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Effects of Sodium Chloride on Prostacyclin-Stimulated Renin Release in Dogs with Filtering and Nonfiltering Kidneys (41473)

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Abstract. The effects of intrarenal infusion of sodium chloride (NaCl) on prostacyclin (PGI_2)-stimulated hyperreninemia were examined in groups of anesthetized dogs with either a single filtering kidney or a single denervated nonfiltering kidney, a model in which the renal tubules are damaged, and the macula densa is nonfunctional. After control observations, intrarenal infusion of prostacyclin at nonhypotensive doses resulted in significant increments of renin secretion and renal blood flow (RBF) in both preparations. Superimposition of intrarenal NaCl to the ongoing prostacyclin infusion produced a striking decrease of renin secretion in dogs with a filtering kidney. In contrast, dogs with a nonfiltering kidney failed to show a significant change in renin secretion during intrarenal NaCl administration. Renal blood flow remained unaffected by NaCl in both groups. The increment in renal venous plasma sodium concentration of 18–21 meq/liter was similar in both series. It is proposed that the renin response to intrarenal NaCl was mediated through the renal tubules, since renin secretion failed to decrease in the nonfiltering kidney preparation. Thus, the present results indicate that prostacyclin-stimulated renin secretion was modulated by a tubular mechanism, probably the macula densa.

The influence of the renal prostaglandins on renin secretion is well established. It has been demonstrated that intrarenal infusions of arachidonic acid and various prostaglandins, including PGI_2, PGE_2, and PGD_2 can stimulate renin secretion in the dog (1–5). Of the several known renal prostaglandins, it has been suggested that prostacyclin may play a major physiological role in the release of renin (4, 6). Indeed, Frölich *et al.* (7) have postulated that prostaglandin-dependent renin release is probably mediated by PGI_2. Although the mechanism of prostacyclin stimulation of renin is not well defined, studies *in vitro* (8, 9) have demonstrated that PGI_2 exerts a direct action on the juxtaglomerular (JG) cells. Prostacyclin stimulation of renin secretion also has been demonstrated in the nonfiltering as well as the filtering kidney preparation of anesthetized dogs (2, 4, 10). Therefore, it appears that a tubular or macula densa mechanism is not essential for the *in vivo* response to prostacyclin infusion. However, in these earlier studies (4, 10) during intrarenal prostacyclin administration into filtering kidneys, a marked natriuresis also occurred; it is possible that this effect could have attenuated the PGI_2-dependent hyperreninemic response. These considerations, combined with the abundant physiological data which support an important role for a tubular or macula densa mechanism in the control of renin secretion (11, 12), led us to design the present experiments to examine the potential influence of the renal tubular system on prostacyclin-stimulated hyperreninemia. Thus, changes in PGI_2-stimulated renin release were studied in either single filtering or denervated nonfiltering kidneys of dogs before and during the intrarenal infusion of hypertonic NaCl. In a previous investigation, Shade *et al.* (13) demonstrated an inhibition of the hypersecretion of renin secondary to chronic caval constriction during intrarenal infusion of hypertonic NaCl into dogs with filtering kidneys, but not in dogs with nonfiltering kidneys. Therefore, the present experimental design is an approach to examine the importance of the renal tubules and pre-

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sumably the macula densa in the control of prostacyclin-induced hyperreninemia.

Methods. The study involved 13 female mongrel dogs with body weights between 13 and 22 kg. Prior to the acute experiment, the dogs were housed in individual metabolism cages and maintained on a diet that provided approximately 65 meq of sodium and 35 meq of potassium daily for at least 4 days before the acute study and until sodium excretion approximated sodium intake. Water was available *ad libitum*.

