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Effect of aging and obesity on peripheral t3 generation and thyroidal status in congenic la/ntul// cp rats

Abstract

To determine the effects of aging and the obese phenotype on Triiodothyronine (T3) generation and thyroidal status, groups of congenic lean and obese female littermate LA/Ntul//-*cp* rats were maintained on Purina stock diet and house water from 4 until 24 months of age. Body weight and adiposity of obese >>> lean at all post weaning ages studied. Measures of resting oxygen consumption (RMR, VO2) at thermal neutrality (30°C), serum T3, T4, T4:T3 and T3:T4 ratios, tissue T3 concentrations, and T4-5' deiodinase activity in liver, interscapular brown adipose tissue (IBAT), and gastrocnemius muscle (GNM) were determined at each age group. Measures of RMR were greater in lean than obese at each age (p=<0.05) and declined with age in both phenotypes with the most substantial decrease in the obese phenotype. Measures of serum T4 were greater at age 4 months than at both older ages measured in both phenotypes and remained similar thereafter. Serum T3 tended to increase modestly in each age in both phenotypes. Serum T4:T3 ratios decreased with age while serum T3:T4 ratios increased with age in both phenotypes. Measures of tissue T4-5' Type II deiodinase activity were determined in isolated homogenates of liver, IBAT and GNM. Tissue activity levels of outer ring T4-5' deiodinase activity of liver and IBAT showed both phenotype and age effects and decreased with age in both tissues. (Lean > obese; young > older) in both lean and obese phenotypes. GNM deiodinase activity increased only modestly with age in lean but not in obese rats. Liver T3 receptor affinity has also been reported to be decreased in the obese phenotype at 4 months of age. These observations are consistent with impaired sirtuin-mediated and age-associated thyroidal actions in the lean and obese phenotypes and which impairments may be contributory to further age associated decreases metabolic rates observed in the obese phenotype.

Keywords: aging, obesity, thermogenesis, thyroid function, T4-5'-deiodinase, receptor binding

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Introduction

The prevalence of overweight and obese conditions have now attained epidemic proportions in much of Westernized society, where they are commonly associated with NIDDM, hypertension, cardiovascular disorders, osteoarthritis, neurologic dysfunction, and other pathophysiologic comorbidities.[1,2] While patients often undertake a broad variety of dietary and exercise approaches in attempts to remedy their overweight status, even the most noble attempts are often met with less than satisfactory outcomes.[1] The hallmark of clinical approaches typically focus on areas of diet and exercise, in combination with selected pharmacotherapeutic adjuncts, but even when effective, the weight may be regained readily soon after the therapeutic regimen is completed. Overweight and obese patients often present in the clinic with symptoms reminiscent of thyroidal dysfunction or hypothyroidism, but when the conventional laboratory tests are completed the results are often disappointingly within the normal range, thereby suggestive of alternative sources attributed to the excess weight experienced.[3,4–7] In a recent study however, evidence for a syndrome of subclinical hypothyroidism has been reported within a larger subgroup of obese patients, some of whom met the criterion for metabolic syndrome (MeTS). The common denominator of insulin resistance was noted throughout the range of overweight and obesity conditions observed among their patient groups and the impairments in thyroidal functions generally proportionate to the magnitude of overweight status.[8]

Common dietary practices have undergone considerable transition since the original dietary guidelines were suggested when the food pyramid was first introduced over 70 years ago. The recent modifications to the pyramid have shifted recommended proportions of saturated animal fats downward and of carbohydrates upward in attempts to curb an increasing prevalence of cardiovascular disorders.[9] While the emerging lower fat dietary guidelines have been widely accepted by many, palatability and satiety interests required increasing the relative proportions of dietary carbohydrate content to improve palatability in attempts to gain public acceptance. The previously greater fat content has been replaced with constituents of lower caloric density including substitution of carbohydrates and other sweeteners for the decreased fat content. The added carbohydrate sources now typically include sucrose and high fructose corn syrup (HFCS), which when consumed in excess may also contribute to the pathophysiologic clinical sequelae typically associated with obesity and overweight conditions.[9,10]

The development of the congenic corpulent rat has become an important animal model whereby the only difference between the obese and the lean phenotypes is the epigenetic expression of obesity via the corpulent *(-cp*) trait, and has proven to be a highly useful model for studies in obesity and cardiovascular disorders due to its congenic and specific pathogen free status.[11,12] Previous studies in the corpulent rat have demonstrated that the capacity for nonshivering thermogenesis under conditions of thermal neutrality was typically

