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THE INFLUENCE OF THE ADRENAL CORTEX ON THYROID ACTIVITY IN THE RABBIT

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Physical and emotional stresses have been shown to decrease thyroid activity in the rabbit (Brown-Grant, Harris & Reichlin, 1954). Although this depression is not secondary to or dependent upon the activation of the adrenal gland brought about by such stresses, it was found on further investigation of the adrenal cortex-thyroid relationship that activation of the adrenal cortex and the administration of adrenal steroid hormones profoundly influenced thyroid activity in the rabbit. This paper is concerned with the results of these experiments and of others designed to elucidate the mechanism by which these compounds influence thyroid activity. Preliminary reports of these experiments have appeared (Brown-Grant, von Euler, Harris & Reichlin, 1953*a*, *b*).

METHODS

Adult female rabbits of mixed stock weighing 2–3 kg were used. The animals were kept under standard conditions and thyroid activity was studied by the method of 'release curves' previously described (Brown-Grant, von Euler, Harris & Reichlin, 1954). Hypophysectomized and adrenalectomized animals were prepared and completeness of operation checked as previously described (Brown-Grant, von Euler, Harris & Reichlin, 1954; Brown-Grant, Harris & Reichlin, 1954).

Drugs. 11-dehydro-17-hydroxycorticosterone (compound E, cortisone acetate, Merck) was given in suspension in divided doses twice daily. (Figures given in the text refer to total daily dose.) The desoxycorticosterone acetate (DOCA) used was the B.P. (Organon) preparation in oil. Adrenocorticotrophic hormone (ACTH) (Armour, batch nos. 41-L and 79-R), and thyrotrophic hormone (TSH) (Armour, lot no. R377157) were dissolved in 0·9% sodium chloride solution (saline) immediately before use. All drugs were given by subcutaneous injection. Doses are given in the text.

RESULTS

(1) *Effect of cortisone on normal rabbits*

Cortisone in doses of 0·2–25·0 mg/day for up to 8 days has been given to seven normal and one ovariectomized rabbits in nine experiments, while the rate of release of ^{131}I-labelled hormone from the thyroid gland was being studied. In all experiments, the injections of cortisone were preceded and

followed by a period of several days during which control injections (s.c.) of 0·5 ml. saline or 0·5 ml. Merck suspending agent were given twice daily. The control injections had no effect on the rate of release of thyroidal ^{131}I.

In seven experiments cortisone in doses of 10 mg/day (5 expts.), 20 mg/day (1 expt.), 25 mg/day (1 expt.) produced a prompt (within 12 hr) and marked reduction in the rate of ^{131}I release which was maintained throughout the period of cortisone administration (Fig. 1). In five cases the release of ^{131}I was completely inhibited, and in the other two was reduced to 5% and 2%/day as compared with 11% and 33%/day respectively in the control periods. After stopping cortisone there was a prompt return to the previous rate of release.

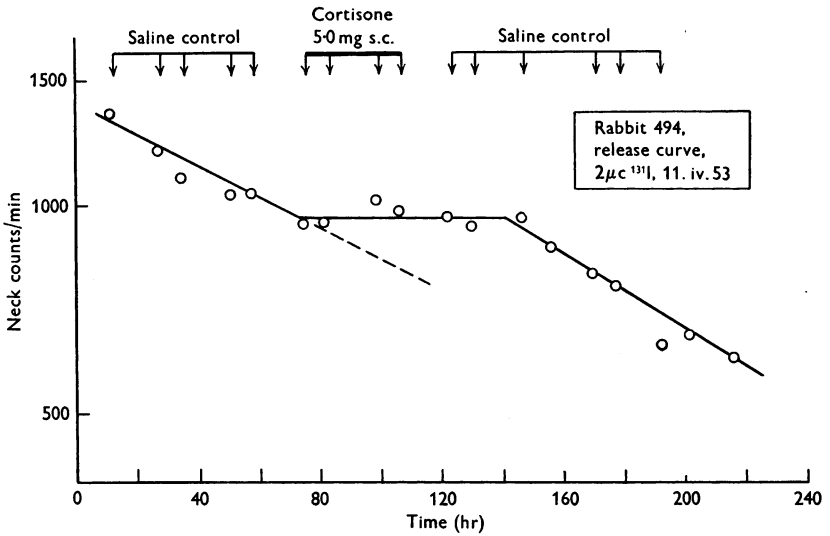

Fig. 1. The effect of subcutaneous injections of cortisone (5 mg twice daily) on the release of ^{131}I from the thyroid gland of the rabbit.

