A Lack of a Direct Action of Glucagon on Kidney Metabolism, Hemodynamics, and Renal Sodium Handling in the Dog

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Although several reports suggest that pharmacologic amounts of glucagon may promote natriuresis, the influence of a physiological or even pathophysiological increase in circulating glucagon levels on kidney function has never been convincingly demonstrated. The present study was therefore undertaken to determine whether a moderate increase in plasma glucagon concentration of blood perfusing the kidney may influence kidney function and promote urinary sodium excretion. To this end, glucagon was infused directly into one renal artery of anesthetized dogs at a rate of 1 ng · kg^{-1} · min^{-1}, calculated to increase glucagon concentration in the blood perfusing the kidney within the pathophysiologic range and thus to levels seen in some catabolic states such as poorly controlled diabetes or starvation. The contralateral kidney was infused with saline only. The estimated concentration of glucagon in blood perfusing the hormone-infused kidney increased with glucagon infusion from 227 pg · mL^{-1} during the control period to mean of 779 pg · mL^{-1}. There was a significant increase in glucagon extraction by this kidney, from 33% in baseline conditions to 61% upon intrarenal infusion of the hormone, and hence venous glucagon levels were only slightly higher than in the contralateral kidney. Despite a more than threefold increase in glucagon levels in blood perfusing the hormone-infused kidney versus the contralateral kidney, this experimentally induced hyperglucagonemia was without influence on renal plasma flow (RPF), glomerular filtration rate (GFR), renal vascular resistance, renal uptake of oxygen and energy-providing substrates. Excretion of Na^+, K^+, Cl^-, and PO_4^{3-} was likewise unaffected. These results indicate that hyperglucagonemia, at least of a magnitude comparable to that seen in starvation or diabetic decompensation, is devoid of any detectable direct influence on renal hemodynamics or tubular function.

IT HAS BEEN suggested that besides its major role in the regulation of hepatic glucose production, glucagon may also influence renal function. This possibility was first put forward by Staub et al,[1] who reported that intravenous (IV) administration of glucagon to dogs caused a strong diuretic effect with a concomitant increase in sodium, potassium, chloride, and phosphate excretion. That glucagon may exert a direct influence on the kidney has also been suggested by other investigators, who demonstrated an increase in urinary flow and ion excretion when the hormone was infused directly into the renal artery.[2-4] Moreover, a number of studies have proposed that the increase in circulating glucagon levels may be responsible for changes in renal function occurring during starvation. Indeed, the increase in renal sodium and water excretion attending the early phase of total starvation is concomitant with a transient increase in glucagonemia.[5] Furthermore, when infused in pharmacological amounts, glucagon was shown to enhance fasting natriuresis and to prevent antinatriuresis of carbohydrate refeeding.[6,7]

In vitro and micropuncture studies have shown that glucagon may decrease sodium reabsorption in the proximal convoluted tubule while increasing sodium reabsorption in the thick ascending limb of Henle's loop, in the distal tubule, and at the level of the collecting duct.[8-10] This could explain the lack of a net influence of glucagon on renal sodium handling observed in several studies.[8,11-13] However, other studies indicated that glucagon may exert a direct action on the kidney,[1-4,6,7] but the mechanism of this renal effect of glucagon still awaits elucidation, and it remains to be established whether physiologic changes in glucagonemia modify renal hemodynamics and/or sodium excretion. Indeed, in most of the above-mentioned studies, glucagon was administered in pharmacologic amounts. The present study was therefore designed to assess the direct influence of pathophysiologic increases of glucagon levels on renal function. To this end, kidney function was studied in normal anesthetized dogs during intrarenal infusion of glucagon in amounts reproducing a pathophysiologic increase of the hormone in blood perfusing the kidney.

