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THE EFFECT OF PRETREATMENT WITH PROPYL THIOURACIL
ON THE ACCUMULATION OF ASTATINE-211
BY THE THYROID GLAND OF THE RAT

Patricia W. Durbin, Joseph G. Hamilton, and Marshall W. Parrott

May 24, 1954

Berkeley, California
THE EFFECT OF PRETREATMENT WITH PROPYL THIOURACIL ON THE ACCUMULATION OF ASTATINE-211 BY THE THYROID GLAND OF THE RAT*

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May 24, 1954

For a number of years it has been known that a variety of chemical agents act as antithyroid drugs, and that their effect is to reduce or almost completely prevent the organification of iodine and subsequently the production of the thyroid hormone.1,2 Propyl thiouracil and related antithyroid drugs have found extensive use in recent years in the treatment of human thyrotoxicosis.3,4

Astatine is the heaviest member of the halogen group, and certain of its chemical properties resemble those of iodine. There are, however, some rather significant dissimilarities.5 Although 18 radioactive isotopes of astatine have been identified, no stable isotopes of this element are known to exist.6 The particular radioisotope used in these and other studies is the 7.3-hour At211, which decays by the emission of alpha particles and 89-kev x-rays.**

The capacity of the thyroid gland to concentrate and retain At211 has been demonstrated in experimental animals and man.7,8,9,10 The present studies were undertaken in order to determine the possible effect of propyl thiouracil upon the accumulation and retention of At211 by the thyroid gland of the rat and to compare this effect with that obtained using carrier-free I131. It was also hoped that these experiments would help to shed some light on the mode of entry of astatine into the thyroid gland and on its chemical state in that organ.

*This work was done under the auspices of the U. S. Atomic Energy Commission
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‡Divisions of Medical Physics, Experimental Radiology, and Medicine, and Crocker Laboratory, University of California, Berkeley and San Francisco, California
**Sixty percent of the At211 nuclei decay by K-capture to form Po211 with a 0.5-second half-life, and 40% decay by alpha-particle emission to form Bi207
METHODS

The animals employed for these studies were 75-day-old female Sprague-Dawley rats that weighed about 165 grams. All the animals used were received from the dealer at the same time and had been maintained for three weeks prior to the start of the experiment on tap water and a pelleted stock diet which is in general use throughout the University of California Radiation Laboratory.* Both food and water were given ad lib.

Propyl thiouracil was administered to 20 rats in the drinking water at a concentration of 0.1% by weight for 11 days. On the tenth day, 10 of these rats were each given 5 microcuries of $^{211}$At and 10 were each given 6 µc of $^{131}$I. Both $^{211}$At and $^{131}$I were administered intravenously. Ten rats that had received no pretreatment served as controls. Five of these were each given 5 µc of $^{211}$At and five each received 6 µc of $^{131}$I.

Twenty-one hours after the administration of the radiohalogens the rats were sacrificed with chloroform, and the thyroids were dissected out and weighed. The $^{211}$At and $^{131}$I contents of the thyroid glands were measured with an NaI-TII scintillating crystal gamma counter. It was possible to measure the $^{211}$At in this manner, since its radioactive decay is associated with an 80-kev x-ray.

RESULTS

The results of these experiments are shown in Table I. The single most impressive observation is the nearly twentyfold enhancement of the accumulation of $^{211}$At in the thyroid glands of the animals treated with propyl thiouracil. This is in distinct contrast to the diminution of the accumulation of $^{131}$I in the thyroid glands of the animals treated with this drug, a result that has been shown previously by Taurog et al.¹ In fact, the concentration of $^{211}$At by the thyroid glands of the treated animals is more than three times the concentration of $^{131}$I in this group.

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*This diet is similar in composition to "Diet 14" developed by the University of California Institute of Experimental Biology and contains a fairly large amount of added iodide. To every 270 pounds of feed there is added 300 ml of a 0.45% solution of KI.