decreased by an average of 20% under most environmental conditions, and the impairment was found to be attributed to a combination of sympathetic and thyroidal actions.[13–15] Moreover, in studies with the corpulent rat strains, parameters of nonshivering thermogenesis in response to parameters of diet and environment were also decreased in the obese phenotype.[13] In addition to the impaired thermic responses to factors of diet and environment, measures of serum T3 concentrations were also often found to be lower in littermates of the obese male and female phenotype, suggestive of a physiological subclinical hypothyroid state, where only modest deficits may account for excess weight gain.[6,13,15,16] Aging contributes additional impairments in the thermogenic responses to diet and cold environment in the obese phenotype.[17,18] Although the physiologic mechanisms that are operative for the impaired thermic responses in aging remain unclear they do appear to include decreases in mitochondrial oxidative activity, a primary source of oxygen utilization in mammalian tissues.[17,19,20] The biochemical mechanism of the NST component of thermogenesis in most warm-blooded animals including rodents occurs in large part via thermogenic activity in brown adipose tissue, where specialized mitochondria demonstrate a neuroendocrine-mediated activation and uncoupling of oxidative phosphorylation of ATP to ADP, resulting in the obligatory generation of heat that can be utilized to maintain body temperature regulation following alterations in diet and thermal environment.[13,19,21] Other tissues including liver and skeletal muscle also contribute to metabolic heat production, albeit via well- established biochemical mechanisms in intermediary substrate metabolism rather than the specialized mitochondrial process common to BAT.[21] Glucose uptake in BAT is essential for BAT thermogenesis to progress, and Marette[22] demonstrated that insulin resistance is a major factor in the impaired thermogenic responses in obese rats.[22] In addition, Tyzbir et al reported that mitochondrial activity in liver tissues of lean Sprague Dawley rats became increased in parallel to serum T3 concentrations following a thermogenic diet and decreased with advancing age in when followed up to 4 months of age, but hepatic thermogenic activity responses to a longer duration of aging and to the obese phenotype remain unclear.[19] Historically most related studies have been conducted in younger male animals. In previous studies in the corpulent rat strains, it was reported that factors of diet, cold exposure, and sympathomimetic responses to norepinephrine were impaired in the obese phenotype of both the LA/Ntul//*-cp* and the T2DM-prone SHR/Ntul//*-cp* strains.[13,16] Thus, the purpose of the present study was to determine the effects of aging and obesity on parameters of T3 generation in key metabolic tissues including BAT, liver and skeletal muscle, and their association with the impaired thermogenesis in aging and obesity in a congenic female animal model highly predisposed to obesity without the usual comorbidities of NIDDM or hypertension.

Materials and methods

Groups of lean and obese female LA/Ntul//*-cp* rats were fed Purina chow diet throughout the duration of the study to construct a 2 x 3 experimental design consisting of 2 phenotypes (lean and obese) and 3 age points (4, 14, and 24 months of age, comprising the projected lifespan of the obese phenotype. Animals were maintained in show box cages lined with 1 inch of pine shavings, with free access to Purina chow and house water, maintained at 20-21 °C, 50% RH and a reverse light cycle (Dark phase 0800-2000 daily). Animals were routinely studied during the dark phase and were fasted overnight (approximately 8 hours) prior to measures of fasting blood glucose, insulin, RMR, or thyroidal parameters. Measures of daily food consumption were obtained over a 24-hour period as described by Venula[23] and measures of live body weight as a measure of ongoing wellness obtained periodically with an Ohaus animal balance to the nearest gram. Measures of resting metabolic rate were determined at thermal neutrality (30°C) in fasted, quietly resting animals via a Collins small animal respiration apparatus fitted with a 4 liter chamber and maintained at 30°C in a closed circuit circulating water bath and corrected for factors of altitude and relative humidity.[13] At 4, 14 and 24 weeks of age groups of lean and obese rats were sacrificed by cervical dislocation, and bloods collected for hormone analysis. The retroperitoneal, dorsal, and interscapular adipose tissue depots and the gastrocnemius muscle and liver were dissected in their entirety and weighed to the nearest mg. Approximately 100 mg aliquots of IBAT, Gastrocnemius, and liver tissue were homogenized and prepared for assay of Type II thyroxine 5'-deiodinase activity in the presence of dithiothreitol (DTT) as described elsewhere (McKee and Tulp).[24] Measures of tissue and serum T4 and T3 were determined via solid phase RIA. The plasma half-life of T4 in 4-month-old male rats was determined following the intravenous injection of 1 µCi of 1-131-T4, and collection of 100 µl aliquots of blood in heparinized micro tubes via tail bleeding for up to 8 hours post infusion and plotting the rate of decline in plasma radioactivity. Data were analyzed via standard statistical procedures including descriptive statistics, ANOVA, Student's t test, and Pages L test for detection of trend analysis.[25,26] The study was approved by the Institutional Animal Care and use committee.

Results

The effects of the obese phenotype on longevity are depicted in Figure 1 and show that typical lifespan of lean animals of either sex projected longevity exceeded that of their obese littermates by approximately 25% when fed the same stock diets and environmental conditions throughout their lifespan. In addition, females of both phenotypes survive longer than their male counterparts, with lean females often surviving beyond 48 months of age. The damaging effects of obesity on projected lifespan were highly significant (p = < 0.01) in both genders. The effects of aging and obesity on final body weights from the present study are depicted in Figure 2.

