International Scholars Journals

African Journal of Internal Medicine ISSN: 2326-7283 Vol. 11 (2), pp. 001-004, February, 2023. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Editorial

Subclinical Hypothyroidism: does it occur in Obesity and Metabolic Syndrome? Evidence for impaired thyroid hormone receptor affinity from animal studies

Orien L Tulp[1], O F Obidi[3], T C Oyesile[3,] Frantz Sainvil[1], Rolando Branly[1], and Aftab Awan[2], Michael Anderson[1], and George P Einstein[1]

[1]College of Medicine, University of Science, Arts and Technology, Montserrat, BWI, MSR 1110 and [2]Cambridge University, Cambridge, UK, University of Lagos, Nigeria[3].

Accepted 08 March, 2023

Abstract

To determine the potential for subclinical thyroidal actions as a contributing factor for hormonal regulation of energy balance and the development of obesity and metabolic syndrome, studies of resting and catecholamine stimulated metabolism, thyroid hormone half life, hormone bind characteristics and weight gain, groups of lean and obese congenic LA/Ntul//-cp rats were offered stock or high energy diets and parameters of thyroid hormone action determined. The obese phenotype demonstrated impaired thermic responses to diet and environment and cold induced thermoregulation, in association with decreases in plasma T3 but not T4 concentrations. The plasma half life of T4 was 50% longer in obese than in lean littemates, while the half life of T3 was similar in both phenotypes. Measures of nuclear thyroid hormone receptor density were similar in both phenotypes, but receptor affinity for T3 was diminished in the obese phenotype, consistent with impaired thyroidal actions as a contributing factor for subclinical hypothyroidism in the obese phenotype of this strain.

Key Words: Obesity, Hypothryoidism, Hyperinsulinemia, Hyperamylinemia, Research, Rats.

Obesity and its pathophysiologic sequela have become a burgeoning medical issue not only in Africa but worldwide.[1]Patients often experiment with any number of a broad assortment of dietary and exercise approaches to resolve their body weight and other issues often with little or no lasting success. While obese and overweight patients may sometimes present with symptoms suggestive of disordered carbohydrate and thyroidal parameters including hypothyroidism, the usual routine thyroid battery of labs come back, they may identify markers of insulin resistance, but often fail to identify any obvious abnormal findings in their hypothalamic-thyroidal axis. However, when we turn to the findings in animal studies we may discover a possible basis for the patients' apparent symptomology. Laurberg et al. noted that small differences in thyroid function alone have been associated with up to a 5 kg annual difference in body weight.[2]A syndrome of carbohydrate sensitivity may also be reported by some patients while attempting to control their ease of weight gain, but even after careful monitoring of the types and amounts of carbohydrates consumed, may still often report lingering weight control issues but which fall in the category of overweight but well short of that required for a diagnosis of metabolic syndrome on initial presentation.[3,4]The extent to which disorders in glucose uptake and oxidation via down regulation of insulin-dependent GLUT4 transporter expression and activity in skeletal muscle and other peripheral

Corresponding Author. Email: o.tulp@usat.edu

tissues projects yet an additional complication without an easy resolution for the obese individual.[5]

Animal studies may hold a clue for the easy weight gain phenomena. In several strains of genetically obese rodents, where the epigenetic expression of obesity usually occurs as an autosomal recessive trait, we often note that disordered parameters of thyroid hormone activity may lead us to a possible explanation for the apparent clinical dilemma experienced by the above referenced patients.[5] During early growth (preweaning, 1 to 21 days of age), the lean phenotype and pre- obese offspring of parental strains that carry the recessive trait appear of normal weight and outward dimensions. However, during the postweaning growth phase (21-42 days of age in rodents) the obese phenotype begin to visibly and progressively express the oncoming signs of obesity via relative hyperphagia of an unconfirmed origin, greater physical and circumferential dimensions, and an altered stance and gait.[5-7]During the adolescence growth phase (over 42 days of age), the physical and clinical markers indicative of the obese phenotype 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.[6] 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[7] 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 did not prevent the further progression of obesity in the obese phenotype.[7] In addition, upon attaining adulthood, metabolic parameters indicative of the obese state including measures of plasma T3, resting and norepinephrine stimulated metabolic rates, and vanilmandelic acid (VMA) excretion as a measure of overall sympathetic activity, became decreased in comparison to the same parameters in their lean littermates. In addition, elevations in both plasma insulin and amylin were found to be increased in the obese phenotype, leading to a state of insulin resistance in the obese phenotype, also especially common stigmata in visceral obesity in humans.[7-9]Parameters ofenergy expenditure have long been known to be heavily influenced via hormonal regulation, including parameters of sympathetic, thyroidal and Insulin actions, and Marette et al have reported that the expression of the insulin-dependent GLUT4 glucose transporter was decreased by an average of 40% in skeletal muscle, a major contribution to insulin resistance in the obese state.[5,9-11]

