Kidney International, Vol. 1 (1972), p. 27–37

Quantitative influence of non-hormonal blood factors on the control of sodium excretion by the isolated dog kidney

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Quantitative influence of non-hormonal blood factors on the control of sodium excretion by the isolated dog kidney. On the basis of experiments performed on isolated dog kidneys, thus eliminating extrarenal hormonal controls, an attempt has been made to evaluate the influence of arterial blood pressure and several non-hormonal blood parameters on fractional sodium excretion. The roles of plasma protein concentration as modulated by filtration fraction, total renal plasma flow, hematocrit, arterial pressure and plasma potassium concentration on overall fractional sodium reabsorption have been evidenced and quantitatively evaluated. Although the control of sodium reabsorption by renal plasma flow and by hematocrit can be ascribed partly to changes in filtration fraction and postglomerular plasma protein concentration, other mechanisms appear to be involved as well. Variations in filtration fraction and postglomerular plasma protein concentration play little, if any, role in the induction of pressure natriuresis. The autonomous and quantitative response of the kidney to blood dilution during saline diuresis represents the cumulative results, not only of the dilution of pre- and postglomerular plasma proteins, but also of the simultaneous decrease of hematocrit and increase of renal plasma flow. The implications of these results for the understanding of the adjustment of sodium balance in acute and chronic conditions are discussed.

Rôle comparatif de facteurs sanguins non hormonaux, dans le contrôle de l'excrétion sodée par le rein isolé de chien. A partir d'expériences réalisées sur des reins isolés de chien, excluant les influences hormonales extrarénales, les effets comparés de la pression artérielle et de plusieurs paramètres sanguins non hormonaux sur l'excrétion fractionnelle du sodium ont été étudiés systématiquement. Les rôles joués par le taux des protéines plasmatiques et la fraction filtrée, par le débit plasmatique rénal, l'hématocrite, la pression artérielle, le taux plasmatique du potassium ont été démontrés et évalués quantitativement. Le contrôle de la réabsorption du sodium par le débit plasmatique rénal et par l'hématocrite n'est que partiellement dû aux variations de la fraction filtrée et de la concentration des protéines plasmatiques post-glomérulaires; d'autres mécanismes interviennent. Les variations de la fraction filtrée et de la concentration des protéines plasmatiques post-glomérulaires n'interviennent que peu ou pas du tout dans l'induction de la natriurèse consécutive à l'hypertension artérielle. La réponse autonome et quantitative du rein à la dilution du sang dans les conditions de la diurèse saline représente la conséquence cumulative, non seulement de la dilution des protéines plasmatiques pré- et postglomérulaires, mais aussi de la diminution de l'hématocrite et de l'augmentation du débit plasmatique. La signification de ces résultats pour la compréhension de l'ajustement de la balance sodée dans les conditions aiguës et chroniques est discutée.

Accepted in revised form June 10, 1971

Adjustments of urine sodium excretion are mainly related to the influence on the kidney of hormones such as aldosterone, angiotensin, vasopressin and perhaps "natriuretic hormone" on the one hand, and less specific factors such as blood dilution or concentration, arterial and venous pressures, and perhaps nervous control on the other hand. The respective contribution of these various parameters to both permanent and rapid adjustments of sodium excretion has not been fully elucidated. Besides glomerular filtration, fractional tubular reabsorption is modulated by non-hormonal factors such as blood pressure, hematocrit, blood flow, and plasma potassium concentration [1–21]. Various mechanisms may be involved such as the intrarenal distribution of blood flow [4, 22], eventually related to the vascular action of antidiuretic hormone (ADH) [23], and changes in interstitial pressure [8]. Redistribution of filtration and

reabsorption between cortical and juxtamedullary nephrons after saline loading has been demonstrated in the rat [24] but not in the dog [25].

Postglomerular plasma oncotic pressure appears to represent an important determinant of sodium reabsorption, as demonstrated in the whole animal [2, 8, 26–31], in the isolated kidney preparation [3, 13] and by micropuncture experiments [26, 32–34]. While the dilution of plasma proteins is liable to explain, at least partly, the rapid natriuretic response after saline loading, the modulation of postglomerular plasma protein concentration, depending on filtration fraction [35], might control glomerulotubular balance to some extent [26, 27].

The present work represents an attempt to evaluate, on a semi-quantitative basis, the influence of postglomerular plasma protein concentration, renal plasma flow, hematocrit, arterial pressure and plasma potassium concentration on overall fractional sodium reabsorption, and to investigate to what extent the influences of plasma flow, hematocrit and arterial pressure can be related to the peritubular and postglomerular plasma protein concentration as modulated by filtration fraction. Isolated dog kidneys have been perfused with heparinized blood via a pump-oxygenator system. Both blood and kidneys originated from randomly selected animals. Moreover, uniform technical conditions and elimination of several known (and perhaps unknown) extrarenal factors during artificial perfusion reduced the number of parameters under study, thus allowing a statistical analysis of their quantitative role. The purpose of the present work was to analyze the correlations on the basis of a great number of individual results. When two or more determinants of sodium reabsorption appeared to be related to each other, the calculation of partial correlations after successive elimination of selected parameters allowed an evaluation of their respective influences on sodium reabsorption. Moreover, the magnitude of these influences has been assessed by the calculation of regression coefficients.

