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Does clinical hypothyroidism occur in obesity? here is what the lab rats may be telling us about hope on the horizon

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Introduction

Historically many patients may present with symptoms suggestive of hypothyroidism or disordered thyroidal parameters, but when the usual labs come back, they often fail to identify any obvious failings in their hypothalamic-thyroidal axis. However, when we turn to the findings in lab rats we may discern the real culprit in the patients' apparent symptomology. Patients often experiment with any number of a broad assortment of dietary and exercise approaches to resolve their body weight and other issues with little success. Indeed, Laurberg et al. noted that small differences in thyroid function alone have been associated with up to 5 kg difference in body weight.[1] Some patients may also experience symptoms of being overly sensitive to dietary carbohydrates, but even after careful monitoring of the types and amounts of carbohydrates consumed, may still often harbor lingering weight control issues but which fall well short of that required for a diagnosis of metabolic syndrome on initial presentation.[2,3]

If we examine the findings in genetically obese rodents, however, where the epigenetic expression of obesity usually occurs as an autosomal recessive trait, we often note that parameters of thyroid hormone activity may lead us to a possible explanation for the apparent clinical dilemma experienced by the above referenced patients.[4] During preweaning growth (1 to 21 days of age) , the lean and soon to be obese offspring of parental strains that carry the recessive trait appear of normal weight and outward dimensions, but during the post weaning growth period (21-42 days of age) the obese phenotype begin to visibly and progressively express the oncoming signs of obesity via greater circumferential dimensions, altered stance and gait, and relative hyperphagia of an unconfirmed origin.[4,5] By the age of adolescence (over 42 days of age), the clinical markers indicative of the obese phenotype now become well established, while growth and development of the lean phenotype is physiologically and physically unremarkable in animals that are both homozygous of heterozygous for the lean phenotype.[4] During the post-pubertal growth period, the hormonal and biochemical parameters become suggestive of the biochemical pathways and physiologic mechanisms that will culminate in their hyperphagia[5] and obesity phenotype, regardless of the dietary or environmental conditions imposed. Pair feeding to their lean littermates and up to 2 hours of vigorous running wheel activity per day could not prevent the further progression of obesity in the obese phenotype.[6] In addition, upon attaining adulthood, measures of plasma T3, Resting and Norepinephrine stimulated metabolic rates, and vanilmandelic acid (VMA) excretion, a measure of sympathetic activity, became decreased in comparison to the same parameters in their lean littermates, while elevations in both plasma insulin and amylin became increased, leading to a state of insulin resistance in the obese phenotype, also especially common stigmata in visceral obesity in humans.[6,7] Parameters of energy expenditure have long been known to be heavily influenced via hormonal regulation, including parameters of sympathetic, thyroidal and Insulin actions.[8,9]

Brown adipose tissue is a major organ for the expression of nonshivering thermogenesis in mammalian species, and dissections of the Interscapular brown fat depot, including determinations of IBAT mass and cellularity were consistently greater in the obese phenotype of several strains of genetically obese rats.[4,8] The increases in IBAT mass and cellularity in the cited studies were disproportionate to the diminished RMR and thermic responses to adrenergic stimulation observed among the obese rat strains. It is noteworthy that early overnutrition imposed via a highly palatable cafeteria diet to normally lean rats during postweaning growth (21 to 42 days postweaning) resulted in significant elevations in IBAT mass and cellularity, resting and norepinephrine stimulated thermogenesis, VMA and plasma T3.[7,10] The commonly observed hyperinsulinemia among obese human and animal subjects is also associated with varying magnitudes of insulin resistance, and which impacts on carbohydrate, lipid and protein energy control, including aspects of glucose, lipid and amino acid homeostasis, and modulation of the rate of insulin regulated protein turnover, the most biochemically and energetically expensive of the three macronutrient sources at 4 high energy phosphate bonds per peptide bond formed.[4] Thus, the dilemma leading to the development of their obesity even in the presence of commonly recommended dietary changes applied to the obese phenotype remains suggestive of hormonally mediated dysregulation within the hypothalamic-thyroidal/insulinogenic-end organ axis.

