Weight, succinic acid dehydrogenase, and SH-group concentration of the thyroid glands after single injection of 15 IU of thyrotrophic hormone

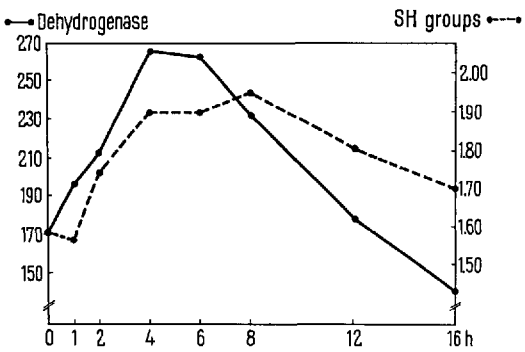
h after injection	Number of animals	Body weight g		Thyroid gland: Weight mg		Succinic dehydrogenase[a]			SH-groups 10^{-5} moles/g		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	P[b]	Mean	S.D.	P[b]
0	8	280	25.4	16.9	2.92	171	48.2		1.58	0.168	
1	8	286	25.5	17.9	1.78	198	62.5	> 0.05	1.56	0.158	> 0.05
2	8	283	18.9	17.4	2.17	211	65.6	> 0.05	1.74	0.218	> 0.05
4	8	280	48.6	15.8	4.83	265	94.3	< 0.01	1.90	0.304	< 0.05
6	8	284	30.9	16.6	1.84	262	91.4	< 0.05	1.90	0.202	< 0.01
8	8	287	22.7	18.0	1.67	232	58.6	< 0.05	1.95	0.221	< 0.001
12	8	286	54.0	16.8	3.30	178	54.7	> 0.05	1.80	0.245	< 0.05
16	8	279	45.5	18.3	3.20	140	20.3	> 0.05	1.70	0.283	> 0.05

[a] µg of reduced tetrazolium salt/100 mg of fresh weight.
[b] P value compared with controls.

SH-groups is slower, reaching its maximum in 8 h. The drop is also slower. The difference from the control level is still significant 12 h after the injection, but no longer after 16 h. These results are also plotted in the graph. No statistically significant differences can be demonstrated in the weight of the thyroid in the different groups.

It has been established in recent long-term experiments that succinic acid dehydrogenase activity is a sensitive indicator of thyroid activity[7]. Succinic acid dehydrogenase participates in the oxidative processes of the cell as an enzyme associated with the cycle of Krebs. On the other hand, it has been shown that TSH increases the oxygen consumption of thyroid cells[12]. The succinic acid dehydrogenase concentration is thus illustrative of the effect of TSH on the oxidative metabolism of the thyroid cell.

A correlation has been stated between SH-groups and the percentage of epithelium of the thyroid[8]. This, in turn, gives a reliable picture of the function of thyroid cells[13].



Changes in thyroid succinic acid dehydrogenase and SH-group concentration of the rat after single injection of TSH.

Both the succinic acid dehydrogenase and the SH-groups are thus good indicators of the activity of thyroid cells. The methods introduced earlier for the measuring of acute changes of thyroid function[2,5–7] are laborious or demand special apparatus. The results obtained in the present work show that it is possible to measure the TSH-induced change in the activity of thyroid cells by the relatively simple methods of determining succinic acid dehydrogenase and SH-groups. It is suggested that these methods could be used generally for the determination of thyroid function in acute experimental conditions.

Zusammenfassung. Es wurde die Wirkung einer TSH-Injektion auf den Gehalt der Bernsteinsäuredehydrogenase und der SH-Gruppen in der Schilddrüse der Ratte untersucht. 4 h nach der Injektion von TSH erfolgte ein signifikanter Anstieg der Bernsteinsäuredehydrogenase und SH-Gruppen. Die Methode ist deshalb zur Untersuchung der Schilddrüsenaktivität im kurzfristigen Versuch geeignet.

O. KYTÖMÄKI und U. K. RINNE

Department of Anatomy, University of Turku (Finland), June 18, 1963.

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An Extrarenal Effect of Hydrochlorothiazide

Chlorothiazide and its analogues, well known for their saluretic effect, have been reported to decrease the urinary volume in patients with *Diabetes insipidus*[1–3]. This effect has also been demonstrated in experimental animals[4,5]. No satisfactory explanation of the antidiuretic action has been given, although some authors have pointed to a renal mechanism[2,6]. Recently an indirect effect of chlorothiazide has been suggested, *viz.* attenuation of thirst through sodium depletion[7]. Although the mechanism of thirst is not yet finally established, some evidence is available for an osmotic-sensitive region in the hypothalamus[8,9]. Activation of this area presumably depends on sodium movement across the cell membrane and therefore may be modified by drugs which impede sodium transport. To

test this possibility, it seemed profitable to study the effect of hydrochlorothiazide on water-intake in nephrectomized animals, as here renal effects of the drug are eliminated. Furthermore, ERBE and WELLER have recently reported that no change occurs in plasma electrolytes following administration of chlorothiazide to nephrectomized rats and dogs[10], although BEAVERS has previously shown an alteration in plasma potassium and sodium in nephrectomized dogs[11].

