Effect of Reserpine on Thyroid Activity in Rats.* (24742)

RICHARD C. MOON† AND CHARLES W. TURNER
Dept. of Dairy Husbandry, University of Missouri, Columbia

A number of investigations have indicated reserpine may alter thyroid function. It has been shown reserpine administration decreased O_2 consumption in rats(1) and guinea pigs(2), but not in man(3). Other studies indicate the drug may increase(4), decrease (5,6) or exert no effect upon thyroidal I^{131} uptake(3). Since results of previous investigations are somewhat contradictory it seemed desirable to reinvestigate the problem in rats employing thyroid secretion rate and thyroidal I^{131} release rate as indices of thyroid function.

Materials and methods. Adult female rats of Sprague Dawley-Rolfsmeyer strain weighing 230-280 g were kept in a room artificially illuminated during daylight hours and at uniform temperature of 78 ± 1°F. Each rat was injected i.p. with 2 μc carrier-free I^{131}. Forty-eight hours were allowed for I^{131} fixation by thyroid and excretion of excess isotope. External thyroid counts were taken at this time and every 48 hours thereafter by first anesthetizing each animal with ether, then placing it on lead plate with neck resting on a scintillation probe. Care was taken in placement of the animal to insure the same geometrical relationship at each successive counting period. Thyroidal radioactivity was measured with scintillation counter, Nuclear-Chicago (N.C.) Model DS 5, connected to pulse height analyzer, N.C. Model 1810, which, in turn, was connected to a rate meter, N.C. Model 1620A. Conventional corrections were made for background and decay of the isotope. *Determination of thyroid secretion rate (TSR).* Each of 43 rats was injected subc. with .05 μg/100 g l-thyroxine for 2 consecutive days beginning 4 days after I^{131} injection. Thyroxine dose was increased at .05 μg/100 g increments, each dose administered for 2 consecutive days, with thyroid count made on day of each increase. TSR was determined by plotting the percent previous count with thyroxine dose. The dose which prevented further thyroidal I^{131} output in each rat (95-100% of previous count) was estimated as its TSR. One day prior to start of thyroxine injections reserpine was injected subc. daily at doses of 5, 10 or 50 μg/100 g/day until the TSR was established. Statistical comparison of TSR of reserpine-treated rats was made with control values obtained concurrently with rats of the same strain, sex and body weight range(7). *Determination of thyroidal I^{131} release rate.* Thyroidal I^{131} release rate was determined in 3 groups of 5 rats each. Daily thyroid counts were made for 12 days commencing 48 hours after I^{131} injection. Beginning 7 days after I^{131} injection, animals in each group received 5 daily subc. injections of either 5, 10 or 50 μg/100 g reserpine. Thyroidal I^{131} release curve was constructed by plotting the average percent dose against time in days. Average hourly release thyroidal I^{131} (k'4) was calculated by the method of Brownell(8).

Results. Average TSR of rats receiving 5 and 10 μg/100 g reserpine was .23 μg/100 g and that of animals injected with 50 μg/100 g was .135 μg/100 g l-thyroxine (Table I). This represented a decrease of 84-90% when compared with control TSR of 1.4 μg/100 g l-thyroxine. The difference between TSR's

TABLE I. Effect of Reserpine on Thyroxine Secretion Rate and Body Weight.

Dose reserpine, μg/100 g/day	No. of rats	TSR, μg/100 g l-thyroxine/day	% change body wt at 10 days
Control*	10	1.40 ± .179†	− 2.2 ± .572
5	10	.230 ± .015‡	+ 6.3 ± 1.051‡
10	23	.230 ± .011	+ 6.4 ± .429
50	10	.135 ± .019	−22.4 ± .511

* Data from Grosvenor and Turner(7).
† Mean ± stand. error.
‡ Significant at .1% level.

* Contribution from Dept. of Dairy Husbandry, Mo. Agr. Exp. Sta. Journal Series No. 1943. Approved by the Director.

† Postdoctoral Fellow of NIH. Investigation supported in part by research grants from P.H.S.

