EFFECT OF GRADED DOSES OF CARBIMAZOLE AND PROPYLTHIOURACIL ON THE SYNTHESIS OF THE THYROID HORMONES

By

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ABSTRACT

The effect of graded doses of carbimazole on hormonal synthesis in the thyroid gland was studied in the rat, and compared with that of graded doses of propylthiouracil. The synthesis of thyroxine and triiodothyronine was totally inhibited by 3–5 mg of carbimazole daily; at this dose the ratio \( \frac{\text{DIT} + \text{MIT}}{1^-} \) was the same as for untreated controls. A dose of 1–3 mg of propylthiouracil also inhibited the synthesis of thyroxine and triiodothyronine, but at this dose the ratio \( \frac{\text{DIT} + \text{MIT}}{1^-} \) was much lower than for the controls. The dose of carbimazole that inhibits the formation of thyroxine and triiodothyronine seems to have little effect on the iodination of the tyrosine radicals and on the formation of mono- and diiodotyrosine.

The inhibition of the synthesis of thyroid hormones by antithyroid drugs was for a long time ascribed to a decrease in the oxidation of inorganic iodine and in the iodination of tyrosine (Astwood 1954). Later investigations, however, have shown that other steps in the synthesis are more easily inhibited than this initial iodination. Thionamides have been found to influence both the iodination of tyrosine radicals to form mono- and diiodotyrosine, and the coupling of iodotyrosines to form iodothyronines. Which step of hormone synthesis is, relatively, most affected also depends on the dose of the anti-
thyroid substance administered (Richards & Ingbar 1959; Slingerland et al. 1959; Mayberry & Astwood 1960; Lino et al. 1961; Shimoda 1964). 1-methyl-3-carbethoxy-2-thioglyoxal lone (carbimazole) was introduced by Lawson (1951). The aim of the present study was to examine the effect of graded doses of carbimazole on the various steps of synthesis of the thyroid hormones, and to compare this with the effect of graded doses of a thiourea derivative, propylthiouracil.

MATERIALS AND METHODS

The study was made on 60 adult albino rats of the Sprague-Dawley strain weighing 220–280 g. Ten days before the experiments were started the animals were fed an iodine-poor diet (rat bread containing 0.1 μg of iodine/g, and water ad libitum). In the first experiment propylthiouracil or carbimazole was administered intraperitoneally for 3 days in a mixture of polyethylene glycol and distilled water (2:1). Propylthiouracil (in doses of 0.5, 1 and 3 mg) was administered to 3 groups of 3 rats each and carbimazole (in doses of 3, 5, 7, 10, 30, 60 and 120 mg) to 7 groups of rats.

The last dose of the antithyroid drug was administered 12 hours before sacrifice. Twenty-four hours before the rats were killed 200 μc of 131I NaI was administered intraperitoneally. The animals were killed under ether anaesthesia and the thyroid glands removed and placed in ice-cold Ringer’s solution. The total radioactivity of the gland was measured with a well type scintillation counter (Tracerlab). The glands of each group animals were pooled, homogenized and hydrolysed at 37°C with crude pancreatic at pH 8.5 for 40 hours and with papain at pH 5.0 for 18 hours, as previously described (Bois & Larsson 1958). The total hydrolyzate (2 ml) was extracted six times with 2 ml of n-butanol saturated with 0.5 per cent sodium thiosulphate solution and six times with 2 ml of n-butanol. More than 95 per cent of the original radioactivity was recovered in the extract. After evaporation in vacuo of the neutral butanol extract, the dry residue was suspended in a mixture of absolute alcohol and concentrated ammonium hydroxide (3:1). The extract was chromatographed on no. 1 Whatman paper in a system of n-butanol, dioxane (free from peroxides) and 2 N ammonium hydroxide (4:1; 4) by means of a one-dimensional descending technique; the samples were duplicated. The radioactivity in the strips was measured with a scintillation counter at 350 000 counts/min/μc 131I over a background of 20 counts/min, and autoradiographed. The peaks were identified by running parallel nonradioactive standards consisting of monoiodotyrosine, diiodotyrosine, 3,5,3-triiodothyronine and thyroxine. Four rats serving as controls were not given antithyroid substances but were otherwise treated in the same way as the test animals; in order to check the individual variation in the distribution of 131I on the chromatograms these glands were not pooled.

