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Urinary Sodium and Calcium in Various Dog Models and Relationship to Endogenous Plasma Glucagon

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Summary. Clearance studies were performed in 23 dogs undergoing extracellular volume (ECV) expansion by saline in order to evaluate relationship between endogenous glucagon and renal excretion of sodium and calcium. In control animals plasma glucagon (pGl) rose following 120 minutes of ECV expansion and was further increased by additional infusion of arginine. In pancreatectomised dogs ECV expansion failed to increase pGl. Both fractional and absolute urinary excretion of sodium in pancreatectomised dogs were markedly lower compared to control dogs. The difference in renal sodium excretion between control and pancreatectomised animals cannot be explained by the sum of nonhormonal factors influencing sodium excretion. In thyro-parathyroidectomised dogs renal sodium excretion was lower than in control dogs, but significantly higher than in pancreatectomised dogs. The arginine-induced increase of glucagon was associated with an increase of renal sodium and calcium excretion in each group under study without any change in glomerular filtration rate. In control dogs all parameters of renal sodium and calcium excretion investigated in this study were linearly correlated. Thyroparathyroidectomy did not influence the relationship between renal sodium and calcium excretion. Hyperglucagonaemia therefore might be one factor contributing to the hypercalciuria associated with renal stone formation. In pancreatectomised dogs undergoing ECV expansion there was no significant correlation between renal sodium and calcium excretion. Pancreatic hormones might be involved in the coupling of renal sodium and calcium excretion.

Key words: Extracellular fluid - Glucagon - Renal haemodynamics - Renal sodium excretion - Renal calcium excretion.

The major clinical significance of hypercalciuria is its relation to the genesis of renal stones. It has been estimated that about 50 percent of patients with renal stones have hypercalciuria on a low calcium diet. Besides increased gastrointestinal absorption of calcium or enhanced release of minerals from bone as the underlying disturbances, a decrease in renal tubular reabsorption of calcium may play a role in causing hypercalciuria in certain situations (28, 29).

Walser (43) pointed out the linear relationship between calcium and sodium tubular reabsorption following infusion of various substances in the dog. Cooke et al. (30) and Eknoyan et al. (12) found a correlation between calcium and sodium excretion in patients with hypercalciuria. The natriuretic effects of exogenous glucagon are well established (31, 36, 38). Less attention has been given to the possible role of endogenous glucagon in the regulation of renal sodium exretion: the hyperglucagonaemia during fasting is accompanied by elevated renal sodium excretion (34), presumably caused by antagonism between glucagon and aldosterone (26). In chronic renal failure plasma glucagon is markedly elevated (7) with a rapid reversal of hyperglucagonaemia following renal transplantation accompanied by normal sodium excretion (6).

The purpose of this study was to investigate the pattern of plasma levels of endogenous glucagon and their relationship to renal sodium and calcium excretion under conditions of ex-

tracellular volume expansion by saline infusion, which would be the basic pathophysiological condition for the release of yet hypothetical natriuretic agents (3, 18, 24, 41). Our hypothesis was that saline ECV expansion might result in a fall in blood glucose and stimulate glucagon secretion. Plasma glucagon was additionally stimulated by infusion of arginine in normal, pancreatectomised, thyro-parathyroidectomised and glucose-substituted dogs.

METHODS

Mongrel dogs of either sex weighing 18-25 kg were used. Animals were deprived of food, but not of water for 12 hours prior to the experiment. They were anaesthetised with thiopental-Na and then given small maintenance doses as required. The animals were ventilated with a respirator via an endotracheal tube. Rectal temperature was monitored (Telco, Siemens, Erlangen) and a fall below 36° C was prevented by keeping all infusion tubes at a constant temperature.

Cannulae were inserted into the right femoral artery (blood sampling), the left femoral artery (blood pressure measurement) and into the right jugular vein (for infusions). 250 ml of blood were withdrawn into a citrate-dextrose bottle prior to the experiment in order to replace the total volume of blood samples taken during the experiment. Laparotomy was performed via a sigmoid incision with the animal supine to obtain access to the pancreas as well as to the left kidney. The left ureter was cannulated for urine collection. Left renal arterial blood flow was measured electromagnetically (Statham) and recorded (Schwarzer-Knott).

When the surgical procedures had been completed, control blood samples were taken. Sodium chloride (0.9 per cent) was then infused at a rate of 0.5 ml/kg body weight/min until the end of the experiment. 120 minutes after starting the saline infusion, urine was collected over 3 timed clearance periods ("saline"). Arginine-hydrochloride was then infused as a stimulus for glucagon secretion (20, 42) at a rate of 31 mg/kg body wt/min for 15 minutes and starting at the time of arginine infusion, 3 further clearances were performed ("arginine"). The experiment was completed by a further 20 minute clearance period. Blood samples were withdrawn at the midpoint of each clearance period.