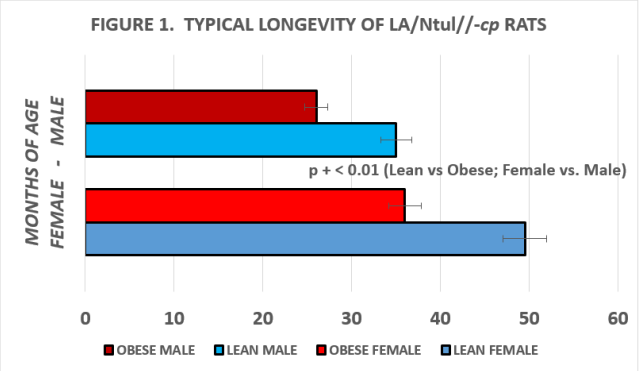

Figure 1 Projected longevity of LA/Ntul//*-cp* rats. Data are the mean ± 1 SD of over 700 rats from our colony. Rats were sustained on house water and Purina rodent chow throughout their lifespan. Rats were accommodated in pairs in Plexiglas shoebox cages lined with 1 inch of fresh pine shavings. Data extrapolated from.[13]

The effects of obesity and aging on resting metabolic rates (RMR) are depicted in Figure 3 and indicate that the RMR of lean rats were greater than the obese phenotype at each age studied. In addition, the RMR decreased progressively with advancing age in both phenotypes. When the effects of norepinephrine (NE) on resting oxygen consumption were determined, the NE response in the lean rats was greater than in their obese littermates, and the NE response

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tended to decrease in magnitude with advancing age. The increase from NE in lean averaged 25% at all ages studied, while the increase in VO2 following NE in the obese rats was similar at the 4 month age but was only 2 to 5% greater than the RMR at ages 14 and 24 months. The differences between lean and obese at each age studied were significant (p = < 0.05) by ANOVA for RMR and RMR+NE.

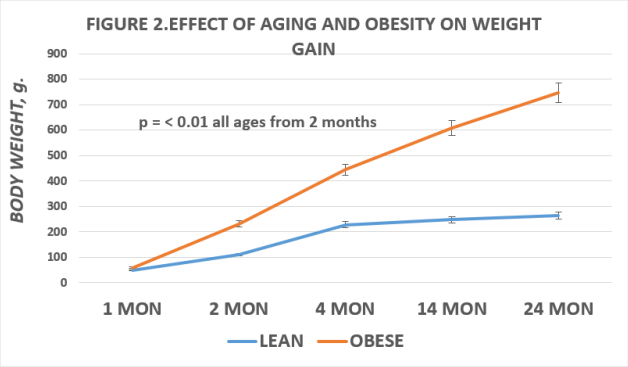

Figure 2 Indicate that the body weights of the obese phenotype were also significantly greater at each age studied.

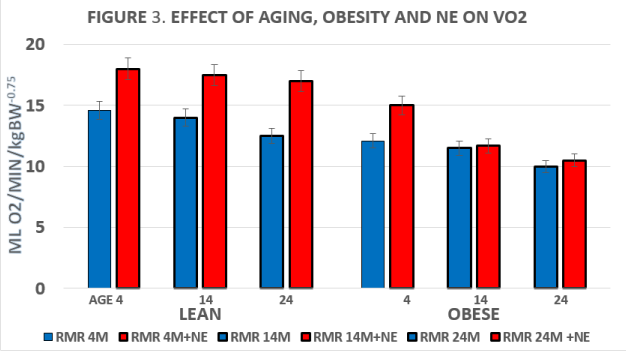

Figure 3 The effects of aging and obesity on RMR ± NE, 100 µg/100 g BW, s.c. Data are mean ± 1 SEM, n = 6-8 rats/group.

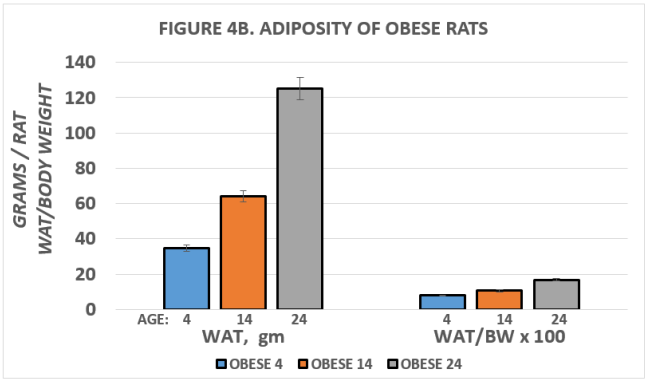

Figure 4B Adiposity of obese rats at 4, 14, and 24 months of age. Data are mean ± 1 SEM, n = 6 to 8 rats / group, and represent the sum of retroperitoneal and dorsal fat pads (left panel) and sum of retroperitoneal and dorsal fat pads / body weight x 100 at each age studied. P = < 0.01 via ANOVA. The mean values at each age are indicated above each column.

