Antithyroid Action of 3-Amino-1,2,4-triazole*

NICHOLAS M. ALEXANDER

From the Radioisotope Service, Veterans Administration Hospital, West Haven, Connecticut, and the Department of Biochemistry, Yale University, New Haven, Connecticut

(Received for publication, June 26, 1958)

It was first shown by Heim et al. (2, 3) that 1 hour after 3-amino-1,2,4-triazole has been injected into rats, there is a marked inhibition of liver and kidney catalase, a lesser inhibition of liver peroxidase, and no inhibition of erythrocyte catalase activity. In view of this rather selective action towards tissue hydroperoxidases, it seemed possible that aminotriazole should exhibit antithyroid activity by inhibiting thyroid iodide peroxidase (4, 5), if such an enzyme exists (6). In essence, the action of aminotriazole would resemble that of propylthiouracil (7), whereby the thyroid gland is prevented from forming organically bound iodine, but can still concentrate plasma iodide.

This report demonstrates that aminotriazole inhibits thyroid 

EXPERIMENTAL

Experiments were performed with male Sprague-Dawley rats which were kept on Purina chow and tap water ad libitum. Injected compounds were dissolved with 1 ml. of isotonic saline and given intraperitoneally. Aminotriazole purchased from the American Cyanamid Company was purified by extracting it with an azeotropic mixture of methanol and benzene (cf. 8). The dried aminotriazole crystals were dissolved in a minimum amount of water and decolorized with charcoal. The white triazole thus crystallized melted at 153-154° (corrected).

The percentage of uptake of injected 

RESULTS

A typical experiment demonstrating the effect of aminotriazole on thyroid iodine metabolism is shown in Table I. Rats weighing 200 gm. were injected with 1 mg. of aminotriazole followed in 1 hour by radioiodine. The animals were then killed at 30 minutes, 60 minutes, and 240 minutes; these are designated as Aminotriazole 30, 60, and 240, and controls injected with isotonic saline solution are shown as Control 30, 60, and 240. It is seen that aminotriazole markedly inhibits thyroid 

* A preliminary account has appeared in abstract form (1).

† Hereafter, 3-amino-1,2,4-triazole will be referred to as aminotriazole.
TABLE I

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>$^{131}$I uptake</th>
<th>$^{131}$I soluble in trichloroacetic acid</th>
<th>T:S*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 30</td>
<td>1.22</td>
<td>9.3</td>
<td>40</td>
</tr>
<tr>
<td>Aminotriazole 30</td>
<td>0.26</td>
<td>94.8</td>
<td>64</td>
</tr>
<tr>
<td>Control 60</td>
<td>1.72</td>
<td>9.5</td>
<td>23</td>
</tr>
<tr>
<td>Aminotriazole 60</td>
<td>0.57</td>
<td>95.4</td>
<td>70</td>
</tr>
<tr>
<td>Control 240</td>
<td>2.18</td>
<td>5.0</td>
<td>25</td>
</tr>
<tr>
<td>Aminotriazole 240</td>
<td>0.18</td>
<td>84.3</td>
<td>71</td>
</tr>
</tbody>
</table>

* Ratio of thyroid to plasma radioiodide concentration.

TABLE II

<table>
<thead>
<tr>
<th>Experimental group*</th>
<th>Average thyroid weight</th>
<th>2-hour $^{131}$I uptake</th>
<th>T:S†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (4)</td>
<td>18.8</td>
<td>1.4</td>
<td>22</td>
</tr>
<tr>
<td>Aminotriazole-fed for 12 days (1)</td>
<td>47.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotriazole-fed for 20 days (3)</td>
<td>67.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotriazole-fed for 37 days (3)</td>
<td>97.3</td>
<td>1.4</td>
<td>56</td>
</tr>
</tbody>
</table>

* Figures in parentheses refer to the number of animals used.
† Ratio of thyroid to plasma radioiodide concentration.

