Effect of Graded Renal Ablation on Kidney and Serum Insulin-Like Growth Factor-I (IGF-I) and IGF Binding Proteins in Rats: Relation to Compensatory Renal Growth

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Kidney insulin-like growth factor-I (IGF-I) increases transiently following unilateral nephrectomy, thus preceding the compensatory renal growth. The aim of the present study was to investigate the effect of different degrees (1/7 to 2/3) of renal ablation on kidney and serum IGF-I and IGF binding proteins (IGFBPs) during a 7-day study period. All nephrectomized rats exhibited an increase in the weight of the remaining renal tissue. Kidney IGF-I measured in kidney pieces close to and away from the resected area increased transiently and more significantly away from the resected area, with significant correlation to the amount of tissue resected (day 1, $r = .73$, $P < .0001$; day 2, $r = .49$, $P < .05$; and day 7, $r = .48$, $P < .05$). No changes in kidney IGFBPs or serum IGF-I were observed. Serum IGFBP-4 correlated to the degree of renal resection, as did changes in serum urea and creatinine. In conclusion, significant correlations were observed between local changes in kidney IGF-I and serum IGFBP-4 levels and the degree of renal ablation, suggesting a role for IGF-I as a renotropic factor and, further, that IGFBP-4 is removed to a major extent through the kidney.

A ROLE FOR GROWTH HORMONE (GH) and insulin-like growth factor-I (IGF-I) as renotropic factors in conditions characterized by rapid renal growth has recently been suggested.[1-4] Following unilateral nephrectomy in rats, a transient increase in kidney IGF-I has been demonstrated preceding the early compensatory renal growth.[1] The transient IGF-I increase is not consistently associated with increased levels of IGF-I mRNA in adult rats,[5] as it has been reported in immature rats.[6,7] In a recent study, it was demonstrated that IGF-I increased in regenerating kidney tissue following different degrees of renal infarction[8]; however, no correlation was observed between infarct size and kidney IGF-I accumulation. Local changes in kidney IGF-I may be involved in compensatory renal growth, as demonstrated in a study by Andersson et al,[9] where immunoreactive kidney IGF-I increased significantly more in renal cortex compared with renal medulla in the remaining kidney following unilateral nephrectomy. In another study where unilaterally nephrectomized rats were treated with a somatostatin analog (octreotide) as a potent inhibitor of GH and IGF-I production, both the transient kidney IGF-I accumulation and renal growth were inhibited, giving further evidence for IGF-I as an important factor in compensatory renal hypertrophy.[4]

IGF-I is bound to IGF binding proteins (IGFBPs), of which six are known today (IGFBP-1 to IGFBP-6),[10] and previous studies demonstrate that IGFBPs may function as carriers and/or modulators of IGF-I activity.[10-12] In a recent study in experimental diabetes, a transient increase in kidney IGFBP-3 and IGFBP-1 was observed concomitantly with the renal tissue IGF-I increase and preceding the early diabetic renal growth.[13,14] Further, kidney IGFBP-1 and IGFBP-5 mRNA are increased in early and long-term experimental diabetes, and this may account partly for the increase in kidney IGF-I observed.[15,16]

The aim of the present study was to investigate changes in kidney IGF-I and IGFBPs following different degrees of renal ablation to relate this to the degree of compensatory renal hypertrophy. Surgical ablation of renal tissue was performed, since this method allows a more precise determination of renal mass removed compared with renal infarction. In addition, changes in serum IGF-I, IGFBPs, urea, and creatinine were determined following different degrees of renal ablation.

