MECHANISM OF THE GOITROGENIC ACTION OF COBALT

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UDC 616.441-003.822-036.21-02:546.73

Administration of cobalt chloride or unithiol (sodium dithiol-2,3-dimercaptopropanesulfonate) to albino rats inhibits the ability of the thyroid of these animals to absorb I^{131} and facilitates its elimination with the urine. The weight of the thyroid increases. If both preparations are given simultaneously, these phenomena do not occur. Hypotheses concerning the mechanism of the goitrogenic effect of cobalt and unithiol and their interaction are suggested.

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The role of cobalt in the onset of endemic goiter has been inadequately studied. Investigations in foci of the disease have not established in every case a direct relationship between its severity and the cobalt content in the external environment [3, 4, 6, 7, 11]. Conversely, experimental results indicate that cobalt lowers the ability of the thyroid to absorb iodine, and leads to an increase in its weight and to change in its histological structure [5, 15, 17, 18, 19].

The combined effect of cobalt and sulfur-containing substances on thyroid function has received little study. Meanwhile, the goitrogenic action of some of these substances present in plants of the Cruciferae family has been reported by many authors [19, 20, 22-25]. An increased content of sulfhydryl groups has been found in white cabbages grown in inhabited areas of Orenburg regions with a bad goiter record [13].

The object of the present investigation was to study experimentally the effect of combined administration of cobalt and unithiol, containing two active sulfhydryl groups, on thyroid function.

EXPERIMENTAL METHOD

Experiments were performed on young male albino rats weighing initially 100-180 g. All the animals were kept on an ordinary laboratory diet.

The rats were divided into 4 groups. The animals of group 1 received unithiol in a dose of 20 mg/kg, those of group 2 cobalt chloride in a dose of 4 mg/kg daily, those of group 3 the same doses of cobalt chloride and unithiol simultaneously, and the rats of group 4 were controls.

It has been shown [12] that unithiol retains its pharmacodynamic properties when administered both by mouth and parenterally. However, to rule out any possibility of interaction in the gastro-intestinal tract, cobalt was given with the drinking water and unithiol injected subcutaneously. The control rats received 0.3 ml physiological saline by subcutaneous injection.

The animals were kept in groups in cages with wire mesh walls and roof. The experiment continued for 60 days.

The indices used as criteria of changes taking place in the rats were their general condition, weight, thyroid function determined by absorption of radioactive iodine and its elimination with the urine, weight of the thyroid, and pulse rate determined from the number of waves on the ECG recorded by a type ÉKPS-4 electrocardiograph with an ink writer.

I^{131} was injected intramuscularly in a dose of 5 μCi and the rats were kept in individual metabolic cages. The degree of absorption of isotope by the thyroid was determined in the living animals 15 min and 2, 6, 8, 24, and 48 h after injection. Its elimination from the animal was measured in 8-h and 24-h samples of urine. The radioactivity was measured as γ-radiation by a B-3 scintillation counter. The radioactivity in percent was determined relative to a reference standard, making allowance for the background.

Department of General Surgery, Orenburg Medical Institute (Presented by Active Member of the Academy of Medical Sciences of the USSR V. V. Zakusov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 3, pp. 51-54, March, 1968. Original article submitted June 18, 1966.

TABLE 1. Absorption of I^{131} by the Thyroid and Its Elimination with the Urine (in %; M±m)

Animals	Emission from thyroid, intervals of measurement (hours)						Content of isotope in urine		
	¼	2	6	8	24	48	8	24	48
Receiving unithiol	11.62±2.7	15.3±2.5	19.1±3.5	19.2±2.8	23.1±3.6	19.5±2.0	30.1±3.1	38.6±3.1	7.7±1.1
" cobalt	13.6±2.5	19.4±2.5	24.8±2.6	24.8±3.7	26.0±4.0	25.3±2.2	18.2±7.3	35.1±7.0	7.7±1.1
" cobalt and unithiol	11.7±1.1	21.4±2.3	27.4±2.8	30.1±2.6	33.4±0.7	33.1±0.3	12.0±0.6	35.1±7.0	12.8±1.8
Control	11.3±0.6	23.2±1.0	34.3±1.0	40.9±1.1	52.9±1.6	34.7±0.8	14.5±0.4	21.5±2.5	10.7±2.7

TABLE 2. Weight of Thyroid and Pulse Rate of Experimental Animals (M±m)

