# Tissue Norepinephrine of Rats Given Chlorothiazide* (35603)

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The mechanism by which thiazide drugs lower the blood pressure of hypertensive patients is not known. During the first few days of administration of these agents, their natriuretic action which results in reduction in total extracellular fluid volume, including plasma volume, undoubtedly is important. With continued therapy, however, sodium balance of the body is restored and plasma volume returns toward normal (1), so that other explanations for the sustained antihypertensive effect of these drugs must be sought. Support for a mechanism unrelated to natriuresis is obtained from the fact that diazoxide, a sodium-retaining thiazide, has a marked hypotensive action (2).

It is of interest that diazoxide given orally to rats acutely increases the level of circulating total catecholamines (3). Hypertensive patients treated with thiazides show a diminution in excretion of urinary catecholamines (4). Thiazide-fed rats' hearts, kidneys, and adrenal glands have decreased epinephrine contents (5). It is possible that these alterations in catecholamine metabolism due to thiazide administration might be related to the decreased peripheral arterial resistance which is found when therapy with these agents is prolonged (1).

The present studies were carried out to determine the effect of chlorothiazide administration to rats on the norepinephrine content of the heart, aorta, and mesenteric arteries.

*Materials and Methods.* Male Sprague-Dawley rats wieghing approximately 250 g were given sodium chlorothiazide 100 mg/kg of body weight in drinking water daily for 2 weeks. Similar rats served as controls. Animals were killed by decapitation and the heart, aorta, and mesenteric arterial vascular bed were quickly removed. Heart was minced, weighed, then immediately frozen in liquid nitrogen. Six rat aortas were weighed, pooled, and similarly frozen. Mesenteric arteries were obtained by the method of Koletsky (6), weighed, then frozen in liquid nitrogen. Frozen tissue was ground with a mortar and pestle, transferred to a glass homogenizer tube, covered with 5.0 ml of 0.8 *N* perchloric acid, and homogenized. Tubes were kept in ice water. Subsequent tissue norepinephrine contents were done according to the method of Moore and Brody (7).

TABLE I. Norepinephrine Contents of Mesenteric Artery, Aorta, and Heart of Normal Rats and of Rats Given Chlorothiazide.[a]

| | Normal rats ($\mu$g/g of wet tissue) | Chlorothiazide-treated rats ($\mu$g/g of wet tissue) |
|---|---|---|
| Mesenteric artery | $0.262 \pm 0.101$ ($N = 51$) | $0.235 \pm 0.088$ ($N = 49$) |
| Aorta | $0.140 \pm 0.098$ ($N = 8$) | $0.094 \pm 0.078$ ($N = 8$) |
| Heart | $0.158 \pm 0.039$ ($N = 36$) | $0.157 \pm 0.074$ ($N = 38$) |

[a] Values given as mean $\pm$ SD; $N$ equals number of determinations and is the same as the number of rats except for aorta where each determination represents six rat aortas.

*Results.* The norepinephrine contents of mesenteric artery, aorta, and heart of normal rats and of rats given chlorothiazide are shown in Table I. Although the mean norepinephrine contents of the chlorothiazide treated rats' mesenteric arteries and aortas were less than those of normal rats, the differences were not statistically significant, $p$ values being $<0.20 >0.10$ and $<0.40 >0.30$, respectively.

*Discussion.* There is evidence that the ad-

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ministration of thiazide drugs causes alterations in catecholamine metabolism. For example, both quinethazone and polythiazide given orally to rats for 20 days tended to reduce the tissue concentration of catecholamines in heart, kidney, and adrenal gland (5, 8). In heart, there was a significant decrease in epinephrine content; norepinephrine was not diminished. In our study of chlorothiazide administration to rats the norepinephrine content of heart likewise was not reduced.

In an effort to determine the mechanism by which thiazide drugs decrease peripheral resistance, the effect of chlorothiazide administration on the norepinephrine content of aorta and mesenteric artery was studied. Although these tissues in chlorothiazide-fed rats had a lower concentration of norepinephrine than did similar tissues of normal rats, the differences did not reach statistical significance. The data, therefore, fail to confirm an association between decreased norepinephrine content of the arterial vascular tree and prolonged chlorothiazide administration. As the tissue contents of catecholamines reflect the complex balance of the formation, uptake, storage, and release of catecholamines, however, such contents need not necessarily correlate with the level of circulating catecholamines and their physiological actions on the arterioles.

*Summary.* The mean norepinephrine contents of aortas and mesenteric arteries of rats given chlorothiazide for 2 weeks were lower than the mean norepinephrine contents of these tissues of normal rats, but the differences between the respective means were not statistically significant. The mean norepinephrine content of the heart of rats given chlorothiazide was the same as that of control rats.

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