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EFFECTS OF THYROXINE AND KSCN ON CAPACITY OF RAT THYROID GLAND TO ACCUMULATE ASTATINE^{211}

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EFFECTS OF THYROXINE AND KCN ON CAPACITY OF RAT THYROID TO ACCUMULATE ASTATINE^{211} *

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The discovery and production of Element 85, astatine^{211} (1) was closely followed by studies of the thyroidal accumulation of this, the heaviest of the halogen elements (2). It has been clearly established that the thyroid glands of rats, guinea pigs, monkeys, and man selectively concentrate the 7.3 hour isotope, At^{211}, to a degree which is similar to, but lower than that of I^{131} (2,3,4,5,6). It has been further established that the thyroid stimulating hormone (TSH) increases while iodide decreases the thyroidal accumulation of both At^{211} and I^{131} (2,3). Two recent reports indicate, however, that the thiouracil type of anti-thyroid compound enhances the thyroidal uptake of At^{211} in rats in contrast to lowering the I^{131} uptake (4,6). Since the mechanism of the thiouracil induced enhancement of At^{211}

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uptake has not been satisfactorily understood or explained, it seemed of interest to study the effects of other classes of anti-thyroid compounds upon the capacity of the thyroid gland to accumulate At^{211}. It is the purpose of this paper to present data which suggest that depressed thyroid function, as produced by the administration of exogenous thyroxine, results in a lowered thyroidal accumulation of both At^{211} and I^{131}, that thiocyanate depresses the thyroidal accumulation of At^{211} and that thiocyanate apparently discharges At^{211} from the thyroid gland.

Methods. The animals used in these studies were young female Sprague-Dawley rats that had been maintained for at least 2 weeks after receipt from the dealer on tap water and a pelleted stock diet*** which is general use throughout the University of California Radiation Laboratory. Both food and water were given ad lib. Food was withdrawn following the intravenous administration of either At^{211} or I^{131}†. The At^{211} was prepared by a modification of the method described by Garrison et al (7). Following

*** This diet is similar in composition to "Diet 14" developed by the University of California Institute of Experimental Biology and has been found to contain 2.5 µg of iodine per gram.

† Processed, carrier-free I^{131} was obtained from Oak Ridge National Laboratory, Oak Ridge, Tennessee.

pretreatment with either thyroxine or KSCN and the administration of the isotopes, the animals were sacrificed with chloroform at intervals of from 1 to 18 hours. The thyroid glands were dissected and weighed to the nearest 0.2 mg on a torsion balance. The x-ray activity of the At^{211} or the γ-ray activity of the I^{131} were measured with an NaI-Tl scintillating crystal gamma counter which has been described elsewhere (3).

Thyroxine was given subcutaneously in a series of 8 daily injections at a level of 230 mg/kg/injection in a volume of 0.1 ml of isotonic saline††. The last injection of thyroxine was given 4 hours before the administration of the radiohalogens. An equal number of rats received daily injections of a similar volume of isotonic saline and served as controls. One-half of the thyroxine treated group received 30 μc of At^{211} and the other half, 10 μc of I^{131}. The sham injected control group was divided and received the same amounts of At^{211} or I^{131} as above. The number of animals in each group is shown in Table I.

Potassium thiocyanate was given subcutaneously at a level of 80 mg/kg/injection in a volume of 0.2 ml. Each rat received 20 μc of At^{211}. The number of rats in each group, the time schedule and the number of KSCN

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†† Pure crystalline l-thyroxine (Merck). One hundred mg was dissolved in 182 ml of 0.0035 N NaOH, made isotonic with NaCl and the pH was adjusted to 8.5.

injections and the interval between the administration of the At^{211} and the sacrifice of the animals is shown in Table II.

Results: Thyroxine. The results of 3 daily subcutaneous injections of thyroxine (230 μg/kg/day) on the 18 hour thyroidal uptake of I^{131} or At^{211}, body weight, and thyroid weight are presented in Table I. The thyroxine dosage was sufficient to depress the growth rate as measured by body weight to a statistically significant degree ($P < 0.01$), but did not appear to affect thyroid weight. The thyroxine dosage depressed the thyroidal accumulation of both I^{131} and At^{211} below that of non-thyroxine treated control rats. It should be noted that the thyroid uptake values for both At^{211} and I^{131} are somewhat low. This is presumably due to the presence of a relatively large amount of stable iodine in the diet employed.

KSCN. Table II shows the accumulation of At^{211} by the thyroid gland of the rat 1, 4, and 18 hours following its intravenous injection with and without the administration of KSCN. A subcutaneous injection of 20 mg of KSCN 1.5 hours before At^{211} injection when the rats were sacrificed at either 1 or 4 hours after the administration of At^{211} resulted in a lower thyroidal accumulation of At^{211} as compared to the controls. Rats that received 2 KSCN injections, 1.5 hours before the At^{211} was given and

another KSCN injection 14 hours later with an interval between At^{211} administration and sacrifice of 18 hours, had lower thyroid At^{211} values than the controls. When the interval between the administration of At^{211} and sacrifice was 18 hours, a single injection of KSCN 1.5 hours before sacrifice also produced lower thyroid accumulation of At^{211}.