Two rabbits were given gradually increasing doses of cortisone, 0·2–20 mg/day in one case and 0·2–40 mg/day in the other. No effect was seen with the lower doses, but a decrease in the rate of release was produced by a dose of 6 mg/day (but not 3·2 mg/day) in one case and by 10 mg/day (but not 4 mg/day) in the other. Higher doses did not reduce the rate of release further in these two experiments. One animal returned to a normal slope 24 hr, and the other 80 hr, after stopping cortisone administration.

(2) *Effect of ACTH administration in normal rabbits*

The effect of activating the adrenal glands by administration of adrenocorticotrophic hormone was investigated in six experiments on five rabbits. Twice daily injections of ACTH in doses of 4 mg/day (3 expts.) 10 mg/day

(2 expts.) and 20 mg/day (1 expt.) were given to rabbits while on release curves. Control injections of saline were given before and after ACTH administration in all but one experiment. In each case the effect was to produce a prompt (within 12 hr) and marked inhibition of release of thyroid hormone; the characteristics of the response were identical with those following cortisone administration (Fig. 2).

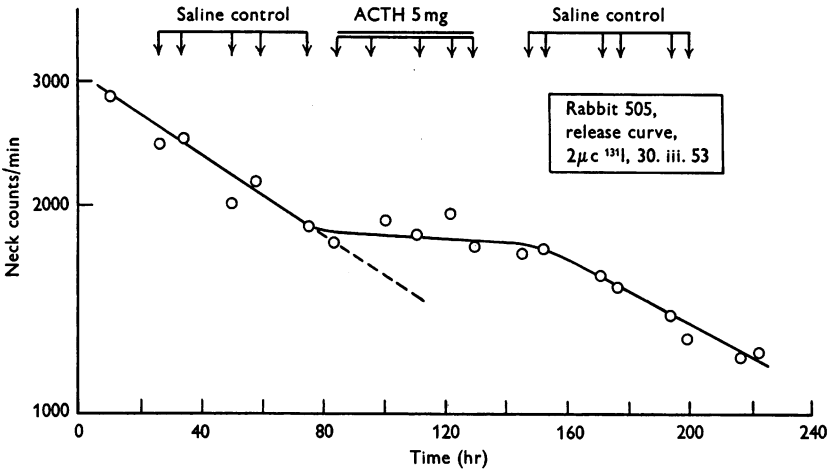

Fig. 2. The effect of subcutaneous injections of ACTH (5 mg twice daily) on the release of ^{131}I from the thyroid gland of the rabbit.

(3) *Effect of DOCA administration in normal rabbits*

Although there is no evidence that desoxycorticosterone is secreted by the adrenal cortex, it was of interest to see whether DOCA possessed similar thyroid-inhibiting properties to those of cortisone.

The effect of DOCA on the rate of release of thyroid hormone has been studied in ten experiments on ten rabbits. DOCA was administered in 5 or 10 mg doses for 2–5 days. In eight cases no effect was seen. In one case 10 mg/day produced a slight decrease in the rate of ^{131}I release, and in another animal 5 mg/day produced a complete inhibition for 24 hr, followed by a return to the rate of release seen in the control period, although injections of DOCA were continued.

(4) *Experiments on adrenalectomized rabbits*

In order to obtain greater control over the concentration in the blood of circulating cortical steroids, adrenalectomized rabbits were used. The rate of release of thyroidal ^{131}I was observed whilst varying the maintenance dose of cortisone, in eight adrenalectomized animals.

