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Renal Hemodynamic Response to Osmotic Diuresis in Man.* (32330)

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The rate of glomerular filtration in normal man remains essentially constant under most circumstances, even with marked changes in renal blood flow(1). In a study of the urinary concentrating mechanism it was observed unexpectedly that filtration rate decreased during osmotic diuresis(2). Depression of filtration rate in the dog has been reported during infusion of hypertonic glucose and glucose with mannitol(3). This response has also been described during infusion of hypertonic solution of mannitol in the anaesthetized dog following laparotomy and has been attributed to increased medullary blood flow(4). In the present study in man no evidence for shunting of blood was obtained, since depression of filtration rate during osmotic diuresis occurred without a significant change in either renal blood flow or extraction ratio of p-aminohippurate. It is suggested rather that an increase in proximal intratubular pressure is responsible, at least in part, for the depression of glomerular filtration.

Methods. Patients were selected from the wards and outpatient clinics of the Third and Fourth (New York University) Divisions of Bellevue Hospital. Observations were made in 12 normotensive subjects without evidence of cardiovascular or renal disease. All subjects were maintained on regular hospital diets. Fluid restriction was imposed for periods ranging from 16 to 24 hours prior to the test. Pitressin® (20 units of vasopressin) was injected intramuscularly. After urethral catheterization, priming doses of inulin and para-aminohippurate were administered, followed by sustaining infusions at 2 ml per minute, delivering Pitressin at a rate of 1 mU (milliunit) per kg per hour.

Blood and urine specimens were collected over 30 to 45 minutes for determination of "basal" (control) rates of glomerular filtration (GFR), renal plasma flow (RPF) and osmolal clearance (C_{osm}) and during an infusion of 10% mannitol solution at 20 ml per minute for 47 to 98 minutes. In 3 subjects (T.S.,

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TABLE I. Renal Hemodynamics During Infusion of Hypertonic Mannitol.

