State-Dependent Expression of Pressure Diuresis in Conscious Rats (44522)

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Abstract. **In 1967, Guyton and Coleman modeled pressure diuresis as the underlying, essential, long-term mechanism that regulates arterial pressure when sodium intake changes. Other mechanisms that influence renal function interact with pressure diuresis to achieve sodium balance and determine the blood pressure. Increases in sodium intake suppress sodium conserving mechanisms and activate natriuretic mechanisms; decreases in sodium intake have the opposite effect. If the Guyton-Coleman model is correct, then pressure diuresis should be more readily detected in animals on a high-salt diet than in animals on a low-salt diet. We measured spontaneous changes in arterial pressure and urine flow in conscious rats fed low-salt (0.4% NaCl) and high-salt (8.0% NaCl) chow. For 10 rats fed a high-salt diet, arterial pressure and urine flow were positively correlated in 19 of 32 (59%) trials. In 10 rats fed a low-salt diet, a positive correlation was observed in 10 of 33 (30%) trials. Chi-square analysis revealed that differences in Na^+ content of the diet were significantly associated with the probability of a positive relationship between blood pressure and urine flow. These results support the hypothesis that the expression of pressure diuresis across time is dependent on the state of sodium balance.**

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The direct influence of arterial pressure on urine flow is known as pressure diuresis (1), a phenomenon probably first described by Ludwig in 1843 (2). In 1967, Guyton and Coleman (3) created a computer model of the circulation to examine arterial pressure control. Pressure diuresis was placed at the center of their model for the regulation of steady-state arterial blood pressure. Their model predicted that pressure diuresis is essential in pressure regulation by the following sequence: i) an increase in arterial pressure produces an increase in urine flow; and ii) the resultant loss of water and salt reduces the blood volume and thus restores arterial pressure. The Guyton-Coleman model has endured because numerous experiments support its validity (4–12) and because it is difficult to find data or design experiments that disprove its essential elements.

Pressure diuresis is intrinsic to the kidney and can be observed in the functionally isolated kidney (9). However, in the intact organism, pressure diuresis acts in concert with all the other mechanisms that restore sodium balance in response to changes in dietary sodium content. Thus the activity of the pressure diuresis mechanism in the intact organism is masked by changes, for example, in autonomic activity (13) that may act on the kidney both *via* influencing renal hemodynamics and *via* changes in renin secretion. Therefore, in the intact organism, the expression of pressure diuresis might be expected to be state-dependent. That is, conditions that suppress sodium-conserving mechanisms (for example, an increase in Na^+ intake) should expose the intrinsic effect of arterial pressure on urine flow, and conditions that increase the activity of sodium-conserving mechanisms should have the opposite effect. If this hypothesis is correct, then a high-salt diet should increase the relative amount of time that spontaneous pressure diuresis occurs unopposed by sodium conserving mechanisms, because a high-salt diet decreases the operation of antidiuretic mechanisms that act superimposed on pressure diuresis.

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That is, changes in salt-retaining mechanisms accompanying a high-salt diet should cause the influence of spontaneous changes in arterial pressure on urine flow to be expressed more frequently and therefore to be more easily detected. Conversely, decreasing dietary salt intake should increase the activity of antidiuretic mechanisms and decrease the activity of diuretic mechanisms, making spontaneous pressure diuresis more difficult to detect. The purpose of this study was to evaluate the contribution of the short-term pressure diuresis mechanism to the regulation of urine formation in the intact conscious rat ingesting a high- or low-sodium diet. For this purpose, we used a recently developed model for determining the effects of spontaneous changes in arterial blood pressure on urine flow in conscious, unrestrained rats (14) and tested the effects of ingesting a high- or low-sodium diet on spontaneous pressure diuresis.

