CIBA FOUNDATION COLLOQUIA
ON ENDOCRINOLOGY

VOLUME 10

Regulation and Mode of Action of Thyroid Hormones

Editors for the Ciba Foundation

G. E. W. WOLSTENHOLME,
O.B.E., M.A., M.B., B.Ch.

and

ELAINE C. P. MILLAR,
A.H.-W.C., A.R.I.C.

With 114 Illustrations

LONDON
J. & A. CHURCHILL LTD.
104 GLOUCESTER PLACE, W.1
1957
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Vol. 10  Regulation and Mode of Action of Thyroid Hormones
A leaflet giving details of available earlier volumes in this series, and also the Ciba Foundation General Symposia, and Colloquia on Ageing, is available from the Publishers.
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PREFACE

As the Ciba Foundation had included fifteen conferences on endocrinological subjects in its first forty small, international and multi-disciplinary meetings, with only slight reference to the thyroid, it was clearly high time to devote a colloquium entirely to the subject. In a three-day meeting of our usual fairly relaxed conversational type, it was impossible even then to consider all aspects of thyroid physiology, and it was decided to concentrate our attention at one end on the regulation of the thyroid gland, and at the other on the character and mode of action of its hormones.

This colloquium would not have taken place without the interest, support and advice of Sir Charles Harington and Dr. Rosalind Pitt-Rivers, and in the event all members of the conference enjoyed and admired the chairmanship of Dr. Pitt-Rivers, the first lady to occupy this position on one of these occasions.

The facilities of the Ciba Foundation are such as to compel us to limit membership to about thirty, always a distressingly hard task of selection. Our experience fully confirms that in our circumstances a group of up to thirty in size can converse in a coherent, co-operative manner, whereas above this number people tend to remain isolated in their separate nationalities, disciplines and opinions. In a large company, members are also much more guarded in their expressions, for fear of offending unknown people, where it is not possible easily to be aware of the identities of all people present.

For those who could not be invited to join us at this meeting, the papers and the discussions they aroused, are reproduced extensively in this volume. We hope that the reader will obtain from it not only information and ideas, but also a sense of participation in a friendly occasion.

Although this will be the thirty-fourth book containing the
papers and discussions of one of the Ciba Foundation's conferences, it may be helpful to add a few explanatory words about the Foundation and its other activities. It is an international centre, established as an educational and scientific charity under the laws of England. It owes its inception and support to its Founder, CIBA Ltd. of Switzerland, but is administered independently and exclusively by its distinguished British Trustees.

The Foundation provides accommodation for scientific workers who visit London from abroad, organizes and holds international conferences, conducts (in conjunction with the Institut National d'Hygiène) a postgraduate medical exchange scheme between England and France, arranges informal meetings for discussion, awards two annual lecture-ships, has initiated a scheme to encourage basic research relevant to the problems of ageing, assists international congresses and scientific societies, is building up a library service in special fields, and generally endeavours to give aid in all matters that may promote international co-operation in scientific research.
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CHAIRMAN'S OPENING REMARKS

Rosalind Pitt-Rivers

My first duty is a very agreeable one: to thank the Ciba Foundation on behalf of us all for arranging this symposium on the regulation and mode of action of thyroid hormones. This is the first of the Ciba Foundation meetings which has been devoted exclusively to the thyroid gland, and it comes at a time most opportune for us; we can now take stock of some of the discoveries in this field which have been made in the past ten or fifteen years.

During this time the use of the radioactive isotope of iodine $^{131}$I has contributed largely to our knowledge. It has allowed us to study dynamic aspects of iodine metabolism in man and animals in health and disease and to investigate alterations in thyroid function as influenced by other endocrine organs. The part played by the hypothalamus in the control of the thyroid by the anterior pituitary has received special attention, and the relationship of the adrenals and of the pancreas to certain aspects of thyroid function is now beginning to be investigated.

In the biochemical field, chromatography of $^{131}$I-labelled thyroid products has enabled us to detect and separate iodinated compounds which are present in biological material in amounts too small to be investigated by the older analytical methods. These studies have led to the discovery of $3:5:3'$-triiodothyronine, which joins thyroxine as one of the thyroid hormones.

Recently two other iodinated thyronines have been demonstrated in the thyroid and in other tissues; further, tetraiodothyroacetic acid (TETRAC) and triiodothyroacetic acid (TRIAC), which have been postulated as likely metabolites of thyroxine and triiodothyronine, have been detected in...
tissues and tissue homogenates after administration of the parent amino acids \textit{in vivo} and \textit{in vitro}. Whether these new compounds also have a place among the thyroid hormones is not yet established, but they merit further investigation.