MATERIALS AND METHODS

Animal Protocol

Male Wistar rats (Møllegaards Avlslaboratoire, Eiby, Denmark) with a mean body weight of 206 ± 3 g were studied (N = 124). Rats were housed two to three rats per cage in a room with a 12-hour (6:30 AM to 6:30 PM) artificial light cycle and controlled temperature (21° ± 2°C) and humidity (55% ± 2%). The animals had free access to standard rat chow (Altromin, Lage, Germany) and tap water throughout the experiment. Animals were randomized into five groups matched for body weight: C, control rats, sham-operated (n = 12); and groups 2, 3, 4, and 5, subjected to increasing degrees of renal ablation and designated NA, NB, NC, and ND. NA rats had a resection of two poles of one kidney, thus leaving one normal functioning kidney and the remaining part of the resected kidney (n = 28). NB rats had a unilateral nephrectomy (n = 28). NC rats had a unilateral nephrectomy and resection of one pole of the remaining kidney (n = 28). And ND rats had a unilateral nephrectomy and resection of two poles of the remaining kidney (n = 28). The surgical procedure was performed under sodium barbital anesthesia (50 mg/kg body weight intraperitoneally [IP]), and the kidneys were exteriorized and encapsulated through a flank incision and resected renal tissue was weighed. Rats in group NA were subjected to resection of two poles from the left kidney only. Unilateral nephrectomy was performed in groups NB, NC, and ND; and further, in the same session, one or two poles were resected from the remaining kidney from animals in groups NC and ND. During resection of the poles, penetration to the renal pelvis was avoided and hemostasis was achieved using mild compression with a sterile gauze swab. In sham-operated control rats, both kidneys were exteriorized and decapsulated and afterwards replaced in the abdomen. The amount of renal tissue removed from animals in the different groups was as follows: NA, 214 ± 5 mg; NB, 825 ± 8 mg; NC, 956 ± 11 mg; and ND, 1,039 ± 14

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mg. Based on this, we termed the different groups ⅓ to ⅔ nephrectomized rats, respectively. Control animals were examined by day 0 and day 7, six rats each day. Animals subjected to nephrectomy were examined by days 1, 2, 4, and 7, seven rats from each group every day.

During the study period, animals were weighed daily and food intake was measured. By the end of the experiments, the rats were anesthetized with sodium barbital (50 mg/kg body weight IP), with blood drawn from the retrobulbar venous plexus followed by dissection of the rats to obtain the kidneys. The kidneys were weighed (wet weight) and macroscopically separated into three pieces; one piece was obtained from the surgical area of the kidney and thus contained both regenerating kidney and scar tissue and was termed "total kidney remnant." The two other pieces were obtained distant from this zone thus representing hypertrophying kidney tissue only and being termed "scar-free kidney remnant."

Kidney and Serum IGF-I Measurements

Kidney IGF-I extraction was performed according to the method used by D'Ercole et al,[17] and serum IGF-I was extracted using acid-ethanol extraction. IGF-I radioimmunoassay was performed as previously described.[18,19] Intraassay coefficient of variation (CV) was 5.4% and interassay CV 9.3%.

IGFBPs

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and Western ligand blot analysis were performed according to the method of Hossenlopp et al[20] as previously described.[14] Autoradiographs of ligand blots were scanned using a laser densitometer (CS-9001PC; Shimadzu, Kyoto, Japan). Relative densities of the bands were measured as arbitrary absorbency units per millimeter squared.

Serum Urea, Creatinine, Potassium, and Sodium

Serum urea, creatinine, K^+, and Na^+ levels were measured using conventional laboratory techniques.

Statistical Analysis

Results are given as the mean ± SEM. Differences between groups were analyzed by one-way ANOVA in combination with the Duncan test for multiple comparisons, or for data not following a normal distribution, the Kruskall-Wallis test followed by the Mann-Whitney test. Regression analysis was also performed by the statistical package SOLO (BMDP Statistical Software, Los Angeles, CA). P less than .05 was considered statistically significant in a two-tailed test.

RESULTS

Body Weight

Body weight changes in the experimental groups are shown in Fig 1. Initially after the anesthesia and surgical procedure, a decrease was observed in all groups followed by an increase in body weight, which was most pronounced in control, NA, and NB rats. The groups with the most pronounced degree of renal ablation, NC and ND, were characterized by a significantly lower body weight increase compared with the sham-operated control rats from day 2 and NA and NB rats from day 5 and throughout the study period ($P < .05$).

Food Intake

A marked reduction in 24-hour food intake in anesthetized animals was observed by day 1 after the surgical procedure compared with day 0 ($P < .05$). In animals with the most pronounced degree of renal ablation, a more marked reduction in food intake was observed for the first few days after the surgical procedure; however, at the end of the study period, no significant difference in food intake was observed between any of the groups (data not shown).

