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Effect of 1-Methyl-2-Mercaptomidazole (Methimazole-Tapazole) on Feed Consumption in the Rat.* (30129)

C. E. HENDRICH AND C. W. TURNER†

Department of Dairy Husbandry, University of Missouri, Columbia

In the estimation of the thyroid hormone secretion rate (TSR) in rats in our laboratory(1), a goitrogen, methimazole or tapazole, has been used to block the recycling of I^{131} resulting from the metabolism of thyroïdal- I^{131} . By blocking the uptake of I^{131} by the thyroid gland, the apparent release rate of thyroïdal- I^{131} is increased and the end-point at which thyroïdal- I^{131} is blocked by increasing levels of thyroxine (T_4) is more readily determined.

While the goitrogen, propylthiouracil, has been shown to accelerate the rate of thyroïdal- I^{131} release(2), methimazole was apparently without extra thyroïdal effects in the rat(3).

The present study was initiated to determine the effect of methimazole on feed consumption of the rat. If methimazole seriously depressed consumption, it would constitute an objection to its use, since decreased feed consumption depresses TSR of rats(4). In previous work, it has been shown that thyroparathyroidectomy depressed food intake 13% in a period of 10 to 16 days(6).

Materials and methods. Eighteen female Sprague-Dawley Rolfmeyer rats with a mean body weight of 215 g were placed in metabolism cages constructed so as to prevent feed loss and coprophagy. Temperature was maintained at $78 \pm 1^\circ\text{F}$ and artificial illumination was provided during normal daylight hours. Purina Lab Chow with an energy value of 4.41 calories per g and 23.4% total protein was provided daily and resulting residues were weighed back. Mean daily feed

consumption was determined for a period of 10 days, followed by the mean feed consumption at 10-day intervals for 30 days under the influence of methimazole.

For normal controls, a second group of 18 rats weighing 231 g were fed for 30 days. Their mean daily feed consumption was determined at 10-day intervals to compare with the experimental group. The level of methimazole which has been used to prevent the recycling of I^{131} in TSR studies has been 400 $\mu\text{g}/100$ g bw/day by subcutaneous injection. Prior to the 10-day control feeding period, I^{131} was injected into each rat to determine normal uptake of I^{131} by the thyroid gland measured externally by a scintillation detector. After 2 weeks, and again after 4 weeks of methimazole feeding I^{131} was again injected to determine the uptake of I^{131} . Four days after methimazole was withdrawn and again after 7 days, I^{131} was injected to determine the % uptake.

The mean pituitary and thyroid gland weights of a control group of 10 rats was compared with a group of 10 rats at the end of the 30-day methimazole feeding experiment and of a group of 8 rats 7 days after methimazole withdrawal.

Results. The mean feed consumption of the 18 normal control rats weighing 231 g during the first 10-day period was 13.35 g/day or 5.78 g/100 g bw/day. During the second 10-day period these rats consumed 13.34 g/day or 5.63 g/100 g bw/day, a reduction of 3%. During the final 10-day period feed consumption was 13.73 g/day and 5.70 g/100 g bw, a decrease of 1% (Table I). Since the feed consumption of the control group during the 30-day period was essentially constant, the effect of methimazole on

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TABLE I. Effect of Methimazole on Feed Consumption and on Pituitary and Thyroid Weights of Female Rats.

Feeding periods	No. of animals	Body wt (g)	Feed consumption		Reduction (%)	Mean pituitary wt (mg)	Mean thyroid wt (mg)
			Per day (g)	g/100 g/bw			
Control group							
10 days	18	215	13.74	6.40 $\pm$.08		(10) 11.08 $\pm$.44	(10) 10.96 $\pm$.81
Methimazole							
10 days	18	224	13.38	5.97 $\pm$.09	6.72*		
20 "	18	228	13.03	5.72 $\pm$.07	10.63*		
30 "	18	231	13.82	5.98 $\pm$.08	6.56*	(10) 16.55 $\pm$.52	(10) 21.78 $\pm$.91
Control group							
10 days	18	231	13.35	5.78			
20 "	18	237	13.34	5.63	3		
30 "	18	241	13.73	5.70	1		
Withdrawal							
7 days						(8) 14.53 $\pm$ 1.06	(8) 16.73 $\pm$ 1.17

* Statistically significant at $P = .005$.

feed consumption is related to the mean feed consumption of the experimental group prior to treatment.

The mean normal feed consumption of the 18 experimental rats weighing an average of 215 g during a 10-day control period was 13.74 g/day or 6.40 g/100 g bw/day. After 10 days on methimazole, mean daily consumption decreased to 13.38 g or 5.97 g bw/100 g bw, a reduction of 6.72% from the control period. After 20 days, feed consumption was reduced to a mean of 13.03 g/day or 5.72 g/100 g bw, a reduction of 10.63% below the control period. After 30 days, feed consumption increased slightly to 13.82 g/day or 5.98 g/100 g bw, a reduction of 6.56% below the control level. Analysis of variance indicated the feed reductions were statistically significant at $P = 0.005$.