Subject	Elapsed time,* min	Urinary vol, ml/min	C_{osm}, ml/min	GFR ml/min	GFR % Change	ERBF ml/min	ERBF % Change	Filtration fraction	EF_{Na} × 100, %	Hematocrit, %
L.K., ♀,	Control	1.2	3.4	169		1243		.25	.92	45.0
29 yr	20	1.5	4.0	164	— 3.0	1223	— 1.6	.24	1.15	43.8
	41	8.6	13.4	125	—26.0	1178	— 5.2	.18	3.55	42.3
	52	10.3	14.8	112	—33.7	1059	—14.8	.18	4.17	41.4
	61	12.1	16.5	115	—31.9	1027	—17.3	.19	4.60	40.7
	73	13.3	17.7	104	—38.5	975	—21.5	.18	5.14	39.8
S.R., ♀,	Control	.7	2.1	121		1244		.17	.64	42.8
26 yr	34	7.0	11.8	86	—28.7	1147	— 7.8	.12	3.77	39.1
	40	9.2	14.3	91	—24.8	1130	— 9.2	.12	4.64	37.8
	47	11.2	16.8	91	—24.6	1170	— 6.0	.12	6.01	36.8
B.P., ♀,	Control	.7	1.9	139		1070		.23	.39	43.0
23 yr	23	5.0	9.6	105	—24.5	1030	— 3.7	.17	.94	40.0
	36	6.6	11.5	91	—34.4	967	— 9.6	.15	1.42	38.0
	48	8.0	13.5	84	—39.4	890	—16.8	.15	1.78	35.9
E.S., ♀,	Control	.6	1.8	151		1050		.26	.35	45.2
20 yr	32	8.3	14.9	131	—13.2	1025	— 2.4	.22	2.70	41.0
	44	10.7	17.4	126	—16.6	940	—10.5	.22	3.68	39.0
	54	13.5	21.0	122	—19.2	920	—12.4	.21	4.58	36.5
G.M., ♂,	Control	1.3	2.9	139		1115		.22		44.0
33 yr	45	13.4	19.0	105	—24.5	1070	— 4.0	.17		42.0
	65	19.2	24.3	106	—23.8	1220	+10.1	.15		42.0
H.C., ♂,	Control	1.1	3.3	114		1105		.18		42.0
28 yr	45	10.7	14.7	84	—26.4	1005	— 9.1	.13		37.0
	56	13.2	21.8	86	—24.6	1008	— 8.9	.14		37.0
T.S., ♂,	Control	1.9	3.4	116		1010		.18		35.1
43 yr	40	5.0	7.7	90	—10.4	1063	+ 5.3	.15		33.8
	52	9.1	12.2	83	—28.4	980	— 3.0	.12		32.0
	61	12.0	15.3	95	—17.9	1015	+ .5	.13		32.0
	121	10.4	13.5	94	—19.0	962	— 4.8	.14		32.7
	181	7.6	10.4	94	—18.9	944	— 6.6	.15		34.5
	241	6.1	9.0	89	—23.3	1000	— 1.0	.14		35.7
	301	5.4	8.6	95	—18.1	1060	+ 5.0	.14		36.4
	361	4.9	8.3	117	+ .9	1040	+ 3.0	.18		35.6
	421	4.3	7.4	106	— 8.7	1000	— 1.0	.16		34.3
R.W., ♂,	Control	1.7	3.4	123		1235		.17		43.0
24 yr	20	2.4	4.6	122	— .8	1185	— 4.1	.18		42.0
	30	3.3	5.7	109	—11.4	995	—19.5	.19		41.0
	68	5.8	9.4	116	— 5.7	1122	— 9.2	.17		40.0
	78	8.7	12.7	96	—21.7	1015	—17.8	.16		38.5
	98	10.8	15.1	99	—19.1	1090	—11.8	.15		38.0
C.M., ♂,	Control	1.0	3.0	110		732		.27		38.0
59 yr	33	1.1	9.8	101	— 8.2	735	+ .4	.21		35.0
	52	5.1	11.7	78	—29.1	615	—16.0	.19		34.0
	62	7.7	14.4	83	—24.6	567	—22.5	.23		35.0
	122	10.0	12.9	86	—21.8	570	—22.1	.24		37.5
	152	8.7	11.0	94	—14.6	620	—15.3	.24		37.0
	172	6.8	9.5	91	—17.3	587	—19.8	.24		36.0
	192	5.8	9.0	92	—16.4	600	—18.0	.24		36.0
R.P., ♂,	Control	2.0	4.7	130		823		.27		41.0
40 yr	39	4.7	9.0	121	— 6.9	806	— 2.7	.25		39.0
	55	9.6	15.0	110	—15.4	744	— 9.6	.24		37.3
	65	14.3	19.6	104	—20.0	859	+ 4.4	.19		37.5
	75	14.6	19.7	101	—22.3	755	— 8.3	.22		38.0
R.C., ♂,	Control	2.0	4.1	133		985		.23		41.0
48 yr	40	7.0	10.2	123	— 7.5	1014	+ 3.0	.19		37.5
	52	14.4	17.3	104	—21.8	880	—10.7	.19		36.5
	68	19.9	22.5	105	—21.0	977	— .8	.17		38.3
	124	12.2	15.2	104	—21.8	940	— 4.6	.19		41.0
	184	6.6	8.8	120	— 9.8	1110	+12.7	.19		41.5

TABLE I (continued)

Subject	Elapsed time,* min	Urinary vol, ml/min	C_{osm}, ml/min	GFR ml/min	GFR % Change	ERBF ml/min	ERBF % Change	Filtration fraction	EF_{Na} × 100, %	Hematocrit, %
J.T., ♂, 22 yr	Control	2.0	4.6	128		1250		.17		39.6
	41	8.4	13.3	119	— 7.6	1350	+ 8.0	.14		37.0
	53	17.8	23.0	98	—25.4	1260	+ .8	.12		34.5
	63	24.6	30.0	112	—13.5	1380	+10.4	.13		35.0

* Elapsed time from start of mannitol infusion. Figures in italics indicate collection periods following discontinuation of mannitol.

C.M., and R.C.) observations were continued for 360, 130 and 116 minutes beyond the period of mannitol infusion. In 4 subjects (T.S., R.P., R.C. and J.T.) renal vein catheterization was performed and extraction ratio for p-aminohippurate (E_{PAH}) determined during the control period and during mannitol infusion.

Chemical methods for determination of inulin and para-aminohippurate have been previously reported. Osmolality of plasma and urine was determined in a Fiske osmometer.

Effective renal blood flow (ERBF) was calculated by correcting renal plasma flow for hematocrit [ERBF = ERPF/(1 — hematocrit)].