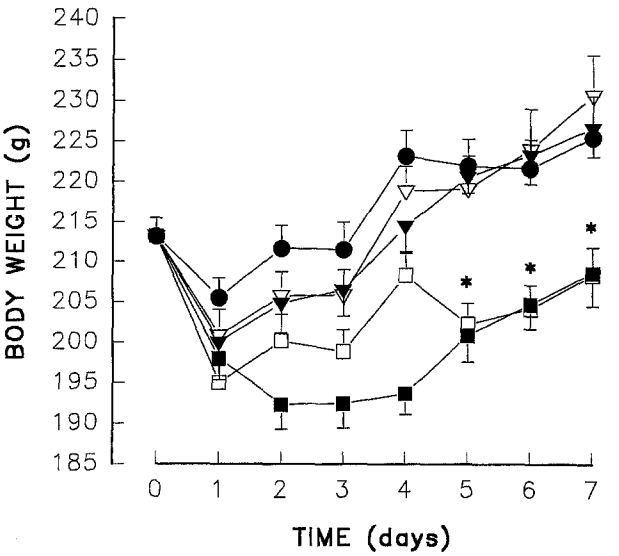

Fig 1. Changes in body weight during the study period in the 5 experimental groups: sham-operated controls (●) and NA (▽), NB (▼), NC (□), and ND (■) rats. Values are the mean ± SEM. *$P < .05$: NC and ND *v* controls, NA, and NB rats by days 5, 6, and 7.

Kidney Weight

Kidney weight changes in the experimental groups are shown in Fig 2. In NA animals, no change in the weight of the unoperated normal kidney (NA-1) was observed. However, in the remaining kidney following excision of the two kidney poles (NA-2), a significantly smaller kidney weight was observed by day 7 compared with day 1 and day 4 ($P < .05$). In NB rats, a significant increase in the weight of the remaining kidney was observed, amounting to 15% by the end of the study period compared with controls investigated by day 0 ($P < .05$). In NC animals, a significant increase in the weight of the remaining kidney tissue was observed from day 1 to day 4 ($P < .01$); however, the day 7 kidney weight was not different from the weight observed by day 1. A similar parallel pattern was observed in the ND group, which was subjected to the most pronounced renal ablation; however, the kidney weight was significantly higher than the day 1 weight ($P < .05$).

Kidney IGF-I

Changes in kidney IGF-I levels in the scar-free kidney remnant are shown in Fig 3A, and in total kidney remnant in Fig 3B. A significantly higher level of IGF-I was observed in the former, and the relative changes in kidney IGF-I levels observed in the scar-free kidney remnant were significantly higher than in the total kidney remnant. Kidney IGF-I levels were similar in the sham-operated control by day 0 and day 7, and there was no difference in IGF-I level in the two separate kidney parts (Fig 3A and B).

In NA rats, in which two poles were resected and one kidney was left undamaged, the scar-free kidney remnant (NA-2)

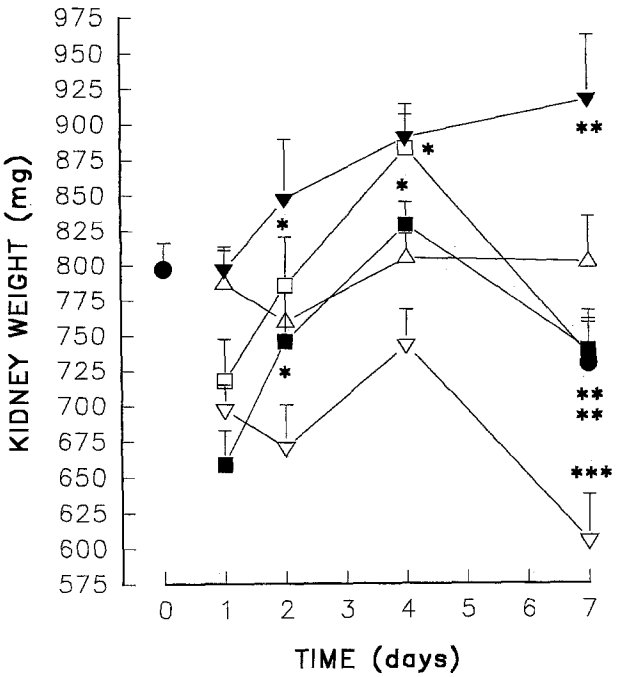

Fig 2. Changes in kidney weights during the study period in the 5 experimental groups: sham-operated controls (●), NA-1 (the undamaged kidney, △), NA-2 (resected kidney, ▽), NB (▼), NC (□), and ND (■). Values are the mean ± SEM. *$P < .01$: NC and ND days 2 and 4 *v* day 1. **$P < .05$ *v* day 1. ***$P < .05$: NA-2 day 7 *v* days 1 and 4. ****$P < .01$: NC and ND day 7 *v* day 4.

showed a small but significant increase in kidney IGF-I from day 2 and for the rest of the study period ($P < .05$; Fig 3A), while no change was observed in the total kidney remnant (Fig 3B) and in the undamaged kidney (NA-1). NB and NC rats showed a transient increase in kidney IGF-I by days 1 and 2, leveling off by day 4 to day 7. A similar but much more pronounced increase was observed in ND animals, which had the most severe degree of kidney resection. By day 1 and at the end of the study period, the kidney IGF-I increase was significantly higher than in all other groups ($P < .05$).

