Increasing Age Impairs the Thyroid Hormone Response to Overfeeding[1] (43078)

Harvey L. Katzeff[2]

Department of Medicine, North Shore University Hospital, Manhasset, New York 11030 and Department of Medicine, Cornell University Medical College, New York, New York 10021

Abstract. **Aging in both man and rodent is associated with increases in body weight and body fat. In young adult rats, mixed calorie overfeeding increases triiodothyronine production and decreases weight gain efficiency compared with chow diets. This study was undertaken to determine whether 4- and 14-month-old adult rats have similar responses in thyroxine (T_4) and triiodothyronine (T_3) metabolism during mixed calorie overfeeding. Four- and 14-month-old male Sprague-Dawley rats were each separated into two groups ($n = 14$): control (CHOW) versus chow + mixed calorie (CAFE) overfeeding for 28 days. The 4-month-old CAFE-fed rats ingested 662 ± 54 extra kcal over 28 days and gained 147 ± 7 vs 113 ± 5 g ($P < 0.01$) for their age-matched CHOW group. The 14-month-old CAFE group ingested 309 ± 45 extra kcal and gained 58 ± 6 g weight vs −12 ± 5 g for their age-matched CHOW group ($P < 0.01$). Serum T_4 concentrations were unchanged during overfeeding or aging. The serum T_3 concentration was increased 24% in the 4-month-old CAFE group compared with the age-matched CHOW group ($P < 0.05$), but there was no difference in the serum T_3 concentration between the 14-month-old CAFE and CHOW groups. The metabolic clearance and production rates of T_3 and T_4 were decreased in the 14-month-old vs 4-month-old groups ($P < 0.01$). The T_3 metabolic clearance rate was increased in the CAFE versus CHOW group in the 4-month-old groups (137.3 ± 11.2 vs 103.0 ± 10.1 ml/kg/hr, $P < 0.01$) but unchanged in the 14-month-old CAFE and CHOW groups (47.6 ± 6.6 vs 53.4 ± 5.3 ml/kg/hr, not significant). Liver type I iodothyronine 5′-deiodinase activity increased during overfeeding in the young (63.6%, $P < 0.02$) but not in the older rat group. T_4 and T_3 production rates were decreased in the older rats and did not increase during overfeeding as observed in the young adult rat.** [P.S.E.B.M. 1990, Vol 194]

In young adult rats, overfeeding is associated with increases in (i) triiodothyronine production, (ii) release of norepinephrine from the sympathetic nervous system, and (iii) brown adipose tissue thermogenesis (1–3). These physiologic responses are thought to be responsible for an increase in energy expenditure (nonshivering thermogenesis) and a decrease in weight gain efficiency (4, 5). The increase in the conversion of thyroxine (T_4) to triiodothyronine (T_3) during overfeeding is thought to be necessary for an increase in adaptive thermogenesis (6–8). Genetically obese Zucker rats and *ob/ob* mice have both abnormalities in thyroid hormone metabolism, energy expenditure, and brown adipose tissue thermogenesis which promote deposition of triglyceride in adipose tissue (9–16). The role of thyroid hormone abnormalities in the pathogenesis of these genetic models of obesity is unclear.

Aging in man and rodents is associated with an increase in fat mass and resistance to the effects of specific hormones, including norepinephrine, released from the sympathetic nervous system (17–20). Resistance to thermogenic hormones may be responsible for a portion of the observed increase in weight gain efficiency and increase the proportion of fat to lean body mass in older rats (18, 19). Controversy exists as to whether there are alterations in serum concentrations

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[2] To whom requests for reprints should be addressed at Department of Medicine, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030.

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of T_4 and T_3 in aging, both in humans and rodents (20–24). *In vitro* studies of Type I iodothyronine 5′-deiodinase activity report decreased enzyme activity in aged rats but *in vivo* thyroid hormone kinetic studies are contradictory as to whether T_4 and T_3 metabolism are normal (22, 23). In addition, it is unknown whether increasing age alters the observed increase in T_3 production in response to overfeeding observed in young adult rats. This study was undertaken to determine whether older rats have similar responses in T_4 and T_3 metabolism as do young adult rats in response to mixed calorie overfeeding.

