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Cortisone-provoked Depression of Plasma Tyrosine Concentration: Relation to Enzyme Induction in Man*

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Within 5 hours after administration of corticosteroids to experimental animals, the activity of hepatic tyrosine- α -ketoglutarate transaminase is increased five- to tenfold (1-8). This enzyme catalyzes the initial step in tyrosine degradation and is one of several mammalian enzymes the activity of which is rapidly and substantially elevated by corticosteroids (9). Adrenal steroids also depress the concentration of tyrosine in plasma (10-11). The reduced level of tyrosine in plasma has been attributed to the increased hepatic activity of tyrosine transaminase, i.e., an increased rate of degradation of tyrosine by the enzyme would be expected to diminish the plasma concentrations of the amino acid (10).

The thyroid status of the animal has been recently shown to modify the typical corticosteroid-induced elevations of hepatic tyrosine transaminase activity. Massive amounts of hydrocortisone are required to elevate enzyme activity in thyroxine-treated rats, whereas in hypothyroid rats, even a small dose of hydrocortisone elevates enzyme activity maximally (12). Thyroxine, in further contrast to adrenal corticosteroids, produces elevations of the plasma level of tyrosine, and thyroidectomy decreases the concentration of tyrosine in plasma (13, 14).

Despite extensive investigations of the alterations in the activity of tyrosine transaminase in experimental animals, only limited attention has

been paid to the possible existence of steroid-inducible enzymes in man. It is known from analyses of specimens of human liver that the pathway of tyrosine oxidation proceeds by the same sequence of reactions as in animal liver, and that the human tyrosine- α -ketoglutarate transaminase has properties similar to those of the animal enzyme (15, 16). It seemed likely, therefore, that the responses of the human transaminase to hormonal stimulation would also be similar to those described in animal liver.

The finding in patients with thyrotoxicosis, as well as in thyroxine-treated animals, of increased concentrations of tyrosine in plasma (17-19) suggested a means of investigating the inducibility of the tyrosine transaminase system in man. Experiments were conducted to determine whether cortisone administration depresses the concentration of tyrosine in plasma of normal adult subjects, and secondly, whether cortisone has greater or lesser effects in patients with abnormal thyroid function. If enzyme induction were being modified by thyroid hormone, then subjects with hyperthyroidism and myxedema should differ from euthyroid subjects in their responses to cortisone. Measurements were therefore made of tyrosine concentrations in plasma of hyperthyroid, euthyroid, and hypothyroid subjects after an overnight fast and 3 hours after ingestion of a standard quantity of tyrosine.

Methods

Patient selection. The subjects investigated were fifteen hyperthyroid, fourteen euthyroid, and four hypothyroid subjects, all of whom were inpatients at Johns Hopkins Hospital. Clinical information is summarized in Table I. The diagnosis of hyperthyroidism and myxedema was based upon unequivocal clinical and laboratory evidence. In hyperthyroid subjects, protein-bound iodine levels in serum ranged from 11.3 to 20.0 μ g per 100 ml serum, and 24-hour uptakes of radioactive iodine

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TABLE I
Clinical summary of patients studied*

