Short-term effects of various sugars on antinatriuresis and blood pressure changes in normotensive young men[1-4]

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ABSTRACT This is a report of the effects of sugars on salt metabolism and on blood pressure. Twenty young men, none of whom had a personal or family history of hypertension, were orally hydrated after an overnight fast and required to lie recumbent for 6 h except for urinary voiding and blood pressure measurements which were performed at ½ h intervals. Venous blood samples were drawn at hourly intervals. The volunteers were kept constantly hydrated by giving them water to drink equivalent to the volumes of urine voided. Two hours from the start of the experiment each subject was given one of the following sugars: glucose, fructose, sucrose, galactose, lactose, or water alone. After oral hydration the subjects appeared to develop natriuresis and kaliuresis. This was quickly abolished by ingestion of either glucose, fructose, sucrose, or lactose, but not by galactose or water alone. Fructose was the most potent antinatriuretic agent. Both glucose and sucrose significantly elevated systolic blood pressure. This lasted for 2 h after glucose ingestion and 1 h after sucrose ingestion. *Am J Clin Nutr* 1983;38:84–94.

KEY WORDS Salt metabolism, blood pressure, normotensive men, glucose, fructose, sucrose, lactose, galactose

Introduction

Total fasting of either obese or lean subjects causes a marked natriuresis which often lasts for 4 to 5 days (1–3). This natriuresis can be abolished quickly by feeding glucose (4–6), and to some extent by feeding protein (7), but not by feeding fat (8).

Kruck and Krecke (9) observed that natriuresis can be induced by hydration of subjects who have fasted overnight. Lindeman et al (10) who also studied this phenomenon, noted this natriuresis in some, but not all, apparently normal individuals. During the period of salt loss, however, ingestion of glucose promptly brought about salt conservation. Of even greater interest was the observation that persons who had hypertension exhibited, on the average, a greater than normal degree of natriuresis when fasted. Administration of glucose resulted in a greater average antinatriuresis in hypertensive than in normal subjects (11). Recent evidence (12, 13) suggests that the red cell membrane sodium transport system may be abnormal in hypertensives. Furthermore, some normotensive subjects born of one or both hypertensive parents also exhibit this abnormality (13, 14). Urinary excretion of sodium is partly mediated by sodium/potassium ATPase systems which are located in the kidney tubules. Factors that control these transport systems are largely unknown although there has been some speculation that they are under hormonal control (15–18).

The alleged (19–25) association of sugar with hypertension is not well defined. Ahrens et al (23) noted that rats retained more salt when fed with sucrose. The increase in blood pressure that occurred in these rats was attributed to an increased retention of sodium.

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If an exaggerated antinatriuresis, induced by glucose feeding, is indeed characteristic of hypertensive patients, it is conceivable that a normotensive person born of hypertensive parents might exhibit a similar response to glucose.

The purpose of this study was to examine the effects of the commonly available sugars—glucose, fructose, sucrose, galactose, and lactose—on sodium excretion in fasted, hydrated, normotensive men. We anticipate that this study may be a prelude to an evaluation of the antinatriuretic effects of these sugars in normotensive individuals born of either one or both hypertensive parents.

Methods

Twenty healthy young men were chosen on the basis of normal blood pressure (below 140/90 mm Hg) and normal body weight (as defined by the Metropolitan Life Insurance Tables). None of them had any major illness and all had parents with normal blood pressure. The volunteers consumed an unrestricted diet and were asked to continue normal activities. On the evening before the test, they were required to fast for 12 h. Only water was allowed after 6 PM. On arrival at the clinic at 6 AM, each was asked to empty his bladder and discard the urine. Immediately thereafter, each was given a loading dose of distilled water equivalent to 20 ml/kg weight. The subjects rested comfortably in a supine position for the next 6 h, but were allowed to stand and void at will. All urine voided after 6:00 AM was saved. To maintain a constant state of hydration they were replenished at intervals with a volume of water equal to the amount of urine voided. At 8 AM each subject was given 1 g/kg of one of the five test sugars dissolved in water (22% w/v). The sugars were assigned to an individual in a random fashion according to a Latin square design. Thus, each man received each of the five sugars at different times. Urinary voiding followed by replenishment was carried out for a further 4 h. For analyses, urinary voidings were pooled at 2-h intervals (specimen I, 6 to 8 AM; specimen II, 8 to 10 AM; and specimen III, 10 to 12 noon). These periods (I, II, III) were designated the "presugar," "sugar," and "post sugar" periods, respectively. Blood samples were collected at regular intervals to coincide with the midpoints of periods I, II, and III. Blood pressure was measured in the sitting position at hourly intervals by means of a mercury column sphygmomanometer with standard cuff. Systolic pressure was recorded as the highest level at which successive sounds were heard. Diastolic pressure was recorded at the disappearance of sound (Korotkoff phase V). Two trained nurses were responsible for blood pressure measurements and were assigned to the subjects in a random fashion. Blood pressure data for each of the five sugars were analyzed by repeated analysis of variance. Multiple-range comparisons of individual means were done by the Newman-Keuls method on those sugars with a significant overall F value. Differences between means that exceeded the critical q_r value were considered significant at the 0.05 level (26).

Hematocrit values were determined by a micromethod, and plasma glucose was measured by the glucose oxidase reaction on a Beckman glucose analyzer. Serum insulin was measured by radioimmunoassay (Amersham/Searle). Urinary aldosterone was determined by radioimmunoassay (Diagnostic Products Co). Urinary sodium and potassium were determined by flame photometry. Rates of urinary excretion of sodium and potassium during the presugar, sugar, and postsugar periods were analyzed by paired *t* test and analysis of variance.

This research protocol was approved by the Executive Committee of the Medical Staff at The University of Nebraska Medical Center.