Materials and Methods

Experimental Protocol. Twenty-eight 4-month-old male Sprague-Dawley rats were obtained from Hilltop Farms, Taconic, NY. Animals were then housed in Plexiglas cages (two animals per cage) until the animals were 14 months of age prior to the experimental period and then separated into individual cages for 28 days. A second group of male 4-month-old Sprague-Dawley rats ($n = 28$) were also obtained from the same source and all animals underwent testing within a 3-month period. The 4- and 14-month-old rats were each separated into two groups ($n = 14$) of chow diet (CHOW) and mixed calorie overfeeding (CAFE) to produce a 2 × 2 experimental design. All animals were fed Purina rat chow (21% protein, 4% fat, and 75% carbohydrate; Ralston Purina Corp.) and pellet intake and water were measured weekly. The CAFE groups were also given premeasured amounts of a variety of palatable high-calorie foods daily and food consumption was measured daily (3). The composition of the CAFE diet actually ingested was 18% protein, 50% fat, and 21% carbohydrate in both age groups.

Thyroxine and triiodothyronine metabolic clearance and production rates were measured by a constant infusion of either $[^{125}I]T_4$ or $[^{125}I]T_3$. One half ($n = 7$) of each of the four groups of animals were infused with $[^{125}I]T_4$ and the other half received $[^{125}I]T_3$. On Day 21 of the experiment, an osmotic minipump (model 2001; Alza Corp., Palo Alto, CA) was subcutaneously implanted distal to the interscapular brown adipose tissue (BAT) pad on the dorsal surface of the experimental animal. The pumps contained either 4.8 μCi of $[^{125}I]T_4$ or $[^{125}I]T_3$ (sp act, 1200 μCi/μg; New England Nuclear, Waltham, MA). These pumps released fluid into the subcutaneous tissues at a rate of 1.15 ± 0.05 μl/hr. The radioactive hormone solutions were prepared by dilution into a solution of 0.9 *M* NaCl + 100 mg/ml bovine serum albumin (Sigma) and then dialyzed versus 0.9 *M* NaCl + 0.1 m*M* NaH_2PO_4 to remove free iodine prior to filling of the pumps. An aliquot of each tracer was chromatographed with a high-pressure liquid chromatography system (55:45 methanol:water, pH 3.0, 1 ml/min) using a C_{18} μBondapak 4.5- × 30-cm column (Waters Associates, Braintree, MA) to ensure that the tracer was >99% pure. On Day 28, animals were sacrificed by decapitation. Serum was separated immediately and aliquots were frozen at −20°C for thyroid hormone determinations. Liver and brown adipose tissue were removed, weighed, and frozen immediately at −78°C for 5′-deiodinase enzyme activity determinations to be performed within 2 weeks. Flash-freezing the organs for up to 3 months produces a decline in 5′-deiodinase activity of less than 10% (10).

Biochemical Methods. The specific activities of $[^{125}I]T_4$ and $[^{125}I]T_3$ in serum were determined by column separation. One milliliter of serum was combined with 2 ml of 0.2 *M* acetic acid and then placed on a C_{18} minicolumn (Setpak; Waters Associates). The minicolumn was washed with 5 ml of 0.1% H_3PO_4 and 3 ml of H_2O to remove free iodine, and the thyroid hormones were then eluted with 3 ml of methanol. The methanol was dryed under N_2 and resuspended in 200 μl of high-pressure liquid chromatography elution buffer. One-hundred-microliter samples were then centrifuged at 15,000 rpm in a microfuge and the supernatant was injected into the high-pressure liquid chromatography. Thyroid hormones were eluted using a 4.5- × 30-cm C_{18} μBondapak column (Waters Associates). The buffer was 55:45 methanol:H_2O (pH 3.0) using H_3PO_4 at a flow rate of 1 ml/min. Fractions were collected at 1-min intervals and counted in a gamma detector. The ratio of $[^{125}I]T_4$ and $[^{125}I]T_3$ to total counts in serum was 91.2 ± 2.3% and 50.2 ± 1.5%, respectively. Standards using known quantities of tracer in charcoal-stripped iodothyronine-free rat serum produced a 95.1 ± 1.4% recovery of T_4 and a 92.0 ± 0.4% net recovery of T_3. The infusion rate of tracer into each animal was determined directly by measuring the total initial counts placed into the minipumps and then determining the radioactivity remaining in the pumps removed at decapitation 168 hr later. There was less than 0.1% damping of counts due to the geometry and composition of the pumps, compared with a solution of 0.238 ml of tracer (volume of pumps). The metabolic clearance rate of both T_4 and T_3 were calculated as the infusion rate of each isotope divided by the concentration of $[^{125}I]T_4$ and $[^{125}I]T_3$ in serum. Serum concentrations of T_3 and T_4 were measured by sensitive and specific radioimmunoassays using thyroid hormone-depleted rat sera for standards (25). The production rates of T_4 and T_3 were calculated as the total serum concentration × metabolic clearance rate.

