Evidence That Insulin-like Growth Factor I Increases Renal Plasma Flow and Glomerular Filtration Rate in Fasted Rats

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Abstract

The mechanisms whereby growth hormone may increase renal plasma flow (RPF) and GFR are not known, but circumstantial evidence has implicated insulin-like growth factor I (IGF-I) as a mediator of this effect. This study examined whether an infusion of IGF-I will increase RPF and GFR, whether this effect occurs quickly, and if this effect is dependent on eicosanoids or peptide hormones known to affect renal function. Rats fasted for 3 d to reduce IGF-I and IGF-I plasma binding proteins were anesthetized; then the rats received an intravenous injection of 25 μg/kg IGF-I, and an infusion of 25 μg/kg IGF-I within 20 min. Controls received infusion of the vehicle. RPF (para-aminohippurate clearances), GFR (inulin clearances), renal vascular resistance (RVR), mean arterial blood pressure (MABP), plasma IGF-I, and glucose concentrations were measured repeatedly. At the end of the 20-min infusion, plasma IGF-I tended to be increased in the animals that received IGF-I ($P = 0.069$), but did not increase in the control rats. IGF-I induced a significant and sustained fall in RVR and rise in RPF and GFR without any change in MABP. A small, transient, but significant decrease in plasma glucose concentrations was observed during IGF-I but not during vehicle infusion. Indomethacin, but not somatostatin, blocked the renal response to IGF-I infusion. Thus, IGF-I infusion increases RPF and GFR and reduces RVR in fasted rats. This effect requires the presence of eicosanoids but does not seem to require other peptide hormones suppressed by somatostatin.

Introduction

There is abundant evidence that growth hormone increases renal plasma flow rate (RPF)[1] and GFR in humans (1). Patients with acromegaly and elevated circulating growth hormone levels have increased RPF and GFR (2). After pituitary ablation, RPF and GFR fall to normal; this fall precedes the reduction in kidney size (2). Moreover, injections of growth hormone in man increase RPF and GFR. However, the elevation in RPF and GFR does not occur for at least several hours after the injection (3, 4). These findings suggest that growth hormone may increase RPF and GFR by stimulating the release of one or more mediators.

Several lines of evidence suggest that insulin-like growth factor-I (IGF-I) may be one such mediator. First, growth hormone stimulates the secretion of IGF-I in the kidney and other organs and causes a rise in plasma IGF-I. Second, the increase in plasma IGF-I after growth hormone injection only occurs after several hours, at approximately the same time that RPF and GFR rise (3, 4). Moreover, after growth hormone injection, the elevations in RPF, GFR, and plasma IGF-I persist at a time when plasma growth hormone has decreased to baseline values (3). Third, in cases of growth hormone deficiency or excess, RPF, GFR, and plasma IGF-I co-vary in the same direction (i.e., all are reduced or increased) (3, 4). Fourth, IGF-I receptors have been identified in the kidney (5).

Although the foregoing studies demonstrate a temporal relationship between elevations in IGF-I, renal hemodynamics, and growth hormone, they do not prove that IGF-I causes the increase in RPF and GFR. Studies therefore were undertaken to test more directly the following questions: (*a*) Does an intravenous infusion of IGF-I increase RPF and GFR in rats? (*b*) Does this effect occur as quickly as would be expected if IGF-I mediates the renal effects of growth hormone? (*c*) Is this effect mediated by eicosanoid compounds or by other peptides that affect renal function?