Animals were divided into 4 groups.
Group 1 (n = 5) Control group.
Group 2 (n = 8) Pancreatectomy. Pancreatectomy was carried out prior to saline infusion.
Group 3 (n = 5) Glucose infusion. 50 percent glucose was infused 50 minutes prior to the first saline clearance period (prime: 0.2 g/kg body wt; sustain: 0.7 mg/kg body wt/min).
Group 4 (n = 5) Thyro-parathyroidectomy (T-Px). Glands were removed 2 days prior to the experiment. Two hours prior to the experiment calcium was infused to maintain serum calcium in the range of 1.75-1.90 mmol/l. In this group the experiment was followed by an identical second part after a 2 hour interval in which l-thyroxine-Na (prime: 10 µg/kg body wt; sustain 2 µg/kg body wt/hour) was added to the saline infusion.

Blood glucose was measured enzymatically, sodium and calcium by flame emission and absorption photometry (Zeiss PMQ II), respectively. Plasma glucagon was determined by radioimmunoassay (2) using antibody 30K (Dallas Diabetes Foundation) which cross-reacts less than 10 percent with glucagon-like immunoreactivity (GLI), crystallized porcine glucagon (kindly donated by Dr. M. Root, Lilly Ltd., Indianapolis) served as standard reference. Plasma insulin and thyroxine were assayed by radioimmunoassay (44) and competitive protein binding assay (35). Glomerular filtration rate (GFR) was determined by inulin infusion (prime: 0.15 g/kg body wt; sustain: 1.5 mg/kg body wt/min) in order to maintain a plasma inulin concentration of 30-50 mg/dl. Inulin was determined using the β-indolylacetic acid colour reagent (15).

Mean values are given ± SEM (standard error of the mean). The differences between mean values were assessed by Student's t-test for paired data, since prior examination by Kolmogoroff-Smirnow test demonstrated a Gaussian type of distribution. The level of significance was set at $p < 0.05$.

RESULTS

Plasma Glucagon (pGl) (Fig. 1)

In group 1 pGl rose following expansion of ECV (control: 197 ± 30 pg/ml; saline: 347 ± 59 pg/ml; $p < 0.005$) and, further, following arginine-hydrochloride (550 ± 53 pg/ml; $p < 0.005$). In group 2 control values were comparable to those of the control group (192 ± 31 pg/ml). Volume expansion decreased pGl to 169 ± 8 pg/ml ($p < 0.01$), addition of arginine increased it to 215 ± 34 pg/ml ($p < 0.05$). Following removal of the pancreas in this group insulin fell from control values of 9.1 ± 2.3 to 1.4 ± 0.3 µU/ml and did not change during arginine infusion. Elevation of blood glucose to near 120 mg/dl in group 3 (Fig. 2) did not abolish, but diminished the rise of pGl following ECV expansion

