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INCREASE OF GLOMERULAR FILTRATION RATE FOLLOWING AMINOACID INFUSION IS SUPPRESSED BY INDOMETHACIN IN NORMAL SUBJECTS

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Summary

Simultaneous creatinine, inulin and PAH clearances were measured every 30 minutes in 11 healthy women two hours before, during and two hours after infusion of a 10% aminoacid solution. The identical protocol was repeated one week later after blocking prostaglandin synthesis by indomethacin. Following aminoacid infusion glomerular filtration rate (GFR) rose by about 40 per cent compared to pre-infusion values. Administration of indomethacin completely abolished this rise of GFR. Prostaglandins may be involved in the mechanism responsible for the variation of GFR after aminoacid administration.

Introduction

It has long been recognized that dietary protein intake has a strong influence on GFR [1]. According to a recent theory [2] sustained high protein intake leads to glomerular hyperfiltration and may cause progressive glomerulosclerosis with subsequent deterioration of renal function in diseased kidneys.

In addition to protein ingestion [3] GFR increases following intravenous aminoacid infusion [4] and glucagon administration [5]. The underlying mechanism, however, has not been elucidated. Based upon animal studies it has been hypothesized that the rise in GFR might be associated with an increased hepatic secretion of a hormone-like substance and that the action of this hormone on glomerular function may involve prostaglandins [6].

Therefore the variation of GFR and renal blood flow following aminoacid infusion was studied in 11 healthy volunteers and the identical experimental protocol was repeated after inhibition of prostaglandin synthesis by indomethacin.

Materials and methods

Eleven healthy female volunteers aged 22–28 years, all of whom had been fully informed of the nature of the study before giving their written consent were investigated.

None had evidence of hypertension, systemic or renal disease as judged by no history of medical illness, normal blood pressure, normal results of routine laboratory analysis, urine analysis, normal 24-hour creatinine clearance and less than 300mg urinary protein excretion over 24 hours.

All subjects were studied while on normal ad libitum protein diets. The investigations were started after an overnight fast, subjects were supine during investigation, standing up only during voiding. The study was started with a water load of 1,000ml. Thereafter urine losses were replaced by equal amounts of water. During the first hour of the experiment all volunteers received a standard breakfast containing 6.6g of protein and a total of 590kcal.

After an equilibration period of two hours, simultaneous creatinine, inulin and PAH clearances every 30 minutes were measured. Continuous intravenous infusion of 250ml/hr of either glucose 5% (from 0 to 4hr and 6 to 8hr) or 250ml/hr of a commercially available aminoacid solution (Aminosteril 10%) (from 4 to 6hr) was performed. A week later the same experimental protocol was repeated after blocking prostaglandin synthesis by oral administration of 100mg indomethacin immediately before starting the experiment and 50mg indomethacin after four hours.

Inulin and PAH were determined photometrically, using standard methods. Creatinine was measured according to Jaffe. Clearances were corrected for a body surface area of $1.73m^2$. Values are shown as means ± SEM. Significance between means was calculated using the Student's 't' test.

Results

Aminoacid infusion in all subjects studied was followed by an increase in GFR and renal blood flow.

Mean inulin clearance rose from a pre-infusion value of 106ml/min to a maximum of 145ml/min after two hours of aminoacid infusion ($p<0.0005$) (Figure 1). The mean rise in creatinine clearance was less pronounced: pre-infusion value 122.8ml/min, after two hours of aminoacid infusion 150.5ml/min ($p<0.001$).

Renal blood flow measured by PAH clearance rose from 535ml/min to a maximum of 671ml/min ($p<0.002$) after aminoacid infusion (Figure 2). Prostaglandin inhibition by indomethacin completely abolished this rise in GFR and renal flow as shown in Figures 1 and 2.

Mean values of urine output, urine electrolytes and plasma renin activity are listed in Table I.

Urine volume (ml/min) remained constant during the whole experiment. After aminoacid infusion an increase in urine sodium and potassium excretion was observed, which was not influenced by prostaglandin inhibition. Plasma renin activity remained unchanged during aminoacid infusion. As expected, prostaglandin inhibition resulted in lower plasma renin activity values.

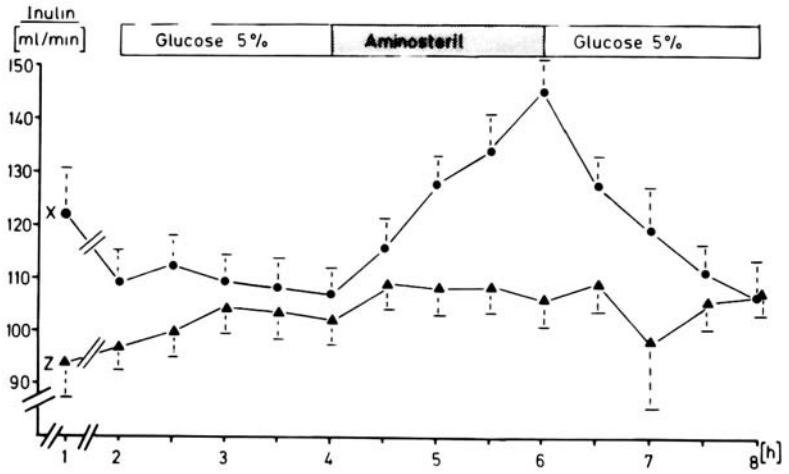

Figure 1. Mean values ± SEM of inulin clearance after glucose 5% and aminoacid (Aminosteril 10%) infusion in 11 healthy volunteers.
▲= prostaglandin inhibition with 150mg indomethacin
●=no prostaglandin inhibition

