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

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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 thyorid 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 At^{211}, which decays by the emission of alpha particles and 89-kev x-rays.**

The capacity of the thyroid gland to concentrate and retain At^{211} has been domonstrated 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 At^{211} by the thyroid gland of the rat and to compare this effect with that obtained using carrier-free I^{131}. 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.

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**Sixty percent of the At^{211} nuclei decay by K-capture to form Po^{211} with a 0.5-second half-life, and 40% decay by alpha-particle emission to form Bi^{207}

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 At^{211}** and 10 were each given 6 μc of I^{131}. Both At^{211} and I^{131} were administered intraveneously. Ten rats that had received no pretreatment served as controls. Five of these were each given 5 μc of At^{211} and five each received 6 μc of I^{131}.

Twenty-one hours after the administration of the radiohalogens the rats were sacrificed with chloroform, and the thyroids were dissected out and weighed. The At^{211} and I^{131} contents of the thyroid glands were measured with an NaI-TlI scintillating crystal gamma counter. It was possible to measure the At^{211} 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 At^{211} in the thyroid glands of the animals treated with propyl thiouracil. This is in distinct contrast to the diminution of the accumulation of I^{131} 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 At^{211} by the thyroid glands of the treated animals is more than three times the concentration of I^{131} 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 At^{211} are given elsewhere.[11]

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 At^{211} and I^{131} in the Female Sprague-Dawley Rat*

	Propyl Thiouracil Water	P**	Tap water
Animal weight	156.4 ± 1.68 g	<0.02	164.8 ± 2.88 g
Thyroid weight	37.4 ± 1.31 mg	<0.01	15.2 ± 0.61 mg
Thyroid uptake percent administered At^{211}	3.82 ± 0.26	<0.01	0.23 ± 0.0025
Thyroid concentration percent At^{211}/g wet tissue	105.4 ± 6.61	<0.01	16.2 ± 1.8
Thyroid uptake percent administered I^{131}	1.13 ± 0.16	<0.01	7.28 ± 1.47
Thyroid concentration percent I^{131}/g wet tissue	30.3 ± 4.5	<0.01	445 ±83.3

*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 I^{131} and At^{211} 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 I^{131} and At^{211} in the thyroid gland of the rat.[8] The uptake of At^{211} in the treated rats is far greater than has been seen previously, even when they had been maintained on a low-iodine diet.[8]

DISCUSSION

These results were quite unexpected. A possible explanation for the tremendous increase in the thyroidal uptake of At^{211} 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.[1] From the results of the experiments described here it appears that the effect of propyl thiouracil on the accumulation of At^{211} by the thyroid gland is quite different from its effect on the uptake of I^{131}. 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, At^-, At^0, AtO^-, and a higher oxidized state.[5] It is likely that in the thyroid gland there are enzymes capable of oxidizing At^0 to AtO^-, 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 At^0 to AtO^- 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 I^{131} and At^{211} in normal and propyl-thiouracil-treated rats. A very marked enhancement of the accumulation of At^{211} in the thyroid gland has been observed following administration of propyl thiouracil. This is in contrast to the diminution of the uptake of I^{131} by the thyroid glands of the rats receiving propyl thiouracil.

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