**The physical and chemical procedures for the preparation of $^{211}$At are given elsewhere.**
Table I

The Effect of the Administration of 0.1 Percent Propyl Thiouracil in the Drinking Water for 11 Days on the Body Weight, Thyroid Weight, and Thyroidal Uptake of Intravenously Administered $\text{At}^{211}$ and $\text{I}^{131}$ in the Female Sprague-Dawley Rat*

<table>
<thead>
<tr>
<th></th>
<th>Propyl Thiouracil</th>
<th>Tap water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal weight</td>
<td>156.4 ± 1.68 g</td>
<td>164.8 ± 2.88 g</td>
</tr>
<tr>
<td>Thyroid weight</td>
<td>37.4 ± 1.31 mg</td>
<td>15.2 ± 0.61 mg</td>
</tr>
<tr>
<td>Thyroid uptake percent administered $\text{At}^{211}$</td>
<td>3.82 ± 0.26</td>
<td>0.23 ± 0.0025</td>
</tr>
<tr>
<td>Thyroid concentration percent $\text{At}^{211}$/g wet tissue</td>
<td>105.4 ± 6.61</td>
<td>16.2 ± 1.8</td>
</tr>
<tr>
<td>Thyroid uptake percent administered $\text{I}^{131}$</td>
<td>1.13 ± 0.16</td>
<td>7.28 ± 1.47</td>
</tr>
<tr>
<td>Thyroid concentration percent $\text{I}^{131}$/g wet tissue</td>
<td>30.3 ± 4.5</td>
<td>445 ± 83.3</td>
</tr>
</tbody>
</table>

*Standard error of the mean = $\sqrt{\frac{\sum d^2}{n(n - 1)}}$

**For calculation of P see Fisher**\(^12\).
It should be noted that the values for the uptake of both $^{131}$I and $^{211}$At in the thyroid glands of the control animals are somewhat low. This is presumably due to the presence of a relatively large amount of stable iodine in the diet employed. It has been shown that the administration of stable iodide decreases the accumulation of both $^{131}$I and $^{211}$At in the thyroid gland of the rat. The uptake of $^{211}$At in the treated rats is far greater than has been seen previously, even when they had been maintained on a low-iodine diet.

**DISCUSSION**

These results were quite unexpected. A possible explanation for the tremendous increase in the thyroidal uptake of $^{211}$At following the administration of propyl thiouracil is presented here with the understanding that it is highly speculative.

The apparent action of propyl thiouracil and related antithyroid drugs is to prevent the organification of iodine. From the results of the experiments described here it appears that the effect of propyl thiouracil on the accumulation of $^{211}$At by the thyroid gland is quite different from its effect on the uptake of $^{131}$I. The inorganic chemistry of astatine is complex and not too well understood, and nothing is known about its biochemistry. Astatine has been shown to possess at least four valence states, $^{\text{At}}-$, $^{\text{At}}^0$, $^{\text{At}}0^-$, and a higher oxidized state. It is likely that in the thyroid gland there are enzymes capable of oxidizing $^{\text{At}}^0$ to $^{\text{At}}0^-$, the lowest of the oxidized states, which thus tend to rob the thyroid gland of its accumulated astatine. In the presence of propyl thiouracil it may very well be that the oxidation of $^{\text{At}}0$ to $^{\text{At}}0^-$ is prevented, so that the continued accumulation and retention of astatine in some type of loose organic binding is possible.

**SUMMARY**

A study has been made of the accumulation of $^{131}$I and $^{211}$At in normal and propyl-thiouracil-treated rats. A very marked enhancement of the accumulation of $^{211}$At in the thyroid gland has been observed following administration of propyl thiouracil. This is in contrast to the diminution of the uptake of $^{131}$I by the thyroid glands of the rats receiving propyl thiouracil.
ACKNOWLEDGMENTS

The authors wish to thank Dr. Warren M. Garrison, for his continued interest in this work and his many helpful suggestions; Mr. G. B. Rossi and the crew of the 60-inch cyclotron, who were responsible for the production of the astatine; and Mrs. Marilyn Williams, for technical assistance.
BIBLIOGRAPHY