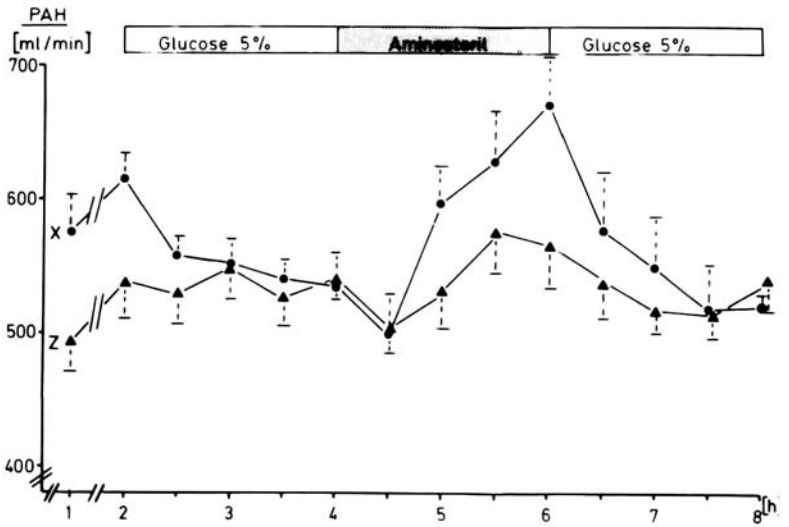

Figure 2. Mean values ± SEM of PAH clearance after glucose 5% and aminoacid (Aminosteril 10%) infusion in 11 healthy volunteers.
▲=prostaglandin inhibition with 150mg indomethacin
●=no prostaglandin inhibition

TABLE I. Mean values of urine volume (ml/min), urine sodium (Na^+ IU), urine potassium (K^+ IU), and plasma renin activity (PRA) in 11 healthy volunteers after glucose and aminoacid (Aminosteril) infusion

		Glucose 5%						Aminosteril 10%				Glucose 5%			
Time (hours)		1.0	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
Urine volume (ml/min)	x	11.8	16.2	15.9	15.9	16.2	15.7	14.7	14.3	14.8	14.2	11.0	14.8	16.2	15.3
	z	9.8	11.1	11.8	12.6	12.9	13.4	12.9	10.4	9.8	9.4	7.2	11.1	12.9	13.3
Urinary Na^+ (mmol/L)	x	8.4	7.4	7.8	9.7	11.4	12.8	16.3	18.6	21.5	28.4	49.5	35.9	27.2	20.4
	z	11.4	6.5	7.7	7.6	9.8	11.8	15.1	14.4	21.0	36.0	45.1	25.9	26.6	13.3
Urinary K^+ (mmol/L)	x	4.5	2.5	3.0	4.0	5.3	6.6	6.8	6.3	5.3	7.0	20.1	14.2	13.2	7.9
	z	4.9	3.5	3.5	3.8	4.8	5.9	9.1	7.6	9.9	16.0	23.3	12.3	11.0	9.1
PRA (ng/ml/hr)	x						2.2	1.9	1.9	1.9	1.7	1.8	1.7	1.5	1.6
	z						1.3	1.2	1.1	1.0	0.9	1.0	1.0	1.0	1.0

x=no prostaglandin inhibition

z=prostaglandin inhibition with 150mg indomethacin

Discussion

It is widely accepted that GFR in healthy persons is remarkably stable from day to day, and that only minor changes of GFR occur after variation of fluid intake or after exercise. Earlier investigations showed, however, that protein intake, aminoacid and glucagon infusions have a significant effect on GFR in humans and animals [3–5]. The ability of dietary protein ingestion to influence GFR has been extensively studied in recent years and has led to the concept of a renal functional reserve which may be considered analogous to cardiac functional reserve, representing the capability of the organ to augment its function under increased physiological demands [7]. During pregnancy and in burn patients GFR increases significantly, as does the filtration rate of the remnant kidney after unilateral nephrectomy.

From studies on isolated rat kidneys it has been shown that direct administration of aminoacids to the renal artery causes only a small rise in GFR [8] in contrast to systemic aminoacid administration, lending support to the hypothesis that increased uptake of aminoacid by the liver causes the secretion of a hormone-like substance named glomerulopressin [9], which is capable of increasing GFR. Renal prostaglandins are involved in the haemodynamic autoregulation of the kidney and there is evidence from animal experiments that indomethacin inhibits the effect of glomerulopressin [10], suggesting that renal prostaglandins mediate the effects of this hormone-like substance on renal blood flow and GFR. The time course of the increase of GFR after aminoacid infusion in our experiments might suggest the involvement of hepatic aminoacid metabolism inducing the release of glomerulopressin.

It can be speculated from our results in normal volunteers that prostaglandins play an important role in the complicated mechanism of adapting GFR to different metabolic requirements.

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