Animals	No. of animals	Mean body weight at end of experiment (in g)	Relative weight of thyroid (per 100 g body weight)	Pulse rate (per 15 sec)
Receiving unithiol	28	230	13.3±3.1	66.3±3.8
" cobalt	18	249	9.1±1.6	76.0±3.3
" cobalt and unithiol	12	238	7.7±1.7	78.4±1.1
Control	10	301	7.05±1.0	91.4±1.9

EXPERIMENTAL RESULTS

The results of investigations of thyroid function (Table 1) showed a decrease in the ability of the gland to absorb radioactive iodine in all groups of experimental animals by comparison with the controls. During all measurements the thyroid of rats receiving cobalt absorbed much less isotope than the controls ($P = 0.01$). Absorption was less still by rats receiving unithiol. After simultaneous administration of cobalt and unithiol, the thyroid retained its ability to absorb radioactive iodine more intensively than after their administration separately ($P = 0.01$).

The rate of accumulation of labeled iodine in the thyroids and the rate of its elimination were judged from the ratios between the percentage absorption after 24 and 48 h, and the percentage absorption during measurements at the other intervals.

Radioactivity in the thyroid glands of all groups of animals reached a maximum at 24 h. However, the rate of accumulation of isotope by the glands of the experimental animals was below this index in the controls. The fall in radioactivity to 48 h likewise was slower than in the controls.

A sharp increase in elimination of the isotope in the first 8 h was observed with the rats receiving unithiol. When cobalt and unithiol were given simultaneously, the elimination of I^{131} with the urine was not significantly different from that in the control.

The relative weight of the thyroid and pulse rate of the animals of the various groups are given in Table 2.

The relative weight of the thyroid of the rats receiving cobalt was increased by 30% ($P = 0.01$), and their pulse rate was slowed to 76 ($P = 0.02$). These changes were still more marked after administration of unithiol. In the animals receiving both preparations together, the weight of the thyroid and the pulse rate were not statistically different from normal.

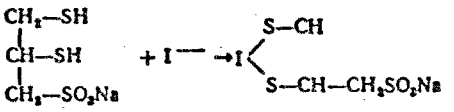
The facts described above give some idea of the mechanism of the goitrogenic action of these preparations. In the case of cobalt it is explained in the modern view of the nature of its biological action. It is now generally accepted that cobalt forms a chemical bond in the body with sulfhydryl groups, which play an important role in the activity of many enzymes responsible for carbohydrate, lipid, and protein metabolism [12]. Cobalt thus disturbs the function of these enzyme systems.

Work has recently been published showing the presence of free sulfhydryl groups in the colloid and thyroid epithelium [1], and demonstrating that their distribution in the thyroid tissue is dependent on its structure and functional state [2, 10].

There are reports in the literature that the ability of the thyroid to accumulate iodine depends on the presence of SH-groups in the gland [21].

Cobalt, by combining with SH-groups in the thyroid, thus blocks its ability to absorb iodine from the blood. This is in agreement with data [9] showing that, if the iodine content of the diet is the same, its absolute content in the thyroid tissue of rats falls with an increase in the cobalt content in the food.

The neutralizing action of unithiol on the goitrogenic effect of cobalt can be explained from this standpoint. Unithiol forms a cyclic metal – unithiol complex with cobalt in the body, facilitating its elimination in the urine [25]. The possibility is not ruled out that the mechanism of attachment of iodide to unithiol during its oxidation into iodine may be similar:



If the possibility of participation of SH-groups of the thyroid in the oxidation or transport of iodide is accepted, the thiol compounds containing these groups (including unithiol) must compete with them. By binding iodine, they may be responsible for endogenous iodine deficiency. This may probably have caused the increased elimination of I^{131} in the urine in our experiments during the first hours after administration of the isotope to rats receiving unithiol. This would fully explain the neutralizing action of cobalt on the goitrogenic effect of unithiol when they are administered together. By fixing unithiol, it leaves the sulfhydryl groups of the thyroid active.

It is perfectly possible that both these mechanisms may take place in the pathogenesis of endemic goiter.

Under the conditions of a natural iodine deficiency, either an insufficient or an excessive intake of cobalt into the body may disturb iodine metabolism in the thyroid if the food products contain appropriate amounts of thiol compounds possessing active sulfhydryl groups in their composition.

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