Results

Oral hydration alone (***Table 1, Figs 1 and 2***)

Sodium excretion. Oral hydration alone in nine subjects who fasted overnight appeared to produce natriuresis. Sodium excretion rose from a mean value of 11.27 ± 1.08 mmol in period I to 16.53 ± 1.18 in period III ($p < 0.001$)

Potassium excretion. An apparent kaliuresis was also observed in these nine subjects. Potassium excretion rates in period II (9.07 ± 0.59 mmol and period III (9.26 ± 0.64 mmol) were significantly different from period I:−6.77 ± 0.59 mmol ($p < 0.05$ and $p < 0.01$, respectively).

*Sugar feeding and sodium excretion (Table 1, **Figs 2, 3, and 4**)*

Glucose. Glucose feeding caused a significant antinatriuresis of about 7 mmol ($p < 0.05$). Sodium excretion 2 h after the sugar load returned to presugar values, and were significantly different from period II ($p < 0.01$).

Fructose. Fructose feeding brought about a significant fall in sodium excretion of about 7 mmol with respect to period I ($p < 0.01$) and period III ($p < 0.001$).

Sucrose. Sucrose ingestion caused a modest (4 mmol) but significant depression of sodium excretion ($p < 0.05$). Sodium excretion in period III returned to presugar values, and were significantly different from period II ($p < 0.001$).

Galactose. Galactose did not produce a significant antinatriuresis; however, sodium excretion 2 h later (period III) rose significantly ($p < 0.01$) with respect to period II.

TABLE 1
Short-term metabolic responses to various sugars*

Treatment	period	$U_{Na}V$	$U_K V$	$V_{ml\ min}$	U_{aldo}	P_{glu}	P_{ins}	H_t
		mM/2 h	*mM/2 h*		*μg/2 h*	*mM*	*μU/ml*	
Water	I	11.27 ± 1.03[a]	6.77 ± 0.59[b]	15.0 ± 1.2	1.45 ± 0.28[b]	4.6 ± 0.2		44.0 ± 2.2
	II	14.22 ± 1.39	9.07 ± 0.81[a]	14.5 ± 0.7	0.51 ± 0.09[a]	4.5 ± 0.1	14.3 ± 3.1	43.0 ± 2.1
	III	16.53 ± 1.18[b]	9.26 ± 0.64[a]	14.2 ± 0.6	0.39 ± 0.05[a]	4.5 ± 0.1	17.0 ± 5.2	44.1 ± 2.0
Glucose	I	16.16 ± 3.30[b]	8.29 ± 1.14[b]	15.0 ± 0.8	1.69 ± 0.20[b]	4.4 ± 0.1[b]		44.3 ± 2.3
	II	8.53 ± 1.06[a]	4.20 ± 0.39[a]	15.0 ± 1.2	0.58 ± 0.08[a]	6.1 ± 0.3[a]	95.1 ± 16.8[a]	43.8 ± 2.3
	III	16.03 ± 2.94[b]	8.40 ± 1.04[b]	17.0 ± 1.2	1.08 ± 0.16[a]	3.7 ± 0.1	21.8 ± 3.8	44.6 ± 2.8
Fructose	I	13.73 ± 2.06[b]	6.67 ± 0.60[b]	15.8 ± 1.4[b]	1.43 ± 0.15[b]	4.4 ± 0.1		45.4 ± 1.8
	II	6.18 ± 0.63[a]	3.20 ± 0.31[a]	11.0 ± 1.1[a]	0.74 ± 0.16[a]	4.6 ± 0.1	36.6 ± 5.3	45.1 ± 1.8
	III	14.56 ± 2.01[b]	6.93 ± 0.90[b]	13.5 ± 0.7	1.00 ± 0.13[a]	4.2 ± 0.1	29.3 ± 5.9	44.8 ± 1.7
Sucrose	I	14.92 ± 1.89[b]	6.38 ± 0.63[b]	15.0 ± 1.1	1.20 ± 0.19[b]	4.5 ± 0.1[b]		43.9 ± 2.6
	II	10.77 ± 1.24[a]	3.85 ± 0.42[a]	14.5 ± 1.3	0.52 ± 0.06[a]	5.6 ± 0.2[a]	82.7 ± 12.2a	44.0 ± 2.4
	III	17.05 ± 1.67[b]	7.39 ± 0.80[b]	16.3 ± 1.1	0.77 ± 0.11[a]	4.1 ± 0.1	19.4 ± 3.5	44.5 ± 2.4
Galactose	I	13.26 ± 3.26[ab]	5.96 ± 0.71[b]	15.0 ± 1.2	1.53 ± 0.20[b]	4.5 ± 0.1		44.0 ± 2.2
	II	11.18 ± 1.63[a]	4.51 ± 0.34[a]	15.8 ± 1.1	0.61 ± 0.07[a]	4.2 ± 0.1	31.6 ± 4.4	43.7 ± 2.0
	III	16.33 ± 2.12[b]	6.98 ± 0.74[b]	16.6 ± 1.3	0.77 ± 0.13[a]	4.2 ± 0.1	23.5 ± 3.6	44.1 ± 2.3
Lactose	I	12.83 ± 2.63[b]	5.42 ± 0.63[b]	15.0 ± 1.2	1.41 ± 0.17[b]	4.5 ± 0.1[b]		44.8 ± 2.4
	II	8.66 ± 1.18[a]	3.54 ± 0.31[a]	14.3 ± 1.5	0.67 ± 0.10[a]	5.1 ± 0.2[a]	52.8 ± 9.7[a]	44.5 ± 2.5
	III	14.43 ± 1.43[b]	6.46 ± 0.49[b]	15.8 ± 1.3	0.84 ± 0.13[a]	4.1 ± 0.1	22.7 ± 4.3	44.7 ± 2.5

* Effects of oral hydration alone (nine subjects) and ingestion of five sugars on urinary secretion of sodium ($U_{Na}V$), potassium ($U_k V$), urinary flow ($V_{ml/min}$), aldosterone (U_{aldo}), and plasma glucose (P_{glu}), insulin (P_{ins}), and hematocrit (H_t) in 20 normotensive young men.

The experimental period of 6 h was divided into three periods (PI, PII, PIII) representing presugar, sugar, and postsugar periods.