The capacity of the thyroid gland for organic binding of the trapped iodine, was taken as the ratio between the amount of labelled mono- and diiodotyrosine and the amount of iodide in the homogenate, \( \frac{\text{DIT} + \text{MIT}}{1} \). The amount of triiodothyronine and thyroxine in the homogenate was taken as a measure of the coupling of the iodo tyrosine to form iodothyronines.

In a separate group of 20 animals the effect of long-term treatment with carbimazole was studied after daily administration of 30 mg of carbimazole for 6 weeks.

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RESULTS

For the non-pooled controls the distribution of $^{131}$I between the various compounds was almost the same, and the variations between animals was small.

As the dose of antithyroid drug was increased, the proportion of labelled tyrosines in the gland diminished and that of free iodide increased (Table 1). The ratio \( \frac{\text{DIT} + \text{MIT}}{I^-} \) in the homogenate thus decreased steadily with the increased dose of the drug.

The homogenate still contained detectable amounts of labelled thyronines at a dose of 1 mg of propylthiouracil, but not at 3 mg, at which dose the ratio \( \frac{\text{DIT} + \text{MIT}}{I^-} \) was about unity (Table 1).

The smallest amount of carbimazole for which no labelled thyronine was detectable was 5 mg; at this dose the ratio \( \frac{\text{DIT} + \text{MIT}}{I^-} \) was 17, which was about the same as for the controls. For a ratio of unity a dose of carbimazole twelve times greater (60 mg) was required (Table 1). When 30 mg carbimazole was given daily over a period of 6 weeks the proportion of mono- and diiodo-tyrosine was almost the same as after administering the same dose over a short period.

The weight of the thyroid gland was 38.2 ± 1.7 as against 19.1 ± 1.2 for the control group.

Table 1.
The percentage distribution of radioactivity in the thyroid gland of rats given graded doses of carbimazole and propylthiouracil (PTU). Paper chromatography of pooled, hydrolyzed thyroid glands; 3 rats in each group, 4 controls, not pooled (S.E. indicated).

<table>
<thead>
<tr>
<th></th>
<th>Carbimazole (mg/day)</th>
<th>PTU (mg/day)</th>
<th>Untreated controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3  5  7  10  30  60 120</td>
<td>0.5 1 3</td>
<td></td>
</tr>
<tr>
<td>DIT + MIT</td>
<td>91.7 94.3 91.6 86.2 50.9 30.8 5.0</td>
<td>87.2 67.8 47.8 47.8</td>
<td>74.0±0.32</td>
</tr>
<tr>
<td>I^-</td>
<td>3.7 5.6 8.2 13.8 15.4 27.0 80</td>
<td>10.6 30.6 51.8</td>
<td>4.0±0.46</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>2.8 -- -- -- -- --</td>
<td>1.5 1.3 --</td>
<td>16.5±0.95</td>
</tr>
<tr>
<td>Trit</td>
<td>1.7 -- -- -- -- --</td>
<td>0.4 0.3 --</td>
<td>5.5±0.26</td>
</tr>
<tr>
<td>DIT + MIT</td>
<td>-- -- -- -- -- --</td>
<td>-- -- --</td>
<td></td>
</tr>
<tr>
<td>I^-</td>
<td>25 17 11 6 3 1 0.06</td>
<td>8 2 1</td>
<td>18</td>
</tr>
</tbody>
</table>
DISCUSSION

At the smallest dose of carbimazole that inhibited coupling so effectively that the thyroid gland homogenate contained no detectable amounts of labelled thyronine, the ratio \( \frac{\text{DIT} + \text{MIT}}{\text{I}^-} \) was still the same as for the controls. For 1 mg of propylthiouracil, the highest dose at which detectable amounts of labelled thyroxine and triiodothyronine were still present, the ratio was much lower than for the controls. The most reasonable explanation of this difference between the drugs is that moderate doses of carbimazole, unlike propylthiouracil, at first inhibit the coupling of iodotyrosines to form thyronines, and that much larger doses are needed before the iodination of tyrosine radicals, is also inhibited. It should, however, be borne in mind that in the gland the ratio \( \frac{\text{DIT} + \text{MIT}}{\text{I}^-} \) is dependent not only on the rate at which the organic binding of iodine to the tyrosine radicals occurs but also on the rate at which the mono- and diiodotyrosine is cleared. Whatever the explanation, there is a difference in the effect of the two compounds at the different steps. This difference could be used for a relatively selective inhibition of the coupling of tyrosines in the thyroid gland and it could account for the greater uptake of radioiodine by the thyroid gland during treatment with carbimazole than during a clinically similarly effective treatment with thiourea derivatives (Wijnbladh 1960).

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REFERENCES


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