All acute experiments were performed in the postabsorptive state. On the morning of the experiment, the dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and supplemental small doses of the drug were administered as needed to maintain a satisfactory level of anesthesia. Polyethylene catheters (fr. 8) were inserted into the femoral vessels and their tips advanced to the inferior vena cava and abdominal aorta. The arterial catheter was connected via a Statham P23Db strain gauge pressure transducer to a Hewlett Packard 7702B recorder in order to monitor mean arterial pressure (MAP). The femoral vein catheter was used for the administration of creatinine and replacement of blood. Both kidneys were exposed via retroperitoneal flank incisions and a unilateral nephrectomy was performed to remove any influence of this kidney on renin secretion. The contralateral renal artery was fitted with an electromagnetic flow probe connected to a model 501 Carolina Electronics flowmeter for determination of renal blood flow. Number 22-gauge needles attached to polyethylene tubes were inserted in the renal artery (distal to the flow probe) for infusion of solutions with a Harvard syringe pump and into the renal vein in order to obtain renal venous blood samples. A ureteral polyethylene 100 catheter was also positioned near the renal pelvis and urine was collected in a graduated cylinder. After a priming solution of creatinine was given, a constant infusion was maintained throughout the experiment in order to determine creatinine clearance (C_{Cr}). In addition, an isotonic NaCl infusion into the renal artery was begun. All intrarenal solutions including prostacyclin, isotonic NaCl, and hypertonic NaCl were given at a constant rate of 0.59 ml/min. Prostacyclin sodium salt was prepared by dissolving 1 mg in 1 ml of 1 *M* Tris buffer; this solution was diluted to 100 ml with 0.05 *M* Tris buffer (pH 9.4). The final dilution for the desired concentration was made with isotonic NaCl. Concentrations of plasma arterial sodium, potassium, and creatinine were determined from blood samples obtained at the midpoint of each period and in the urine collected over the entire clearance interval. Blood for the measurements of renal venous plasma sodium (RVP Na) was obtained at the end of each period. From these data, C_{Cr} and electrolyte excretion were calculated. During the last 4 min of each period, renal venous and arterial blood samples were collected for measurement of plasma renin activity (PRA) and hematocrit. Mean arterial pressure and RBF were recorded continuously. Following surgical preparation, a 60-min equilibration period was allowed before initiation of the following two experimental series. In all experiments, blood withdrawn for sampling was replaced with an equal volume of fresh donor blood from a normal dog.

Experiment 1. Intrarenal PGI_2 and superimposed NaCl infusion in anesthetized dogs with a single filtering kidney ($N = 7$). Three 15-min control renal clearance periods with intrarenal infusion of isotonic NaCl were obtained. In the subsequent two periods, prostacyclin was given intrarenally at a rate of 1.0×10^{-8} g/kg/min. This was followed by two periods of prostacyclin infusion at a rate of 1.5×10^{-8} g/kg/min. This latter dose of prostacyclin was continued throughout the remainder of the experiment in order to achieve maximal stimulation of renin release without a concomitant drop in MAP. During the next three periods, PGI_2 and hypertonic NaCl were given together intrarenally. The hypertonic NaCl solution was administered in a concentration calculated to increase the existing RVP Na concentration an additional 20 meq/liter for each individual experiment and the range for the group was 2.42–5.84 meq/min. Finally, two recovery

periods with infusion of PGI_2 alone were obtained.

Experiment 2. Intrarenal PGI_2 and superimposed NaCl infusion in anesthetized dogs with a single denervated nonfiltering kidney ($N = 6$). A denervated nonfiltering kidney was produced in each dog 4 days before the acute experiment. The nonfiltering kidneys were prepared according to the method of Blaine *et al.* (14). Briefly, under anesthesia with pentobarbital, one of the dog's kidneys was exposed via a retroperitoneal flank incision. The renal artery was occluded for 2 hr with a serrafine clamp. After restoration of blood flow, the ureter was ligated and cut. Finally, the kidney was denervated. Four days later the acute experiment was performed and an identical protocol described for series No. 1 was followed, except that due to the absence of filtering capacity, ureteral catheterization was omitted; consequently, measurements of C_{Cr} and electrolyte excretion were not obtained. Also in this series, the concentration of hypertonic NaCl infusion was adjusted to increase the existing RVP Na concentration an additional 20 meq/liter for each individual experiment. Since the renal plasma flow in the nonfiltering kidney was substantially reduced when compared to the filtering kidney, the rate of infusion of hypertonic NaCl was less than in the filtering kidney series, and it ranged from 1.6 to 2.5 meq/min. At the end of each experiment, these kidneys were decapsulated and a solution of lissamine green dye was injected into the renal artery to verify the nonfiltering status. This was accomplished by the failure to observe the appearance of dye within the renal tubules. This criterion was fulfilled in each of the dogs reported in this series.

Analytical methods. Plasma and urine electrolyte and creatinine concentrations were determined by standard techniques. PRA was measured by radioimmunoassay for angiotensin I(A-I) with the technique described by Sealey et al., (15). Renin secretion rate was calculated by multiplying the difference between renal venous and arterial PRA concentration by renal plasma flow. Renal plasma flow (RPF) was calculated from the formula RPF = RBF × 1 − HCT. Hematocrits were determined by the microcapillary tube method.

The results are presented as an average of the control and each of the different experimental categories. The data were analyzed by the χ^2 sign test for differences between categories. A P value of <0.05 was considered significant.

