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Research Article

Determination of T4-5' deiodinase activity and metabolic sequelae in peripheral tissues of congenic lean and obese LA/Ntul//-cp rats

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Abstract

Thyroid hormones are well established entities that readily mediate numerous essential biochemically-mediated elements of normal development, growth and energy metabolism (EM) expressed at the genomic level in response to alterations in diet and environment. A family of three highly specific Iodothyronine deiodinases consist of a subfamily of three deiodinase enzymes that exert important roles in the activation and deactivation of thyroid hormones in virtually all somatic tissues of vertebrate organisms. Thus, thyroid hormones can directly bring about genomic-mediated variations in gene expression and in the rate of metabolism including pathways of energy expenditure and in the conservation of energy utilization in peripheral tissues. Groups of lean and obese animals were subjected to measures of resting and norepinephrine stimulated VO2, measures of plasma insulin and glycemic parameters, tissue T3 and total in vitro deiodinase activity in multiple tissues, T4 half-life, and T3 nuclear hepatic receptor binding occupancy. The VO2 of resting and dose related NE stimulated VO2 of lean > obese, and serum and tissue T3 of lean > obese, and T4-5' deiodinase activity of lean > obese in liver and obese > lean in IBAT. T3 receptor occupancy was decreased and T4 half-life was prolonged in the obese phenotype. These results indicate that net T4 activation to T3 and hepatic T3 nuclear receptor binding is decreased in the obese phenotype, and despite the increase in IBAT mass, the decreases in thyroidal actions and hyperinsulinemia are likely contributors to the decreased capacity for resting and NE-stimulated thermogenesis and contributors to greater adiposity in the obese phenotype of this strain.

1. Introduction

Thyroidal hormones contribute essential roles to the efficiency and metabolic regulation of energy metabolism in man and animals [1]. While some active T3 is released from thyroidal tissue, the iodothyronine deiodinases that act on T4 are strategically located in peripheral tissues in the intracellular compartment, thus generating partially deiodinated thyroidal entities that are in close proximity to thyroid hormone (TH) genomic receptor domains and where they can bring about both activation or inactivation of thyroid hormone mediated metabolic activities [2, 3]. These actions include converting the inactive prohormone L-tetraiodothyronine (T4) to the hormonally active L-triiodothyronine (T3) form via a Type 1 deiodinase (EC 1.21.99.4) or a Type II deiodinase (EC 1.21.99.3) in the outer ring of the hormone. These deiodination actions are typically accomplished by stereospecific deiodination of the outer (β) benzene ring 5'- iodine [3, 4]. Alternatively, a physiologically inactive iodothyronine may be generated by removal of the inner (α) tyrosyl ring at the 5 position to from 3', 5', 3 iodothyronine from the T4 substrate via D-III deiodinase (EC 1.21.99.5), commonly referred to as 'reverse T3' (or rT3), that is accomplished by removing the iodine from the 5 position on the inner (α) tyrosyl ring of the iodothyronine [1–3, 5, 6]. The D-III

deiodinase can also inactivate hormonally active T3 to form diiodothyronine (T2) to terminate the hormonal activity of T3. The Iodothyronine deiodinases including Type 1 deiodinase (EC 1.21.99.4 and EC 1.21.99.3 (Type II deiodinase) and Type III deiodinase (EC 1.21.99.5) are a subfamily of strategically located membrane associated deiodinase enzymes that provide essential actions important in the activation and deactivation of thyroid hormones. The D-I and D-III enzymes are plasma membrane-associated entities, where they may facilitate the respective deiodination actions upon T4 initial entry into the cells and tissues. In contrast, D-II is strategically located internally on the endoplasmic reticulum (ER) membrane, in close intracellular proximity to epigenetic receptor domains [5, 6]. All naturally occurring thyroid hormones are formed biosynthetically as the L-enantiomers, while the synthetic D-enantionmers can also undergo deiodination but are virtually devoid of most but not all thyroidally mediated metabolic actions aside from their lipid lowering effects [7]. The hormonal actions of thyroidal entities are expressed via interaction of triiodothyronine (T3) with two thyroid hormone receptors (THRs), THR-α- and THR-β that reside on thyroid hormone response elements (TREs) located on TH promotor regions of their target genes [8]. In so doing, they normally mediate transcription events via both genomic and some non-genomic mechanisms. The TH α- and β- receptor affinity for T3 is much greater than for T4, however, necessitating outer ring deiodination of the T4 prohormone to hormonally active T3 to most efficiently impinge on the TREs.

