Reserpine and Thyroid Function. (21980)

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The introduction of reserpine with its mild sedative effects into common clinical use raises the question of the influence of this agent on thyroid function. Reserpine is generally assumed to act upon certain medullary centers(1), but the experiments of McQueen *et al.*(2) and of Kuschke and Gruner(3) appear to indicate a direct peripheral action as well. Very little work has been reported in the literature which would indicate whether reserpine exerts any influence either directly on the thyroid gland, or, through the hypothalamic-pituitary-thyroid axis, upon thyroid function. Certain observations, particularly the reserpine-induced bradycardia(4) and the effect of reserpine upon weight gain in "constitutional leanness"(5) could indicate an anti-thyroid activity of the drug. Moreover, Kuschke and Gruner(3) have reported that in the rat the effect of parenterally administered thyroxine upon the BMR is prevented by the administration of reserpine in large doses. However, the two published reports on the effect of Rauwolfia preparations on thyroid function as measured by the basal metabolic rate agree in finding no consistent effect. Erban and collaborators(6) found no effects in rats with a number of commercial preparations, and Moyer and associates(7) found no consistent changes in a small series of patients. Moyer also studied his patients by means of a radioiodine uptake test and obtained no consistent changes due to 6 weeks' medication with several crude Rauwolfia preparations. Since many patients entering thyroid clinics give a history of treatment with Rauwolfia preparations, it was considered important to establish whether this drug exerted any appreciable influence upon any of the commonly used criteria of thyroid function. A study was therefore undertaken in 18 chronically ill patients receiving reserpine at a level commonly used for the reduction of blood pressure.

To reconcile our results with those of Kuschke and Gruner the effect of reserpine in very high doses on thyroid function was also studied in a small number of rats.

Methods. Eighteen male patients were included. Blood pressure was determined daily throughout the study period. Base line values were obtained for the following criteria of thyroid function: (a) Serum total cholesterol, determined by the method of Kanter, Goodman and Yarborough(8); (b) 24-hour thyroidal radioiodine uptake; (c) 24-hour urinary radioiodine excretion; (d) serum protein-bound stable iodine, determined by Barker's (9) method; and (e) the 24-hour thyroxine synthesis measured according to Morton(10). In addition, the effect of a standard dose of adrenaline upon the level of circulating eosinophiles was determined by Thorn's(11) method. After completion of the base-line studies all patients received reserpine (Serpasil-Ciba) at a level of 0.125 mg t.i.d. for 2 days. The dose was then raised to 0.25 mg t.i.d. for another 24 days. In 2 patients the dose had to be reduced to 0.125 mg t.i.d. again after 1 and 11 days at the higher level, respectively, because of side effects. On the last 2 days of drug administration the battery of thyroid function and Thorn tests were repeated.

In the animal experiment 6 male Sprague-Dawley rats were injected intravenously with 0.40 mg/kg of serpasil in solution 2 hours before tracer iodine administration, and then received 0.60 mg/kg by subcutaneous injection every 3 hours. Four control rats received similar volumes of the vehicle furnished by Ciba Pharmaceuticals at the same time. Twenty-four hour thyroidal radioiodine uptake was determined and serum hormonal iodine synthesis were measured in all animals by the methods of Morton(10) and of Ingbar (12)

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TABLE I. Post-Serpasil Thyroid Parameters as % of Pre-Treatment Level with Standard Deviations.

Group	No.	Cholesterol	24-hr I^{131} uptake	PBI	Urinary excretion*	Tx/To†
Whole	18	101 ± 22	96 ± 54	112 ± 16	111 ± 43	92 ± 41
+++	8	102 ± 28	110 ± 73	113 ± 24	118 ± 50	99 ± 46
++	7	99 ± 16	90 ± 34	110 ± 8	99 ± 23	77 ± 34
±	3	101 ± 16	67 ± 6	115 ± 13	120 ± 73	135 ± 19

+++ = Decrease of 20% or more in the mean systolic blood pressure. ++ = Moderate decrease in blood pressure. ± = Doubtful effect on blood pressure.

* 24 hr urinary excretion of radioiodine.

† % of 24 hr serum I^{131} activity present as hormonal iodine.