The expression of nonshivering thermogenesis in mammalian species occurs to a large extent in brown adipose tissue in addition to thermogenic activities in skeletal muscle and liver tissues. In rodents, dissections of the interscapular brown fat depot (IBAT), including determinations of IBAT mass and cellularity were consistently greater in the obese phenotype of several strains of genetically obese rats.[7,11] 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.[9,12] 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.[6] 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 axis and ininsulinogenic-mediated parameters.

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. Thus, these observations suggested that the hypothalamus played a pivotal role in the expression of the obese phenotype in the Zucker fatty rat.[12] Administration of I^{131} T4 and I^{131} 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.[14] 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.[15]Because the peripheral conversion of T4 to T3 normally provides a significant proportion of plasma T3 availability and mediation of thyroidal actions in mammalian species, this represents a possible explanation at least in part for the abnormalities in plasma T3 concentrations. Gavin et al reported that T4 deiodination to T3 was impaired in adult-onset diabetes (NIDDM or Type II diabetes) reflecting a link between insulin resistance and peripheral T4 deiodination and which finding is further supported by the findings of decreased expression of GLUT4 glucose transporters by Marette et al.[1,5,16] The authors attributed to the dysregulation to insulin resistance of NIDDM, 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.[16-19] 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.[14,20,21] 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.[19] 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 and at least three isoforms of T4-5'deiodinase activity (D-1, D-2 and D-3) expressed in different tissues,[22] 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.[22,23] 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.[21]

SUMMARY AND CONCLUSIONS

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. The typical laboratory findings often reflect the presence of normal plasma concentrations of the routinely measured thyroidal parameters including bound and free fractions of T4, T3 and of TSH, thus failing to meet the usual criterion for a diagnosis of a thyroidal disorder. Currently there aren't any known reliable assays to assess intracellular binding characteristics for thyroid hormones, 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 and possible crippling impact on the health care resources of many counties by year 2030. Current clinical recommendations pertaining to adjustments in diet, exercise and lifestyle practices will likely remain among the accepted clinical recommendations, but are not likely to resolve the dilemma in its entirety. Thus, the burgeoning incidence of obesity and its common sequelae of NIDDM and hypertension indicate a serious need for additional research in his area, as the current trends in the increasing prevalence of obese and overweight conditions will in all likelihood become a global priority to identify and more fully characterize at the molecular, tissue, and organ system levels of organization. It is imperative that doable resolutions to the critical issues of overweight and obese conditions must be found, as an urgency is emerging that signals that of a metabolic and global health epidemic tantamount to a tsunami if left unattended.[25]

ACKNOWLEDGEMENTS

The authors thanks the numerous authors cited in this editorial for their noteworthy contributions over time to this topic.

REFERENCES

1. **1.** George P Einstein[1], O F Obidi[4], Orien L Tulp[2], T C Oyesile[3].The Prevalence of Adult Obesity in Africa. Einstein Institute, Medicine, Graduate College, University of Science Arts & Technology, Olveston, Montserrat, Microbiology, University of Lagos, Lagos, Nigeria. Experimental Biology April 1-6, 2016, Faseb J 30(S1).
2. Laurberg P., Knudsen, N. , Andersen, S., Carlé, C., A., Pedersen, IB., and Karmisholt, J. Thyroid Function and Obesity. Eur Thyroid J. 2012 Oct; 1(3): 159–167. 2012. doi: 10.1159/000342994. PMCID: PMC3821486. PMID: 24783015
3. Weinandy, L. A carb intolerance may be the reason weight loss is difficult. Health News. Pp 1-4, Ohio State Univ, 2017.
4. Reaven, GM. Syndrome X: A Short History. Ochsner J. 2001 Jul; 1993. 3(3): 124–125. PMCID: PMC3385776
5. Marette, A., Atgie, C., Liu, Z., Bukowiecki, LJ and Klip, A. Differential regulation of GLUT1 and GLUT4 glucose transporters in skeletal muscle of a new model of Type II

diabetes: The obese SHR/Ntul//-*cp* Rat. Diabetes 42:1195-1201. 1993.

