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Research Article

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Seven normal human volunteers were placed on three sodium intake diets: (*a*) ad lib. sodium intake, (*b*) high sodium intake, and (*c*) low sodium intake. Plasma prostaglandin A, E, and F concentrations were measured by radioimmunoassay.

Mean prostaglandin A levels on the ad lib. diet were 1.60 ng/ml. Prostaglandin A levels decreased 49% to 0.82 ng/ml on the high sodium intake and increased 34% to 2.14 ng/ml on the low sodium intake. Prostaglandin A levels increased 161% on the low sodium diet in comparison with levels on the high sodium diet. Plasma prostaglandin E and F concentrations did not change significantly during variation in sodium intake.

These results show that dietary sodium content markedly effects plasma prostaglandin A levels and that prostaglandins may play a role in the physiologic mechanism of sodium homeostasis.

The Effect of Chronic Sodium Loading and Sodium Restriction on Plasma Prostaglandin A, E and F Concentrations in Normal Humans

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ABSTRACT It has been suggested that prostaglandins may be involved in the control of sodium homeostasis. Prostaglandin A and prostaglandin E have been shown to increase renal blood flow and urinary sodium excretion and prostaglandin A has been shown to stimulate aldosterone release. The purpose of this study was to determine the effect of chronic sodium loading and sodium restriction on plasma prostaglandin A, E, and F concentrations.

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INTRODUCTION

In 1965 Lee, Covino, Takman, and Smith (1) presented evidence that prostaglandin E_2 (PGE_2),[1] and medullin, later renamed prostaglandin A_2 (PGA_2) were present in the renal medulla, the portion of the kidney known to have vasodepressor properties (2). Nissen (3) demonstrated that a period of salt repletion in salt-depleted rats induced an increase in the number of lipid droplets in renal medullary interstitial cells. By the use of tissue culture techniques Muirhead et al. (4) showed that these renal interstitial cells contain prostaglandins A_2, E_2, and $F_{2\alpha}$. In addition to the presence of prostaglandins in the renal medulla, increased levels of prostaglandin-like material have been demonstrated in renal venous blood in response to a number of physiologic stimuli (5–9).

The evidence that prostaglandins were present in renal medulla and seemed to respond to physiologic stimuli led workers to study the effect of prostaglandins on blood pressure and renal function. Prostaglandins E and A have been shown to increase renal blood flow, urine volume, free water clearance, and sodium excretion when infused in dogs (10–14). Renal effects in hypertensive man are similar to those in dogs when PGA is infused at low concentrations, however at higher concentrations a vasodepressor effect predominates (15–17). In addition, recent studies in man have indicated that PGA increases aldosterone secretion independent of changes in ACTH, renin, and serum electrolytes (18, 19).

Thus a growing body of evidence suggests that prostaglandins play a role in the regulation of blood pressure and salt and water balance. Investigation of this relationship, however, has been hampered by the absence of a specific, reliable assay that could be applied to large numbers of samples. Recently we have developed (20, 21) a radioimmunoassay for prostaglandins which incorpo-

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[1] *Abbreviations used in this paper:* PGA, prostaglandin A, PGE, prostaglandin E; PGF, prostaglandin F; PGB, prostaglandin B.

TABLE I

Effect of Sodium Intake on Blood Pressure, Serum Sodium, Serum Potassium, Serum Creatinine, Creatinine Clearance, Sodium Excretion, Plasma Renin Activity, and Weight