Levels of 5′-deiodinase activity in liver and brown adipose tissue were measured by modification of the method of Gavin *et al.* (26). Liver tissue was homogenized (Tissumizer; Cole-Parmer) and diluted to 2% (v) in 0.5 *M* Tris + 0.25 *M* sucrose + 6 m*M* EDTA + 10 m*M* dithiothreitol (pH 7.2). Homogenates were centrifuged at 600*g* for 10 min and the supernatant was used for the incubation. The total volume of the incubation homogenate was 1 ml and 160 μg of T_4 in 10 μl of 0.01 M NaOH was added as substrate (final concentration, 0.2 μM) to start the incubation. The incubation duration was 60 min and a 50-μl aliquot of the homogenate was removed at time 0 min and time 60 min and placed into 450 μl of chilled, charcoal-stripped sera containing 10 mm of propylthiouracil to stop the reaction. This serum was immediately frozen and stored for later analysis using a T_3 radioimmunoassay with appropriate standards. Brown adipose tissue 5′-deiodinase activity was measured using a 12.5% homogenate with 10 mM dithiothreitol. Thyroxine was added to make a final concentration of 0.2 μM for the liver incubation and 0.2 nM for the brown adipose tissue incubation. Protein concentrations of homogenates were measured using the Lowry method (27). Activity was expressed as the picomoles of T_3 generated per minute per 100 mg of protein.

Statistical Analysis. All data are represented as the mean ± SD. The comparisons between age and diet groups were performed by a two-way analysis of variance (28).

Results

Food intake and weight gain were greater in the CAFE groups compared with their age-matched controls (Table I). In the 4-month-old group, the CAFE diet increased caloric intake 26% and weight gain was increased 17% compared with the CHOW-fed group after 28 days (both $P < 0.01$). The caloric intake of the 14-month-old *ad libitum*-fed CHOW rats was lower than that measured in their younger counterparts (384.8 ± 18.8 vs 639.2 ± 17.8 kcal/week, $P < 0.001$) but the 4-month-old rats were still gaining weight whereas the 14-month-old rodents lost 12 g over 28 days. The CAFE diet increased food intake 20% in the aged rats and produced a weight gain (58.4 ± 6.0 vs −12.0 ± 5.1 g, $P < 0.01$) compared with the 14-month-old CHOW group. Total wet BAT weight and BAT protein content were both increased in the CAFE groups compared with their age-matched counterparts ($P < 0.01$), but overfeeding in the aged rat produced a smaller increase in BAT tissue. The 14-month-old CHOW group had similar total BAT and BAT protein weight as the 4-month-old CHOW group but the BAT/body weight ratio was lower as a proportion of total body mass.

Thyroid Hormone Metabolism. Serum T_4 concentrations were similar in the CHOW- and CAFE-fed animals in both the 4-month-old (5.5 ± 0.8 vs 5.7 ± 0.4 μg/dl) and 14-month-old groups (5.2 ± 0.3 vs 4.9 ± 0.3 μg/dl) (Table II). There was a small decline in serum T_4 levels (10%, $P < 0.10$) that did not reach significance when the 14-month-old rats are compared with their 4-month-old counterparts. The serum T_3 concentration was increased in the 4-month-old CAFE group compared with the age-matched CHOW group ($P < 0.05$), but there was no difference in the serum T_3 concentration between the 14-month-old CAFE and CHOW groups. The metabolic clearance rates of T_4 were decreased in the 14-month-old age groups with no changes observed during overfeeding. There were also no differences in absolute T_4 production rates between the CAFE and CHOW groups but when calculated per kilogram of body weight the aged rats had decreased T_4 production rates. The T_3 metabolic clearance rate (MCR) was increased in the CAFE versus CHOW group in the 4-month-old groups (137.3 ± 11.2 vs 103.0 ± 10.1 ml/kg/hr, $P < 0.01$) but was unchanged in the 14-month-old CAFE and CHOW groups (47.6 ± 6.6 vs 53.4 ± 5.3 ml/kg/hr, not significant). The T_3 MCR and production rates (PR) were decreased when the 14-month-old groups were compared with the 4-month-old animals ($P < 0.005$). The 14-month-old groups had a markedly decreased T_3 MCR compared with their 4-month-old counterparts (−60%). The decrease in T_3 MCR in the aged groups can be explained, in part, by differences in caloric intake. As shown in Figure 1, there is a strong linear relationship between T_3 PR and caloric intake ($r = 0.95$, $P < 0.001$).