Methods

The pump-oxygenator device has been described previously, as have the technical prerequisites for the proper functional performance of perfused organs [15, 36]. In each experiment, kidney and blood were taken from two different dogs submitted to pentobarbital anesthesia (30 mg/kg i.v.). Kidney weight ranged between 14 and 72 g. Blood donors, weighing between 14 and 37 kg, received a previous injection of heparin (1250 IU/kg i.v.). The amount of perfusing blood was identical in all experiments (450 ml). In order to reduce initial vasoconstriction, 25 mg promethazine (Phenergan®, Specia), which exhibits a transient vasodilating action, were added to the blood before starting the perfusion. Temperature was kept constant at 37.5° C. In order to compensate for excretory and metabolic losses, a solution containing 2 g glucose, 2 g urea and 1.5 g potassium chloride/100 ml Ringer's solution was infused continuously at a rate of 6 ml/hr. These amounts have been established experimentally as necessary to keep the composition of the blood within the initial range. The duration of the perfusion was 2.5 hours; urine was collected during four successive 30 min periods and quantitatively replaced by half-diluted Ringer's solution. The first sample was discarded. Arterial blood samples were taken in the midst of each collection period. A priming dose of 90 mg creatinine was added at the beginning of the perfusion and was followed by a continuous infusion of 6 ml/hr of Ringer's solution containing creatinine at a concentration of 2 g/100 ml at the level of the renal vein. In order to avoid the development of massive water diuresis, 0.1 IU vasopressin (Sandoz) was added after 30, 60, and 90 minutes.

Renal blood flow was measured by the venous output into a graduated pipette; the hematocrit was measured in Wintrobe tubes. Sodium and potassium determinations were made by flame photometry, creatinine by the Folin-Wu technique adapted to the Technicon auto-analyzer, plasma proteins by refractometry under periodical control by the Kjeldahl technique. Postglomerular plasma protein concentration was calculated from the preglomerular (systemic) concentration and from the filtration fraction according to Bresler's formula [35]. Plasma oncotic pressure was calculated from the plasma protein concentration by Keys' formula [37].

Detailed information concerning the functional performance of perfused kidneys has been presented elsewhere [15].

Regression equations and correlation coefficients were determined by the usual formulas as well as partial correlation coefficients by successive elimination of variables. For details of the study of partial correlation, we refer the reader to the books of Schwartz [38] and Quenouille [39].

Results

The average results are presented in Table 1. The correlations, partial correlations and regression equations are presented in Table 2. They have been calculated, for each parameter, from 221 individual measurements obtained during 76 perfusion experiments.

The following abbreviations have been used in the presentation and discussion of results:

NaE: sodium excretion (% of filtered load).

PP: preglomerular plasma protein concentration (g/liter).

PGPP: postglomerular plasma protein concentration (g/liter).

H: hematocrit (vol %).

PNa: plasma sodium concentration (mEq/liter).

PK: plasma potassium concentration (mEq/liter).

RPF: total renal plasma flow (ml/min/g kidney wt).

GFR: glomerular filtration rate (ml/min/100 g kidney wt).

FF: filtration fraction (%).

AP: arterial pressure (mm Hg).

Fractional sodium excretion and postglomerular plasma protein concentration (Table 2). While a significant correlation was not found between NaE and PP (line 1), a very significant negative correlation was observed between NaE and PGPP (line 2 and Fig. 1). Since AP, H, and PK influenced NaE in various ways, these variables were successively eliminated; the resulting partial correlation was not significantly altered thereafter (lines 3–5).

Fractional sodium excretion and glomerular filtration rate (Table 2). As shown in line 7, NaE seemed to be significantly related to glomerular filtration rate (GFR). However, both NaE and GFR were related to AP (lines 44 and 52), while NaE also appeared to be related to RPF (line 14). After the elimination of AP and RPF, the partial correlation between NaE and GFR became insignificant (line 9). The well known interdependence of GFR and RPF was observed and did not depend on AP (lines 19 and 20). Elimination of the variables PK (line 59) and PGPP (line 2) induced no significant change (line 11).

Fractional sodium excretion and renal plasma flow (Table 2). A positive correlation was found between NaE and RPF (line 14). Since both of these parameters were related to AP (lines 44 and 53), it was therefore

Table 1

Average results

	AP, mm Hg				Overall values	
	110	130	150	170		
Number of experiments	15	36	8	17	76	
Number of collection periods	51	80	22	68	221	
Plasma proteins, g/liter	66.30 (0.79)	69.50 (0.58)	75.90 (0.41)	75 (0.75)	71.13 (0.62)	<0.001 [51]
Hematocrit, vol. %	51.80 (0.42)	51.10 (0.42)	53.60 (0.41)	50.70 (0.79)	51.40 (0.56)	NS
Plasma sodium, mEq/liter	147.90 (2.01)	150.50 (0.38)	148.70 (0.47)	148.70 (1.37)	148.20 (1.37)	NS
Plasma potassium, mEq/liter	4.43 (0.07)	4.50 (0.04)	4.54 (0.06)	4.36 (0.04)	4.44 (0.04)	<0.001 [58]
Renal plasma flow, ml/min/g	2.40 (0.06)	2.49 (0.04)	2.10 (0.03)	3.57 (0.13)	2.77 (0.10)	<0.001 [53]
Glomerular filtration, ml/min/100 g	37.80 (0.62)	44.22 (0.90)	35.60 (0.57)	46.90 (1.05)	42.71 (0.87)	<0.01 [52]
Filtration fraction, %	17.86 (0.49)	18.64 (0.42)	17.55 (0.42)	15.20 (0.44)	17.29 (0.44)	<0.01 [54]
Post-glomerular plasma proteins, g/liter	81.80 (1.30)	85.60 (0.86)	92.50 (0.75)	89.20 (1.13)	86.52 (0.94)	<0.01 [55]
Sodium excretion, % of filtered load	2.57 (0.15)	3.67 (0.16)	5.50 (0.17)	7.18 (0.33)	4.68 (0.25)	<0.001 [44]

Standard error of the mean is given between brackets after each value. In the last column, statistical significance of the overall correlation between each parameter and arterial pressure is given on the basis of the corresponding correlation coefficients; the numbers between brackets refer to these coefficients and regression equations presented in Table 2.