MATERIALS AND METHODS

Animal Preparation and Surgical Procedure

The experiments were performed on nine mongrel dogs of both sexes with a body weight of 30 ± 2 kg (mean ± SE). All dogs were fed the same commercial diet and were fasted overnight before the experiment, with free access to tap water. Anesthesia was induced by intramuscular injection of morphine (2 mg · kg^{-1}), followed 30 minutes later by an IV injection of sodium pentobarbital (30 mg · kg^{-1}). After tracheotomy, the animals were intubated and ventilated with room air. Ventilation rate was adjusted to stabilize baseline arterial pH at approximately 7.4. One catheter was inserted into the right humeral artery and advanced into the abdominal aorta to the level of the renal arteries for arterial blood sampling and blood pressure measurement. Heart rate was calculated from arterial pressure tracing. Another catheter was inserted into the right humeral vein for simultaneous perfusion of *p*-aminohippuric acid ([PAH] Sigma Chemical, St Louis, MO), inulin (Sigma), and pentobarbital. To catheterize both kidneys for venous sample collections, two Simmons Type III catheters (Bard, Galway, Ireland) were inserted into the femoral veins and advanced under radiologic control into both renal veins. The position of venous catheters was checked by three criteria: location corresponding to the level of the second to third lumbar vertebrae, renal venous P_{O_2} at least 50 mm Hg, and venous pH similar to arterial pH. The renal arteries of both kidneys were catheterized through the femoral

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arteries with Renal PII catheters (Bard). These catheters have two side holes and an open end, thus delivering the perfusate containing glucagon homogenously to the arterial blood. Both ureters were catheterized with polyethylene tubing through a small suprapubic incision. This experimental setting was designed to maximally reduce the surgical injury related to kidney catheterization.

After surgery, a second dose of sodium pentobarbital was administered (15 mg · kg^{-1}), and anesthesia was maintained throughout the experiment by IV perfusion of pentobarbital at the rate of 0.05 mg · kg^{-1} · min^{-1}. Heparin was injected IV (3 mg · kg^{-1}) at the end of the surgical preparation, and a second equivalent dose was administered 1 hour before the first blood sampling. After the experiment, position of the catheters was checked twice, first by injection of contrast product (Urografin 76%; Schering, Berlin, Germany) and then at necropsy. The mean weight of glucagon-infused and contralateral kidneys was 73 ± 2 and 72 ± 2 g, respectively.

Experimental Procedure

During surgery, each dog received an initial IV infusion of saline solution consisting of 0.9% sodium chloride (30 mL · kg^{-1} infused in 30 minutes) followed by continuous perfusion of saline at the rate of 2 mL · min^{-1}. After positioning the catheters, a priming dose of PAH (2 mg · kg^{-1}) and insulin (15 mg · kg^{-1}) was administered, followed by perfusion of PAH (4 μg · kg^{-1} · min^{-1}) and inulin (11 μg · kg^{-1} · min^{-1}) at the rate of 2 mL · min^{-1}. After 90 minutes, arterial blood and renal venous blood and urine samples were collected from both kidneys for baseline measurements. Blood samples for clearance determinations and assessment of renal uptake of different substrates were taken in the middle of urinary collections, each lasting 30 minutes. After the control collection, glucagon (Glucagon Hypokit; Novo, Copenhagen, Denmark) prepared in saline solution supplemented with 3 g · L^{-1} bovine serum albumin (BSA) in 0.9% NaCl (saline-BSA) was infused into one renal artery, while the contralateral kidney was infused with saline-BSA solution at a rate of 0.16 mL · min^{-1} to provide reference values. Glucagon was infused at a rate of 1 ng · min^{-1} · kg^{-1}. This infusion rate was calculated on the basis of renal plasma flow (RPF) determined in our previous studies[14,15] to reach local glucagon concentrations similar to those measured in pathophysiological conditions. The infusion rate of glucagon was adjusted to compensate for adsorption of the hormone to the perfusion system, which was a mean of 36%.

Urine was collected from 30 to 60 minutes and from 75 to 105 minutes of glucagon or saline-BSA infusion, and blood was sampled at the midpoint of each urine collection, ie, after 45 and 90 minutes.

