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A HIGH-SALT MEAL PRODUCES NATRIURESIS IN HUMANS WITHOUT ELEVATING PLASMA ATRIOPEPTIN

MARK A. SAVILLE, PAMELA G. GEER, BIN C. WANG, ROBERT J. LEADLEY, JR., AND KENNETH L. GOETZ

Division of Experimental Medicine, St. Luke's Hospital and Foundation, Kansas City, Missouri 64111, and Department of Physiology, University of Kansas Medical Center, Kansas City, Kansas 66103

Abstract. The effects of a high-sodium meal on plasma atrial natriuretic peptide (atriopeptin) and renal sodium excretion were studied in eight normal human subjects. As expected, sodium excretion and urine osmolality increased following the meal. Plasma atriopeptin levels did not increase, however, after the high-sodium meal. In a control experiment, consumption of a low-sodium meal by six of the same subjects did not increase either urinary sodium excretion or plasma atriopeptin concentration. We conclude that the natriuresis elicited by a high-salt meal is not mediated by the atrial peptides. © 1988 Society for Experimental Biology and Medicine

Introduction. Consumption of a high salt diet for several days has caused human subjects to develop modest, but significant, elevations of circulating atriopeptin in most (1-4), but not all (5), of the studies that have been reported. The concentration of atriopeptin in plasma was 1.4- to 3.3-fold greater after several days on a high salt diet than it was when the same subjects consumed a low-salt diet (1-4). Although it was suggested that the elevation in circulating atriopeptin may have contributed to the increase in renal sodium excretion that accompanied the increased sodium intake (1-4), several investigators have reported that sustained elevations of plasma atriopeptin produced by chronic intravenous infusion do not appreciably increase sodium excretion (6-8).

If atriopeptin is a physiological regulator of renal sodium excretion, its plasma concentration might be expected to increase acutely in response to a high-sodium meal and to correlate with a period of augmented renal sodium excretion. Homcy and associates (9) reported that ingestion of 85 g of salted potato chips led to elevated plasma levels of atriopeptin in human subjects; however, sodium excretion was not measured in that study. Verburg and his colleagues (10) observed concomitant increases in plasma atrial peptides and urinary sodium excretion in dogs after the animals had ingested a meal containing 125 mmol of sodium. The present investigation was designed to determine whether ingestion of a single high-salt meal by human subjects would produce an increase in circulating atriopeptin levels that might correlate with the postprandial increase in renal sodium excretion.

Materials and Methods. Eight healthy volunteers (five women, three men; age 24-55) participated in the study. All

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subjects were laboratory personnel who remained on their usual diets prior to the study. Routine work activities were performed by each subject during the experiment in order to mimic normal daily living conditions as closely as possible. We limited the number of hormones measured to minimize blood loss. The study was approved by the Institutional Review Board of St. Luke's Hospital. All volunteers gave informed consent.

At 0630 on the day of the experiment, after having had nothing to eat or drink since 2300 the previous day, the subjects drank 2 ml of water per kg of body weight; they subsequently drank an identical amount of water at hourly intervals until the experiment ended. At 0730 the subjects emptied their bladders and began timed urine collections (four 1-hr urine collections followed by two 2-hr collections). At 0830 the subjects consumed either a high-salt (100 mmol sodium) or low-salt (4 mmol sodium) breakfast along with 350 ml of a beverage that did not contain caffeine. This liquid was provided in addition to the hourly water ration. Each meal consisted of approximately 340 calories, but the high-salt meal was supplemented with sodium chloride that was dissolved in the hourly water ration and consumed immediately before the food was eaten. All eight subjects participated in the high-salt study and six of these same subjects participated in the low-salt study. The high-salt experiment was performed at least one month prior to the low-salt experiment.

Venous blood samples were taken from a forearm vein immediately before the meal and at the midpoint of each subsequent urine collection period. The samples were analyzed for plasma atriopeptin, renin activity, sodium, potassium, osmolality, and hematocrit. Once each hour the subjects were seated comfortably for 1 min before blood pressure was determined by a blood pressure cuff on the arm and heart rate was determined by palpation. These measurements routinely preceded venipuncture. No attempt was made to maintain cardiovascular variables at basal conditions during the experiments. Mean arterial blood pressure was calculated as follows: diastolic pressure + 1/3 (systolic - diastolic pressure).