$V_{ml/min}$ for PI and PII represent urinary flow 1 h before and after sugar refeeding. (Values for PIII are mean urinary flow for that period.)

P_{glu} for PI and PII represent values 1 h before and after sugar refeeding respectively. Data for PIII represent values determined 3 h after sugar refeeding.

P_{ins} for PI and PII represent values 1 h before and after sugar refeeding.

H_t for PI and PII represent values 1 h before and after sugar refeeding. Data for PIII represent values determined 3 h after sugar refeeding.

All data shown are mean ± SEM—data with different letters are significantly different; $p < 0.05$ (paired t test).

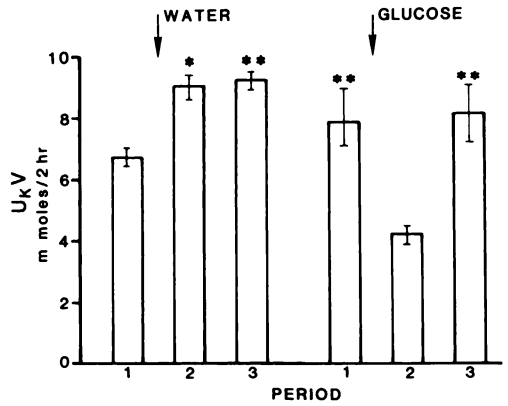

FIG 1. Mean urinary excretion of potassium (U_kV) after oral hydration alone (nine subjects) and after refeeding with glucose (20 subjects). The 6-h experimental period was divided into three periods, PI, PII, and PIII which represented presugar, sugar, and postsugar periods, respectively. Data analyzed by paired *t* test (PI vs PII and PII vs PIII). *; **; ***; $p < 0.05$; $p < 0.01$; $p < 0.001$, respectively.

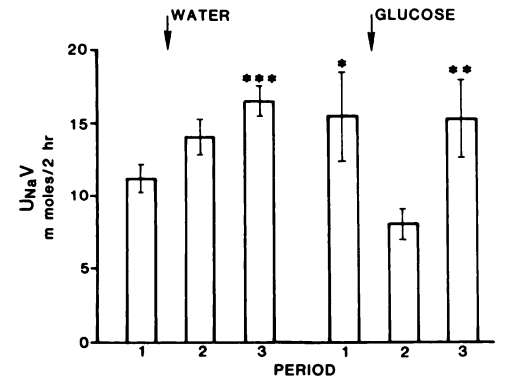

FIG 2. Mean urinary excretion of sodium ($U_{Na}V$) after oral hydration alone (nine subjects) and after refeeding with glucose (20 subjects). Experimental conditions similar to Figure 1.

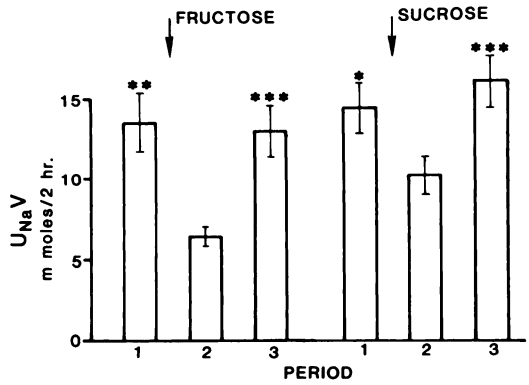

FIG 3. Mean urinary excretion of sodium ($U_{Na}V$) after ingestion of fructose or sucrose (20 subjects). Experimental conditions similar to Figure 1.

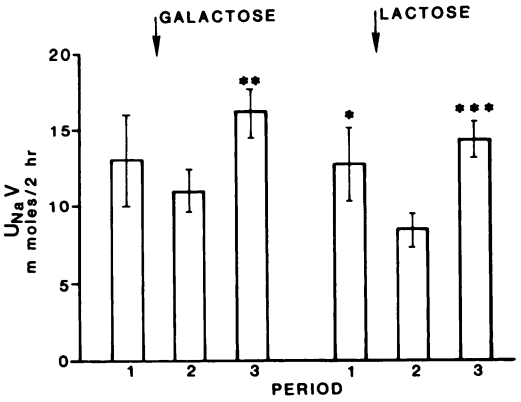

FIG 4. Mean urinary excretion of sodium ($U_{Na}V$) after ingestion of galactose or lactose (20 subjects). Experimental conditions similar to Figure 1.

Lactose. A small depression in sodium excretion (4 mmol) was observed after lactose ingestion. This was significantly different from base-line ($p < 0.05$) and sodium excretion in period III ($p < 0.001$). In all cases sodium excretion rates 2 h after ingestion of all five sugars were similar to sodium excretion during the presugar period (period I).

Comparison of the antinatriuretic effect of the five sugars (***Fig 5***)

Analysis of variance showed that the antinatriuretic effect of fructose alone is significantly greater than that produced by sucrose or galactose ($p < 0.01$).

Sugar refeeding and potassium excretion (Table 1)

All five sugars (glucose, fructose, sucrose, galactose, and lactose) produced significant antikaliuresis ($p < 0.01$ for glucose, sucrose, fructose and lactose; $p < 0.05$ for galactose). Potassium excretion returned to presugar values 2 h after the sugar drink (period II). Excretion rates in period III, however, were significantly greater than in period II ($p < 0.01$ after each sugar).

Hematocrit (Table 1)

Neither ingestion of water alone nor with sugar produced any significant changes in blood hematocrit values.