The effects of aging and obesity on thyroidal parameters are depicted in Figures 5A and 5B, and the effects of aging and obesity

Adiposity was estimated by adding the sum of the mass of the retroperitoneal and dorsal WAT depots, depicted in the left panel of Figure 4A and indicates that the sum of the two depots increased progressively at each age studied. These depots were selected to represent both an abdominal and a subcutaneous depot. When expressed as a proportion to body weight, the ratio also increased with each age. The adiposity of the obese rats is depicted in Figure 4B and indicates that the sum of the two depots also increased progressively with each advancing age, and the absolute mass was markedly greater than occurred in their lean littermates fed the same regimen. As depicted in the right panel of Figure 4B, the proportion of WAT mass also increased with age, and the absolute ratios also represented a greater proportion of body weight represented by the adipose tissue depots. Figure 1

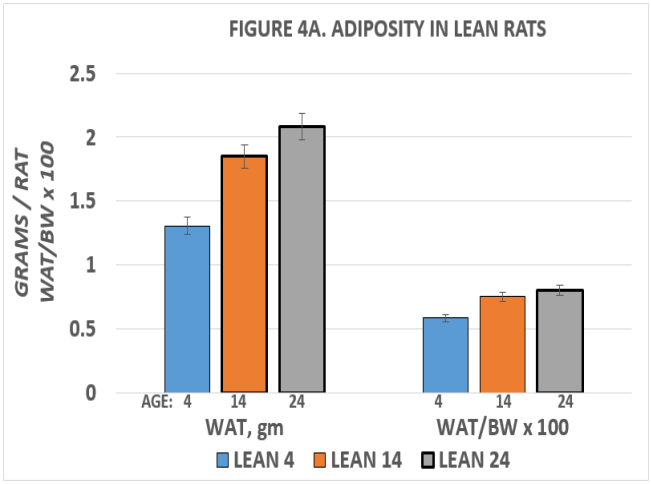

Figure 4A Adiposity of lean rats at 4, 14, and 24 months of age. Data are mean ± 1 SEM, n = 8 rats / group. Data represents the sum of retroperitoneal and dorsal fat pads (left panel) and sum of retroperitoneal and dorsal fat pads / body weight x 100 at each age studied. P = < 0.01 via ANOVA. The mean values at each age are indicated above each column.

on T4-5' deiodinase activity in Figures 6A-C. In Figure 5, serum T4 concentrations at each age studied are depicted in the left panel, and serum T3 concentrations in the right panel. Serum T4 concentrations were greater at 4 months than at 14 or 24 months in both phenotypes and were similar in lean and obese at all 3 ages studied. In contrast, serum T3 concentrations tended to increase only modestly in both phenotypes with advancing age and were within the normal physiological range in both phenotypes and at all ages studied. Serum T4/T3 ratios (left panel) and T3/T4 (right panel) are depicted in figure 5B and indicate that T4/T3 ratios of lean animals were greater than in obese animals, and decreased with age in both phenotypes. Serum T3/T4 ratios reflect the reciprocal of the T4/T3 ratios as depicted in the right panel of Figure 5B and increased with advancing age in both phenotypes. The generation of T3 from T4 occurs via the actions of a family of three distinct iodothyronine deiodinase enzymes, termed D-I, D-II, and D-III.[27] Both D-1 and D-II bring about the removal of an iodine from the 5' or outer ring position, yielding a physiologically active form of T3, while D-III removes the iodine moiety from the inner ring, 5 position, rendering an inactive hormone often referred to as 'reverse T3, or rT3.[28] In the present study, we assayed for D-II activity in liver, interscapular brown adipose tissue, and gastrocnemius skeletal muscle (Figures 6A-6C respectively).

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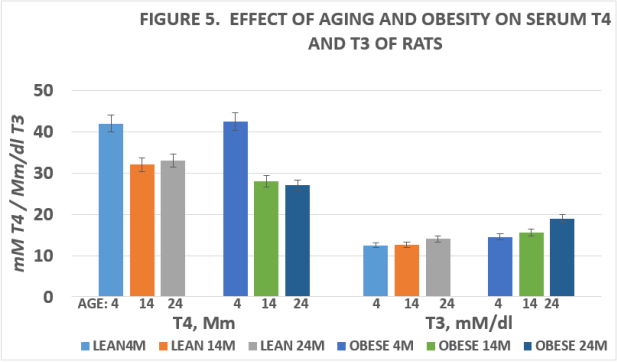

Figure 5 Effects of aging and obesity on serum T4 and T3 of rats. Data are mean ±1 SEM, n = 8 rats/group.