Analyses

Arterial and venous blood samples were analyzed for plasma free fatty acids (FFA),[16] glucose (Beckman Glucose Analyzer 2; Beckman Instruments, Fullerton, CA), and lactate.[17] PAH[18] and inulin[19] levels were measured in urine and arterial and venous plasma for determination of RPF and glomerular filtration rate (GFR), respectively. Arterial pH and Po_2 were determined using a blood gas analyzer (model 613; Instrumentation Laboratory, Boston, MA). Blood oxygen content was measured by a Lex-O_2-con analyzer (Lexington Instruments, Waltham, MA). Uptake of lactate, glucose, and FFA by the kidney was calculated with the following formula: $Q_S = [RPF \cdot A_S] - [RPF - V) \cdot RV_S]$, where Q_S is net renal uptake (+) or release (−) of a substrate, S; V is urine flow; RV_S is renal venous plasma concentration of S; and A_S is arterial plasma concentration of S. Renal uptake of these energy-providing substrates was expressed as micromoles per minute per gram of kidney. Oxygen uptake was obtained from the arteriovenous difference of whole-blood oxygen content and renal blood flow that was calculated from RPF and the hematocrit and was expressed as micromoles per minute per gram of kidney. Sodium and potassium levels were measured by flame photometry (Instrumentation Laboratories, Boston, MA). Chloride level was measured by coulometric titration with a chloride titrator (CMT 10; Radiometer, Copenhagen, Denmark). Phosphate was assayed by the method of Bailey,[20] and adenosine 3′,5′-cyclic monophosphate by radioimmunoassay (Rianen Assay System; Du Pont, Billerica, MA). Glucagon concentration was measured in peripheral arterial and renal plasma.[21] Insulin[22] and cortisol[23] levels were measured in arterial plasma. Renal vascular resistance was calculated as the mean aortic pressure divided by RPF and expressed as millimeters of mercury per min per gram per milliliter.

The calculated concentration of glucagon in blood perfusing the hormone-infused kidney was obtained as (RPF × infusion rate of the hormone) + arterial systemic glucagon concentration. The percentage of renal glucagon extraction was calculated as [(A − V)/A] × 100, where (A − V) represents the arteriovenous difference of the hormone, and A the arterial level of glucagon.

Statistical Analysis

ANOVA was used to test the significance of differences in the general evolution of parameters of renal function in glucagon-infused versus saline-infused kidney. Intragroup differences, as well as differences from baseline values determined during glucagon or saline infusions, were evaluated by paired Student's *t* test. *P* less than .05 was considered to indicate significance. All data are expressed as the mean ± SE.

RESULTS

The concentration of glucagon in arterial blood of the hormone-infused kidney increased from a measured value of 227 pg · mL^{-1} in baseline conditions to a mean calculated value of 779 pg · mL^{-1} during infusion of glucagon ($P < .001$). The latter glucagon level represents an average of measurements taken at 45 and 90 minutes of glucagon infusion. Concomitantly, a significant increase in glucagon levels ($P < .005$) was measured in systemic arterial blood, and thus in blood perfusing the contralateral kidney. However, during the infusion, renal arterial glucagonemia was significantly lower in the contralateral than in the glucagon-infused kidney (Table 1). The concentration of glucagon measured in the renal vein increased slightly upon glucagon infusion, but this increase was comparable to that documented for the contralateral kidney (Table 1).

Renal extraction of glucagon, which was a mean of 32% under control conditions, remained stable in the contralateral saline-infused kidney. By contrast, the extraction rate of the hormone by the glucagon-infused kidney increased significantly ($P < .001$) to a mean of 61% (Table 1).

During glucagon infusion, RPF, GFR, and renal vascular resistance remained unchanged with respect to baseline values and were similar in hormone- and saline-infused kidneys (Table 2). Infusion of glucagon was devoid of any influence on heart rate, arterial pH, mean arterial pressure, plasma levels of energy-providing substrates, arterial concentrations of insulin, cortisol, sodium, and potassium, or the hematocrit (Table 3).