Results. *Experiment 1. Effects of intrarenal PGI_2 and hypertonic NaCl infusion in anesthetized dogs with a single filtering kidney.* Infusions of PGI_2 at nonhypotensive doses of 1.0 and 1.5 × 10^{-8} g/kg/min significantly increased renin secretion from 147 ± 70 to 357 ± 146 and 416 ± 131 ng A-I/min, respectively (Fig. 1). Superimposition of hypertonic NaCl during PGI_2 administration resulted in an increase in RVP Na concentration of approximately 18 meq/liter ($P < 0.05$) (Table I) and a threefold increase in renal sodium excretion ($P < 0.05$) (Table I). Also, the filtered load of sodium appeared to increase in 6 out of 7 animals although the increment did not reach the 5% level of significance for the group. These changes were correlated with a significant reduction of renin secretion from 416 ± 131 to 157± 51 ng A-I/min (Fig. 1), a value that was not different from con-

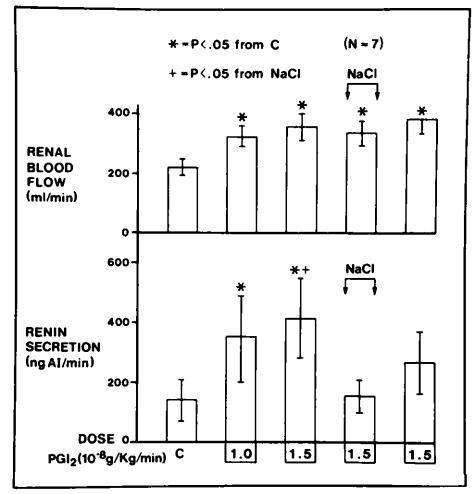

FIG. 1. Responses to intrarenal PGI_2 and NaCl infusions in dogs with a single filtering kidney. Values are expressed as means ± SE.

TABLE I. CHANGES IN CARDIOVASCULAR AND RENAL HEMODYNAMIC FUNCTION DURING PGI_2 AND NaCl INFUSION INTO FILTERING KIDNEYS OF ANESTHETIZED DOGS ($N = 7$)

		PGI_2 infusion at 1.0 or 1.5 $\times 10^{-8}$ g/kg/min					
				NaCl			
	C	1.0	1.5	1.5	1.5	1.5
MAP mm Hg	134 ± 4	133 ± 5	131 ± 4	131 ± 5		131 ± 4
RVR mm Hg/[ml/min]	0.67 ± 0.10	0.44* ± 0.06	0.40* ± 0.06	0.42* ± 0.05		0.38* ± 0.05
C_{Cr} ml/min	39 ± 3	40 ± 5	42 ± 5	38 ± 4		39 ± 5
RVP Na meq/L	143 ± 1	143 ± 1	143 ± 1	161*† ± 2		154 ± 3
RVP K meq/L	3.9 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.1*† ± 0.1		3.4* ± 0.1
E_{Na} μEq/min	76 ± 24	156* ± 30	165* ± 27	538*† ± 69		520* ± 70
E_K μEq/min	37 ± 5	58* ± 8	66* ± 8	61 ± 7		90* ± 14
UV ml/min	0.51 ± 0.15	1.12* ± 0.20	1.25* ± 0.02	2.97*† ± 0.35		3.01* ± 0.31

Note. Values are expressed as mean ± SE. Abbreviations are explained in text. Sodium and potassium excretion rates are represented by E_{Na} and E_K. The asterisk (*) indicates statistically significant P value for the noted period compared with control. The dagger (†) indicates statistically significant P value for noted period compared to the immediately preceding one.

trol. During the recovery period with infusion of PGI_2 alone, renin secretion appeared to rise toward the prehypertonic NaCl level, but the increment was not significantly different from the control (Fig. 1); however, both RVP Na and urinary sodium excretion remained elevated during the recovery (Table I). PGI_2 infusion induced a significant increase in the renal blood flow which was not attenuated during hypertonic NaCl administration (Fig. 1). Likewise, renal vascular resistance (RVR) was decreased with PGI_2 infusion (both doses) ($P < 0.05$) and remained attenuated during the hypertonic NaCl infusion and recovery period ($P < 0.05$) (Table I). Creatinine clearance and MAP were not detectably changed throughout the experiment (Table I). PGI_2 significantly increased renal potassium excretion, but there were no further consistent changes in the excretion of this electrolyte during hypertonic NaCl administration (Table I); during the recovery period, potassium excretion was again elevated ($P < 0.05$) (Table I). In addition, renal venous plasma potassium (RVP K) concentration decreased slightly ($P < 0.05$) during hypertonic NaCl infusion and during the recovery period ($P < 0.05$) (Table I).