NS = not significant.

Table 2

Regression equations and total and partial correlation coefficients between fractional sodium excretion, postglomerular plasma protein concentration, glomerular filtration, renal plasma flow, filtered fraction, hematocrit, arterial pressure, plasma potassium concentration (221 values for each parameter)

Line	Correlations (total and partial)	r	$2P$	Regression equations
1	NaE/PP	−0.045	NS	
2	NaE/PGPP	−0.29	<0.001	NaE = 11.38 − 0.078 (±0.35) PGPP
3	NaE/PGPP eliminating AP	−0.45	<0.001	
4	NaE/PGPP eliminating AP and H	−0.29	<0.001	
5	NaE/PGPP eliminating AP, H and PK	−0.30	<0.001	
6	PK/PGPP	−0.17	0.01	PK = 5.348 − 0.011 (± 0.009) PGPP
7	NaE/GFR	0.23	<0.001	NaE = 0.067 (±0.039) GFR + 1.82
8	NaE/GFR eliminating AP	0.16	<0.05	
9	NaE/GFR eliminating AP and RPF	0.03	NS	
10	NaE/GFR eliminating AP, RPF and PK	−0.03	NS	
11	NaE/GFR eliminating AP, RPF, PK and PGPP	−0.07	NS	
12	PK/GFR	−0.20	<0.01	PK = 5.047 − 0.013 (±0.009) GFR
13	PGPP/GFR	0.14	0.05	PGPP = 80.34 + 0.146 (±0.14) GFR
14	NaE/RPF	0.41	<0.001	NaE = 1.075 (±0.32) RPF + 1.7
15	NaE/RPF eliminating AP	0.33	<0.001	
16	NaE/RPF eliminating AP and GFR	0.28	<0.001	
17	NaE/RPF eliminating AP, GFR and PGPP	0.19	<0.01	
18	PK/RPF	0.01	NS	
19	GFR/RPF	0.31	<0.001	GFR = 2.55 (±1.05) RPF + 35.65
20	GFR/RPF eliminating AP	0.27	<0.001	
22	FF/RPF	−0.48	<0.001	FF = 22.85 − 1.99 (±0.49) RPF
23	FF/RPF eliminating AP	−0.45	<0.001	
24	FF/RPF eliminating AP and H	−0.32	<0.001	
25	PGPP/RPF	−0.39	<0.001	PGPP = 97.86 − 4.06 (±1.30) RPF
26	PGPP/RPF eliminating AP	−0.47	<0.001	
27	PGPP/RPF eliminating AP and H	−0.32	<0.001	
28	NaE/H	−0.41	<0.001	
29	NaE/H eliminating AP	−0.43	<0.001	
30	NaE/H eliminating AP and PGPP	−0.34	<0.001	
31	NaE/H eliminating AP, PGPP and RPF	−0.21	<0.01	
32	NaE/H eliminating AP, PGPP, RPF and PK	−0.26	<0.001	
33	PK/H	−0.14	<0.05	PK = 53.782 − 0.018 (±0.017) H
34	GFR/H	−0.07	NS	
35	RPF/H	−0.41	<0.001	RPF = 6.68 − 0.75 (±0.23) H
36	RPF/H eliminating AP	−0.42	<0.001	
37	FF/H	0.46	<0.001	FF = 0.36 (±0.09) H − 1.22
38	FF/H eliminating AP	0.46	<0.001	
39	PP/H	0.55	<0.001	PP = 0.61 (±0.13) H + 39.77
40	PGPP/PP	0.78	<0.001	PGPP = 1.18 (±0.12) PP + 2.64
41	PGPP/H	0.56	<0.001	PGPP = 1.09 (±0.22) H + 31.58
42	PGPP/H eliminating AP	0.56	<0.001	
43	PGPP/H eliminating AP and PP	0.24	<0.001	
44	NaE/AP	0.48	<0.001	NaE = 0.08 (±0.02) AP − 6.354
45	NaE/AP eliminating PP	0.53	<0.001	
46	NaE/AP eliminating GFR	0.51	<0.001	

Table 2 (continued)

Line	Correlations (total and partial)	*r*	2*P*	Regression equations
47	NaE/AP eliminating PP and RPF	0.47	<0.001	
48	NaE/AP eliminating GFR and RPF	0.45	<0.001	
49	NaE/AP eliminating PP, GFR and RPF	0.50	<0.001	
50	NaE/AP eliminating PP, GFR, RPF and PK	0.45	<0.001	
51	PP/AP	0.36	<0.001	PP = 0.14 (+0.05) AP + 51.54
52	GFR/AP	0.20	<0.01	GFR = 0.11 (±0.07) AP + 27.35
53	RPF/AP	0.28	<0.001	RPF = 0.02 (±0.01) AP + 0.06
54	FF/AP	−0.18	<0.01	FF = 24.57 − 0.052 (±0.037) AP
55	PGPP/AP	0.20	<0.01	PGPP = 0.12 (±0.08) AP + 69.81
56	PGPP/AP eliminating PP	−0.14	0.05	
57	H/AP	0.04	NS	
58	PK/AP	−0.32	<0.001	PK = 6.146 − 0.012 (±0.005) PA
59	NaE/PK	−0.28	<0.001	NaE = 10.158 − 1.226 (±0.57) PK
60	NaE/PK eliminating AP	−0.15	0.05	
61	NaE/PK eliminating PGPP	−0.35	<0.001	
62	NaE/PK eliminating AP and PGPP	−0.21	0.001	

Twice standard deviation is given between brackets for each regression coefficient.

necessary to eliminate the possibility that this positive correlation depended mainly on AP. This was not the case, since the correlation coefficient was not significantly changed after the elimination of AP (line 15). Moreover, GFR, which was related to RPF (line 19) could also be removed without suppressing the significant relationship between NaE and RPF (line 16).

