PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 181, 357–363 (1986)

The Effect of Sodium Intake on Renal Prostaglandin Production[1] (42265)

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Abstract. The effect of chronic alterations in dietary sodium intake on renal arachidonic acid (AA) metabolism was studied in male Wistar rats who were maintained for 14 days on a diet consisting of sodium-deficient food and either deionized water (low salt intake, LSI), 1% saline (normal salt intake, NSI), or 2% saline (high salt intake, HSI). 24 h Urinary Sodium (UNaV) and plasma renin activity (PRA) measurements were shown to validate the dietary protocol. Microsomal preparations from the cortices and medullae were incubated with radiolabeled exogenous AA, and endogenous urinary prostaglandin (PG) levels were assayed by RIA to quantify renal PG synthesis. Cortical $PGF_{2\alpha}$ and PGE_2 synthesis was found to be the greatest following LSI. In contrast, medullary $PGF_{2\alpha}$ was shown to be the least following LSI and to increase with increased sodium intake. Likewise, urinary $PGF_{2\alpha}$ levels significantly increased with increasing sodium intake. Changes in urinary PGE_2 levels showed the same trend as $PGF_{2\alpha}$ but did not achieve statistical significance. These data show that dietary sodium differentially affects renal cortical and medullary PG synthesis and may reflect physiological differences in the regulation of cyclooxygenase in these zones. These data further suggest that the major source of urinary PGs is the renal medulla since the relationship of urinary levels to sodium intake mimics that described for the synthesis of PGs by the medullary tissue.

The kidney by virtue of its role in preserving the osmolality of body fluids has the remarkable ability of conserving as well as eliminating sodium. It is now recognized that there are major interactions between the electrolytes and a number of hormonal systems in the kidney. The renin–angiotensin system is an important regulator of both blood pressure and volume through its activities on the vasculature and the adrenal–renal axis (1). There is evidence to suggest that the renin–angiotensin system, as well as sodium directly, may interact with the renal prostaglandin (PG) pathway and modulate the homeostatic control of blood volume and pressure (2). The PGs have been an area of intense interest due to the proven ability of some of these compounds to affect both fluid balance and blood pressure. The PGs have been shown to dilate arterial beds as well as to induce both a diuresis and natriuresis when infused into conscious animals (3).

Renal PGs are synthesized in both the cortex and the medulla of the kidney, with the major sites being the vasculature, glomeruli, renomedullary interstitial cells, and collecting ducts (4–7). There have been numerous studies which have proposed a relationship between dietary salt intake and PG production, yet the results have proven to be contradictory and inconsistent when one considers the differences in experimental protocols. The findings reported in the literature range from elevations in PG levels associated with increasing sodium intake to decreased renal synthesis under the same conditions. An example of such opposite findings is seen in the data of Lifschitz *et al.* (8) and of Davila *et al.* (9). On the one hand, Lifschitz noted no significant change in urinary PGE_2 excretion following chronic alterations in sodium intake in the rabbit; while on the other, Stahl and co-workers (10) demonstrated enhanced PGE_2 excretion following sodium depletion in the same species. Likewise, Davila reported that urinary PGE_2 and $PGF_{2\alpha}$ levels decreased during high salt intake and increased during low salt intake, in rabbits, while Weber *et al.* (11) showed a decrease in urinary PGE_2 levels and a slight increase in $PGF_{2\alpha}$ levels in the urine following salt loading. Contrasting results also exist for studies involving humans and rats. In a study by Tan *et al.* (12) in contrast to the rabbit, oral sodium loading over a period of weeks was

[1] Supported by The Joseph Alexander Foundation and The Frank Strick Foundation.

0037-9727/86 $1.50

found to increase urinary PGE_2 excretion. However, a recent study by Sinaiko and Green (13), in which rats were maintained on high, normal, and low sodium diets for six days, found that there was no significant difference in urinary PGE_2 levels in response to dietary salt. The effect of dietary sodium on the biosynthetic capacity of the renal parenchyma has also been studied extensively using renal slices, homogenates, and microsomal preparations (14). These data are equally contradictory (15). To understand better the mechanism by which the kidney regulates blood pressure and volume, we examined the effects of chronic alterations in sodium intake on renal arachidonic acid (AA) metabolism. We measured both cortical and medullary biosynthetic capacity and urinary PG levels simultaneously so as to better identify the renal sites and stimuli for PG production.