Metabolic effects of endogenous thyroid hormones directly and indirectly impact multiple parameters of macronutrient energy metabolism at several levels of organization in this rodent strain, thereby impacting aspects of carbohydrate, protein, and lipid metabolism. In addition, the presence of insulin resistance in the obese phenotype from weaning also impacts the efficiency of energy metabolism and storage, including the efficiency of protein synthesis and degradation, key elements of protein turnover, thereby decreasing the ATP requirements normally consumed in the processes of protein synthesis, and further contributing to the efficiency of energy storage and depot-specific fat accretion [9–11]. Moreover, the decreases in insulin sensitivity in muscle and adipose tissue depots contributes to the impaired glucose disposal in peripheral tissues following meals in the obese phenotype [12–16]. Parameters of nonshivering thermogenesis following alterations in diet and environment are also impaired in the obese phenotype of this and other genetically obese rodent strains, including the thermic responses to adrenergic stimulation [17, 18]. Adrenalectomy has been shown to decrease the magnitude of insulin resistance, and improve the capacity for nonshivering thermogenesis (VO2) within 21 days post-surgery, presumably via a restoration of GLUT4 activity in peripheral tissues, a primary factor in restoring the efficiency of glucose uptake in skeletal muscle and adipose tissues during the fasting and postprandial states of glucose disposal [13, 14]. In addition, thyroid hormones principally T3 improve the sensitivity of adrenergic receptor actions, thereby contributing to the restoration and normalization of the thermic responses to diet and environment [1]. Thyroid hormone actions also enhance the preferential oxidation of glucose as a metabolic energy source, with corresponding improvements in resting energy expenditure in insulin-dependent tissues [18].

2. Methods

Groups of lean and obese littermates(n= 6-8 rats/group) were obtained from the Drexel colony at 5 weeks of age and placed in plexiglass showbox cages lined with one inch of pine shavings. Rats were maintained on Purina rodent chow (formula 5012) and house water ad libitum in littermate pairs (1 lean plus 1 obese) from weaning throughout the study under conventional laboratory environment (22$^{\circ}C$, 50% RH, on a reverse light cycle (light 8 PM to 6 AM). A colony-wide weighing was conducted where approximately 700 male and female animals of both lean and obese phenotypes were weighed [19]. At 8 weeks of age, lean and obese littermate female rats were subjected to determination of resting metabolic rate in a Collins small animal thermogenesis apparatus fitted with a 1 cubic foot plexiglass closed circuit metabolic chamber and RMR expressed / kg of Body Weight- at thermal neutrality (30$^{\circ}C$) during the mid dark cycle after a brief 6 hour fast and expressed as kg $BW^{-0.75}$ to adjust for differences in body size and surface area as outlined by Klieber and Yang [20, 21].VO2 was determined before and after administration of norepinephrine (100 or 200 μg/kg BW, s.c. on separate days). At 16 weeks of age, animals were sacrificed by acute cervical dislocation and blood, liver, kidneys, gastrocnemius muscle and IBAT harvested, weighed to the nearest mg. The tissues were homogenized in a phosphate buffer and measures of total T4-5' deiodinase activity in the presence of dithiothreitol (DTT, 3 μg) to determine the maximum combined activities of D-1 and D-II respectively [22]. Measures of tissue and plasma T3 and plasma T4 were determined by radioimmunoassay and expressed as ng T3/dl of plasma or of homogenate after a 120 minute incubation at 37°C in a shaking water bath at 50 cycles per minute [22]. Liver tissues were homogenized in a chilled phosphate buffer, and measures of T3 nuclear receptor binding over a broad range of physiologic and supraphysiologic T3 concentrations at 37$^{\circ}C$ determined as outlined by Hillgartner and Romsos [23, 24]. Data were analyzed via standard statistical procedures, and trend analysis was determine via Page's L test for trend analysis [25, 26]. The study was approved by the Intuitional animal care and use committee (IACUC).

3. Results

The metabolism of thyroid hormones is depicted in the schematic in Figure 1, which depicts the transformation of the prohormone levo-tetraiodothyronine (L-T4) to its metabolically active and inactive forms of T3, rT3 and T2 respectively. The active T3 formation is depicted on the left side of Figure 1 via Type I Deiodinase (D-I) and Type II deiodinase (D-II), and its metabolically inactive inner ring form of rT3 via Type III deiodinase (D-III) is depicted on the Right side of the diagram. Both T3 and rT3 are further inactivated to T2 (3,3'T2) devoid of nuclear binding or other physiologic activity. The iodine moieties that are thereby generated may be recaptured and recycled by the thyroidal epithelium, where they may contribute to the iodination of additional thyroglobulin tyrosyl residues during the de novo formation of additional L-T4. This reuptake of iodine moieties is highly beneficial to human health as dietary iodine availability is often sparse in many remote parts of the global land masses, especially in landlocked locales distant from the oceans and in iodine unsupplemented foodstuffs.

