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Diuretic Agents and Glucose Reabsorption (38741)

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A correlation between glomerular filtration rate (GFR) and proximal tubular sodium reabsorption with glucose reabsorption has been demonstrated by several investigators (1–3). Recently Kurtzman and coworkers, as well as others, reemphasized that correlation (4–6).

Since glucose reabsorption is linked in some fashion to proximal tubular sodium reabsorption, one would expect glucose reabsorption to be suppressed when proximal sodium reabsorption is inhibited. Accordingly, we studied diuretics known to have a proximal tubular sodium inhibitory effect to determine if they had a similar inhibitory effect on glucose reabsorption. We infused acetazolamide, chlorothiazide, ethacrynic acid and furosemide to glucose loaded dogs.

Materials and Methods. Twenty-six clearance experiments were done on 26 female mongrel dogs. Five percent dextrose in water containing iothalamate ^{125}I was infused at 0.5 ml/min throughout each experiment as a marker of GFR. All the clearance periods were of ten minute duration. 50% dextrose in water was infused at rates sufficient to maintain a blood glucose level constant above 450 mg/100 ml. After the blood glucose concentration reached the desired level an equilibration period of 30 min or more was allowed. Arterial pCO_2 was maintained between 35 and 45 mmHg during each experiment. After equilibration, three control periods were collected followed by six to nine experimental periods. The experimental period started with the administration of the diuretic. There were four experimental groups, the first consisting of four dogs which received acetazolamide 10 mg/kg injected intravenously at the beginning of the first experimental period followed by a constant infusion of 1 mg/min during the rest of the experiment. Group 2 consisted of four dogs receiving chlorothiazide 10 mg/kg injected intravenously at the beginning of the 1st experimental period followed by an infusion of 1 mg/min throughout the remaining periods. Group 3 consisted of eight dogs which received 2 mg/kg ethacrynic acid injected intravenously at the beginning of the 1st experimental period followed by 1 mg/min through the remainder of the experiment. Group 4 consisted of ten dogs receiving furosemide intravenously, 10 mg/kg at the beginning of the experimental period followed by an infusion of 1 mg/min. During each experiment all urinary losses were constantly replaced with Ringer's lactate solution. Methods of sample collection and analysis were identical to those previously described (4). Each animal was weighed before and after each experiment.

Results. None of the animals studied had a weight change that exceeded 100 g. Table I presents a summary of data obtained in the four groups of animals studied. The first three control periods were compared with the last three experimental periods.

Group I—Acetazolamide. GFR decreased by 21% and TG decreased by 28%. TG/GFR was unchanged. Fractional sodium excretion increased significantly from 2.70% ± 1.53 to 10.3% ± 4.33. Figure 1 plots TG/GFR against (^{C}Na/GFR) × 100 using the data from all control and experimental periods in this group. As can be seen, TG/GFR is not significantly different in relation to low or high fractional sodium excretion ($Y = 3.07 - 0.01X$, $r = 0.16$, NS). Thus, no depression of glucose re-

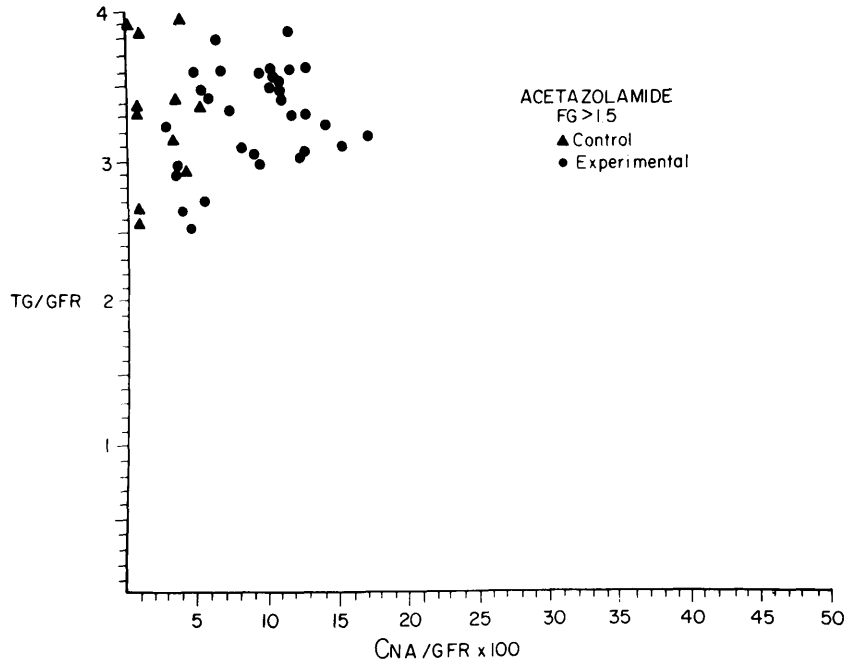

FIG. 1. Effect of acetazolamide on glucose reabsorption (FG = Filtered Glucose/Reabsorbed Glucose).

absorption was observed with administration of acetazolamide.