Plasma glucose (Table 1)

Plasma glucose values 1 h after ingestion of glucose, sucrose, or lactose were significantly elevated above base-line values ($p <$

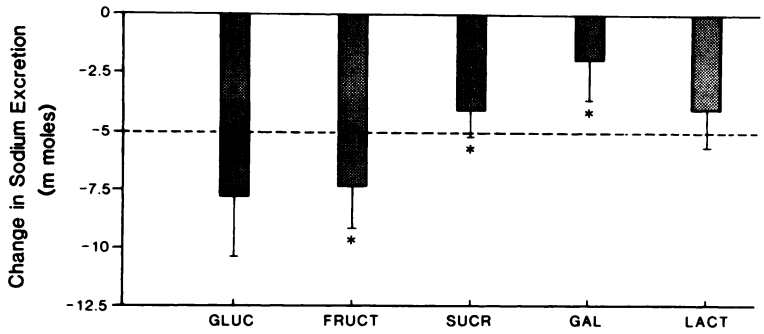

FIG 5. Degree of antinatriuresis after sugar refeeding: absolute change in sodium excretion measured; (the difference in excretion between PII and PI after refeeding with glucose, fructose, sucrose, galactose, or lactose). Values are means ± SEM for 20 normotensive subjects. The *dotted line* represents the overall mean change produced by the five sugars. Data analyzed by ANOVA show that fructose is significantly different from galactose $p < 0.01$ and sucrose $p < 0.01$.

0.001 after glucose and sucrose and $p < 0.01$ after lactose). Neither fructose nor galactose elevated plasma glucose.

Plasma insulin (Table 1)

Insulin determinations were done on blood samples obtained at 1 and 3 h after sugar load. Plasma insulin values were significantly raised at 1 h (relative to the 3-h sample) after glucose, sucrose, and lactose ingestion ($p < 0.01$ for glucose and lactose and $p < 0.001$ for sucrose). Neither fructose nor galactose raised insulin levels.

*Blood pressure (**Table 2**)*

Glucose ingestion significantly raised mean systolic blood pressure by about 10 mm Hg (1 h) and 8 mm Hg (2 h). Thereupon blood pressure returned to presugar values. Mean systolic blood pressure 1 h after sucrose load was significantly raised (8 mm). Neither oral hydration alone nor any of the remaining sugars tested caused changes in blood pressure. Diastolic pressure was not influenced by any experimental treatments.

Aldosterone (Table 1)

After oral hydration alone, there was a progressive fall in urinary excretion of aldosterone. Aldosterone excretion during period II (0.51 ± 0.09 μg/2 h) and period III (0.39 ± 0.05 μg/2 h) was depressed by 25 to 30% relative to period I (1.45 ± 0.28 μg/2 h); ($p < 0.001$). Similarly, ingestion of each of the five sugars depressed urinary aldosterone in period II ($p < 0.001$). Comparisons between mean excretion rates in period III after ingestion of each of the five sugars and after oral hydration alone, show that ingestion of sugars caused a significant elevation of aldosterone excretion ($p < 0.05$ after galactose, $p < 0.01$ after sucrose and lactose, and $p < 0.001$ after fructose and glucose).

*"Exaggerated" response after sugar refeeding (**Table 3**)*

Certain individuals responded to the ingestion of sugars with a profound reduction in sodium excretion. Individuals who had a reduction of 30% or more in sodium excretion were considered to possess an exaggerated antinatriuretic response. Fifteen of 20 individuals responded with an exaggerated antinatriuresis after fructose, 10 after glucose, nine after lactose, eight after sucrose, and three after galactose.

Discussion

Experts disagree on whether or not oral hydration with water alone can produce a substantial degree of natriuresis in healthy persons. Metzger et al (27) observed no increase in urinary excretion of sodium after a sustained water load, whereas Kruck and Krecke (9) and Lindeman et al (10) reported significant natriuresis after oral hydration.

A possible explanation for this discrepancy could be the length of the fast before the experiment. In our studies and in those of Kruck and Krecke (9) and Lindeman et al (10) subjects were fasted for at least 12 h, whereas Metzger et al (27) reported that only

TABLE 2
Systolic (Sys) and diastolic (Dias) blood pressure responses after ingestion of water and various sugars (mean ± SEM)*

Time (h)		−1	0	+1	+2	+3	+4
Water	Sys	118 ± 14	117 ± 13	116 ± 8	118 ± 12	115 ± 14	120 ± 17
	Dias	86 ± 9	82 ± 11	84 ± 9	85 ± 11	82 ± 9	87 ± 10
Glucose	Sys	112 ± 11	111 ± 10	121 ± 11†	119 ± 11†	117 ± 14	116 ± 12
	Dias	81 ± 10	81 ± 9	82 ± 9	84 ± 10	81 ± 10	81 ± 8
Fructose	Sys	121 ± 10	118 ± 10	122 ± 12	121 ± 10	121 ± 10	120 ± 13
	Dias	86 ± 9	86 ± 8	86 ± 8	87 ± 8	89 ± 8	88 ± 9
Sucrose	Sys	119 ± 8	115 ± 10	124 ± 10†	119 ± 11	116 ± 10	119 ± 11
	Dias	85 ± 8	83 ± 8	85 ± 9	86 ± 7	84 ± 9	85 ± 9
Galactose	Sys	113 ± 15	114 ± 14	120 ± 13	115 ± 15	117 ± 14	117 ± 13
	Dias	81 ± 13	83 ± 9	84 ± 9	82 ± 12	86 ± 9	86 ± 9
Lactose	Sys	116 ± 12	117 ± 9	121 ± 14	123 ± 13	118 ± 11	119 ± 11
	Dias	84 ± 10	84 ± 10	86 ± 8	87 ± 7	87 ± 9	86 ± 7

* Multiple range comparisons of individual means were done by the Newman Keuls method on those sugars with a significant overall F value.
† $p < 0.05$. All comparisons evaluated the blood pressure at 0 h and at 1, 2, 3, or 4 h, respectively.

TABLE 3
Percentage of normotensive young men who showed "exaggerated"* antinatriuresis after ingestion of various sugars

Sugar	%
Glucose	50
Fructose	75
Sucrose	40
Galactose	15
Lactose	45

* "Exaggerated" = a reduction of at least 30% in amount of sodium excreted after sugar ingestion.

breakfast was withheld. Fluctuations in sodium excretion, however, may also be attributed to diurnal variations (28).

