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Assessment of the degradation of thyroid hormones in man during bed rest

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BALSAM, ALAN, AND LYNN E. LEPPO. *Assessment of the degradation of thyroid hormones in man during bed rest.* J. Appl. Physiol. 38(2): 216–219. 1975.—The effect of bed rest on the absolute turnover rates of thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), was evaluated in man. Bed rest resulted in physical deconditioning, measured by a decreased rate of maximal oxygen consumption; physical deconditioning was associated with no significant alterations in the metabolic clearance of T_4 and T_3. Plasma concentrations of these iodothyronines were not changed as a result of bed rest. Absolute hormone turnover rates were similar in control and bed-rest subjects. The data suggest that the degradation of thyroid hormones is not influenced by physical deconditioning or hypodynamia.

L-thyroxine; L-triiodothyronine; hypodynamia

PHYSICAL CONDITIONING (1) and physical deconditioning (2) in man are associated with diverse physiological alterations. Previous investigations have demonstrated a relationship between physical conditioning and the metabolism of thyroxine (T_4) (4, 5). Increased degradation of T_4 has been noted in thoroughbred race horses (5) and track athletes (4) in training. The effect of physical deconditioning on the secretion and metabolism of thyroid hormones in man is, however, uncertain. Recent studies of the effect of hypodynamia in man disclosed increased plasma binding of triiodothyronine (T_3) (6, 17) and increased concentration of T_4 (17) associated with bed rest. These changes have been attributed to increased hormone binding by plasma proteins due to contraction of the extracellular fluid volume during bed rest (6). The present study was undertaken to examine the effect of physical deconditioning induced by bed rest on the metabolism of thyroid hormones; radioisotopic methods were used to assess simultaneously the degradation rates of T_4 and T_3.

MATERIALS AND METHODS

Fourteen male volunteers, aged 18 to 23 yr, participated in a study designed to assess the peripheral turnover of thyroid hormones during bed rest. Complete physicals and clinical laboratory examinations were normal in all subjects; no past history of thyroid disease was elicited. The participants were divided into two equal groups: the experimental group was maintained in the supine position at bed rest for 17 days; the control group was permitted normal activity during the same period.

Seventy-two hours after the beginning of bed rest, all subjects received intravenous injections of a combined dose containing 74 μCi L-[^{131}I]triiodothyronine ([^{131}I]T_3)—specific activity 31 μCi/μg—and 37 μCi L-[^{125}I]thyroxine ([^{125}I]T_4)—specific activity 69 μCi/μg—diluted in 1% human serum albumin in normal saline. The labeled iodothyronines were obtained from Abbott Laboratories, N. Chicago, Ill. The hormones were dialyzed separately in normal saline as described previously (10) and were then diluted and combined. The hormone preparation was sterilized by passage through a Swinex millipore filter (0.22 μm). Hormone turnover was assessed from the plasma disappearance kinetics of injected tracer iodothyronines. Heparinized blood samples were obtained 10 min and 2, 5, 10, and 24 h postinjection, twice daily during the following 4 days, and once daily thereafter until 2 wk after the injection. During the turnover study, subjects ingested Lugol's iodine, 5 drops daily.

Plasma iodothyronine activity was taken as the difference between trichloroacetic acid (TCA)-precipitable activity and radioactivity that was not extractable with ethanol (9). All specimens were assayed for radioactivity, together with a dilution of the injected dose, in a dual-channel gamma spectrometer and expressed as a percent of the injected dose.

Single-compartment analysis was applied to the plasma disappearance curve of T_4. Following equilibration of the hormone in the distribution space during a 24- to 48-h period postinjection, the plasma disappearance curve of T_4 approximated a straight line on semilog plot (Fig. 1). A straight line was fitted to the linear portion of the curve by the least squares method. The plasma fractional exit rate is the slope of this straight line, and the hormone distribution space is the reciprocal of the antilog of the ordinate intercept. The metabolic clearance rate is taken as the product of the fractional exit rate from plasma and the hormone distribution space. The concentration of T_4 in plasma was measured by column chromatography at BioScience Laboratories, Van Nuys, Calif. The absolute degradation rate of T_4 was determined as the product of the metabolic clearance and the concentration of the hormone in plasma.