Materials and Methods

Animal Preparation. All surgical and experimental procedures in this study were in accordance with U.S. animal protection laws and were approved by the Institutional Animal Care and Use Committee of the Medical College of Ohio (Toledo, OH). Twenty male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) with body weights between 400 and 600 g were randomly divided into two experimental groups. Ten animals were placed on high-salt chow (8% NaCl; Teklad, Harlan Industries, Madison WI) (high-salt group). Ten animals were fed low-salt chow (0.4% NaCl; Teklad) (low-salt group). The animals received water *ad libitum* and were maintained on a 12:12-hr light:dark cycle.

After 2 weeks on the assigned diets, each rat was anesthetized with a mixture of ketamine (Aveco Co., Inc., Fort Dodge, IA; 100 mg/kg ip) and xylazine (Mobay Corp., Shawnee, KS; 20 mg/kg ip). Normal body temperature was maintained by placing the rat on a heating pad. A midabdominal incision was made, and the ureters were exposed. Catheters (0.01" ID × 0.03" OD Tygon tubing; Norton Plastics and Synthetics, Akron, OH) were inserted into the ureters with the tips placed just distal to the renal pelvis. The catheters were secured to the ureters with 3–0 silk ties and to the underlying psoas muscle with 5–0 silk sutures. A 7-cm trocar, fashioned from 16-gauge stainless steel tubing, was used to tunnel the ureteral catheters through the dorsal wall of the abdomen. The catheters were then tunneled subcutaneously to exit separately at the base of the tail. The abdominal incision was closed with 5–0 and 3–0 silk interrupted sutures. Each exteriorized end of the ureteral catheter was inserted into a 2-cm section of 18-gauge stainless steel tubing. To stabilize the catheters, the sections of steel tubing were inserted ≈ 1 cm underneath the skin, and the catheters were secured to the steel tubing with Super Glue (alpha cyanoacrylate; International Adhesives Corp., Pembroke, FL). The exteriorized portions of the steel tubing were secured to the skin of the tail with cranioplastic cement (Plastics One, Roanoke, VA) such that ≈ 1 cm of the steel tubing protruded from the base of the tail. The ends of the exteriorized catheters were cut flush with the tip of the steel tubing.

The left femoral artery was isolated and cannulated with a catheter that was constructed from a 6-cm segment of Teflon tubing (0.015" ID; Small Parts, Inc., Miami, FL) inserted into a 25-cm segment of Tygon tubing (0.02" ID). The catheter was secured to the artery with 3–0 silk ties, tunneled dorsally beneath the animal's skin, and exited at the nape of its neck. The arterial catheter was secured to the animal's skin with Super Glue. Following surgery, the animal was returned to its home cage, provided with rat chow at the appropriate salt content and water *ad libitum*, and weighed daily. All animals were given at least 3 days to recover from surgery before being studied.

Experimental Setup. During the experiments, the rats were housed individually in a polycarbonate cage identical in size and shape to their home cage. A siphoning system and an analytical balance were employed to continuously collect and weigh the urine produced throughout the experiment (15). In brief, Tygon extension tubing was connected to the ureteral catheters to establish a continuous column of fluid from the urine in each ureteral catheter to a collection reservoir on the pan of the balance. The extension tubing exited the cage *via* a 38 × 14-cm, T-shaped, 5-mm wide slot in the floor of the cage. The center of the "T" was at the center of the floor, and each arm reached close to the side of the cage. By this arrangement, movement of the animals within the cage was minimally restricted during data collection. Water was available throughout the duration of the recording period.