A negative correlation was found between FF and RPF (line 22 and Fig. 2) which was independent of AP and H (lines 23 and 24). The negative correlation between PGPP and RPF (line 25) also proved to be independent of AP and H (lines 26 and 27). Changes in PGPP could therefore account to some extent for the modulation of NaE by RPF; however, they were not the only factors involved, since after elimination of AP, GFR and PGPP, the correlation between NaE and RPF, though less, was still very significant (line 17).

Fractional sodium excretion and hematocrit (Table 2). There was a very significant negative correlation between NaE and H (line 28). GFR was independent

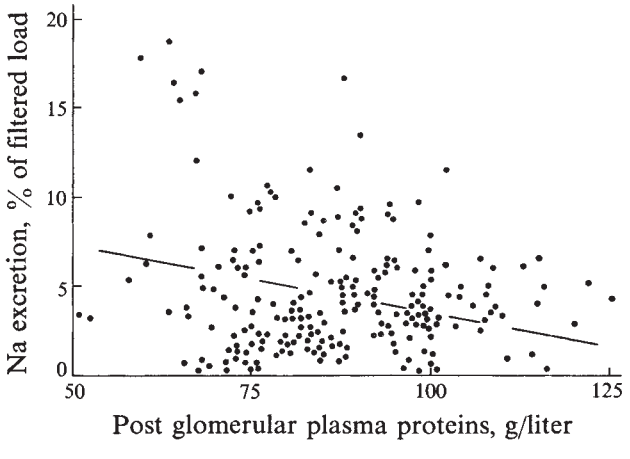

Fig. 1. Correlation between post-glomerular plasma protein concentration and sodium excretion expressed in % of filtered load.

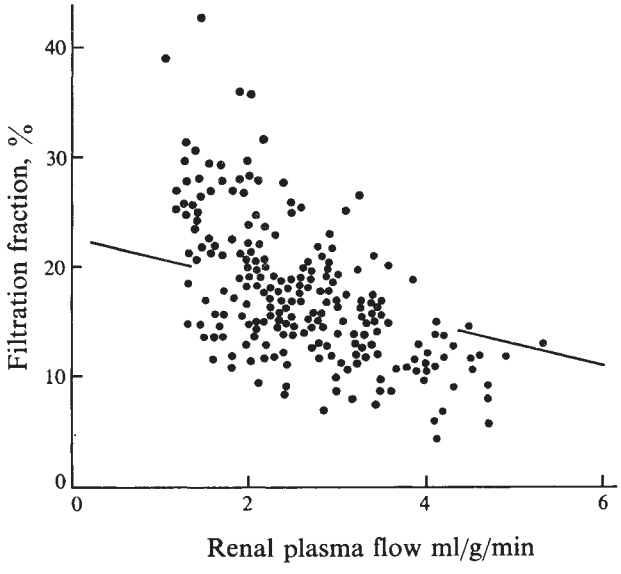

Fig. 2. Correlation between renal plasma flow and filtration fraction.

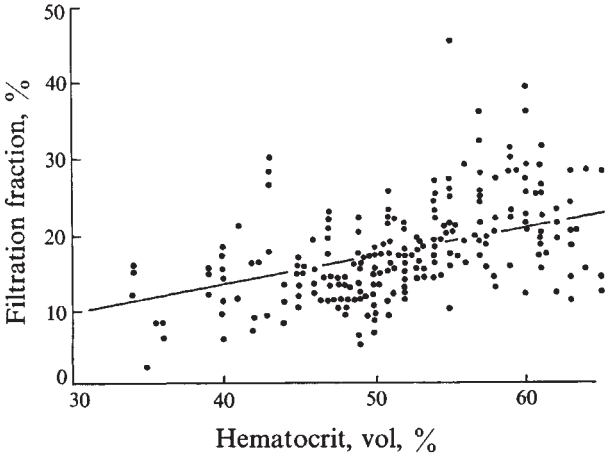

Fig. 3. Correlation between hematocrit and filtration fraction.

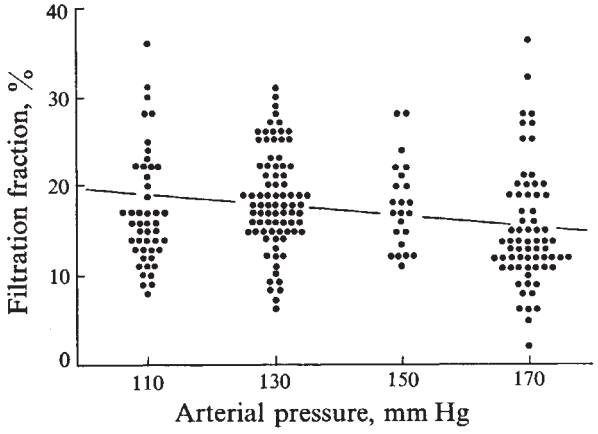

Fig. 4. Correlation between arterial pressure and filtration fraction.

of H (line 34); on the contrary, a strong negative correlation was observed between H and RPF (line 35), and this correlation was totally independent of AP (line 36). The result was a strongly positive correlation between FF and H (line 37 and Fig. 3), independent of AP (line 38). PGPP increased with hematocrit (line 41), also independent of AP (line 42), but more than should have been expected from the increase of FF. PGPP was strongly related to PP (line 40), and PP to H (line 39), the differences of H between the blood donors depending partly on overall hemodilution or hemoconcentration. However, the positive relationship between PGPP and H was still very significant after the elimination of AP and PP (line 43), as should have been expected from the correlation between FF and H mentioned above. Thus, the modulation of NaE by H could be related to some extent to the changes in FF and PGPP, but not entirely; the correlation between NaE and H was still very significant after the elimination of PGPP. The changes in total renal plasma flow related to hematocrit also appeared partially responsible for the control of NaE, further elimination of renal plasma flow reducing the strength of the correlation (line 31, $X^2=2.9$, $2P=0.05$). Final correlation after removal of AP, PGPP and RPF was still significant (line 31); other parameters, still undefined, appear therefore to account for the relationship between NaE and H.