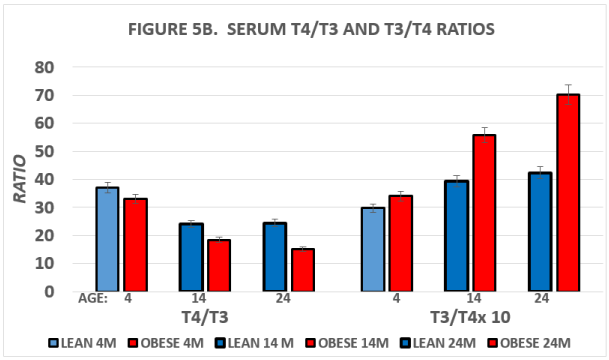

Figure 5B Effects of aging and obesity on plasma T4/T3 and T3/T4 ratios. Data are mean ± 1 SEM, n= 8 rats/group.

In liver (Figure 6A) T4-5' deiodinase activity decreases with advancing age in both phenotypes, while T4-5' deiodinase active was consistently greater in the lean than the obese phenotype at all three ages (Left panel of Figure 6A). Corresponding tissue T3 concentrations are depicted in the right panel, and also reflect decreases in 5'-deiodinase activity with advancing age in both phenotypes, but in contrast to the activity levels in the left panel, the deiodinase activity was similar in both phenotypes. Brown adipose tissue is also an active tissue for T3 generation, and the effects of age and obesity on deiodinase activity are depicted in Figure 6B. The deiodinase activity in IBAT was found to decrease with advancing age, and the activity in lean phenotype was greater than in the obese phenotype at each age studied. Tissue IBAT T3 concentrations are depicted in the right panel and indicate that tissue concentrations of T3 tended to be greater in the lean than the obese phenotype at 4 months of age but were similar in both phenotypes at 14 and 24 months of age. The tissue T4-5' deiodinase activity of gastrocnemius muscle is depicted in Figure 6C, and indicates that deiodinase activity in this skeletal muscle was less than in the liver and IBAT tissues, and tended to increase with age in the lean phenotype, while decreasing with advancing age in the obese phenotype. In contrast, tissue T3 concentrations were similar in both phenotypes at all ages.

In other studies, the overall T4 clearance of ^{131I} in the obese phenotype was found to be decreased by approximately 50% when studied under similar environmental conditions, suggestive of differences in receptor affinity in the obese phenotype, rather than differences in the bio regulatory phases of T3 generation in peripheral tissues.[28–30] The plasma half-life of $^{131I\text{-}T4}$ was determined in a smaller group of 4 month-old male lean and obese littermates fed the same diet from weaning. The $T4_{1/2}$ of T4 averaged 3.6 hours in the lean phenotype, and 6.8 hours in the obese phenotype, consistent with a systemic decrease in the activity of outer ring T4-5' deiodinase activity and in the peripheral generation of T3 in peripheral tissues of the obese phenotype of male littermates. Considering that the deiodinase activity rates in the three tissues identified are expressed per mg of tissue, the liver contributed the greatest mass of the three tissues analyzed and may suggest that the liver may be a predominant tissue in overall peripheral T3 production in this animal model, and the results of the longer plasma T4 survival time in male littermates are consistent with that observation. Figure 7

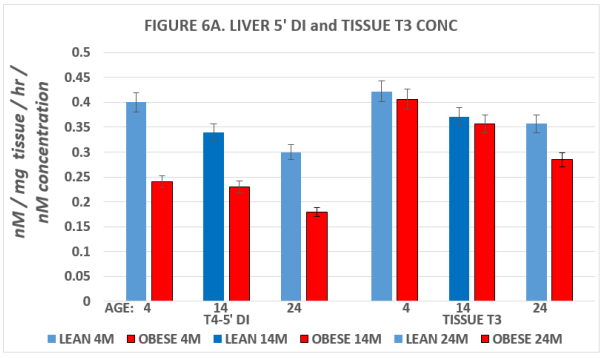

Figure 6A Effect of age, obesity, and phenotype of Type II T4-5' deiodinase activity in liver. Data are mean ± 1 SEM, n= 8 rats/group. Deiodinase activity is depicted in the left panel, and tissue T3 concentrations in the right panel.

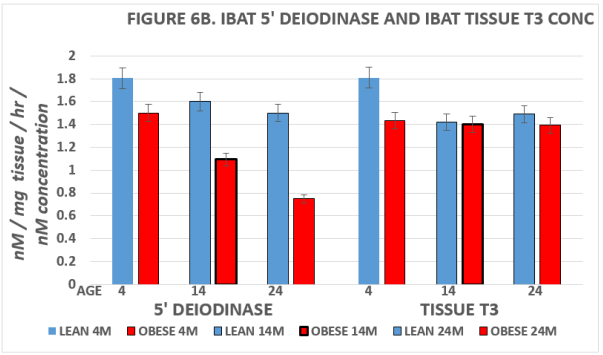

Figure 6B Effect of age, obesity, and phenotype of Type II T4-5' deiodinase activity in IBAT. Data are mean ± 1 SEM, n= 8 rats/group. T4-5' Deiodinase activity is depicted in the left panel, and tissue T3 concentrations in the right panel. Blut = lean rats, red = obese rats.