Experimental Protocol. All recording sessions were conducted in a quiet, well-lighted, 22°C room during the animals' light cycle (between 9 AM and 3 PM). This period was selected so that animals would be relatively quiet during the recording sessions. The rats were prepared for continuous recording of arterial pressure and urine flow, and a recording of approximately 2 hr duration was made from each animal on a daily basis as long as the animal remained healthy, and the catheters remained patent. The goal was to obtain uninterrupted recording of spontaneous changes in arterial pressure and urine flow from healthy, relatively undisturbed animals. Therefore, changes in body weight, normal grooming behavior, and normal arterial pressure were criteria used as indications of possible deterioration in the animal's health. Any animal whose health was questionable was removed from the study. The recording session was interrupted only if the arterial catheter extension tubing became excessively tangled or crimped, or if the animal bit through the arterial or ureteral tubing. The situation was corrected immediately, and the recording session then resumed. If the recording session had to be interrupted more than three times within a 30-min period, the session was terminated. Usable sections of data from sessions that were terminated early were included in analysis as

long as data collection was able to proceed for at least 20 min without interruption. Following the recording session, the animal was returned to its home cage. After completing the study, all rats were euthanized with 150 mg/kg ip sodium pentobarbital.

Measurements. The arterial catheter was connected to a Gould-Statham P23Db pressure transducer (Gould, Medical Products Division, Oxnard, CA), and the signal was amplified with a SensorMedics Dynograph Recorder R611 (Anaheim, CA). Mean arterial pressure was obtained by damping the analog pressure signal electronically (time constant = 0.78 sec). The voltage output was led to a Tektronix 5031 dual beam oscilloscope (Tektronix, Inc., Beaverton, OR) for display and to a DT 2801 analog-to-digital converter (Data Translation, Marlboro, MA) housed within an AST 386/33 computer (model 5 V, AST Research, Inc., Taiwan, R.O.C.). The damped arterial pressure signal was digitally sampled at 20 Hz and then averaged every 10 sec to obtain a 0.1-Hz signal. Communication between the analytical balance and the computer was established *via* an RS232 data interface. Data were collected to an ASCII file (Po-Ne-Mah Digital Acquisition Analysis and Archive Systems, Po-Ne-Mah, Inc., Storrs, CT) at 0.1 Hz. Urine flow was calculated from the change in weight of the urine reservoir every 10 sec and was expressed in µl/min. These paired arterial pressure and urine flow measurements, which covered the same 10-sec intervals, were used for data analysis.

Data Analysis. The data were examined, and obviously aberrant values were discarded. Aberrant values were defined as those that occurred sporadically and differed by more than 50% from preceding or following values. Observation suggested that these aberrant values arose from rapid positional changes by the animal that distorted the arterial and ureteral catheters. These discarded data represented less than 2% of the total observations. A linear regression analysis of urine flow on arterial pressure was performed on the data from each recording session. The slope of the regression line, the correlation coefficient (R), and the significance of the slope were determined. In addition, the Chi-squared statistic was calculated to compare the distribution of positive, nonsignificant, and negative slopes of the regression lines in the high-salt versus low-salt groups. Data were expressed as the mean ± SEM. Significance was ascribed if $P < 0.05$.

Results

The spontaneous changes with time in urine flow and arterial blood pressure during a 104-min recording session in a rat on the high-salt diet are shown in Figure 1. These same data are presented in Figure 2 showing the correlation between urine flow and blood pressure. For this session, there was a significant positive correlation between urine flow and arterial blood pressure ($P < 0.001$, R = 0.44). Sixty-five recording sessions were made in all; 32 from the 10 rats in the high-salt group and 33 from the 10 rats in the

