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Original article

Effects of glucagon on diuresis, renal plasma flow and glomerular filtration in sheep

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Summary —The effects of intravenous infusion of glucagon (100 $ng \cdot kg^{-1} \cdot min^{-1}$) on diuresis, renal plasma flow and glomerular filtration rate were studied in conscious sheep. Diuresis began to decrease upon initiation of glucagon infusion, down to 50% of its baseline value at the end of glucagon infusion. Glomerular filtration rate was also decreased by 75%. With regard to renal plasma flow, the decrease started at the beginning of glucagon infusion, but remained restricted. It was not possible, from these results, to explain the reduced diuresis by a decrease in renal plasma flow; the observed anti-diuretic effect could be the consequence of a modification of either the filtration coefficient or water tubular reabsorption.

renal plasma flow / glomerular filtration / glucagon / sheep

Résumé — Effets du glucagon sur la diurèse, le débit plasmatique rénal et la filtration glomérulaire chez le mouton. *Les effets de la perfusion intraveineuse de glucagon (100 $ng \cdot kg^{-1} \cdot min^{-1}$) sur la diurèse, le débit plasmatique rénal et le débit de filtration glomérulaire ont été étudiés chez le mouton vigile. Dès le début de la perfusion de glucagon, on observe une diminution de la diurèse, qui se trouve réduite de moitié à la fin de la perfusion de glucagon. La filtration glomérulaire diminue également (–75%). En ce qui concerne le débit plasmatique rénal, la diminution survient dès le début de la perfusion de glucagon mais reste d'amplitude limitée. Avec nos résultats, il n'est pas possible d'expliquer la réduction de la diurèse par une diminution du débit plasmatique rénal; l'effet antidiurétique observé pourrait être la conséquence, soit d'une modification du coefficient de filtration, soit d'une modification de la réabsorption tubulaire d'eau.*

débit plasmatique rénal / filtration glomérulaire / glucagon / mouton

* Correspondence and reprints

INTRODUCTION

According to current literature, low-protein-fed sheep reduce their renal elimination of urea; the urea retained returns to the digestive tract to be transformed into amine nitrogen by the reticulo-ruminal microorganisms. Cirio and Boivin (1990) confirmed the previous reports of many authors (Ergene and Pickering, 1978; Gans and Mercer,1962; Leng *et al,* 1985; Rabinowitz *et al,* 1973) that in sheep, this sparing mechanism appears to result in part from decreases in glomerular filtration.

Conversely, the intake of a protein-rich diet increases glomerular filtration in a number of species (dog: Premen *et al,* 1985, Woods *et al,* 1991; human: Penner *et al,* 1990). Intravenous infusion of amino-acid solutions has similar effects (dog: Brown and Navar, 1990; rat: Chen Chu *et al,* 1992; human: Castellino *et al,* 1986, Maggiora *et al,* 1991). Several authors have attributed a mediator role to glucagon for the hyperfiltration induced by amino acids (Friedlander *et al,* 1990; Wada *et al,* 1991). Also, glucagon intravenous infusion increases diuresis and glomerular filtration in rats (Ahloulay *et al,* 1992) and in dogs (Ueda *et al,* 1977; Aki *et al,* 1990).

In ruminants, intravenous infusion of most amino acids increases blood glucagon concentration in sheep (Kuhara *et al,* 1991). Also, infusion of some amino-acid solutions increases diuresis and glomerular filtration in this species (Faix and Leng, unpublished results).

The relationship between renal function and blood glucagon concentrations in sheep has not yet been established. We therefore set out, as a first step, to study the effects of glucagon intravenous infusion on diuresis, renal plasma flow (RPF) and glomerular filtration rate (GFR) in this species.

MATERIALS AND METHODS

Six 9-month-old female lambs (20–25 kg) kept in individual boxes were divided into 2 groups (C = controls and G = glucagon); they were fed a maintenance standard diet, and could drink *ad libitum.* After a fortnight's habituation, a vesicular balloon probe was fitted permanently for continuous urine collection with a peristaltic pump. A catheter was fitted in each of the jugular veins for infusions and blood sampling.

