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Effect of physical training on the metabolism of thyroid hormones in man

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BALSAM, ALAN, AND LYNN E. LEPPO. *Effect of physical training on the metabolism of thyroid hormones in man.* J. Appl. Physiol. 38(2): 212–215. 1975.—The effect of a 6-wk program of physical training (track running) on the peripheral metabolism of thyroxine (T_4) and triiodothyronine (T_3) was evaluated in a group of 11 men. Measurements were made of hormone turnover, urinary and fecal clearances, plasma hormone concentrations, and hormone binding by plasma proteins in all subjects before and after training. After training, metabolic clearance of T_3 was increased 8.5% above the pretraining level due to an increased deiodinative clearance of this hormone. No significant change was observed in plasma T_3 concentration. The absolute degradation of T_3 increased 10.3% after training. In contrast, no significant change in the metabolic clearance of T_4 was detected. Significantly decreased plasma concentration of total T_4 after 4 and 6 wk of training was apparently not due to decreased hormone binding by plasma protein since no significant alteration in the dialyzable fraction of T_4 was detected. The absolute degradation rate of T_4 was decreased 8.8% after training. Possible implications of the observed differential impact of training on the degradation of T_4 and T_3 regarding thyroid hormone economy are discussed.

L-thyroxine; L-triiodothyronine; iodothyronine turnover

ENHANCED METABOLISM of thyroid hormones has been noted previously in association with intensive physical training in a number of species (1, 5, 6). Irvine observed increased degradation of thyroxine (T_4) in horses after a 3-mo program of physical training (5). He extended this observation to man, demonstrating increased absolute turnover of T_4 in track athletes in training (6). We have reported increased metabolism of T_4 and triiodothyronine (T_3) in the rat after rigorous training by treadmill running for 12 wk (1). On the other hand, the effect of mild training and brief periods of muscular exercise on the degradation of thyroid hormones is less certain. Lashoff and co-workers observed no change in the disappearance rate of radiothyroxine in a group of subjects who had walked 14 miles in 4–4.5 h (7). Irvine noted an increased fractional degradation rate of T_4 in nonathletic individuals after 6 days of daily bouts of muscular exercise by track running (6). De Nayer et al. (3) found a decreased serum concentration of free T_4 after a brief bout of strenuous exercise, whereas Terjung and Tipton (13) observed an increase in free T_4 after submaximal exercise in man.

This study was undertaken to evaluate the metabolism of iodothyronines in a group of young men (nonathletes) before and after a 6-wk program of track running. Assessment of hormonal metabolism included measurement of *a*) absolute degradation rates of T_3 and T_4 based in the plasma disappearance kinetics of injected tracer hormones, *b*) urinary and fecal hormonal disposition, and *c*) hormone binding by plasma proteins.

METHODS AND MATERIALS

Eleven male volunteers between the ages of 18 and 25 yr participated in a study designed to evaluate the effect of physical training on metabolism of thyroid hormones. Hormonal metabolism was quantified before and after a 6-wk training program. The training regimen consisted of daily morning and afternoon timed sprints on a level 3-mile outdoor course. Subjects ran between 4 and 6 miles in the two daily sessions. The mean ± SD sprinting rate of the groups was 7.57 ± 0.946 mph (range 6.10–9.10 mph). Hormone turnover was assessed with the use of L-[^{131}I]triiodothyronine and L-[^{125}I]thyroxine purchased from Abbott Laboratories, N. Chicago, Ill. The labeled hormones were diluted in 1% human serum albumin, dialyzed separately in isotonic saline, sterilized by millipore filtration, and stored at −20°C until used. Turnover of the thyroid hormones was measured before and after training as follows. A dose containing 65 μCi [^{131}I]T_3 and 32 μCi [^{125}I]T_4 was injected intravenously, and heparinized blood samples were obtained at 10 min and 2, 5, 10, and 24 h, twice daily during the following 5 days, and daily thereafter for 8 days. During the posttraining study blood specimens were obtained before exercise to avoid transient contraction in plasma volume associated with acute bouts of exercise. To avoid the possibility of detraining, subjects continued exercising during the second turnover study. Thyroidal utilization of radioiodine released during metabolism of the hormones was precluded by ingestion of Lugol's iodine, 5 drops daily. Plasma concentrations of tracer iodothyronines were measured as the difference between trichloroacetic acid-precipitable and ethanol-nonextractable radioactivity (9). Plasma samples were counted with a dilution of the injected dose in a dual-channel gamma spectrometer, and appropriate correction was made for the appearance of ^{131}I counts in the ^{125}I window setting.