Methods

General protocol. Male Sprague-Dawley and Munich Wistar rats were fasted, with free access to water, for 60–72 h to reduce plasma binding proteins and IGF-I (6). Anesthesia was induced by injecting Inactin (Byk-Gulden, Konstanz, FRG) 120 mg/kg body wt i.p. Rats were placed on a heating table (Harvard Apparatus, S. Natick, MA) that maintained a constant temperature of 36–38°C. A polyethylene (PE) 240 or 260 catheter (Clay Adams Div., Becton, Dickinson & Co., Parsippany, NJ) was inserted into the trachea. PE-50 catheters were placed in the left femoral artery, left internal jugular vein, and bladder. The bladder was ligated around the catheter to reduce the dead space. A quantity of normal saline equal to 1.5% of body weight was then infused intravenously over 15 min to replace fluid losses. A constant infusion of Ringer's lactate solution containing [^{3}H]inulin (15 μCi/ml) and [^{14}C]para-aminohippurate (PAH), (0.6 μCi/ml) (both from ICN Radiochemicals, Irvine, CA) was started at a rate of 1.7 ml/h. Blood pressure was recorded using a transducer (P23DB; Gould-Statham,

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1. *Abbreviations used in this paper:* HCT, hematocrit; IGF, insulin-like growth factor; MABP, mean arterial blood pressure; PAH, para-aminohippurate; RPF, renal plasma flow rate; RVR, renal vascular resistance.

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Inc., Cleveland, OH) and an amplifier with a recorder (model 8805 C; Hewlett-Packard Co., Waltham, MA). At the conclusion of the study, blood samples were obtained simultaneously from the left renal vein and femoral artery to determine the renal extraction of PAH, which was considered to be constant throughout the procedure in each animal. After the above procedures, the following studies were carried out.

Study 1. After a 75–105-min equilibration period, eight male Sprague-Dawley rats, weighing 246±7 (SEM) g, underwent 12 20-min urine clearance periods. The first two clearance periods were designated as baseline. At the beginning of the third period, the rats were given an intravenous injection of 25 μg/kg IGF-I in 0.2 ml of normal saline over ~ 45 seconds. This was followed by a continuous infusion of 25 μg/kg IGF-I in 0.3 ml of normal saline; the total time for bolus injection and continuous infusion of IGF-I was 20 min, which was the duration of the third clearance period. Seven Sprague-Dawley rats, weighing 251±6 g, served as controls. These animals were treated in an identical fashion except that they received the same quantity of acetic acid diluted in normal saline as vehicle instead of the IGF-I solution. Before and at the end of the IGF-I or vehicle infusion, 200 μl of arterial blood were withdrawn for measurement of plasma IGF-I and glucose. At the midpoint of each of the 12 clearance periods, ~ 70 μl of arterial blood were collected in heparinized capillary tubes for determining the hematocrit and plasma concentrations of inulin and PAH.

The IGF-I used is a recombinant DNA-derived human IGF-I analogue (generously provided by Dr. Kathrine Fagin, Amgen, Thousand Oaks, CA). Its amino acid sequence differs from human IGF-I only in position 59, at which threonine was substituted for methionine. The peptide was dissolved in 0.1 M acetic acid to form a stock solution in a concentration of 1 mg/ml. This solution was further diluted with normal saline for the infusion studies.

Study 2. The following six groups of male Munich Wistar rats were studied: groups 1a, 2a, and 3a received IGF-I injections and infusions as indicated in study 1; their body weights were 254±22, 218±4, and 205±6 g, respectively. Groups 1b, 2b, and 3b received the vehicle infusion as described for study 1; their body weights were 260±10, 211±6, and 217±6 g, respectively. Groups 2a and 2b received a constant infusion of indomethacin, 2.5 mg/kg/h (Sigma Chemical Co., St. Louis, MO). A stock solution of indomethacin, 3.57 mg/ml, with sodium carbonate anhydrous, 114 mg/ml was added to the Ringer's lactate solution (groups 2a and 2b) containing the radioactive PAH and inulin. Groups 3a and 3b were infused continuously with 2.5 μg/h somatostatin (SRIF) (Sigma Chemical Co.). This dose of SRIF has been demonstrated to block the release of several peptide hormones, including glucagon, growth hormone, and insulin (7). The SRIF was added to the PAH and inulin solution. Thus, there was no difference in the volumes infused in any of the six groups in study 2.

