Mechanism of Anti-Hypertensive Action of Quinethazone.* (28694)

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It was recently demonstrated that a non-diuretic thiazide compound, diazoxide, effectively lowers the blood pressure of renal hypertensive rats in association with a decrease in potassium content of the aorta wall and no change in water or sodium content(1). It was suggested that the anti-hypertensive action of thiazides might be mediated through reduction in potassium content of arterial smooth muscle. This deduction was based on the similarity of reported vascular responses following thiazide administration and those observed in other experimental conditions where the aorta wall content of potassium had been reduced.

It was considered worthwhile to determine whether other anti-hypertensive drugs, not related to thiazides, might have a similar selective effect on the aorta wall potassium content. A clinically proven diuretic with anti-hypertensive properties, quinethazone† (7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-OXO-6-sulfamyl-quinazoline) was chosen for such a study.

Methods. Five- to 6-week-old Long Evans male rats were subjected to Grollman's figure-of-eight renal ligation method of inducing hypertension. Twelve weeks later a group of hypertensive rats with systolic blood pressures averaging 188 mm Hg, were fed a stock diet to which was added an amount of quinethazone calculated to provide a daily intake of approximately 50 mg/kilo body weight. After 2 weeks the blood pressures averaged 136 mm Hg. The animals were then sacrificed. The aortas were rapidly removed, stripped of adventitia, promptly weighed, then oven-dried at 100°C, extracted with ether to remove fat, and the residue weighed to determine the water content. The residue was then digested with 0.75 N nitric acid and assayed for chloride by the Cotlove amperometric method and for potassium and sodium by flame photometry.

A similar procedure was followed with groups of normal and hypertensive rats fed stock diet. Blood was obtained from all 3 groups of rats for sodium and potassium analyses.

Results. The accompanying Table demonstrates the sodium, potassium, and water distribution between intra-cellular and extra-cellular compartments of aorta wall tissue of rats fed quinethazone. These data were calculated by standard formulae from the results of tissue and blood analyses for water, sodium, potassium and chloride. In addition, previously published data on the effect of diazoxide administration to hypertensive rats are included to allow for a more convenient comparison with those obtained with quinethazone.

It is readily noted that quinethazone had no significant effect on sodium or water distribution in arterial tissue of hypertensive rats. However, there was an approximate 20% decrease in the intra-cellular content of potassium of such rats as compared to similar rats fed stock diet. These results are practically identical to those obtained with diazoxide.

Discussion. The present experiment reveals that the drug quinethazone, lowers blood pressure of renal hypertensive rats to almost normotensive levels. Even though this compound has a potent effect on sodium and water excretion, there was no diminution of these components in the arterial tissue. There was, however, a significant reduction in intra-cellular potassium content. These results coincided with those obtained with the thiazide, diazoxide. It is most interesting that this latter compound is not a diuretic and actually causes some sodium retention(2). It is apparent therefore that the actions of these drugs on kidney excretory function have no special relationship to their anti-hypertensive qualities.

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TABLE I. Distribution of Electrolytes and Water in Aorta Wall.*

	No. of rats	H_2O (g)		Na (meq)		K (meq)	
		Extra-cell	Intra-cell	Extra-cell	Intra-cell	Intra-cell	
Normal	18	18.0 ±.4†	174 ± 1.0	23.4 ±.3	1.4 ±.08	11.0 ±.13	
Hypertensive + stock diet	16	22.4 ±.6	217 ± 1.4	28.2 ±.7	2.9 ±.10	14.9 ±.27	
Hypertensive + diazoxide	14	20.9 ±.7	210 ± 1.8	27.1 ±.5	3.1 ±.11	12.3 ±.21	P <.01
Hypertensive + quinethazone	16	21.3 ±.9	206 ± 2.0	26.8 ±.8	2.8 ±.18	12.0 ±.32	P <.01

* Per 100 g fat-free dry wt. † Standard deviation.

Numerous reports from this laboratory have indicated that under a number of conditions there has been a positive correlation between blood pressure level and concentration of potassium in arterial tissue(3). It has been suggested that the blood pressure level of renal hypertensive animals is regulated by this cation acting on arterial tone and thus influencing peripheral resistance. This hypothesis appears to be supported by the evidence that diazoxide(2) as well as other thiazides(4) induce a lowering of peripheral vascular resistance in association with a reduction in aorta wall potassium content(1). It is, therefore, deduced that the anti-hypertensive action of thiazides may be mediated through this effect on arterial muscle potassium. Likewise, quinethazone which differs chemically and pharmacologically from the thiazides may exert its anti-hypertensive effect through a similar mechanism.

Summary. Quinethazone lowers blood pressure of renal hypertensive rats in association with a decrease in potassium but no change in water or sodium contents of aorta wall. The anti-hypertensive effect of quinethazone, like the thiazides, may be mediated through this electrolyte alteration in arterial muscle.

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Influence of Type and Level of Gas Environment on Anterior Pituitary Lactogen Production *in vitro*.* (28695)

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Anterior pituitaries (AP) freed from hypothalamic control and cultured *in vitro* are capable of considerable net synthesis of lactogen(1,2,3). Although Meites and co-workers (1,4) reported greater lactogen production by pituitaries cultured in an environment of 95% O_2 – 5% CO_2 than by pituitaries cultured in an air environment, they did not indicate the level of gas flow. The purpose of this investigation was to determine the influence of type of gas environment on lactogen production and level of 95% O_2 – 5% CO_2 gas flow that resulted in maximal lactogen production *in vitro*.

Materials and methods. Primary anterior pituitary explants from 3-month-old, female, hooded Norway rats were cultured *in vitro*

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