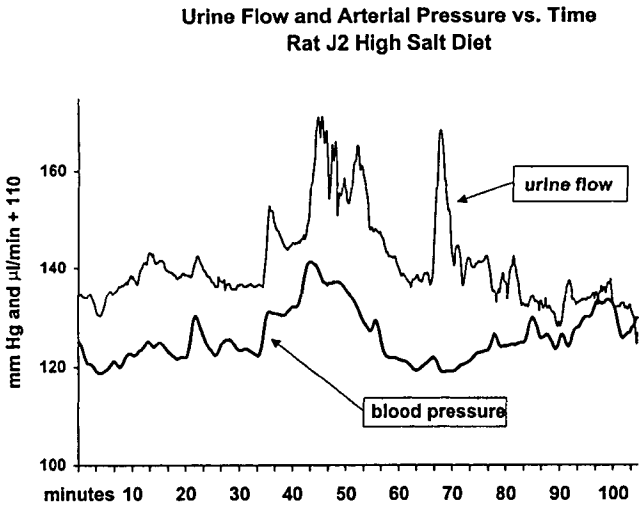


Figure 1. A rat on the high-salt diet: spontaneous changes in urine flow and blood pressure. Results of a single recording session. One minute moving averages of urine flow and blood pressure are shown. To facilitate comparison between the blood pressure and urine flow, 110 has been added to the urine flow values.

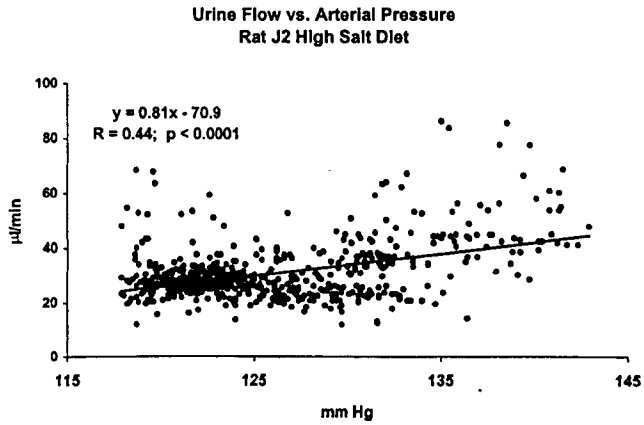


Figure 2. A rat on the high-salt diet: correlation between urine flow and blood pressure. Data are for the same recording session as shown in Figure 1. The 10-sec average values for blood pressure and urine flow are graphed.

low-salt group. Each rat participated in from one to six of these sessions. Of these 65 sessions, 11 ended prematurely due to the rat repeatedly chewing through its ureteral catheters. The briefest recording session was 45 min long. Table I compares the mean duration of recording sessions, body weight (at the time of surgery), mean of all the arterial pressure values, and urine flow for the two groups of rats. As can be seen in the table, the only significant difference between the groups was for body weight. After 2 weeks on their respective diets, the high-salt group was ≈ 10% lighter than the low-salt group. This difference in body weight may be due to differences in palatability of the two diets (16). For each rat in each recording session, the linear regression of urine flow on arterial pressure was calculated. For rats on high-salt chow, 19 slopes of the linear regressions showed a significant positive correlation, 6 were positive but not significant, and 7 of the slopes were negative (Table II). In

Table I. Comparison Between High and Low Salt Groups

	High salt (8% NaCl)	Low salt (0.4% NaCl)	Probability
Number of sessions	32	33	
Mean duration of sessions, min	59.6 ± 33.7	64.2 ± 28.8	NS
Body weight, g	419 ± 3.59	466 ± 19.6	$P = 0.038$[a]
Arterial pressure, mm Hg	123 ± 1.75	124 ± 1.54	NS
Urine flow, µl/min	27.6 ± 2.22	30.1 ± 2.2	NS

[a] Two-tailed *t* test.