Metabolic clearance rate (MCR) of T_4 was determined from the plasma disappearance of [^{125}I]T_4, with the use of

TABLE 1. *Effect of physical training on the metabolism of thyroxine*

Subj	Age, yr	Wt, kg		k/day		V_t, liters		MCR, liters/day		UC, liter/day		FC, liter/day		PT_4, μg/100 ml		TD_4, μg/day	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
15	18	66	69	0.105	0.110	10.5	9.66	1.10	1.06	0.942	0.850	0.157	0.208	6.12	5.66	67.32	60.0
16	19	71	76	0.106	0.115	10.2	9.07	1.08	1.05	0.797	0.863	0.283	0.183	6.27	4.90	67.76	51.45
17	24	74	76	0.128	0.130	12.7	13.6	1.63	1.77	1.24	1.40	0.386	0.369	5.66	5.05	92.26	89.39
18	26	78	76	0.114	0.117	12.0	12.0	1.36	1.41	1.09	1.17	0.271	0.239	5.81	5.36	79.02	75.58
19	18	63	63	0.104	0.108	10.7	10.5	1.11	1.13	0.945	0.929	0.161	0.204	6.43	6.58	71.37	74.35
20	18	71	74	0.097	0.103	10.6	10.2	1.03	1.05	0.837	0.965	0.197	0.086	5.51	4.44	56.75	46.62
21	20	60	54	0.106	0.115	11.2	10.9	1.18	1.26	1.03	1.04	0.154	0.213	5.97	4.59	70.45	57.83
22	19	69	71	0.093	0.094	10.1	11.0	0.934	1.03	0.736	0.883	0.198	0.149	7.19	6.27	74.06	64.58
23	23	58	61	0.102	0.093	9.83	10.7	1.00	0.998	0.795	0.832	0.208	0.166	6.58	6.12	65.80	61.08
24	20	66	68	0.114	0.102	9.06	9.69	1.03	0.984	0.804	0.813	0.228	0.171	8.11	7.04	83.53	69.27
25	20	64	63	0.090	0.103	9.37	9.59	0.845	0.986	0.685	0.858	0.160	0.128	6.73	6.73	56.87	66.36
Mean		67.3	69.2	0.105	0.108	10.6	10.6	1.12	1.16	0.900	0.964	0.219	0.192	6.40	5.70	71.38	65.14
± SD		6.02	5.81	0.011	0.011	1.08	1.28	0.215	0.242	0.167	0.179	0.071	0.073	0.752	0.902	10.65	11.95
P		<0.02		NS		NS		NS		<0.05		NS		<0.001		<0.05	

Plasma disappearance kinetics and degradation rate of thyroxine measured before (pre) and after 6 wk of physical training (post). Abbreviations: k, plasma fractional disappearance rate; V_t, distribution space; MCR, metabolic clearance rate; UC, urinary clearance rate; FC, fecal clearance rate; PT_4, plasma thyroxine concentration; TD_4, thyroxine degradation rate. Statistical comparison by Student *t*-test for paired observations.