Group 2—Chlorothiazide. GFR, TG, and TG/GFR underwent no significant change. Fractional sodium excretion increased from 1.5% ± 1.40 to 9.3% ± 1.92 ($P < 0.001$). Figure 2 plots TG/GFR against (^{C}Na/GFR) × 100 using data from all control and experimental periods in this group ($Y = 3.36 - 0.02X$, $r = 0.34$, NS). Chlorothiazide does not depress glucose reabsorption.

Group 3—Ethacrynic acid. The effect of ethacrynic acid on glucose reabsorption is shown in Table I. GFR and (^{C}Na/GFR) × 100 increased significantly ($P < 0.01$ and $P < 0.001$ respectively). TG decreased from 185.9 ± 48.04 to 169.7 ± 39.66 (NS) and TG/GFR decreased from 3.05 ± 0.22 to 2.54 ± 0.41 ($P < 0.02$). Figure 3 plots TG/GFR against (^{C}Na/GFR) × 100 using all control and experimental values in this group ($Y = 3.14 - 0.02X$; $r = 0.67$, $P < 0.01$). It has recently been demonstrated that increases in GFR up to 100% are accompanied by a parallel increase in TG (6). The fact that ethacrynic acid leads to an increase in GFR and to a simultaneous decrease in TG demonstrates that this drug has an inhibitory effect on glucose transport.

Group 4—Furosemide. Table I shows that GFR was unchanged and (^{C}Na/GFR) × 100 increased significantly ($P < 0.001$). TG and TG/GFR decreased slightly but not significantly after furosemide. Figure 4 plots TG/GFR against (^{C}Na/GFR) × 100 using all control and experimental values in this group ($Y = 3.29–0.03X$, $r = 0.52$, $P < 0.01$). Thus furosemide causes a modest decrease in TG/GFR which is not significant when the first control values are compared with the three last experimental values, but which is significant when all the experimental values are analyzed.

Discussion. Glucose reabsorption is linked in some fashion to sodium reabsorption; volume expansion with saline depresses glucose reabsorption and conversely volume contraction enhances it (3–5). More recently it has been demonstrated that absolute glucose reabsorption varies linearly with glomerular filtration rate (4–6). The aim of this study was to evaluate the effects of acetazolamide, chlorothiazide, ethacrynic acid and furosemide on glucose reabsorption. All four diuretics have been shown to have

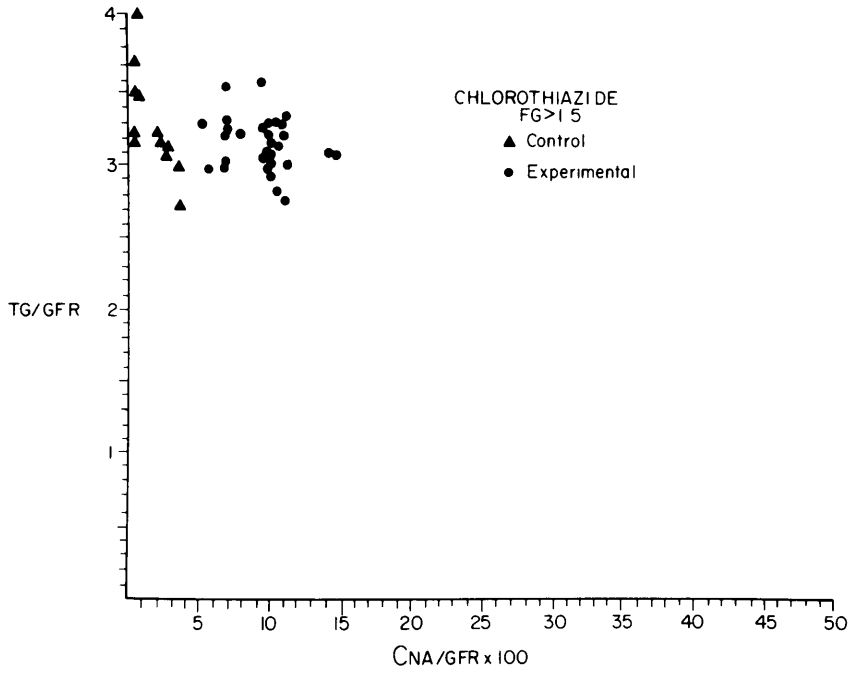

FIG. 2. Effect of chlorothiazide on glucose reabsorption.

