Effects of Norethandrolone on the Transport and Peripheral Metabolism of Thyroxine in Patients Lacking Thyroxine-Binding Globulin

OBSERVATIONS ON THE PHYSIOLOGICAL ROLE OF THYROXINE-BINDING PREALBUMIN

LEWIS E. BRAVERMAN, THEODORE AVRUSKIN, MICHAEL J. CULLEN, APOSTOLOS G. VAGENAKIS, and SIDNEY H. INGBAR

From the St. Elizabeth's Hospital and Department of Medicine, Tufts Medical School, and the Thorndike Memorial Laboratory and the Harvard Medical Service, Boston City Hospital, and the Department of Medicine (Endocrinology), Children's Hospital Medical Center, and the Departments of Medicine and Pediatrics, Harvard Medical School, Boston, Massachusetts 02118

ABSTRACT Studies of the effect of norethandrolone on the transport and peripheral metabolism of thyroxine were carried out in four patients lacking thyroxine-binding globulin. Before norethandrolone administration, values for serum protein-bound iodine (PBI) were decreased (1.8 ±0.5 μg/100 ml) and the proportion of free thyroxine increased (0.036 ±0.008%). As a result, values for the absolute concentration of free thyroxine iodine were at the lower end of the normal range (0.63 ±0.12 mμg/100 ml). During the control thyroxine-turnover study, the thyroxine distribution space was strikingly increased (18.2 ±7.9 liters) and the fractional rate of thyroxine turnover moderately increased (17.1 ±11.3%/day), as compared to the expected mean values for normal subjects. Therefore, calculated values for the daily rate of thyroxine clearance were increased even more, ranging between 255 and 500% of normal values. However, owing to the low PBI in these patients, the daily disposal of thyroxine iodine was similar to that expected in normals on the basis of age and weight. During the administration of norethandrolone, the thyroxine-binding capacity of the thyroxine-binding prealbumin increased strikingly in all patients, values averaging 162% of those found during the control period. This increase was associated with a highly significant increase in PBI (133% of control values) and a small but significant decrease in the proportion of free thyroxine, resulting in no significant change in the absolute concentration of free thyroxine iodine. In all four patients, administration of norethandrolone was associated with a pronounced decrease in the thyroxine distribution space to values which averaged 69% of those found during the control period. Values for the fractional rate of thyroxine turnover increased slightly. As a result, thyroxine-clearance rate decreased in all patients. Owing to the reciprocal changes in clearance rate and PBI, no significant change in total daily thyroxine disposal was observed. The present studies reveal that when the thyroxine-binding prealbumin is increased in patients lacking thyroxine-binding globulin, several indices of peripheral thyroxine transport and metabolism are altered. However, these changes were small, even in the absence of thyroxine-binding globulin. It is suggested, therefore, that the effect of changes in thyroxine-binding prealbumin would be even smaller in individuals in whom thyroxine-binding globulin is present.

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INTRODUCTION

Recent studies have indicated that in vitro the thyroxine (T_4)-binding globulin (TBG)[1] is the principal protein to which endogenous T_4 is bound (1, 2). Contrary to

[1] *Abbreviations used in this paper:* AFT_4I, absolute concentration of free thyroxine iodine in serum; HSA, human serum albumin; PBI, protein-bound iodine; PFT_4, proportion of free thyroxine in serum; T_4, thyroxine; TBG, thyroxine-binding globulin; TBPA, thyroxine-binding prealbumin; TDS, thyroxine distribution space.

indications provided by early electrophoretic studies (3, 4), only a small proportion of endogenous T_4 is bound by the thyroxine-binding prealbumin (TBPA) (1, 2). Few data have been available, however, concerning the role of TBPA in T_4 transport in vivo. A variety of illnesses are associated with decreased T_4-binding by TBPA (3–6); however, it is difficult to ascribe any changes in T_4 metabolism which may occur in these circumstances to alterations in TBPA, since they might also be due to other concomitants of the illness, such as fever, hepatic injury, decrease in TBG, etc. (7, 8). Indeed, in the postoperative state, there is little correlation between decreases in TBPA and alterations in T_4 turnover (9). Salicylate and certain of its congeners inhibit T_4-binding by TBPA and accelerate T_4 turnover (10). Although this was taken as evidence of a significant role of TBPA in the transport of T_4, more recent studies have shown that salicylate also displaces T_4 from binding sites on albumin,[2] and may influence the intrinsic cellular metabolism of the hormone. Hence, under known conditions in which binding of T_4 by TBPA is decreased, little can be concluded concerning the significance of concomitant changes in T_4 binding by TBPA and changes in T_4 metabolism.