In spite of the large amount of work which has been done on the mode of action of thyroid hormones, we are still in the dark as to its exact nature. Much of this effort has been directed to the investigation of effects at a sub-cellular level and it is now thought that one of the thyroid's actions is to control the liberation of energy released during biological oxidations. It does indeed seem reasonable that hormones which contribute so much to the control of energy in the whole animal should have as their target some part of the control mechanism of coupled high energy phosphate reactions. It is however unlikely that this is the whole story, and future work may show that the overall thyroid hormone effect is only manifested in a physiological system which includes other endocrine glands, since these exert so great an influence on thyroid function \textit{in vivo}.

One result of the spurt in thyroid research has been some divergence of opinion about a number of problems. The Ciba Foundation now offers us an opportunity to air these differences and help to resolve them by an exchange of information and by discussion.
HYPOTHALAMUS-PITUITARY-THYROID RELATIONSHIPS*

G. W. HARRIS and J. W. WOODS
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Maudsley Hospital, London

Previous work (Brown-Grant, von Euler, Harris and Reichlin, 1954; Brown-Grant, Harris and Reichlin, 1954a, b), which was briefly reported by Harris (1955a) at a Ciba Foundation Colloquium, demonstrated that the $^{131}$I output method forms a simple and direct technique for observing changes in thyroid activity in the rabbit. The necessary procedures may be carried out without anaesthesia and afford a period of 10–18 days, in any one experiment, in which changes in thyroid activity may be detected. In the work cited above, it was found that with the animals under standardized conditions the rate of release of thyroidal radioactivity follows an exponential curve and that a decreased or increased activity of the gland is associated with a decreased or increased slope of the curve respectively. Stressful or noxious stimuli were uniformly found to produce inhibition of the thyroid gland, and evidence was adduced that this effect was mediated by the hypothalamus and anterior pituitary gland. Since such stimuli uniformly lead to increased activity of the adrenal cortex it was pointed out that under many, if not all, conditions of environmental change a reciprocal relationship seemed to be maintained between the thyroid and adrenal cortex. A study of the effect of administration of adrenocorticotrophic hormone (ACTH) or cortisone on thyroid activity in the adrenalectomized rabbit showed that inhibition of the thyroid gland occurred when the blood concentration of adrenal corticoids was increased.

* The original work reported in this paper was carried out during the tenure by one of us (J. W. W.) of a Fellowship of the American Cancer Society, and aided by a grant from the Research Fund of the Maudsley Hospital.
The aim of the present experiments was to investigate any changes in thyroid activity produced by prolonged electrical stimulation of the hypothalamus in the unanaesthetized rabbit. Green and Harris (unpublished, cited by Harris, 1955b) stimulated various regions of the hypothalamus and pituitary gland of unanaesthetized rabbits and studied their oxygen uptake. No consistent changes were observed but the limitations of this method for assessing thyroid activity prevented any definite conclusions from being drawn. Colfer (1949) found histological signs of increased thyroid activity in rats and rabbits after prolonged electrical stimulation of the hypothalamus. An increased discharge of thyrotrophic hormone (TSH) was reported by Ellis and Wiersma (1945) following repeated electronarcosis in dogs and guinea pigs. Del Conte, Ravello and Stux (1955) confirmed these findings in the guinea pig and reported a rise in blood concentration of TSH within 80 minutes of electroshock. In view of these data and the well-established fact that electrical stimulation of the region of the median eminence of the hypothalamus evokes anterior pituitary secretion of ACTH (rabbits, de Groot and Harris, 1950; dogs, Hume and Wittenstein, 1950; cats and monkeys, Porter, 1953, 1954), and of gonadotrophic hormone (Harris, 1937, 1948; Markee, Sawyer and Hollinshead, 1946) it seemed reasonable to suppose that similar stimulation might evoke discharge of TSH.

The method used for detecting changes in thyroid activity of the rabbit, in the present study, is the $^{131}$I output method as described previously. Electrical stimulation is performed by a modification of the remote control method of de Groot and Harris (1950). This technique makes it possible to stimulate the hypothalamus of the unanaesthetized, unrestrained rabbit. A small secondary coil is implanted subcutaneously over the lumbar spine and connected by flexible leads to glass-insulated platinum electrodes inserted into the hypothalamus or pituitary region. During an experiment the animals are housed in cages surrounded by a large primary coil, and stimulation applied at appropriate times by passing condenser
discharges through the field coil at 50 cyc./sec. The pulses induced in the secondary are alternating with a duration 0.5-0.7 m.sec. The primary circuit is provided with an interrupter which makes it possible to stimulate with on:off periods of any desired ratio—\( \frac{1}{4} \) min. on : \( \frac{1}{4} \) min. off in the present experiments. The intensity of stimulation is controlled by the position of the rabbit's cage relative to the primary coil and by the capacitance of, and voltage applied to, the condenser bank discharging through the primary coil.

