MECHANISM OF THE ANTIGOITROGENIC ACTION OF IODINE AND SALTS OF CERTAIN METALS DURING ADMINISTRATION OF 6-METHYLTHIOURACIL

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Experiments in vitro showed that 6-methylthiouracil (6-MTU) can form complexes with cobalt, zinc, manganese, copper, lead, and nickel and also can react with iodine in an alkaline medium while not reacting with potassium iodide. It is postulated that this may account for the antigoitrogenic action of iodine and trace elements when given together with 6-MTU, and also for the difference between the prophylactic effect of iodine and of potassium iodide.

6-Methylthiouracil (6-MTU) has a goitrogenic action in man and animals and deprives the tissues of iodine, copper, and manganese [3, 5-7, 10, 11, 14]. The effect of trace elements on goiter development is taken as evidence of their role in the genesis of endemic goiter. If rabbits receive copper or manganese and 6-MTU with their diet, the goitrogenic action of 6-MTU is sharply reduced or abolished, and the internal organs are deprived of iodine, copper, and manganese to a lesser degree. This suggested that these agents, in certain doses, act like iodine and prevent the onset of endemic goiter [2, 10, 11]. During simultaneous administration of cobalt and 6-MTU, the high thyrotropic activity of the pituitary [1], observed when 6-MTU is given alone [5], was depressed.

The object of the investigation described below was to examine the mechanism of antagonism between 6-MTU and trace elements with regard to their action on the thyroid gland.

EXPERIMENTAL METHOD AND RESULTS

A solution of 100 mg 6-MTU was prepared in 50 ml distilled water made alkaline with ammonia. Next, 0.5% solutions of cobalt and calcium chlorides and of manganese, copper, zinc, lead, and nickel sulfates were mixed in separate tubes in the ratio of 1 : 1 with the solution of 6-MTU. Reactions of solutions of the salts of these metals with ammonia were used as the control (Table 1).

TABLE 1. Color of Precipitate after Reaction of Salt of Metals with 6-MTU and Ammonia

Metals reacting	Solution of 6-MTU	Ammonia
Lead	Purple	Black
Copper	Muddy turquoise blue	Blue
Cobalt	Pale yellow	Pale yellow
Manganese	Blue-green	Green
Zinc	Milky	White floccules
Nickel	Cloudy green	Lilac
Calcium	Solution remains transparent	

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The amorphous precipitate formed in the tubes was separated by filtration. On the addition of hydrochloric acid to the filtrate is remained translucent, but on its addition to the 6-MTU solution, the latter acquired the appearance of a suspension [18]. The difference between the color of the precipitate in the control and experimental tubes and the absence of 6-MTU in the filtrate are evidence of the formation of complexes between 6-MTU and all the metals used except calcium, and of the precipitation of the complex. On the addition of Lugol's solution or iodine to the suspension or solution of 6-MTU, they were decolorized, but no visible reaction took place with potassium iodide.

A possible mechanism of the antithyroid action of thiourea is the fixation of iodine in the thyroid gland during its conversion into molecular iodine [17]. Under these circumstances the appearance of an SH-group in its structure leads to the formation of a formamidine disulfide complex [15]. In acid and neutral media, thiourea formed complexes with several trace elements [15].

The ability of SH-groups to react with certain metals and to be oxidized by iodine is well established [4, 13]. As the present experiments showed, under certain conditions 6-MTU, which has a thiocarbamido group in its structure, can also form complexes with metals and react with iodine. It may be assumed that other synthetic (mercaptoimidazole, thiouracil, mercazolyl) and natural (5-vinyl-2-thiooxazolidone or goitrin, ergothioeine) antithyroid compounds possessing reactogenic SH- or thiocarbamido-groups in their structure will form complexes under certain conditions with trace elements and will react with iodine.

In experimental investigations 6-MTU and salts of metals were given by mouth, and the possibility of their contact was a real one, while the alkaline reaction in the small intestine creates favorable conditions for their chemical interaction. Other evidence that this reaction can take place in the body is given by the decrease in content of trace elements in the tissues during administration of 6-MTU [2, 11, 14].

Both in solution and in suspension, 6-MTU does not react with potassium iodide but reacts rapidly with iodine. Without denying the great importance of potassium iodide for restoration of normal thyroid function and for the prevention of endemic goiter, it can be considered that one aspect of the antigoitrogenic use of Lugol's solution and of iodine in the treatment of thyrotoxicosis by 6-MTU [3, 6, 8, 9, 12] is neutralization of part of its dose while still in the gastro-intestinal tract. With respect to 6-MTU and, possibly, its natural analogue with a thiocarbamido group – goitrin – iodine and potassium iodide differ in value in the prevention of goiter.

This is confirmed indirectly by the observations of Clements [16] in Tanzania. Consumption of milk containing goitrin in that country led to the appearance of goiter in children despite prophylactic administration of potassium iodide (10 mg every week).

The possibility is not ruled out that in the presence of natural goitrogens containing reactogenic groups in their structure, not only iodine but also other trace elements capable of forming complexes with them may have a prophylactic action in foci of endemic goiter.

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