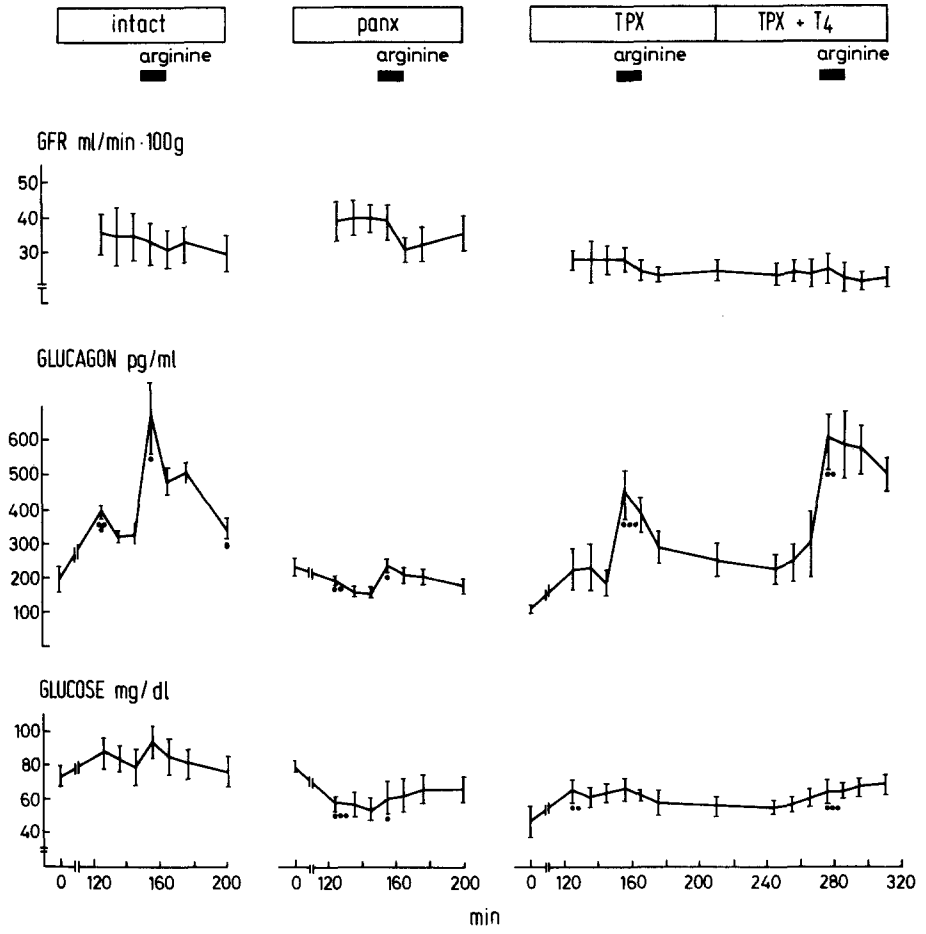


Fig. 1. Changes of glomerular filtration rate (GFR), plasma glucagon concentration and blood glucose in different groups under study: pancreatectomised (panx), thyro-parathyroidectomised group devoid of T_4 (T-Px), and with substitution of T_4 (T-Px+T_4). Black bars indicate duration of arginine infusion (31 mg/kg body wt/min). Mean values ± standard error of the mean (SEM). Zero time (0 min): control values. P values (·: <0.05; ··: <0.01; ···: <0.005; o: <0.001) indicate significant difference between control and saline (mean of 3 periods), and between saline and additional arginine infusion (mean of 3 periods)

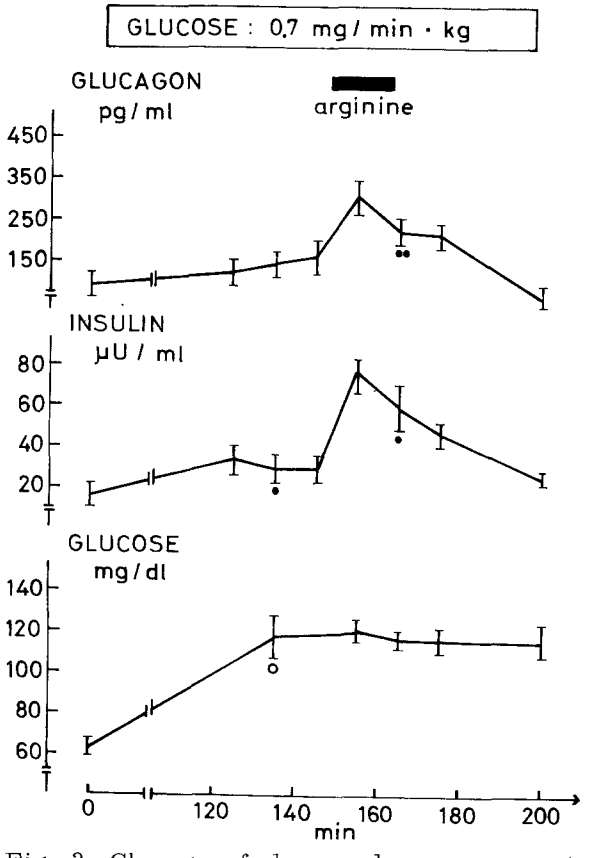


Fig. 2. Changes of plasma glucagon concentration, plasma insulin concentration and blood glucose in dogs with simultaneous administration of saline and glucose, and additional arginine infusion

(control: 150 ± 32 pg/ml; saline: 198 ± 29 pg/ml; $p > 0.05$). The response of pGl to exogenous arginine, however, was unimpaired (arginine: 300 ± 39 pg/ml; $p < 0.01$). Plasma insulin also rose following arginine (Fig. 2) indicating that amino acid sensitive B-cell receptors of the islets were intact during the experiment and that enhanced glucagon secretion was not due to disturbed insulin secretion. Control values of pGl in T-Px dogs were lower than in other groups (113 ± 11 pg/ml). However, ECV expansion increased pGl to a comparably greater extent (saline: 212 ± 58 pg/ml; arginine: 371 ± 58 pg/ml; $p < 0.01$). Thyroxine substitution did not impair secretory activity of A-cells.