two different kinetic models. In the standard single-compartment analysis, the MCR is taken as the product of the plasma fractional removal rate and the volume of distribution. The MCR of T_4 was also determined by the method of Tait (12) as the quotient of the total injected dose and the area subtended by the plasma disappearance curve. The definite integral $\int_0^t p\,dt$, where p denotes the plasma concentration of radioactive hormone and t is elapsed hours, was approximated by using a two-compartment model.[1] Since the difference in the values of the MCR of T_4 calculated by these techniques was slight (2%), the single-compartment data analysis of T_4 before and after training is presented. The MCR of T_3 was determined by the single-compartment method and an integral technique. The area beneath the plasma disappearance curve of T_3 was approximated by a two-compartment model with an asymptote,[2] since this model gave a statistically better fit to the observed T_3 data than a two-compartment model without an asymptote[1] ($P < .001$). As previously demonstrated by Surks et al. (11), the MCR of T_3 calculated from the single-compartment model exceeds the value obtained by an integral method. In the present study, the magnitude of overestimation by single compartment calculations was approximately 51%. Comparative pre- and posttraining MCR data of T_3 presented were calculated using the two-compartment model with the asymptote.

Plasma concentration of total T_4 was determined by column chromatography at BioScience Laboratories, Van Nuys, Calif. Plasma concentration of T_3 was measured by radioimmunoassay.[3] Total plasma thyroxine concentrations were measured in duplicate before training and after 4 and 6 wk of training. Duplicate plasma T_3 measurements were performed on specimens obtained before and after 6 wk of exercise. Daily degradation rates of the iodothyronines were calculated as the product of the MCR and the plasma concentration of the hormones. Plasma binding of T_4 was assessed by equilibrium dialysis (10). Complete urinary and fecal collections were obtained daily during the turnover studies. Urinary and fecal clearances were computed as the product of the MCR and the fraction of excreted radioactivity in urine and feces respectively. Stastical analyses were performed by the Student *t*-test for paired observations and analysis of variance (Table 2).

[1] Area $= \int_0^t (\alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t})\,dt$.

[2] Area $= \int_0^t (\alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t} + \alpha_3)\,dt$.

[3] Measured by Drs. M. I. Surks and J. H. Oppenheimer.

RESULTS

Metabolism of T_4 (Table 1). With use of the standard single compartment model to analyze the plasma disappearance of [^{125}I]T_4, the parameters of T_4 turnover, distribution and metabolism were calculated before training (mean ± SD): fractional turnover, 0.105 ± 0.011 per day; volume of distribution, 10.6 ± 1.08 liters; metabolic clearance rate, 1.12 ± 0.22 liters/day; urinary clearance, 0.90 ± 0.17 liters/day; fecal clearance, 0.22 ± 0.07 liters/day; and absolute degradation rate 71.4 ± 10.7 μg/day. These data substantially agree with values published in the literature for euthyroid man (8). After training, no significant changes were detected in the plasma fractional turnover rate or distribution space of T_4. Metabolic clearance of T_4 was not increased significantly. Cumulative total recovery of injected ^{125}I-T_4 (mean ± SD (% dose)) in urine and feces during the 14-day turnover studies: pretraining, 74.3 ± 4.90; posttraining, 71.0 ± 3.95 ($P < .05$). A 7.1% increase in the urinary clearance of T_4 was detected after training. Fecal clearance was not altered as a result of training. Plasma concentration of total T_4 was diminished during training, but no significant change in free T_4 concentration was demonstrated (Table 2). The T_4 degradation rate was diminished 8.7% after training due to a similar diminution in the concentration of T_4 in plasma.

Metabolism of T_3 (Table 3). A two-compartment model was used to analyze the plasma disappearance of T_3. Baseline values for T_3 kinetic parameters (mean ± SD) were:

TABLE 2. *Effect of physical training on plasma concentrations and plasma protein binding of thyroxine*