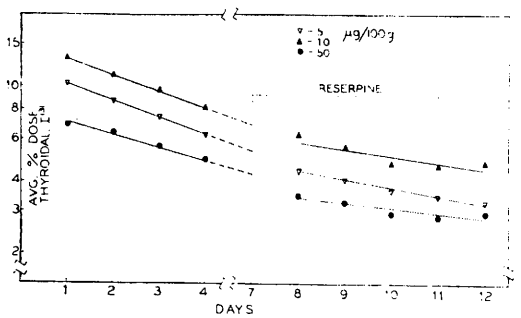

FIG. 1. Effect of reserpine on thyroidal I^{131} release.

of the high and low reserpine groups was significant ($P<.001$). A definite break in the thyroidal I^{131} release curve was evident upon administration of reserpine (Fig. 1). Average hourly release of thyroidal I^{131} (k'4) during the experimental period was significantly less than during the control period at all doses of reserpine employed (Table II). Body weight was reduced markedly in animals receiving 50 μg 100 g reserpine, while those rats injected with the 2 lower doses exhibited significant increases ($P<.001$) in weight.

Discussion. Thyroidal I^{131} release rate has many advantages over thyroidal I^{131} uptake as a criterion of thyroid function as it allows for detection of slow changes in thyroid activity which may not be noted by the single observation usually employed in uptake studies. It is also less dependent upon circulating level of I^{127} or upon changes in renal excretion of I^{131}. Furthermore, it is of sufficient duration to allow both control and experimental periods of observation. One minor discrepancy is evident in determining thyroid activity by this method, *i.e.*, the reutilization of I^{131} which is released upon degradation of radioactive hormone released by the thyroid. However, only about 11% of the radioactivity lost by the thyroid in any one day is reaccumulated as I^{131} (9). Although rate of release of thyroidal ^{131} is an index of thyroid activity, it does not, however, indicate the quantity of thyroid hormone which is secreted under any given set of conditions. The technic proposed by Pipes *et al.* (10), and later modified (9,11), appears to be much more sensitive than thyroidal I^{131} release rate in detecting changes in thyroid activity. It also has the added advantage of estimating secretion rate in terms of l-thyroxine. The contradictory results obtained with reserpine in previous I^{131} uptake studies may be due to the lack of sensitivity of this method as compared with thyroidal I^{131} release rate and TSR determination, for the results of the present experiments clearly indicate that reserpine inhibits thyroid activity. It is likely that maximum inhibition is produced by the dosages of reserpine employed since average TSR of animals receiving 5 or 10 μg 100 g is the same. The significantly lower TSR of those treated with 50 μg 100 g reserpine is probably due to the added effect of inanition upon thyroid activity, as it was observed animals of this group exhibited a marked reduction in body weight. The mechanism by which reserpine inhibits thyroid function is unknown. It has been suggested reserpine inhibits the organic-binding of I^{131} (5,6). If organic-binding of I^{131} was a factor, an apparent increase in release rate would be expected since the thyroid would be unable to hold the recycled I^{131}. The opposite result was obtained in these experiments. It has also been suggested that reserpine antagonizes thyroxine (1,2). Although this mechanism warrants further investigation, it is likely reserpine inhibits thyrotropin secretion, possibly through the hypothalamo-hypophyseal system, since pharmacological studies (12) have indicated the primary site of action of reserpine to be the hypothalamus. It is also of interest to note that secretion of at least 2 other hormones of the adenohypophysis, ACTH (13) and gonadotropin (14), is inhibited by reserpine. Decrease in body weight exhibited by animals receiving 50 μg/100 g reserpine is probably due to a decreased food intake. Increases in body weight of rats in-

TABLE II. Effect of Reserpine on Average Hourly Release Thyroidal I^{131} (5 Rats in Each Group).

Dose reserpine, μg/100 g/day	Avg k'4	
	Control period	Reserpine period
5	.00640 ± .00098*	.00311 ± .00073†
10	.00637 ± .00098	.00278 ± .00119†
50	.00540 ± .00025	.00190 ± .00057‡

* Avg k'4 error.
† Significant at .5% level.
‡ " 1 % "

jected with the 2 lower doses of reserpine may result from an increased deposition of fat which may occur during a hypothyroid state.