The significant fall in aldosterone excretion after water hydration, as observed in our study, would suggest that changes in extracellular fluid volume may have taken place, an enlargement of which should cause a fall in aldosterone secretion (29, 30). The observed natriuresis might be due to net loss of sodium from extracellular fluid compartments or could indicate a sodium surfeit (4). An increase in potassium excretion, however, pari passu with sodium excretion, would fail to support the concept that changes in aldosterone activity mediate the observed natriuresis of oral hydration. This natriuresis was not due to obligatory cation coverage of an increased excretion of organic anions, since hydrated individuals who have fasted overnight show no measurable changes in urinary excretion of organic acids (31).

Lindeman et al (10) and Kraikitpanitch et al (11) observed that the natriuresis of oral hydration after an overnight fast can be abolished by a glucose meal. This effect is somewhat analogous to antinatriuresis after a glucose meal in subjects undergoing salt loss as a result of prolonged fasting (1, 5, 6, 32, 33). In the present study we observed that glucose, fructose, sucrose, and lactose, but not galactose, produced a significant antinatriuresis.

Involvement of aldosterone in mediating this response apparently is not necessary since, in the present study, there was a fall in aldosterone excretion after the sugar loads. Further evidence against aldosterone involvement comes from the studies of Gersing and Bloom (34) and Kolanowski et al (35) who observed that low doses of spironolactone (a natriuretic drug and a potent aldosterone antagonist) do not prevent sodium retention in response to glucose ingestion after a period of starvation. Aldosterone, however, may exhibit varying degrees of potency that range from normal to less than normal during early fasting, and become super normal during carbohydrate refeeding (36). The excretion rate of aldosterone may not by itself indicate biological activity. Radioactive aldosterone has

been shown to attach itself to receptor sites along the collecting ducts of rabbit nephrons (37). Histological examinations have shown selective deposits of glycogen in this region (38). The biopotency of aldosterone may be influenced by the simultaneous presence of glycogen deposits which would be replenished by carbohydrate refeeding.

Nevertheless, there may be other factors that reduce urinary sodium, when fasted subjects are refed carbohydrates. Our observations show that all sugars that elevate both plasma glucose and insulin levels also produce significant antinatriuresis. The sugars were administered on a weight basis; hence, lactose and sucrose upon hydrolysis would provide half the amount of glucose as glucose itself. These sugars also produced a lower degree of antinatriuresis compared to glucose itself. One might assume that the potential of a given sugar to produce antinatriuresis depends on its glucose moiety. However, fructose ingestion did not elevate either glucose or insulin levels but did cause significant antinatriuresis. The possible reasons for this will be discussed shortly.

In the present study sodium and potassium excretion returned to presugar values within 2 h after sugar ingestion. Coincidentally, plasma glucose and insulin values also returned to base-line levels. This observation suggests that plasma glucose or plasma insulin levels may mediate the antinatriuresis or the antikaliuresis of carbohydrate feeding.

That insulin may play a role in the renal handling of sodium after glucose refeeding of fasted subjects was suggested by the work of Kolanowski et al (33). However, more direct evidence of insulin involvement came from the studies of DeFronzo et al (39) who found that injection of insulin reduced the natriuresis of subjects undergoing volume expansion. Infusion of insulin while keeping blood glucose levels constant also produced similar antinatriuretic changes (40). This observation would seem to rule out elevated blood glucose per se as a mediator of antinatriuresis. There is convincing evidence that insulin stimulates sodium transport across amphibian epithelia (41, 42); apparently insulin has a direct stimulatory action on the sodium pump (43).

While discussing insulin involvement in mediating antinatriuresis, however, it is also necessary to consider the role of glucagon since insulin-to-glucagon molar ratios may dictate the nutrient fluxes available to the cell (44, 45). Aside from this, glucagon has been shown to possess natriuretic properties. This conclusion was based on the observation that during fasting natriuresis, glucagon levels and renal sodium excretion increase in concert (46, 47). Pharmacological doses of glucagon cause both natriuresis and hyperglycemia (48, 49). However, it is controversial whether glucagon at physiological doses has natriuretic properties or not (46, 50). Although the insulin/glucagon molar ratio has no influence on sodium metabolism during fasts which extend for days (51), the relative levels of these two hormones may be important in determining sodium excretion after short (overnight) fasting. We did not observe any significant correlations between either plasma glucose or insulin values and the degree of natriuresis.

There is some evidence that antinatriuresis brought about by carbohydrate feeding is a result of increased reabsorption of sodium in the proximal tubule (10, 32). Other workers maintain that both proximal and distal sites are involved in mediating this response (52, 53). A point worthy of consideration is that sodium reabsorption in the distal tubules of the kidney is an energy requiring process. The kidney is capable of efficient gluconeogenesis, which takes place primarily in the cortex (54). The medullary portion, however, is not capable of gluconeogenesis and, therefore, may derive its energy primarily from circulating or stored carbohydrates (55). Studies performed in rabbits indicate a rapid turnover of glycogen in the medullary portion of the kidney (55) and, in the absence of gluconeogenesis, one may assume glycogen levels would be somewhat diminished after an overnight fast. Therefore, in such circumstances, availability of glucose would presumably become a critical factor in determining whether or not active transport systems are mobilized. Perhaps conditions that produce an increase in circulating glucose and insulin also initiate glycogen formation, which may then be involved in the provision of energy for active transport processes in the collecting duct (38).

The transient nature of the antinatriuresis and antikaliuresis we observed is in contrast to the sustained antinatriuretic effect of car-

bohydrate feeding after a prolonged fast described by Katz et al (7) and Wright et al (52). In these instances renal excretion of sodium was depressed for a couple of days even though the fast continued. This would be expected since, in prolonged fasting, the individual is in a negative sodium balance (1, 2), and the antinatriuresis initiated by carbohydrates simply redresses this imbalance.

All of the carbohydrates tested gave a significant antikaliuresis. This is probably due to shifts of potassium intracellularly. After a carbohydrate meal there is a net influx of potassium into liver and skeletal muscle (56, 58). This is evidenced by a significant fall in plasma potassium (5, 10, 39). Decreased urinary potassium excretion cannot be attributed to a reduction in the filtered load since the rate of potassium excretion is governed to a large extent by potassium *secretion* by the kidney tubule (59, 60).