Renal excretion of sodium, potassium, and chloride

Table 1. Comparison of Arterial and Renal Venous Glucagon Levels and Renal Extraction of Glucagon During Intrarenal Perfusion of Glucagon

	Baseline	During Perfusion 45 min	During Perfusion 90 min	P
Arterial glucagon (pg · mL^{-1})				
Saline	227 ± 47	428 ± 103*	403 ± 81*	<.001
Glucagon		787 ± 90†	771 ± 74†	
Renal venous glucagon (pg · mL^{-1})				
Saline	156 ± 32	321 ± 90*	280 ± 66*	NS
Glucagon	154 ± 36	345 ± 85*	312 ± 56*	
Glucagon extraction (%)				
Saline	30.7 ± 3.91	29.3 ± 4.90	32.1 ± 5.13	<.001
Glucagon	33.4 ± 3.05	59.7 ± 5.13†	61.0 ± 4.47†	

NOTE. Glucagon was infused at the rate of 1 ng · min^{-1} · kg^{-1} into one renal artery, whereas the contralateral kidney was infused with saline-BSA. Values are the mean ± SE (n = 9). *P* values indicate significance of the difference in evolution between glucagon-infused and contralateral control kidney (ANOVA).

*$P < .05$ *v* baseline.

†$P < .01$ *v* baseline.

(Table 4) increased slightly during glucagon infusion, but this increase was significant only for sodium and chloride, and it was similar to that documented for the contralateral saline-infused kidney. Phosphate and cyclic adenosine monophosphate (cAMP) renal excretions were stable and remained unaffected by glucagon or saline infusion (Table 4). Only lactate and oxygen were significantly taken up by the kidney, not only in baseline conditions but also during glucagon or saline infusion. By contrast, there was no net uptake of FFA or glucose, both substrates being even slightly released both in control conditions and upon glucagon or saline infusion. Thus, intrarenal infusion of glucagon was devoid of any effect on substrate uptake or release by the kidney (Table 5).

Table 2. Effects of Intrarenal Glucagon Infusion on RPF, GFR, and Renal Vascular Resistance

	Baseline	During Perfusion 45 min	During Perfusion 90 min
RPF (mL · min^{-1} · g^{-1})			
Saline	1.22 ± 0.13	1.22 ± 0.12	1.16 ± 0.11
Glucagon	1.24 ± 0.15	1.21 ± 0.13	1.20 ± 0.12
GFR (mL · min^{-1} · g^{-1})			
Saline	0.48 ± 0.05	0.48 ± 0.04	0.50 ± 0.06
Glucagon	0.49 ± 0.05	0.49 ± 0.04	0.52 ± 0.05
Renal vascular resistance (mm Hg · g · min · mL^{-1})			
Saline	53.9 ± 5.28	50.6 ± 3.54	55.3 ± 5.94
Glucagon	54.4 ± 5.84	51.4 ± 3.84	53.3 ± 5.03

NOTE. Glucagon was infused at the rate of 1 ng · min^{-1} · kg^{-1} into one renal artery, whereas the contralateral kidney was infused with saline-BSA. Values are the mean ± SE (n = 9).

Table 3. Effects of Intrarenal Glucagon Infusion at the Rate of 1 ng · min^{-1} · kg^{-1} in Anesthetized Dogs on Blood pH, Heart Rate, Mean Arterial Pressure, and Energy-Providing Substrate, Insulin, and Cortisol Levels in Peripheral Arterial Plasma