Iodothyronine 5′-Deiodinase Activity. There was

Table I. Animal Characteristics

	4-month-old Chow	4-month-old Cafe	14-month-old Chow	14-month-old Cafe
Final body weight (g)	542 ± 6	590 ± 6	654 ± 17	704 ± 26
Weight gain (g/28 day)	103 ± 5	147 ± 7[a]	−12 ± 5	58 ± 6[a]
Caloric intake (kcal/week)	639.2 ± 17.8	804.8 ± 16.5[a]	384.8 ± 18.8	462.0 ± 25.0
BAT wet weight (g)	0.58 ± 0.12	1.55 ± 0.23[a]	0.53 ± 0.15	0.82 ± 0.14[a]
BAT (protein content, mg)	23.4 ± 2.5	47.5 ± 4.9[a]	21.3 ± 2.0	38.0 ± 3.3

[a] $P < 0.01$ versus age-matched control.

Table II. Measures of Thyroid Hormone Metabolism *In Vivo*

	4-month-old CHOW	4-month-old CAFE	14-month-old CHOW	14-month-old CAFE
Serum T_4 (μg/dl)	5.5 ± 0.8	5.7 ± 0.4	5.2 ± 0.3	4.9 ± 0.3
Serum T_3 (ng/dl)	81 ± 4	99 ± 5^a	81 ± 3	79 ± 3
T_4 MCR (ml/kg/hr)	16.2 ± 1.5	14.4 ± 2.1	8.7 ± 0.7^b	9.3 ± 1.3^b
T_3 MCR (ml/kg/hr)	103.0 ± 10.1	137.3 ± 11.2^a	53.4 ± 5.3^b	47.6 ± 6.6^b
T_4 PR (ng/kg/hr)	891 ± 113	827 ± 149	453 ± 66^b	455 ± 67^b
T_3 PR (ng/kg/hr)	127.1 ± 21.0	178.9 ± 17.2^a	65.9 ± 12.9^b	60.4 ± 12.0^b

[a] $P < 0.05$ versus CHOW.
[b] $P < 0.01$ vs 4-month old (analysis of variance).

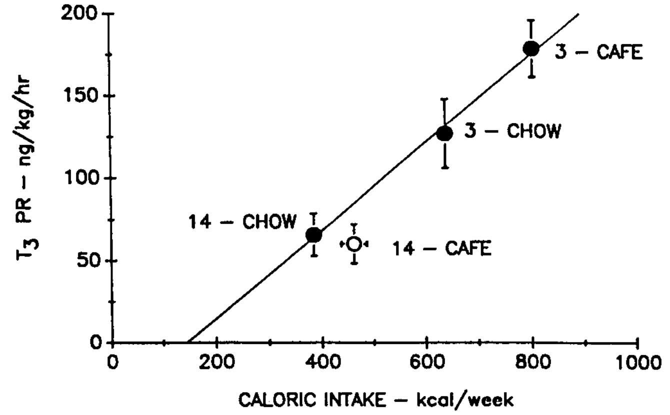

Figure 1. The mean production rate of T_3 (ng/min/kg) for each of the four groups of rodents are plotted versus the total caloric intake (kcal) over 28 days. All groups except for the 14-month-old mixed calorie overfed group (14-month-old CAFE) are linearly related ($r = 0.95$, $P < 0.001$).

almost a 2-fold increase in liver but not BAT 5′-deiodinase activity during the overfeeding diet in the young adult rat group ($P < 0.02$) (Table III). In the aged rat groups, overfeeding produced no change in enzyme activity in either the liver or BAT. However, the aged CHOW-fed rats also had a 2-fold increase in liver 5′-deiodinase activity compared with their younger counterparts ($P < 0.02$).

Discussion

This study reports that weight-stable 14-month-old rats voluntarily increased their caloric intake and body weight when presented with a variety of palatable foods (cafeteria diet). In spite of this 20% increase in caloric intake, the older rats did not increase either their T_3 serum concentrations or metabolic clearance and production rates as did the 4-month-old young adult rats. In addition, both the T_4 and T_3 metabolic clearance and production rates during chow feeding were lower in the older adult rat.

The most probable explanation for the decrease in T_4 and T_3 production rates in the 14-month-old rats is the fact that both older groups (CHOW + CAFE) ingested fewer calories than their diet-matched 4-month-old counterparts. In previous studies, T_3 production rates were correlated to the level of caloric intake in both man and rodent (6–8, 13, 29). Thus, without invoking any abnormality in thyroid hormone regulation, the lower T_4 and T_3 production rates in the CHOW-fed aged rats can be explained by their lower level of calorie intake. Previous studies of elderly men and rodents also reported a lower level of calorie intake than their younger counterparts, but the differences have not been as large as those reported in this study (30–34). Since two of the major determinants of calorie intake are body mass and growth rate, the fact that the young rats increased their body weight almost 50% and their final body weight was almost as great as the older rats accounted for the large difference in calorie intake between the 4- and 14-month-old rat groups in this study. Also interstrain variability on maximum weight