**Results**

(a) **Before complete adrenalectomy**

Electrical stimulation has been applied to the hypothalamus or pituitary gland of 27 animals in 41 experiments. Fifteen of these rabbits were normal, 5 had been subjected to ovariec-tomy and right adrenalectomy, and 7 to right adrenalectomy. Stimulation for periods of several days (usually 48 hr.) resulted in transient inhibition of thyroid activity in 22 experiments (Figs. 1 and 4), no change in 16, a questionable
response in 1, and in only 2 experiments (on one normal rabbit) was a definite increase in thyroid function seen. In no case was a detrimental effect on the rabbits observed.

(b) After complete adrenalectomy

In view of the data indicating first, that increased ACTH secretion may follow electrical stimulation of the hypothalamus, and secondly, that an increased blood concentration of adrenal corticoids inhibits the secretion of TSH, it was decided to repeat the experiments in completely adrenalectomized rabbits maintained on constant daily doses of cortisone. Eighteen of the 27 rabbits reported above have been studied after complete adrenalectomy, and a striking change in the thyroid response has been observed in many cases. Forty-eight experiments on these animals showed that 12 rabbits now responded to the electrical stimulation with a marked

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RABBIT 1071. 27.12.55

![Graph](image)

**Fig. 2.** The effect of hypothalamic stimulation on $^{131}$I release from the thyroid after adrenalectomy.
increase in thyroid activity (Figs. 2 and 3) (previous to adrenalectomy, they had shown thyroid inhibition in 10 experiments, and no change in thyroid activity in 6 experiments). The increase in thyroid function was assessed not only by measuring the rate of loss of thyroidal radioactivity, but in 5 experiments on 4 rabbits by simultaneous measurements of the total plasma radioactivity or the plasma $^{131}$I.

![Graph](image)

**Fig. 3.** The effect of hypothalamic stimulation on $^{131}$I release from the thyroid, and on the $^{131}$I concentration in the plasma.

The results indicated that the blood concentration of thyroid hormone was increased up to four-fold (Fig. 3). It is significant that hypothalamic stimulation maintained, in some cases, an increased level of thyroid activity even in the presence of a raised concentration of thyroid hormone in the blood.

The precise localization of the region stimulated has not yet been determined by histological study in all the animals, but
the available studies (see Fig. 5) and the radiographic evidence suggest that it is stimulation of the anterior part of the median eminence of the tuber cinereum which results in increased thyroid activity.

Five of the rabbits that showed a marked acceleration of thyroid activity during stimulation eventually died, suddenly and unexpectedly, whilst being stimulated.

(c) Cortisone-treated animals

Seven rabbits with the left adrenal gland intact were given high daily doses of cortisone (5–40 mg.) in an attempt to at

![Graph](image)

**Fig. 4.** To show the effects of hypothalamic stimulation before and during cortisone administration on a rabbit with the left adrenal gland intact. Note (1) the reduced rate of release during the control periods whilst under cortisone administration, and (2) the reversal by cortisone of the effect produced by hypothalamic stimulation.

least partially blockade ACTH secretion, and subjected to electrical stimulation. Four of these animals in 6 experiments responded with an increased rate of release of thyroidal radioactivity (Fig. 4).
Fig. 5. Microphotographs of a horizontal section through the hypothalamus of rabbit 1074. Bi-polar electrodes have been implanted; the site of one electrode (x) may be seen as a circular hole in the anterior part of the median eminence. The site of the other electrode (also x) was traced through serial sections and found to be in the anterior part of the third ventricle. 100 μ thick; Weigert's haematoxylin, × 9. III V., third ventricle; I.C., internal carotid arteries; M.B., mammillary body; T.L., temporal lobe of brain.
**Discussion**