A weak negative correlation was found between H and PK (line 33). Nevertheless, further elimination of the variable represented by PK did not change the relationship between NaE and H significantly (line 32).

Fractional sodium excretion and arterial pressure (Table 2). High AP resulted in high NaE (line 37). RPF increased significantly with AP (line 46); this increase, as judged from the regression equation, is moderate, as should be expected because of autoregulatory mechanisms. GFR increased slightly more (line 45), resulting in a weak negative correlation between FF and AP (line 47 and Fig. 4).

In the experiments performed at high arterial pressure, PP was moderately increased (line 51); this represented an experimental artefact: the higher urine output at high arterial pressure resulted in some degree of concentration of the perfusing blood, and the replacement of urine occurred only at the end of each collection period while the blood samples were drawn in the midst of these periods. As a consequence, PGPP increased with AP (line 55). The results demonstrate that the changes in FF and PGPP play a minor role in "pressure natriuresis" although there is a weak negative correlation between PGPP and AP after elimination of the artefactual increase of PP (line 56). That PP, GFR, and RPF (and therefore FF and PGPP) are of little influence on "pressure natriuresis" is further demonstrated by the fact that successive elimination of the variables PP, GFR, and RPF did not induce any change in the correlation between NaE and AP (lines 47–49).

A negative correlation between PK and AP (line 58) can be ascribed to increased urinary losses of potassium during perfusion at high pressure [11]. Removal of the variable PK does not alter the correlation between NaE and AP significantly (line 50).

Fractional sodium excretion and plasma potassium concentration (Table 2). A positive correlation between NaE and PK was evidenced (line 59), thus confirming previous results [12]. This correlation was not sup-

pressed by elimination of the variables AP and PGPP (lines 60–62) to which PK appeared to be related (lines 58 and 6).

Discussion

Postglomerular plasma protein concentration. The quantitative relationship between PGPP and overall fractional reabsorption of sodium can be evaluated on the basis of the present experiments. According to the regression coefficient (Table 2, line 2), an increase of 10 g/liter of PGPP results in an increase of tubular reabsorption of $0.78 \pm 0.37\%$ of filtered load. In order to compare this value with other experimental results involving supplementation with serum albumin, thus changing the albumin-globulin ratio, plasma oncotic pressures have been calculated according to Keys' formula [37]. If the present results are expressed in terms of the relationship between overall fractional sodium reabsorption and postglomerular oncotic pressure, it is found that an increase of the oncotic pressure of 150 mm H_2O induces an increase of sodium reabsorption corresponding to $3.3 \pm 1.5\%$ of the filtered load. From our previous experiments on paired isolated kidneys involving unilateral correction of plasma oncotic pressure by serum albumin after *in vitro* saline loading [13], the average calculated value is 5.6%. From the experiments performed on the whole dog by Kramer, Boylan and Keck [28], we computed a value of 4%. On the basis of a systematic study on the whole dog, Vereerstraeten [29] and Vereerstraeten and Toussaint [30] found a value of 7.5%. While it is impossible to ascribe statistical significance to the differences between these values, it does appear clear that the results are of the same order of magnitude, whether they are obtained from the whole animal or from the isolated organ. The importance of postglomerular oncotic pressure for the control of overall tubular reabsorption thus receives further confirmation.

Glomerular filtration rate. Overall fractional sodium excretion increased moderately with filtration rate; according to the regression equation (Table 2, line 7) a 10 ml variation of GFR induced a variation of overall tubular reabsorption of $0.67 \pm 0.39\%$ of the filtered load. However, the correlation is much weaker after elimination of the influence of AP (Table 2, line 8), and it disappears totally after elimination of RPF (Table 2, line 9). It is well known that GFR and RPF are normally inter-related, a fact which was confirmed by the present results (Table 2, lines 19 and 20). It appears that the moderate increment of NaE related to an increment of GFR is primarily due to the concomitant increase of RPF via a mechanism that will be discussed later.

Renal plasma flow. The influence of renal plasma flow on sodium reabsorption can be ascribed partly to its influence on FF (Table 2, lines 22–24) and therefore on PGPP (Table 2, lines 25–27). However, the correlation remains significant after successive elimination of PGPP, AP, and GFR (Table 2, lines 15–17); the natriuresis caused by increased renal plasma flow cannot therefore be explained completely by the concomitant variations of PGPP and total GFR. According to the regression equation (Table 2, line 14), a variation of 1 ml of RPF corresponds to a variation of NaE of $1.075 \pm 0.32\%$ of filtered load ($1.075 \pm 0.74\%$ after elimination of the variables AP, GFR, and PGPP).