Subj	Pretraining			Training					
				4 Weeks			6 Weeks		
	T_4, μg/100 ml	DF	FT_4, ng/100 ml	T_4, μg/100 ml	DF	FT_4, ng/100 ml	T_4, μg/100 ml	DF	FT_4, ng/100 ml
15	6.12	0.0678	2.766	5.74	0.0774	2.962	5.66	0.0703	2.653
16	6.27	0.0517	2.161	4.90	0.0695	2.270	4.90	0.0730	2.385
17	5.66	0.0777	2.932	4.90	0.0652	2.130	5.05	0.0768	2.2586
18	5.81	0.0688	2.665	5.28	0.0749	2.636	5.36	0.0543	1.940
19	6.43	0.0583	2.499	6.35	0.0747	3.162	6.58	0.0790	3.465
20	5.51	0.0628	2.307	5.28	0.0581	2.045	4.44	0.0670	1.983
21	5.97	0.0715	2.846	5.36	0.0620	2.215	4.59	0.0766	2.344
22	7.19	0.0559	2.679	6.81	0.0587	2.665	6.27	0.0562	2.349
23	6.58	0.0666	2.922	7.11	0.0608	2.992	6.12	0.0534	2.179
24	8.11	0.0505	2.730	7.42	0.0463	2.290	7.04	0.0645	3.027
25	6.73	0.0556	2.495	6.58	0.0592	2.597	6.73	0.0511	2.293
Mean	6.398	0.0625	2.6365	5.975	0.0643	2.5422	5.704	0.0657	2.4731
± SD	0.752	0.0088	0.2479	0.911	0.0093	.3810	0.902	0.0104	0.4493
P				<0.02	NS	NS	<0.005	NS	NS

Parameters measured at noted intervals before and during training. T_4, plasma concentration of total thyroxine; DF, dialyzable fraction; FT_4, plasma free thyroxine.

TABLE 3. *Effect of physical training on metabolism of triiodothyronine*

Subj	MCR, liters/day		UC, liter/day		FC, liter/day		PT_3, ng/100 ml		TD_3, μg/day	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
15	21.6	22.5	18.5	17.8	3.15	4.73	119	132	27.3	30.2
16	19.9	19.2	16.1	15.9	3.87	3.34	127	136	25.0	24.1
17	29.5	29.8	25.0	25.4	4.49	4.42	127	115	35.5	31.6
18	26.5	26.5	22.8	23.0	3.69	3.49	129	135	30.7	32.9
19	24.0	25.5	22.7	21.7	1.38	3.78	143	135	38.2	38.2
20	18.3	18.8	15.4	17.6	2.95	1.19	145	169	26.2	30.1
21	21.6	24.6	18.2	20.9	3.38	3.73	97	115	24.5	31.0
22	20.0	23.4	17.2	20.8	2.79	2.61	158	154	32.1	35.5
23	17.4	22.0	14.2	18.8	3.22	3.22	129	136	27.2	34.4
24	17.2	20.3	14.4	17.4	2.82	2.85	143	144	26.1	30.0
25	17.4	20.6	14.9	18.6	2.53	2.00	129	142	24.6	32.6
Mean	21.22	23.02	18.13	19.81	3.115	3.215	131.5	137.5	28.85	31.87
± SD	4.02	3.37	3.77	2.82	0.803	1.025	16.0	15.4	4.66	3.63
P	<.01		<.02		NS		NS		<.02	

Plasma disappearance kinetics and degradation rate of [^{131}I]T_3 measured before (pre) and after training (post), MCR, UC, FC, metabolic, urinary, and fecal clearances, respectively. PT_3, plasma concentration of total T_3; TD_3, T_3 degradation rate.

metabolic clearance rate, 21.22 ± 4.02 liters/day; urinary clearance, 18.13 ± 3.77 liters/day; fecal clearance, 3.12 ± 0.80 liters/day; absolute degradation, 28.8 ± 4.66 μg/day. These measurements, which depend on the two-compartment analysis of metabolic clearance of T_3, are similar to the results obtained by others with the use of integral techniques (11). A small but significant increase (8.5%) in the metabolic clearance of T_3 was observed after training. The increased metabolic clearance appeared to be due to an increased urinary clearance of T_3. Fecal clearance of the hormone was not altered. Cumulative recovery of injected [^{131}I]T_3 in urine and feces (mean ± SD (% dose)): pretraining, 94.0 ± 4.33, posttraining, 97.7 ± 9.11 ($P > 0.05$). Plasma concentration of radioassayable T_3 was unchanged. The daily degradation rate of T_3 was increased 10.5% due to the increased metabolic clearance of T_3.