Kidney IGF-I levels in the scar-free kidney remnant correlated significantly with the amount of kidney tissue resected. However, the correlation was most pronounced by day 1 ($r = .68$, $P < .001$) and day 2 ($r = .65$, $P < .001$), whereas it was absent by day 4 ($r = .38$, $P = .06$) and day 7 ($r = .31$, $P = .12$). In the total kidney remnant, a significant correlation was observed by day 1 ($r = .73$, $P < .0001$), day 2 ($r = .49$, $P < .05$), and day 7 ($r = .48$, $P < .05$), but it was absent by day 4 ($r = .024$, $P = .12$).

Kidney IGFBPs

In kidney tissue, four distinct bands of IGFBPs were identified with apparent molecular weights of 38 to 47 (doublet), 30, and 24 kd. The 38- to 47-kd doublet probably corresponds to the IGF binding subunit of IGFBP-3 (Fig 4A), and the 30-kd band to IGFBP-1, IGFBP-2, and IGFBP-5 (Fig 4B), since these IGFBPs have similar molecular weights in rats, and the 24-kd band to IGFBP-4 (Fig 4C). Only small amounts of IGFBP-3 were observed, whereas the 30-kd IGFBPs and IGFBP-4 showed a predominant band on the ligand blots. No significant changes in kidney IGFBPs were observed in any of the groups throughout the study period.

Serum IGF-I

Sham-operated control rats exhibited a significant decrease in serum IGF-I from day 0 to the end of the study period (1,043 ± 95 *v* 737 ± 86 μg/L, $P < .05$). No changes in serum IGF-I were observed over the study period in the different nephrectomized groups (Fig 5).

Serum IGFBPs

In serum, four distinct bands of IGFBPs were observed with molecular weights as already described for kidney IGFBPs, and

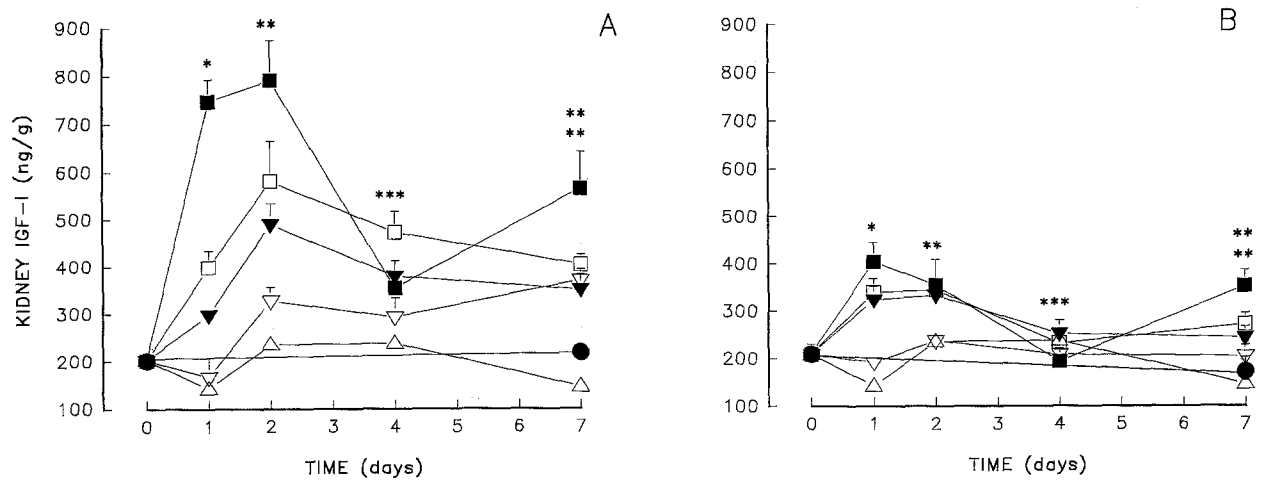

Fig 3. Changes in kidney IGF-I levels in (A) scar-free kidney remnants and (B) total kidney remnants observed in the 5 experimental groups during the study period: sham-operated controls (●), NA-1 kidney (△), NA-2 kidney (▽), NB (▼), NC (□), and ND (■). Values are the mean ± SEM. Correlations between kidney IGF-I and renal tissue removed by day 0 are presented as *r* and *P* values by each day. (A) *$r = .68$, $P < .001$ by day 1; **by day 2, $r = .65$, $P < .001$; ***by day 4, $r = .38$, $P = .06$; and ****by day 7, $r = .31$, = 0.12. (B) *$r = .73$, $P < .0001$ by day 1; **by day 2, $r = .49$, $P < .05$; ***by day 4, $r = .024$, $P = .12$; and ****by day 7, $r = .48$, $P < .05$.