Table II. Slopes of Regression Lines Relating Urine Flow to Blood Pressure

High-Salt Chow			Low-Salt Chow		
Session	Slope	*P* Value	Session	Slope	*P* Value
D2	1.1	0.0001	D3	3.38	0.0001
J2	0.89	0.0001	G2	2.01	0.0001
C3	0.81	0.0001	C2	0.99	0.0001
D1	0.79	0.0001	F4	0.71	0.0001
J6	0.67	0.0001	B4	0.67	0.0011
F2	0.66	0.0006	D1	0.64	0.0009
A1	0.45	0.0126	E1	0.46	0.0001
B2	0.43	0.0001	A1	0.42	0.0005
C2	0.37	0.0001	F2	0.38	0.0001
H3	0.35	0.0001	I1	0.15	0.0001
A3	0.34	0.0001			
J1	0.34	0.0001	C1	0.24	0.0921
J5	0.3	0.0001	J1	0.14	0.0992
A4	0.27	0.0167	C3	0.08	0.4598
A2	0.26	0.0001	H2	0.08	0.5974
B1	0.22	0.0006	B1	0.02	0.6677
H4	0.22	0.0059	F3	0.02	0.7778
I3	0.15	0.0022			
I2	0.08	0.0001	B5	−0.09	0.2704
			B3	−0.14	0.5558
F1	0.43	0.0585	H5	−0.15	0.0628
G3	0.2	0.1768	A2	−0.16	0.1004
G1	0.2	0.1703	D2	−0.21	0.2738
J4	0.19	0.098	G1	−0.16	0.0058
E1	0.1	0.5183	C5	−0.28	0.0001
J3	0.01	0.8507	F1	−0.31	0.0001
			B2	−0.32	0.0212
I1	−0.26	0.0146	H3	−0.32	0.0024
C1	−0.28	0.0139	C4	−0.35	0.0001
H1	−0.46	0.0059	F5	−0.42	0.0001
F4	−0.81	0.0001	H4	−0.48	0.0001
H2	−0.97	0.0001	E2	−0.59	0.0001
F3	−1.13	0.0001	H1	−0.62	0.0001
G2	−1.43	0.0001	J2	−0.86	0.0001
			A3	−1.36	0.0001

Note. Data are separated by the sign of the slope.

contrast, for the rats on the low-salt chow, 10 slopes were significantly positive, 11 were either positive or negative but not statistically significant, and 12 were negatively correlated. This distribution of slopes between high- and low-salt groups was compared by Chi-square analysis; $\chi^2 = 10.0$, $0.001 < P < 0.005$. This significant difference in the distribution of slopes between the low- and high-salt groups, with more positive and significant slopes in the high-salt than the low-salt group, is consistent with the hypothesis that pressure diuresis is expressed to a greater extent in animals on a high-salt intake when antidiuretic mechanisms are suppressed and diuretic mechanisms activated. These observations are graphically depicted in Figure 3 (high-salt group) and Figure 4 (low-salt group), with the slope of the regression line drawn over the actual arterial pressure range for each individual animal in each recording session.

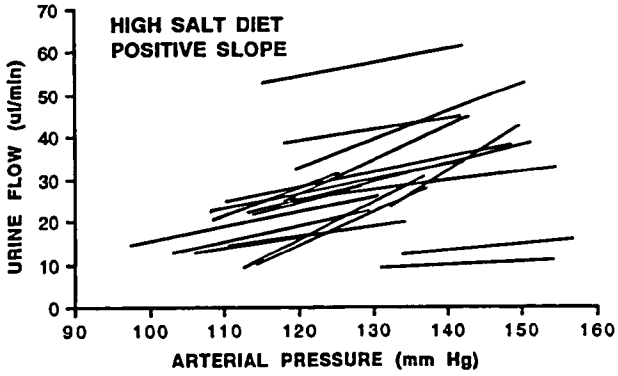
In contrast to the greater number of recording sessions with positive correlations in the rats on high-salt chow, the opposite was true for significant negative correlations. From the rats on low-salt chow, there were 12 recording sessions in which the slope was negative and significantly different from zero, compared with 7 sessions with negative slopes for the rats on high-salt chow (Table I).