The effect of age, gender and phenotype on body weight is depicted in Figure 2, and indicates that while body weights were similar in the two phenotypes at weaning, the obese phenotype gained weight more rapidly and soon surpassed the average weights of their lean littermates by a factor of two by adolescence and early adulthood, despite having been fed the same dietary regimen and environmental conditions throughout the duration of postweaning growth and development. Moreover, the accelerated rate of growth and weight gain continued well into adulthood, while weight gain in the lean phenotype became stabilized by ten weeks of age in both males and females with little change thereafter. The obese phenotype began to exhibit evidence of moderate hyperphagia soon after weaning, which appears to have continued thereafter, and which in addition to epigenetically mediated metabolic factors may at least partially contribute to the added weight gain in the

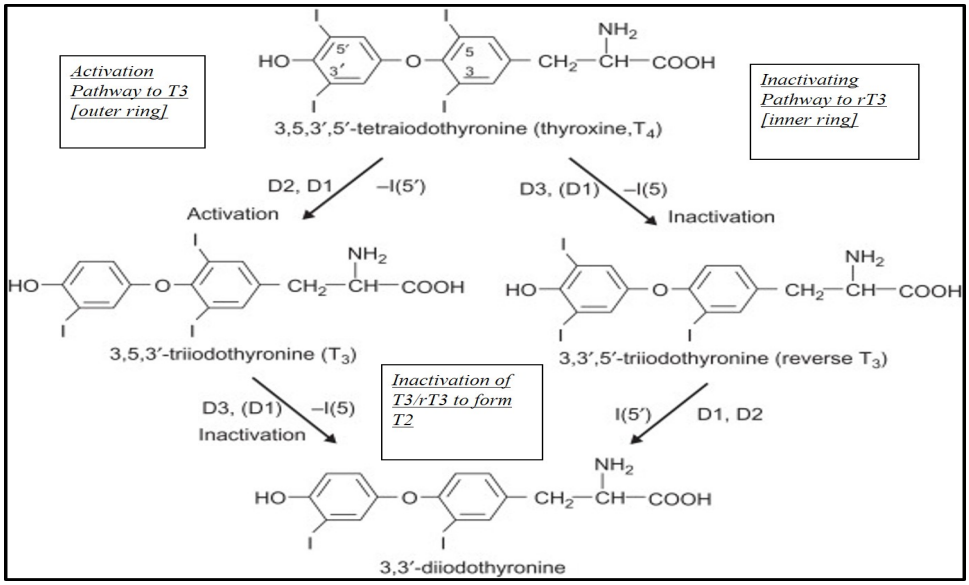

Figure 1: Schematic of iodothyronine deiodination in peripheral tissues. T4 = tetraiodothyroiine; T3 = triiodothyronine; T2 = diiodothyronine. IDI = T1 5' deiodinase; IDII = T2 5-deiodinase; IDIII = T3 deiodinase. Outer benzene ring also referred to as the β-ring, located on the left side of the molecule as indicated, while the inner tyrosyl ring on the right side as depicted is often referred to as the α-ring. -I(5') removal of outer 5' position iodine; -I(5) = removal of inner 5 position iodine; -I(5) = removal of inner ring 5' position iodine; I(5') = removal of outer ring 5' position iodine. Ref modified from multiple refs [3–5].

obese phenotype.

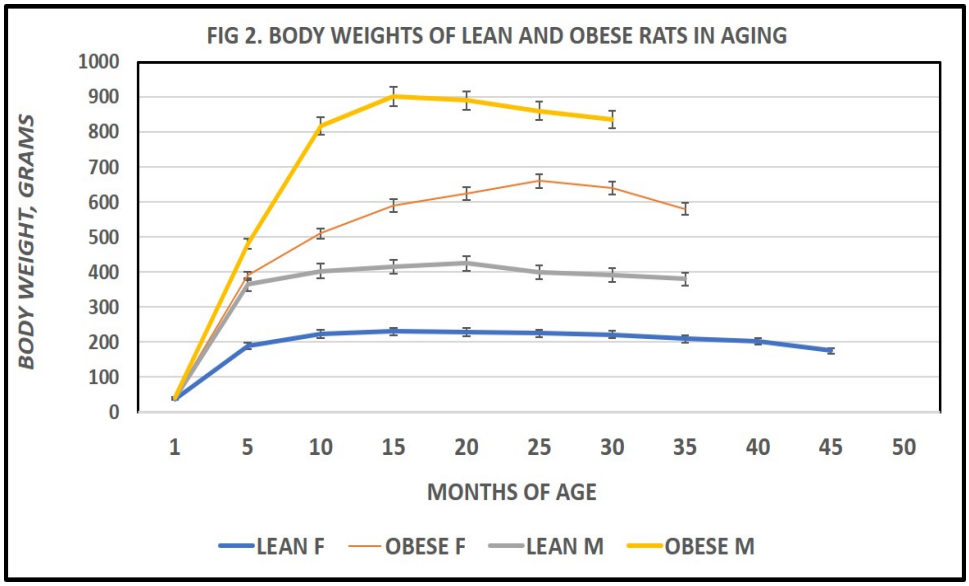

Figure 2: Effect of age, phenotype and gender on body weights of LA/Ntul//-cp rats. Data were obtained from taking live weights of approximately 700 animals, fed standard Purina Lab chow from weaning. Data points are mean ± 1 SEM of 5-10 animals per data point. F = female; M = male.