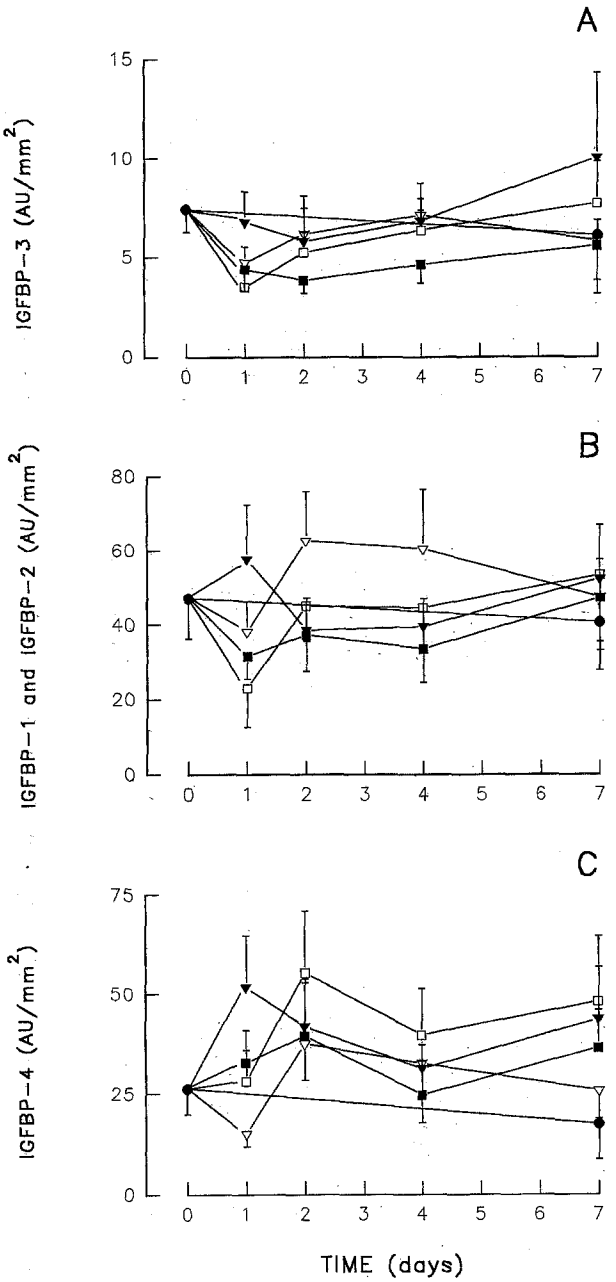

Fig 4. Changes in kidney (A) IGFBP-3, (B) IGFBP-1 and -2, and (C) IGFBP-4 levels observed in the 5 experimental groups during the study period: sham-operated controls (●), NA (▽), NB (▼), NC (□), and ND (■). Values are the mean ± SEM.

are shown in Fig 6A, B, and C. IGFBP-3 constituted the largest fraction, followed by a smaller band of 30-kd IGFBPs and by IGFBP-4. No significant changes were observed in serum IGFBP-3 or 30-kd IGFBPs throughout the study period. A significant increase was observed in the IGFBP-4 band in these groups with the most severe reduction in kidney mass by day 1 compared with control rats by day 0 (NB, NC, and ND *v* controls, $P < .05$). Positive correlations between IGFBP-4 and the amount of kidney tissue resected by day 0 were observed by day 1 ($r = .47$, $P = .02$) and day 7 ($r = .45$, $P = .03$), but only a tendency was observed by day 2 ($r = .39$, $P = .08$) and day 4 ($r = .41$, $P = .06$).

Serum Urea Creatinine, Na^+, and K^+

Serum creatinine and urea concentrations are shown in Table 1. All groups subjected to increasing degrees of renal ablation had higher serum urea and creatinine by day 1 compared with control rats ($P < .05$). The increase in urea and creatinine correlated significantly with the degree of renal ablation (day 1: urea, $r = .31$ and $P = .004$, and creatinine, $r = .33$ and $P = .001$; day 2: urea, $r = .24$ and $P = .013$; and creatinine, $r = .60$ and $P = .001$; day 4: urea, $r = .54$ and $P = .0001$, and creatinine, $r = .62$ and $P = .0001$; day 7: urea, $r = .55$ and $P = .001$, and creatinine, $r = .53$ and $P = .001$).

