Effects of Cortisone on Thyroidal Iodine Uptake in Hypophysectomized, Nephrectomized Rats* (34120)

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Administration of cortisone for short periods of time reduced thyroidal uptake of radioiodine (1–3) in both intact and hypophysectomized rats given TSH and cortisone (4, 5). Concomitantly, in hypophysectomized animals there was an increased renal clearance of iodide while thyroidal clearance was unaltered (4). The decreased thyroidal uptake of ^{131}I was attributed to a corticoid-induced increase in renal iodide clearance. In support of this hypothesis, cortisone reportedly increased ^{131}I uptake in both bilaterally nephrectomized animals with intact pituitaries or hypophysectomized animals treated with TSH (5).

In contrast, stress-induced decrease of ^{131}I uptake persisted after bilateral nephrectomy (6). Since the effects of stress are mediated at least in part by adrenocorticoids, the role of the kidney in the effect of corticoids on the thyroid remains unclear. In addition, thyroid weight and protein anabolism are decreased in intact rats after cortisone treatment (7). In an attempt to resolve some of these differences, we have investigated the action of cortisone on thyroid gland iodide metabolism in hypophysectomized rats that were maintained on homologous pituitary homogenates and bilaterally nephrectomized just prior to ^{125}I treatment.

Methods. Twenty-eight male rats of the Rolfsmeyer strain (Rolfsmeyer, Inc., Madison, Wisconsin) were hypophysectomized, placed on Purina Rat Chow, and given a solution of .85% NaCl, 5% dextrose, and .15% tetracycline in water to drink. Of these, 14 received pituitary replacement therapy by daily subcutaneous injections of rat pituitary homogenates. Rat pituitary glands which had been collected at hypophysectomy and quickly frozen were homogenized in 1 ml of 0.85% NaCl. The homogenate was divided into small portions and frozen. Prior to injection the homogenate was thawed and mixed. Each rat received the equivalent of 1 pituitary (0.2 ml of homogenate) each day. Control animals identical in weight and sex were maintained under the same conditions as the experimental rats. On Day 8 after hypophysectomy, daily subcutaneous injections of cortisone 5 mg/day/rat were administered to seven hypophysectomized and eight control rats. On postoperative Day 14, all animals were bilaterally nephrectomized through flank incisions under ether anesthesia. One hour after nephrectomy, each animal received 2 μCi $Na^{125}I$ in 0.5 ml 0.85% NaCl ip. Cortisone was given at this time in the indicated groups. Eighteen hours after the radioiodide injection the animals were sacrificed under ether anesthesia. The thyroids were dissected out, weighed, and placed in test tubes for counting. Completeness of hypophysectomy was checked at sacrifice by examination of the sella turcica. Animals that died after nephrectomy or animals in which pituitary remnants were found were rejected from the study. The thyroid samples were counted in a Nuclear Chicago well-type scintillation counter equipped with a single-channel analyzer. A standard of the injected solution was counted at the same time. The data were analyzed by Student's t test.

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Result. Cortisone treatment caused a significant reduction in thyroid weight in both pituitary-intact and hypophysectomized–pituitary replaced groups. However, cortisone treatment did not reduce the total radioiodine uptake in bilaterally nephrectomized animals. This occurred in both hypophysectomized pituitary-replaced animals and those with intact pituitaries. Since cortisone reduced thyroid weight but not radioiodine uptake, there was a significant increase in the percentage of uptake of ^{125}I per mg of gland tissue. Although pituitary replacement therapy alone had no effect on thyroid gland weight it did increase the glands avidity for ^{125}I. The percentage of uptake by thyroid glands of the pituitary-injected rats was essentially double that of their respective pituitary-intact controls (Table I).

Discussion. Although several hypotheses have been proposed to explain the effect of cortisone on iodide metabolism in the thryoid gland of the intact animal, the mechanism of action still remains unclear. Reduction in iodide uptake by cortisone could be accomplished by several mechanisms. Increased renal clearance of iodide could account for the decreased gland uptake (4, 5). However, in man the thryoid-suppressive effect can be differentiated from the renal effect of the hormone (8, 9). Furthermore, nephrectomy abolished the thyroid-suppressive effect of administered steroid (5) in hypophysectomized rats although it was ineffective in stressed animals with intact pituitaries (6). This apparent inconsistency could be explained by a different extrathyroidal iodide pool in a stressed intact rat and hypophysectomized animal receiving cortisone treatment. Iodide clearance varies markedly with the intake of water and electrolytes, and cortisone increased the iodide clearance of adrenalectomized and hypophysectomized–adrenalectomized animals, but not of intact animals (10). Thus cortisone treatment prior to nephrectomy could have depleted the extrathyroidal iodide pool in the hypophysectomized–TSH-maintained animal while not affecting the intact rat.