Results (Table I). GFR was reduced during rapid intravenous infusion of hypertonic mannitol solution in all 12 normotensive subjects. Significant depression usually occurred in about 30 minutes and was maximal in from 34 to 65 minutes. Maximal decrease in GFR averaged —26.9% (range —19.2 to —39.4%) (Fig. 1).

ERBF during the maximal reduction in GFR decreased less than 10% in 7 of the 12 subjects; the average change in ERBF was —10.0% (range —21.5 to +0.8%) (Fig. 2).

E_{PAH} did not change significantly: in subject T.S., from a control value of 86.7 to 83%; in R.P., from 90.9 to 90.6%; in R.C., from 76.5 to 83.5%; and in J.T., from 88.1 to 85.3%.

Plasma osmolality increased in the majority of subjects during mannitol infusion, generally from 3.0 to 10.0 mOsm per liter. The hematocrit decreased an average of 3.7%.

A curve relating depression in GFR to C_{osm} was derived by plotting individual values for each subject and then averaging interpolated values for GFR at 1.0 ml per minute increments in C_{osm} (Fig. 3). Data at C_{osm} below 9.0 ml/min were obtained infrequently because of early, rapid increases in C_{osm}, and in most instances when early urine collection periods were taken, the data were discarded to avoid washout errors. However, in 6 subjects in whom such data were obtained, small

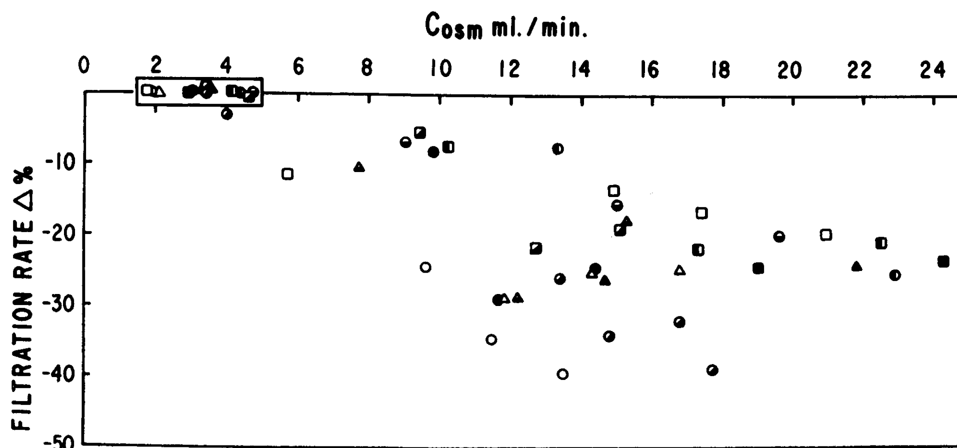

FIG. 1. Depression of filtration rate during increasing osmotic diuresis. The different symbols represent individual subjects. Control values are enclosed in upper left corner.

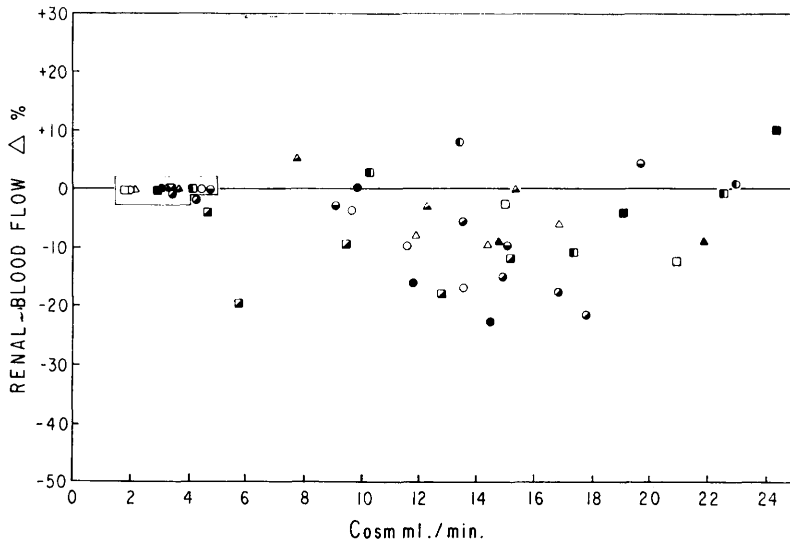

FIG. 2. Renal blood flow during increasing osmotic diuresis. The different symbols represent individual subjects. Control values are enclosed in upper left corner.

decreases in GFR (less than 10%) were observed. As C_{osm} increased from 10.0 to 15.0 ml/min, GFR decreased abruptly to an average depression of —23.0%. With further increases in C_{osm} to 22.0 ml/min, GFR showed no further change.