Naturally occurring increases in TBPA, comparable in magnitude to those seen in the case of TBG, are unknown. Agents which are known to increase TBPA include the androgenic-anabolic steroids (11, 12) and glucocorticoids in large doses (13). These agents also decrease thyroxine (T_4) binding by TBG, however, and, in the case of the androgenic-anabolic steroids, the changes in peripheral T_4 metabolism which they induce are characteristic of those seen when T_4 binding by TBG is decreased (11, 14). Hence, any changes in T_4 metabolism which might result from the increase in TBPA are obscured. The present studies were designed to overcome this difficulty. Steroid induced increases in TBPA were produced in four patients with the syndrome of idiopathic absence of TBG. Here, concomitant decreases in T_4 binding could not occur, and hence the effects of increases in TBPA on peripheral T_4 metabolism could be observed.

METHODS

Studies were conducted in four male patients in whom the T_4-binding capacity of TBG was unmeasurably low (< 1.0 $\mu g T_4$/100 ml). Patient S.F. was studied in the spring of 1968. Patients J. D. and A. D., who were brothers, and E.D., who was their uncle, were studied in the fall of 1969. After a period in which control observations of T_4 transport and turnover were made, patients were started on treatment with 20–40 mg of norethandrolone per os daily. On the 17th day of treatment, a base line blood was drawn for determination of radioactivity remaining from the first T_4 injection. This proved to be negligible. The second measurement of T_4 turnover was then begun with a fresh injection of ^{131}I-labeled T_4. Treatment with norethandrolone was continued until the second turnover study was completed.

The kinetics of the peripheral metabolism of T_4 were measured with the aid of ^{131}I-labeled T_4 by methods previously described (15), special care being taken in the preparation of counting standards in order to minimize errors in the calculated volume of the T_4 distribution space. Labeled T_4 was diluted in sterile 1% human serum albumin (HSA) to a final concentration of 10 μCi/ml. Either 2.0 or 5.0 ml was administered as a single intravenous injection. Immediately thereafter, counting standards were prepared to their final dilution in 1% HSA (human serum albumin) to minimize adsorption of T_4 to glassware and were promptly pipetted into counting tubes. Blood samples were drawn daily for 7–9 days, serum samples separated, and their radioactivity compared to that in the counting standards. Both the zero-time intercept and the slope of the plasma T_4-^{131}I disappearance curve were determined from the semilogarithmic regression equation calculated by the method of least squares. Data obtained during the first 24 hr after injection of T_4-^{131}I were excluded from the latter calculation to permit ample time for completion of T_4 distribution.

Binding capacities of TBG and TBPA for T_4 were determined by both reverse-flow and conventional filter paper electrophoresis in glycine-acetate buffer, pH 8.6 (16). Values for the binding capacity of TBG were obtained from the reverse-flow system, while those for TBPA were obtained from conventional electrophoresis. Values presented represent the mean of measurements made in samples of serum obtained on two separate days during each study period.

The proportion of free T_4 in serum was measured in triplicate in samples obtained on 2 separate days of each study period. Analyses were conducted by an equilibrium dialysis technique in which 1 ml of undiluted serum was dialyzed against 9 ml of phosphate buffer, 0.1 M pH 7.4. T_4-^{131}I in the dialysate was separated from radioiodide by trichloracetic acid precipitation after addition of normal human serum. Absolute concentrations of free T_4 iodine were calculated as the product of the mean value of the proportion of free T_4 and the mean value of the protein-bound iodine (PBI) during each study period.

In order to assess the significance of any small changes in serum PBI, which might occur as a result of treatment, all PBI values were measured in duplicate, five separate samples during each study period being analyzed in patient S.F. and eight or nine separate samples being analyzed for each study period in the remaining three patients.[3]

Statistical analyses were carried out by means of the *t* test or, when appropriate, the paired *t* test, as described by Snedecor (17).