Table III. Idothyronine 5′-Deiodinase Activity[a]

	4-month-old CHOW	4-month-old CAFE	14-month-old CHOW	14-month-old CAFE
Liver	12.9 ± 2.4	21.1 ± 2.6^a	23.2 ± 2.5^b	23.9 ± 4.3^b
BAT	0.95 ± 0.24	1.06 ± 0.18	1.13 ± 0.09	1.02 ± 0.15

[a] Enzyme activity = pmol/min/100 mg protein).
[b] $P < 0.02$ vs 4-month-old CHOW.

achieved in the aged rat model is an important reason for the differences reported (32, 34).

The effects of increasing age on thyroid hormone metabolism has been controversial. In human studies, investigators report both decreased and normal serum T_4 and T_3 concentrations (20, 21). Much of the conflict appears to be secondary to the types of subjects that were studied. When unrecognized hypothyroidism was excluded by measuring blood thyroid-stimulating hormone levels and only healthy elderly adults who were weight maintained were studied, normal serum T_4 and T_3 concentrations were obtained (32). In the rodent model of aging, there are also conflicting reports of thyroid hormone metabolism (22–24). Both normal or decreased T_4 and T_3 levels in serum have been reported, but there has been no standardization of nutritional intake with increasing age.

Jang and DiStefano (24) report that 11-month-old chow-fed rats had increased T_3 production compared with their 5-month-old counterparts. Unfortunately they did not report the level of food intake and the body weight of their Sprague-Dawley rats was such that it suggested that these animals were still growing and ingesting a greater quantity of food than the weight-stable aged rats reported in this study. Frolkis and Valueva (23) reported a decrease in T_3 MCR in their 12-month-old rats compared with the 1- to 2-month-old rats but again no caloric intake data were reported. It is possible that differences in rate of growth and caloric intake are responsible for the variability of reported results of thyroid hormone levels in the literature.

It is theorized that increased conversion of T_4 to T_3 in nonthyroidal tissues during overfeeding promotes increased thermogenesis and decreases weight gain efficiency (7). The lack of this adaptive mechanism may therefore promote excessive weight gain. This study was not designed to measure the efficiency of weight gain but the aged cafeteria-fed rats appeared to be more efficient weight gainers than young overfed rats (difference in weight gain between CAFE and CHOW in young and old groups 44 g/662 kcal vs 70 g/309 kcal, Table I). In addition to an alteration in resting thermogenesis, differences in spontaneous physical activity or the caloric density of the weight gain could also account for the differential weight gain between the young and aged overfed rats.

Older rodents appear to have normal basal or resting O_2 consumption and lean body mass but several groups have reported decreases in cold-, diet-, and norepinephrine-induced BAT thermogenesis in older rats (35–38). The findings of Donda *et al.* (39) and this study which report that Type II 5′-deiodinase activity in older rats is unchanged suggest normal regulation of this enzyme with aging. Another factor to consider is the age-related decreases in serum thyroid hormone concentrations which may depress intracellular T_3 levels in BAT, although intracellular T_3 levels in the anterior pituitary are normal (39). Overall, there are little data to indicate that age-related changes in thyroid hormone metabolism affect BAT thermogenesis.

It is uncertain whether the determination of 5′-deiodinase activity *in vitro* is consistent with the *in vivo* measurements of T_3 production in rodents. Although several groups have reported decreased Type I 5′-deiodinase activity during starvation, Kinlaw *et al.* (40) report that the cause of the decrease in T_3 production was a decrease in T_4 availability and that the proportion of T_4 converted to T_3 was normal. Measurements of 5′-deiodinase activity both *in vitro* and *in vivo* during aging have also been inconclusive. This study found an increase in Type I 5′-deiodinase activity in the chow-fed older rodents but no increase during overfeeding in the older rat group, but Ooka (22) reports decreased activity. Frolkis and Valueva (23) report increased conversion of T_4 to T_3 *in vivo* and *in vitro* in several tissues including heart and skeletal muscle. Thus, it is unclear whether our observation of no alteration in 5′-deiodinase activity during overfeeding in the older group has any physiologic significance.

Fourteen-month-old rats have decreased T_4 and T_3 production rates compared with young adult rats. Mixed calorie overfeeding is associated with a rise in T_3 but not T_4 metabolic clearance and production rates in young adult rats and is not observed in overfed older rats. Whether these alterations in thyroid hormone metabolism with increasing age promotes excessive fat deposition needs to be addressed.

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