The reversal of the thyroid response to electrical stimulation of the tuber cinereum after adrenalectomy may be explained in several ways. The most likely hypothesis seems to be that some substance is liberated from the adrenal glands during hypothalamic stimulation, which in turn inhibits either TSH secretion or the thyroid gland itself. This substance might originate in the adrenal medulla or cortex, since it is known that either adrenaline (Haigh, Reiss and Reiss, 1954; Brown-Grant, Harris and Reichlin, 1954a; Brown-Grant and Gibson, 1956) or adrenal cortical steroids (Myant, 1953; Brown-Grant, Harris and Reichlin, 1954b) may inhibit thyroid activity in the rabbit. It is unlikely that adrenal medullary secretion is involved since (a) localized stimulation of the tuber cinereum probably does not evoke secretion of adrenaline (Magoun, Ranson and Hetherington, 1937), (b) the dose of adrenaline necessary to produce prolonged inhibition of the thyroid gland of the rabbit is high (Brown-Grant, Harris and Reichlin, 1954a), and (c) rabbits with an adrenal gland intact may respond to stimulation with increased thyroid function if under high cortisone administration. It is probable that adrenal cortical secretion is the factor involved, since (a) localized stimulation of the tuber cinereum results in increased secretion of ACTH (de Groot and Harris, 1950; Hume, 1952), (b) the dose of adrenal steroids necessary to produce prolonged inhibition of the thyroid gland in the rabbit seems within the physiological range (Brown-Grant, Harris and Reichlin, 1954b; Brown-Grant, 1956), and (c) rabbits with an intact adrenal in which ACTH release is presumably blocked with large doses of cortisone show a thyroid response. It is probable that adrenal steroids affect thyroid activity by suppressing the secretion of TSH from the anterior pituitary, since cortisone was found not to influence the response of the thyroid gland of the hypophysectomized rabbit to injection of exogenous TSH (Brown-Grant, Harris and Reichlin, 1954b).
The present findings are of interest in a consideration of the aetiology of Graves's disease, for two reasons.

First, the fact that localized stimulation of the rabbit’s hypothalamus can result in increased thyroid activity is compatible with the thesis expressed in so many clinical accounts that emotional stress is an important aetiological factor in the onset of Graves's disease. The occurrence of hyperthyroidism following a severe fright was mentioned by Parry (1825) when he first described the disease. The publications of Crawford (1897), Maranon (1921), Deutsch (1923), Lewis (1925), Bram (1927), Moschcowitz (1930), Goodall and Rogers (1933) may be quoted from amongst the large number dealing with this subject. Further reference to the literature on the relationship of psychic trauma to Graves’s disease may be found in the more recent papers of Lidz and Whitehorn (1950) and Mandelbrote and Wittkower (1955).

Secondly, the fact that stimulation of the hypothalamus is effective in the adrenalectomized rabbit rather than the normal is compatible with much data indicating a state of absolute or relative deficiency of the adrenal cortex in patients with Graves’s disease. Emphasis was first placed on this point by Marine and Baumann (1921) and Marine (1930). The data at the present time may be summarized as follows:—

1. The occurrence of thyrotoxicosis in cases already suffering from Addison’s disease has been reported (Rössle, 1914), and the frequency of onset of Graves’s disease under these circumstances has been given as ten times that in previously normal subjects (Frederickson, 1951). Oppenheimer (1937) described the onset of hyperthyroidism following X-ray damage to the adrenal cortex in man.

2. The excretion of 17-ketosteroids seems reduced in patients with Graves’s disease (Fraser, Forbes, Albright, Sulkowitch and Reifenstein, 1941; Shadaksharappa, Calloway, Kyle and Keeton, 1951; Corvilain, 1958). The excretion of reducing steroids may be normal or slightly increased (Shadaksharappa, Calloway, Kyle and Keeton, 1951; Talbot, Wood,
Hypothalamus-pituitary-thyroid Relationships

Worcester, Christo, Campbell and Zygmuntowicz, 1951) although the formaldehydogenic steroids are decreased (Daughaday, Jaffe and Williams, 1948). Daughaday and co-workers (1948) also report that a severe exacerbation of the thyrotoxic state was accompanied by a fall in the excretion of formaldehydogenic steroids and such an observation provides a rational basis for the treatment of thyroid crisis with administration of cortisone. In a more recent study Levin and Daughaday (1955) found the excretion of urinary 17-keto- and 17-hydroxysteroids to be within the normal range in hyperthyroidism. The surprising factor, on a priori consideration, is that urinary excretion of adrenal steroids is not greatly increased in Graves’s disease, since the administration of exogenous thyroxine results in adrenal hypertrophy (Wallach and Reineke, 1949; and others), an increased excretion of 17-hydroxysteroids in the guinea pig (Levin and Daughaday, 1955) and of 17-ketosteroids in man (Corvilain, 1953). The physical and mental states of thyrotoxic patients would also seem to afford a strong stimulus to adrenal cortical hyperfunction.