Experiment 2. Response to intrarenal PGI_2 and hypertonic NaCl infusion in anesthetized dogs with a single denervated nonfiltering kidney. As in experiment 1, infusion of nonhypotensive doses of PGI_2 at a rate of 1.0 and 1.5 $\times 10^{-8}$ g/kg/min resulted in a significant increase in renin secretion from 119 ± 30 to 456 ± 53 and 463 ± 42 ng A-I/min, respectively (Fig. 2). Intrarenal infusion of hypertonic NaCl produced a significant increase in RVP Na concentration of approximately 20 meq/liter (Table II). In contrast to series 1, the superimposition of hypertonic NaCl did not suppress renin secretion which remained elevated from the control at a rate of 365 ± 29 ng A-I/min ($P < 0.05$) (Fig. 2). This value was not significantly different from the level of 463 ± 42 ng A-I/min obtained with the infusion of PGI_2 alone (Fig. 2). During the recovery period, renin secretion appeared to remain elevated but the change did not reach statistical significance at the 5%

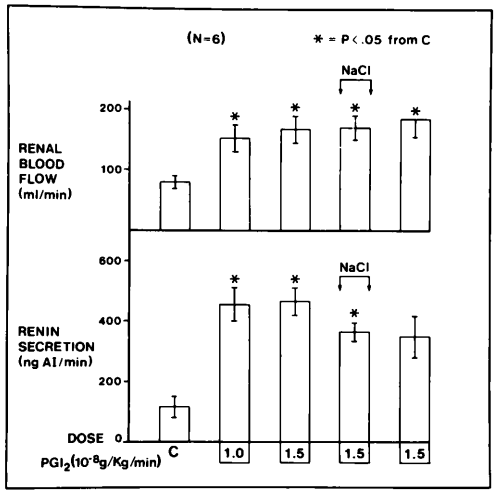

FIG. 2. Responses to intrarenal PGI_2 and NaCl infusions in dogs with a single denervated nonfiltering kidney. Values are expressed as means ± SE.

level. Renal blood flow significantly increased ($P < 0.05$) and RVR decreased ($P < 0.05$) during the administration of PGI_2 and these changes were unaffected by the administration of hypertonic NaCl (Fig. 2, Table II). As with the filtering kidney, RVP K concentration appeared to decrease slightly with the infusion of hypertonic NaCl (Table II), but the change was not significant. Finally, as in the first series, MAP remained unchanged throughout the experiment.

Discussion. The results of the present study demonstrate the active participation of an intact renal tubular mechanism in the modulation of prostacyclin-stimulated renin release. In the present experiments and in agreement with previous reports from this laboratory (4), intrarenal infusion of nonhypotensive doses of PGI_2 significantly stimulated renin release in dogs with either single filtering or nonfiltering kidneys. During this hyperreninemic state, the influence of the renal tubular mechanism was evaluated by intrarenal infusion of hypertonic NaCl, an intervention that is well known to inhibit renin release (13, 16). Accordingly, in our first series of experiments with filtering kidneys, the superimposition of hypertonic NaCl on the ongoing PGI_2 infusion significantly reduced renin secretion to the control level. This suppression was associated with an increment in RVP Na concentration, in the filtered load of sodium, and in sodium excretion. On the other hand, in dogs with a nonfiltering kidney, in an identical protocol NaCl infusion failed to attenuate significantly renin release, even though the increment in RVP Na concentration was similar to the level achieved in dogs with filtering kidneys. Comparison of renin secretion during hypertonic NaCl infusion in the filtering and nonfiltering kidney series clearly indicates that in the absence of a tubular mechanism, hypertonic NaCl was ineffective in reducing renin release. It seems reasonable to suggest that the renal tubular mechanism was mediated by the macula densa in the series with the filtering kidney.