The concentration of atriopeptin in plasma was determined by radioimmunoassay. All plasma samples were extracted with Sep-Pak C_{18} cartridges (Waters Associates) and evaporated to dryness. Plasma extracts were reconstituted in assay buffer to one-fourth of the original volume of the plasma samples to enable low concentrations of atriopeptin to be detected by radioimmunoassay. Standards (α-human atrial natriuretic polypeptide, Peninsula Laboratories) ranged from 0-100 pg/assay tube. Antibody to α-human ANP (Peninsula Laboratories) and ^{125}I-labeled α-hANP tracer (Amersham Corporation) were combined with standards or concentrated plasma extracts and determined in triplicate. Antigen-antibody complexes were precipitated with goat anti-rabbit IgG serum and normal rabbit serum (Peninsula Laboratories). The recovery of ^{125}I-labeled α-hANP and unlabeled α-hANP added to plasma was 66% and 63%, respectively. The atriopeptin values were not corrected for losses during extraction. The minimal detectable amount of atriopeptin was 1.5-3 pg/tube. Intra- and inter-assay coefficients of variability were 4.1% and 16.7%, respectively. Plasma renin activity was measured by radioimmunoassay with reagents supplied by a commercially-available kit (Clinical Assays). Urinary and plasma electrolytes were measured by flame photometry, and osmolality was measured by freezing point depression. Hematocrit was measured in capillary tubes after centrifugation.

Statistics. All results are reported as means ± SE. Data for each variable were evaluated by an analysis of variance for repeated measures. Dunnett's test was used to determine which means differed statistically from the control period. P values of less than 0.05 were considered to be statistically significant.

Results. High-sodium meal. The effects of a high-salt meal on plasma atriopeptin concentration and renal variables are shown in Figure 1 (solid lines). Atriopeptin concentration was 31.9 ± 5.4 pg/ml prior to eating and did not change significantly following

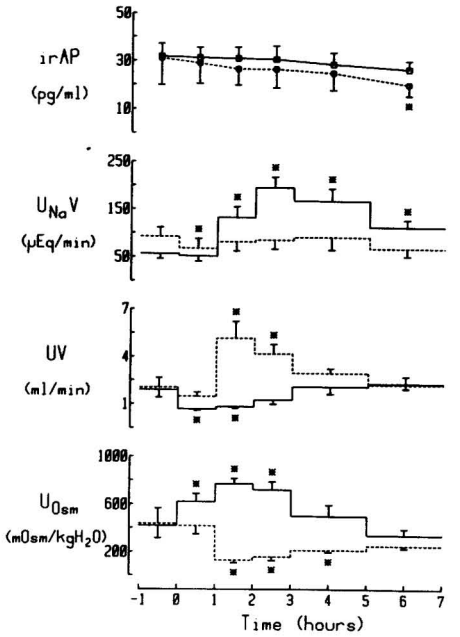

Fig 1. Effects of a high-salt (solid lines) and a low-salt (dashed lines) meal on plasma immunoreactive atriopeptin concentration (irAP), urinary sodium excretion rate (UNaV), urine flow rate (UV), and urine osmolality (UOsm) in healthy human subjects. Values shown correspond to the hour before (control) and seven hours after ingestion of the high- or low-salt breakfast consumed at 0830 hrs. Note that the last two experimental periods are each two hours long. *P < 0.05 compared to control value.

ingestion of the meal, although it tended to fall progressively to 26.9 ± 3.6 pg/ml by the final period. Urinary sodium excretion rate was unchanged from the pre-meal rate of 56.7 ± 11.0 μEq/min during the first hour after the high-salt breakfast, but increased thereafter and peaked at 346% of the pre-meal sodium excretion rate during the third hour after the meal. Urine flow rate (UV) decreased during the first two hours after the high-sodium meal before returning to near the control rate of 1.9 ± 0.5 ml/min. Urine osmolality averaged 418 ± 105 mosm/kg H_2O prior to the high-salt meal and increased during the three hours immediately following the breakfast.