The effects of phenotype on plasma glycemic parameters and adiposity are presented in Table 1, and indicate that by 16 weeks of age, fasting plasma insulin concentrations and the insulin to glucose ratios were markedly elevated in the obese phenotype, indicative of insulin resistance but without the confounding impact of overt non-insulin diabetes myelitis (NIDDM) since none of the animals demonstrated overt glycosuria or OGT responses consistent with a diabetic state. Historically. IR but not NIDDM has been reported to occur in this strain to date [18, 19, 27]. Biometric data including liver mass and fat pad mass of principle adipose tissue depots is presented, and indicates that the liver mass of obese animals was doubled that of their lean littermates at 16 weeks of age, and began to reflect early visible signs of fatty liver formation. Both retroperitoneal and dorsal fat pad weights were also significantly greater, 23-fold and 5- fold respectively. In addition, interscapular brown adipose tissue mass, a normally thermogenic tissue, was also markedly greater n the obese than in the lean phenotype and all fat pad measures were significant at the $p < 0.001$ level.

The effects of phenotype and norepinephrine administration on VO2, corrected for difference in body mass and surface area in quietly resting animals are depicted in Figure 3 and indicate that phenotype effects were present in resting metabolic rates, Lean > obese in all measurements depicted. The resting VO2 of lean rats averaged 20% greater in the lean than in their obese littermates. The effect of NE administration resulted in a ˜25% increase in VO2 at the lower dose, and a 50% increase at the higher dosage. In contrast, in the obese littermates the NE-induced increase averaged 20% above baseline and increased only modestly to 24% above baseline following the greater dosage level.

Table 1: Insulin status, liver and fat pad depot weights of lean and obese rats

Phenotype	N	Insulin µU/ml	Ins:Glc	Liver, G	RP, g	Dorsal, g	IBAT, g
Lean	12	30± 5	5.55±0.13	6.06±0.33	0.81±0.10	0.33±0.04	0.27±0.02
Obese	12	139±15	23.99±1.51	12.64±0.59	15.84±3.30	1.67±0.11	0.95±0.11
P =		< 0.001	< 0.01	< 0.001	< 0.001	< 0.001	< 0.001

Plasma fasting insulin, Insulin:glucose ratios, fat pad and liver weighs of lean and obese LA/Ntul//-cp rats at 16 weeks of age. Data are mean± 1 SEM, n=12 rats/phenotype. Insulin reported as µU/ml; Insulin:Glucose reported as molar ratios. RP = retroperitoneal fat depot. P= < 0.001 to < 0.01, student's 'T' test.

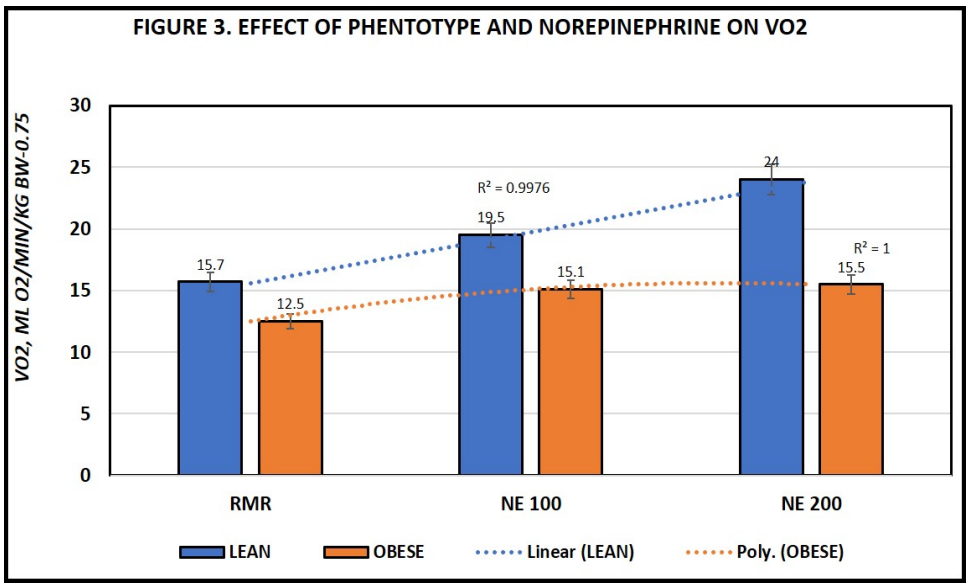

Figure 3: Effect of norepinephrine on resting VO2 in lean and obese rats. Data are mean ± 1 SEM, n = 6 rat/group. Phenotype effects for p = ¡ 0.05 (Lean vs Obese) at each dosage level.

The effect of phenotype on tissue and serum T4 and T3 are depicted in Figures 3 and 4 respectively. In Figure 4, plasma T3 concentrations are depicted at 6 and again at 16 weeks of age in normally fed and reared rats and indicate that T3 concentrations in lean rats were similar at both ages. In contrast, plasma T3 concentrations of obese rats were modestly lower than in their similarly fed lean littermates at both ages studied and the differences between lean and obese rats were significant at the p = < 0.05 level.