Patient	Age Race Sex	PBI	RAI uptake at 2 and 24 hours	Fasting plasma tyrosine concen- tration		Plasma tyrosine concentration 3 hours after tyrosine load	
				Before cortisone	After cortisone (1 day)	Before cortisone	After cortisone (1 day)
		$\mu\text{g}/100\text{ ml}$	%	$\mu\text{g}/\text{ml}$		$\mu\text{g}/\text{ml}$	
Hyperthyroid							
(1) L.T.	45 NF	13.3	86/90	31.4	35.7		
(2) C.W.	46 NF	14.0	58/81	28.1	16.8	46	55
(3) G.W.	27 NF	12.0	32/71	24.4	24.9	41	44
(4) M.E.	44 NF	16.2	41/67	23.8	19.6		
(5) G.C.	34 NF	18.0	52/61	21.8	18.6	113	72
(6) E.P.	36 NM	17.0		21.6	18.9		
(7) C.S.	38 NF	20.0	80/64	19.4	25.1	42	49
(8) R.B.	40 NM	13.3	58/74	19.0	24.7	64	93
(9) T.B.†	62 NM	7.0		18.8	17.3	36	49
(10) M.C.	51 NF	15.5	80/86	18.5	18.6	112	65
(11) F.B.	36 NF	15.6	69/76	16.7	15.0		
(12) F.D.	23 NF	14.6		16.3	13.2	56	89
(13) O.M.	47 NF	11.3		15.2	18.2		
(14) N.C.	35 NF	18.3	70/77	14.5	15.0	36	31
(15) C.P.	41 NF	11.3		9.3	14.6		
Hypothyroid							
(1) R.J.	68 NF	2.9	10/10	12.4	9.7		
(2) G.C.	35 NF	2.3	4/9	12.7	13.2	28	22
(3) A.H.	45 CF	2.6	2/2	13.5	11.5	43	37
(4) M.U.	59 CF	1.2	3/4	8.3	7.7	23	16
Clinical diagnosis							
Euthyroid							
(1) L.M.	57 CM						
			Obesity; mild bronchitis; chronic gouty arthritis	18.5	16.2	23	28
(2) A.S.	35 NF		Anxiety	16.8	9.8	51	32
(3) N.B.	27 NF		Obesity, mild hypertension	15.7	15.5	25	16
(4) A.H.	45 CF		Hypothyroid, treated	15.3	14.0	29	20
(5) L.L.	23 NM		Erythema nodosum	14.8	12.6	34	34
(6) W.C.	59 NM		Hypertension; mild congestive heart failure	14.6	12.9		
(7) M.C.	51 NF		Hyperthyroid, treated	13.8	13.9		
(8) O.W.	62 NF		Iron-deficient anemia; ASCVD; old stroke	13.6	7.9		
(9) G.P.	42 NM		Mild hypertension	12.8	9.5		
(10) S.W.	29 NM		Mild chronic bronchitis	12.6	11.8	36	29
(11) M.M.	30 NF		Diarrhea, treated	12.1	11.4	43	31
(12) C.P.	55 NF		Esophagitis	11.4	11.4		
(13) G.P.	45 NM		Thrombophlebitis	11.2	10.4		
(14) A.C.	55 NM		Mucous colitis, in remission	9.7	11.3	37	31

* PBI = protein-bound iodine; RAI = radioactive iodine. N = negro; C = Caucasian. ASCVD = arteriosclerotic cardiovascular disease.

† Normal subject treated with triiodothyronine 300 μg per day for 10 days.

by the thyroid gland from 61 to 90% of the administered dose, as shown in Table I. Additional laboratory confirmation of hyperthyroidism was provided by elevations in the measurements of basal metabolic rate (range = +35% to +95%), and of I^{131} -triiodothyronine uptake by red blood cells (24% to 40%), with depressions of the serum cholesterol concentration (90 to 170 mg per 100 ml serum). One normal subject was included in the group of patients with thyrotoxicosis after he had been receiving 300 μg per day of triiodothyronine in divided doses for 10 days. At that time there was elevation of the basal metabolic rate to +50% and depression of the

serum cholesterol concentration to 135 mg per 100 ml plasma, in association with marked tachycardia, sweating, nervousness, and weight loss.

In hypothyroid subjects, as shown in Table I, protein-bound iodine levels in serum ranged from 1.2 to 2.9 μg per 100 ml serum, and 24-hour uptakes of radioactive iodine by the thyroid gland were from 2 to 10% of the administered dose. The return phase of reflexes was uniformly delayed; assays of thyroxine iodine in serum by column exchange techniques¹ were below normal in

¹ Bio-Science Laboratories, Los Angeles, Calif.

all patients, and there were low measurements of basal metabolic rate (-24% to -34%).

Fourteen control subjects were selected from the general hospital population; the average age of the controls was 39.0 years, as compared to the average age of hyperthyroid subjects of 40.3 years. Each of the control subjects was convalescent from a mild illness and was studied shortly before discharge. All were unequivocally euthyroid on clinical examination by several observers, and the majority had one or more confirmatory tests of thyroid function performed. One previously hyperthyroid and one previously hypothyroid patient, both of whom had been studied earlier, were included in the control group after they had been rendered euthyroid by appropriate therapy. Clinical diagnoses are shown in Table I.

All subjects were fully ambulatory and were receiving a standard hospital diet at the time of the investigation.

Procedures. Effects of cortisone administration upon the concentrations of tyrosine in plasma were determined 1) after an overnight fast and 2) 3 hours after ingestion of known amounts of tyrosine. Two types of studies were performed.