Following discontinuation of mannitol infusion in 3 subjects C_{osm} decreased slowly to values of 7.4, 8.9, and 8.8 ml/min. GFR returned toward control values and remained in the same relationship to C_{osm} as had been observed during rapidly increasing osmotic diuresis.

Sodium excretion fraction (EF_{Na}) increased along with C_{osm} throughout the mannitol infusion.

Discussion. The renal hemodynamic response to rapid infusion of a hypertonic solution of mannitol was characterized by decrease in GFR, with a lesser decrease in ERBF, and unchanged E_{PAH}. This pattern of response may be attributed to an increase in intratubular pressure initially or as a result of increased interstitial pressure, to a change in arteriolar resistances, or to a combination of these phenomena.

In view of the known action of mannitol as a non-reabsorbable solute, it seems reasonable to consider first the possible role of a primary increase in intratubular pressure. Rapid infusion of mannitol results in a high concentration of non-reabsorbable solute in the glomerular filtrate, which in turn decreases salt and water reabsorption in the proximal tubule. With the resultant increase in volume flow, an increase in intratubular pressure would occur if there were resistance to outflow at any site in the nephron. Gottschalk

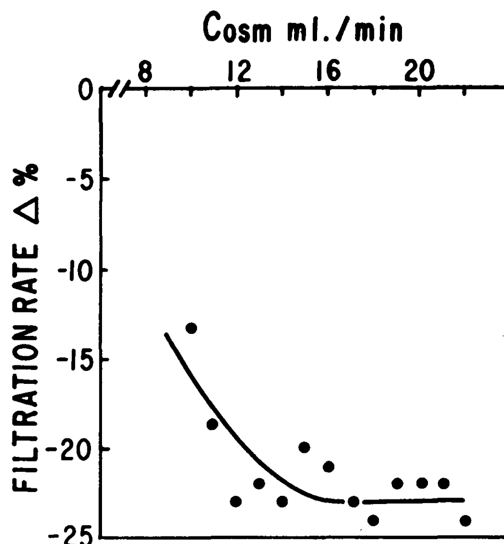

FIG. 3. Relationship between filtration rate and solute load. The observed values for GFR were plotted against C_{osm} for individual subjects. From the separate plots an average curve was derived utilizing values interpolated at increments of 1 ml/min C_{osm}.

has observed that osmotic diuresis in the rat is associated with an increase in proximal tubular volume and hydrostatic pressure(5). Koch, while confirming this observation, has reported in addition that mannitol depresses GFR in the rat(6). In the dog, transit time from glomerulus to urinary bladder remains constant during osmotic diuresis, suggesting that an increase in tubular volume occurs *pari passu* with decrease in proximal tubular fluid reabsorption. Our data suggest that increase in intratubular pressure may occur during mannitol infusion in man and that GFR decreases, at least in part, as a result of increased pressure opposing filtration.

On the other hand, if mannitol infusion should increase interstitial fluid volume in the kidney and, thereby, interstitial pressure, increased intratubular pressure might arise by this mechanism and oppose glomerular filtration. Data quantitating changes in interstitial fluid volume in man during osmotic diuresis are not available at this time.

Entirely apart from consideration of intratubular and interstitial pressure, the mechanism by which GFR is reduced by mannitol infusion may involve changes in segmental renal resistances in the arteriolar and venular beds. At this time we cannot weight the relative importance of intratubular volume, interstitial pressure, or vasomotor changes in the renal response to mannitol infusion.

Our data are sparse below a C_{osm} of 9.0 ml per minute, but in each instance in which such values were obtained, GFR was decreased at these lower solute loads, suggesting that the effect of non-reabsorbable solute may appear early. As C_{osm} increases from 9.0 to 15.0 ml/min, increases in intratubular volume and pressure could occur and account for the marked decrease in GFR. The observation that GFR shows no further reduction as C_{osm} is increased from 15.0 to 22.0 ml/min indicates that effective filtration pressure becomes constant and suggests that intratubular pressure reaches a maximum value or that undefined regulatory mechanisms become operative.