DISCUSSION

The present study has detected small changes in the metabolism of T_4 and T_3 as a result of the training program. The degradation rate of T_3 was increased by approximately 10%, while the degradation rate of T_4 was slightly decreased after training. The metabolic clearance of T_3 was significantly increased after training, but no change was detected in the metabolic clearance of T_4. A significant diminution in the plasma concentration of total T_4 was observed after 4 and 6 wk of training, apparently unrelated to decreased hormonal binding by plasma proteins, since there was no change in the dialyzable fraction of T_4. Slight but significant increases in the urinary clearances of T_4 and T_3 were noted as a result of training, but no changes in the fecal hormonal clearances were found. In the case of T_4, however, the apparent increase in urinary clearance may be attributable to dissimilar recovery of the dose observed in the two turnover studies. In contrast, no significant difference in the recovery of tracer T_3 was noted in the pre- and posttraining turnover studies.

The effect of exercise and physical training on thyroid activity and the peripheral metabolism of thyroid hormones has been examined in a number of studies by diverse measurements of glandular function and hormone degradation. Bondy and Hagewood (2) observed a fall in the plasma PBI in rats 2 h after swimming. Escobar del Rey and Morreale de Escobar (4) noted accelerated disappearance of [^{131}I]T_4 in rats trained to exercise daily for 2–3 wk. Winder and Heninger (14) demonstrated increased hepatic concentration and reduced serum concentration of T_4 in rats trained on an exercise wheel for 6 wk. Irvine (5) observed a 65% increase in the T_4 degradation rate in thoroughbred race horses in training. We have observed that physical training in the rat is associated with stimulation of the metabolism of T_4 and T_3, with increased hepatic uptake and fecal disposition of both iodothyronines (1). In human beings, Lashoff et al. (7) noted no change in the butanol-extractable iodine or in the disappearance rate of radiothyroxine as a result of long-distance walking. Moreover, these authors could detect no change in the serum protein-bound iodine in subjects after a strenuous bout of swimming (7). In contrast, Irvine noted that the T_4 absolute degradation rate in athletes in training was substantially greater than that in nonathletic sedentary controls (6). He further observed that the absolute degradation rate of T_4 of nonathletes after 4–6 days of exercise exceeded that of resting nonathletes by approximately 40% (6). However, since the measurement of absolute degradation in nonathletes depended on determining the fractional turnover rate in these subjects over a period of only 2 days, this finding appears to be of uncertain significance.

In contrast to Irvine's findings, we have noted a slight decrease in the absolute turnover of T_4 in our subjects after training. These divergent observations may be, at least in part, related to differences in experimental design. Thus, although the daily energy expenditure of the subjects in the present study and in the track athletes in Irvine's study was

of similar magnitude, in the latter study the athletes had just completed a season of intensive training with a daily energy output approximately double that expended in the off-season study. On the other hand, our subjects had not trained prior to the study. Thus, the intensity and length of training may be important factors in the previously noted stimulatory effect of training on T_4 metabolism in man.

In conclusion, we have observed decreased absolute turnover of T_4 and increased absolute turnover of T_3 after 6 wk of physical training. The decreased degradation rate of T_4 was related to a fall in the plasma concentration of this hormone. The etiology of the lowered plasma concentration of T_4 during and after the training regimen is uncertain. No change in the binding of T_4 by plasma proteins was detected by equilibrium dialysis. Additional causes of the diminished plasma T_4 concentration would include preferential secretion of T_3 compared to T_4 by the thyroid gland and increased conversion of T_4 to T_3 by peripheral tissues. In the face of the documented increased disposal of T_3 after training, increased generation of T_3 by either of these mechanisms would result in increased delivery of hormone to biological effector sites to maintain the euthyroid state. The impact of the differential effects in the degradation rates of T_3 and T_4 noted posttraining on the pituitary secretion of thyrotropin (TSH) is also uncertain. Negative feedback inhibition of TSH secretion would be expected in the presence of either increased T_3 generation from extrathyroidal conversion of T_4 or preferential T_3 secretion by the thyroid gland. Clearly, direct measurements of TSH secretion and hormone interconversion would be requred to validate or negate these hypothetical consequences of the alterations in hormone degradation noted after training in the present study.

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