RESULTS

Control observations (Tables I and II). Before the administration of norethandrolone, values for the serum PBI averaged 1.8 $\pm$0.5 μg/100 ml (mean $\pm$SD). Binding of more than a trace of T_4 by TBG could not be detected in the sera of any of the four patients studied, even when specimens were enriched with only small tracer quantities of labeled T_4. As judged from conventional

[2] Braverman, L. E., A. E. Foster, and S. H. Ingbar. Unpublished observations.

[3] PBI determinations carried out at the Boston Medical Laboratory, Waltham, Mass.

TABLE I

The Effect of Norethandrolone on the Peripheral

Patient	Age	Sex	Body wt	PBI		T_4 distribution space	
				Control	Rx*	Control	Rx
			kg	*μg/100 ml*		*liters*	
S. F.	39	M	72.2	1.5 ±0.2‡	2.1 ±0.2	19.8 (11.9)	14.7
A. D.	7½	M	18.3	1.3 ±0.3	1.6 ±0.2	8.2 (3.1)	6.2
J. D.	12½	M	51.8	2.2 ±0.2	2.8 ±0.3	17.6 (9.3)	13.1
E. D.	23½	M	67.8	2.2 ±0.2	3.1 ±0.2	27.3 (11.5)	14.5
Mean				1.8	2.4	18.2 (8.9)	12.1
SD				0.5	0.7	7.9 (4.1)	4.0

Numbers in parentheses represent the expected values for each patient in respect to age and weight.

* Norethandrolone administered daily for 26 days to patients (S. F. and E. D., 40 mg; J. D., 30 mg; A. D., 20 mg).

‡ Mean ±SD for serum PBI measured in duplicate on multiple samples during each study period.

electrophoretic analysis, T_4–binding capacities of TBPA averaged 183 ±79.5 μg/100 ml.

In all patients, the proportion of free thyroxine (PFT_4) in serum was above the normal range (0.019–0.025%), values averaging 0.036 ±0.008%. Values for the absolute concentration of free thyroxine iodine in serum (AFT_4I) calculated as the product of the PBI and PFT_4, averaged 0.63 ±0.12 mμg/100 ml, a value within, but the lower end of, the normal range (0.5–1.6 mμg/ml).

In view of the markedly different ages and body sizes of the four patients studied, control values for the several aspects of peripheral T_4 metabolism were examined in relation to the expected mean for comparable age and size (18). In all patients, a striking increase in thyroxine distribution space (TDS) was seen. Values ranged between 166 and 264% and averaged 216% of those expected. A similar, but less striking, increase in the fractional rate of T_4 turnover was also noted, values ranging between 126 and 179% of the expected normal. Calculated values for the daily rate of T_4 clearance, the product of TDS and fractional turnover rate, were increased even more, ranging between 255 and 500% of normal values for individuals of comparable age and weight. In each of the four patients studied, values for the daily disposal of T_4 iodine, calculated as the product of clearance rate and PBI, were similar to those normally expected on the basis of age and size. As a result of the low values for PBI, calculated values of the extrathyroidal T_4 pool were subnormal in all patients, but not markedly so, owing to the concomitant increase in TDS.

Effects of norethandrolone (Tables I and II). During the administration of norethandrolone, quantitatively small but proportionately moderate increases in PBI occurred in all patients. During the control period, PBI's in the four patients averaged 1.8 ±0.5 μg/100 ml, whereas after 17–26 days of norethandrolone administration, values averaged 2.4 ±0.7 μg/100 ml., a change which was highly significant for the group as a whole when assessed by the paired t test ($P < 0.02$). Multiple measurements of PBI in each patient permitted analyses of the significance of the increase which occurred in each individual patient. These revealed that the increase in PBI which occurred during norethandrolone treatment was statistically significant in each except A. D., in whom the change was of marginal significance.

In all patients, administration of norethandrolone was associated with a pronounced decrease in TDS, values during treatment averaging 69% of those obtained during the control period, ($P < 0.02$). Values for fractional turnover rate increased in all patients, but this change was of significant magnitude only in patient E. D. T_4–clearance rate decreased in all patients to values which averaged 80% of those seen during the control period ($P < 0.02$). As a result of reciprocal changes in clearance rate and PBI, no significant change in total daily T_4 disposal was observed in any of the patients. The peripheral T_4 pool was essentially unchanged during norethandrolone administration.