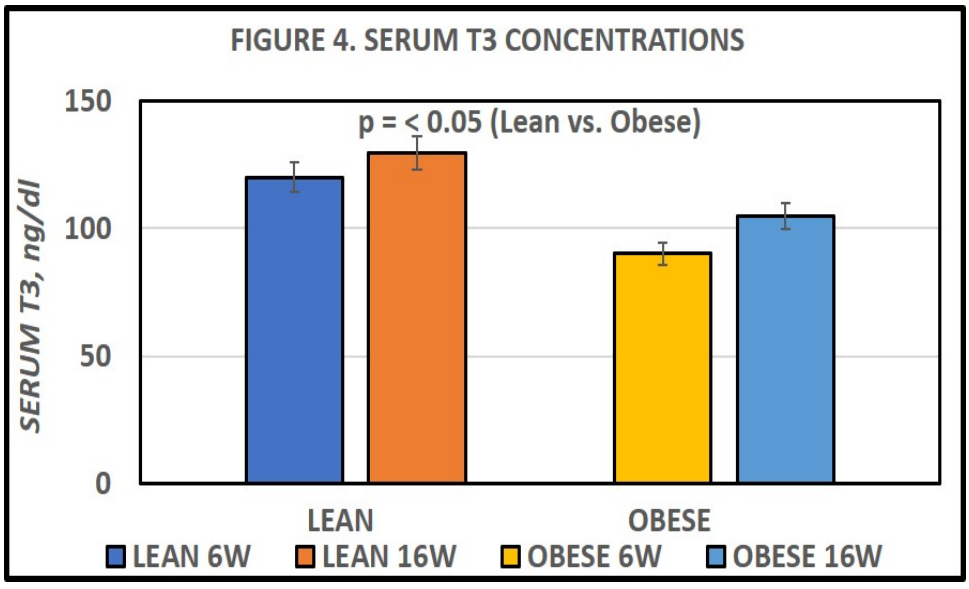

Figure 4: Plasma T3 concentrations at 6 and 16 weeks of age. Data are mean ± 1 SEM, n = 6 rats/group. P = < 0.05 for phenotype effects at both 6 and 16 weeks of age.

In Figure 5, plasma T4 concentrations are depicted at 6 and again at 16 weeks of age in normally fed and reared rats and indicate that T4 concentrations in lean rats were similar at both ages. In contrast, plasma T4 concentrations of obese rats were lower than in their similarly fed lean littermates at both ages studied and the differences between lean and obese rats were significant at the p=0.05 level at both ages studied.

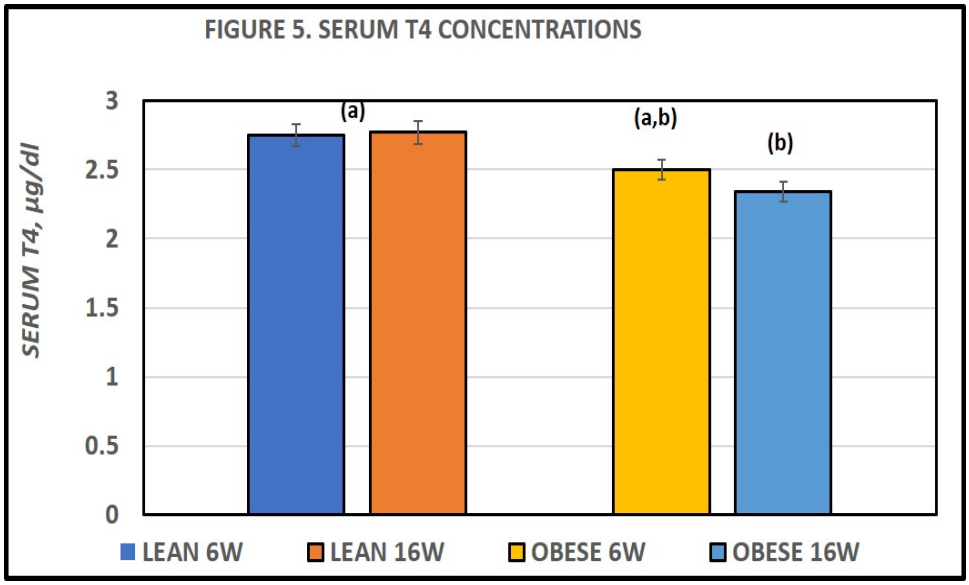

Figure 5: Plasma T4 concentrations at 6 and 16 weeks of age. Data are mean ± 1 SEM, n = 6 rats/group. The letters above each bar indicate differences via Student-Newman-Keuls subgroup analysis.

Tissue T3 concentrations in three tissues are depicted in Figure 6, and indicate that tissue T3 concentrations in liver homogenates in lean rats tended to be modestly greater in the lean than in their obese littermates at 16 weeks of age (exact p = 0.065), while tissue t3 concentrations in kidney tissue homogenates were similar in both phenotypes. Tissue T3 concentrations in IBAT homogenates are depicted in the far right panel, and indicate that like kidney homogenates, IBAT tissue T3 concentrations were similar in both phenotypes mhen measurd at 16 weeks of age. Note that the absolute concentrations presented do not reflect the greater organ mass in the obese phenotype, which if computed would likely reflect a greater organ-wide T3 quantity on the basis of net mass/organ.