Methods. *Treatment of animals.* Male Wistar rats (225–235 g) were maintained for a period of 14 days on sodium-deficient food (ICN) supplemented with either deionized water (low sodium intake, LSI); 1% saline (normal sodium intake, NSI); or 2% saline (high sodium intake, HSI) *ad libitum.* At the end of the 13-day equilibration period, the animals were placed in metabolic cages for a 24-hr period in which fluid intake and urine output were measured. Since voiding time varied resulting in differing lengths of urinary retention in the bladder, no preservatives were added to the urinary samples. However, all samples were processed in the same manner following 24-hr collection. Twenty-four-hour urinary sodium and potassium were measured by direct potentiometry (Nova Biomedical). In addition, body weight and blood pressure, measured by tail-cuff sphygmomanometry (16), were recorded.

The rats were sacrificed by decapitation. Blood was collected in heparinized tubes for plasma renin determination by the method of Sealey and Laragh (17).

Preparation of tissues. Kidneys were excised, placed on ice, and frozen. The cortices and medullae were separated by dissection, and homogenates were made using a polytron homogenizer (w:v, 1:3) in 0.1 *M* potassium phosphate buffer (pH 7.8) containing 1% bovine serum albumin and 10 m*M* EGTA. The homogenates were centrifuged at 10,000*g* for 15 min. The resulting supernatant was then centrifuged at either 50,000*g* for 2 hr (Sorvall RC5 B) or 100,000*g* for 1 hr (Beckman Ultracentrifuge). Microsomal pellets were washed three times with cold phosphate buffer and were resuspended in 0.1 *M* potassium phosphate buffer (pH 7.8) in a volume equal to one-fourth of the original tissue weight.

Incubations. Microsomal incubations containing 1 μg (300,000 cpm) 1-[14-C]-AA, 100 μl tissue, 10 μl epinephrine (final concn. 1 m*M*), in a total volume of 180 μl were carried out for 30 min at 37°C, and were stopped by acidification to pH 3.5 with 4 *N* formic acid. The reactions were extracted twice with 2 vol of ethyl acetate, evaporated under N_2 and reconstituted in a few drops of chloroform: methanol (2:1). The concentrates were spotted on TLC plates along with authentic prostaglandin standards and developed in system C (chloroform:methanol:acetic acid:water; 90:8:1:0.8) to separate prostaglandins. While system C does not permit the separation of PGE_2 and 6-keto-$PGF_{1\alpha}$, this was not of concern, since in parallel incubations using system A9, no 6-keto-$PGF_{1\alpha}$ was detected (unpublished observations). Plates were put in cassettes with Kodak X-OMAT film and autoradiographs were produced. Appropriate bands on the TLC plates were cut, placed in RIA-Solve (RPI) scintillation fluor, and counted in a Packard Tri-Carb counter. Microsomal protein estimations were made by fluorometric assay of proteins (18), and prostaglandin synthesis expressed as nanogram product per milligram microsomal protein per 30-min incubation.

Urinary prostaglandin assays. Radioimmunoassays of PGE_2 and $PGF_{2\alpha}$ were carried out as follows: Urinary samples were extracted on ODS silica columns by the method of Powell (19), and the eluate was evaporated to dryness and the residue resuspended in RIA buffer (0.05 *M* potassium phosphate, pH 7.4, containing 0.9% NaCl and 0.1% BSA). Specific antibodies raised against keyhole-limpet hemocyanin (KLH)-conjugates of PGE_2 and $PGF_{2\alpha}$ in rabbits were used along with ^3H-label to assay the content of these metabolites in the sample. Each tube assayed consisted of a total volume of 200 μl and contained buffer, unlabeled standard (1–200 pg) or unknown, antibody (1:10,000 dilution), and tritiated standard (2500–3000 cpm) (Amersham). Tubes

were allowed to equilibrate overnight at 4°C. Bound and free ligands were separated by the addition of dextran charcoal followed by centrifugation at 3000 rpm. The supernatant was decanted, suspended in RIA-Solve (RPI), and counted in a Packard Tri-Carb scintillation counter. Specific performance characteristics of these antisera have been previously described by Weisman *et al.* (20). Analysis of data derived from the use of internal standards has shown inter- and intra-assay variability to be less than 10% for each of the assays.