The inulin, PAH, and indomethacin or somatostatin infusions were given for 200 min, from the beginning of a 120-min equilibration period until the end of four 20-min urine clearance periods. After the first 80 min of equilibration, 25 μg/kg IGF-I or vehicle was given as a bolus injection, followed by a continuous infusion of 25 μg/kg IGF-I or vehicle. As in Study 1, the duration of time for the bolus injection and continuous infusion was 20 min. Note that there was an interval of 20 min between the end of the IGF-I or vehicle infusion and the first urine collection period. Thus, study 2 was designed to shorten the period during which the rats were anesthetized to ~ 230 min and yet to allow the animals sufficient time to respond to the compounds administered. Plasma was obtained for measurement of glucose before, at the midpoint (i.e., 10 min after the IGF-I or vehicle injection), and at the end of the infusion of IGF-I or vehicle. At the midpoint of each of the four urine clearance periods, ~ 70 μl of blood was collected from the femoral artery in a heparinized capillary tube for determination of hematocrit and plasma inulin and PAH.

Laboratory analyses. The radioactivity of [^{14}C]PAH and [^{3}H]inulin in plasma and urine was measured with a liquid scintillation counter (Beckman Instruments, Fullerton, CA). Plasma for the determination of IGF-I concentrations was frozen at −70°C immediately after collection. IGF-I in plasma was measured with a disequilibrium RIA performed by Nichols Institute, San Juan Capistrano, CA. However, a specific anti-rat-IGF-I antibody, kindly provided by Dr. Louis Underwood was used. Acid-ethanol extractions were not performed. Thus, the results of the plasma IGF-I concentration may underestimate the total plasma concentration of IGF-I (8, 9). Plasma glucose was measured by the glucose oxidase method using a glucose analyzer (model 27; Yellow Springs Instruments, Yellow Springs, OH).

GFR was calculated as the clearance of inulin. RPF and renal vascular resistance (RVR) were calculated from the PAH clearances, renal extraction of PAH (E_{PAH}), hematocrit (HCT), and mean arterial blood pressure (MABP) as follows: (*a*) RPF (microliters/minute) = C_{PAH}/E_{PAH}, and (*b*) RVR (millimeters of mercury/microliter/min) = MABP/RPF/(1 − HCT/100).

Statistical analyses. Data are presented as mean and SEM. Statistical comparisons of renal hemodynamics were performed by analysis of variance (ANOVA) and Duncan's multiple comparison test. In study 2, the grand means of the measurements in each rat were also compared by unpaired *t* tests. Significance of changes in plasma glucose and IGF-I levels were tested by paired (comparison within groups) or unpaired (comparison between groups) *t* tests. Statistical significance was taken as $P < 0.05$. All statistical calculations were performed with Clinfo II software (Bolt, Beraneck, and Newman, Cambridge, MA).

Results

Study 1. RPF and GFR at baseline were not different in the two groups of rats. The grand means (microliters per minute per 100 grams) for baseline RPF in the IGF-I-treated and control rats were 2,459±133 (SEM) and 2,801±79, respectively (Fig. 1). The grand means for GFR (microliters per minute per 100 grams) at baseline were 720±28 and 768±24 in the IGF-I treated and control groups, RPF and GFR both appeared to rise during the 20 min that IGF-I was administered and became significantly greater than baseline during the first 20 min after cessation of the infusion (Fig. 1). These values remained elevated above baseline throughout the first five 20-min clearance periods after the infusion. The maximum values for RPF and GFR were observed during the fourth and third clearance periods, respectively, after the IGF-I infusion, and were 3,247±103 ($P < 0.05$ vs. baseline) and 898±43 ($P < 0.05$) μl/min/100 g. Thereafter, both RPF and GFR began to fall toward baseline. The maximum percent increase above baseline values for RPF and GFR in the IGF-I-treated rats was 29.9±3.2 ($P < 0.05$) and 24.7±2.9% ($P < 0.05$), respectively.