	Systolic BP, *mm Hg*			Diastolic BP, *mm Hg*		
Salt intake	Ad lib.	High	Low	Ad lib.	High	Low
Mean ±SEM	115±4	121±4	111±4	79±2	78±2	76±2
% Change ±SEM		+5.4±2.5	−4.5±1.4		−1.1±1.8	−3.4±0.9
P value		NS	<0.02		NS	<0.01
	Serum sodium, *meq/liter*			Serum potassuim, *meq/liter*		
	Ad lib.	High	Low	Ad lib.	High	Low
Mean ±SEM	139.3±0.3	138.3±0.6	137.0±0.4	3.97±0.08	4.10±0.07	3.97±0.09
% Change ±SEM		−0.3±0.3	−1.7±0.3		+3.4±1.5	+0.0±0.8
P value		NS	<0.002		NS	NS
	Mean BP, *mm Hg*			Serum creatinine, *mg/100 ml*		
	Ad lib.	High	Low	Ad lib.	High	Low
Mean ±SEM	96±3	100±3	93±3	0.96±0.05	0.95±0.05	1.15±0.08
% Change ±SEM		+3.8±1.8	−3.7±0.7		−1.6±0.9	+21.3±6.7
P value		NS	<0.002		NS	<0.02
	Creatinine clearance, *ml/min*			Urinary sodium, *meq/24 h*		
	Ad lib.	High	Low	Ad lib.	High	Low
Mean ±SEM	117.8±11.3	130.7±9.7	97.8±10.6	151.3±15	230.9±10.1	10.4±2.0
% Change ±SEM		+13.5±4.6	−17.1±5.2		+59.1±12.2	−91.6±2.3
P value		<0.03	<0.02		<0.005	<0.001
	Weight, *lb*			Plasma renin activity, *ng/ml per h*		
	Ad lib.	High	Low	Ad lib.	High	Low
Mean ±SEM	151.6±13.1	157.2±13.2	149.7±12.6	1.49±0.12	0.61±0.03	8.49±0.75
% Change ±SEM		1.1±0.4	3.7±0.5		−58.4±2.3	455.8±60.8
P value		<0.04	<0.001		<0.001	<0.001

* Mean of weight, renin, and blood pressure for each person represents the average of measurements during 4 days of ad lib. diet, and the final 3 days of the high and low sodium-intake periods. Mean of creatinine clearance, urinary sodium, serum sodium, serum potassium, and serum creatinine represents the average of measurements taken on the last 2 days of each dietary period.

rates these qualities. Using this technique we have shown in a previous study (22) that plasma and renal tissue levels of PGA increase in rats on a sodium-restricted diet, while PGA levels decrease in sodium-loaded animals.

The purpose of the present study was to investigate the effect of sodium loading and sodium depletion on plasma levels of prostaglandins A, E, and F in man.

METHODS

Experiments were carried out in seven human volunteers from whom informed consent was obtained, using a protocol approved by the Clinical Investigation Committee of the Yale University School of Medicine.

There were four male and three female volunteers ranging in age from 22- to 36-yr old. Drugs were not taken during the course of the study with the exception of an estrogen-progestin oral contraceptive by K. J. None of the subjects had a history of serious illnesses of any type. One subject (J. G.) had a questionably enlarged liver; his liver function studies were normal.

The course of the experiments lasted 14 days during which each subject went on three diets: (*a*) a 4 day, ad lib. dietary control period during which the subject ingested his usual daily sodium intake, (*b*) a 5 day duration ad lib. diet supplemented by six 1-g sodium chloride tablets per day, which was calculated to yield a total of over 200 meq sodium intake per day, and (*c*) 5 days of a 10 meq sodium diet prepared by the metabolic dietary kitchen of the Clinical Research Center. In one group of subjects the low sodium diet followed the high sodium diet after a 1 day interval (subjects R. Z., J. G., D. S., K. J.), in the second group after a 7 day interval (subjects B. K., G. D., and G. S.). Potassium and caloric intake were not controlled. For comparison to control (ad lib. diet) data, only data

TABLE II

Effect of Sodium Intake on Plasma Prostaglandin A, E, and F Levels

Subject	Salt intake	Prostaglandin A			Prostaglandin E			Prostaglandin F		
		Ad lib.	High	Low	Ad lib.	High	Low	Ad lib.	High	Low
			ng/ml			*ng/ml*			*ng/ml*	
B. K.		1.73	0.99	2.37	0.20	0.24	0.25	0.36	0.47	0.36
D. S.		1.60	1.00	1.72	0.32	0.27	0.22	0.32	0.35	0.44
G. D.		1.35	0.82	1.90	0.31	0.22	0.20	0.29	0.25	0.30
G. S.		1.71	0.86	2.27	0.21	0.22	0.31	0.35	0.28	0.49
J. G.		1.75	0.74	2.13	0.23	0.21	0.27	0.44	0.32	0.31
K. J.		1.61	0.64	2.20	0.22	0.26	0.28	0.40	0.31	0.42
R. Z.		1.44	0.71	2.36	0.29	0.23	0.25	0.48	0.50	0.39
Mean ±SEM		1.60±0.06	0.82±0.05	2.14±0.09	0.25±0.02	0.24±0.01	0.24±0.01	0.38±0.03	0.35±0.04	0.39±0.03
Mean %Δ ±SEM			−48.3±3.3	+34.3+6.5		−4.3±7.2	+5.2±12.1		−5.6±8.0	5.4±9.8
P value			<0.001	<0.001		NS	NS		NS	NS