Blood Glucose

Blood glucose in the control group was slightly increased after 120 minutes of ECV expansion (control: 74 ± 3 mg/dl; saline: 83 ± 9 mg/dl; $p < 0.05$), while it declined in the pancreatectomised group (control: 78 ± 4 mg/dl; saline: 57 ± 7 mg/dl; $p < 0.005$). In the T-Px group control values of blood glucose reached a nadir of 46 ± 8 mg/dl, corresponding well with the rather low pGl values of this group.

Table 1. Effects of arginine infusion on fractional sodium excretion (FE_{Na}), urinary sodium excretion ($U_{Na} \cdot V$), fractional calcium excretion (FE_{Ca}) and total urinary calcium excretion ($U_{Ca} \cdot V$) in different groups under study

Group		FE_{Na}	$U_{Na} \cdot V$	FE_{Ca}	$U_{Ca} \cdot V$
		percent	mol/min	percent	mol/min
Control	S	6.02±2.02	340.4±45.6	7.35±1.90	11.51±3.49
	A	9.69±2.90	565.8±82.1	13.68±3.17	21.59±7.18
	p	0.05	0.05	0.01	0.05
Panx	S	0.49±0.15	38.2± 6.5	0.72±0.15	1.00±0.19
	A	1.61±0.39	76.2±12.9	1.81±0.41	2.45±0.58
	p	0.01	0.05	0.05	0.05
T-Px	S	2.63±1.02	119.2±13.8	4.92±1.37	6.02±1.73
	A	6.62±2.50	273.1±20.1	11.36±3.88	13.75±4.96
	p	0.05	0.01	0.05	0.05
T-Px+T_4	S	3.21±0.68	128.9 ± 5.4	5.15±1.41	6.99±2.02
	A	7.74±2.07	285.1± 6.6	11.27±3.98	15.41±5.80
	p	0.05	0.01	ns	=0.05

Values are the average of 3 saline (S) and 3 arginine (A) clearance periods ± SEM. P-values indicate statistical differences between these values. All values of $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ are calculated for 100 ml GFR. Panx (Pancreatectomised), TPx (Thyroparathyroidectomised), S (Saline), A (Arginine).

Urinary Sodium Excretion (Table 1)

Both absolute ($U_{Na} \cdot V$) and fractional (FE_{Na}) renal sodium excretion in group 2 were much lower than in the control group. In the T-Px group $U_{Na} \cdot V$ was also impaired compared to the control group. As GFR in the latter group was lower than in the pancreatectomised group (T-Px: 27.4±4.8 ml/min/100 g kidney weight; panx: 40.1±5.6 ml/min/100 g kidney wt; Fig. 1), differences in FE_{Na} between both groups became more pronounced. Administration of Thyroxine to T-Px dogs slightly enhanced FE_{Na}. Arginine infusion increased both $U_{Na} \cdot V$ and FE_{Na} in all groups under study without any increase, but a slight decrease of GFR in each group (Fig. 1).

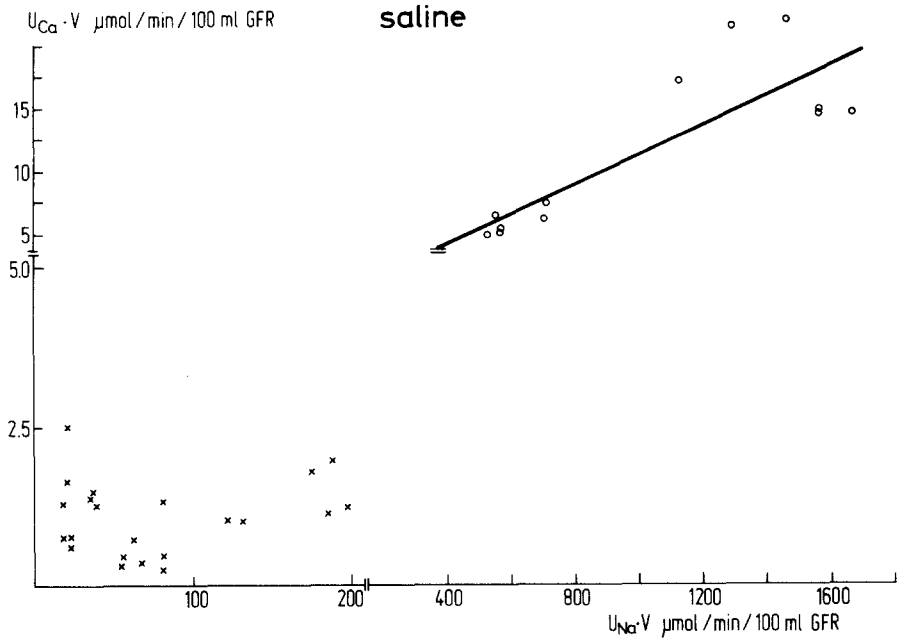
Urinary Calcium Excretion (Table 1)

In pancreatectomised dogs renal calcium excretion was depressed to about 10 per cent that of control dogs. In T-Px dogs calcium excretion was diminished compared to the control group, but markedly greater than in the pancreatectomised group. Substitution of thyroxine induced a small increase in renal calcium excretion.