In the first study, samples of heparinized plasma were obtained from all subjects at 9 a.m., after an overnight fast. The blood samples were centrifuged at $2,000 \times g$ for 15 minutes, and the plasma was separated and recovered. Samples of the plasma from fasting subjects were then frozen promptly and remained at -15°C until the time of assay. Base-line levels of tyrosine in fasting subjects were generally determined on samples of plasma obtained on two or three successive mornings.

Each patient then received intramuscular injections of cortisone acetate, U.S.P., 50 mg, at 1 p.m., 5 p.m., and 9 p.m., and the following morning at 1 a.m., 5 a.m., and 9 a.m. A single specimen of plasma from each fasting subject was obtained immediately after the last injection and was labeled "cortisone 1 day."

Six hyperthyroid, five euthyroid, and four hypothyroid subjects continued to receive a total of 300 mg cortisone acetate during a second 24-hour period. Injections of cortisone acetate, 100 mg, were given at 1 p.m. and 11 p.m. and at 7 a.m. on the following morning. Specimens from fasting subjects were again obtained at 9 a.m. and were labeled "cortisone 2 days." A schedule of frequent injections of cortisone during a 48-hour period was employed because investigations of the tyrosine- α -ketoglutarate transaminase system in rat liver have previously shown that the enzyme has a very rapid turnover (20), and that a continuous supply of corticosteroid is required to maintain enzyme activity in the fully induced state (21).

In the second study, samples of heparinized plasma were obtained after an overnight fast in eight of the euthyroid, nine of the hyperthyroid, and three of the hypothyroid subjects. Each subject then received an oral load of L-tyrosine,² 50 mg per kg body weight, suspended in orange juice. Samples of heparinized plasma were ob-

tained exactly 3 hours after ingestion of tyrosine. Cortisone was then administered for a 1-day period, as described above. Identical oral loads of tyrosine were fed on the following morning, and samples of heparinized plasma were obtained 3 hours later.

Chemical methods. Tyrosine was assayed in duplicate by a fluorometric method (22). Under conditions of the assay, recoveries of added tyrosine from fasting plasma samples were 87 to 100%. Samples from plasma obtained 3 hours after ingestion of tyrosine were diluted 1:5 with water before readings were performed, because of quenching of fluorescence at high concentrations of tyrosine. All results were expressed as micrograms per milliliter plasma.

Results

Results of measurements of tyrosine levels in fasting hyperthyroid and euthyroid subjects after 0, 1, and 2 days of cortisone administration are shown in Figure 1 and Table I. Concentrations of tyrosine in hyperthyroid fasting subjects averaged $19.9 \pm 1.4 \mu\text{g}$ per ml (standard error of the mean) and were significantly greater ($p < 0.001$) than were the levels of $13.8 \pm 0.6 \mu\text{g}$ per ml measured in euthyroid subjects. There was no significant correlation in individual hyperthyroid subjects between the plasma tyrosine levels and any of the measurements of thyroid function. Levels in the four hypothyroid fasting subjects averaged $11.7 \pm 1.1 \mu\text{g}$ per ml. The concentrations of tyrosine in plasma of all three groups of subjects were similar to those reported previously (19).

After 1 day of administration of cortisone, at which time each subject had received a total of 300 mg cortisone acetate in divided doses, plasma levels of tyrosine in euthyroid subjects were decreased in eleven of fourteen subjects compared to levels before treatment with cortisone. There was an average decrease in all subjects of $1.9 \pm 0.7 \mu\text{g}$ per ml, with p value using paired data < 0.02 . After 2 days of injection of cortisone, decreases in the concentrations of tyrosine in plasma of fasting subjects were observed in all six euthyroid subjects studied; the average decrease from base-line levels was $3.9 \pm 0.8 \mu\text{g}$ per ml (p value < 0.01).

In the four hypothyroid subjects, tyrosine concentrations in plasma from fasting subjects decreased an average of $1.3 \mu\text{g}$ per ml after 1 day of cortisone treatment. After 2 days of treatment, mean concentrations had decreased an average of $3.0 \mu\text{g}$ per ml (not shown in Table I).

In hyperthyroid subjects, by contrast, no con-

² California Corp. for Biochemical Research, Los Angeles, Calif.