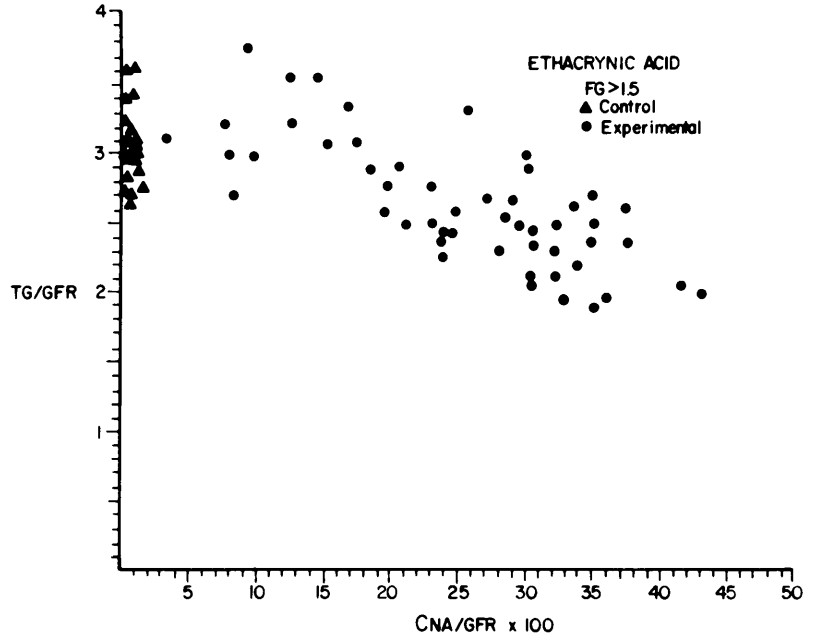

FIG. 3. Effect of ethacrynic Acid on glucose reabsorption.

an effect on the proximal tubule (7–13). Since glucose reabsorption is linked to sodium reabsorption one might expect these diuretics to depress glucose reabsorption. Our results demonstrate that only furosemide and ethacrynic acid depress glucose reabsorption. Ethacrynic acid led to an increase in GFR (by a mechanism that is not clear)

TABLE I. EFFECT OF DIURETICS ON GLUCOSE REABSORPTION.

	GFR[a] ml/min		TG[b] mg/min		TG/GFR mg/ml GFR		$\frac{C_{Na}}{GFR} \times 100$[c] %		Plasma Glucose mg/100 ml	
	C	E	C	E	C	E	C	E	C	E
Acetazolamide (n = 4)	52.6 ± 4.79	40.1 ± 7.3	173.1 ± 40.41	124.0 ± 30.77	3.25 ± 0.50	3.06 ± 0.33	2.70 ± 1.53	10.3 ± 4.33	533 ± 16.86	542 ± 13.58
	$P < 0.05$		NS		NS		$P < 0.01$		NS	
Chlorothiazide (n = 4)	57.9 ± 7.11	52.7 ± 8.7	189.2 ± 10.01	159.8 ± 19.60	3.30 ± 0.34	3.06 ± 0.13	1.50 ± 1.40	9.3 ± 1.92	477 ± 58.12	506 ± 20.20
	NS		NS		NS		$P < 0.001$		NS	
Ethacrynic Acid (n = 8)	58.9 ± 12.28	67.5 ± 13.5	185.9 ± 48.04	169.7 ± 39.66	3.05 ± 0.22	2.54 ± 0.41	0.60 ± 0.53	29.5 ± 7.46	497 ± 45.35	525 ± 50.95
	$P < 0.01$		NS		$P < 0.02$		$P < 0.001$		NS	
Furosemide (n = 10)	54.9 ± 14.70	53.9 ± 13.0	175.7 ± 32.12	154.7 ± 45.20	3.09 ± 0.31	2.84 ± 0.04	0.96 ± 0.87	20.9 ± 5.28	503 ± 37.33	547 ± 70.50
	NS		NS		NS		$P < 0.001$		$P < 0.05$	

[a] Glomerular filtration rate.
[b] Absolute-glucose reabsorption.
[c] Fractional sodium excretion.