Relationship between Renal Sodium and Calcium Excretion

The upper panel of Figure 3 shows the linear relationship between $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ following ECV expansion in control dogs ($y = 0.39 + 0.46x$; $n = 12$; $r = 0.8387$; $p < 0.001$). $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ were not significantly correlated in pancreatectomised dogs.

Following additional arginine (Fig. 3, lower panel) the slope of the regression line between $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ was increased insignificantly in control dogs ($y = 3.71 + 0.61x$; $n = 12$; $p < 0.001$). Under these experimental conditions the relationship between $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ also in the pancreatectomised group became significant ($y = 1.29 + 0.21x$; $r = 0.5695$; $p < 0.01$). The comparison of regression coefficients for $U_{Na} \cdot V$ versus $U_{Ca} \cdot V$ between control and pancreatectomised groups revealed a significant difference ($p < 0.01$). The



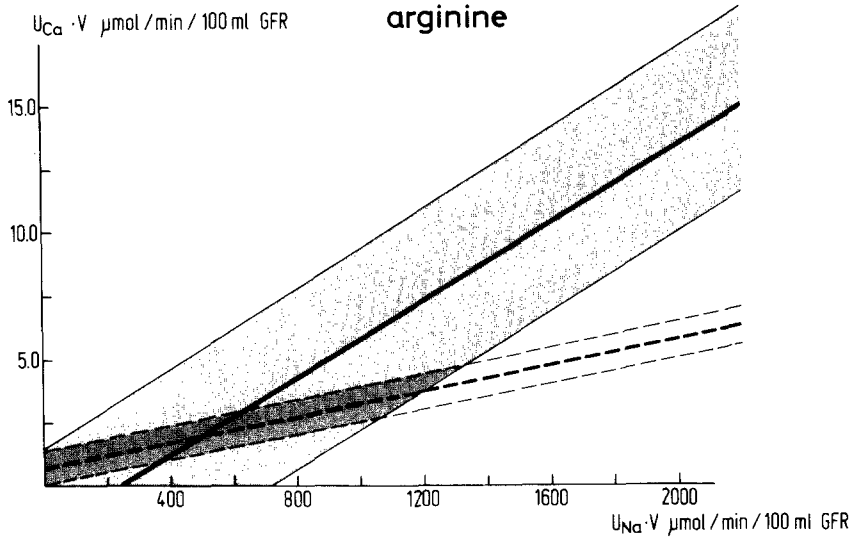


Fig. 3. Relationship between urinary excretion per unit glomerular filtrate of sodium and calcium. Upper panel: Clearance periods in 4 control dogs (n = 12; o) and 8 pancreatectomised dogs (n = 22; x) during intravenous saline infusion alone; regression equation for control dogs: y = 0.39 + 0.46 x; r = 0.8387; p <0.001). Lower panel: Regression lines and 95 per cent confidence range for clearance periods during saline infusion and additional arginine-hydrochloride in control dogs (full lines; n = 15; y = 3.71+0.61x; r = 0.8972; p <0.001) and pancreatectomised dogs (broken lines; n = 24; y = 1.29 + 0.21x; r = 0.57; p <0.01)

pattern of correlation between FE_{Na} and FE_{Ca} was identical to $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ and, therefore, is not shown in the figures.

In Figure 4 regression lines are delineated for the relation between urine concentrations of sodium, (Na_U), and calcium, (Ca_U) in control dogs, as well as in thyro-parathyroidectomised dogs without (T-Px) and with substitution of thyroxine (T-Px+T_4). Since there was no difference in regression coefficients between "saline" and "arginine" values in either group, all respective data were pooled for each animal group and recalculated. The regression lines for both the T-Px and the T-Px+T_4 groups do not differ significantly from the regression line for control dogs (y = 0.16 + 0.34x; n = 30;