In the control rats, there were no changes in RPF or GFR during the study (Fig. 1). RPF was significantly greater in the IGF-I-treated versus control rats during the second and third periods after the IGF-I infusion. Similarly, GFR was significantly greater in the IGF-I treated versus control rats during the fourth and fifth periods after the infusion.

RVR during baseline was similar in the IGF-I- and vehicle-treated rats (Fig. 1); the grand means (millimeters of mercury μl/min per 100 grams) were 0.023±0.002 and 0.022±0.002, respectively. RVR began to fall during the IGF-I infusion and was significantly below baseline for the first five periods after the infusion. The lowest RVR occurred during the third clearance period after finishing the IGF-I infusion and was 0.017±0.001 mmHg μl/min per 100 g. This constituted a 26.1±3.9% decrease below baseline ($P < 0.05$). RVR was significantly lower in IGF-I treated rats as compared with controls during the second and third clearance periods after the IGF-I or vehicle infusion.

The grand mean for the filtration fraction in the experi-

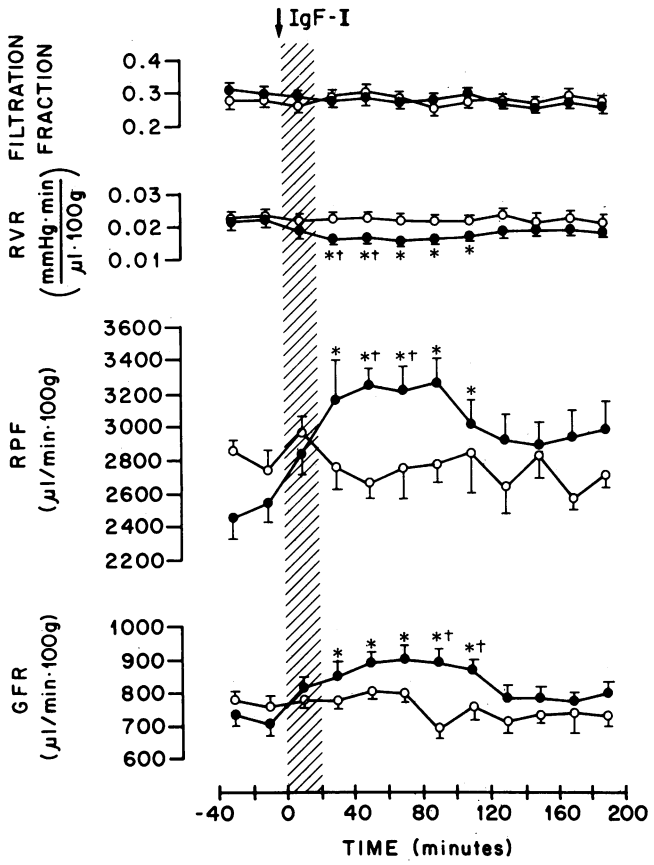

Figure 1. GFR, RPF, RVR, and filtration fraction (FF) before, during, and after infusion of IGF-I or vehicle in study 1. ●, IGF-I-treated rats (n = 8); ○, indicate controls (n = 7). The shaded bar marks the 20-min duration of the IGF-I or vehicle infusion. Bars indicate SEM. *Different from baseline, $P < 0.05$. †Different from control, $P < 0.05$.

mental and control rats during baseline was 0.30±0.01 and 0.28±0.01, respectively (P = NS, Fig. 1). The grand mean for MABP during baseline in the IGF-I-treated and control rats was 115±7 and 119±6 mmHg, respectively (P = NS). Neither filtration fraction nor MABP changed in either group during the study. The HCT also did not vary between the two groups. The grand mean of the HCT was 49.4±0.2 and 49.1±0.2 vol% in the IGF-I-treated and control rats.

Baseline plasma IGF-I values, immediately before commencing infusion of IGF-I or vehicle, were 0.5±0.1 and 1.0±0.3 U/ml, in the experimental and control groups, respectively (P = NS). Plasma IGF-I at the end of the infusion tended to increase only in the experimental rats, to 1.0±0.2 U/ml (P = 0.069). At the end of infusion in the control rats, plasma IGF-I was 0.8±0.3 U/ml, which was not different from baseline in control animals or from postinfusion values in the IGF-I rats.