No effect of norethandrolone on the essentially absent T_4 binding by TBG was noted. Values for the T_4-binding capacity of TBPA, however, increased strikingly in all patients, values averaging 162% of those found during the control period. These changes were associated with a consistent decrease in PFT_4, the mean changing from 0.036 ±0.008 to 0.030 ±0.005 per cent. Al-

Metabolism of Thyroxine (T_4) in Patients Lacking TBG.

Fractional turnover rate		Clearance rate		Extrathyroidal T_4I		T_4 disposal rate	
Control	Rx	Control	Rx	Control	Rx	Control	Rx
%/day		*liters/day*		*μg*		*μgT_4I/day*	
14.0 (9.1)	14.4	2.8 (1.1)	2.1	297 (595)	309	41.6 (54.1)	44.5
24.4 (13.6)	28.6	2.0 (0.4)	1.8	107 (155)	99	26.1 (20.1)	28.3
17.2 (12.2)	17.6	3.0 (1.1)	2.3	387 (465)	367	66.6 (56.7)	64.6
12.8 (10.2)	18.3	3.5 (1.2)	2.7	601 (575)	450	76.9 (58.7)	82.4
17.1 (11.3)	19.7	2.8 (0.9)	2.2	348 (447)	306	52.8 (47.4)	54.9
5.2 (2.0)	6.2	0.6 (0.4)	0.4	205 (203)	150	23.2 (18.3)	23.5

though small (average decrease 14%), this change was significant for the group as a whole ($P = 0.02$). Values for AFT_4I increased slightly in two of the four patients during norethandrolone administration, the mean changing from 0.63 ±0.12 to 0.72 ±0.14 mμg/100 ml. This difference was not statistically significant, however.

No changes in total serum protein, albumin, or globulin concentrations were induced by norethandrolone administration.

DISCUSSION

The present studies were undertaken to determine whether the increase in the T_4-binding activity of TBPA in serum induced by the adrogenic-anabolic steroid, norethandrolone, would be associated with significant changes in the binding and peripheral metabolism of T_4. To exclude effects on T_4 metabolism secondary to the decrease in TBG which this steroid induces, studies were conducted in four patients in whom T_4-binding by TBG in serum was lacking.

The control studies carried out in these patients before norethandrolone administration constitute, to our knowledge, the largest single series of studies of peripheral T_4 metabolism in patients lacking TBG. Hence, the abnormalities found during the control state seem worthy of consideration. In all four patients, serum PBI was markedly decreased, varying between 1.3 and 2.2 μg/100 ml. In all, the PFT_4 was increased. Values for the AFT_4I fell at the lower end of the normal range in all four patients, a finding similar to that reported by Hennemann, Beckers, Docter, Dolman, and De Nayer (19). A pronounced increase in total T_4-clearance rate was also observed, values ranging between 2.5 and five times those expected on the basis of age and weight. As a result of these opposing changes, values for the total daily disposal of hormonal iodine, calculated as the product of PBI and T_4-clearance rate, were within the normal range. These changes, too, are concordant with those previously reported (20–25). However, an examination of the component functions of the T_4-clearance rate, i.e., T_4-distribution space and fractional turnover rate, revealed some differences from the findings in certain of the earlier reports. Particularly noticeable in this respect was the increase in TDS, values of which ranged between 166 and 264% of the expected normal. The proportionate increases in TDS were greater than in fractional turnover rate, values of which ranged from 126 to 179% of the expected normal. In several of the previously reported cases, the increase in TDS seemed less marked, and the increased T_4-clearance rate was largely due to an increased value of fractional turnover rate (20–22). In others, however, the findings more nearly resemble those presently reported, in that both TDS and fractional turnover rate were substantially increased, particularly the former (23–25). The explanation for this seeming variation in the extent of abnormality in TDS in patients lacking T_4 binding by TBG is unknown.