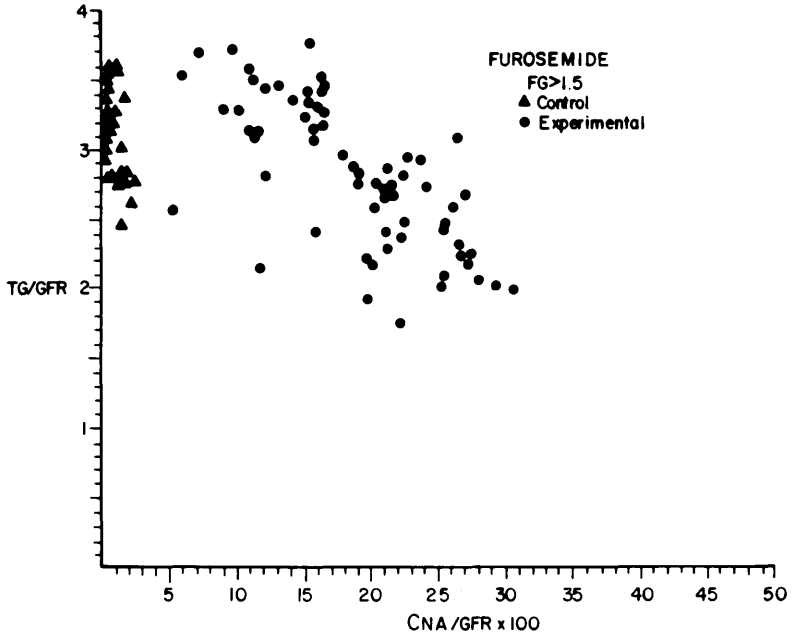

FIG. 4. Effect of furosemide on glucose reabsorption.

and a decrease in TG, thus resulting in a significant decrease in TG/GFR. In other words, ethacrynic acid administration disrupts glomerular-tubular balance for glucose. This strongly suggests that ethacrynic acid, by its action on the proximal tubule, has some inhibitory effect on glucose reabsorption. An alternative explanation for this effect is a distal action of ethacrynic acid on glucose transport.

Glucose reabsorption has been thought to take place mainly in the proximal tubule. A recent study however, suggested that significant amounts of glucose may be reabsorbed in the distal nephron (14). Although ethacrynic acid has a proximal effect its main site of action is in the diluting segment of the loop of Henle (7). Ethacrynic acid could depress glucose reabsorption by blocking distal reabsorption though this mechanism seems less likely than that attributable to a proximal effect. The effects of furosemide on glucose reabsorption are much more modest. GFR was unchanged after furosemide but TG decreased, leading to a significant decrease in TG/GFR when all points are analyzed. Furosemide could depress glucose reabsorption, in a fashion similar to ethacrynic acid, by acting either on the proximal or distal nephron (8, 9).

Acetazolamide, a diuretic with a well known proximal action, did not have any effect on TG/GFR. Absolute glucose reabsorption was lower after acetazolamide, but this seems to have resulted from a drop in GFR (13). Chlorothiazide also did not show any significant effect on TG/GFR.

The inhibitory effect of ethacrynic acid and furosemide on glucose reabsorption was observed when fractional sodium excretion exceeded 20%. The lack of effect of acetazolamide and chlorothiazide on glucose reabsorption may be explained by the fact that fractional sodium excretion never exceeded 20% with these drugs. It is possible that if smaller dosages of ethacrynic acid and furosemide had been used to produce lower levels of fractional sodium excretion (equivalent to those obtained with acetazolamide and chlorothiazide), that no effect of these diuretics on glucose reabsorption would have been demonstrated.

Summary. Acetazolamide, chlorothiazide, ethacrynic acid and furosemide were infused to glucose loaded dogs. Glucose reasorption was unchanged after acetazolamide

and chlorothiazide. Ethacrynic acid depressed glucose reabsorption significantly. Furosemide caused a modest decrease in glucose reabsorption which was not significant when the control values were compared with the last three experimental values, but which was significant when all experimental values are analyzed. These diuretics most likely depress glucose reabsorption by acting on the proximal tubule, though a distal effect cannot be excluded.

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