from the last 3 days of each experimental period were used for calculation of mean prostaglandin levels. "*P*" values were determined by the Student *t* test.

Blood pressures, weights, and blood samples for prostaglandin and renin levels were taken daily between 8 and 9 a.m. Blood pressures were taken in the sitting position. Blood samples for determination of creatinine, electrolytes, and hematocrit were obtained on the last 2 days of each experimental diet. 24-h urine collections were made during the last 2 days of each experimental diet period for measurement of sodium, potassium, and creatinine content.

Blood for renin determinations was collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA), blood for prostaglandin in heparinized vacutainers. Blood was centrifuged (1,200 *g*) immediately at 4°C, and after the red cells were removed, plasma was stored at −20°C until analysis. Sodium and potassium were determined by flame photometry. Creatinine was measured on a Technicon Auto-Analyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Plasma renin activity was measured by radioimmunoassay (23).

Prostaglandins were determined as previously reported from our laboratory (20, 21). Briefly, extraction is performed twice with 5 vol of distilled ethyl acetate at pH 3.5–4.0. The A, E, and F prostaglandins were separated on a 0.5 g silicic acid column using increasing methanol concentrations in benzene/ethyl acetate (60/40: vol/vol) for elution. After chromatographic separation, PGA and PGE were measured by radioimmunoassay using an antiserum prepared in rabbits by immunization with a bovine serum albumin-prostaglandin E_2-conjugate. PGF was measured using an antiserum prepared in rabbits by immunization with a bovine serum albumin-prostaglandin $F_{2\alpha}$-conjugate.

Since this method does not distinguish between prostaglandins A_1 and A_2, E_1 and E_2, or $F_{1\alpha}$ and $F_{2\alpha}$, the concentrations reported are of the total prostaglandins for each type and are designated simply as PGA, PGE, and PGF, respectively. Prostaglandin A cannot be separated from prostaglandin B by column chromatography. The low cross-reactivity of the antiserum with PGB in comparison with PGA and the lack of an enzyme system in humans to convert PGA to PGB in the plasma (24) indicates that contamination of the sample with prostaglandin B is of minor concern.

RESULTS

A summary of measurements of blood pressure, serum sodium, serum potassium, serum creatinine, creatinine clearance, sodium excretion, weight, and plasma renin activity is shown in Table I.

High salt diet. The high salt diet led to an increase in weight in all subjects except G. S. The mean increase for the group was 1.1% of control body weight ($P < 0.04$). This was associated with increased urinary sodium excretion from an average base line of 151 meq/day to an average of 230 meq/day. There was no significant change in blood pressure or in serum sodium or potassium concentrations. Although serum creatinine did not change significantly, creatinine clearance increased from 117.8 to 130.7 cm^3/min ($P < 0.03$).

As expected, plasma renins were lower during the high salt diet than during ad lib. or low salt diet in every subject.

Low salt intake. The 10 meq sodium diet led to a mean weight loss of 3.7%. Systolic, diastolic, and mean blood pressures fell in every individual, averaging 4.5, 3.4, and 3.7% decrease from baseline values, respectively. Mean serum sodium fell 2.3 meq/liter, ($P < 0.002$) but serum potassium did not change from control levels. Every subject reached urinary sodium outputs of less than 10 meq/day by the 5th low sodium day except G. S. who excreted 21 meq/24 h. Mean serum creatinine rose significantly from 0.96 to 1.15 mg/100 ml ($P < 0.02$). Renin levels rose over base-line values in every subject during salt restriction.