An interesting observation is that galactose feeding, which did not have any antinatriuretic effect, produced a significant antikaliuresis. This would suggest that processes which lead to sodium reabsorption after carbohydrate feeding are independent of potassium metabolism. It is not entirely clear what mediates the antikaliuresis of carbohydrate feeding. DeFronzo et al (39) have suggested that the intracellular potassium concentration of kidney tubular cells may dictate secretion rates of potassium.

Fructose is the only sugar that seems to have a different action. The antinatriuretic effect of fructose cannot be attributed to a rise in plasma glucose or insulin. All of our subjects who ingested fructose (1 g/kg) developed watery diarrhea. In most cases this diarrhea occurred within 40 to 60 min of ingesting the fructose load and lasted for about 45 min. Osmotic diarrhea brought about by any poorly absorbed solute causes a shift of electrolytes and water into the bowel with subsequent excretion in the feces. In the present study, a significant fall in urine output occurred in the first 20 min after fructose loading (Table 1). Antidiuretic hormone has been thought to augment sodium transport in the ascending limb of the loop of Henle (61). However, it is very unlikely that the observed antinatriuresis resulted from antidiuretic hormone action since, under conditions of water diuresis, this hormone is virtually absent. A substantial loss of water from the intestinal tract may have contributed to the fall in urine output. Furthermore, a subsequent transient decrease in extracellular fluid volume could explain some of the antinatriuretic effects of fructose.

Galactose ingestion did not influence sodium excretion by the kidney. This we attributed to its apparent inability to raise blood glucose and insulin in our group of subjects (as observed 1 h after galactose ingestion); galactose per se does not stimulate insulin release in humans (62). The lack of hyperglycemia after galactose ingestion has been reported previously (63). In some cases ingestion of large amounts of galactose produces a hypoglycemic response (64, 65). Haworth and Lord (63) noted that galactose feeding did not produce a rise in plasma glucose although total blood carbohydrates were elevated. The inference is that galactose feeding produces a rise in plasma galactose but not plasma glucose. The availability of plasma galactose for glucogenesis would be minimal since the renal threshold for galactose is low (66) and significant urinary excretion of galactose would probably occur. Apparently, in the liver galactose is metabolized into glucose intermediates but under certain conditions does not produce a net increase in circulating glucose; and this may well explain our observations.

Systolic blood pressure is known to be influenced by ingestion of a meal. Grollman (67) reported that ingestion of sucrose resulted in a rapid and transient response in metabolism, cardiac output, and pulse rate of healthy human volunteers. Systolic pressure was increased while diastolic pressure was unchanged. These blood pressure fluctuations are unique not only to sugars but also are shared by proteins and, to a much lesser extent, by fats (68). In the present study, only glucose and sucrose produced elevation of systolic blood pressure. We did not observe significant blood pressure responses to fructose, galactose, or lactose. For reasons already stated, we assume that fructose was absorbed only minimally from the intestinal lumen.

The lack of a significant response after lactose loading is intriguing. Seven of the 20 subjects experienced intestinal discomfort and diarrhea, and the stress resulting from this may have contributed to the wide fluc-

tuations in their blood pressure readings. None of the subjects had a history of lactose intolerance. The lack of response after galactose loading, however, is not easily explained.

There is evidence that overfeeding rats with sucrose produces an increased sympathetic activity in the heart muscle (69). Catecholamines have been implicated in the development of hypertension in young salt-sensitive hypertensive rats (70). Increased circulating levels of epinephrine would certainly produce increases in systolic blood pressure and smaller increases in diastolic blood pressure (71). It is possible that the elevated systolic pressure observed after glucose and sucrose was mediated by epinephrine.

There are some practical implications of our observations. Saline mixtures containing appropriate concentrations of glucose or sucrose (72, 73) and corn syrup and milk (74) have been used successfully for oral therapy in diarrheal diseases. In some patients who do not have access to food, periods of fasting would conceivably induce natriuresis which could lead to hyponatremia in those who had already experienced a salt loss. Therefore, in addition to the properties of some sugars to promote water and salt absorption in the intestinal lumen, the potential for promoting salt conservation (as a result of antinatriuresis) and antikaliuresis may be a further factor in recommending a particular type of sugar for oral therapy.

Kraikitpanitch et al (11) observed that fasted subjects who developed antinatriuresis after glucose ingestion could be divided into two groups—those who gave an exaggerated antinatriuresis and those who responded only moderately. The subgroup of hyperresponders (Table 3) showed no association between their dietary intake of salt (estimated by questionnaire) and their degree of antinatriuresis. Also, those subjects who showed an exaggerated response with one sugar did not necessarily have a similar response to the other sugars; for example, only two of our 22 subjects had a "hyperresponse" to all five sugars. The criteria for a hyperresponse are defined arbitrarily by defining a cutoff point. Nevertheless, if the observations of Kraikitpanitch et al (11) are correct, a majority of hypertensive patients exhibit exaggerated antinatriuresis after glucose loading. It should be informative to evaluate the response of hypertensives to different sugars.