Plasma renin activity tended to increase initially and then decline (NS) from the control value after consumption of the high-sodium meal (Table I). Plasma sodium concentration increased significantly during the first hour after eating and then slowly declined. Plasma osmolality rose from the pre-meal level of 287.9 ± 1.7 to 293.6 ± 2.0 mosm/kg H_2O during the second hour after the high-salt meal before returning to control levels. Hematocrit decreased within thirty minutes after consumption of the high-salt breakfast and remained below pre-meal levels throughout the study. Heart rate declined modestly, but significantly, during the latter stages of the experiment. Mean arterial pressure was unchanged.

Low-sodium meal. The effects of a low-sodium meal on plasma atriopeptin concentration and renal variables are shown in Figure 1 (dashed lines). Atriopeptin concentration declined progressively following the low-salt meal from a control level of 31.1 ± 11.0 to 20.4 ± 4.6 pg/ml at the end of the experiment. Much of the decrease in atriopeptin concentration in the final period can be attributed to one subject whose atriopeptin level decreased from a control value of 85.6 to 43.1 pg/ml at the end of the study. Control sodium excretion rate was 92.5 ± 19.5 μEq/min and did not differ significantly from the corresponding value obtained before the high-sodium meal. Sodium excretion did not increase following ingestion of the low-sodium breakfast, but urine flow increased significantly from a control rate of 2.0 ± 0.6 to a peak of 5.2 ± 1.1 ml/min. Urine osmolality decreased significantly from a control value of 432 ± 132 mosm/kg H_2O to 129 ± 24 mosm/kg H_2O within two hours after consuming the low-salt meal.

Plasma renin activity was elevated during the first two hours after the low-sodium meal (Table I). Plasma sodium concentration was decreased significantly during the first hour after the meal and remained depressed throughout the remainder of the study. Plasma osmolality did not change following the low-salt breakfast.

Table I

Effect of High- and Low-Sodium Meals on Plasma Levels of Renin Activity, Sodium, Osmolality, and on Hematocrit, Heart Rate, and Mean Arterial in Normal Human Subjects

		Time after consumption of meal (h)					
		Control	0.5	1.5	2.5	4.0	6.0
PRA	Hi	2.6±0.8	3.5±0.8	2.6±0.4	2.1±0.5	1.5±0.3	2.1±0.4
	Lo	1.7±0.6	3.3±1.1*	3.8±0.8*	2.7±0.6	2.0±0.6	2.4±0.6
P_{Na}	Hi	142.1±0.7	144.5±0.5*	144.2±0.9	143.4±0.9	140.4±0.7	140.0±1.5
	Lo	143.4±1.0	141.5±0.9*	140.7±0.9*	141.4±1.2*	139.7±0.8*	136.6±0.7*
P_{Osm}	Hi	287.9±1.7	293.2±1.1	293.6±2.0*	289.4±2.4	288.5±2.2	282.8±2.3
	Lo	283.6±3.1	283.4±2.9	281.6±1.9	283.4±1.5	281.1±1.5	281.4±0.9
Hct	Hi	43.4±1.2	41.9±1.1*	41.0±1.0*	40.7±1.0*	40.8±1.2*	41.4±1.2*
	Lo	43.8±1.2	43.5±1.1	43.1±1.3	43.1±1.2	42.9±1.2*	42.9±1.1*
HR	Hi	73±2	73±3	77±3	68±2*	66±3*	67±2*
	Lo	64±4	69±3*	71±3*	68±3	64±4	65±4
MAP	Hi	90±4	91±4	87±4	89±3	87±5	87±4
	Lo	97±5	95±4	90±3*	90±4*	93±4	93±3

Values are means ± SE. Control values were obtained 30 minutes before meal consumption. All values are n=8 for high- and n=6 for low-salt meal. Abbreviations are Hi, high salt meal; Lo, low salt meal; plasma renin activity, PRA (ng AI/ml/h); plasma sodium concentration, P_{Na} (μEq/ml); plasma osmolality, P_{Osm} (mosm/kg H_2O); hematocrit, Hct (%); heart rate, HR, (bpm); mean arterial pressure, MAP, (mmHg). * $P < 0.05$ compared with control value.

tocrit did not change immediately the low-salt meal, but decreased he end of the experiment. Heart increased modestly early in the eriment, and mean arterial pressure declined.