High-performance liquid chromatographic confirmation of product identity. PGs eluted from the ODS column with methyl formate were evaporated to dryness and the residue resuspended in HPLC mobile phase (water: acetonitrile:benzene:acetic acid; 65:35:0.2: 0.1). The sample coeluting with standard using a Waters fatty acid analysis column (21) was collected and evaporated to dryness and resuspended in RIA buffer. The RIA was performed as previously described.

Statistical analysis. All parameters were analyzed by one-way analysis of variance and considered to differ significantly at $P < 0.05$. All values are expressed as means ± SEM.

Results. The animals were randomly assigned to one of the dietary groups. Body weight, blood pressure, urine volume, and urinary electrolytes were measured for each of the groups ($n = 8$) prior to subjecting them to the various diets and were found not to differ significantly. Following the 13-day equilibration, in which the animals were maintained on the respective dietary protocols, these same parameters were measured, with the inclusion of plasma renin activity (PRA). At this point, the 24-hr urine volume (UV), urinary sodium (UNa) (Table I), and PRA (Table II) differed significantly between the groups. In addition, the output of fluid and sodium was found to be almost identical to the intake, suggesting that the animals had achieved metabolic balance (Table I). The final body weight and kidney weight also differed between the groups with the HSI and LSI animals failing to increase their body weight to the same extent as the NSI group (Table II). Likewise, the kidney weight was found to be proportional to the body weight in these groups. This decrease in weight gain associated with these diets has been seen previously (unpublished observations).

Analysis of renal cortical and medullary PG synthesis (PGE_2 and $PGF_{2\alpha}$) reveals a differential synthetic pattern of these compounds between the cortex and the medulla with respect to salt intake. In addition to the previously reported data which has shown the renal medulla to be a greater producer of PGE_2 and $PGF_{2\alpha}$, we found that renal cortical microsomal preparations from animals maintained on the LSI diet produce significantly more PGE_2 and $PGF_{2\alpha}$ than NSI animals (Table III). In addition, the cortical PG production of animals subjected to the LSI protocol did not differ from the HSI group; however, the difference between HSI and NSI did not achieve statistical significance. In contrast to the PG production observed in the cortex, the medullary microsomes were found to respond differently to chronic alterations in sodium intake. As can be seen in Table III, which shows the biosynthetic capacity of the medulla from

TABLE I. SODIUM BALANCE FOLLOWING 14-DAY EQUILIBRATION TO DIETARY PROTOCOL

	Intake/24 hr		Output/24 hr	
Group	Volume (ml)	Sodium (meq)	Volume (ml)	Sodium (meq)
LSI $n = 8$	61.25 ± 8.75[a]	Not detected[a]	48.5 ± 8.3[a]	Not detected[a]
NSI $n = 8$	51.62 ± 6.47	8.7 ± 0.8	35.5 ± 5.7	8.7 ± 0.4
HSI $n = 8$	176.25 ± 24.49	60.0 ± 7.8	163.8 ± 23.9	63.0 ± 1.9

Note. LSI = Low sodium intake. NSI = Normal sodium intake. HSI = High sodium intake.
[a] All groups differ significantly.

TABLE II. PHYSIOLOGIC PARAMETERS FOLLOWING 14-DAY EQUILIBRATION TO DIETARY PROTOCOL

Group	Body weight (g)	Kidney weight (g)	Blood pressure (mm Hg)	Plasma renin activity (ng Al/ml/hr)
LSI $n = 8$	242.88 ± 7.48	1.90 ± 0.08	129.4 ± 5.8*	13.35 ± 2.12**
NSI $n = 8$	304.50 ± 11.77***	2.19 ± 0.07	111.9 ± 5.5	2.05 ± 0.22
HSI $n = 8$	220.62 ± 12.94	2.12 ± 0.08	129.7 ± 8.0	0.65 ± 0.07

Note. LSI = low sodium intake. NSI = Normal sodium intake. HSI = High sodium intake.
* LSI > NSI, LSI = HSI; $P < 0.05$.
** All groups differ significantly; $P < 0.05$.
*** NSI > LSI, LSI = HSI; $P < 0.05$.

animals maintained on the various diets, the LSI medulla produces the least PGE_2 and $PGF_{2\alpha}$ of the three groups and synthesis increases with increasing sodium intake such that HSI synthesis is significantly greater than that of the LSI group (HSI PGE_2 15.23 ± 2.13 ng > LSI PGE_2 6.98 ± 1.98 ng). This pattern of synthesis is strikingly different from that which we have described for the cortex.