For each animal, the experimental protocol included an equilibration period (1 h), a control time (C: 3 x 15-min periods) and an experimental time (E: 6 x 15-min periods). Throughout the experiment, we infused an isotonic NaCl solution containing 6 $mg \cdot ml^{-1}$ *p*-amino hippuric acid (PAH) (for RPF measurement) and 27.5 $mg \cdot ml^{-1}$ inulin (IN) (for GFR measurement), in a jugular vein at the rate of 1 $ml \cdot min^{-1}$. This infusion followed a priming dose (50 mg PAH and 1 g IN), so as to obtain a stable blood concentration after 1 h. During the experimental time (90 min), we added glucagon (Novo Nordisk Pharmaceutique, Boulogne, France) (100 $ng \cdot kg^{-1} \cdot min^{-1}$) to the infusions of the glucagon group animals. The animals were deprived of food and water during the sessions to prevent any interference by food or water intake. For clearance calculation, urine was collected separately for each 15-min period, with 1 blood sampling at the midpoint of each period (5 ml on heparin iodoacetate). Diuresis was determined by weighing. The RPF (PAH clearance) and the GFR (IN clearance) were calculated in the conventional way as the product of urine flow and urinary concentration divided by plasma concentration. Plasma and urine samples were analyzed for inulin according to Vurek and Pegram (1966), and *p*-amino hippuric acid by the Piaget and Liefooghe method (in Lecoq, 1967).

We also systematically measured blood glucose, using an enzymatic method (Glucose enzymatique PAP, bioMérieux, France) and we investigated possible glycosuria in animals from the G group using reagent strips (Multistix 10 SG, Bayer Diagnostics, UK).

For each sheep, we calculated the mean of the results obtained for the 3 periods of the control time and for the 6 periods of the experimental time, to obtain a control value and a experimental value for each animal. The percentage variation between experimental and control

times for each parameter and each animal was calculated as Δ% = (EXP–CON) x 100/CON. All results are expressed as means ± SEM. The statistical significance of differences between the control and experimental times for each control and glucagon-receiving group was determined by comparing means using a paired *t*-test.

RESULTS

Results for both groups are expressed as absolute values in table I. Figure 1 shows the evolution of the parameters studied, expressed as percentages of the control values. Upon initiation of glucagon infusion, a decrease in diuresis was observed. After 30 min, this diuresis was reduced to 60% of the initial level. It then fluctuated and was reduced by 50% at the end of glucagon infusion (fig 1a). Glomerular filtration rate also began to decrease at the beginning of glucagon infusion, and was down to 25% of the initial value at the end of infusion (fig 1b). The decrease in renal plasma flow occurred upon initiation of the glucagon infusion, but remained restricted (fig 1c). Glycemia increased from 0.84 ± 0.02 $g \cdot l^{-1}$ during the control time to 1.87 ± 0.06 $g \cdot l^{-1}$, 45 min after starting glucagon infusion. No glycosuria was observed.

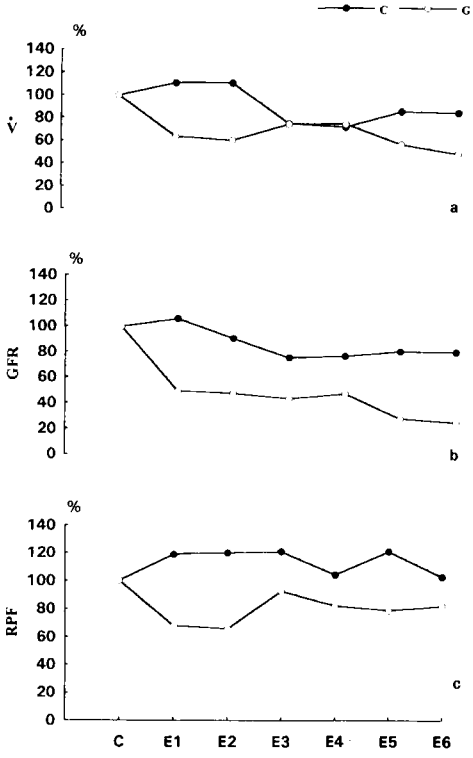

Fig 1. Evolution of a) diuresis (V̇), b) glomerular filtration rate (GFR), and c) renal plasma flow (RPF), during the experimental time (E1–E6) in the control and in glucagon-infused sheep. Values are expressed as percentages of the average of control periods (C).

DISCUSSION

The aim of this study was to show the effects of glucagon infusion on renal function in sheep. Contrary to what has been described in other species (Ueda *et al*, 1977; Aki *et al*, 1990; Ahloulay *et al*, 1992), glucagon infusion under our experimental conditions induced a sharp decrease in diuresis.

