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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 kg⁻¹ 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 glomé- rulaire chez le mouton. Les effets de la perfusion intraveineuse de glucagon (100 ng kg⁻¹ min⁻¹) sur la diurèse, le débit plasmatique rénal et le débit de filtration glomérique 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 glomérique 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 glomérique / 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 Bolvin (1990) confirmed the previous reports of many authors (Ergene and Pickering, 1976; 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.


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·ml⁻¹ p-amino hippuric acid (PAH) (for RPF measurement) and 27.5 mg·ml⁻¹ inulin (IN) (for GFR measurement), in a jugular vein at the rate of 1 ml·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·kg⁻¹·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 mid-point 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 an 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 con-
trol and glucagon-receiving group was deter-
mined 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 infu-
sion, 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 glu-
cagon infusion (fig 1a). Glomerular filtrat-
ion rate also began to decrease at the be-
ginning 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·l⁻¹ during the control time to 1.87 ±
0.06 g·l⁻¹, 45 min after starting glucagon
infusion. No glycosuria was observed.

DISCUSSION

The aim of this study was to show the ef-
effects of glucagon infusion on renal function
in sheep. Contrary to what has been de-
scribed in other species (Ueda et al, 1977;
Aki et al, 1990; Ahloulay et al, 1992), glu-
cagon 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 ani-
mals, a statistical significance should be
reached. Renal plasma flow also de-
creased but the effect was not as pro-
nounced.

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 ex-
perimental conditions (Ergene and Pick-
ering, 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 de-
crease in renal plasma flow. The anti-
diuretic 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·kg\(^{-1}·\text{min}^{-1}\)).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Glucagon-infused</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CON</td>
<td>EXP</td>
</tr>
<tr>
<td>(\dot{V}) (ml·min(^{-1}))</td>
<td>0.93 ± 0.42</td>
<td>0.84 ± 0.30</td>
</tr>
<tr>
<td>GFR (ml·min(^{-1}))</td>
<td>90.96 ± 2.63</td>
<td>77.61 ± 11.69</td>
</tr>
<tr>
<td>RPF (ml·min(^{-1}))</td>
<td>314.96 ± 19.44</td>
<td>361.56 ± 72.81</td>
</tr>
</tbody>
</table>

\(CON\) = control time; \(EXP\) = experimental time; \(\Delta\%) = \text{variation percentage between CON and EXP, calculated as (\(EXP - CON\)) \times 100/CON for each animal; values are expressed as means ± SEM; significant difference by paired-\text{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 1200 ng·kg⁻¹·min⁻¹ according to the authors, diuresis was always increased. The dose that we used (100 ng·kg⁻¹·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 anesthesia. 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 non-ruminant 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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