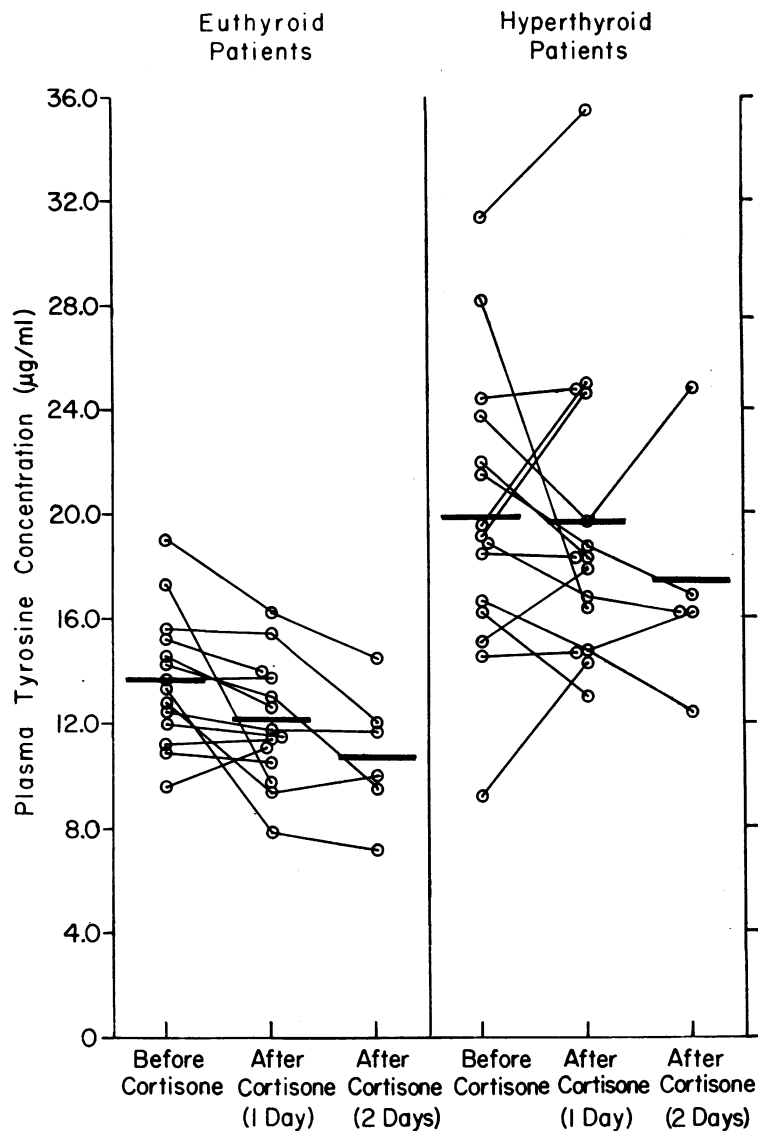


FIG. 1. CONCENTRATIONS OF TYROSINE IN PLASMA OF FASTING EUTHYROID AND HYPERTHYROID SUBJECTS, BEFORE AND AFTER ADMINISTRATION OF CORTISONE. Each subject received 300 mg per day of cortisone acetate in divided doses by intramuscular injection for 1 or 2 days. Samples of heparinized plasma were obtained at 9 a.m. after an overnight fast and were assayed for tyrosine concentration. The short horizontal lines refer to the mean of each group. Corresponding patients are listed consecutively in Table I beginning with the one whose plasma concentration of tyrosine was highest.

sistent decreases in tyrosine levels occurred after cortisone administration. The levels of tyrosine in plasma of fasting subjects were decreased in only seven of the fifteen hyperthyroid subjects after 1 day of cortisone administration and were actually increased in four subjects. The mean levels recorded after cortisone ($19.7 \pm 1.5 \mu\text{g}$ per ml) did

not differ from the base-line levels recorded before cortisone treatment ($19.9 \pm 1.4 \mu\text{g}$ per ml). After 2 days of cortisone administration, decreases in plasma levels of tyrosine were noted in only three of five hyperthyroid subjects, as shown in Figure 1. These differences were not statistically significant ($p > 0.1$).