No significant changes in serum Na or K were observed (data not shown).

DISCUSSION

The present study confirmed that IGF-I increases transiently in the remaining kidney following unilateral nephrectomy in rats.[1,4] In addition, increasing degrees of renal ablation were followed by increasing degrees of kidney IGF-I accumulation in positive correlation to the amount of kidney tissue resected. Finally, local IGF-I changes occurred primarily in the scar-free kidney remnant.

The degree of renal ablation was followed by corresponding changes in body weight, food intake, and serum urea and creatinine levels. Immediately after the surgical procedure, markedly elevated levels of serum urea and creatinine were observed. However, in groups with the smallest kidney resection, the animals were able to compensate with normalization of serum urea and creatinine. In animals with the most severe kidney reduction, only a partial restoration of serum urea and creatinine was observed, indicating that renal function was not fully restored.

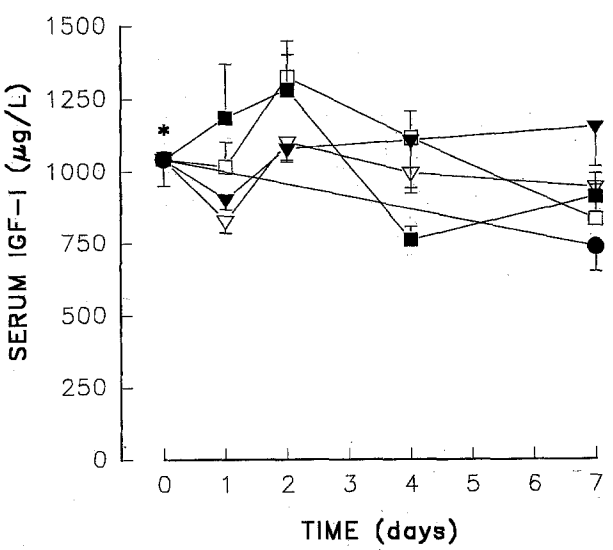

Fig 5. Changes in serum IGF-I during the study period in the 5 experimental groups: sham-operated controls (●), NA (▽), NB (▼), NC (□), and ND (■). Values are the mean ± SEM. *$P < .05$: control rats day 0 *v* day 7.

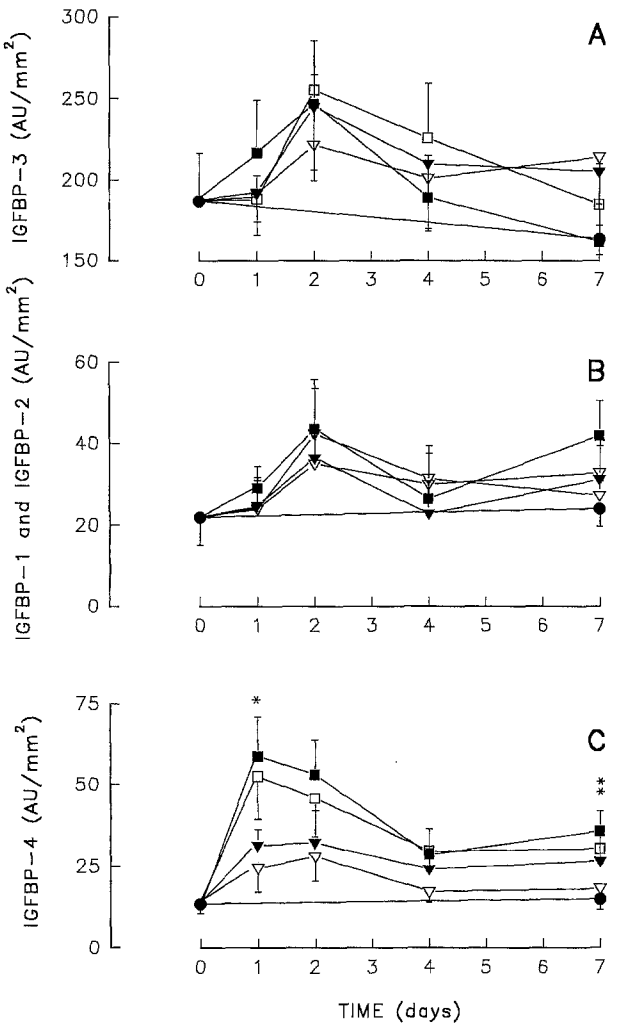

Fig 6. Changes in serum (A) IGFBP-3, (B) IGFBP-1 and -2, and (C) IGFBP-4 levels observed in the 5 experimental groups during the study period: sham-operated controls (●), NA (▽), NB (▼), NC (□), and ND (■). Values are the mean ± SEM. Correlations between serum IGFBP-4 and renal tissue removed by day 0 are shown as *r* and *P* values by each day: *day 1 (*r* = .47, *P* = .02); **day 7 (*r* = .45, *P* = .03).