The disappearance of T_3 from plasma was measured for 7 days following injection of the dose. The plasma disappearance of T_3 24–48 h postinjection did not exhibit a pattern of single exponential decay, as noted in the case of T_4, but appeared curvilinear in a semilog plot (Fig. 1). Thus, the metabolic clearance of T_3 was calculated as the quotient

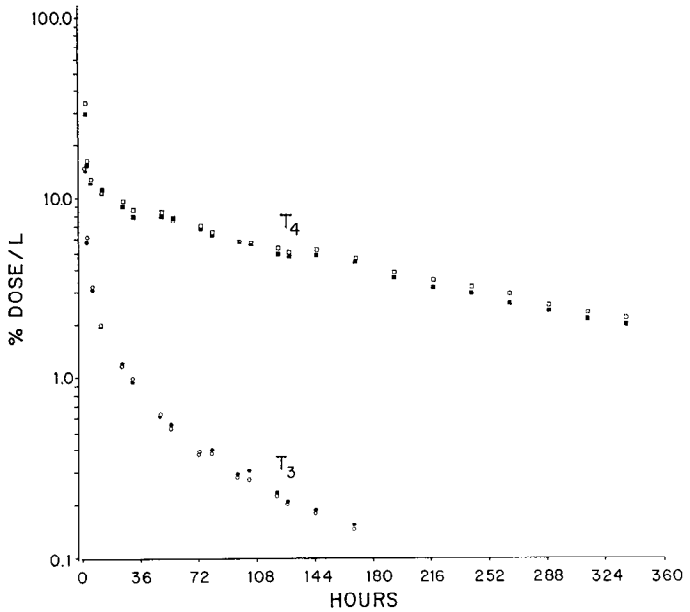

FIG. 1. Mean plasma disappearance curves of simultaneously injected [^{131}I]T_3 and [^{125}I]T_4 in seven controls and seven subjects during bed rest. Radioactive plasma hormone concentrations: T_4, ■ = control, □ = bed rest; T_3, ● = control, ○ = bed rest.

of 100, the total percent dose injected, and the area subtended by the plasma disappearance curve, as proposed by Tait (16). The application of this technique to the measurement of the metabolic clearance of T_3 was suggested by Oppenheimer et al. (10). The concentration of T_3 in plasma was assessed by radioimmunoassay in duplicate on a sample obtained on *day 10* of bed rest (15.)[1] The absolute degradation of T_3 was calculated as the product of the metabolic clearance and the concentration of this iodothyronine in plasma.

The binding of T_4 by plasma proteins was evaluated by equilibrium dialysis of diluted plasma (11). The dialyzable fraction is proportional to the original free hormone in undiluted plasma.

RESULTS (TABLE 1)

Physical deconditioning was documented in the bed rest group by measuring the rate of maximal oxygen consumption ($\dot{V}O_2$) before and immediately following bed rest (11). The mean level of oxygen consumption decreased 19.5% in the inactive group: $\dot{V}O_2$, ml/kg lean body mass per min (mean ± SE) pre-bed rest, 65.5 ± 2.4; post-bed rest, 52.7 ± 1.7 ($P < 0.001$, by the "paired" *t*-test). A smaller, nonsignificant decrease in the rate of maximal oxygen consumption and marked variability in individual measurements were noted in the control group: prestudy, 64.7 ± 2.3; poststudy, 56.7 ± 12.5 ($P > 0.05$, nonsignificant).

The fractional disappearance of thyroxine (T_4) from plasma was not significantly slowed during bed rest (Table 1). The mean plasma fractional removal of T_4 was decreased 10.2% compared with that measured in controls; however, the decrease was not statistically significant ($p > 0.05$). The volume of distribution of T_4 and the metabolic clearance of this hormone were not significantly altered. The mean concentration of plasma T_4 (avg concn of *days 1, 10,* and *17*) was not significantly increased in the experimental subjects. The mean ± SE dialyzable fraction of T_4 (DF) and free T_4 concentration (FT_4, ng/100 ml) (avg of *days 1, 10,* and *17*) were not significantly altered: DF, control 0.0602 ± 0.00586, bed rest 0.0589 ± 0.00404 ($P > 0.05$), FT_4, control, 2.51 ± 0.329, bed rest 2.61 ± 0.204. The absolute degradation rate of thyroxine was not changed. The metabolic clearance of T_3 was unaltered during bed rest[2] (Table 1). The plasma concentration and the absolute degradation of T_3 were similarly unchanged.

DISCUSSION

Previous studies of thyroid activity during bed rest have delineated changes in plasma levels of T_4 and in the in vitro assessment of plasma T_3 binding. Vernikos-Danellis and co-workers (17) noted a prompt decrease in the T_3 resin uptake that was sustained during 56 days of bed rest. Additionally, a transient increase in the mean daily concentration of T_4 was observed by these investigators during the first 10 days of bed rest. Leach et al. (6) noted a significantly decreased T_3 resin uptake in a group of subjects after 6 days of bed rest. An attendant nonsignificant increase in the concentration of T_4 was observed. The changes in serum T_4 levels and plasma hormonal binding were noted in association with a significantly decreased plasma volume measured by the dilution of intravenously injected radioiodinated albumin (6). The detection of a contracted plasma volume during bed rest by Leach et al. confirmed earlier observations of Miller et al. (7). These investigators observed a 15% reduction in the plasma volume of subjects after 11 days of a 28-day period of bed rest.