The negative correlation between FF and RPF means that the changes in total GFR are not proportional to the changes of total RPF, suggesting that in the present experimental conditions, postglomerular vascular resistance plays, together with preglomerular arterial tone, an important role in the modulation of effective filtration pressure. That PGPP alone cannot account exclusively for the influence of RPF on natriuresis would be expected in view of previous experimental findings. Among other mechanisms, consideration must be given to washout of solutes in the interstitium resulting in greater delivery from the ascending limb of Henle's loop [5], as well as an intrarenal redistribution of blood flow and glomerular filtration [4, 22]. Moreover, it appears from several studies on the influence of various vasodilating drugs [5, 40–43] that these pharmacological agents do not modulate sodium excretion by only one identical mechanism.

Hematocrit. The natriuretic response to changes of hematocrit involves several other intrarenal factors as well. One of them appears to be the concomitant changes in FF and PGPP; this finding is in good agreement with the results of Nashat et al [11] and of Schrier and Earley [18] on the whole dog, and of Brenner and Galla [2] in the rat, as is the independence of glomerular filtration from hematocrit [11]. According to Nashat et al [10], cortical blood flow is not modified by the changes of packed red cell volume [10] while medullary flow changes inversely; special attention is paid to the changes in medullary osmotic gradient as the consequence of hemodynamic factors [11]. A mechanism such as described by these authors

might be responsible, together with the proximal effect of postglomerular peritubular oncotic pressure, for the variations not only of urine concentration, but also of sodium excretion related to hematocrit.

The regression equation indicates that a 10% increase of hematocrit corresponds to a decrease of $1.9 \pm 0.6\%$ in fractional sodium excretion ($1.9 \pm 0.9\%$ after elimination of the variables AP, PGPP, RPF, and PK).

Arterial pressure. According to the regression equation (Table 2, line 44), an increment of arterial pressure of 10 mm Hg induces an increment of $0.8 \pm 0.2\%$ in fractional excretion of filtered sodium load. The results demonstrate clearly that the increase of NaE with arterial pressure does not depend on GFR and RPF, and that variations of FF are of minor importance. These data are in good agreement with the fact that because of autoregulation, there is little change of either GFR or RPF over a wide range of arterial pressure [6, 19, 21]. Moreover, AP does not interfere significantly with the correlations between PGPP and RPF (Table 2, lines 25 and 26), RPF and H (Table 2, lines 35 and 36), FF and H (Table 2, lines 37 and 38), PGPP and H (Table 2, lines 41 and 42). According to the work of Thurau and Deetjen [21], the mechanism of "pressure natriuresis" is related to changes in medullary blood flow (which is not autoregulated) which induce variations of the osmotic cortico-papillary gradient. Several workers [6, 19, 44, 45] point to the same explanation based on an impairment of sodium transport in the ascending limb of Henle's loop. MacDonald and de Wardener [7], investigating the relationship between arterial pressure and saline natriuresis, observed a relationship between sodium excretion and arterial pressure, and an inverse correlation between natriuresis and the fall in plasma protein concentration; these authors suggested that the exaggerated sodium excretion of hypertensive patients given saline intravenously might be partly due to the direct effect of arterial hypertension. The problem of the interaction between "pressure natriuresis" and "saline natriuresis" has also been investigated by Bank et al. [1] and by Craig et al. [3]. In a previous work [17] we have found that the isolated dog kidney responds to increased perfusion pressure with a natriuresis, and that the further addition of saline to the perfusing blood results in a more rapid quantitative excretion of the extra saline load than that observed at a normal perfusion pressure. These experiments demonstrated that the autonomous response of the kidney to both hypertension and blood dilution was additive, one common mechanism possibly being represented by changes in the medullary circulation due to the combined effect of blood dilution and arterial hypertension.

Plasma potassium concentration. In previous experiments on paired isolated dog kidneys, we have found that the increase of sodium excretion which follows the *in vitro* addition of saline to the blood was partly corrected by subsequent restoration of plasma potassium concentration in the absence of changes of filtered sodium load; restoration of the plasma potassium concentration thus improved the tubular reabsorption of sodium [12]. From these previous experimental results [12], it can be computed that a decrement of 1 mEq/liter of plasma potassium results in an increment of NaE corresponding to $1.0 \pm 0.4\%$ of filtered load. From the regression coefficient obtained in the present study, a value of 1.23 ± 0.57 is computed (1.23 ± 0.76 after removal of AP and PGPP); both values are identical. The influence of potassium concentration on tubular sodium reabsorption has also been observed by Vogel and Tervooren [46] in amphibian kidneys perfused with potassium-free solutions and by Maude [47] during stop-flow microperfusion of proximal tubules in rat kidney cortex slices. A role of potassium in active transport of sodium by the toad bladder has been evidenced by Essig and Leaf [48]. However, opposite results have been presented by various authors in the more complex conditions occurring in the whole animal [49, 50, 51, 52]. It is not possible so far to explain these discrepancies. The influence of plasma potassium concentration on sodium handling by the tubules is of considerable pathophysiological interest; however, plasma potassium concentration is not likely to play a major role in the induction of saline diuresis, since its decrease after saline infusion is no more than moderate [29].

General. These results demonstrate the influence of blood dilution or concentration on sodium excretion as modulated by tubular reabsorption of the filtered sodium load. They provide further evidence of the role of postglomerular plasma protein concentration depending on both plasma dilution and filtration fraction. After saline infusion, the fall of plasma protein concentration due to blood dilution is further enhanced by the concomitant decrease of filtration fraction. The experiments demonstrate however that other parameters related to blood dilution, such as changes of hematocrit and renal plasma flow, also

interfere with the overall fractional reabsorption of sodium, and that their influence does not depend entirely on changes of the postglomerular plasma protein concentration.