In experiments on four rabbits it was found possible to alter the rate of ^{131}I release, and maintain a new rate indefinitely, by varying the maintenance dose of cortisone in the range of 0·2–5·0 mg/day. Within this range increasing dosage reduced the rate of release, and vice versa (Fig. 3). The rate of release in these experiments was varied in the range 5–40% thyroidal ^{131}I content per day.

Five rabbits were given doses of 10 mg cortisone/day for periods up to 3 days, during a release curve. In each case there was complete or almost complete inhibition of release of thyroid hormone, as was found at this dose level in the intact animal.

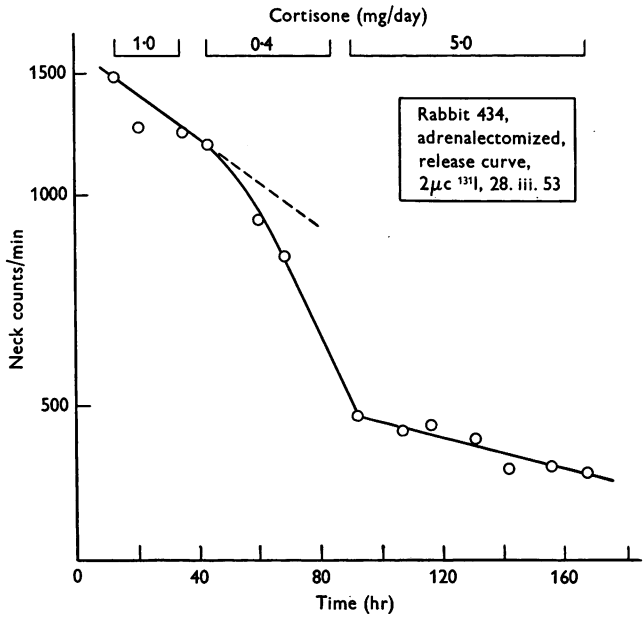

Fig. 3. The effect of varying the daily maintenance dose of cortisone on the release of ^{131}I from the thyroid gland of the adrenalectomized rabbit.

The effect of stopping cortisone maintenance therapy was investigated in five animals. In three experiments there was a gradual slowing of the rate of release over 12–48 hr after stopping cortisone. The slower rate was maintained for the period of several days over which observations were made. In one experiment there was an initial acceleration, followed by a rate of release slower than that observed while the animal was receiving low dosage of cortisone. In the fifth experiment no change was observed following withdrawal of cortisone. In two of these animals, subsequent resumption of low (0·2 and 0·4 mg/day) dosage of cortisone produced an acceleration, whereas still higher doses again slowed the release.

In view of the findings of Soffer, Gabrilove & Dorrance (1951) that ACTH administration will reduce the uptake of ^{131}I by the thyroid of adrenalectomized rats maintained on DOCA, the effect of ACTH on the rate of release of thyroid hormone in two adrenalectomized rabbits on a constant maintenance dose of cortisone was investigated. Both animals were given 5 mg of ACTH twice daily (total dose 15 mg). The specific effect of ACTH on the thyroid could not be studied because the preparation used was sufficiently toxic to cause the death of these adrenalectomized animals. Following the injection there was, however, a prompt and complete inhibition of release of ^{131}I, lasting 36 and 23 hr, at which time the animals died.