Discussion. The consumption of a high-sodium meal by the subjects in this study was followed by a substantial natriuresis that was not accompanied by an increase in circulating atriopeptin. One may conclude, therefore, that the postprandial increase in urinary sodium excretion was not mediated by atrial peptides. Rather, the natriuresis may have been caused by a decrease in renal nerve activity (11), by a release of a natriuretic hormone that inhibits Na^+-K^+ATPase (12), or by stimulation of central receptors such as the circumventricular organs involved in salt appetite control (13). The absence of natriuresis following the low-sodium breakfast demonstrated that the natriuretic response evoked by the high-sodium breakfast was caused by the 100 mmol sodium load, a substantial physiological stimulus, and not simply by the act of eating or by diurnal factors.

Consumption of the high-salt meal increased plasma sodium and osmolality and induced an increase in sodium excretion and urine osmolality while urine flow decreased significantly. Although plasma vasopressin levels

were not measured in these experiments, it is probable that plasma vasopressin increased in response to the elevated plasma osmolality (14) and thereby increased renal free water reabsorption which in turn reduced urine volume and increased urine osmolality. In contrast, plasma sodium decreased and plasma osmolality tended to decline when the breakfast contained only a small amount of sodium; urine osmolality became hypotonic, presumably because plasma vasopressin levels had decreased.

The small fluctuations in heart rate and blood pressure that occurred most likely are attributable to minor alterations in the activity of our subjects during the experiment. As mentioned earlier, the subjects performed routine duties to ensure that our results would reflect responses obtained during normal living conditions.

There is good evidence that atrial distension increases circulating levels of atriopeptin in experimental animals (15, 16) and human subjects (17, 18). It is unlikely, however, that the atria of our subjects were distended appreciably during the course of the present experiments. An estimation of changes in blood volume using hematocrit values and the Van Beaumont formula (19) indicated that a maximal increase in blood volume of 4.7% occurred in our subjects three hours after ingestion of the high-salt meal. Small increases in plasma volume are distributed primarily to dependent portions of the venous system, i.e. to areas below heart level, and it is unlikely that the small increase in plasma volume would produce significant elevations in atrial pressures in our subjects who remained either upright or seated throughout the experiment. It also is noteworthy that the small but significant increases in plasma sodium and osmolality that occurred after the high-salt meal were unable to increase circulating atriopeptin levels. Nevertheless, the renal response of our subjects was appropriate for each stimulus.

The results of our experiments contrast with those of Homcy et al. (9) who reported that an increase in plasma atriopeptin occurred in human subjects following ingestion of 85 g of salted potato chips. It is difficult to compare the two studies because the amount of salt contained in the potato chips was not specified, and Homcy et al. did not indicate whether liquids were consumed with the chips. They also did not measure urinary sodium excretion. Verburg and colleagues (10) reported an elevation of circulating atrial peptides in conscious dogs that correlated with the natriuresis following ingestion of a meal containing 125 mmol of sodium. This sodium load, however, was approximately four times greater on a body weight basis than the amount of sodium given to our human subjects. Whereas water intake was controlled in the present investigation, water was available ad libitum to the dogs in Verburg's study, a factor that may have contributed to a greater postprandial increase in blood volume.

As mentioned in the introduction, most studies indicate that consumption of a high-salt diet for several days by human subjects induces approximately a 2-fold increase in the concentration of atriopeptin in plasma. It therefore has been suggested by some investigators (1-4) that the elevated peptide concentration may contribute to the augmented natriuresis elicited by the increased salt intake. We are aware of no evidence, however, to suggest that an approximate doubling of plasma atriopeptin could be responsible for an appreciable part of the massive increase in renal sodium excretion necessary to preserve sodium balance when subjects increased their sodium consumption by 6.5- to 35-fold (1-4). Further evidence compatible with the view that atriopeptin plays a minimal role in eliciting the natriuresis induced by high sodium intake comes from studies in which chronic salt loading was not accompanied by increases in circulating atriopeptin (5, 20, 21); nevertheless, urinary sodium excretion increased appropriately in response to the salt load.

In summary, ingestion of a high-sodium meal elicited a postprandial increase in urinary sodium excretion. Circulating levels of atriopeptin did not increase following the high-sodium meal. Consequently, we conclude that the postprandial natriuresis that follows

a high-salt meal is not mediated by atrial peptides.

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