Results of the second study are shown in Figure 2 and Table I. Three hours after ingestion of tyrosine, plasma levels of tyrosine in thyrotoxic subjects were consistently elevated compared to levels in euthyroid subjects, as previously reported (18). When 300 mg cortisone acetate in divided

doses had been administered during a 24-hour period to euthyroid subjects, plasma levels of tyrosine 3 hours after an oral load were decreased in six of the eight individuals compared to corresponding levels in plasma before administration of cortisone. In one subject there was no change

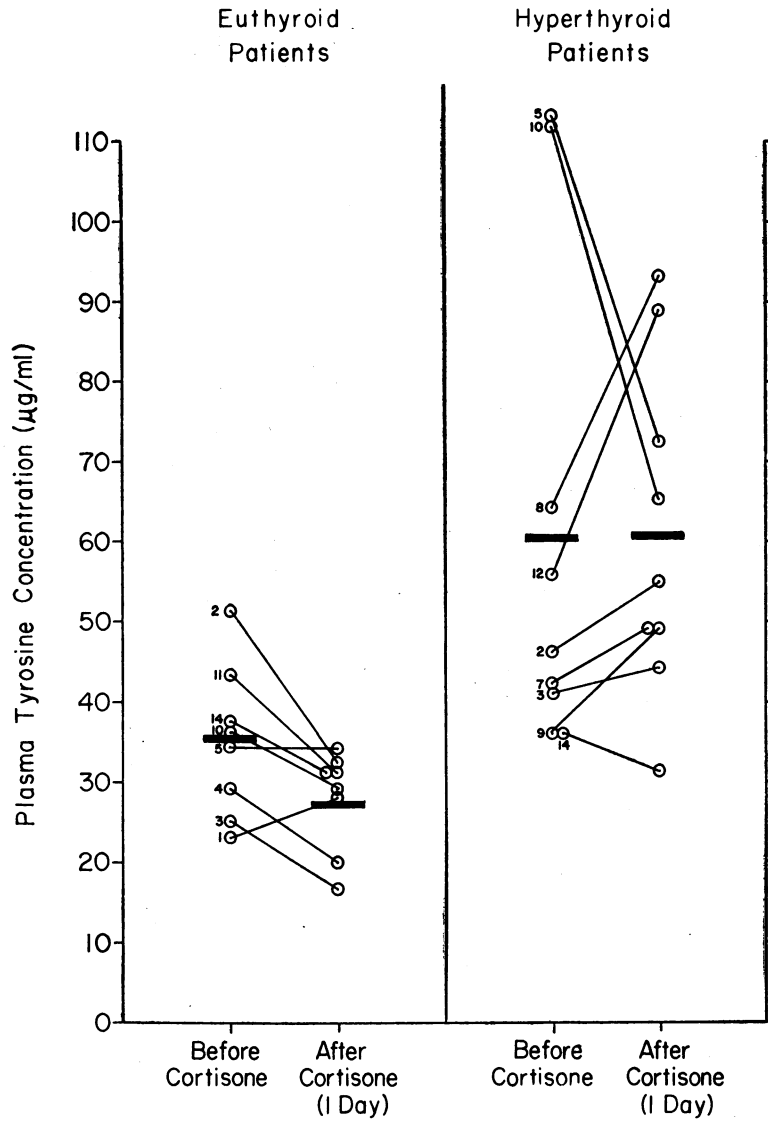


FIG. 2. CONCENTRATIONS OF TYROSINE IN PLASMA AFTER INGESTION OF AN ORAL LOAD OF TYROSINE IN EUTHYROID AND HYPERTHYROID SUBJECTS, BEFORE AND AFTER ADMINISTRATION OF CORTISONE. Each subject received an oral load of tyrosine (50 mg per kg body weight) at 9 a.m., and plasma was obtained exactly 3 hours later. A repeat load of tyrosine was given after administration of cortisone acetate, 300 mg in divided doses, during a 24-hour period. The short horizontal lines refer to the mean of each group. The numbers written to the left of the individual points refer to the patients listed in Table I.

in the plasma levels, and in another subject a slight increase in the plasma concentration of tyrosine. An average decrease of $7.1 \pm 2.6 \mu\text{g}$ per ml was recorded for all subjects ($p < 0.025$).

In all three hypothyroid subjects, cortisone resulted in an appreciable decrease in plasma levels of tyrosine 3 hours after an oral load, as shown in Table I.