There was no difference in the plasma glucose concentrations obtained immediately before the infusion in the experimental and control animals, 103±5 and 109±4 mg/dl, respectively. At the end of the infusion, plasma glucose had fallen slightly but significantly in the IGF-I-treated rats to 94±3 mg/dl (infusion vs. baseline value, $P < 0.05$). In the control rats, the plasma glucose did not change during the infusion and averaged 108±3 mg/dl; the latter value was significantly greater than the plasma glucose levels observed at the end of the IGF-I infusion ($P < 0.05$).

Study 2. As in study 1, the grand means of RPF and GFR were greater and RVR was less in the rats infused with IGF-I as compared with controls (Groups 1a and 1b, Table I, Fig. 2). The IGF-I treated rats, in comparison to controls, displayed a 36.0±4.1% ($P < 0.05$) greater RPF, a 30.3±6.1% ($P < 0.05$) greater GFR, and a 27.1±4.0% lower RVR ($P < 0.05$). When indomethacin was infused (Groups 2a and 2b), the augmentation in RPF and GFR and the reduction in RVR induced by IGF-I infusion were abolished (Table I, Fig. 2). On the other hand, SRIF did not inhibit the IGF-I-induced rise in RPF and GFR or the fall in RVR. With the SRIF infusion, the rats given IGF-I displayed an increase in RPF and GFR of 28.7±4.5% ($P < 0.05$) and 19.7±2.8% ($P < 0.05$) and a decrease in RVR of 23.7±2.3% ($P < 0.05$) as compared with the controls that received SRIF but were infused with vehicle instead of IGF-I (Table I, Fig. 2).

The percent changes in RPF, GFR, and RVR in the IGF-I vs. control rats in Groups 1a and 1b were similar to the percent changes in these parameters in the animals given SRIF (i.e., groups 3a vs. 3b). However, both the IGF-I- and vehicle-treated rats given SRIF (groups 3a and 3b) tended to have a lower RPF and GFR in comparison to the rats not given SRIF (groups 1a and 1b) (Table I). The MABP, filtration fraction, and hematocrit were not different in any of the six groups (Table I, Fig. 2). During the IGF-I infusion, plasma glucose fell slightly in groups 1a and 2a but not in the rats given SRIF (Table II). Plasma glucose did not change in any group of vehicle-treated rats. However, in both groups of animals pretreated with SRIF, plasma glucose was greater at each time of

Table I. Renal Hemodynamics in the Six Groups of Rats in Study 2

Group/Treatment		RPF	GFR	RVR	FF	MABP	HCT
	n	*µl/min per 100 g*		*mmHg·min/µl per 100 g*		*mmHg*	*Vol %*
1a/IGF-I	6	3,620±273*	963±29*	0.016±.002*	0.27±.01	113±5	50.5±0.6
1b/Control (vehicle)	6	2,653±220	736±26	0.022±.002	0.29±.02	117±6	51.6±0.7
2a/Indomethacin + IGF-I	6	2,810±74	849±30	0.022±.001	0.32±.02	114±3	50.4±0.8
2b/Indomethacin + Veh.	5	2,707±212	805±50	0.021±.002	0.30±.01	114±5	50.4±0.3
3a/Somatostatin + IGF-I	8	2,793±136*	806±24*	0.021±.001*	0.29±.01	112±4	50.8±0.6
3b/Somatostatin + Veh.	4	2,173±161	676±29	0.027±.002	0.32±.02	114±4	50.3±1.3

Values are the grand mean±SEM of the mean values from individual rats obtained during the four clearance periods after equilibration. Veh., vehicle. Compared with the respective control in each group by t test: * $P < 0.05$.