(5) *Experiments on hypophysectomized rabbits*

Among various hypotheses put forward to explain the action of cortisone in depressing thyroid function, it has been suggested that cortisone may reduce the sensitivity of the thyroid gland to thyrotrophic hormone. Several workers have found that the increase in the uptake of ^{131}I by the thyroid gland produced by injection of TSH in the hypophysectomized rat may be abolished or greatly reduced by concurrent administration of cortisone or ACTH. This finding however, is not universal (see discussion for references to previous work), and so a similar investigation was carried out in the hypophysectomized rabbit. The procedure adopted was as follows. Hypophysectomized animals were injected with a sufficiently large dose (4–12 μc) of ^{131}I to provide a satisfactory initial counting rate 48 hr later (1000–3000 counts/min). The rate of release of thyroidal ^{131}I is very low in the hypophysectomized rabbit, the slope of release curve being less than 1 %/day in many cases. After a control period of several days, a single injection of freshly prepared TSH (250–1000 μg) in saline was given. The dose varied according to the sensitivity of the individual animal to the hormone preparation used, but was constant in any one experiment. The result of the injection was a prompt and marked discharge of ^{131}I from the gland, lasting about 18 hr, followed by a return to the previous very slow rate of release. After stabilization at the new level, cortisone 10 or 40 mg/day was given. This had no effect on the slope of the release curve; 36 hr after the first injection of cortisone and while cortisone administration was continued, a second dose of TSH was given, and a second discharge of ^{131}I from the gland produced. Following a return to the previous slow rate of release, cortisone administration was stopped. After a period of several days to allow any effects of the cortisone to wear off, a third dose of TSH was given. The results were recorded by determining the fall in ^{131}I content produced by each dose of TSH and expressing this as a percentage of the gland content of ^{131}I at the time of injection of TSH. A typical experiment is illustrated in Fig. 4, and the results of six experiments in five animals are given in Table 1, when the responses to TSH alone are compared with the

responses to TSH during the administration of cortisone. It may be seen that there is no significant difference in the effect produced by TSH during the administration of cortisone (in amounts sufficient to inhibit completely the release of ^{131}I in normal and adrenalectomized animals) and the effect of TSH alone.

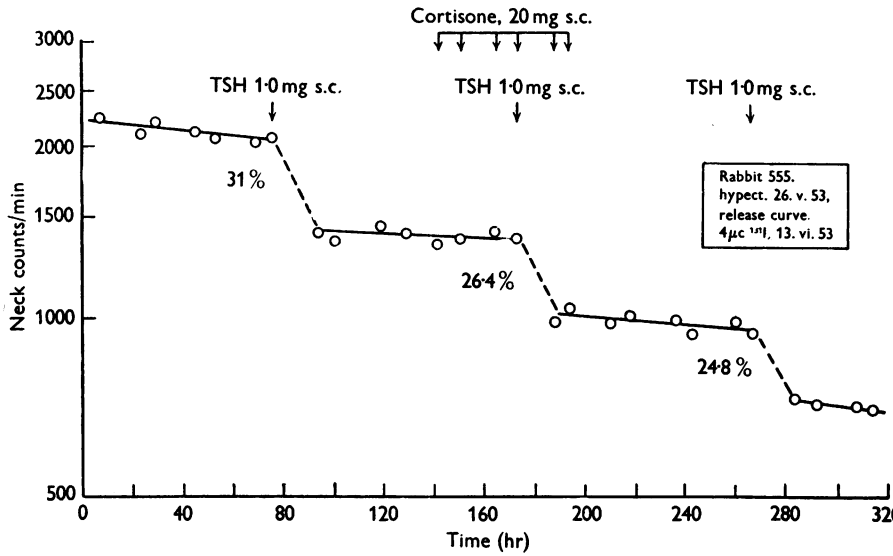

Fig. 4. The effect of cortisone on the response of the thyroid gland to injection of TSH in the hypophysectomized rabbit.

TABLE 1. The effect of cortisone on the thyroid response of the hypophysectomized rabbit to TSH

Rabbit	Dose of TSH (μg)	% fall after 1st injection TSH (alone)	% fall after 2nd injection TSH (with cortisone)	% fall after 3rd injection TSH (alone)	Dose of cortisone (mg/day)
542	250	29·3	16·5	13·2	40
544	500	25·6	14·4	8·1	10
548	500	9·8	13·6	20·6	10
555	500	29·4	26·4	15·5	10
555	1000	31·0	26·1	24·1	40
556	500	24·0	15·0	15·8	40

DISCUSSION

Cortisone and ACTH have been shown to depress the rate of release of ^{131}I-labelled hormone from the thyroid gland of the rabbit. This observation is in agreement with the bulk of previous work dealing with the effects of ACTH and cortisone on thyroid function.