Materials and Methods. Male rats (180–250 g) of HU strain were bilaterally nephrectomized under ether anaesthesia, according to the method described by MARKOWITZ et al.[12]. Hydrochlorothiazide was injected s.c.; the control group was given an equal volume of the solvent alone ($NaHCO_3$ 1%). Each experimental group consisted of 4–6 rats. Water intake from a graduated bottle was determined every 8 h. To avoid water loss a glass tube was fitted to the bottle and the water was sucked by the rats. Preliminary experiments have shown that on the usual diet the rats survived nephrectomy for 4–6 days. Results were evaluated only for the first 2 days, excluding the initial 8 h following operation, in order to avoid possible effects of anaesthesia and of the stress of operation.

Results and Discussion. The administration of hydrochlorothiazide (10 mg/kg) consistently decreased water intake in the nephrectomized fed rats. In the combined results of 4 experiments, hydrochlorothiazide lowered water intake to 67% ± 13 of control. Sham operated rats did not differ from the control. Subcutaneous administration of hypertonic sodium chloride solution (5 ml/kg of a 3% solution) considerably increased water intake, to 160% of controls (Figure 1). The surplus in water intake was abolished after injection of hydrochlorothiazide (Figure 1).

If the nephrectomized rats were starved, injection of hydrochlorothiazide caused an increase of water intake (Figure 2). It is well known that in starved animals water intake is depressed[9,13]. If, however, starved, nephrectomized rats were injected s.c. with hypertonic solutions of sodium chloride to stimulate their sensation of thirst, administration of hydrochlorothiazide diminished water consumption considerably (Figure 2).

The present results demonstrate that hydrochlorothiazide can decrease water intake in the nephrectomized rat, an unexplained exception being under starvation of the operated animals. The rise in water consumption induced by hydrochlorothiazide under starvation may be due to increased water loss from the intestine, although this factor has not been quantitatively determined. When the urge to drink is increased, either by food intake or by hypertonic NaCl injected s.c., the drug inhibits water consumption significantly (Figure 1 and 2).

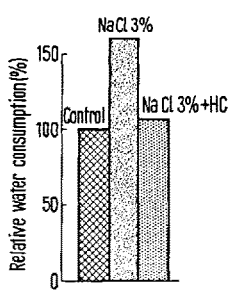

Fig. 1. Effect of hydrochlorothiazide on polydipsia induced by hypertonic NaCl. Control = nephrectomized rats; NaCl 3% = nephrectomized rats injected s.c. with 5 ml/kg of 3% NaCl. NaCl 3% + HC = as before with addition of hydrochlorothiazide 10 mg/kg s.c. Results expressed as ratio of water intake of treated animals to that of control animals.

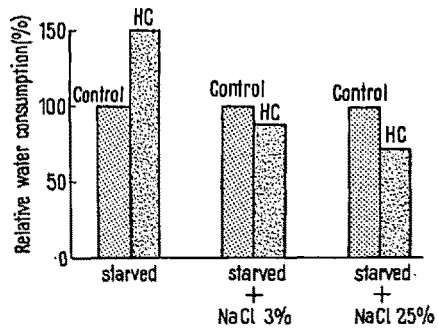

Fig. 2. Modification of hydrochlorothiazide effect on water intake by starvation and hypertonic NaCl. Control = nephrectomized rats treated as denoted below columns of each experiment. NaCl 3%, NaCl 25%—injection of 5 ml/kg s.c. of the respective solutions. HC = nephrectomized rats treated in each experiment as the control and in addition hydrochlorothiazide 10 mg/kg s.c. Results expressed as in Figure 1.

Since the effect of hydrochlorothiazide on drinking has been presently shown in the absence of kidneys, it is probably not due to salt depletion, which is the mechanism suggested by GOODMAN and CARTER in patients with *Diabetes insipidus*[6]. As mentioned above, ERBE and WELLER have not found any change in the concentration of electrolytes in plasma following chlorothiazide in nephrectomized rats[10]. Therefore it is suggested that hydrochlorothiazide decreases water intake through a change in permeability of the cells involved in the regulation of thirst. The unexplained rise in water consumption induced by hydrochlorothiazide under starvation is now being further studied[14].

Résumé. L'hydrochlorothiazide diminue la consommation d'eau chez des rats néphrectomisés normalement alimentés ou bien ayant reçu par injection du sel hypertonique.

J. GUTMAN

Department of Pharmacology, The Hebrew University Hadassah Medical School, Jerusalem (Israel), April 22, 1963.

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