3. In an investigation on thyroid-adrenocortical relationships in man, Hill, Reiss, Forsham and Thorn (1950) found that administration of ACTH or cortisone depressed the uptake of $^{131}$I by the thyroid and lowered the concentration of blood protein-bound iodine, although they noted that exogenous TSH was still active in the presence of a high concentration of adrenal steroids in the blood. They also observed that ACTH and cortisone therapy might be of benefit to patients with Graves’s disease and that the best results were obtained in early cases and in those with a good adrenal response to ACTH.

4. Marine (1930) reported that post-mortem examination of thyrotoxic patients revealed the presence of a small adrenal cortex, and such signs of adrenal hypofunction as lymphoid hyperplasia and a large thymus gland. LeCompte (1949)
measured the width of the adrenal cortex and found a significant narrowing in cases of Graves's disease. Kraus (1923) described a similarity of the human pituitary in cases of Addison's disease and thyrotoxicosis. Perhaps more significant in this context is the report of Crooke and Russell (1935) that the thyroid gland in cases of Addison's disease may be histologically similar to that of Graves's disease. Boyd (1944) summarizes the position by stating: "The more completely the matter is studied the more clearly does an underlying relationship become evident between three such apparently different conditions as exophthalmic goiter, status lymphaticus and Addison's disease."

It is likely that the normal human, as well as laboratory animals, responds to emotional or physical stress with an increased activity of the adrenal cortex. It is possible that if, for some reason, the adrenal cortical response fails to occur, and the inhibitory effect of a raised blood concentration of adrenal corticoids on TSH secretion is lacking, thyroid hyperactivity may ensue.

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DISCUSSION

Greer: Prof. Harris, as I understand it, your hypothesis is that adrenocortical hormones inhibit the production of TSH when they are given in excess. There are considerable data in the literature showing an inhibition of thyroidal uptake and release and a lowering of the protein-bound iodine in animals and man given large doses of cortisone, yet there is no inhibition of the goitre produced by the administration of antithyroid drugs when cortisone is given simultaneously.

I wonder how you tie this together. Do you believe that the effect of adrenal hormones may be transient and if they are continued for a longer period of time they have no effect; or do you believe there are two mechanisms involved? In other words, do you think cortisone exerts more inhibition on the metabolic activity of the thyroid than on its growth?

Harris: The position with regard to the thyroid-inhibiting action of the adrenal steroids is certainly not clear in all its aspects. The action does not seem to be species-specific to the rabbit, since thyroid inhibition following administration of ACTH and adrenal steroids has been reported in the human (Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W. (1950). J. clin. Endocrin., 10, 1375) and in the rat (Brown-Grant, K. (1956). J. Physiol., 131, 58). The mechanism whereby a raised blood concentration of adrenal steroids results in a diminution of thyroid activity appears to involve the rate of release of pituitary TSH. The reason for saying this is that administration of cortisone to the hypophysectomized rabbit does not effect the thyroid response to exogenous TSH (Brown-Grant, K., Harris G. W., and Reichlin, S. (1954). J. Physiol., 126, 41). Now if it is true that the adrenal corticoids act at a pituitary or hypothalamic level to affect the rate of release of pituitary TSH, and this seems to be the case, then your point is why was no inhibitory action of the adrenocortical hormones demonstrated in the experiments involving the administration of goitrogens. I should like to ask first, though, how far it would have been possible to measure or observe any inhibition if such had been present.

Greer: D'Angelo, I believe, first reported such results. He found an increase in the size of the goitre produced with propylthiouracil when rats were given cortisone in addition. Dr. Florsheim, in our laboratory, has been repeating and amplifying these experiments. In some experiments he also finds that the goitre in the cortisone-treated group is larger, while in others there is no difference. When there is a threefold enlargement of the thyroid, such as one gets in these experiments, I would think that any appreciable inhibition of thyrotrophin production by cortisone would show up quantitatively.

Harris: If any inhibitory action of cortisone could be quantitatively measured under these conditions then I have no explanation to offer. However, experiments involving the use of goitrogens may not be so simple as they appear at first sight. In the normal and in the adrenalectomized rabbit there is no doubt that increasing the blood concentration of cortisone tends to decrease the rate of thyroid secretion. Dr. Brown-Grant (1956. J. Physiol., 131, 58) has found this to be true also