Lowered uptake of ^{131}I by the thyroid gland has been reported, by many workers, to follow ACTH or cortisone administration in man (see Berson & Yalow, 1952; Kuhl & Ziff, 1952), and in the rabbit (Myant, 1953). Similarly,

cortisone and ACTH administration in the rat has been found to depress thyroid activity as judged by ^{131}I uptake (Money, Kraintz, Fager, Kirschner & Rawson, 1951; Albert, Tenney & Ford, 1952; Perry, 1951; Verzar & Vidovic, 1952; Migeon, Gardner, Crigler & Wilkins, 1952), by histological criteria (Cheymol, Delsol & Pazin, 1952) and by thyroid weight (Mercier-Parot & Tuchmann-Duplessis, 1951). However, Eucortone (Allen and Hanburys) and cortisone have been reported not to depress thyroid activity in the rat as judged by uptake of ^{131}I (Paschkis, Cantarow, Eberhardt & Boyle, 1950; van Middlesworth & Berry, 1951) and by thyroid weight (Winter, Silber & Stoerk, 1950; O'Neal & Heinbecker, 1953*b*). Cortisone administration has occasionally been reported to increase thyroid activity as judged by histological criteria (Higgins, Woods & Kendall, 1951; Halmi & Barker, 1952; Moszkowska & LeRoy, 1953).

In our experiments, DOCA had no consistent effect on thyroid function in the rabbit. Although DOCA has been reported to reduce the uptake of ^{131}I by the thyroid gland of the rat (Money *et al.* 1951; Perry, personal communication) and man (Zingg & Perry, 1953), negative results, with which our findings are in agreement, are reported by Paschkis *et al.* (1950) and Migeon *et al.* (1952) (rat-^{131}I uptake), Perry (personal communication) (rat-^{131}I output) and Mercier-Parot *et al.* (1951) (rat-histological criteria).

In two experiments, ACTH was found to be effective in reducing thyroid activity in the adrenalectomized rabbit. A similar result, using uptake of ^{131}I, was reported by Soffer *et al.* (1951) in the adrenalectomized rat. Since the hormone preparation used in our experiments was highly toxic to the adrenalectomized animal, it seems likely that the ACTH acted as a non-specific stress to reduce thyroid activity.

In the adrenalectomized rabbit, cessation of cortisone maintenance therapy (0·2–0·5 mg/day) resulted in a diminution in the rate of release of thyroidal ^{131}I. This may be due to the state of adrenal insufficiency. Resumption of small daily doses of cortisone increases the release of ^{131}I, a result which may be compared with the effect of cortisone on thyroid activity in the Addisonian patient (Hill, Reiss, Forsham & Thorn, 1950). Larger doses of cortisone again inhibit the release in the rabbit, and the uptake in the Addisonian.

The majority of workers find that ACTH and cortisone depress at least certain aspects of thyroid function, but little is known of the mechanism by which this effect is brought about. It has been suggested that ACTH and cortisone may (1) produce an *apparent* decrease in ^{131}I uptake by the thyroid by increasing the renal clearance of ^{131}I, (2) decrease the sensitivity of the thyroid gland to circulating TSH, or (3) decrease the rate of TSH secretion by the pituitary gland.

If the uptake of ^{131}I by the thyroid gland is used as a measure of thyroid activity, the results may be influenced by changes in extra-thyroidal disposal

of ^{131}I as well as by genuine changes in thyroid activity (see Berson & Yalow, 1952; Riggs, 1952). Cortisone and ACTH are known to promote renal excretion of iodide and so tests based solely on the uptake of ^{131}I by the thyroid gland, or urinary excretion of ^{131}I, are unreliable during cortisone or ACTH treatment. However, definite evidence that thyroid activity is depressed by ACTH and cortisone have been obtained by methods independent of changes in renal function (thyroid clearance of ^{131}I, rate of secretion of ^{131}I-labelled hormone from the thyroid, thyroid histology and weight).