6. Tulp, OL. Charactics of thermognesis, obesity and longevity in the LA/Ntul//-cp rat. ILAR J 32:32-39

7. Huang, HJ, Young, AA, Koda, JE, Tulp, OL et al. Hyperamylinemia, hyperinsulimnemia and insulin resistance in genetically obese LSA/N-cp rats. Hypertension 1992: 19(Suppl 1) 101-109.

8. Tulp, OL. Effects of aging, phenotype, and carbohydrate feeding on caloric efficiency and adiposity in the LA/Ntul//-cp rat. Adv Obes Weight Control Manag. 2021:11(1):5-11. DOI. 10.15406 / aowmc.2021.11.00329.

9. Tulp, OL and Jones, CT. Effects of increased energy expenditure on weight gain and adiposity in the LA/Ntul//-cp Rat. Comp Biochem Physiol 86A (1):67-72. 1987.

10. Tulp, OL, Awan, AR and Einstein, GP. Treatment with α-methylparatyrosine inhibits sympathetic but not thyroidal responses to diet induced thermogenesis in lean cafeteria overfed rats. Curr Trends in Toxicicol Pharma Res 2022:2(1): 1-6. DOI.10.53902/CTTPR.2022.02.000504. ,Atgie, C, Liu, Z,

11. Marette, A., Atgie, C., Liu, Z., Bukowiecki, LJ and Klip, A. Differential regulation of GLUT1 and GLUT4 glucose transporters in skeletal muscke of a new model of Type II diabetes. Diabetes 42:1195-12-1. 1993.

12. Cannon, B and Nedergaard, J. Brown Adipose Tissue: Function and Physiological Significance. Physiol Rev 84: 277–359, 2004; 10.1152.

13. Danforth, E Jr. Hormonal control of thermogenesis. Life Sci. 28:1821-1827. 1981

14. Tulp, OL, Frink, R and Danforth, E Jr. Effect of overfeeding–induced hyperplasia of brown adipose tissue on the development of white adipose tissue and body composition in postweaning rats. Am J Clin Nutr. 34(4):619. 1981.

15. Tulp, OL, Chen, Q and Tso, P. ICV implant of lean hypothalamic tissue normalized energy expenditure prior to weight change in obse Zucker rats. Proceedings, Western Branch of ACS fall meeting, p.234. 1995.

16. Tulp, O.L., Paz Nava, M., Black, D.E. and Young, N.L. Genetic determinants of T3 receptor affinity and thermogenesis in LA/Ntul//-cp rats. Proceedings, XV International Congress of Nutrition, IUNS, p 481, 179A. 1983.

17. Hyde, D.L, Kelly, L.J. and Tulp, O.L.. The effect of exogenous thyroid hormone administration on body weight loss in th.e corpulent rat. Proceedings of Maine Biology and Medical Assoc, p.43, 1983.

18. Gavin, L.A., McMahon F.A., and Moeller, M. The mechanism of impaired T3 production in diabetes. Diabetes 1981. 30:694-699.

19. Carter, Su-C., Okamoto, K. Effect of insulin and glucocorticoids on glucose transporters in rat adipocytes. Am J Physiol 1987. 252(4) E441-E453.

20. Kahn, S.E., Hull, R.L and Utzschneider, K.M. Adiposity and IR: Mechanisms linking obesity to insulin resistance and type 2 diabet.es. *Nature*vol 444, pp 840–846 (2006).

21. James D.E., Brown R., Navarro J., Pilch P.F. (May 1988). "Insulin-regulatable tissues express a unique insulin-sensitive glucose transport protein". Nature. 333 (6169): 183–5. *Bibcode*:*1988Natur.333..183J*. *doi*:*10.1038/333183a0*. *PMID 3285221*. *S2CID 4237493*.

22. Young, N.L. PhD Thesis: Adaptive thermogenesis and thyroid hormone function in the LA/N-corpulent rat. 182 pp. Drexel University. (O. Tulp, D Klurfield and D Kritchevski, advisors). 1991.

23. Anyetei, C.S., Roggero, V.R., and Allison, L.A.. Thyroid hormone receptor localization in target tissuesJ Endocrinol. 2018 Apr; 237(1): R19–R34. PMCID: PMC5843491; NIHMSID: NIHMS944236, and PMID: 29440347

24. Sabatino, L., Vassalle, C., Del Seppia, C., and Iervasi, G. Deiodinases and the Three Types of Thyroid Hormone Deiodination Reactions. Endocrinol Metab (Seoul).vol 36(5): 952–964. 2021. doi: 10.3803/EnM.2021.1198. PMCID: PMC8566136. PMID: 34674502

25. Kelly, T., Wang, W., Chen, C.S. et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (London) 32(9):1431-1437. 2008.