Consistent with previous studies, animals exposed to unilateral nephrectomy (group NB) showed a 15% increase in contralateral kidney weight after a study period of 7 days.[1,4] In the two groups with the most severe reduction in renal mass (NC and ND), marked increases of the remaining kidney tissue were observed from day 1 to day 4 compared with day 1. However, by day 7, only ND rats had significantly higher kidney weights compared with the day 1 value. The apparent decrease in kidney weight by day 7 was not caused by differences in renal ablation performed by day 0, since similar amounts of kidney tissue were resected. However, it may be questionable to use the day 1 values as a reference value for increases in kidney weight, since renal hypertrophy may already start within 24 hours after nephrectomy, as demonstrated by Mulroney et al,[6] and thus show an inflated reference value. In addition, surgical manipulation with edema may cause some increase in remaining kidney weight, especially during the first postoperative days. However, if a theoretical day 0 value was estimated by subtracting the average amount of removed tissue from the average day 0 kidney weight in control rats, the degree of renal growth by day 7 was 17% in NB rats, 21% in NC rats, and 40% in ND rats.

As previously demonstrated, kidney IGF-I increased in the remaining renal tissue after reduction in renal mass.[1,5,21] The mechanism(s) behind the increase in kidney IGF-I may be an increase in uptake from the circulation or preurine due to increased binding to IGF receptors or IGFBPs or in local IGF-I production, and/or a combination of the factors. No changes in serum IGF-I have been demonstrated in the above-cited studies[1,5,21,22] or in the present study, which may suggest that serum IGF-I only contributes to a minor degree to IGF-I accumulation. It has previously been demonstrated that kidney IGF-I mRNA increases in the remnant kidney following uninephrectomy.[6,7,21] Mulroney et al[6,7,23] reported that this is primarily observed in immature or prepubertal rats, not in postpubertal rats as used in the present experiment. However, an increase in IGF-I mRNA has recently been demonstrated also in adult rats,[8,24] and increased local IGF-I production may thus be involved in the IGF-I accumulation observed in the present study. Increased IGF binding to kidney cell membranes has been demonstrated in immature rats, but not in adult rats, following uninephrectomy[7]; this may be due to binding to specific receptors and IGFBPs. In that study, only IGF-II binding was significantly increased in immature rats, and no significant changes were observed for IGF-I binding in either immature or adult rats. Kidney IGFBPs may be co-involved in IGF-I accumulation by trapping IGF-I from the circulation; however, data on changes in kidney IGFBP peptide and mRNA levels in models of

Table 1. Changes in Serum Urea (mmol/L) and Creatinine (μmol/L) in Sham-Operated Controls and Rats Subjected to Increasing Degrees of Renal Ablation (NA, NB, NC, and ND) Investigated During the 7-Day Study Period

		Experimental Groups			
Day	Controls	NA	NB	NC	ND
0					
Urea	3.9 ± 0.6*				
Creatinine	43 ± 1*				
1					
Urea		5.5 ± 0.8	5.8 ± 0.6	8.5 ± 0.8	11.0 ± 0.6†
Creatinine		51 ± 3	55 ± 3	78 ± 7	86 ± 5†
2					
Urea		5.9 ± 1.1	5.7 ± 1.4	8.8 ± 0.4	11.1 ± 0.8‡
Creatinine		46 ± 2	53 ± 6	70 ± 2	83 ± 2‡
4					
Urea		5.4 ± 0.3	6.5 ± 0.4	7.7 ± 0.2	10.5 ± 0.8§
Creatinine		43 ± 3	51 ± 2	56 ± 2	62 ± 2§
7					
Urea	5.7 ± 0.3	5.8 ± 0.3	6.8 ± 0.3	8.6 ± 0.4	8.9 ± 0.3‖
Creatinine	37 ± 1	43 ± 2	51 ± 2	66 ± 2	62 ± 3‖

NOTE. Correlations are between the amount of kidney tissue resected by day 0 and serum urea and creatinine by the different days.