The effect of ACTH and cortisone on the sensitivity of the thyroid gland to TSH has been investigated by a number of workers using hypophysectomized animals. Conflicting results have been obtained. Cortisone and ACTH are reported to reduce the increase in ^{131}I uptake by the thyroid gland produced by injections of TSH in the hypophysectomized rat (Woodbury, Ghosh & Sayers, 1951; Rawson, 1952; Verzar & Vidovic, 1952; Epstein, Cantarow, Friedler & Paschkis, 1953). However these results are again open to the criticism that changes in renal excretion may have influenced the thyroid iodine uptake. The renal clearance of ^{131}I has been shown to be abnormally low in the hypophysectomized rat (Albert, Tenney & Lorenz, 1952). Ingbar (1953) has shown that cortisone produces an increased renal excretion of ^{131}I in hypophysectomized rats and that this change in renal excretion is sufficient to account for the *apparent* reduction in uptake of ^{131}I by the thyroid of these rats when treated with TSH and cortisone as compared with TSH alone. He further showed that the thyroidal clearance of plasma iodide in hypophysectomized rats was markedly increased by the administration of TSH but was unaffected by the concomitant administration of cortisone. In our own work, cortisone in doses greater than those necessary to inhibit completely the release of thyroid hormone in normal or adrenalectomized rabbits had no significant effect on the discharge of hormone from the thyroid gland of the hypophysectomized rabbit following the injection of TSH. The conclusion that cortisone does not affect the response of the thyroid to TSH is in agreement with Ingbar (1953) and other workers who have used methods of measuring thyroid activity that are independent of changes in renal excretion of ^{131}I (Halmi, 1952; Halmi, Bogdanove, Spirtos & Lipner, 1953; O'Neal & Heinbecker, 1953*a*). Alterations in the ability of the thyroid to respond to TSH do not then provide an adequate explanation for the effects of ACTH and cortisone on thyroid function.

A suppression of TSH secretion seems the most probable explanation for the effects produced by ACTH and cortisone on the thyroid gland. Two experimental findings have been thought by some workers to be contrary to this view. First, Albert *et al.* (1952) and Perry (1951) have observed that cortisone and ACTH do not affect the rate of release of ^{131}I from the rat thyroid, although they decrease the uptake of ^{131}I. Since thyroxine administration,

which is known to depress pituitary TSH secretion, reduces both uptake and rate of release this has been cited as evidence that cortisone and ACTH cannot be acting in the same way. However, both in the work reported in this paper and in the work of Myant (1953) cortisone has been shown to reduce the rate of release of thyroid hormone in the rabbit. The failure to demonstrate an inhibitory effect on the rate of release in the rat may be due to inadequate dosage of cortisone, as Bondy & Hagewood (1952) have shown that administration of 12·5 mg/day cortisone produces a significant fall in the protein-bound iodine concentration of the blood in 3 days in the rat. Secondly, it has been suggested (d'Angelo, Stevens, Paschkis & Cantarow, 1953) that if cortisone and ACTH act to depress pituitary TSH secretion then they might prevent the development of a goitre and the histological changes in the thyroid that follow the administration of goitrogenic drugs. Although several workers (see d'Angelo *et al.* 1953; O'Neal & Heinbecker, 1953*b*) have found that cortisone and ACTH do not interfere with the action of goitrogens, this finding does not exclude the possibility that in the normal animal ACTH and cortisone act by depressing pituitary TSH secretion.

From the work reported in this paper and a review of the literature it seems probable that cortisone and ACTH act to depress thyroid activity in the intact animal principally by a suppression of pituitary thyrotrophic hormone secretion. The mechanism by which such a reduction in anterior pituitary TSH secretion might be brought about is still a matter of speculation; in view of the importance of the adrenal-thyroid relationship in both clinical and experimental endocrinology this is a question which merits further detailed investigation.

SUMMARY

1. Measurements of the output of radioactive thyroid hormone showed that ACTH and cortisone depressed thyroid activity in the rabbit. DOCA had no significant effect.

2. In the adrenalectomized rabbit variations in the maintenance dose of cortisone were followed by marked changes in thyroid activity.

3. Cortisone did not influence the response of the thyroid gland of the hypophysectomized rabbit to TSH administration.

4. It seems probable, from this work and the data in the literature, that cortisone and ACTH act mainly by suppressing pituitary thyrotrophic hormone secretion.

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