Prior to the 10-day control feeding period, I^{131} was injected into each rat to determine the percentage uptake by the thyroid glands. Of the I^{131} injected a mean of 28.1% was taken up by the thyroid glands. That the level of methimazole administered was effective in blocking I^{131} uptake was shown by the reduction to 2.4% after 2 weeks and to 1.4% after 24 days.

At the end of the 30-day period, methimazole was withdrawn. Four days later, the mean I^{131} uptake had increased to 8.93%

and after 7 days to 23.97%. Thus the metabolism of methimazole appears rapid and uptake of I^{131} is quickly restored to normal.

A group of 10 normal rats was sacrificed at the end of the experiment to serve as controls. Mean thyroid weight was 10.96 $\pm$.81 mg and mean pituitary weight 11.08 $\pm$.44 mg. After 30 days of methimazole administration a group of 10 experimental animals was sacrificed. Mean thyroid weight of these animals increased to 21.78 $\pm$.91 mg and pituitary weight to 16.55 $\pm$.52 mg. Seven days after withdrawal of methimazole, the mean thyroid weight of the 8 remaining experimental rats was 16.73 $\pm$ 1.17 mg and the pituitary weight was 14.53 $\pm$ 1.06 mg. Thus, while methimazole was quickly metabolized and normal uptake of I^{131} restored, the mean weight of the pituitary and thyroid glands had not returned to control levels.

Discussion. Brimblecombe and Pearce(5) reported that when methimazole was introduced into the drinking water of rats at a level of 0.12%, their normal consumption of water of 15 ml/day was reduced $\frac{1}{2}$ and at a level of 0.4%, water consumption was reduced to 3 ml/day. When methimazole was introduced by stomach tube at the rate of 1 ml of a 1.6% solution, feed consumption was reduced from 15.5 g/day to 8.3 g on day 14 and water intake from 17.0 to 12.2 ml/day.

Their metabolic rate was reduced 27%.

In the present study methimazole was injected subcutaneously at a level of 400 μ g/100 g bw, a level which had been shown by previous study to block the recycling of I^{131} resulting from the metabolism of thyroidal- I^{131} . At this level, methimazole depressed feed consumption a maximum of 10.63% during the 10th to 20th days. This was a significant reduction in feed consumption as compared to the control period ($P = .005$).

In a study of the effect of feed restriction on thyroid secretion rate (TSR) in the same strain of rats, Grossie and Turner(4) observed that an 8% reduction in feed intake had no effect on TSR during the period of 3 to 14 days. A 17% reduction in feed resulted in a non-significant reduction of 8% in TSR.

Since the duration of the period required to estimate the TSR in rats never exceeds 10 to 14 days, it is concluded that the reduction in feed consumption would not influence the estimation of TSR. It should be pointed out that increasing levels of thyroxine (T_4) are administered during the test period up to the level secreted. Thus the metabolic rate would not be seriously reduced and the reduction in feed consumption would probably be less than indicated by this study where replacement therapy was not practiced.

That the level of methimazole administered was effective in blocking I^{131} uptake by the thyroid gland was shown by the marked reduction from 28.08% of the injected dose to 2.43% after 14 days and to 1.36% after 24 days. During the 30-day experiment the thyroid glands increased from a mean of 10.96 to 21.78 mg, an increase of 98.72%, then decreased to 16.73 mg or 23.19% during the 7 days of the withdrawal period. At the same time the mean pituitary weight increased from 11.08 to 16.55 mg, an increase of 33.05%, then decreased to 14.53 mg, a reduction of 12.21% during the withdrawal period.

The rapid metabolism of methimazole is

indicated by an uptake of 8.93% of I^{131} four days after withdrawal and 23.97% uptake after 7 days.

In a previous study of the effect of thyro-parathyroidectomy on feed intake(6), it was shown that after 10 to 16 days feed intake was reduced 13% and after 56 to 62 days feed intake was reduced 23.6%. Thus in the comparable period, feed intake was reduced by similar amounts by thyroidectomy and methimazole.

Summary. The mean daily feed consumption of a group of 18 female Sprague-Dawley Rolfmeyer rats weighing a mean of 215 g during a 10-day period was 6.40 g/100 g bw. The rats were then injected subcutaneously daily with 400 μ g/100 g bw of methimazole to block iodine uptake. After 10 days mean daily feed consumption was reduced to 5.97 g/100 g bw, a reduction of 6.72%, after 20 days to 5.72 g, a reduction of 10.63%, and after 30 days to 5.98 g, a reduction of 6.56%. The reductions in feed were statistically significant at $P = 0.005$ at each time interval. The I^{131} uptake was reduced from 28.08% to 1.36% after 24 days of treatment. Mean thyroid weight increased from $10.96 \pm .81$ mg to $21.78 \pm .91$ mg, an increase of 98.72% during the 30-day period, then decreased to 16.73 mg during a 7-day withdrawal period. Since reduction of feed intake to the extent observed has been shown to have no significant effect on TSR determination, it was concluded that methimazole could be used safely in estimation of TSR.

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