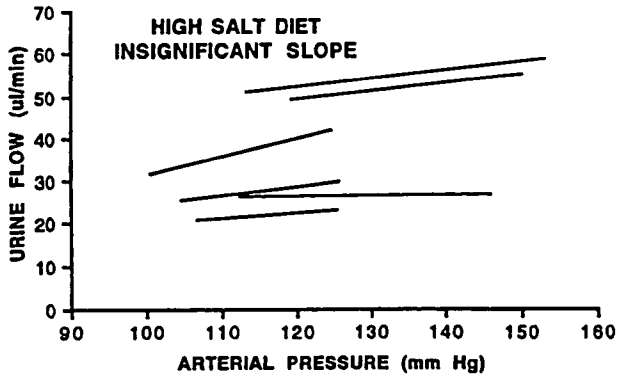
For rats on the high-salt diet, mean arterial pressure was higher ($P = 0.0112$) during recording sessions in which the slope of the regression line was significantly positive (126.8 ± 2.0 mmHg) than during sessions in which the slope was negative (116.4 ± 2.3 mmHg). However, urine flow was not significantly different between these two groups. For rats on the low-salt chow, the significance and direction of the slope of the regression line between arterial pressure and urine flow was not associated with any significant differences in mean arterial pressure or mean urine flow.

Discussion

This study is the first attempt to determine whether expression of pressure diuresis is dependent upon the state of sodium balance in conscious, unrestrained rats responding to spontaneous changes in blood pressure during normal operation of all of the mechanisms regulating renal function. The results supported the hypothesis that spontaneous pressure diuresis is expressed more frequently when sodium-conserving mechanisms are suppressed by high-salt intake than when these mechanisms are activated by low-salt intake. Rats on a high-salt diet displayed pressure diuresis as indicated by a positive correlation between urine flow and blood pressure in 19 out of 32 (59%) recording sessions. In contrast, rats on a low-salt diet displayed pressure diuresis in only 10 of 33 sessions (30%). (Although only urine flow was measured in this study, we assume that Na^+ excretion is proportional to urine flow during pressure diuresis (9, 10).)

Based on Guyton's concept that pressure diuresis is a long-term mechanism, the logical view has developed that changes in arterial pressure that result from changes in blood volume probably require hours or days to develop, so that pressure diuresis is postulated to act long-term rather than in response to moment-to-moment changes in arterial pressure. How may this view be reconciled with the present study showing significant correlations between moment-to-





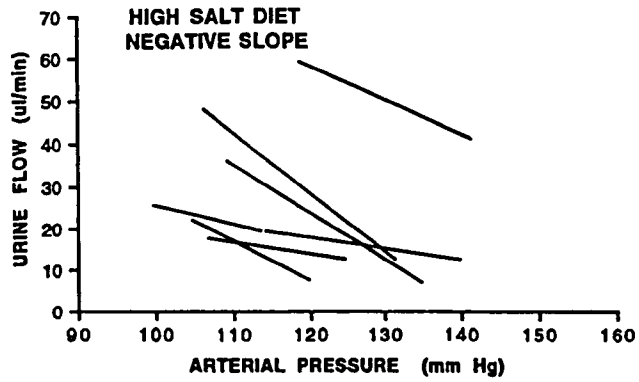
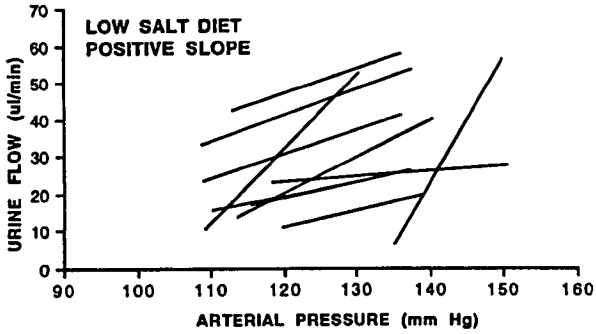
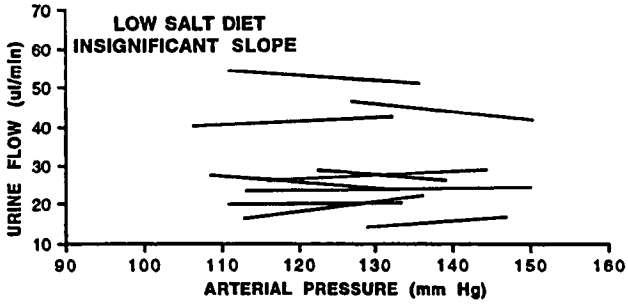


Figure 3. High-salt group: spontaneous blood pressure and urine flow. Each line represents the linear regression for one recording session comparing the urine flow for each 10-sec collection with the average damped arterial pressure signal for the same 10-sec interval (see Materials and Methods). The lines are extended over the actual arterial pressure range for the session. Results are sorted according to the sign of the slope.