The fall in glomerular filtration rate was very important and one can reasonably consider that with a greater number of animals, a statistical significance should be reached. Renal plasma flow also decreased but the effect was not as pronounced.

The decreases in diuresis and GFR therefore appear to be unlinked to RPF variations. This absence of correlation was also reported in sheep under different experimental conditions (Ergene and Pickering, 1978; Leng *et al*, 1985; Le Bas *et al*, 1993). It is not possible from our results to explain the decrease in diuresis by the decrease in renal plasma flow. The antidiuretic effect observed could be the con-

Table I. Diuresis ($\dot{V}$), glomerular filtration rate (GFR) and renal plasma flow (RPF) in controls and glucagon-infused sheep (100 $ng \cdot kg^{-1} \cdot min^{-1}$).

	Control			*Glucagon-infused*		
	CON	*EXP*	*Δ%*	*CON*	*EXP*	*Δ%*
$\dot{V}$ ($ml \cdot min^{-1}$)	0.93 ± 0.42	0.84 ± 0.30	−2.79 ± 9.06	0.61 ± 0.06	0.38 ± 0.13*	−64.43 ± 10.45
GFR ($ml \cdot min^{-1}$)	90.96 ± 2.63	77.61 ± 11.69	−14.98 ± 10.39	125.31 ± 61.06	53.59 ± 24.31	−57.09 ± 11.65
RPF ($ml \cdot min^{-1}$)	314.96 ± 19.44	361.56 ± 72.81	18.32 ± 31.49	441.69 ± 93.88	389.94 ± 84.91	−9.89 ± 9.64

CON = control time; EXP = experimental time; Δ% = variation percentage between CON and EXP, calculated as (EXP − CON) x 100/CON for each animal; values are expressed as means ± SEM; significant difference by paired *t*-test between EXP and CON in each group: * = $P < 0.05$.

sequence of either a modification of the filtration coefficient, or of water tubular reabsorption.

The interspecies differences in renal response to glucagon intravenous infusion could be explained by the differences in the dose used. In monogastric animals, and with doses ranging from 6 to 1 200 $ng \cdot kg^{-1} \cdot min^{-1}$ according to the authors, diuresis was always increased. The dose that we used (100 $ng \cdot kg^{-1} \cdot min^{-1}$) was within the range used in monogastric animals and always induced typical hyperglycemia without glycosuria.

In contrast with most trials performed in other species, our animals were conscious. The differences in response to glucagon may therefore be due to general anaesthesia. Nevertheless, we found the same results in anaesthetized sheep. Indeed, during renal micropuncture experiments, glucagon carotid infusion reduced or even stopped glomerular filtration (unpublished results). In other species, the diuretic effect of glucagon was also observed in unanesthetized animals (Premen *et al,* 1985).

With the present state of knowledge, we are unable to explain the differences in renal response between sheep and nonruminant species. The effects of intravenous glucagon infusion on glomerular filtration rate are indeed conflicting. A few authors have found increased glomerular filtration rate in dogs (Staub *et al,* 1957) and in humans (Elrick *et al,* 1958), whereas others only found systematic increases in glomerular filtration rate when the hormone was infused in the portal bloodstream (Premen *et al,* 1985; Lang *et al,* 1990). Thus, glucagon appears to act by a liver-borne mechanism (Lang *et al,* 1992). One can reasonably think that the hepatic effect of glucagon in sheep is different from the hepatic effect in other species. This difference may be linked to the nutritional and metabolic characteristics of ruminants. However, we found that glucagon infusion in a mesenteric vein also reduces glomerular filtration in sheep (unpublished results) and so a direct effect of the hormone on the sheep kidney cannot be ruled out.

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REFERENCES

Ahloulay M, Bouby N, Machet F, Kubrusly M, Coutaud C, Bankir L (1992) Effects of glucagon on glomerular filtration rate and urea and water excretion. *Am J Physiol* 263 (Renal Fluid Electrolyte Physiol 32) F24-F36

Aki Y, Shoji T, Hasui K, Fukui K, Tamki T, Iwao H, Abe Y (1990) Intrarenal vascular sites of action of adenosine and glucagon. *Jpn J Pharmacol* 54, 433-440

Brown SA, Navar LG (1990) Single-nephron responses to systemic administration of amino acids in dogs. *Am J Physiol* 259 (Renal Fluid Electrolyte Physiol 28) F739-F746