Irvine (4) has suggested that physical inertia may slow the degradation of T_4, based on turnover measurements in inactive subjects. He observed that the mean fractional degradation rate of T_4 in a group of sedentary human controls was approximately 10% lower than the corresponding age and sex corrected figure obtained from the data on T_4 turnover compiled by Oddie et al. (8). However, this observation could not be evaluated statistically. In the present study, a similar insignificant slowing of the fractional degradation rate of T_4 was noted. The small magnitude of these changes appears to raise doubt of their possible biological significance.

The effect of drug-induced sleep in the course of sleep therapy on the plasma protein-bound iodine concentration and plasma T_4 turnover was assessed in a study by Reichlin, Koussa, and Witt (12). Accelerated turnover of T_4 and no change in plasma PBI was noted as a result of sleep therapy. The implications of these data regarding physical inertia are limited. Moreover, phenobarbital administered in daily dosage of 240–260 mg in this study may have been responsible for the increased T_4 turnover, since hepatic smooth endoplasmic reticulum induction by this agent is associated with augmented metabolism of T_4 in the rat (9).

The current study provides quantification of the absolute

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

[2] The impact of 10 days' bed rest on T_3 turnover was assessed since the hormone was injected on the third day of bed rest and the relatively short biological half-life of T_3 (1–1.5 days) permitted the measurement of T_3 turnover in plasma for only 7 days.

TABLE 1. *Quantification of the turnover of thyroid hormones during bed rest*

			T_4 Kinetics					T_3 Kinetics		
	Age, yr	Wt, kg	k/24 h	V_t, liters	MC, liter/24 h	PT_4, μg/100 ml	TD_4, μg/24 h	MC, liters/24 h	PT_3, ng/100 ml	TD_3, μg/24 h
Control subj										
1	19	98	0.114	13.25	1.52	5.1	77.5	25.5	143	36.5
2	19	62	0.136	9.25	1.26	5.8	73.1	19.8	141	27.9
3	23	72	0.105	10.66	1.12	6.3	70.6	18.9	153	28.9
4	19	63	0.124	9.15	1.14	5.5	62.7	17.6	146	25.7
5	18	70	0.110	10.56	1.16	7.0	81.2	21.9	128	28.0
6	18	85	0.134	12.61	1.68	5.8	97.4	26.7	156	41.7
7	20	63	0.106	9.81	1.04	6.3	65.5	18.3	118	21.6
Mean	19.4	73	0.118	10.76	1.27	6.0	75.4	21.3	141	30.0
± SE	0.64	5	0.0049	0.61	0.089	0.23	4.39	1.36	5.1	2.57
Rest subj										
8	19	74	0.115	10.94	1.25	6.7	83.8	22.2	133	29.5
9	18	66	0.111	11.04	1.22	5.5	67.1	20.1	121	24.3
10	20	62	0.111	9.93	1.10	6.3	69.3	19.4	158	30.7
11	20	84	0.089	14.53	1.29	7.0	90.3	25.1	159	39.9
12	19	79	0.097	11.28	1.10	7.2	79.2	20.5	157	32.2
13	19	57	0.115	8.36	0.96	8.7	83.5	16.8	147	24.7
14	19	84	0.104	12.13	1.26	5.7	71.8	22.3	162	36.1
Mean	19.1	72	0.106	11.17	1.16	6.7	77.9	20.9	148	31.1
± SE	0.26	4	0.0037	0.72	0.045	0.41	3.27	0.99	5.9	2.15

Plasma turnover of iodothyronines was measured following intravenous injection of L-[^{125}I]thyroxine (T_4) and L-[^{131}I]triiodothyronine (T_3) in 7 control and 7 experimental male volunteers during a 17-day period of bed rest. k, plasma fractional exit rate; V_t, hormone distribution volume; MC, metabolic clearance. PT_4 and PT_3 denote the plasma concentrations of total hormone, and TD_4 and TD_3 signify degradation rates of T_4 and T_3, respectively.

degradation rates of T_3 and T_4 during bed rest. A number of previous studies have demonstrated that primary alterations in the binding of T_4 by plasma proteins result in no changes in hormone flux (3, 13). Thus, increased plasma concentrations of T_4 binding proteins would be expected to result in slowed fractional removal rate, contracted distribution space, increased plasma concentration and unchanged absolute turnover of the hormone. In view of the normal hormone flux measured during bed rest, it is concluded that previously observed changes in the plasma concentration of T_4 and the binding of T_3 and T_4 by plasma in man during bed rest are independent of changes in hormone degradation.

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The voluntary informed consent of the subjects used in this research was obtained in accordance with AFR 80-33.

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