Prostaglandin A. Mean plasma concentrations of prostaglandin A for 4 ad lib. Control days and for the last 3 days of each experimental period are shown in Table II and Fig. 1.

During the ad lib. sodium intake, mean plasma PGA was 1.60 ng/ml. The level fell almost 50% during the high sodium diet to a mean of 0.82 ng/ml. During the

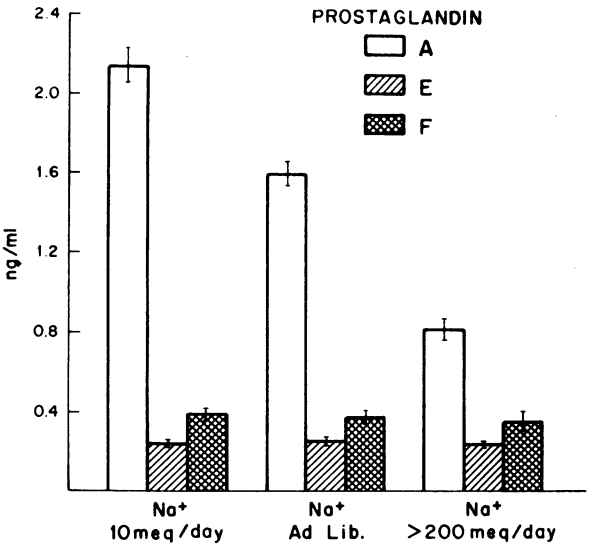

FIGURE 1 Effect of sodium intake on plasma prostaglandin A, E, and F concentrations in normal humans on high, low, and ad lib. sodium intake diets.

low sodium diet, PGA levels rose approximately 34% over base line, and 161% over high sodium intake to 2.14 ng/ml. These changes were significant at $P < 0.001$.

Sequential changes of PGA are shown on a daily basis in Fig. 2. In every subject, PGA levels dropped dramatically during the 2nd day of the high salt diet and plateaued at this new level. The effect of low sodium intake of PGA levels is somewhat more gradual, although this could reflect the effect of the prior salt load. However, there was no difference in the rate of change of PGA in subjects in whom low salt diet immediately followed high salt diets and in those subjects in whom the two dietary periods were separated by 6 days. If prior salt loading had an effect on PGA levels during sodium deprivation, one would expect a difference in the two groups of subjects since it would seem likely that at least in the second group, control conditions would have been reestablished.

Plasma PGA levels rose during the low sodium diet and plateaued during the 4th day in most subjects, although the mean for the dietary period was determined from the last 3 days for statistical purposes. In one subject (D. S.), the levels of PGA did not rise significantly for the period as a whole. We cannot ascribe this response to dietary indiscretion since other parameters changed in expected fashion during this period in this subject.

Prostaglandin E and F. Neither prostaglandin E nor F changed significantly during the dietary periods (Fig. 1).

DISCUSSION

Our results show that circulating plasma levels of prostaglandin A are profoundly influenced by changes in dietary sodium chloride, while levels of prostaglandins E and F are not. It has been shown (25, 26) that both PGE and PGF are almost completely metabolized by passage through the lungs, whereas PGA is not. It is possible that changes in PGE and/or PGF occurred, but were masked by pulmonary metabolism. Nevertheless, the results seem to add weight to the suggestion by many authors that PGA could function systemically as a circulating hormone.

Our experiments do not elucidate the source of circulating prostaglandin A although it seems likely that the kidney contributes to the total. Prostaglandins A, E, and F have been found in the renal medulla, and prostaglandin-like substances have been released in response to several types of physiologic stimuli, including renal nerve stimulation (5), adrenaline (6), bradykinin (7), angiotensin II (8), and ischemia (9). Furthermore, changes in salt balance were noted to effect the numbers of lipid droplets in renal interstitial cells (3). Finally, we have recently shown that changes in rat kidney prostaglandin A content parallel changes in circulating plasma prostaglandin A under conditions of dietary sodium intake similar to those in the present study (22).