The purpose of our study was to determine whether cortisone could exert a direct effect on thyroid glands of hypophysectomized animals that were given pituitary gland replacement therapy in order to obviate the possibility of extrathyroidal iodine depletion. The use of pituitary homogenate provided all the pituitary hormones while eliminating any corticoid-mediated effect on the pituitary–thyroid axis, thus maintaining the hypophysectomized rats in a more normal state. The apparent effectiveness of pituitary replacement is evidenced by the fact that the body weights of the hypophysectomized pituitary replaced animals averaged 217 g while that of the intact controls averaged 200 g. The body weights of control rats and of hypophysectomized pituitary replaced animals treated with cortisone averaged 159 and 151 g respectively. In addition cortisone was equally effective

TABLE I. Effect of Cortisone on Thyroid Gland Uptake of ^{125}I in Nephrectomized Rats.

Group	No cortisone	Cortisone	
Control			
No. of rats	6	8	
Thyroid wt (mg)	14.07 ± 0.48[a]	9.95 ± 0.70	$.01 > p > .001$[b]
% Uptake	7.17 ± 0.96	10.55 ± 2.35	$.2 > p > .3$
% Uptake/mg	0.52 ± 0.07	1.00 ± 0.15	$.05 > p > .02$
Hypophysectomized + pituitary replacement			
No. of rats	7	7	
Thyroid wt (mg)	13.29 ± 1.63	9.53 ± 0.48	$.05 > p > .02$
% Uptake	16.54 ± 2.54	18.19 ± 1.54	$p > .5$
% Uptake/mg	1.22 ± 0.08	1.9 ± 0.71	$.05 > p > .02$

[a] Standard error of the mean.

[b] Analyzed by Student's t test.

in reducing the thyroid gland weights of both groups.

Our observation that cortisone significantly increased radioiodine uptake per milligram in thyroid of hypophysectomized–nephrectomized rats treated with pituitary homogenates is consistent with the histological evidence suggesting thyroidal activation after cortisone treatment (11). In addition, it substantiates Woodbury's observation (5) that nephrectomy unmasks a stimulatory effect of cortisone on thyroidal iodine uptake, particularly since the enhanced uptake in the present study is probably not the result of a depleted extrathyroidal iodine pool. The actions of cortisone in reducing both weight and protein anabolism of the thyroid gland, while apparently enhancing radioiodine uptake remain unresolved and are currently under investigation.

Summary. The effect of cortisone on thyroidal ^{125}I iodide uptake was investigated in hypophysectomized, pituitary-replaced, bilaterally nephrectomized rats. Cortisone reduced thyroid and body weights but did not reduce iodide uptake. Thus, an enhanced uptake of iodide per unit weight of gland resulted. It is unlikely that the enhanced ^{125}I uptake resulted from a depletion of the extrathyroidal iodide pool.

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1. Van Middlesworth, L. and Berry, M. M., Am. J. Physiol. **167**, 576 (1951).

2. Verzar, F. and Vicovic, V., J. Endocrinol. **8**, 321 (1952).

3. Albert, A., Ann. Rev. Physiol. **14**, 481 (1952).

4. Ingbar, S. H., Endocrinology **53**, 171 (1953).

5. Woodbury, D. M., Goates, D. T., Lee, G. R., Williams, C. B., Callster, P. S., and Craighead, J. E., J. Clin. Endocrinol. Metab. **14**, 822 (1954).

6. Asch, L., Compt. Rend. Soc. Biol. **157**, 363 (1963).

7. Yatvin, M. B., Wannemacher, R. W., Jr., and Brown, N. V., Endocrinology **79**, 1079 (1966).

8. Berson, S. A. and Yalow, R. S., J. Clin. Endocrinol. Metal. **12**, 407 (1952).

9. Ling, W. and Perry, F., J. Clin. Endocrinol. Metab. **13**, 712 (1953).

10. Paris, J., Ford, E., Lorenz, N., Keating, F. R. J., and Albert, A., Am. J. Physiol. **183**, 163 (1955).

11. Catz, B., El-Rawi, I., Geiger, E., and Stark, P., J. Clin. Endocrinol. Metab. **13**, 878 (1953).

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