Castellino P, Coda B, De Fronzo RA (1986) Effect of amino-acid infusion on renal hemodynamics in humans. *Am J Physiol* 251 (Renal Fluid Electrolyte Physiol 20) F132-F140

Chen C, Mitchell KD, Navar LG (1992) Role of endothelium-derived nitric oxide in the renal hemodynamic response to amino-acid infusion. *Am J Physiol* 263 (Regulatory Integrative Comp Physiol 32) R510-R516

Cirio A, Boivin R (1990) Débit plasmatique rénal et filtration glomérulaire chez le mouton vigile : influence d'un régime carencé en protéines. *Reprod Nutr Dev* suppl 2 S239-240

Elrick H, Hussman ER, Hald CJ, Whipple N, Staub A (1958) Effects of glucagon on renal function in man. *J Clin Endocrinol & Metab* 18, 813-824

Ergene N, Pickering EC (1978) The effects of urea infusion on glomerular filtration rate and renal plasma flow in sheep fed low and high protein diets. *Q J Exp Physiol* 63, 77-81

Friedlander G, Blanchet-Benqué F, Nitenberg A, Labrie C, Assan R, Amiel C (1990) Glucagon secretion is essential for amino-acid-induced hyperfiltration in man. *Nephrol Dial Transplant* 5, 110-117

Gans JS, Mercer PF (1962) Effect of osmotic diuretics and vasopressin on renal function in sheep. *Am J Vet Res* 23, 230-235

Kuhara T, Ikeda S, Ohneda A, Sasaki Y (1991) Effects of intravenous infusion of 17 amino acids on the secretion of GH, glucagon and insulin in sheep. *Am J Physiol* 260 (Endocrinol Metabol 23), E21-E26

Lang F, Tschernko E, Schulze E, Ottl I, Ritter M, Völkl H, Hallbrucker CH, Häussinger D (1990) Hepatorenal reflex regulating kidney function. *Hepatology* 14, 590-594

Lang F, Tschernko E, Häussinger D (1992) Hepatic regulation of renal function. *Exp Physiol* 77, 663-673

Le Bas A, Cardozo V, Tomeo G, Cirio A (1993) Renal urea retention in Romney Marsh sheep on reduced dietary protein. Proc XXXII IUPS Congress, Glasgow

Lecoq R (1967) *Manuel d'analyses médicales et de biologie clinique.* 2nd ed, Doin, Paris, 2410 pp

Leng L, Szanyiova M, Boda K (1985) The renal response of sheep to a low dietary nitrogen intake. *Physiol Bohemoslov* 34, 147-154

Maggiora E, Silberstein C, Arany E, Salvieda JC, Del Castillo E, Uranga J (1991) Enhanced glomerulopressin production and glomerular filtration rate by amino-acid infusion in normal humans. *Proc Soc Exp Biol Med* 156, 170-174

Penner SB, Bernstein KN, Fine A (1990) Changes in endogenous creatinine clearance in man on a controlled protein diet: effect of route of administration of a protein load. *Clin Invest Med* 13, 233-236

Premen AJ, Hall JE, Smith MJ Jr (1985) Postprandial regulation of renal hemodynamics: role of pancreatic glucagon. *Am J Physiol* 248 (Renal Fluid Electrolyte Physiol 17): F656-F662

Rabinowitz L, Gunther RA, Shoji ES, Freedland RA, Avery EH (1973) Effects of high and low protein diets on sheep renal function and metabolism. *Kidney Int* 4, 188-207

Staub A, Springs V, Stall F, Elrick H (1957) A renal action of glucagon. *Proc Soc Exp Biol Med* 94, 57-60

Ueda J, Nakanishi H, Miyazaki M, Abe Y (1977) Effects of glucagon on the renal hemodynamics of dogs. *Eur J Pharmacol* 41, 209-212

Vurek G, Pegran S (1966). Fluorometric method for the determination of nanogram quantities of inulin. *Anal Bioch* 16, 409-419

Wada L, Don BR, Schambelan M (1991) Hormonal mediators of amino-acid-induced glomerular hyperfiltration in humans. *Am J Physiol* 260 (Renal Fluid Electrolyte Physiol 29): F787-F792

Woods LL, Deyoung DR, Smith BE (1991) Regulation of renal hemodynamics after protein feeding: effects of loop diuretics. *Am J Physiol* 261 (Renal Fluid Electrolyte Physiol 30) F815-F823