	Baseline	During Perfusion 45 min	During Perfusion 90 min
Arterial pH (U)	7.407 ± .004	7.398 ± .009	7.395 ± .008
Heart rate (beats/min)	68 ± 6	68 ± 5	70 ± 6
Mean arterial pressure (mm Hg)	105 ± 7	102 ± 5	102 ± 5
Arterial glucose (mmol · L^{-1})	4.02 ± 0.22	3.73 ± 0.30	3.78 ± 0.26
Arterial lactate (mmol · L^{-1})	1.48 ± 0.15	1.33 ± 0.15	1.16 ± 0.12
Arterial FFA (mmol · L^{-1})	0.34 ± 0.03	0.35 ± 0.05	0.37 ± 0.07
Arterial insulin (ng · mL^{-1})	0.22 ± 0.03	0.27 ± 0.06	0.29 ± 0.05
Arterial cortisol (μg · mL^{-1})	0.17 ± 0.02	0.17 ± 0.03	0.16 ± 0.02
Arterial sodium (mmol · L^{-1})	147.1 ± 0.9	148.8 ± 1.2	148.6 ± 1.1
Arterial potassium (mmol · L^{-1})	3.20 ± 0.08	3.18 ± 0.08	3.11 ± 0.10
Hematocrit (%)	41 ± 1	42 ± 1	42 ± 1

NOTE. Values are the mean ± SE (n = 9).

*$P < .05$ *v* baseline.

DISCUSSION

To evaluate whether a pathophysiologic increase in plasma glucagon concentration may exert a direct effect on kidney function, the hormone was infused directly into the

Table 4. Effects of Intrarenal Glucagon Infusion on Sodium, Potassium, Chloride, and Phosphate Excretion

Renal Parameter	Baseline	During Perfusion 45 min	During Perfusion 90 min
Sodium excretion (μmol · min^{-1} · g^{-1})			
Saline	0.28 ± 0.06	0.37 ± 0.08	0.44 ± 0.11*
Glucagon	0.25 ± 0.05	0.32 ± 0.07	0.38 ± 0.09*
Potassium excretion (μmol · min^{-1} · g^{-1})			
Saline	0.34 ± 0.05	0.40 ± 0.07	0.42 ± 0.08
Glucagon	0.35 ± 0.05	0.38 ± 0.07	0.40 ± 0.09
Chloride excretion (μmol · min^{-1} · g^{-1})			
Saline	0.24 ± 0.04	0.27 ± 0.05	0.31 ± 0.03*
Glucagon	0.22 ± 0.04	0.26 ± 0.07	0.30 ± 0.06*
Phosphate excretion (nmol · min^{-1} · g^{-1})			
Saline	1.07 ± 0.31	1.15 ± 0.27	1.09 ± 0.34
Glucagon	1.13 ± 0.27	1.17 ± 0.37	1.21 ± 0.31
cAMP (pmol · min^{-1} · g^{-1})			
Saline	93 ± 24	87 ± 22	81 ± 26
Glucagon	101 ± 26	89 ± 24	85 ± 25

NOTE. Glucagon was infused at the rate of 1 ng · min^{-1} · kg^{-1} into one renal artery, whereas the contralateral kidney was infused with saline-BSA. Values are the mean ± SE (n = 9).

*$P < .05$ *v* baseline.

Table 5. Effects of Intrarenal Glucagon Infusion on the Uptake of Energy-Providing Substrates and Oxygen by the Kidney

Renal Parameter	Baseline	During Perfusion	
		45 min	90 min
Lactate uptake (nmol mmol · $min^{-1} \cdot g^{-1}$)			
Saline	0.20 ± 0.02†	0.21 ± 0.02†	0.23 ± 0.03†
Glucagon	0.22 ± 0.03†	0.22 ± 0.03†	0.25 ± 0.03†
FFA release (nmol · $min^{-1} \cdot g^{-1}$)			
Saline	0.001 ± 0.004	0.007 ± 0.011	0.010 ± 0.008
Glucagon	0.000 ± 0.004	0.001 ± 0.004	0.009 ± 0.009
Glucose release (μmol · $min^{-1} \cdot g^{-1}$)			
Saline	0.18 ± 0.03†	0.16 ± 0.06*	0.06 ± 0.04
Glucagon	0.15 ± 0.03†	0.11 ± 0.05*	0.04 ± 0.04
Oxygen uptake (μmol · $min^{-1} \cdot g^{-1}$)			
Saline	2.99 ± 0.34†	2.69 ± 0.26†	2.49 ± 0.28†
Glucagon	3.22 ± 0.38†	2.59 ± 0.38†	2.59 ± 0.20†