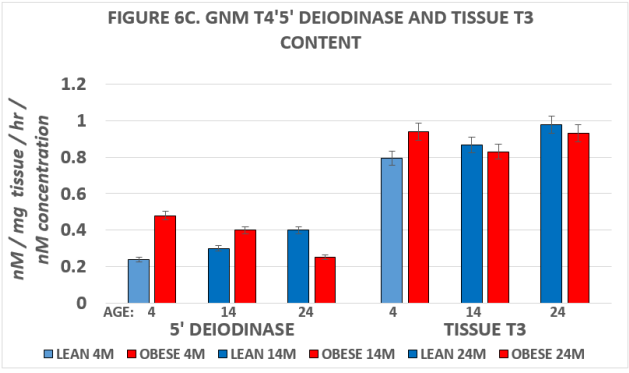

Figure 6C Effect of age, obesity, and phenotype of Type II T4-5' deiodinase activity in gastrocnemius muscle. Data are mean ± 1 SEM, n= 8 rats/group. Deiodinase activity is depicted in the left panel, and tissue T3 concentrations in the right panel.

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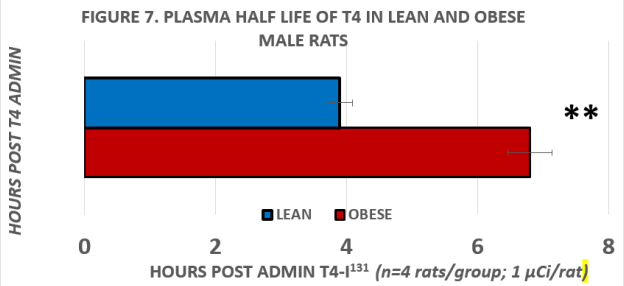

Figure 7 Effect of phenotype on plasma half-life of T4. Data are mean ± 1 SEM, n = 4 male rats/phenotype. ** = P < 0.01 (Student's t Test).

Discussion

Thyroid hormones play essential roles in numerous regulatory aspects of genetic expression and metabolism in man and animals.[28,29,31] Thyroxin (tetra iodothyronine, or T4) is secreted and stored in the thyroid gland where it is stored primarily in the form of thyroglobulin, a 660 kd glycoprotein produced by the follicular cells of the thyroid gland. After the glycoprotein is synthesized, it stores thyroid hormones in the form of T4, small quantities of T3, and iodine.

Once the thyroid hormones are mobilized in response to physiological stimuli, they are released into the circulation as physiologic demands of peripheral tissues dictate. Once released into the general circulation the T4 undergoes deiodination to T3, the physiologically more active form of the hormone via actions of D-1 and D-2 tyrosyl deiodinases in multiple peripheral tissues including the liver and brown adipose tissue. Alternatively inner ring tyrosyl deiodination of T4 via D-3 deiodinase results in formation of rT3, a physiologically inactive analog form of the T3 hormone resulting from the inner ring deiodination.[28] The thyroid hormones T3 and T4 become bound to plasma thyroid binding globulins in circulation and in cells, leaving only a small fraction of free, non-bound hormone that becomes readily available for immediate uptake in peripheral tissues. Once the free active hormone reaches its cytoplasmic environment, it easily identifies with specific genomic binding sites on nuclear and mitochondrial DNA, where it facilitates the epigenetic expression of thyroidal actions on a broad assortment of growth, development and metabolic actions. Of interest, the iodine moieties that are generated following removal from the tyrosyl residues during the deiodination reactions are efficiently taken up against a significant concentration gradient and recycled into the biosynthesis of additional thyroid hormones in the thyroidal epithelium.

Factors of diet and environment are among the best known and documented regulators of T4 deiodination to T3 or rR3 in peripheral tissues: cold exposure, carbohydrate and high energy feeding bring about increases in peripheral T3 generation, while fasting and starvation bring about increases in the physiologically inactive rT3 from T4, thereby contributing to energy conservation during conditions contributing to deficits in energy intake.[28] The rT3 contributes to decreases in resting metabolic rate and in subsequent energy conservation via decreases in T3 availability, receptor binding and actions.[31,32] The cumulative effects of the metabolic processes contributing to energy conservation may be a key to enhance survival duration under prolonged deficits in nutrient and energy availability. Additional thyroidal contributions to conservation of mechanisms of energy expenditure may occur via decreases in the genomic receptor affinity for T3 and may represent likely secondary effects to metabolic processes linked to hyperinsulinemia and/or including the development of insulin resistance, a common hallmark of obesity and T2DM.[33–36] Clinical assessment of thyroidal status typically includes measurement of plasma thyroidal hormones including TSH, which yield important information about thyroidal hormone regulation, including aspects of the feed-back regulation leading to hormone synthesis and release. In contrast, the metabolic actions of thyroid hormones occur intracellularly, therefore assay of plasma hormone levels may fail to adequately address the intracellular actions, while measures of resting metabolic rate may provide supporting evidence. In the present study, measures of both resting and norepinephrine-stimulated oxygen consumption corrected for differences in mass and surface area were decreased in the obese phenotype, and tended to decrease further with advancing age, consistent with a likely decrease in both thyroidal and sympathomimetic contributions to nonshivering thermogenesis and thus reflect a conservation in net energy expenditure in the obese phenotype.