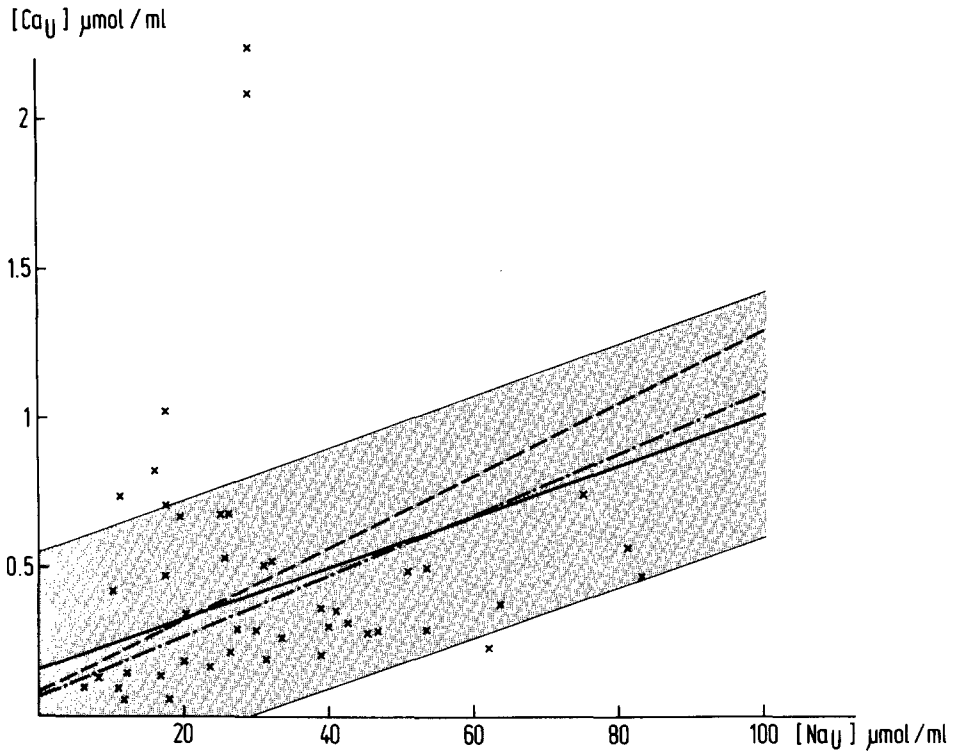


Fig. 4. Relationship between urinary concentration of sodium and calcium. Note that individual values from clearance periods (saline alone and with additional arginine) in pancreatectomised dogs (x) are not correlated. Full lines indicate regression line and 95 per cent confidence range, respectively, of control dogs (n = 30), dotted and broken lines pertain to thyro-parathyroidectomised dogs with substitution of T_4 (T-Px+T_4; n = 30) and devoid of T_4 (T-Px; n = 30). Regression equations. Control dogs: $y = 0.16 + 0.34x$; $r = 0.6592$; $p < 0.001$; T-Px+T_4: $y = 0.07 + 0.40x$; $r = 0.79$; $p < 0.001$; T-Px: $y = 0.08 + 0.48x$; $r = 0.7883$; $p < 0.001$

$r = 0.6592$; $p < 0.001$). From the pancreatectomised animals individual values are depicted. There was no significant correlation between (Na_U) and (Ca_U) in this group.

Physical Factors

Changes of those physiological parameters which are known to influence renal sodium excretion are shown in Table 2. Both renal arterial plasma flow (RPF_a) and mean arterial blood pressure (MAP) in the pancreatectomised as well as in the T-Px group were markedly depressed compared to the control group. When T_4 was re-substituted in the T-Px group, RPF_a further declined, whereas MAP rose. Thus calculated renal vascular resistance (RVR) was strongly elevated following T_4 infusion. Although the flow increasing effect of exogenous glucagon is known (21), the low RPF_a in the pancreatectomised group rather might be a consequence of the blood loss during pancreatectomy rather than lack of glucagon. Despite the low RPF_a of the pancreatectomised group its glomerular filtration rate is comparable with that of the control group (control: 35.3 ± 7.4 ml/min/100 g kidney wt; pancreatectomised: 40.1 ± 5.6 ml/min/100 g kidney wt). In the T-Px group with and without T_4 replacement GFR was lower than in the control group (T-Px: 27.4 ± 4.9 ml/min/100 g kidney wt; T-Px+T_4: 23.7 ± 3.6 ml/min/100 g kidney wt; Fig. 1). Arginine infusion increased RPF_a in all groups under study, but with a slight decrease of GFR in each group. MAP did not change following arginine. "Saline" values of haematocrit were higher in control animals than in both the pancreatectomised and T-Px group, indicating a more pronounced ECV expansion in the latter groups. Postglomerular protein concentration (PGP[1]) in the pancreatectomised

1 Postglomerular protein concentration (PGP) was calculated according to Bresler's formula (8): PGP (g/100 ml) = PP/1-FF, whereby PP = total plasma protein concentration and FF = filtration fraction.

