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## Observations on Mechanism of Potassium Excretion due to Administration of Hydrochlorothiazide. (26226)

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Administration of thiazide diuretics to normal subjects and to patients with compensated congestive heart failure produced only moderate urinary excretion of potassium (K)(1,2). On the other hand, these agents induced much greater kaliuresis in patients with edema and ascites(3-6). This difference suggested to us that aldosterone may influence K loss due to the thiazide diuretics inasmuch as most patients with significant edema and ascites excrete abnormally large quantities of aldosterone in the urine(7). This hormone is believed to promote renal excretion of K only when there is an adequate sodium (Na) transport to the distal tubular site for Na and K exchange (8-10). The present studies in laboratory animals represent an attempt to clarify the influence of aldosterone-like steroids on K excretion with thiazide diuretics.

*Method.* Holtzman rats, 150-200 g, were housed in a constant environment and fed Purina chow biscuits and tap water for 4 days prior to study. Adrenalectomy was performed through a dorsal incision under ether anesthesia and the animals were then maintained on sugar and tap water postoperatively. Approximately 24 hours after adrenalectomy the animals were injected subcutaneously with 2.5 ml of 0.9% saline and with desoxycorticosterone (DOC) as the acetate form in 0.25 ml of ethanol-isotonic saline solvent (28/72 by volume). DOC was used as a standard aldosterone-like steroid(13) because of its availability. Hydrochlorothiazide (H-C) was given subcutaneously in 0.25 to 0.5 ml of ethanol-saline, either alone or in combination with DOC at the time of the saline load. Control injections of solvent were used where indicated. Animals were placed in metabolism cages (4 rats/cage) for collection of a 4-hour sample of urine. Bladders were emptied by suprapubic pressure before and at the end of collection. Urinary sodium and potassium were determined by flame photometric analysis. Statistical comparisons were done by Students "t" test.

*Results.* Table I summarizes the effects of DOC and H-C on Na and K excretion in adrenalectomized rats. DOC alone at doses of 3, 6, and 24 $\mu$g induced a strong retention of Na with only slight insignificant changes in urinary excretion of K. H-C significantly increased urinary output of both Na and K at doses of 0.6 and 1.2 mg/kg ($P<0.05$). There was no significant increase in potassium excretion with the 0.3 mg/kg dose when

TABLE I. Urinary Excretion of Na and K Following Treatment with Desoxycorticosterone and Hydrochlorothiazide in Adrenalectomized Rats.

| Treatment | | | Mean response | |
|---|---|---|---|---|
| DOC, $\mu$g | H-C, mg/kg | No. of measurements | Na | K |
| — | — | 8 | .69 ±.23 | .37 ±.09 |
| 3 | — | 11 | .36 ±.19* | .46 ±.15 |
| 6 | — | 9 | .18 ±.06* | .42 ±.14 |
| 24 | — | 4 | .12 ±.04* | .38 ±.03 |
| — | .3 | 4 | .93 ±.15 | .47 ±.07 |
| — | .6 | 5 | 1.21 ±.25* | .61 ±.15* |
| — | 1.2 | 5 | 1.28 ±.30* | .62 ±.09* |
| 3 | .3 | 3 | .78 ±.07 | .76 ±.07† |
| 6 | .3 | 4 | .56 ±.13 | .75 ±.15† |
| 3 | .6 | 6 | 1.08 ±.17 | .72 ±.03 |
| 6 | .6 | 4 | .75 ±.19 | .70 ±.11 |
| 24 | .6 | 4 | .66 ±.11 | .94 ±.09† |

* $P<0.05$ relative to untreated controls.

† $P<0.05$ relative to corresponding treatment with hydrochlorothiazide (H-C) above.

Na and K = mean meq output/4 hr ± stand. dev. Each measurement = 4 animals.

compared with the untreated control ($P > 0.05 - < 0.10$). In the presence of DOC, however, K excretion with 0.3 mg/kg of H-C was significantly augmented relative to the corresponding response to thiazide or to DOC alone. The same doses of DOC when given with 0.6 mg/kg of H-C did not further increase K excretion. However, when the dose of DOC was increased to 24 μg further K loss occurred. The Na losses induced by H-C were effectively reversed by small doses of DOC as shown in the table. There was progressive reduction of Na excretion without an increase in K excretion when the animals were given increasingly larger doses of DOC alone, suggesting that the steroid promoted reabsorption of Na directly in addition to promoting Na-K exchange, and that this mechanism for direct reabsorption is proximal to the Na-K exchange site.

*Discussion.* Results of our studies suggest that one of the major mechanisms of K excretion following administration of H-C may be the presence of aldosterone-like steroids. The K loss in this situation is believed to result from inhibition of Na reabsorption in the proximal renal tubule by the thiazide diuretic(11) and the resultant delivery of a larger load of Na to the distal tubule, the site of action of aldosterone-like steroids for Na-K exchange. The increase in K excretion with larger doses of H-C alone may be due to carbonic anhydrase inhibition in the renal tubular cells(11,14), or to the delivery of a larger load of Na to the distal tubule where Na-K exchange will occur even in absence of mineralocorticoid hormone.

Since H-C was used in approximately the dosage range for man, on a weight basis, it is possible that K loss seen clinically with the thiazides is a partial response to the presence of aldosterone and not due to the pharmacological effect on the kidney. Some support for the concept is gained by reports of the ability of aldosterone antagonists, *e.g.*, steroidal spirolactones, to prevent the K loss resulting from administration of thiazide diuretics(12,13).

These data suggest that urinary electrolyte response to diuretic agents can be markedly influenced by the presence of aldosterone-like hormones. Endogenous production of aldosterone should be taken into consideration in the study of these agents.

*Summary.* Potassium excretion with hydrochlorothiazide in *adrenalectomized* rats was significantly influenced by the presence of small amounts of DOC. Hydrochlorothiazide alone caused kaliuresis only at relatively large doses. These studies demonstrate that K loss with thiazide diuretics is in part dependent upon body fluid titers of aldosterone-like steroids.

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