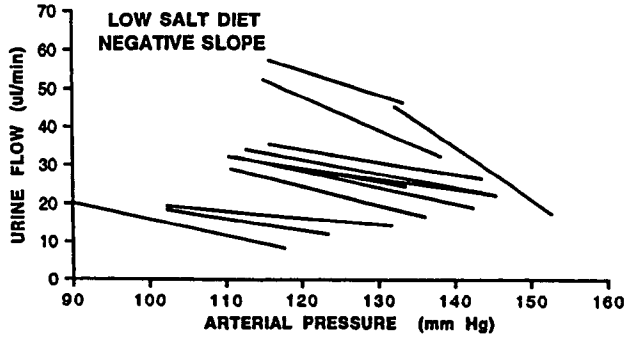


Figure 4. Low-salt group: spontaneous blood pressure and urine flow. Each line represents the linear regression for one recording session comparing the urine flow for each 10-sec collection with the average damped arterial pressure signal for the same 10-sec interval (see Materials and Methods). The lines are extended over the actual arterial pressure range for the session. Results are sorted according to the sign of the slope.

moment changes in arterial pressure and urine flow in relatively brief recordings from conscious animals?

For pressure diuresis to act on a moment-to-moment basis, changes in pressure must be accompanied promptly by changes in urine flow. Our laboratory previously demonstrated that induced changes in arterial pressure in the anesthetized rat are followed by parallel changes in urine flow within 6 sec (17). Additional studies in conscious rats also demonstrated moment-to-moment coupling between arterial pressure and urine flow (14). In conscious dogs, Brand *et al.* (13) demonstrated that changes in arterial pressure induced by behavioral arousal were correlated short-term with directionally similar changes in urine flow. Nafz *et al.* (2) showed reductions in urine flow in conscious dogs within 10 sec following a change in renal perfusion pressure. These results supported the hypothesis that pressure diuresis is sensitive to short-lived, moment-to-moment changes in arterial pressure that produce short-term but significant changes in salt and water excretion. According to this model, the long-term nature of the pressure diuresis

mechanism is presumably the cumulative summation of many short-term changes in urine flow influencing blood volume and thus arterial pressure.

Although pressure diuresis may act on a moment-to-moment basis, in the intact animal it also operates in concert with all the other mechanisms that induce changes in renal function in response to changes in dietary Na^+ intake. (For the sake of this discussion, we take "pressure diuresis" to mean the direct effect of arterial pressure on Na^+ excretion and urine flow as can occur, for example, in the functionally isolated kidney (9).) These mechanisms include the renin-angiotensin-aldosterone system, sympathetic effects on renal hemodynamic and tubular function, and urodilatin. The antinatriuretic effects of all of these mechanisms are suppressed by increased dietary Na^+ intake and activated by decreased sodium intake (18). Thus these mechanisms will act with varying time courses to oppose the expression of pressure diuresis when Na^+ intake is low, but will be suppressed and allow pressure diuresis to be detected when Na^+ intake is high. This model explains our observations that moment-to-moment spontaneous changes in pressure produce significant, parallel changes in urine flow more frequently in rats on a high-Na^+ intake than in rats on a low-Na^+ intake.

