Hydration of Arterial Muscle and Blood Pressure Response.* (29751)

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From a previous study it was suggested that increased water content of arterial muscle induces a dilution of the contractile components resulting in a lowering of peripheral resistance and a depression of blood pressure(1). This hypothesis was based on the assumption that the sodium-potassium ratio of arterial tissue reflected hydration of the muscle cells. In this regard, blood pressure of hypertensive rats subjected to adrenalectomy declined to normotensive levels in association with an elevated sodium-potassium ratio due to an increase in the sodium content. Following prednisolone administration, blood pressure was restored to hypertensive levels concomitantly with removal of the added sodium. Similarly, the blood pressure of renal hypertensive rats fed the antihypertensive compound quinethazone declined to normotensive levels in association with an increase in sodium-potassium ratio of the aorta due to a reduction of the potassium content(2). Preliminary tests revealed that prednisolone administration restored the depressed blood pressure of quinethazone-fed rats to the original hypertensive levels in association with a lowering of the sodium-potassium ratio. This effect provided an opportunity to study the relationship of this ratio to the state of hydration of arterial muscle and its possible role in blood pressure regulation.

Methods. Five- to six-week-old male Long-Evans rats were subjected to Grollman's figure-of-eight renal ligature method for induction of hypertension. Ten to twelve weeks later, hypertensive rats were divided into 4 groups. One group consisted of untreated hypertensive rats (II). A second group (III) was fed a diet containing quinethazone† calculated to provide a daily intake of approximately 100 mg/kg body weight. After two weeks on this diet, at which time the blood pressure levels had declined to almost normotensive values, these rats and those of Group II were sacrificed. The aortas and blood were removed for analyses of the water, sodium, potassium and chloride content as previously described(2).

A third group (IV) was fed the diet containing quinethazone for 2 weeks and was then injected with 2 mg prednisolone acetate‡ subcutaneously 2 times at a 15-hour interval. Four hours after the second injection systolic blood pressures were obtained by microphonic manometer and the animals sacrificed for determination of the electrolytes and water content of aorta and electrolytes of blood. A fourth group (V) of hypertensive rats fed the quinethazone diet for 2 weeks received two subcutaneous injections of 5 mg desoxycorticosterone trimethylacetate 15 hours apart; blood pressure readings were obtained 4 hours after the second injection and rats then sacrificed for similar analyses.

Results. From Fig. 1, it can be observed that the blood pressure of hypertensive rats fed quinethazone for 2 weeks declined to levels approaching normotension. Administration of prednisolone to such rats promptly restored the blood pressure to hypertensive levels while desoxycorticosterone had no pressor effect under similar conditions.

In association with the blood pressure changes, there were significant alterations in the water and electrolyte contents of the aorta wall (Table I). Thus, treatment of hypertensive rats with quinethazone resulted in a reduction of potassium from 15.6 ± .5 mEq to 12.4 ± .4 mEq per 100 g dry weight with no appreciable change in water or sodium content. When these animals were injected with prednisolone, the potassium content remained the same but the water content of aorta declined from 231 ± 5.8 g to

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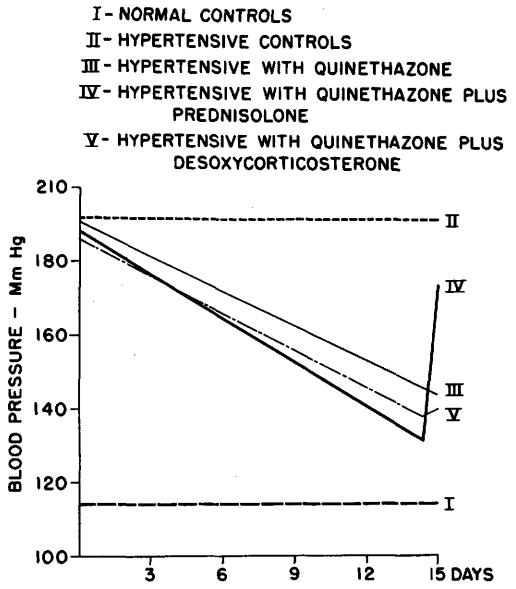

FIG. 1. Schematic representation of depression of blood pressure in hypertensive rats fed quinethazone (100 mg/kg body weight), prompt restoration by administration of prednisolone, and failure to respond to DOCA.