Table 2. Non-hormonal physiological factors influencing renal sodium excretion

		RPF_a	MAP	RVR	PGP	Ht
		ml/min	mmHg	mmHg.min. ml^{-1}	g/100ml	percent
Control	S	274.1±70.1	144±0	0.65±0.12	5.35±0.19	44.0±2.0
	A	330.8±78.9	143±1	0.55±0.09	4.26±0.20	38.0±1.4
	p	<0.001	ns	<0.05	<0.005	<0.01
Panx	S	148.9±16.7	121±2	0.99±0.09	4.53±0.24	37.4±1.5
	A	173.7±32.5	122±2	0.99±0.19	3.69±0.35	32.1±1.9
	p	ns	ns	ns	<0.01	<0.001
T-Px	S	149.9±32.3	128±10	0.67±0.07	5.36±0.59	39.4±1.7
	A	179.7±39.2	129±9	0.61±0.08	4.47±0.45	35.9±2.0
	p	<0.01	ns	<0.05	<0.01	<0.001
T-Px+T_4	S	103.8±21.1	142±10	1.13±0.26	4.64±0.41	37.6±3.0
	A	117.8±22.8	149±8	1.13±0.19	3.92±0.35	33.0±2.7
	p	<0.05	ns	ns	<0.005	<0.005

Abbreviations: RPF_a (renal arterial plasma flow), MAP (mean arterial blood pressure, RVR (renal vascular resistance), PGP (postglomerular protein concentration), Ht (hematocrit). S (saline) A (Arginine). Panx (Pancreatectomised) TPx (Thyroparathyroidectomised)

group was decreased as a consequence of a low total plasma protein concentration, although filtration fraction in these dogs was higher than in the control group. PGP was not influenced by thyroparathyroidectomy.

DISCUSSION

Glucagon functions predominantly as a hormone of glucose homeostasis. The results of the present study suggest that it might be also involved in the regulation of renal sodium and calcium excretion. Sodium excretion regularly increases along with a rise of plasma glucagon mediated by saline alone and or together with exogenous arginine. The failure of plasma glucagon to rise in pancreatectomised, ECV expanded dogs is associated with a very low urinary sodium excretion. The decreased natriuresis of these animals cannot be ascribed to an effect of insulin. This hormone enhances renal tubular sodium reabsorption (10); accordingly, the lack of insulin in pancreatectomised dogs would rather tend to induce an enhanced urinary sodium excretion.

Exogenous glucagon increases the renal excretion of both sodium and calcium, and of other electrolytes (31, 36). Walser (43) reported that calcium clearance in dogs undergoing diuresis induced by various substances was linearly related to sodium clearance. We therefore investigated the relationship between renal calcium and sodium excretion following arginine-induced hyperglucagonaemia. Our study revealed a highly significant correlation between sodium and calcium in control dogs, as well as in thyroparathyroidectomised dogs with or without substitution of thyroxine. Regression coefficients for $U_{Na} \cdot V$ versus $U_{Ca} \cdot V$ of control and T-Px dogs only show small and insignificant differences. Thus the coupling of renal sodium and calcium excretion seems to be rather independent of thyrocalcitonin, parathyroid hormone and thyroxine.

The hypercalciuria induced by endogenous glucagon is not only based upon an enhanced

urine flow, but also upon an increased urinary calcium concentration. Therefore, at least during states of ECV expansion, hyperglucagonemia might contribute to renal calcium stone formation associated with hypercalciuria. However no conclusive evidence is available concerning whether or not renal calcium stone-formers are volume-expanded. There is conflicting data about diurnal sodium regulation in calcium stone formers, which perhaps depends upon the differences in the kind of urine samples collected and analysed, i.e. 24 hour sodium even under balance conditions may be normal (27), whereas timed sodium excretion following a 12 hour nocturnal fasting period was found significantly elevated by us (38). Studies on the state of body fluid compartments appear necessary in order to clarify the interdependence of sodium and calcium excretion in stone disease. Moreover preliminary data indicate that the integrated response of plasma glucagon to a standard meal in stone patients is decreased rather than increased (37). Thus, hyperglucagonaemia as one possible factor underlying renal calcium stone formation in man must remain speculative. Both urinary sodium and calcium excretion in pancreatectomised dogs are depressed. The close linear correlation between renal sodium and calcium excretion however, no longer exists. These results suggest that one role of the pancreatic hormones might be the coupling of renal excretion of sodium and calcium.