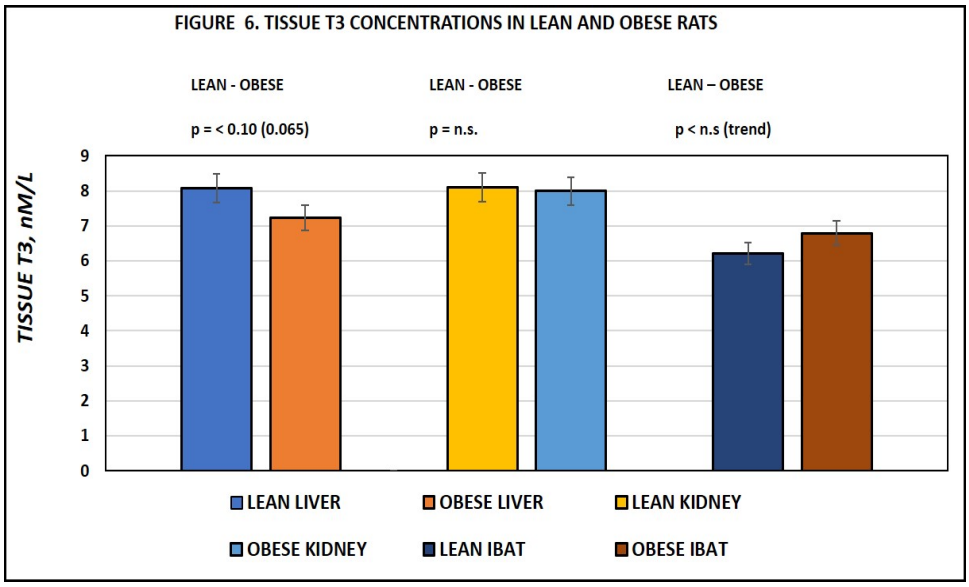

Figure 6: Tisue T3 concentrations in liver, kidney, and IBAT. Data are mean ± 1 SEM, n = 6 rats/group.

Tissue outer ring T4-5'-deiodinase activity in liver, kidney and IBAT is depicted in Figure 7, with lean rats presented in the Left panel, and their obese littermates in the Right panel, indicating individual organ capacity to activate T4 to its metabolically active form of T3. Significant phenotype effects were noted for liver T4-5'-deiodinase activity in liver (Lean 26% > obese) and IBAT (Obese 75% > Lean), while outer ring deiodinase activity in renal homogenates was similar in both phenotypes (mean 0.387 vs 0.386 ng/T3/dl, Lean vs Obese respectively). Overall T4 disappearance data following I-131 T4 at comfortable room temperatures $(22°C)$ are depicted in Figure 8, obtained in a similar-aged group of male littermates. The mean half life of T4 disappearance in lean frats averaged 3.9 hours, while the T4 disappearance half life in their obese littermates averaged 6.8 hours, approximately 75% longer than in their lean littermates. The phenotype effects resulting in the prolonged T4 disappearance was highly significant (p = < 0.01) despite the small N = 4 of the treatment groups. The effects of in vitro T3 receptor binding occupancy in liver homogenates is depicted in Figure 9 and indicates that binding occupancy of lean rats was significantly more avidly than occurred in their obese littermates at both physiologic (< 8 nM) and supraphysiologic (> 10 nM) concentrations. Thus, the net binding activity of lean rats, as determined by computing the area under the curve was approximately 2-fold greater in the lean phenotype, or conversely, T3 receptor binding was decreased by approximately 50% in both substrate concentration ranges of the T3 substrate. The differences in the binding avidity are not immediately apparent from the data presented but may implicate

alterations in silent transporter functions including Sirt1 availability or actions or other molecular actions including the presence of insulin resistance throughout adolescence and adulthood in the obese phenotype.