A state of subclinical hypothyroidism of unconfirmed origin has been described in patients with metabolic syndrome, a condition where the hallmark factors of obesity and insulin resistance are present.[8] In addition, a syndrome of subclinical hypothyroidism has also been described in obese, hyperinsulinemic rats, including demonstration of decreases thyroid hormone receptor affinity in the obese animals that could account for at least in part, the reduced resting metabolic rates commonly reported to occur in the obese animals of this and other strains of obese rodents.[4,16,18] Thus, peripheral generation of T3 is an essential process in the expression of thyroid hormone-mediated effects on genetic expression and metabolism, and likely impacts survival and potential longevity as well.[3,4,6–8,16,18]

Obesity is typically characterized by variable states of hyperinsulinemia and insulin resistance, which may also confound thyroidal actions in peripheral tissues.[3,6,18,33–37] In the present study, we documented marked weight gain and adiposity in the obese phenotype of the non-diabetic corpulent rat, in concert with decreases in both resting and norepinephrine-stimulated metabolic rate, both considered essential constituents of non-shivering thermogenesis (NST). The NST requires both sympathetic and thyroidal actions, both shown to be contributing about half of the total thermogenic response in rats.[13,38] Sympathetic thermogenic actions are mediated principally by norepinephrine via specialized stereospecific cell surface receptors that can discriminate between the various sympathomimetic hormones, while thyroid hormones interact at the level of the genome via a family of highly stereospecific thyroid hormone receptors, where their actions are epigenetic in nature. In the present study, the mechanism of T3 generation in peripheral tissues appears to be largely intact, albeit modestly less active than in their lean littermates. In both phenotypes thyroidal generation tends to decrease with aging, with progressive declines in the T4/T3 ratio, and reciprocal increases in the T3/T4 ratio with advances in aging in both phenotypes. At 24 months of age, the obese phenotype is approaching their maximum longevity. In contrast, the lean phenotype typically experiences an average lifespan of three years or more, and where the differences in longevity between the two phenotypes has been associated with chronic insulin resistance, neurocellular senescence and other factors and longevity declined more rapidly in the obese than the lean phenotype.[9,10] These observations are consistent with those reviewed by Taylor,[18] who also reported age associated declines in thyroidal actions in aging among humans in clinical studies.[18] Measures of free T3 and T4 may have provided additional insight but were not recorded in the present study.

No discussion of thyroidal activation, biologic functions and longevity would be complete without a brief inclusion of the bio physiological actions of sirtuins, regulatory factors also identified as NAD+ dependent deacetylases deriving from liver, brown adipose tissue, and other tissues.[39–50] The group of NAD+-dependent deacetylases are a family (n=7 at last count) of silent information transfer factors that can bring about the enzymatic deacetylation and subsequent activation of some chromatin-based histone proteins, thereby conferring genomic-linked regulatory actions on key regulatory elements of intermediary metabolism, cell survival and cellular replication, all of which can contribute to a healthful longevity.[39,41,44] Sirtuins facilitate their biological actions as a reflection at least in part of the prevailing NAD+/NADH ratio, a biochemical function of cellular oxidation and mitochondrial activity. Thus, both nutritional and environmental factors contribute to the regulation of sirtuin production and cellular activity, in concert with elements of cellular and mitochondrial substrate metabolism**.** [38–43]

The formation and release of sirtuins respond to parameters of caloric intake and nutritional wellness. During periods of starvation, fasting or caloric deprivation for example, SIRT1 release increases, histone deacetylation and resulting activation becomes increased, followed by a reciprocal decrease in thyroidal activity and a consequential decrease in RMR.[39–43] As the deiodination of T4 to T3 decreases, and the alternate pathway of T4 deiodination to hormonally inactive rT3 becomes increased, with the net effect resulting in a decrease in RMR as the individual shifts metabolism from the fed- to the unfed- state.[41,42] In contrast, episodes of caloric intake including normal or overfeeding result in a reversal of the NAD/NADH ratio as derived from macronutrient and substrate oxidation, a suppression of hepatic SIRT1 generation, and a shift in T4-deiodination from the inner 5-position yielding hormonally inactive rT3 to the outer ring 5' position yielding hormonally active T3. [27,50] Thus, the shift in deacetylase activity results in increases in T3 generation, followed by genomic-linked T3-THRβ-subunit association, T3-linked genomic expression, greater mitochondrial activity, and increases in RMR. The formation of high energy phosphate bonds of ATP that are required for many energy-consuming biosynthetic reactions are endergonic and consume energy to produce. Centristically, the cleavage of high energy bonds especially typical of brown adipose tissue and muscular contraction is exergonic with the release of heat energy, with the collective efforts thereby facilitating thermoregulation during excursions in environmental and nutritional conditions and in aging and senescence. With further respect to thyroidal-mediated activity, since Sirt1 release is activated via the NAD+/NADH ratio, thyroidal activity and T3-mediated actions thus become biochemically linked to a mitochondrial function that reflects the relative activity of intermediary metabolism. As in the present study, the overall activity of intermediary metabolism and mitochondrial activity is often estimated in vivo by measures of resting oxygen consumption, or RMR, since active mitochondria are the primary organelles responsible for oxygen utilization during mitochondrial activity, ATP generation and exergonic use.[21]