The considerable amplitude of the modulation of sodium excretion by dilution parameters of the blood and their possible cumulative effect helps to understand the sensitivity and the accuracy of the renal response to blood dilution as demonstrated by the quantitative excretion of a saline load when added *in vitro* to the perfusing blood [16]; the kidney is adjusted, in the sense of a stable equilibrium, to a definite level of blood concentration. Moreover, it is obvious that the various physical and hormonal factors may offset the influence of each other, thus avoiding permanent sodium losses in chronic pathological conditions involving anemia, hypoproteinemia or arterial hypertension [14].

Acknowledgements

This work has been performed with the help of the Fonds National de la Recherche Scientifique of Belgium.

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References

1. Bank, N., Koch, K. M., Aynedjian, H. S., and Aras, M.: Effects of changes in renal perfusion pressure on the suppression of proximal sodium reabsorption due to saline loading. J. Clin. Invest. *48:* 271–283, 1969.
2. Brenner, B. M., and Galla, J. H.: Influence of postglomerular hematocrit and protein concentration on rat nephron fluid transfer. Am. J. Physiol. *220:* 148–161, 1971.
3. Craig, C. M., Mills, I. H., Osbaldiston, G. W., and Wise, B. L.: The effect of change of perfusion pressure and haematocrit in the perfused isolated dog kidney. J. Physiol. (Lond.) *186:* 113, 1966.
4. Earley, L. E., and Friedler, R. M.: Changes in renal blood flow and possibly the intrarenal distribution of blood during the natriuresis accompanying saline loading in the dog. J. Clin. Invest. *44:* 929–941, 1965.
5. Earley, L. E., and Friedler, R. M.: Studies on the mechanism of natriuresis accompanying increased renal blood flow and its role in the renal response to extracellular volume expansion. J. Clin. Invest. *44:* 1857–1865, 1965.
6. Lowitz, H. D., Stumpe, K. O., and Ochwadt, B.: Natrium- und Wasserresorption in den verschiedenen Abschnitten des Nephrons beim experimentellen renalen Hochdruck der Ratte. Pflügers Arch. ges. Physiol. *304:* 322–325, 1968.
7. MacDonald, S. J., and de Wardener, H. E.: The relationship between the renal arterial perfusion pressure and the increase in sodium excretion which occurs during an infusion of saline. Nephron *2:* 1–14, 1965.
8. Martino, J. A., and Earley, L. E.: Demonstration of a role of physical factors as determinants of the natriuretic response to volume expansion. J. Clin. Invest. *46:* 1964–1978, 1967.
9. Nashat, F. S., and Portal, R. W.: The effects of changes in haematocrit on renal function. J. Physiol. *193:* 513–522, 1967.
10. Nashat, F. S., Scholefield, F. R., Tappin, J. W., and Wilcox, C. S.: The effects of changes in haematocrit on blood flow through the different regions of the kidney in anesthetized dogs. J. Physiol. *201:* 639–656, 1969.
11. Nashat, F. S., Scholefield, F. R., Tappin, J. W., and Wilcox, C. S.: The effect of acute changes in haematocrit in the anaesthetized dog on the volume and character of the urine. J. Physiol. *205:* 305–316, 1969.
12. Nizet, A.: Control by plasma potassium concentration of sodium excretion by isolated perfused dog kidney. Pflügers Arch. ges. Physiol. *297:* 162–165, 1967.
13. Nizet, A.: Influence of serum albumin and dextran on sodium and water excretion by isolated dog kidney. Pflügers Arch. ges. Physiol. *301:* 7–15, 1968.
14. Nizet, A.: The role of autonomous renal mechanisms in the control of sodium and water balance. Intern. Urology and Nephrol. *1:* 361–371, 1969.
15. Nizet, A., Cuypers, Y., Deetjen, P., and Kramer, K.: Functional capacity of the isolated perfused dog kidney. Pflügers Arch. ges. Physiol. *296:* 179–195, 1967.
16. Nizet, A., Godon, J. P., and Mahieu, P.: Quantitative excretion of water and sodium load by isolated dog kidney: Autonomous renal response to blood dilution factors. Pflügers Arch. ges. Physiol. *304:* 30–45, 1968.
17. Nizet, A., Godon, J. P., Mahieu, P., and Kramer, K.: Autonomous response of dog kidney to increased blood pressures with and without saline loading. Pflügers Arch. ges. Physiol. *313:* 245–251, 1969.
18. Schrier, R. W., and Earley, L. F.: Effects of hematocrit on renal hemodynamics and sodium excretion in hydropenic and volume-expanded dogs. J. Clin. Invest. *49:* 1656–1667, 1970.

19. Selkurt, E. E., Womack, I., and Dailey, W. N.: Mechanism of natriuresis and diuresis during elevated renal arterial pressure. Am. J. Physiol. *209:* 95–99, 1965.

20. Shuster, A., Alexander, E. A., Lalone, R. C., and Levinsky, N. G.: Renal blood flow, sodium excretion and concentrating ability during saline infusion. Am. J. Physiol. *211:* 1181–1186, 1966.

21. Thurau, K., and Deetjen, P.: Die Diurese bei arteriellen Drucksteigerungen. Pflügers Arch. ges. Physiol. *274:* 567–580, 1962.

22. Hollenberg, N. K., Epstein, M., Guttman, R., Basch, R. I., and Merrill, J. P.: The relationship between intrarenal distribution of blood flow and sodium balance in normal man. J. Clin. Invest. *47:* 48a, 1968.

23. Fisher, R. D., Grundfeld, J. P., and Barger, A. C.: Intrarenal distribution of blood flow in diabetes insipidus: Role of ADH. Am. J. Physiol. *219:* 1348–1358, 1970.

24. Horster, M., and Thurau, K.: Micropuncture studies on the filtration rate of single superficial and juxtamedullary glomeruli in the rat kidney. Pflügers Arch. ges. Physiol. *301:* 162–181, 1968.