Discussion. It has been clearly established that thyroid hormone acts to depress thyroid function by inhibiting the production of TSH by the anterior pituitary (8). In this experiment, the administration of relatively large amounts of thyroxine apparently inhibited pituitary TSH production which, in turn, depressed thyroid function as measured by the decreased thyroidal accumulation of both At^{211} and I^{131}. These findings are in agreement with the previous studies by Hamilton and Soley (1) that exogenous TSH increased the thyroidal uptake of both At^{211} and I^{131}, and further indicate that the thyroidal accumulation of At^{211} is under pituitary control as is the thyroidal accumulation of I^{131}.

It has been demonstrated that thiocyanate inhibits the collection of iodide by the thyroid gland (9). It seems reasonable to interpret the present finding of a lowered thyroidal uptake of At^{211} when thiocyanate was given prior to At^{211} administration to a similar mechanism; that is,

thiocyanate interferes with the capacity of the thyroid gland to concentrate astatide (At^-).

What happens to the astatide after it is collected by the thyroid gland is more difficult to understand. In the case of I^{131}, iodide is presumably oxidized to iodine and this is organically bound (10). Thiouracil blocks the organic binding of iodine, and this is reflected by a lower I^{131} content of the thyroid gland. However, both thiouracil and propyl thiouracil have been shown to increase the accumulation of At^{211} by the thyroid gland (4,6). These results have indicated that the behavior of the thyroid toward At^{211} and I^{131} is not always similar. This is not surprising since the chemistry of astatine and iodine differ in many respects (11). It has been shown that thiocyanate administration after the organic binding of I^{131} discharges little or no I^{131}(9). Since in the present experiment approximately 50% of the At^{211} was discharged when KSCN was given 1.5 hours before an 18 hour At^{211} uptake, it is apparent that the At^{211} accumulated by the thyroid is not organically bound in a manner that is strictly comparable to the organic binding of I^{131}.

Summary. 1. The administration of thyroxine to the intact female Sprague-Dawley rat resulted in a lowered thyroidal accumulation of both

At^{211} and I^{131}. Since it is known that thyroxine inhibits the production of TSH by the pituitary gland, it is suggested that a reduced pituitary function resulted in a reduced thyroidal accumulation of both halogens. It is further indicated that the thyroidal accumulation of At^{211} is under pituitary control.

2. It has been demonstrated that thiocyanate blocks the thyroidal accumulation of astatide, and that since thiocyanate can discharge At^{211} from the thyroid gland, At^{211} probably is not organically bound in a manner similar to the organic binding of I^{131}.

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Table I. Effect of 8 Daily Subcutaneous Injections of Thyroxine (230 μg/kg/day) on 18 Hour Thyroidal Uptake of I^{131} or At^{211}, Body Weight and Thyroid Weight of 55 day old female Sprague-Dawley Rats. Last Thyroxine Injection Given 4 Hours Before IV Administration of Isotope

Treatment	No. Of Rats	Mean Body Wt. Beginning g	Mean Body Wt. at Sacrifice g	Mean Thyroid Wt. mg	Mean ± St.E. Thyroid uptake % of admin. isotope	Mean ± St. E Thyroid conc. % isotope/g wet tissue
Thyroxine + I^{131}	8	121	133	9.8	.73 ± .06	75.4 ± 6.6
Control + I^{131}	10	124	148	12.3	6.00 ± .51	502 ± 46
Thyroxine + At^{211}	10	114	124	9.6	.068 ± .001	6.9 ± .5
Control + At^{211}	9	119	141	9.7	.305 ± .01	32.0 ± 4.3

When mean value is underlined, this indicates that it was tested against the mean immediately below by the t-test (12) and the P value was beyond the 1% level of confidence.

Table II. Effects of a Single or Double Subcutaneous Injection of KSCN on Thyroidal Uptake of At^{211} in 130 day old Female Sprague-Dawley Rats.

Interval between At^{211} IV Injection and sacrifice hr	Interval between KSCN Injection and sacrifice hr	No. of Rats	Mean Body Wt. g	Mean Thyroid Wt. mg	Mean ± St.E Thyroid uptake % of admin. At^{211}	Mean ± St.E Thyroid Con % At^{211}/g wet tissue
1	none	5	252	20.5	.31 ± .02	15.60 ± 1.3
1	2.5	5	254	20.3	.07 ± .01	3.19 ± .1
4	none	5	246	16.8	.32 ± .03	18.95 ± 1.3
4	5.5	5	245	16.7	.10 ± .01	5.85 ± .4
18	none	6	248	19.9	.40 ± .06	20.00 ± 2.1
18	19.5	6	244	18.8	.45 ± .08	23.08 ± 3.3
18	19.5 - 5.5	6	255	18.4	.16 ± .02	8.67 ± .5
18	1.5	6	248	21.0	.22 ± .02	10.37 ± 1.1

When mean value is underlined this indicates that it was tested against the mean of the control non-KSCN injected group of the same interval between At^{211} injection and sacrifice (12) and the P value was beyond the 1% level of confidence.