NOTE. Glucagon was infused at the rate of 1 ng · min^{-1} · kg^{-1} into one renal artery, whereas the contralateral kidney was infused with saline-BSA. Values are the mean ± SE (n = 9).

*Significantly different from zero ($P < .01$).

†Significantly different from zero ($P < .001$).

renal artery while the contralateral kidney was infused with saline only. Renal blood flow, GFR, and renal sodium handling were similar in glucagon- and saline-infused kidneys, which suggests that glucagon is devoid of any significant direct effect on kidney function, at least at physiologic and pathophysiologic concentrations. This conclusion is in keeping with previous observations that glucagon affects renal hemodynamics, water, and mineral excretion only when high pharmacologic doses of the hormone are infused.[2-4,24,25] Moreover, the latter effect may be indirect, resulting from the action of large doses of glucagon on the liver and on protein catabolism.[26]

Plasma Glucagon Levels and Renal Extraction of Glucagon

During glucagon infusion, the calculated concentration of the hormone in blood perfusing the kidney increased to a mean value of 779 pg · mL^{-1}, thus reproducing a pathophysiologic hyperglucagonemia like that of diabetic subjects with insufficiently corrected insulin deficiency. Systemic arterial glucagon levels, and hence glucagon concentration in blood perfusing the contralateral kidney, also increased significantly upon hormone infusion to a mean value of 415 pg · mL^{-1}. However, this concentration was significantly lower than that of arterial glucagon in the glucagon-infused kidney. Since glucagon concentration in venous effluent of the hormone-infused kidney was lower than systemic arterial glucagon levels documented during the infusion, no obvious explanation for the increase in systemic glucagonemia can be provided. The latter cannot be attributed to anesthesia-related stress, since not only heart rate and blood pressure but also plasma cortisol levels remained unchanged during the experimental procedure.

Extraction of glucagon by the kidney averaged 33% of the amount of hormone reaching the organ, not only during the control period but also when saline was infused into the renal artery. This rate of renal glucagon extraction is in agreement with previously reported data.[27-30] Our data also indicate that renal glucagon is considerably enhanced when the filtered load of glucagon is increased, thereby attenuating the increase in glucagon concentration in venous effluent of the glucagon-infused kidney. It has been suggested that, at least under baseline conditions, glucagon is mainly removed by the kidney through glomerular filtration and almost totally hydrolyzed at the level of the proximal tubule,[27,31] since only 2% to 4% of the filtered load of glucagon is found in the urine.[28,29] However, it is noteworthy that during intrarenal glucagon infusion, extraction rate of the hormone was significantly higher than its filtered load; this observation suggests the existence of a peritubular clearance process for glucagon removal by the kidney, as mentioned earlier.[29,32] This observation is in keeping with the previous suggestion[28] that renal clearance of glucagon may play an important role in maintaining arterial concentration of the hormone within the physiological range.

Glucagon Infusion and Renal Hemodynamics

The increase of renal plasma glucagon to pathophysiological levels had no effect on GFR, RPF, or renal vascular resistance, in agreement with the conclusions of other investigators.[12,33] The conclusion that glucagon may exert renal hemodynamic effects only when very high pharmacologic amounts of the hormone are infused[2-4,24,25] is also supported by the observation that intrarenal infusion of glucagon at the rate of 3 ng · kg^{-1} · min^{-1}, ie, three times higher than in our experimental conditions, had no effect on renal hemodynamics in the dog.[34] However, intraportal infusion of glucagon at the same rate produced a significant increase of GFR and RPF.[34] Uranga et al[35] observed a similar hepatic effect of glucagon, and suggested that this apparent effect of the hormone on glomerular filtration may in fact result from an hepatic action of glucagon inducing release by the liver of a hormonal substance called glomerulopressine.