Following discontinuation of the mannitol infusion, GFR returned toward control levels and maintained the same relationship to C_{osm} as was observed during increasing solute load. This observation confirms the causal relationship between increasing solute load and decreasing GFR. The constancy in the relationship of GFR to C_{osm} even though the rate of decline in C_{osm} in the post-infusion period was much slower than its previous rate of increase during the rapid infusion demonstrates that the response to hypertonic mannitol infusion is independent of time.

Increased plasma skimming associated with fall in hematocrit might account for the decrease in GFR, according to the hypothesis of Pappenheimer and Kinter(7). However, decreases in hematocrit were minor in extent, and more importantly, our failure to observe a fall in E_{PAH} eliminates the possibility of plasma skimming.

Doberneck *et al* failed to observe any consistent change in GFR in 6 normal subjects during infusion of hypertonic mannitol (8). These investigators administered 20% mannitol at a rate of 5 ml/min, one-half the rate utilized in the present study, and C_{osm} probably did not reach the levels at which we observed a significant decrease in GFR.

Mannitol infusion in the anaesthetized dog produces a fall in GFR and E_{PAH} and an increase in RPF; this response has been interpreted by Braun and Lilienfield(4) to indicate that mannitol dilates the efferent arteriole of the juxtamedullary glomerulus, permitting increased blood flow to the medulla. Our failure to observe a decrease in E_{PAH} or an increase in ERBF makes this hypothesis untenable in man.

Hypertonic mannital infusion has been shown to increase filtration rate and renal blood flow during experimental hemorrhagic hypotension in the dog(4), and it has been suggested that it be used to prevent acute renal failure in patients subjected to cross-clamping of the abdominal aorta(9). The renal response to mannitol described here was observed in normal man under basal conditions and is not directly applicable either to the experimental animal or to patients undergoing extensive vascular surgery. The possibility exists, however, that increased proximal intratubular volume and pressure

may be factors in the mechanism by which mannitol prevents acute renal failure.

Summary. The hemodynamic response to rapid infusion of hypertonic mannitol was examined in 12 normotensive subjects. At osmolar clearances of 10 to 15 ml/min glomerular filtration rate was decreased in all, the maximal reduction ranging from 19.2 to 39.4%. The maximal reduction in effective renal blood flow was less than 10% in the majority of subjects. Extraction ratio for p-aminohippurate was unchanged in the 4 subjects in whom this measurement was made. The decrease in filtration rate which occurs during osmotic diuresis as induced by mannitol probably results, at least in part, from a reduction in net filtration pressure caused by increased tubular volume and hydrostatic pressure. It is recognized that changes in the interstitial pressure and renal vasomotor activity may also participate in the renal response to hypertonic mannitol infusion.

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Role of Thalamic Gustatory Nucleus in Diet Selection by Normal and Parathyroidectomized Rats.* (32331)

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Until recently, studies on the role of taste in food and water consumption have been fraught with difficulty mainly because a complete elimination of gustatory functions was not technically feasible. Denervation of the taste buds by sectioning of the chordae tympani and IXth nerves was inadequate since in many animals these receptors are found not only on the tongue, but also on the palate and the pharynx(1). Surgical interruption of central gustatory pathways could not be done with certainty because anatomical descriptions of these pathways have been incomplete. An arrangement by which an animal can self-inject food directly into its stomach is novel and valuable(2), but it does not permit an evaluation of central gustatory mechanisms.

At present, destruction of gustatory functions can be accomplished by electrocoagulation of a definite region in the rat thalamus. Behavioral tests indicate that, provided all gustatory neurons of this thalamic region are destroyed, the animals are unable to distinguish between tap water and a quinine hydrochloride solution of high concentration(3). Consequently, this technique for experimental disruption of the gustatory system was used to study the influence of the thalamic gustatory neurons on the selection of particular dietary items under conditions of normal physiological needs and under a heightened need for calcium after parathyroidectomy.

Materials and methods. Young male Sherman rats, weighing 234 ± 11 g (avg ± S. E.), were housed individually in cages fitted with 7 calibrated Richter drinking bottles. Carbohydrates and proteins were made available in the form of dextrose and spray-dried egg whites; fats were offered in

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