Further extrapolation of the proposed role of sirtuins in longevity follow sirtuin-linked actions on the regulation of the cell cycle, with regulatable slowing actions at both the M and the S phase of the cell cycle, thereby improving the regenerative process.[44–48] The cellular impact is to prolong individual cell survival, and permitting continued cellular repair and replication albeit it likely at a slower rate than in a highly fed state. Sirtuin actions are necessary for orchestrating DNA point repair in addition to mitotic and likely successful mitochondrial replication. As an animal or individual ages, hepatic sirtuin production, like insulin and thyroid hormones, also tends to decline with aging. The net effects of age-related functions results in corresponding increases in proportional SIRT1 inactivation of thyroidal activity, decreases in RMR, decreases in the rate of telomere shortening, and further extension of a healthier lifespan. In contrast, during the absence of fasting, hepatic release of sirtuins becomes decreased, and the subsequent rate of telomere shortening may become proportionately accelerated, with ultimate potential decreases in the projected life span in man and animals. Telomeres consists of repetitive DNA sequences, specifically six-base pair TTAGGG sequences. The telomere lengths tend to decrease with aging from childhood and beyond, and once the telomeres attain a critical reduction in base length, continued cellular recovery and proliferation may become irreversibly compromised. Specifically, SIRT1 deacetylates XPA on K63 and K67 of the genome, thereby facilitating its genomic interaction with RPA32, a linked stabilization factor which enhances single-stranded DNA integrity during replication and DNA damage repair.[49] Finally, SIRT1 overexpression following longer durations of fasting in mice was reported to inhibit telomere erosion while its telomere silencing functions during feeding accelerated their shortening.[46] Thus, while the entirety of the molecular interactions of sirtuins remain unclear or incompletely defined, the proposed roles of sirtuins in functional thyroidal activity and healthful longevity represent an important and now-emerging area of scientific interest in man and animals.

Summary and conclusions

The results of this study indicate that essential parameters of thyroidal function and actions, including resting and norepinephrine stimulated thermogenesis, and the peripheral deiodination of T4 to T3 in selected peripheral tissues declines in aging, with further decreases in the obese phenotype of this strain. In contrast, the plasma half-life of T4 is significantly longer in the obese than the lean phenotype, consistent with decreased activity of T4-4'-deiodinase in liver and IBAT, two of the primary peripheral tissues where plasma T3 is generated in rodents. Historically, the role of nutrition and environmental temperatures have been considered key factors in peripheral T4 deiodination and T3 generation. However, the results of this study indicates that factors of obesity and likely insulin resistance may also contribute an additional layer of control over the processes of thyroid hormone generation and genomic actions. The independent presence of insulin resistance, a hallmark of the obese state, may also be a contributing factor and could not be ruled out from this study. The process of protein turnover, consisting of the sum of protein synthesis and degradation in both smooth and striated muscle is a major insulin-linked factor in resting energy expenditure, and was found to be decreased during post weaning growth by 50% or more in the obese phenotype of this congenic strain.[51] Genomic activation via tissue T3 also contributes to the economy of protein metabolism, but major differences in tissue T3 concentrations in the obese phenotype were not apparent in the present study, suggesting that the regulatory mechanisms of thyroid hormone formation and distribution were likely intact, and that the direct source of the economy and energetic expenditure of protein turnover was more likely associated with insulin resistance or receptor affinity than T3-mediated epigenetic expression in the obese phenotype in that study. The cellular affinity for the genomic receptors for T3 however, was decreased in the obese phenotype, consistent therefore with the metabolic economy noted above and in that of the present study by the lower resting and norepinephrine stimulated metabolic rates in the obese phenotype.[29,52]

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Conclusion

The results of this study indicate that key parameters of thyroid hormone generation and actions are decreased in the obese phenotype of the LA/Ntul//-*cp* rat, and that thyroidal parameters become further decreased with advancing aging in both phenotypes.

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Competing interests

The author reports no competing interests.

Use of Artificial intelligence

The author reports that no applications of AI were utilized in the generation of this manuscript

Conflict of interests

The author declares that there are no conflicts of interest.

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