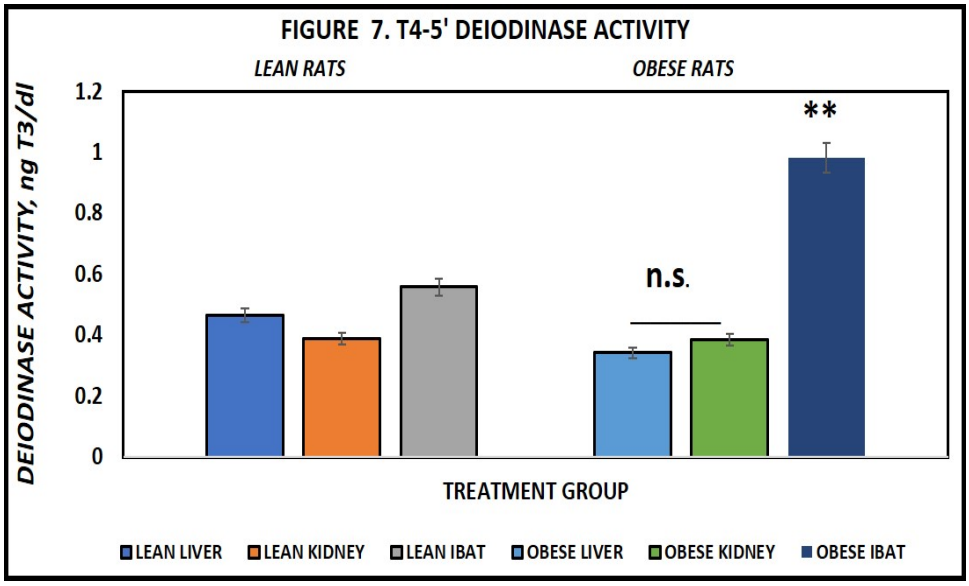

Figure 7: Tisue T4-5' deiodinase activity in homogenates of liver, kidney, and IBAT. Data are mean ± 1 SEM, n = 6 rats/group.

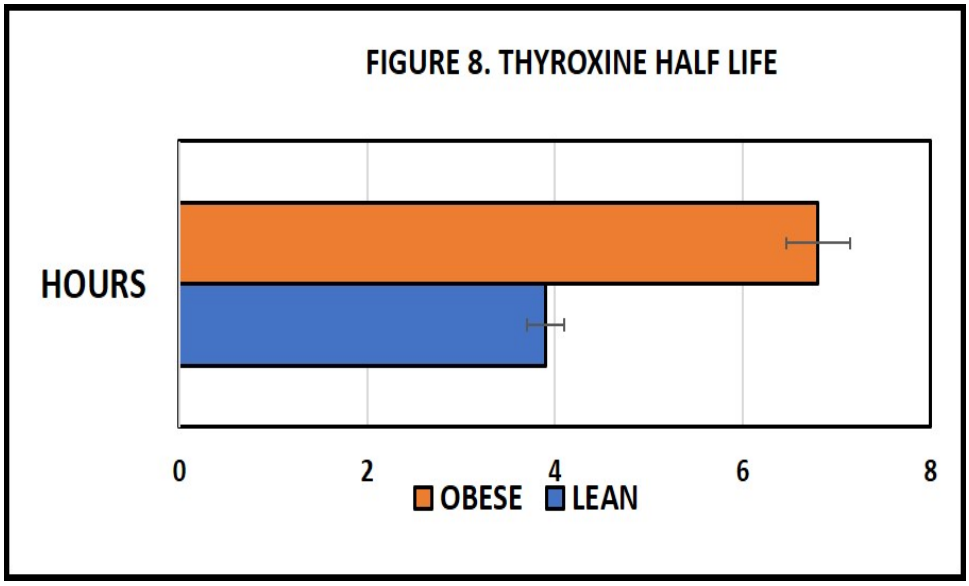

Figure 8: T4 half life in lean and obese rats. Data are mean ± 1 SEM, n = 4 rats/group. Rats were administered 1 µCi of I-131 levothyroxine intravenously via a tail vein, and 100 µl aliquots of blood obtained via tail bleeding for 8 hours post administration and radioactivity determined. P = < 0.01 (lean vs obese).

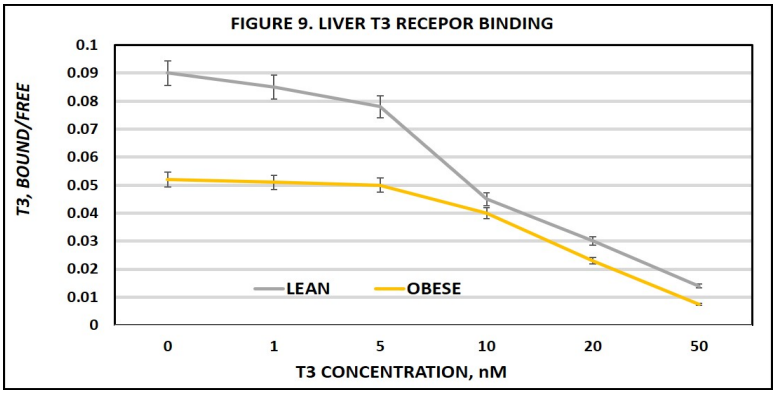

Figure 9: T3 receptor binding in liver homogenates. Data are mean ± 1 SEM, n = 6 rats/group.

4. Discussion

The results presented above indicate that key parameters of thyroidal action are deranged in the obese phenotype of this strain, and are likely contributors to the ease and efficiency of adipose tissue expansion and contributory to the epigenetic expression, energetic efficiency and early onset obesity in the obese phenotype in this strain. The net T4 activation to T3 via outer ring T4-5'-deiodinase activity and prolonged T4 disappearance from plasma are consistent with an intracellular syndrome of subclinical hypothyroidism, which could contribute to an improved efficiency of substrate metabolism, including key parameters associated with protein synthesis and protein turnover. In other studies, measures of net protein turnover, at a cost of 4 high energy phosphate bonds per new peptide bond formed, represents a significant contributor to the economy of daily energy requirements, and a significant component of the energy costs of maintaining resting metabolic rates [9]. Indeed, the energy costs of protein synthesis rank among the most expensive aspects of resting energy requirements and are decreased by the presence of insulin resistance. Insulin resistance of obesity facilitates a decrease in the rate of protein degradation during protein tissue remodeling, which serves as a primary source of amino acid moieties for de novo protein biosynthesis.