Although the stimulus for the elevated prostaglandin A levels in our study was salt deprivation, the mechanism by which this occurs is unclear. It has been suggested that prostaglandin A is a circulating natriuretic hormone, our data indicates that rather than observing an increase in circulating PGA levels on a high sodium diet, an increase occurs with the low sodium diet. An explanation of these observations must be highly speculative. Intraarterial angiotensin II has been shown to release prostaglandin-like substances in the renal venous effluent (8). It is possible that changes in circulating angiotensin II levels with changes in sodium intake are responsible for the observed alterations in plasma PGA levels. Hollenberg et al. (27) have shown a decrease in cortical blood flow on low sodium diets in humans. Changes in intrarenal prostaglandin synthesis may be responsible for changes in renal hemodynamics observed with changes in sodium intake.

It is interesting that both renal nerve stimulation and angiotensin infusion have led to an increase in prostaglandin-like substances in renal venous blood (5, 6, 8). It has been shown that recovery of renal blood flow and urine flow in noradrenalin-infused dogs (6) and angiotensin-infused dogs (8) is accompanied by increasing concentrations of PGE-like substances in renal venous

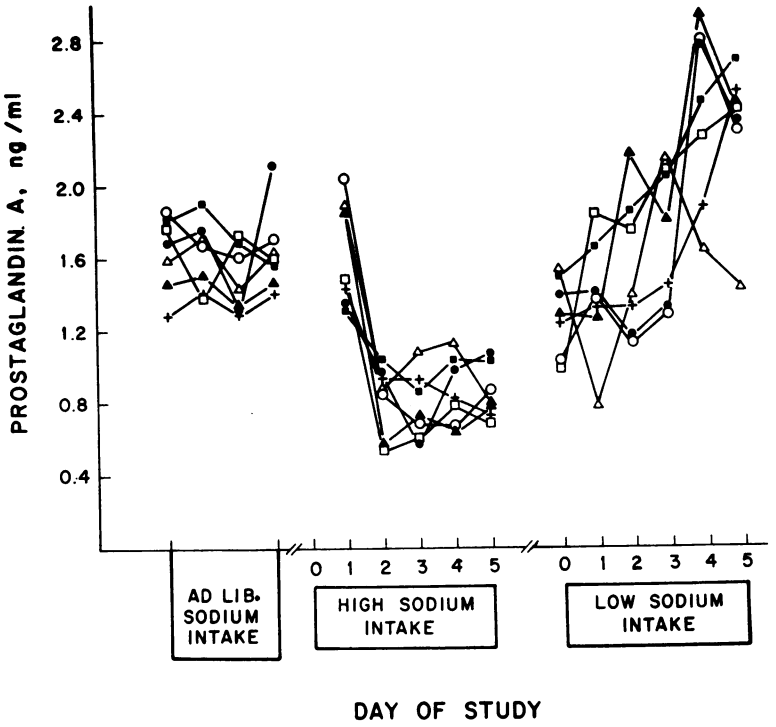

FIGURE 2 Effect of sodium intake on daily plasma prostaglandin A concentrations in normal humans.

effluent. PGA was not estimated in these studies. Thus a change in intrarenal blood flow, whether due to renal nerve stimulation, angiotensin, norepinephrine, or renal ischemia appears to be associated with the release of prostaglandins from the kidney. Intrarenal alterations in medullary and cortical prostaglandin levels may be responsible for the changes in blood flow distribution in response to these stimuli. As a potent vasodilator, prostaglandins could act locally in an intrarenal feedback system, and systemically on peripheral vasculature. In regard to the latter effect, during salt deprivation in the present study when renin levels are extremely high, blood pressure is significantly lower than during the control period. Presumably this is due to the effect of vascular volume contraction, but it is possible that the elevated levels of prostaglandin A play a role as well. Herbaczynaka-Cedro and Vane (28) have shown that animals pretreated with indomethacin, a potent prostaglandin synthesis inhibitor, exhibt greater vasoconstriction in response to intravenous angiotensin than untreated controls. These studies suggest that prostaglandins play an important role in the modulation of the peripheral vasoconstricting effects of angiotensin and thus play a role in blood presure control. In addition to the vasodilatory action, PGA may play another role in sodium homeostasis by contributing to the increased aldosterone production during sodium deprivation.

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