References

1. Gamble JL. Physiological information gained from studies on life raft ration. Harvey Lectures 1947;42:247–73.
2. Bloom WL, Mitchell W. Salt excretion of fasting patients. Arch Intern Med 1960;106:321–6.
3. Stinebaugh BJ, Schloeder FX. Studies on the natriuresis of fasting I: Effect of prefast intake. Metabolism 1966;15:828–37.
4. Bloom WL. Inhibition of salt excretion by carbohydrate. Arch Intern Med 1962;109:80–6.
5. Veverbrants E, Arky RA. Effects of fasting and refeeding I. Studies on sodium, potassium and water excretion on a constant electrolyte and fluid intake. J Clin Endocrinol 1969;29:55–62.
6. North KAK, Lascelles D, Coates P. The mechanisms by which sodium excretion is increased during a fast but reduced on subsequent carbohydrate feeding. Clin Sci Molec Med 1974;46:423–32.
7. Katz AI, Hollingsworth DR, Epstein, FH. Influence of carbohydrate and protein on sodium excretion during fasting and refeeding. J Lab Clin Med 1968;72:93–104.
8. Haag BL, Reidenberg MM, Shuman CR, Channick BJ. Aldosterone, 17-hydroxycorticosteriod, 17-ketosteroid, and fluid and electrolyte responses to starvation and selective refeeding. Am J Med Sci 1967;254:652–8.
9. Kruck F, Krecke HJ. The renal sodium excretion during oral hydration in man. Nephron 2:1965;321–33.
10. Lindeman RD, Adler S, Yiengst MJ, Beard ES. Natriuresis and carbohydrate-induced antinatriuresis after overnight fast and hydration. Nephron 1970;7:289–300.
11. Kraikitpanitch S, Chrysant SG, Lindeman RD. Natriuresis and carbohydrate-induced antinatriuresis in fasted hydrated hypertensives. Proc Soc Exp Biol 1975;149:319–29.
12. Garay RP, Meyer P. A new test showing abnormal net Na^+ and K^+ fluxes in erythrocytes of essential hypertensive patients. Lancet 1979;1:349–53.
13. Canessa M, Adragna N, Solomon HS, Connolly TM, Tosteson DC. Increased sodium-lithium countertransport in red cells of patients with essential hypertension. New Engl J Med 1980;302:772–6.
14. Ambrosioni E, Costa FV, Montebugnoli L, et al. Intralymphocytic sodium concentration: a sensitive index to identify young subjects at risk of hypertension. Clin Exp Hypertension 1981;3:675–91.
15. Bahlmann J, McDonald SJ, Ventom MG, Dewardener HE. The effect of urinary sodium excretion of blood volume expansion without changing the composition of the blood in the dog. Clin Sci 1967;32:403–13.
16. Bengele HH, Houttuin E, Pearce JW. Volume natriuresis without renal nerves and renal vascular pressure rise in the dog. Am J Physiol 1972;223:68–73.
17. DeWardener HE. Natriuretic hormone. Clin Sci Mol Med 1977;53:1–8.

18. Knock CA, DeWardener HE. Evidence in vivo for a circulating natriuretic substance in rats after expanding the blood volume. Clin Sci 1980;411–21.
19. Hall CE, Hall O. Comparative effectiveness of glucose and sucrose in enhancement of hypersalimantation and salt hypertension. Proc Soc Exp Biol Med 1966;123:370–4.
20. Ahrens RA. Sucrose, hypertension and heart-disease: an historical perspective. Am J Clin Nutr 1974;27:403–22.
21. Beebe CG, Schemmel R, Mickelsen O. Blood pressure of rats as affected by diet and concentration of NaCl in drinking water. Proc Soc Exp Bio Med 1976;151:395–9.
22. Caster WO, Parthemos MD. Growth, hemoglobin; cholesterol and blood pressure observed in rats fed common breakfast cereals. Am J Clin Nutr 1976;29:529–34.
23. Ahrens RA, Demuth P, Lee MK, Majkowski JW. Moderate sucrose ingestion and blood pressure in the rat. J Nutr 1980;110:725–31.
24. Srinivasan SR, Berenson GS, Rhadakrishnamurthy B, Dalferes ER, Underwood D, Foster TA. Effects of dietary sodium and sucrose on the induction of hypertension in spider monkeys. Am J Clin Nutr 1980;33:561–9.
25. Preuss HG, Fournier RD. Effects of sucrose ingestion on blood pressure. Life Sci 1982;30:879–86.
26. Winer BJ. Multifactor experiments having repeated measures on the same elements. In: Statistical principles in experimental design. New York, NY: McGraw-Hill Book Co, 1962:298–378.
27. Metzger RA, Vaamonde LS, Vaamonde CA, Papper S. Renal excretion of sodium during oral water loading in man. Nephron 1969;6:11–27.
28. Papper S, Rosebaum JD. Diurnal variation in the diuretic response to ingested water. J Clin Invest 1952;31:401–5.
29. Bartter FC, Liddle GW, Duncan LE, Barber TK, Delea C. Regulation of aldosterone secretion in man: the role of fluid volume. J Clin Invest 1956;35:1306–15.
30. Duncan LE, Jr, Liddle GW, Bartter FC. The effect of changes in body sodium on intracellular fluid volume and aldosterone and sodium excretion by normal and edematous men. J Clin Invest 1956;35:1299–305.
31. Lindeman RD, Adler S, Yiengst MJ, Beard ES. Influence of various nutrients on urinary divalent cation excretion. J Lab Clin Med 1967;70:236–45.
32. Hoffman RS, Martino JA, Wahl G, Arky RA. Effects of fasting and refeeding II. Tubular sites of sodium reabsorption and effects of oral carbohydrate on potassium, calcium, and phosphate excretion. J Lab Clin Med 1969;74:915–26.
33. Kolanowski J, Pizarro MA, DeGasparo M, Desmecht P, Harvengt C, Crabbe J. Influence of fasting on adrenocortical and pancreatic islet response to glucose loads in the obese. Eur J Clin Invest 1970;1:25–31.
34. Gersing A, Bloom WL. Glucose stimulation of salt retention in patients with aldosterone inhibition. Metabolism 1962;11:329–36.
35. Kolanowski J, Desmecht P, Crabbe J. Sodium balance and renal tubular sensitivity to aldosterone during total fast and carbohydrate refeeding in the obese. Eur J Clin Invest 1976;6:75–83.
36. Spark RF, Arky RA, Boulter PR, Saudek CD, O'Brian JT. Renin, aldosterone and glucagon in the natriuresis of fasting. New Engl J Med 1975;292:1335–40.
37. Doucet A, Katz AI. Mineralocorticoid receptors along the nephron: ^{3}H-aldosterone binding in rabbit tubules. Am J Physiol 1981;241:F605–11.
38. Darnton SJ. Glycogen metabolism in rabbit kidney under differing physiological states. Q J Exp Physiol 1967;52:392–400.
39. De Fronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium and phosphate in man. J Clin Invest 1975;55:845–55.
40. De Fronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. J Clin Invest 1976;58:83–90.
41. Herrera FC, Wittembury G, Planchart A. Effect of insulin on short-curcuit-current across isolated frog skin in the presence of calcium and magnesium. Biochem Biophys Acta 1963;66:170–2.
42. Andre R, Crabbe J. Stimulation by insulin of active sodium transport by toad skin: influence of aldosterone and vasopressin. Arch Int Physiol Biochem 1966;74:538–40.
43. Siegel B, Civan MM. Aldosterone and insulin effects on driving force of Na^{+} pump in toad bladder. Am J Physiol 1976;230:1603–8.
44. Marliss EB, Aoki TT, Unger RH, Soeldner JS, Cahill GF, Jr. Glucagon levels and metabolic effects in fasting man. J Clin Invest 1970;49:2256–70.
45. Unger RH, Orci L. Physiology and pathophysiology of glucagon. Physiol Rev 1976;56:778–826.
46. Saudek CD, Boulter PR, Arky RA. The natriuretic effect of glucagon and its role in starvation. J Clin Endocrinol 1973;36:761–5.
47. Saudek CD, Felig P. The metabolic events of starvation. Am J Med 1976;60:117–26.
48. Staub A, Springs V, Stoll F, Elrick H. A renal action of glucagon. Proc Soc Exp Biol Med 1957;94:57–60.
49. Pullman TN, Lavender AR, Aho I. Direct effects of glucagon on renal hemodynamics and excretion of inorganic ions. Metabolism 1967;16:358–73.
50. Forrest JN, Fisher M, Hendler R, Soman V, Sherwin R, Felig P. Contrasting roles of the kidney in the disposal and hormonal action of physiological concentrations of glucagon. Clin Res 1976;24:400A.
51. Kolanowski J, Salvador G, Desmecht P, Henquinj C, Crabbe J. Influence of glucagon on natriuresis and glucose-induced sodium retention in the fasting obese subject. Eur J Clin Invest 1977;7:167–75.
52. Wright HK, Gann DS, Albertsen K. Effects of glucose on sodium excretion and renal concentrating ability after starvation in man. Metabolism 1963;12:804–11.
53. Schloeder FX, Stinebaugh, BJ. Renal tubular sites of natriuresis of fasting and glucose induced sodium conservation. Metabolism 1970;19:1119–28.
54. McCann WP. Renal glucose production and uptake in separate sites, and its significance. Am J Physiol 1962;203:572–6.