The hypothalamic-thyroidal axis normally remains intact in lean littermates. However, when cell suspensions obtained from 14 day-old gestational age rats that had been obtained from homozygous lean rats were implanted into the third ventricle of preadolescent obese Zucker rats, measures of resting metabolic rates and thyroidal, insulin, and other markers of adiposity soon became substantially normalized, while the early stage magnitude of obesity present at the time of the implants and used to confirm the identity of littermates found to be bearing the obese phenotype remained present in the hypothalamic-engrafted animals thereafter.[11] Administration of I^{131} T4 and T3 in the obese phenotype of corpulent rats resulted in similar clearance rats

for T3 but T4 clearance was consistently prolonged by approximately 50% among the obese phenotype.[12] In addition, administration of T4 to postweaning corpulent rats was ineffective in diminishing the development of the obese stigmata among obese animals, thereby suggestive of dysregulation at the level of T4-5' deiodinase activity.[13] The peripheral conversion of T4 to T3 normally provides a significant proportion of plasma T3 availability and mediation of thyroidal actions in mammalian species, and Gavin et al reported that T4 deiodination was impaired in adult-onset diabetes (NIDDM or Type II diabetes).[14] The authors attributed to the dysregulation to insulin resistance, thus implicating a pivotal role for insulin sensitivity in thyroid hormone actions in peripheral tissues. Insulin resistance along with increased glucocorticoid sensitivity impairs the normal intracellular translocation mechanism of GLUT4 glucose transporters.[14–17] which also appears to contribute to the development of peripheral insulin resistance in obesity and NIDDM, and also likely contributes to the dysregulation in thermogenesis, intermediary energy metabolism and in overall energy balance in the obese phenotype of the Corpulent rat and other genetically obese rodent strains.

In recent studies, measures of thyroid hormone nuclear binding and T4-5- deiodinase activity were completed in tissues from young, adolescent lean and obese non-NIDDM LA/Ntul//-cp rats.[12,18,19] Not surprisingly, the T3-recptor binding sites, a presumed genetically predetermined attribute, were found to be similar in number in both the lean and obese phenotype. The T3 receptor binding affinity however was decreased in the liver of obese rats, while plasma and liver T3 concentrations and measures of T4-5' deiodinase activity were modestly to moderately decreased when compared to lean controls in liver tissues obtained from the obese animals.[18] The obese animals of those studies also demonstrated significant insulin resistance as supported by hyperinsulinemia and an increased Insulin to glucose ratio often typical of obesity, and in the cited studies occurred in the absence of indicators of NIDDM. Since there are multiple molecular configurations of the thyroid hormone binding receptors[20] and at least three isoforms of T4-5'deiodinase activity (D-1, D-2 and D-3) expressed in different tissues,[20] the individual tissue-specific responses to nutritional and environmental stimuli may respond differently to the combination of deiodinase activity ant receptor binding events. While both D-1 and D2 are outer ring deiodinases and generate the metabolically and hormonally active form of T3 found in plasma, D-3 represents an inner ring deiodinase and forms metabolically inactive 'reverse' or rT3 in response to decreased availability of nutritional stimuli.[20,21] It remains unresolved if the different isoforms of the thyroid hormone receptors or the tissue specific deiodinases may respond differently in response to variations in nutritional and environmental stimuli other than caloric deprivation. In the studies of exogenous thyroid hormone administration, only T3 but not T4 resulted in weight loss in the obese phenotype of the corpulent rat, while both hormones were effective in the lean littermates.[19]

Thus, there may be hope at the end of the hypothalamic-thyroidal-end organ axis tunnel, in seeking a resolution of the apparent hypothalamic stigmata sometimes presented in obese syndromes, but in the presence of normal plasma concentrations of the routinely measured thyroidal parameters including bound and free fractions of T4, T3 and of TSH. Currently there aren't any known reliable assays to assess intracellular binding characteristics for thyroid hormones or to directly assess deiodinase activities *in vivo* or to detect the metabolic actions of their intracellular activity noninvasively. It has often been said, 'we are what we eat', but the results of our review suggest that in addition to our nutritional, environmental and lifestyle compliments, a genetic component influencing multiple hormonal actions including thyroidal, sympathetic and insulinogenic entities must be considered when considering symptomatic therapeutic measures. Truly, we are 'who we are', not entirely 'what we consume' or our physiologic and environmental interactions in the way of fulfilling energy and nutritional needs. The global burden of obesity and its sequelae continue to increase in the populations world-wide and have been projected to impose a major impact on the health care resources of many counties by year 2030. Thus, the burgeoning incidence of obesity and its common sequelae of NIDDM and hypertension will in all likelihood become a global priority to identify and find doable resolutions to the critical issues of overweight and obese conditions with an urgency that signals that of a metabolic and global health epidemic if left unattended.[22]

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Conflicts of interest

The author declares there is no conflict of interest.

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