Renal Uptake of Substrates and Oxygen

In keeping with previous studies,[14,15,36,37] lactate is the major substrate taken up by the dog kidney under control conditions. During glucagon perfusion and despite the increase in systemic arterial glucagon levels, arterial plasma FFA levels remained stable, whereas arterial glucose and lactate were barely decreased. The similar pattern of these substrate levels was previously documented in anesthetized dogs infused with saline only.[14,15] Since uptake of oxygen and energy-providing subtrates by the kidney remained unchanged and similar in glucagon- and saline-infused kidney, it appears that glucagon is devoid of a direct effect on kidney metabolism. This observation is in accordance with that of Johannessen et al,[38] who demonstrated by the

heat-production technique that glucagon, even at a pharmacologic dosage, had no effect on renal metabolism independent of its GFR-increasing effect.

Renal Excretion of Ions and cAMP

The previously postulated natriuretic effect of glucagon[2] is not confirmed by results of the present study. Indeed, sodium excretion remained comparable for both kidneys when glucagon was infused directly into the renal artery, despite an increase in glucagon concentration in blood perfusing the kidney to a level at least two times higher than levels observed during the natriuretic phase of starvation or in poorly controlled diabetes.[13] Potassium, chloride, and phosphate excretions were also unaffected by glucagon. This is in agreement with results of studies performed on thyroparathyroidectomized rats,[11,12] which report no net effect of a physiologic increase of systemic arterial glucagon levels on renal sodium excretion.

Since a similar slight increase in sodium excretion occurred for both kidneys whatever the concentration of glucagon in blood perfusing each kidney, one could postulate that moderate hyperglucagonemia stimulates sodium excretion, with a maximal stimulatory effect already occurring when glucagon levels were increased to 400 pg · mL^{-1}. However, this interpretation seems unlikely, since we previously observed a similar spontaneous increase in sodium excretion in anesthetized dogs infused with saline alone.[14,15] This interpretation is also in keeping with the recent observation reported by Schwartz-Sorensen et al[11] that even when a fourfold increase in glucagonemia induced a 6% increase in GFR and thus a significant increase in the filtered load of sodium, urinary sodium excretion remained unchanged. This was due to an increase in absolute reabsorption of sodium by the distal tubule, totally counterbalancing the increased load of sodium to this segment of the nephron. As for the previously reported stimulatory effect of glucagon administration on water and ion excretion,[2-4,24,25] it resulted in all likelihood from the vasodilatory effect of the hormone infused at pharmacologic dosage.[26]

Although it has been suggested that glucagon may stimulate adenylate cyclase activity in some parts of the nephron,[9,39] our results indicate that urinary cAMP excretion is not increased when glucagon is infused directly into the renal artery. This observation is in keeping with the observation that the enhancement in urinary cAMP excretion occurring during a systemic infusion of pharmacologic amounts of glucagon is essentially due to increased GFR and plasma cAMP level, resulting probably from a direct effect of glucagon on the liver.[40]

Taken together, the results of the present study are in keeping with our previous suggestion that glucagon can no longer be considered a "natriuretic hormone" responsible for sodium losses during starvation or other catabolic states.[13] However, it cannot be excluded that hyperglucagonemia may influence kidney function in some conditions indirectly through its influence on amino acid metabolism by the liver. Indeed, it has been suggested that such an indirect effect of glucagon may be involved in changes of renal function observed after a protein-rich meal[41] or during amino acid infusion.[42,43] The existence and (patho)physiological relevance of such a mechanism remain to be established, and further investigations are needed to clarify the nature of this postulated indirect effect of glucagon on kidney function.

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