25. Mandin, H., Israelit, A. H., Rector, F. C., Jr., and Seldin, D. W.: Effect of saline infusion on intrarenal distribution of glomerular filtrate and proximal reabsorption in the dog. J. Clin. Invest. *50:* 514–522, 1971.

26. Brenner, B. M., Falchuk, K. H., Keimowitz, R. I., and Berliner, R. W.: The relationship between peritubular capillary protein concentration and fluid reabsorption by the renal proximal tubule. J. Clin. Invest. *48:* 1519–1521, 1969.

27. Brenner, B. M., and Troy, J. L.: Postglomerular vascular protein concentration: Evidence for a causal role in governing fluid reabsorption and glomerulotubular balance by the renal proximal tubule. J. Clin. Invest. *50:* 336–349, 1971.

28. Kramer, K., Boylan, J. W., and Keck, W.: Regulation of total body sodium in the mammalian organism. Nephron *6:* 379–387, 1969.

29. Vereerstraeten, P.: L'intervention de la pression oncotique péritubulaire dans la réabsorption de sodium par le rein du chien. Acta Clin. Belg., suppl. *5*, pp. 3–144, 1969.

30. Vereerstraeten, P., and Toussaint, C.: Mécanismes de l'excrétion du sodium par le rein du chien. Nephron *7:* 15–36, 1970.

31. Vogel, G.: Über die Wirkung transzellulärer osmotischer Gradiente auf die tubulären Transporte von Wasser, Na + und osmotisch aktivem Material. Pflügers Arch. ges. Physiol. *297:* 1255, 1967.

32. Arrizurieta-Muchnik, E. E., Lassiter, W. E., Lipham, E. M., and Gottschalk, C. W.: Micropuncture study of glomerulotubular balance in the rat kidney. Nephron *6:* 418–436, 1969.

33. Lewy, J. E., and Windhager, E. E.: Peritubular control of proximal tubular fluid reabsorption in the rat kidney. Am. J. Physiol. *214:* 943–954, 1968.

34. Windhager, E. E., Levy, J. E., and Spitzer, A.: Intrarenal control of proximal tubular reabsorption of sodium and water. Nephron *6:* 247–259, 1969.

35. Bresler, E. H.: The problem of the volume component on body fluid homeostasis. Am. J. Med. Sci. *232:* 93–104, 1956.

36. Cuypers, Y., Nizet, A., and Baerten, A.: Technique pour la perfusion de reins de chien avec du sang hépariné. Arch. Int. Physiol. Biochim. *72:* 245–255, 1964.

37. Keys, A.: The study of colloidal dimensions, thermodynamic activity and the mean molecular weight of the mixed protein in blood serum. J. Physiol. Chem. *42:* 11–20, 1938.

38. Schwartz, D.: Méthodes statistiques à l'usage des médecins et des biologistes, Paris, Flammarion, 1963.

39. Quenouille, M. H., Introductory Statistics, Oxford, Pergamon Press, 1966.

40. Dirks, J. H., and Seely, J. F.: Micropuncture studies on the effect of vasodilators on proximal tubule reabsorption in the dog. Clin. Res. *15:* 478, 1967.

41. Harsing, L., Köver, G., Malyusz, M., Toth, G., und Harza, T.: Die Wirkung von vasodilatatorischen Substanzen (Papaverin, Acetylcholin) auf die Nierenfunktion. Pflügers Arch. ges. Physiol. *281:* 346–355, 1964.

42. Heller, J., and Novakova, A.: Proximal tubular reabsorption during renal vasodilation and increased arterial blood pressure in saline loaded rats. Pflügers Arch. ges. Physiol. *309:* 250–265, 1969.

43. Vander, A. J.: Effects of acetylcholine, atropine and physostigmine on renal function in the dog. Am. J. Physiol. *206:* 492–498, 1964.

44. Bank, N., Aynedjian, H. S., Bansal, V. K., and Goldman, D. M.: The effect of acute hypertension on sodium transport by the distal nephron. J. Clin. Invest. *48:* 5a, 1969.

45. Buckalew, V. A., Jr., Puschett, J. B., Kintzel, J. E., and Goldberg, M.: Mechanism of exaggerated natriuresis in hypertensive man: Impaired sodium transport in the loop of Henle. J. Clin. Invest. *48:* 1007–1016, 1969.

46. Vogel, G., and Tervooren, U.: Die Bedeutung von Kalium für die renal-tubulären Transporte von Natrium und Calcium und für die Wirkung kardiotonischer Steroide. Pflügers Arch. ges. Physiol., *284:* 103–107, 1965.

47. Maude, D. L.: Stop-flow microperfusion of proximal tubules in rat kidney cortex slices. Am. J. Physiol. *214:* 1315–1321, 1968.

48. Essig, A., and Leaf, A.: The role of potassium in active transport of sodium by the toad bladder. J. Gen. Physiol. *46:* 505–515, 1963.

49. Bank, N., and Aynedjian, H. S.: A micropuncture study of the renal concentrating defect of potassium depletion. Am. J. Physiol. *206:* 1347–1354, 1964.

50. Jones, N. F., Mylle, M., and Gottschalk, C. W.: Renal tubular microinjection studies in normal and potassium depleted rats. Clin. Sci. *29:* 261–276, 1965.

51. Dluhy, R. G., Wolf, G. L., Christlieb, A. R., Hickler, R. B., and Lauler, D. P.: Suppression of plasma renin activity by acute potassium chloride loading. Circulation, 37–38, Suppl. *6:* 1–66, 1968.

52. Vander, A. J.: Direct effects of potassium on renin secretion and renal function. Am. J. Physiol. *219:* 455–459, 1970.