In the present study the nonfiltering kid-

TABLE II. CHANGES IN CARDIOVASCULAR AND RENAL HEMODYNAMIC FUNCTION DURING PGI_2 AND NaCl INFUSION INTO NONFILTERING KIDNEYS OF ANESTHETIZED DOGS ($N = 6$)

		PGI_2 infusion at 1.0 or 1.5 × 10^{-8} g/kg/min			
				NaCl	
	C	1.0	1.5	1.5	1.5
MAP mm Hg	140 ± 4	140 ± 2	140 ± 2	140 ± 2	141 ± 2
RVR mm Hg/ [ml/min]	1.90 ± 0.28	1.02* ± 0.15	0.91* ± 0.12	0.91* ± 0.13	0.86* ± 0.14
RVP Na meq/L	145 ± 1	144 ± 1	143 ± 1	164*,† ± 2	152* ± 1
RVP K meq/L	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.2	4.1 ± 0.2	4.4 ± 0.2

Note. Values are expressed as mean ± SE. Abbreviations are explained in the text. The asterisk (*) indicates statistically significant P value for the noted period compared with control. The dagger (†) indicates statistically significant P value for the noted period compared to the immediately preceding one.

neys were denervated whereas the filtering kidneys were innervated. In the filtering kidneys, it seems unlikely that intrarenal NaCl infusion influenced renal nerve activity with a subsequent effect on renin release. In an earlier study by Shade *et al.* (13) in which the renal nerves were intact in both filtering and nonfiltering kidneys, a similar intrarenal infusion of hypertonic NaCl decreased renin secretion only in the filtering kidney.

The renin secretion response during the recovery phase in the filtering and nonfiltering kidney preparations was variable and requires additional comment. In both groups, renin secretion appeared to be elevated above control levels, but the increments were not statistically significant at the 5% level for either group. Similarly, renin secretion in the recovery period was not different from PGI_2 induced renin secretion prior to hypertonic NaCl infusion. It is possible that the observed increased variability in renin secretion during the recovery phase was related to nonspecific secondary mechanisms, possibly volume expansion. Also, in the filtering kidney series RVP Na and sodium excretion remained elevated during the recovery period and this could have continued to attenuate partially the renin response to prostacyclin infusion. These findings were not unexpected, since similar responses in the recovery phase were observed by Shade *et al.* (13) using a similar protocol of hypertonic NaCl infusion in filtering and nonfiltering kidneys of anesthetized dogs with hyperreninemia due to caval constriction.

The bulk of the early evidence in the literature (11, 12, 16) supports the view that an increased tubular sodium concentration or the load of sodium at the macula densa can attenuate renin secretion. More recently, studies by Kotchen *et al.* (17, 18) have postulated that chloride rather than sodium might be the important ion for this effect. In addition, there is the suggestion (11) that both sodium and chloride are involved in the macula densa sensor mechanism. Regardless of which ion(s) are detected by the macula densa, comparative studies with hypertonic NaCl infusion in the filtering and nonfiltering kidney (13) have provided evidence to support an important role for the tubular system in the control of renin secretion. Inhibition of renin release by hypertonic NaCl has been demonstrated in normal anesthetized dogs with baseline renin secretion (16) as well as in dogs with hyperreninemia induced by caval constriction (13) or by norepinephrine (16). These observations and the present data are consistent with the idea that the macula densa can attenuate both basal and stimulated levels of renin secretion. The above considerations are particularly interesting when applied to prostaglandin-dependent renin release. Under appropriate conditions, it is possible that the natriuresis induced by various endogenous prostaglandins could reflect increased NaCl delivery to the macula densa and a feedback mechanism which functions as a brake on the increase in renin release. A similar postulate has been suggested in a recent review by Henrich (19). Studies by Higashihara *et al.* (20) and Stokes (21) have suggested a PGE_2-dependent inhibition of chloride reabsorption in the thick ascending limb of Henle, but the interpretation of the data has been questioned (22) and conclusive evidence of the action of prostaglandins on tubular sodium and chloride transport is lacking.

The effects of prostacyclin on renal hemodynamic function and electrolyte excretion have been well documented and the present results are in agreement with previous studies (4, 10). In both the filtering and nonfiltering kidney series, the elevation in RBF produced by PGI_2 infusion was not altered by the administration of hypertonic NaCl, while renin secretion was strikingly reduced in the filtering kidney preparation. This finding demonstrates that hypertonic NaCl did not inactivate or directly block the biological action of PGI_2. Other investigators have also reported lack of changes in renal hemodynamic function during intrarenal NaCl infusion with similar protocols in sodium replete dogs (16) or in dogs with caval constriction (13).

In summary, hypertonic NaCl inhibited PGI_2-stimulated renin secretion in the

single filtering kidney while hypertonic NaCl had no effect on PGI_2-dependent renin release in the nonfiltering kidney. Thus an intact tubular mechanism is essential for this response. It is suggested that changes in tubular delivery of NaCl to the macula densa can modulate the hyperreninemia induced by PGI_2.

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