In hyperthyroid subjects, by contrast, plasma levels of tyrosine 3 hours after an oral load of the amino acid were decreased in only three of the nine subjects after administration of 300 mg cortisone. In the remaining six subjects, levels were increased compared to values measured before cortisone. The average plasma concentrations of tyrosine before and after cortisone administration to the hyperthyroid subjects were nearly identical, i.e., $60.7 \pm 10.3 \mu\text{g}$ per ml and $60.8 \pm 6.9 \mu\text{g}$ per ml, respectively.

Discussion

The present experiments demonstrate that cortisone administration reduces the concentration of tyrosine in plasma of euthyroid and hypothyroid subjects within 24 hours of its administration. A further decrease in tyrosine concentration is observed when cortisone is given for a 2-day period. In thyrotoxic subjects, by contrast, no consistent changes in the concentrations of tyrosine in plasma after an overnight fast are noted after either 1 or 2 days of cortisone.

Similar results are obtained when oral loads of tyrosine are fed before and after the subjects have received cortisone. In euthyroid subjects receiving cortisone, levels of tyrosine in plasma 3 hours after an oral load of tyrosine are lower than are levels in these same subjects before cortisone has been given. In thyrotoxic subjects, no consistent decreases in plasma levels can be demonstrated after administration of cortisone.

These results are similar to what one would predict if there were a steroid-inducible tyrosine- α -ketoglutarate transaminase in human liver similar to the enzyme in rat liver in its dependence upon thyroid function. Previous studies have shown that to increase tyrosine transaminase activity, larger doses of corticosteroids are required for hyperthyroid than for euthyroid rats, and for euthyroid than for hypothyroid rats. This dif-

ference in response to corticosteroids has been attributed at least in part to differences in the rate of steroid inactivation (12). Thyroxine enhances the rate of steroid degradation (12, 23-25). It has been postulated that small doses of adrenal steroids are degraded too rapidly by livers of thyrotoxic rats to be effective as stimuli of enzyme synthesis. Only when massive doses of steroids are employed is the capacity of the degradative system exceeded, and enough active steroid accumulates to be effective as an enzyme inducer (12). Similarly, in hypothyroidism, the rate of steroid inactivation is reduced, and even a small amount of administered steroid can be effective in increasing enzyme activity.

It is apparent that adrenal cortical hormones and thyroid hormones have different effects upon tyrosine metabolism, as illustrated diagrammatically in Figure 3. Experiments using α -aminoisobutyric acid and 1-aminocyclopentane-carboxylic acid have shown that cortisone accelerates the uptake of these nonmetabolizable amino acids by the liver (26-29). Therefore, steroids probably act to augment the accumulation of neutral amino acids by the liver. Indeed, one of the earliest effects of cortisone and triamcinolone is to increase the total level of amino acids in liver (30). Increased uptake of tyrosine may facilitate its removal by the hepatic tyrosine transaminase system. After steroid administration, the level of tyrosine in plasma decreases, as shown above. This decrease may be related to the substantial increase in the activity of tyrosine transaminase that also occurs (10). The increase in enzyme activity may produce a transient depletion of tyrosine in liver; after administration of corticosteroids to fasted, adrenalectomized rats, the level of tyrosine in liver was observed by two groups of workers to decrease (10, 31).

Different events occur after thyroxine administration. There is an increase in the activity of tyrosine transaminase in liver of 40%, which is small when compared to the five- to tenfold change produced by corticosteroids (12, 14, 32). Experiments with radioactive tyrosine have shown that thyroxine produces a decrease of approximately one-third in the apparent volume of distribution of tyrosine (33), by mechanisms that have not yet been elucidated. The plasma level of tyrosine increases after thyroxine administration, probably