Urinary levels of PGE_2 and $PGF_{2\alpha}$ were assessed by RIA and are expressed as the total number of nanograms of the PG in a 24-hr urine sample taken immediately prior to sacrifice. $PGF_{2\alpha}$ levels were found to increase significantly with increasing dietary salt intake. While increases in PGE_2 levels failed to achieve statistical significance, a similar trend was observed (Table III). The increase in urinary PG output with increasing salt intake appears to reflect the increase in medullary PG synthesis observed with the microsomal preparation.

Due to the high urinary levels of $PGF_{2\alpha}$ observed in this study and the lack of literature reports corroborating such values, we repeated samples from each group, using the HPLC protocol described, to separate that portion of the sample comigrating with authentic $PGF_{2\alpha}$ standard. The purified sample was then assayed by RIA to confirm the identity of the metabolite. The results of this examination showed that the compound quantified by RIA alone comigrated with authentic standard, and that the values obtained did not differ by greater than 10% between the two methods.

TABLE III. PROSTAGLANDIN PRODUCTION: RENAL CORTICAL AND MEDULLARY PROSTAGLANDIN SYNTHESIS AND 24-hr URINARY PG LEVELS FOLLOWING DIETARY PROTOCOL

	Cortical (ng/mg protein/30′)		Medullary (ng/mg protein/30′)		Urinary (ng/24 hr)	
Group	$PGF_{2\alpha}$	PGE_2	$PGF_{2\alpha}$	PGE_2	$PGF_{2\alpha}$	PGE_2
LSI $n = 8$	2.53 ± 0.38*	1.45 ± 0.14*	15.0 ± 4.2***	6.98 ± 1.98***	60.0 ± 10.2**	26.2 ± 8.5
NSI $n = 8$	1.05 ± 0.14	0.94 ± 0.11	27.9 ± 6.5	13.49 ± 3.73	162.5 ± 32.2	51.7 ± 9.8
HSI $n = 8$	2.12 ± 0.72	1.72 ± 0.42	38.1 ± 7.6	15.23 ± 2.13	649.9 ± 86.8	79.9 ± 23.3

Note. LSI = Low sodium intake. NSI = Normal sodium intake. HSI = High sodium intake.
* LSI > NSI, LSI = HSI; $P < 0.05$.
** All groups differ significantly; $P < 0.05$.
*** HSI > LSI; $P < 0.05$.

Discussion. Since renal PGs have been implicated in the regulation of renal salt and water handling, there has been much interest in the relationship between dietary sodium and renal PG synthesis. Unfortunately, previous studies have resulted in conflicting data. Much of the confusion in this area of research stems from the fact that many of the previous studies were carried out with varying degrees of sodium intake, duration of diet, and differences in species, age, and weight, and lacked the measurement of critical physiologic parameters necessary to validate the dietary protocols. In our experiments, we have shown profound differences in the biosynthetic capacity of the rat renal cortex and medulla in relation to sodium intake and speculate that these differences may reflect compartmentalization for specialized function. It is interesting that the cortex, which is the major producer of angiotensin II (AII), produces elevated quantities of PGE_2 and $PGF_{2\alpha}$ during LSI, when AII levels are maximal (1). This is relevant since AII has been shown in numerous experiments to be a potent stimulus for the production of PGs, and may therefore be responsible for the elevated PG production in the cortices of the LSI animals. The previous reports have suggested that AII, via a receptor-mediated mechanism, increases the activity of phospholipase A_2, the enzyme which releases AA, the substrate for PG production, from the membrane phospholipids (22). However, the fact that our microsomal cyclooxygenase enzyme preparation is devoid of the influences of cytosolic or plasmalemmal enzymes, such as phospholipase A_2, suggests that other factors are involved. In addition, the use of this preparation eliminates the influence of cystolic PG degradative enzymes which might be affected by alterations in sodium intake. It is conceivable that the elevated levels of AII circulating in the LSI animals and the subsequent stimulation of phospholipase may result in an elevated AA release, which in turn either alters the kinetics of the cyclooxygenase enzyme or induces the production of more enzyme protein. The fact that the HSI cortex also produces elevated amounts of PGs at a time when PRA is low suggests a second mechanism for influencing cortical PG production during high sodium intake. The response to alterations in sodium intake is very different in the medulla. In this region, PG production is lowest in the LSI animals and increases significantly with increases in sodium intake. Since increased sodium intake leads to natriuresis and diuresis, synthesis of PGs, which have been shown to be both natriuretic and diuretic, might be predicted.