The extent to which the pressure diuresis mechanism is masked by other mechanisms may be estimated by comparing the slope of the isolated, intrinsic pressure diuresis mechanism to the slope of the relationship between arterial pressure and urine flow in the intact, conscious animal. We previously estimated that the slope of the isolated pressure diuresis mechanism in the rat kidney is 100 times greater than the slope of the arterial pressure-urine flow relationship in the conscious dog (9, 13). In the present study, the slope of the arterial pressure-urine flow relationship in intact rats on a high-salt diet was 0.00025 ml/mmHg. Roman and Cowley (9) observed a slope of 0.002 $ml \cdot min^{-1} \cdot mmHg^{-1} \cdot g\ kidney^{-1}$ for the functionally isolated pressure-diuresis mechanism in anesthetized rats subject to renal denervation and infusion of saturating levels of vasopressin, aldosterone, corticosterone, and norepinephrine. Thus, in the intact rat the slope of the arterial pressure-urine flow relationship was 8-fold less than the slope of the isolated pressure diuresis curve. The lower slope for the arterial pressure urine flow relationship in the intact state compared with the isolated pressure diuresis mechanism presumably results from the interaction of pressure diuresis with all the other mechanisms that affect urine flow. These other mechanisms have the effect of dampening the activity of the intrinsic pressure diuresis mechanism.

The arterial pressure urine flow slope was 100-fold less in the intact dog than in the isolated rat kidney, whereas the slope was only 8-fold less in the intact rat than in the isolated kidney. These differences in slopes between rat and dog may be due to species differences, or may be explained by a greater activation of antinatriuretic and antidiuretic mechanisms in the dog than in the rat due to a lower NaCl intake in the dog (the daily NaCl intake of the dogs was 12.6 mEq/kg/day, and in the present study the NaCl intake of the rats was $\approx$ 93 mEq/kg/day). The higher level of NaCl intake in the rats likely suppressed antinatriuretic mechanisms to a greater extent than in the dog, allowing a greater degree of expression of pressure diuresis in the rat than the dog.

Another aspect of the interaction of intrinsic pressure diuresis with other mechanisms influencing renal function may be revealed by the greater frequency of recording sessions with negative arterial pressure–urine flow slopes in the rats ingesting low-salt chow compared with those on high-salt chow (Table II). The greater frequency of negative slopes in rats on low-salt chow may indicate a greater degree of sympathetic activation in these rats compared with those on high-salt chow. Increased sympathetic activity can simultaneously increase arterial pressure and decrease urine flow, resulting in a negative relationship between pressure and urine flow (19).

We are aware of only one other study of the relationship between spontaneous changes in blood pressure and urine flow, that by Nafz *et al.* (2). These authors found no correlation between spontaneous changes in renal perfusion pressure and urine flow in conscious dogs. One possible explanation for these differing results is that Nafz *et al.* (2) calculated 60-sec average values for urine flow and blood pressure. Urine flow changes within 6 sec after an induced change in arterial pressure (17) and spontaneous variations in blood pressure occurred at frequencies up to 6 cycles/min (20). Consequently averaging blood pressure and urine flow over 60 sec may have obscured a correlation between the two signals.

In summary, we have presented evidence that the expression of spontaneous pressure diuresis in the intact, conscious rat is state-dependent. Increased NaCl intake increases the frequency of expression of pressure diuresis, and decreased NaCl intake has the opposite effect. Our observation that urine flow changes in response to moment-to-moment spontaneous changes in arterial pressure is compatible with a model in which the long-term nature of the pressure diuresis mechanism is explained as the cumulative summation of many short-term changes in urine flow gradually influencing blood volume and thus arterial pressure.

In hypertensive animals in which the pressure diuresis curve is shifted toward higher pressures, a normal or increased salt intake will lead to increased blood pressure as small increases in body NaCl content act in a cumulative manner on the circulation. Thus further study of the expression of spontaneous pressure diuresis in hypertensive animals on high- and low-NaCl diets may show even greater differences in the state-dependent expression of pressure diuresis than we have observed in these normotensive rats.

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