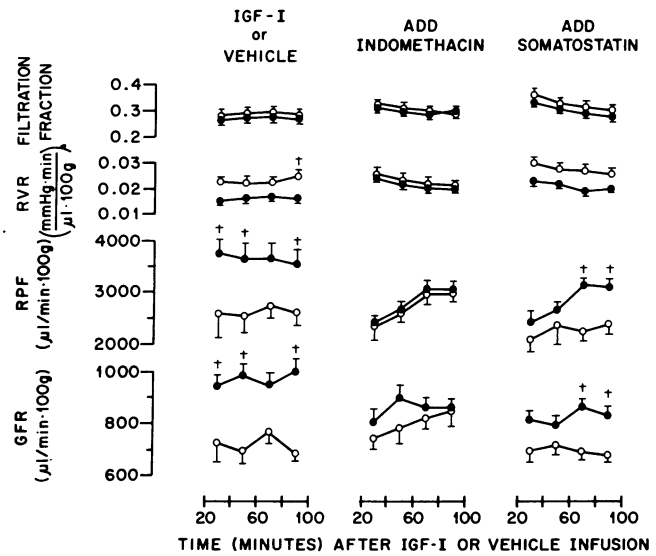

Figure 2. GFR, RPF, RVR, and filtration fraction (FF) after infusion of (●) IGF-I or (○) vehicle in study 2. (*Left*) Rats not treated with indomethacin or SRIF. (*Middle and right*) Rats infused with either indomethacin or somatostatin, for 120 min before commencing the clearance periods. Note that the IGF-I or vehicle infusion was terminated 20 min before the first clearance period was started. Bars indicate SEM. IGF-I versus control: †$P < 0.05$.

measurement in comparison to the four groups of rats not given SRIF.

Discussion

Since the effect of growth hormone on RPF and GFR is delayed (1, 3, 4), this study was carried out to examine whether IGF-I, which is secreted in response to growth hormone, also increases RPF and GFR and, hence, might be a mediator of the growth hormone effects on the kidney. The results indicate that infusions of IGF-I do indeed cause a rapid increase in RPF and GFR and a fall in RVR. These actions appear to occur within 20 min of starting the infusion, are statistically significant within 40 min of the onset, and last for ~ 100 min after terminating the infusion (Fig. 1). There was no change in filtration fraction or MABP during or after the IGF-I infusion.

These effects of IGF-I occurred with plasma levels that were not significantly different from control values and that were not much greater than preinfusion values. It is likely that the plasma IGF-I levels were greater immediately after the priming dose. However, because the half life of free plasma IGF-I after injection in rats is ~ 30 min (10) and because animals received a continuous infusion of IGF-I until the final plasma IGF-I value was obtained, it would seem to be unlikely that the plasma IGF-I was much greater at the end of the priming dose than at the end of the IGF-I infusion. The combination of an acute IGF-I infusion and low plasma IGF-I binding proteins in starved rats probably resulted in a high fraction of free IGF-I in plasma.

The mechanism by which IGF-I increases RPF and GFR is not known. Ichikawa and co-workers studied rats chronically fed isocaloric diets that were high or low in protein and probably low in calories (11). The rats given the low-protein diet had lower single nephron glomerular filtration and plasma flow rates; but their plasma volumes were similar to the rats fed the high-protein diet. The rats fed the low-protein diet also displayed increased afferent and efferent arteriolar resistances, and reduced K_f (glomerular ultrafiltration coefficient); the glomerular transcapillary hydraulic pressure difference was similar in the rats fed the low- and high-protein diets.