TABLE III

<table>
<thead>
<tr>
<th>Experimental group*</th>
<th>Thyroid catalase specific activity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No injection</td>
<td>0.004</td>
</tr>
<tr>
<td>Saline</td>
<td>0.256</td>
</tr>
<tr>
<td>50 mg. aminotriazole</td>
<td>0.115</td>
</tr>
<tr>
<td>1 mg. aminotriazole</td>
<td>0.248</td>
</tr>
</tbody>
</table>

* Four animals, each weighing approximately 200 gm., were used in all groups and were killed 1 hour following injections.
† Average activity obtained with four separate thyroids expressed as microequivalents of H$_2$O$_2$ decomposed in 5 minutes per mg. of nonvolatile organic material.

The catalase activities of the two control groups. Animals injected with 50 mg. of aminotriazole had thyroid catalase activities which were 44 per cent of those of the controls. However, animals receiving 1 mg. of aminotriazole, an amount which markedly inhibits thyroid iodine uptake, had essentially the same catalase activity as the controls.

A recent report (14) has shown that aminotriazole is not readily permeable to the red cell membrane. Thus, aminotriazole in the plasma might have inhibited the erythrocyte catalase released during homogenization of thyroid tissue contaminated with blood. Such a possibility could have explained the result obtained with the injection of 50 mg of aminotriazole but was excluded when the catalase activities of hemolyzed whole blood were found to be the same in these animals as in the controls.

In examining the nonenzymatic reaction between aminotriazole and I$_2$, it was found that when a solution consisting of 0.05 M aminotriazole and 0.005 M I$_2$ was allowed to stand for 30 minutes at pH 7.4, only 17 per cent of the I$_2$ had disappeared. Under identical conditions either in the presence or absence of aminotriazole, 0.05 M tyrosine immediately reacted with all of the I$_2$.

**DISCUSSION**

Antithyroid drugs which block the formation of organic iodine generally contain thiocarbamyl or aromatic groups (15). Compounds with these groups react very rapidly with I$_2$ to form either I$^-$ (16) or iodinated derivatives (17), but the significance of such reactions in vivo is not definitely known (17, 18). In contrast, neither group is found in the aminotriazole molecule and the triazole would not be expected to react with I$_2$ in vivo. But the possibility that aminotriazole metabolites might react with I$_2$ or other oxidized forms of iodine which normally exist in the thyroid has not been excluded.

Because small doses of aminotriazole inhibit thyroid iodine uptake without affecting thyroid catalase activity, the depressed activity produced by larger doses of aminotriazole probably has no bearing on the antithyroid action of the drug. Small amounts of aminotriazole may inhibit thyroid iodide peroxidase activity towards iodide ion without altering the catalase activity and it would be more revealing to assay iodide oxidation by H$_2$O$_2$ and thyroid tissue. Such an assay is complicated by the nonenzymatic oxidation of iodide by H$_2$O$_2$ and the contamination of thyroid tissue by erythrocyte catalase and methemoglobin which behaves as a peroxidase.

Sufficient information was not obtained from these experiments to assess the possible inhibition by aminotriazole of tyrosine iodinase (19) or the presumed H$_2$O$_2$ generating system in the thyroid gland.

**SUMMARY**

In the rat, 3-amino-1,2,4-triazole is a fairly potent antithyroid agent which inhibits the formation of organically bound iodine but does not affect the iodide trap. Continuous ingestion of the triazole causes hyperplasia of the thyroid gland. Large doses of the triazole bring about a 50 per cent inhibition of thyroid catalase activity. Much smaller doses of the drug do not alter the thyroid catalase activity but are effective in inhibiting $^{131}$I uptake by the thyroid gland. It is believed that the decreased thyroid catalase activity is probably not related...
to the antithyroid action of the drug. The mechanism of the antithyroid activity is not known.

Acknowledgment—The technical assistance of Miss A. Panaccone is gratefully acknowledged.

REFERENCES

Antithyroid Action of 3-Amino-1,2,4-triazole
Nicholas M. Alexander


Access the most updated version of this article at http://www.jbc.org/content/234/1/148.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/234/1/148.citation.full.html#ref-list-1