*$P < .05$ *v* all other groups by day 1.

†Day 1 urea ($r = .31$, $P = .004$) and creatinine ($r = .33$, $P = .001$).

‡Day 2 urea ($r = .24$, $P = .013$) and creatinine ($r = .60$, $P = .001$).

§Day 4 urea ($r = .54$, $P = .0001$) and creatinine ($r = .62$, $P = .0001$).

‖Day 7 urea ($r = .55$, $P = .001$) and creatinine ($r = .53$, $P = .001$).

renal-mass reduction are sparse. In the present study, we could not demonstrate any changes in kidney IGFBP levels when examined by Western ligand blotting in whole-kidney homogenates. However, bearing in mind the localized production of IGFBPs (for review, see Flyvbjerg[25]) it may be difficult to detect restricted local changes in kidney IGFBPs when whole-kidney homogenates are examined. This has recently been demonstrated by Evan et al,[24] since IGFBP-2 mRNA was distributed in significantly different amounts in glomerulus > inner stripe > cortex > inner medulla > outer strip. Interestingly, glomerular IGFBP-2 mRNA increased over time in nephrectomized rat kidneys in their study. In experimental diabetes, another model characterized by IGF-I–dependent growth, an early transient increase in 30-kd IGFBPs and IGFBP-3 was observed using Western ligand blotting.[14] In addition, increased IGFBP-1 mRNA levels have recently been reported, and the IGFBP-1 mRNA increase was sustained for up to 6 months in experimental diabetes.[15]

In the present study, kidney IGF-I changes were different depending on the localization. IGF-I increased less markedly in the cut zone of renal tissue, where scar tissue develops (total kidney remnant), whereas more marked increases were observed in renal tissue away from the cut zone (scar-free kidney remnant). This may indicate that IGF-I is involved preferentially in renal hypertrophy and may be involved in the hyperfunction of kidney tissue where undamaged nephrons are localized. In a recent study by Rogers et al,[8] ischemia-induced renal infarction was followed by a similar increase in extractable kidney IGF-I as found in the present study, although the increase was apparently independent of the amount of tissue infarction (½ or 1½). In the present study, we demonstrated that IGF-I increased in correlation with the amount of kidney tissue resected, which supports the hypothesis that IGF-I is involved in the compensatory renal growth following surgical nephrectomy. Furthermore, the greatest increases in kidney IGF-I were observed in groups that by the end of the study period had demonstrated the greatest relative increase in kidney weight. IGF-I may also be involved in the hemodynamic changes observed following renal ablation, since an increase in the glomerular filtration rate (GFR) has been reported.[26,27] It has been shown that IGF-I infusion is followed by an increase in GFR and renal plasma flow in normal rats.[27,28] However, when exogenous IGF-I is administered to rats already subjected to a reduction in renal mass, no effect of IGF-I is observed for the GFR.[27] This may suggest that the increased endogenous kidney IGF-I level following reduction in renal mass makes the kidney resistant to a further increase in GFR induced by exogenously administered IGF-I. The cited studies and data from the present experiment thus provide further evidence for a role of IGF-I in inducing renal hypertrophy and hyperfunction in response to renal ablation.

Changes in serum IGF-I, IGFBP-3, and 30-kd IGFBPs were similar in all nephrectomized groups throughout the study period. In contrast, circulating IGFBP-4 showed a transient increase on days 1 and 2 with a positive correlation to the degree of renal ablation, which may suggest that IGFBP-4 is degraded to a major degree in the kidney. IGFBP-4 is mainly produced in the liver and seems not to be regulated by GH or IGF-I (for review, see Jones and Clemmons[29]). Further, the effect of IGFBP-4 is primarily believed to be inhibitory on IGF-I actions, as demonstrated both in vitro[30-32] and in vivo.[33,34] Thus, it cannot be excluded that the observed increase in serum IGFBP-4 in the present study is partly involved in the growth retardation observed in nephrectomized rats.

In conclusion, it was demonstrated that following graded degrees of renal ablation, a graded increase was observed in kidney IGF-I concentrations in the early phase of compensatory renal hypertrophy. Further, more pronounced kidney IGF-I changes were observed in renal tissue distant from the resected kidney area compared with renal tissue from the cut zone containing scar tissue, which may suggest an action of IGF-I related to undamaged nephrons. Finally, significant correlations were observed between kidney IGF-I, serum urea, serum creatinine, and serum IGFBP-4 and the amount of renal tissue resected.

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