The Role of Glucocorticoids in the
Regulation of Thyroid Function in Man

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ABSTRACT The diurnal variation in thyroidal iodine release previously observed in euthyroid subjects appears to correlate with variations in serum immunoadassayable thyrotropin (TSH). The hypothesis is advanced that this diurnal rhythm seems to be primarily regulated by a negative feedback action of circulating hydrocortisone. The administration of maintenance doses of hydrocortisone to patients with primary adrenal insufficiency and pharmacological doses to euthyroid subjects was accompanied by a acute suppression in both thyroidal iodine release and serum TSH values. An escape from glucocorticoid suppression was observed to occur in 2 or 3 days with the resumption of a near-normal thyroidal iodine release rate but was accompanied by a damping or absence of the normal diurnal rhythm. Withdrawal of pharmacological doses of glucocorticoids in euthyroid subjects and maintenance doses in primary hypoadrenal patients was accompanied by transient stimulation of both serum TSH and thyroidal iodine release values. The study of a patient before and after cryohypophysectomy indicated that the rebound response in thyroid release after steroid withdrawal may be a useful testing procedure to indirectly assess the hypothalamic-pituitary reserve capacity of TSH.

INTRODUCTION

The action of glucocorticoids in altering thyroid function has been an area of considerable investigative interest and confusion. Ingbar and Freinkel reviewing this subject in 1956 concluded that the "weight of evidence" indicated that corticotropin (ACTH) and cortisone probably transiently suppress thyrotropin (TSH) release at the hypothalamic level. But these authors were quick to add that they did not support this concept with any "profound conviction" and that further investigation most certainly was essential to clarify the subject (1). Subsequently, Ducommun, Sakiz, and Guillemin have reported in the rat a reciprocal relationship between TSH and ACTH secretion in response to cold and other extraosseous stimuli (2). Retiene, Zimmerman, Schindler, Neuschwander, and Lipscomb also observed a reciprocal relationship between ACTH and TSH secretion while studying the spontaneous endocrine rhythms in the rat (3). Recently, Wilber and Utiger described both in man in the rat an acute suppression of TSH secretion which occurs after the administration of pharmacological doses of glucocorticoids and a rebound in TSH release after withdrawal (4) of glucocorticoids. It is the purpose of this study to extend these observations, to present evidence concerning the role of glucocorticoids in the regulation of normal thyroid function in man, and to demonstrate that withdrawal from glucocorticoid administration may be a useful testing method for assessing TSH reserve capacity.

METHODS

The subjects employed in this investigation were from the inpatient and outpatient services of the Los Angeles County-University of Southern California Medical Center and were studied at the Clinical Research Center. All studies were performed on euthyroid subjects as determined both by clinical examination and conventional laboratory tests including a protein-bound iodine, triiodothyronine resin uptake, and 24 hr thyroid-131I uptake.

The dual iodine isotopic method used to measure thyroidal iodine release has been described in detail elsewhere (5). Briefly, the method utilizes 131I to endogenously label the thyroid gland and thyroxine-131I (T,131I) to generate a 131I reference source. This 131I reference source acts as an in vivo indicator for the 131I released by the thyroid gland as hormone or iodide. The measurement of 131I/131I activity in serially-timed urine samples allowed the measurement of the thyroidal iodine release rate relative to past and future urine collections. All release studies were performed during

1922 The Journal of Clinical Investigation Volume 49 1970
what has been termed the "release slope phase" (5). During
this phase, the urinary \[\text{I}^3\text{I}/\text{I}^1\text{I}\] ratio values were observed to
predictably rise in a linear manner when plotted on semi-
logarithmic coordinates against time. Therefore, a change
in the slope during this phase could be interpreted as an
alteration in release rate. Serum TSH values were measured
by a double antibody radioimmunoassay method (6). The
materials for the assay were provided, in part, through the
courtesy of the National Pituitary Agency. Assays were
performed independently by two of the authors (D.F. and
M.A.) without the knowledge of the other's tests results.
The TSH value employed in this study was the average of
the values from these two laboratories. All samples in a
single study were performed in the same assay run in order
to eliminate interassay variability. Serum cortisol determi-
nations were performed by the competitive protein-binding
assay technique of Nugent and Mayes (7). Estimation of
serum thyroxine-binding capacity was determined by a modi-
fication of a commercial T\text{r} \text{r} \text{r} \text{r} resin uptake test (Triosorb,
Abbott Laboratories, North Chicago, Ill.) (8). Thyroxine
iodine by column and free thyroxine determinations were
performed at Bio-Science Laboratories, Van Nuys, Calif.
Statistical analysis of the data was performed by conven-
tional paired t test examination. The analysis of changes
in thyroidal iodine release was performed by comparing the
observed changes in values with projected normal values.
These projected values were established by interpolation of
the release slope between the control periods obtained before
and after the testing procedure.

RESULTS

Studies of increased glucocorticoid levels on TSH and
thyroidal iodine release. The administration of phar-
macological doses of prednisolone resulted in a prompt
and significant (\(P < 0.01\)) reduction in serum TSH and
thyroidal iodine release values. This is graphically il-
lustrated for three euthyroid subjects in Fig. 1. After 3
days of suppression, prednisolone withdrawal resulted in
a significant augmentation in TSH and in iodine release
values (\(P < 0.01\)). The augmentation in thyroidal iodine
release persisted for several days and was followed by a
return to a normal release pattern. For comparison a
normal pattern is portrayed in the lower portion of the
figure. The TSH results are similar to those recently
reported by Wilber and Utiger (4) in euthyroid subjects.

When glucocorticoid administration was continued
beyond 3 days, an escape from thyroid suppression was
observed as is illustrated in Fig. 2. Increasing the pred-
nisolone dosage from 5 to 20 mg every 8 hr resulted in
some further suppression, but the increase did not halt
release as was initially observed. During this escape
phase, there was a loss of normal diurnal pattern in
thyroidal iodine release. A similar lack of a normal di-
urnal pattern has been observed in four subjects with
Cushing's disease secondary to bilateral adrenal hyper-
plasia. A representative example of a release pattern in
Cushing's disease is included in this figure for purposes
of comparison. Withdrawal of glucocorticoid adminis-
tration after prolonged suppression was accompanied by

a prompt rebound in thyroidal iodine release which was
again followed in several days by a return to a normal
release pattern. Note that the degree and promptness of
the initial inhibition of release was greater with 5 mg of
prednisolone every 8 hr than with 25 \(\mu\)g of triiodothy-
ronine daily.

Studies of hydrocortisone administration on thyroid
function in subjects with primary adrenal insufficiency.
The withdrawal of maintenance hydrocortisone therapy
in two subjects with primary adrenal insufficiency re-
sulted in a gradual rise in both TSH and thyroidal iodine
release values. The results on two subjects are illustrated
in Fig. 3. Upon resuming maintenance therapy, a prompt
and significant drop (\(P < 0.01\)) in both of these parame-
ters to base line levels was observed. During the with-