These findings suggest a spatial separation of the two major actions of the PGs in the kidney. In the cortex, the vascular elements may produce PGs to counteract the influences of vasoconstrictors such as AII which are elaborated as a consequence of a number of conditions including LSI. In the medulla, during sodium loading, the tubular elements may be stimulated to release PGs by changes in volume, pressure, or sodium directly or through unknown hormonal channels in order to enhance salt and water excretion. It appears likely that distinct pools of cyclooxygenase exist which are linked to specific hormone-dependent lipases responsive to different agonists or stimuli. Although activation of phospholipase may affect cyclooxygenase activity as described above, the possibility also exists that the physiological changes associated with dietary sodium alteration may directly affect cyclooxygenase differentially in distinct regions of the kidney. Such changes in cyclooxygenase activity have been demonstrated in 3T3 cells stimulated by platelet-derived growth factor (23) and in renal cortex following unilateral ureteral obstruction (24).

One of the major objectives of this study was to ascertain the renal source of urinary PGs. Previous studies have shown that urinary PG levels are an indication of renal synthesis but have not provided conclusive evidence for an actual renal location (25). Our finding of a positive relationship between salt intake and urinary levels of PGE_2 and $PGF_{2\alpha}$, which mimics the pattern observed in the medulla, provides strong evidence for a medullary source of these compounds. It is possible that urinary PG levels represent a summation of cortical and medullary synthesis with the large medullary production overshadowing the relatively small cortical activity. Nonetheless, it appears that urinary levels provide a convenient means of assessing medullary synthetic ability.

A recent report by Bing *et al.* (26) which examined the effect of chemical renal medullectomy on urinary PGE_2 levels in relation

to variations in sodium intake provides some insight into this question and is consistent with our findings. This group found that urinary PGE_2 was markedly reduced in medullary damaged rats, consistent with the renal medulla being the major source of urinary PGs. Our analysis of their data for the medullectomized rats shows their PGE_2 levels, when correlated with sodium intake, to directly mimic the cortical pattern which we have described. In addition, the pattern of production, with respect to salt intake, of their normal control group appears to be identical to the pattern we have observed in the urine, as well as the medullary microsomal preparations, we have studied.

Our finding of $PGF_{2\alpha}$ as the major renal AA metabolite in the rat, as confirmed by HPLC analysis, along with alterations in the quantity of this compound with varying sodium intakes, suggests a possible role for this compound in the regulation of kidney function. Therefore, renewed study of this metabolite along with further confirmation of product identity by a more definitive method of PG analysis, such as GC-MS, appears warranted as a result of its prominent production and correlation with sodium intake.

There is no question that more variables than sodium change in these studies. Since urinary volume was altered with varying sodium intakes it is difficult to differentiate between volume-related or direct sodium effects. In addition, there may also be differences in the circulating concentrations of antidiuretic hormone in the groups of rats. Nonetheless, clear differences in PG synthesis are found with alterations in sodium intake. Of importance to this study is that the cortex and medulla respond differently to dietary alterations in sodium and that urinary PG content correlates with medullary synthesis.

The authors thank Soledad Salamone for her excellent assistance in the preparation of this manuscript.

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Received June 7, 1985. P.S.E.B.M. 1986, Vol. 181.
Accepted November 4, 1985.