In addition, the decreases in hepatic T3 nuclear receptor binding studies also support the above findings. Nuclear T3 receptor binding was found to be substantially decreased in the obese phenotype throughout both the physiologic and supraphysiologic concentration ranges examined. This observation is indicative of a syndrome of thyroid hormone resistance, also common in the presence of insulin resistance [12, 28]. Whether this phenomenon occurs as a reflection of the plasma membrane actions of collocated outer ring deiodinases. The D-II deiodinase is also strategically located internally on the endoplasmic reticulum (ER) membrane, in close intracellular proximity to epigenetic receptor domains to enhance the geometric transit to the nuclear receptor binding events. Overall, T4 deiodinase activities in several tissues are decreased in the obese phenotype, and despite the increase in IBAT mass, the decreases in thyroidal actions are likely contributors to the decreased capacity for resting and NE stimulated thermogenesis and greater adiposity in the obese phenotype of this strain. Disordered elements of thyroid hormone actions are often a consideration in diagnosing obesity, but most often, the plasma concentrations of the respective hormonal entities are a reflection of glandular feedback mechanisms, and thus fail to discern insight into the disordered elements of cellular energy metabolism and thus are sometimes referred to as a syndrome of subclinical hypothyroidism [12].

The congenic LA/Ntul//-cp rat model is an excellent animal model to investigate the above parameters, as the only difference between the lean and the obese phenotypes as biological littermates is the epigenetic expression of early onset hypertrophic-hyperplastic obesity in the obese phenotype of the strain, thereby minimizing potentially extraneous research variables [19]. The model demonstrates hyperinsulinemia, hyperamylinemia, and other metabolic sequala of obesity soon after weaning [19, 29]. The obese littermates demonstrate hyperphagia soon after weaning, followed by hyperinsulinemia, hyperamylinemia, moderate glucose intolerance, and insulin resistance but not overt hyperglycemia [27, 29]. In addition, mechanisms of protein turnover, and both thyroidal and sympathetic parameters of non-shivering thermogenesis become impaired during the preadolescent growth and developmental stages by 6 weeks of age [9]. While a central factor supporting all of the above metabolic changes could not be determined from the present studies, the overriding presence of insulin resistance is likely residing close to the origin of the findings in this and other studies of thyroidal actions in obesity, similar to that which occurs in human obesity [30].

5. Conclusions

The results of this study indicate that key parameters of thyroidal actions including peripheral T3 generation and T3 receptor domain binding in peripheral tissues are impaired in the obese phenotype of this unique rodent strain. While the direct causation of thyroidal dysfunctions could not be unequivocally stated, the comorbidity of insulin resistance common to the obese phenotype of this strain is a likely contributor. Insulin resistance, occurring with or in the absence of overt NIDDM results in an economy of energy expenditure, via diminished thermogenic responses to diet and environment, and in a conservation of energy metabolism often in the form of excess fat accretion. The LA/Ntul//-cp rat is a unique rodent model demonstrating the phenomena of obesity-linked insulin resistance in that this model typically doesn't develop the confounding effects of NIDDM, as occurs in some other genetic forms of obesity among rats. In addition, the congenic status of the model minimizes internal variables, since the only differences between lean and obese littermates is the development of early onset obesity and its metabolic comorbidities soon after weaning. Breeding pairs that are heterozygous for the autosomal recessive -cp trait historically produce 25% of offspring that are homozygous for obesity, 25% that are homozygous for lean phenotype, and the remaining 50% that are heterozygous for the -cp trait but remain with a lean habitus virtually indistinguishable from their homozygous lean littermates throughout their lifespan. Parameters of thyroid function contribute a major role in the determinants of the efficiency of metabolic energy balance in man and animals, and when impaired, impact secondary effects on other endocrine systems including those that modulate glycemic and lipogenic responses, in addition to the sympathetic contributions to nonshivering thermogenesis in brown adipose tissue and other organs and tissues. In the present study, despite a significant increase in the mass of brown adipose tissue, the thermogenic responses to both resting and noradrenergic stimulated thermogenesis were impaired, in agreement with previous studies in this and other report of decreased capacity for expression of parameters nonshivering thermogenesis in rodents and including those related to the conservation of energy expenditure during metabolic aspects of protein turnover. While the results of the study cannot be directly applied to human metabolism, the overall mechanisms of carbohydrate and protein metabolism, and of lipid biosynthesis and fat accretion are similar in both human and rodent species, thereby inviting speculation that similar hormonally mediated effects may occur in mankind.

Article Information

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Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

Consent: It is not applicable.

Ethical approval: The study was approved by the Institutional Animal Care and Use Committee of USAT.

Competing Interests: Author has declared that there are no competing interests.

Disclosures: The authors have no disclosures.

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