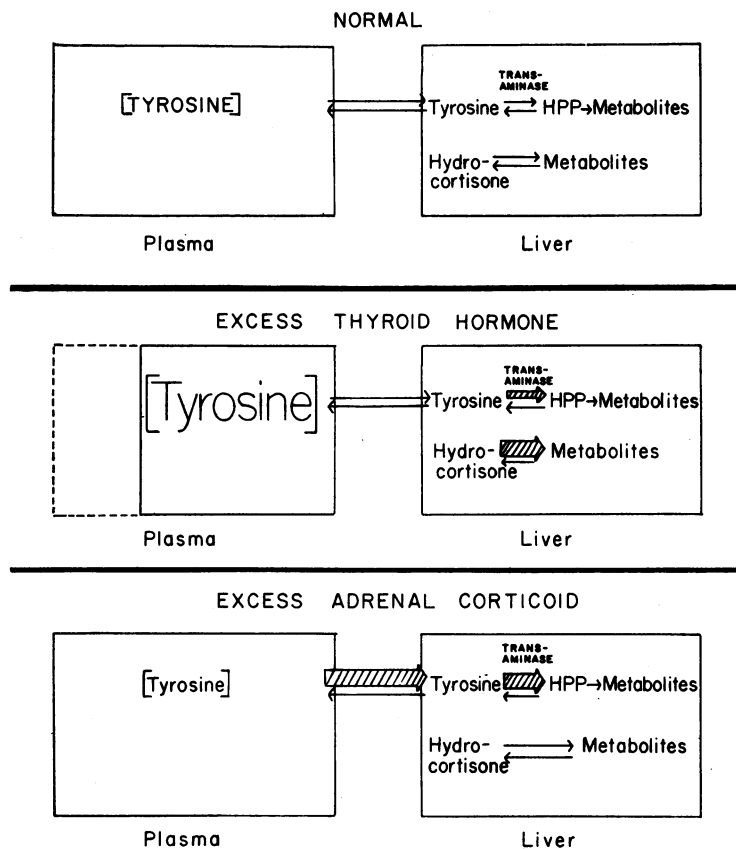


FIG. 3. DIAGRAMMATIC REPRESENTATION OF THE EFFECTS OF THYROID AND ADRENAL CORTICAL HORMONES UPON THE PLASMA CONCENTRATION OF TYROSINE AND THE HEPATIC ACTIVITY OF TYROSINE- α -KETOGLUTARATE TRANSAMINASE. The elevated concentration of tyrosine in plasma after administration of thyroid hormone is symbolized by large letters in brackets in the plasma compartment, and the reduced concentration after cortisone administration by small letters. The reduction in the apparent volume of distribution of tyrosine with excess thyroid hormone is shown by the dotted lines in the central portion of the figure. Thickened, hatched arrows refer either to increased hepatic enzyme activity or to accelerated uptake of amino acid into liver from plasma. HPP = *p*-hydroxyphenylpyruvate.

in part as a consequence of this change in distribution. An additional factor may be the hepatic activity of *p*-hydroxyphenylpyruvate oxidase, which has been reported to decrease after administration of thyroid to animals (34). Because the degradation of hydrocortisone is greatly accelerated by thyroxine (23-25), a given dose of adrenal corticosteroid may be relatively less effective as an enzyme inducer in livers of hyperthyroid than euthyroid rats.

The present report provides evidence that is compatible with the functioning of a steroid-inducible enzyme in euthyroid individuals and with

altered induction in hyperthyroid individuals. Data in the present report are consistent with those of Menkes and Avery (35), who showed that cortisone in larger doses than used here produces marked decreases in the greatly elevated plasma levels of tyrosine in premature infants. Using microbiological techniques, Borden and colleagues (36) were unable to demonstrate any effect of ACTH administration upon the serum levels of tyrosine, although the 24-hour urinary excretion was increased. ACTH and cortisone have been reported to reduce the tyrosyluria of premature infants (37, 38), but the mechanism producing ty-

rosyluria may comprise changes in more than one enzyme (39).

We suggest that corticosteroids may influence amino acid metabolism in man in a manner similar to that described abundantly in experimental animals.

Summary

The administration of cortisone to euthyroid and hypothyroid adult subjects in divided doses for 1 and 2 days produced consistent decreases in the concentration of tyrosine in plasma of subjects after an overnight fast. Cortisone also decreased the plasma levels of tyrosine 3 hours after an oral load of tyrosine, compared to results obtained after oral loading before cortisone.

In hyperthyroid subjects, by contrast, cortisone produced no consistent changes in either the levels of tyrosine in fasting subjects or the levels in plasma 3 hours after an oral load.

The results are consistent with the hypothesis that cortisone depresses the concentration of tyrosine in plasma by increasing the activity of hepatic tyrosine transaminase. This process of enzyme induction appears to be modified in hyperthyroid subjects in a manner entirely analogous to that described in experimental animals.

Thyroid and adrenal cortical hormones differ in their effects upon the metabolism of tyrosine, and the postulated mechanisms have been discussed.

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