The present studies reveal that when norethandrolone is administered to patients lacking TBG in the serum, several indices of peripheral T_4 transport and metabolism are altered. Provided that these changes cannot be ascribed to an effect of norethandrolone itself, then the data provide strong evidence that alterations in TBPA in vivo, in the absence of concomitant changes in TBG, do influence peripheral T_4 metabolism. Thus, during the increase in TBPA associated with norethandrolone ad-

TABLE II

The Effect of Norethandrolone on the Concentration and Binding of Thyroxine (T_4) in the Serum of Patients Lacking TBG

Patient	PBI		TBG		TBPA		PFT_4		AFT_4I	
	Control	Rx*	Control	Rx	Control	Rx	Control	Rx	Control	Rx
	$\mu g/100$ ml		$\mu gT_4/100$ ml		$\mu gT_4/100$ ml		%		$m\mu gT_4I/100$ ml	
S. F.	1.5	2.1	0	0	183	259	0.031	0.028	0.46	0.60
A. D.	1.3	1.6	0	0	72	205	0.048	0.038	0.62	0.61
J. D.	2.2	2.8	0	0	223	350	0.033	0.027	0.72	0.77
E. D.	2.2	3.1	0	0	254	368	0.032	0.029	0.71	0.90
Mean	1.8	2.4	0	0	183	295	0.036	0.030	0.63	0.72
SD	0.5	0.7			79	77	0.008	0.005	0.12	0.14

*Norethandrolone administered daily for 26 days to patients (S. F. and E. D., 40 mg; J. D., 30 mg; A. D., 20 mg).

ministration, serum PBI increased, although not to normal levels. This was accompanied by a proportionately comparable decrease in TDS, so that the content of the extrathyroidal T_4 pool did not change. A small, but consistent and statistically significant decrease in the PFT_4 occurred, but this change was insufficient to restore values from their initially elevated levels to normal. Since the PBI remained abnormally low and the PFT_4 abnormally high, their product, AFT_4I, was not significantly changed and remained within the normal range. Both fractional rate of turnover of T_4 and absolute rate of daily T_4 disposal were not significantly changed.

The nature of the change in peripheral T_4 metabolism which accompanies the increase in TBPA in these patients is different in many respects from that which characteristically accompanies an increase in TBG (6). In both situations, T_4-clearance rate decreases, while serum PBI increases, with the result that total daily disposal of T_4 remains unchanged. However, in the case of increased TBPA, the decrease in T_4-clearance rate is mainly the result of a decrease in TDS, while in the case of an increase in TBG, the decrease in the T_4-clearance rate is mainly the result of a decrease in fractional T_4-turnover rate. In both cases, the proportion of free T_4 decreases, but more so when TBG is increased. The latter difference could be ascribed to the fact that in most situations in which the T_4-binding capacity of TBG is increased, the proportionate increase is greater than that seen in the case of the T_4-binding capacity of TBPA in the present studies. On the other hand, the difference is also consistent with several studies which indicate that TBG has a more profound influence on the binding of T_4 in serum than does TBPA (1, 2, 7). Moreover, since the importance of T_4 transport by TBPA is greatly increased in the absence of TBG, it seems likely that the changes in T_4 metabolism associated with increased TBPA in the present studies would be of lesser magnitude in patients with normal quantities of TBG.

No explanation is apparent for the seemingly differing effects on T_4 metabolism of increases in T_4 binding by TBG and TBPA. The differences are difficult to reconcile within the traditional free thyroxine concept and suggest a more complex role for the transport proteins in the regulation of peripheral hormone metabolism. It could be postulated that TBG restricts the entry of T_4 to a relatively small tissue compartment wherein metabolism of T_4 is rapid. Thus, an increase in TBG would have little effect on TDS, but would have a large effect upon the fractional rate of T_4 turnover. TBPA, in contrast, might restrict the entry of T_4 into a large pool with a slow turnover, hence the reduction principally in TDS when TBPA is increased. These postulated roles for TBG and TBPA, however, do not seem consistent with the large increase in TDS found in the present patients lacking TBG. Schussler has postulated that the free T_4 concentration at the cellular-extracellular interphase, and not in the plasma, is a major determinant of T_4 distribution and disposal and that this, in turn, is greatly influenced by the permeability of individual capillary beds (26). Thus, the differing effects of increases in TBG and TBPA may depend upon their different abilities to penetrate individual capillary membranes. It is apparent, however, that in the present state of knowledge, such considerations are entirely speculative.

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