Following removal of the pancreas there is still a small rise in plasma glucagon following infusion of arginine. This corresponds well to the report of Unger et al. (33) that there are true A-cells in the gastric fundus and in the duodenum of dogs corresponding with the distribution of glucagon, immunologically indistinguishable from pancreatic glucagon. In our study, this "gut glucagon" seems to have natriuretic as well as calciuretic potency, shown by the arginine-induced increase of sodium and calcium excretion in the pancreatectomised dogs. Following arginine the linear relationship between $U_{Na} \cdot V$ and $U_{Ca} \cdot V$ re-appears but not that between (Na_U) and (Ca_U). The regression coefficient of this relationship, however, is significantly lower in these pancreatectomised dogs than in the control group, i.e. renal calcium excretion at a given level of renal sodium excretion is lower than in control dogs. The calciuretic potency of gut may be less than pancreatic glucagon. Further studies are needed to elucidate the effect of gut glucagon on electrolyte metabolism.

Our conclusion that glucagon might be active as a natriuretic agent seems to be contradictory to the work of Levinsky (22), in which he showed that renal sodium excretion increased following saline loading despite ligation of the portal vein and hepatic artery. This statement, however, is based on the results of only three experiments. There are no data concerning changes of other physiological factors influencing sodium excretion. For example, saline ECV-expansion may have depressed postglomerular protein concentration and haematocrit and/or increased renal arterial plasma flow, both resulting in an enhanced renal sodium excretion despite a fall in plasma levels of a natriuretic active agent. Moreover, glucagon may have reached the circulation via alternative venous pathways bypassing the liver.

Starting from the assumption that blood concentration of glucose was the stimulus for glucagon secretion we infused glucose into one group of dogs in an attempt to decrease glucagon release. Plasma glucagon, however, did not fall, but increased slightly. Moreover, in the T-Px group a low blood glucose is associated with a low plasma glucagon. Therefore, glucagon secretion under these experimental conditions must be stimulated by factors other than blood glucose concentration. This interpretation is supported by the report of Iversen (18) that an enhanced release of glucagon is mediated by adrenergic receptor sites of A-cells despite prevailing hyperglycaemia. At present it is not known whether volume expansion represents another form of stress, which, by release of neural transmitters, might stimulate these receptors (18).

Glucagon enhances calcitonin secretion in several animal species (9, 40), which, like parathyroid hormone has natriuretic potency (1, 4, 5, 13, 14). The low urinary sodium excretion in the T-Px dogs can be ascribed to the lack of PTH or calcitonin or the sum of both hormones and only to a small degree to the low plasma glucagon. As the arginine-induced increase in renal sodium excretion is comparable in control and T-Px dogs, the natriuretic effect of endogenous glucagon seems to be independent of the secondary release of calcitonin in the dog.

Michael et al. (25) reported on an increase of FE_{Na} in hypothyroid rats. Our studies do not confirm these results for the dog as T_4 replacement in T-Px dogs does not influence FE_{Na}. However, antinatriuretic effects of T_4 might have been masked by the simultaneous rise in plasma glucagon.

Several authors stress the role of non-hormonal factors in the regulation of urinary sodium excretion (16, 19, 32). The influence of these factors on sodium excretion in our experiment is difficult to evaluate: in the pancreatectomised group postglomerular protein concentration, as well as haematocrit are lower than in the control group, both tending to en-

hance natriuresis in pancreatectomised dogs, whereas low renal arterial plasma flow might have decreased sodium excretion by a fall in postglomerular hydrostatic pressure. Thus the sum of changes in non-hormonal factors might not be the main cause of the low urinary sodium excretion in pancreatectomised dogs.

This is supported by the fact that FE_{Na} in T-Px dogs is about five fold higher than in pancreatectomised dogs despite almost identical RPF_a and even higher PGP.

In studies with exogenous glucagon Levy (23) described a slight, but constant rise in GFR, which was great enough to explain the enhanced natriuresis in these experiments. In our study we failed to produce any increase in GFR by arginine-induced glucagon secretion and therefore no increase in filtered sodium load. Probably the high doses of exogenous hormone used in Levy's study subsequently released greater amounts of calcitonin, which has been reported to be a potent renal vasodilator (11). The low RPF_a in the T-Px group might be explained by the lack of this hormone.

Summarising data from the present study one is inclined to propose that hypercalciuria in renal stone disease should be evaluated along with concomitant changes in urinary sodium and abnormal secretory patterns of gastrointestinal hormones.

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