Results. A. Effects on Thyroid Function. Table I summarizes the results obtained with our group of patients, most of whom were markedly hypertensive prior to therapy. All patients participating in this study were judged to be euthyroid initially from the PBI and radioiodine uptake values. However, the thyroxine synthesis values were below 2% in ⅓ of the patients, which represents the lower limit of the euthyroid range. On recalculating the data by Ingbar's method, 10 patients had serum radio-thyroxine levels below .008% of the administered dose per liter of plasma, and only one patient showed a value above .012% per liter. In previous studies we have found low thyroxine synthesis values in the presence of normal PBI and uptake values in patients with cardiac disease of long duration (13), and we believe this to be a consequence of chronic stress. In Table I the experimental group has also been subdivided according to the effect upon the blood pressure produced by reserpine. Since the blood pressure was quite labile in most of the subjects, the patients were grouped into three categories according to the mean drop in blood pressure produced, with +++ indicating a good response (>20% drop of the mean systolic pressure); ++ a fair one and ± a doubtful or insignificant change due to the drug. The variability of the results may be related to the hypertensive state of most of these patients, since equally varied and random changes were found in two hypertensive subjects who were merely observed during the experimental period without medication, and since similar variability of the I^{131} uptake and BMR have been reported by Moyer(7).

From the results it is clear that reserpine at the levels employed does not affect thyroid function significantly.

B. Effects on the Thorn test. The Thorn test with adrenaline is not universally accepted as a test of the functional state of the hypothalamic-pituitary-adrenal axis. However in healthy individuals a drop of more than 30% of the circulating eosinophiles is produced 4 hours after an injection of 0.2 mg of adrenaline subcutaneously. In only 3 patients out of 14 was a drop of less than 30% observed in the number of circulating eosinophiles before reserpine therapy. After administration of reserpine for 25 days, 11 out of 17 patients showed no significant eosinopenic response. While the Thorn test with adrenaline certainly is not a specific test for pituitary-adrenal function, the reversal of the test under the influence of reserpine is of interest. At least part of the eosinopenic effect of adrenaline is generally assumed to be mediated via effects on cerebral centers higher than the pituitary. Since reserpine depresses afferent impulses to certain subcortical centers(14) and lowers central sympathetic reactivity(15) the results obtained in this study agree with the generally accepted mode of action of reserpine. However, the mechanism by which adrenaline exerts its eosinopenic effect is so poorly understood that it is not permissible to speculate on this basis alone.

C. Effects of reserpine at high dose levels. Since Kuschke and Gruner had observed what appeared to be an antagonism between reserpine and thyroxine in the rat, it became of interest to investigate whether any anti-thyroid activity of reserpine might occur in this species. Employing the drug at low levels of .10 mg/kg/day, the results were similar to those

TABLE II. Thyroid Activity of Rats on High Doses of Serpasil.

Group	No.	24 hr uptake (%)	Tx/To	Tx, % AD/l*
Control	4	8.4 ± 2.1	57.2 ±10.0	.088±.018
Serpasil	6	23.3 ± 4.1	10.8 ± 5.2	.18 ±.07

* Serum thyroxine-I^{131} as % of administered I^{131} dose/l of serum.

obtained in man, with neither the 24-hour uptake nor the thyroxine synthesis significantly affected. It was then decided to use reserpine at a dose level which had been shown to raise significantly the arousal in the brain stem of the rat(16). Under the conditions specified the data in Table II were obtained. It is significant that the reserpine-treated animals showed the symptoms of hypotensive shock: nasal congestion, somnolence and ptosis, as well as diarrhea. There was an obvious interference with renal excretion of iodide: Serum inorganic radioiodide levels were 20 times those in the controls 24 hours after tracer administration. This explains both the higher thyroidal uptake and the higher thyroxine synthesis value as calculated by Ingbar's method. It is possible that poor absorption of peripherally administered thyroxine due to the reserpine-induced hypotension also explains Kuschke and Gruner's results.

Summary. Reserpine at the dose levels employed clinically for the treatment of hypertension does not affect thyroid function in man. The effects of large doses in the rat appear to be due to hypotensive effects and interference with the renal excretion of iodide.

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