55. Lee JB, Vance VK, Cahill GF, Jr. Metabolism of C^{14}labeled substrates by rabbit kidney cortex and medulla. Am J Physiol 1962;203:27–36.
56. Fenn WO. The deposition of potassium and phosphate with glycogen in rat livers. J Biol Chem 1939;128:297–307.
57. Fineberg SE, Merimee TJ. Effects of comparative perfusions of equimolar, single component insulin and proinsulin in the human forearm. Diabetes 1973;22:676–86.
58. Hoffman RS, Martino JA, Wahl G, Arky RA. Fasting and refeeding III. Antinatriuretic effect of oral and intravenous carbohydrate and its relationship to potassium excretion. Metabolism 1971;20:1065–73.
59. Malnic G, Klose RM, Giebish G. Micropuncture study of renal potassium excretion in the rat. Am J Physiol 1964;206:674–86.
60. Brenner BM, Berliner RW. The transport of potassium. Handbook Physiol 1973;(sect 8):497–519.
61. Ullrich KJ, Kramer K, Boylan JW. Present knowledge of the countercurrent system in the mammalian kidney. Progr Cardiovasc Dis 1961;3:395–431.
62. Samols E, Dormandy TL. Insulin response to fructose and galactose. Lancet 1963;1:478–9.
63. Haworth JC, Lord JD. Variation of the oral galactose tolerance test with age. J Pediatr 1963;63:276–82.
64. Hartmann AJ, Grunwaldt B, James DH, Jr. Blood galactose in infants and children. J Pediatr 1953;43:1–8.
65. Dormandy TL, Leak D, Grant M. Hypoglycemia induced by galactose. Lancet 1959;2:269–71.
66. Gammeltoft A, Kjerulf-Jensen K. The mechanism of renal excretion of fructose and galactose in rabbit, cat, dog and man. Acta Physiol Scand 1943;6:368–84.
67. Grollman A. The cardiac output of man in health and disease. London: Baillier, Tindale and Company, 1932:95–100.
68. Aperia A, Carlens E. Vergleich Zwischen der Wirkung von Fett, Kohlenhydrat and Eiweiss auf den Kreislauf des Menschen. Skand Arch fur Physiol 1931;63:151–63.
69. Young JB, Landsberg L. Stimulation of the sympathetic nervous system during sucrose feeding. Nature 1977;269:615–17.
70. Battarbee HD, Funch DP, Dailey JW. The effect of dietary sodium and potassium upon blood pressure and catecholamine excretion in the rat. Proc Soc Exp Biol Med 1979;161:32–7.
71. Weiner N. Norepinephrine, epinephrine and the sympathomimetic amines. In: Goodman LS, Gilman AG, eds. The pharmacological basis of therapeutics. New York, NY: Macmillan Publishing Co Inc, 1980:138–53.
72. Chatterjee A, Mahalanabis D, Jalan KN, et al. Evaluation of a sucrose/electrolyte solution for oral rehydration in acute infantile diarrhea. Lancet 1977;1:1333–5.
73. Field M. New strategies for treating watery diarrhea. New Engl J Med 1977;297:1121–2.
74. Chung AW, Viscorova B. The effect of early oral feeding versus early oral starvation on the course of infantile diarrhea. J Pediatr 1948;33:14–22.