197 ± 6.3 g, and the sodium content from 29.7 ± 7 mEq to 25.0 ± 1.0 mEq. Desoxycorticosterone administration to such rats had relatively little effect on these constituents.

It is also apparent that in conjunction with the anti-hypertensive effect of quinethazone, the ratio of aorta sodium to potassium increased from the initial value of 1.96 ± .03 to 2.40 ± .03. Following administration of prednisolone to such rats and reversal of blood pressure, this ratio was reduced to 2.00 ± .04. The ratio was unchanged by administration of desoxycorticosterone. Under these conditions there is an inverse correlation between blood pressure and sodium-potassium ratio of the aorta.

Similarly an inverse correlation is found between the ratio of water to potassium content of the aorta and blood pressure. Thus quinethazone feeding increased this ratio from the initial value of 15.5 ± .5 to 18.6 ± .6. Administration of prednisolone to hypertensive rats fed quinethazone lowered the ratio to 15.4 ± .6. When such rats were treated with desoxycorticosterone, there was no change in the ratio which approximated that of normotensive controls.

A similar relationship can be found between blood pressure levels and the ratio of intra-cellular water to potassium of the aorta. This can be converted to a positive correlation between blood pressure and concentration of intra-cellular muscle potassium (Table II). For this purpose the values for these

TABLE I. Water and Electrolyte Content of Aortas.*

	Rats	H_2O (g)	Cl (mEq)	Na (mEq)	K (mEq)	Na (mEq) / K (mEq)	H_2O (g) / K (mEq)
Normal	16	199 ± 4.2†	19.7 ± .5	25.9 ± .6	11.5 ± .2	2.25 ± .02	17.3 ± .4
						$p < .01$	$p < .01$
Hypertensive	16	247 ± 5.1	23.7 ± .7	30.6 ± .8	15.6 ± .5	1.96 ± .03	15.5 ± .5
						$p < .01$	$p < .01$
Hypertensive & quinethazone	16	231 ± 5.8	22.3 ± .6	29.7 ± .7	12.4 ± .4	2.40 ± .03	18.6 ± .6
						$p < .01$	$p < .01$
Idem + prednisolone	14	197 ± 6.3	18.8 ± .6	25.0 ±1.0	12.5 ± .4	2.00 ± .04	15.4 ± .6
						$p < .01$	$p < .01$
" + desoxycorticosterone	12	220 ± 5.2	19.9 ± .5	28.8 ± .8	11.9 ± .7	2.42 ± .04	18.4 ± .7

* Per 100 g fat-free dry wt.

† Standard error.

TABLE II. Concentration of Arterial Muscle Potassium.

	Intra-cell H_2O (g)*	Intra-cell K (mEq)	K (mEq/l) intra-cell water	
Normal	49 ± 1.2†	10.8 ± .2	220 ± 4.4	
				$> p < .01$
Hypertensive	53 ± .9	14.7 ± .5	277 ± 5.1	
				$> p < .01$
Hypertensive and quinethazone	49 ± 1.6	11.6 ± .4	236 ± 4.8	
				$> p < .01$
Idem + prednisolone	43 ± 1.3	11.9 ± .4	276 ± 3.9	
				$> p < .01$
" + desoxycorticosterone	57 ± 2.1	11.2 ± .8	197 ± 8.7	

* Per 100 g fat-free wt. † Standard error.

constituents were obtained by standard formulae based on the assumption that almost all chloride is confined to tissue extracellular space. It can be noted that the values for intracellular water of aorta muscle are unrealistic when compared to other muscle such as skeletal or myocardial. This may be accounted for by the fact that considerable quantities of chloride are bound to the collagen and elastin present in arterial tissue with a consequent distortion of values for intra- and extracellular water(3). However, since the fiber content of the aortas of the experimental animals in the different groups is apparently comparable, the increment of chloride associated with the non-cellular elements may be considered constant for practical purposes. Under such conditions the values in Table II may be considered valid for demonstrating relative hydration of arterial muscle. It can be seen from this Table that untreated hypertensive rats had an arterial muscle potassium concentration of 277 ± 5.1 mEq per liter of muscle water compared to 220 ± 4.4 mEq/l in normal rats. Hypertensive rats fed quinethazone showed a reduction in concentration of potassium to 236 ± 4.8 mEq/l. Following administration of prednisolone to such rats the concentration of muscle potassium was elevated to 276 ± 3.9 mEq/l. Desoxycorticosterone administration to similar rats diluted muscle potassium somewhat.