These findings may be relevant to this study in which rats were starved for 60–72 h. Their low RPF and GFR at baseline may have been related to malnutrition. Since plasma IGF-I is decreased in protein-calorie malnutrition (12), low IGF-I may have caused the reduction in renal function. When these latter rats were given IGF-I, RPF, and GFR increased to normal levels. In addition, RVR fell, but filtration fraction and MABP did not change. This is consistent with the possibility that the IGF-I infusion reduced both afferent and efferent arteriolar resistances. Hence, it is possible that low IGF-I reduces RPF and GFR during starvation by increasing afferent and efferent arteriolar resistances and, possibly, decreasing K_f. It is not known, whether infusion of IGF-I in larger doses or for a longer duration will cause abnormally high values for RPF and GFR. The present study also suggests a role for eicosanoids in the actions of IGF-I on the kidney. The infusion of indomethacin blocked the IGF-I induced changes in renal hemodynamics (Fig. 2, Table I). Hence, it is possible that IGF-I increases RPF and GFR and lowers RVR by enhancing the synthesis of vasodilating eicosanoids. It is noteworthy that IGF-I stimulates the synthesis of 6-keto-PGF_{1a} and PGE_2 in cultured rat liver cells in the presence of tumor promoters (13).

In groups 3a and 3b in study 2 we examined whether the action of IGF-I on renal function is dependent on other peptide hormones. SRIF blocks the release of several peptide hormones including renin, insulin, glucagon, and growth hormone (7, 14). A rise in plasma glucagon and growth hormone concentrations can increase RPF and GFR and lower RVR; this effect occurs acutely with glucagon and is delayed for several hours with growth hormone (3, 15). Injection of IGF-I

Table II. Plasma Glucose Concentrations in the Six Groups of Rats in Study 2 before, at the Midpoint, and at the End of the 20-min IGF-I or Vehicle Infusion

Group	*n*	Treatment	Before infusion*	Infusion midpoint	End of infusion
1a	6	IGF-I	100±4‡	96±4§	96±5§
1b	6	Control (vehicle)	100±2	101±2	100±2
2a	6	Indomethacin + IGF-I	95±3	94±2	90±2§
2b	5	Indomethacin + vehicle	105±4	107±4	107±4
3a	8	SRIF + IGF-I	132±8‖	131±10‖	126±9‖
3b	4	SRIF + vehicle	126±3‖	125±3‖	123±4‖

* These values were obtained before the infusion of IGF-I or vehicle but after the onset of the infusion of indomethacin or somatostatin in groups 2a, 2b, 3a, and 3b.

‡ Mean±SEM.

§ Significantly lower than the values obtained from the same group of rats before the onset of the infusion, $P < 0.05$.

‖ Significantly greater than the control rats that did not receive indomethacin or somatostatin, $P < 0.05$. The comparisons were made between plasma specimens obtained at the same time of the infusion period.

may increase plasma glucagon and growth hormone and reduce insulin, probably due to the IGF-I induced decrease in plasma glucose (16) (Table II). Therefore, it seemed important to exclude the possibility that a rise in glucagon or growth hormone levels could have increased the renal hemodynamics after IGF-I infusion. In this study, infusion of SRIF did not impair the IGF-I-induced rise in RPF and GFR and fall in RVR. This finding suggests that the IGF-I induced rise in renal hemodynamics is independent of a number of peptide hormones including insulin, glucagon, and growth hormone.

The rats infused with SRIF and vehicle (group 3b) tended to have lower RPF and GFR and higher RVR as compared with the animals not infused with SRIF (group 1b). SRIF may lower GFR in healthy man (17). This effect of SRIF might be due to the suppression of one or more peptide hormones that act on the kidney.

IGF-I is synthesized in many tissues including the kidney (18). Some investigators suggest that IGF-I acts locally where it is synthesized, as an autacoid, and that plasma IGF-I does not play a physiological role (18, 19). This study, however, provides evidence that systemic infusion and changes in plasma levels of IGF-I can affect renal function.

This study also suggests that IGF-I may play a role in the regulation of renal function. The evidence is that IGF-I infusion increases RPF and GFR and reduces RVR. Moreover, two commonly occurring phenomena that alter plasma IGF-I levels, growth hormone administration and nutritional intake, also affect renal function (1, 3, 11, 12, 20). Further studies are clearly needed to examine the role of IGF-I in the regulation of renal function, particularly in malnutrition.

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