Summary. Reserpine at doses of 5, 10 or 50 μg/100 g/day inhibits thyroid activity in rats. Thyroidal I^{131} output is decreased significantly and thyroid secretion rate is reduced approximately 84-90% below control values. It is suggested reserpine alters thyroid function through inhibition of thyrotropin secretion.

1. Kuschke, H. J., Gruner, H., *Klin. Wchnschr.*, 1954, v32, 563.

2. De Felice, E. A., Smith, T. C., Dearborn, E. H., PROC. SOC. EXP. BIOL. AND MED., 1957, v94, 171.

3. Ford, R. V., Livesay, W. R., Miller, S. I., Moyer, J. H., *Med. Rec.*, 1953, v47, 608.

4. Goodman, J. R., Florsheim, W. H., Tempereau, C. E., PROC. SOC. EXP. BIOL. AND MED., 1955, v90, 196.

5. Mayer, S. W., Kelly, F. H., Merton, M. E., *J. Pharmacol. and Exp. Therap.*, 1956, v117, 197.

6. Pokorny, C., Wilkinson, P. N., McCuster, E. N., Hellwig, C. A., *Growth*, 1957, vXXI, 89.

7. Grosvenor, C. E., Turner, C. W., PROC. SOC. EXP. BIOL. AND MED., 1958, v99, 517.

8. Brownell, G. L., *J. Clin. Endocrinol.*, 1951, v11, 1095.

9. Reineke, E. P., Singh, O. N., PROC. SOC. EXP. BIOL. AND MED., 1955, v88, 203.

10. Pipes, G. W., Blincoe, C. R., Hsieh, K., *J. Dairy Sci.*, 1950, v33, 384.

11. Perry, W. F., *Endocrinol.*, 1951, v48, 643.

12. Plummer, A. J., Earl, A., Schneider, J. A., Trapold, J., Barrett, W., *Ann. N. Y. Acad. Sci.*, 1954, v59, 8.

13. Wells, H., Briggs, F. N., Munson, P. L., *Endocrinol.*, 1956, v59, 571.

14. Barraclough, C. A., Sawyer, C. H., *ibid.*, 1957, v61, 341.

Received December 8, 1958. P.S.E.B.M., 1959, v100.

Effect of Meprobamate on Limbic System of the Brain. (24743)

MILTON KLETZKIN AND FRANK M. BERGER
Wallace Lab., Division of Carter Products, New Brunswick, N. J.

During an investigation relating to site of action of meprobamate(1) recordings of brain waves from various cortical and subcortical leads were studied. Spontaneous potentials picked up from thalamus are slowed in frequency and increased in amplitude after administration of small doses of the drug. Larger doses caused similar changes in cerebral cortex but did not affect potentials in the hippocampus, fornix, amygdala and other limbic structures(2). The present study describes effects of meprobamate upon seizure discharges initiated by direct stimulation of the limbic system and upon activation patterns produced by stimulation of the reticular formation.

Methods. Twenty-five adult male cats were prepared under ether anesthesia. Bipolar electrodes were placed stereotaxically in midbrain reticular formation, hippocampus, amygdala, anterior thalamic nuclei, septum and gyrus cinguli, and cortical electrodes were introduced through cranial burr holes. Wound margins and pressure points were infiltrated with xylocaine, the animals immobilized with succinylcholine given intravenously by a slow injection apparatus. Respiration was maintained with respiratory pump. At least one hour was allowed for elimination of ether before start of experiment. Recordings were taken with Grass electroencephalograph, Model IIID, and AEL 104 stimulator supplied the trains of rectangular pulses used. At end of each experiment the brain was removed and electrode positions verified.

Results. The limbic system was stimulated in 2 ways; directly and indirectly. Direct stimulation (1 msec pulse; 150/sec. 4-10 volts; 5-7 sec.) of the hippocampus produced high voltage afterdischarges which usually persisted for 35-50 seconds. These afterdischarges almost always spread to other limbic structures and ended simultaneously and abruptly in all leads. Duration of these elec-