Discussion. These results reveal that the anti-hypertensive effect of quinethazone was promptly reversed by administration of prednisolone. This is apparently a specific action of an anti-inflammatory steroid since the mineralocoid, desoxycorticosterone, was ineffective.

The distribution of water and electrolytes of the arterial wall offers a possible explanation of the shifts in blood pressure. In this regard, Tobian and associates suggested that in hypertensive animals, the hydration from an increased sodium content of artery wall caused a narrowing of the lumen and an elevated peripheral resistance. Friedman and Allardyce considered that excess sodium of the smooth muscle cells induced a sustained contraction of the peripheral arteries and a similar increase in resistance to blood flow(5). The results reported here demonstrate likewise that the arteries of renal hypertensive rats contain excess sodium and water as well as potassium. However, quinethazone feeding lowered blood pressure concomitantly with a reduction in potassium content but no change in water and sodium. Following prednisolone treatment to such rats, blood pressure was restored to hypertensive levels with removal of the excess sodium and water. Thus, a different interpretation may be made when blood pressure changes are studied in the light of the relationship between the potassium and the sodium and/or water contents of artery wall.

The results of the present study confirm a previous suggestion of an inverse correlation between blood pressure and ratio of aorta sodium to potassium(1). A similar correlation between blood pressure and ratio of aorta water to potassium has been disclosed and extended to the ratio of intra-cellular water to potassium. Inversion of this latter ratio indicates a positive correlation between

blood pressure and concentration of arterial muscle potassium. It is suggested therefore that the reversal of the anti-hypertensive effect of quinethazone by prednisolone may be related to the induction of a higher concentration of arterial muscle potassium through mobilization of intracellular water. This concept presupposes that the data obtained from analyses of aorta tissue may be extrapolated to smaller arteries and that alterations in peripheral resistance are mainly responsible for blood pressure changes.

With these considerations in mind, sufficient data are available to postulate that arterial muscle potassium has a regulatory effect on peripheral resistance. It is well known, for instance, that potassium is a vital component in the contractile mechanism of smooth muscle of arteries as well as other organs. In addition, recent reports indicate that this cation may influence basal arterial tone. Thus, Bevan and Osher reported that while potassium sensitized the contraction of artery strips to norepinephrine, it shortened the resting length of the strips through direct action on smooth muscle cells(6). Barr *et al* also showed that shortening of artery strips was a positive function of intra-cellular potassium(7). Furthermore, Laszt and Hamoir maintain that vascular muscle contains "tonactomyosin," a protein which regulates tone under the direct influence of cellular potassium(8).

It follows that the anti-hypertensive effect of quinethazone may, in part, result from loss of arterial tone through dilution of arterial muscle potassium. On the other hand, prednisolone could reverse this anti-hypertensive effect by restoring tone through mobilizing cellular water and concentrating muscle potassium. This effect may shed some light on the mechanism by which anti-inflammatory steroids are known to improve circulation in a variety of hypodynamic states.

Summary. Presnisolone, but not desoxycorticosterone, administration reverses the anti-hypertensive effect of quinethazone. The elevation of blood pressure is associated with an increase in concentration of arterial muscle potassium through the mobilization of cellular water. The direct influence of potassium on arterial tone may be involved in this relationship.

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Mechanism of Dextran Sulfate Inhibition of Attenuated Poliovirus.* (29752)

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In recent years reports on the effect of sulfated polysaccharides on several viruses have been published. The viruses studied include picornaviruses such as polio(1-3), encephalomyocarditis virus (EMC)(4) and foot-and-mouth disease virus (FMDV)(5,6), herpes simplex virus(7) and myxoviruses such as influenza A2 and B(8). The effect of sulfated polysaccharides on plaque size has primarily been investigated. With poliovirus and FMDV the effect of agar extracts and/or

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