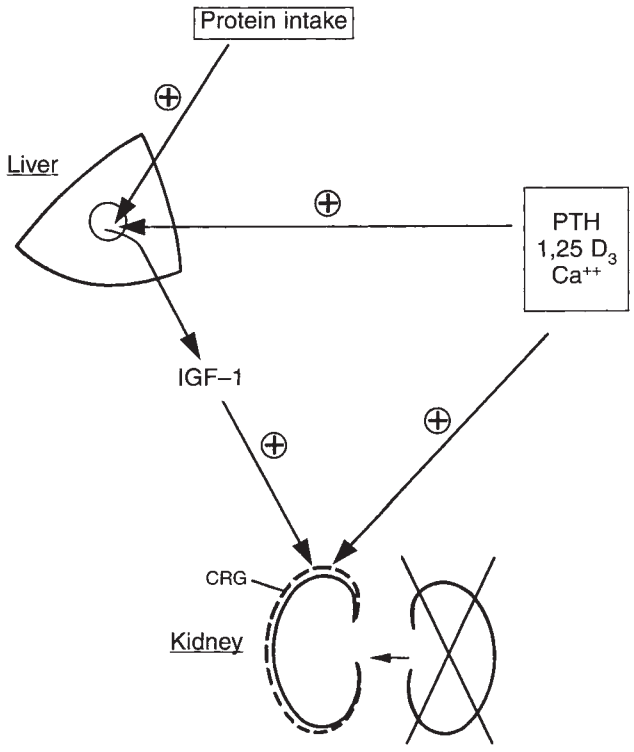

Fig. 5. *Schematic representation of effects of calciotropic factors on IGF-1 production and compensatory renal growth (CRG).* Calciotropic factors affect at the hepatic level the production of IGF-1 in response to variations in the protein intake. In addition, PTH, 1,25 D_3 either directly or indirectly via their calcemic activity can also modulate the magnitude of the compensatory renal growth (CRG) in response to nephronal reduction.

the magnitude of the compensatory renal growth in response to nephronal reduction [20, 21].

In conclusion, the results of the present study provide strong indirect evidence that calciotropic hormones such as PTH and 1,25-dihydroxyvitamin D_3 and/or the associated change in plasma calcium concentration modulate the hepatic IGF-1 production induced by high protein diet. The consequent elevation of the circulating level of IGF-1 could be responsible for the protein-dependent kidney hypertrophy in rats with a reduced renal mass. This effect on the remaining nephrons might play a significant role in the acceleration of renal function deterioration induced by a high protein diet.

Acknowledgments

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