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EDITORIAL

Do refined carbohydrates, glycemic index, subclinical hypothyroidism, and insulin resistance contribute to the brain senescence of subjective cognitive decline in aging in man and animals? Here is what the lab rats are saying

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Abstract

The onset and progression of subjective cognitive decline (SCD) in aging typically occurs gradually over an extended duration, often escaping recognition by friends and family during the early stages of the disorder. The incidence of SCD in developed counties, where the abundant consumption of refined carbohydrate sources is also commonplace, is virtually staggering, currently approaching over 10% of the population over age 45 with no definitive end in sight.[1] The development of SCD has been associated with factors of socioeconomic, educational, metabolic and pathophysiological comorbidities, including diet and impaired insulin sensitivity common to obesity, Type 2 and 3 diabetes (T2DM; T3DM). While early intervention is preferable for the treatment of many illnesses and disorders, effective remedies for the senescence of aging and SCD remain a challenge for the practicing clinician, in part because the metabolic and nutritional factors which initiate the process remain largely unclear. The development of symptoms consistent with subclinical hypothyroidism (SCHT) are also commonplace among the aged. The independent contributions of thyroidal dysregulation and insulin resistance to dysregulation of energy balance, although strongly linked, some aspects remain unclear and incompletely known. Several recent studies have now associated obesity and insulin resistance (IR) to brain senescence in aging congenic obese rats. Several studies also support a link between chronic hyperinsulinemia, epigenetic expression of obesity, brain shrinkage and decreased brain protein and cellular deoxyribose nucleic acid (DNA) content in a congenic rodent model of early onset obesity.

Aging congenic obese LA/Ntul//-*cp* rats develop obesity and hyperinsulinemia soon after weaning regardless of diet and which pathophysiologic stigmata persist throughout their lifespan. The stigmata of insulin resistance may become further aggravated when fed a high glycemic index diet. Groups of lean and obese rats were fed USDA-formulated nutritionally complete isoenergetic diets continuing cornstarch (ST) or sucrose (SUC) as the only carbohydrate source from weaning until 10.5 months of age. Longevity of obese << lean in both sexes. Obese rats were found to exhibit SCHT and decreased brain mass associated with IR, and accompanied with proportionate decreases in brain lipid, protein and DNA content in the obese but not the lean phenotype. In addition, the decreases in brain mass, protein and DNA composition were of greater magnitude when fed the SUC vs the ST diets in both phenotypes. These observations are suggestive of an increased potential for a contribution of the metabolic sequelae of insulin resistance as a pathophysiologic factor in the progression of brain shrinkage and presumed cognitive decline in the aging obese, hyper insulinemic rat, analogous to clinical observations which may occur in senescence, dementia and Alzheimer's disease in aging populations and implicate the glycemic index of the refined carbohydrate source as a contributory factor.

Keywords: carbohydrates, glycemic index, subclinical hypothyroidism, insulin resistance, epigenetics, rats, aging, nootropics, senescence.

Introduction

In a recent publication, the issue of dietary quality vs. quantity suggested that the higher glycemic index and magnitude of insulin resistance impacted parameters of cardiovascular health and an acceleration of dietary factors that contribute to epigenetic aging.[1] Considering that industrialized societies are consuming more refined sugars and ultrarefined manufactured foods *per capita* now than at any time in past history, it is timely that an examination of the metabolic effects of excess carbohydrate consumption on parameters of health might be well served.[2-4] Refined sugars contribute to increases in insulin resistance, which contributes to systemic inflammation and to various comorbidities of obesity and T2DM.[1,2,5-7] With the ready availability and prevalence of refined sugars as sweeteners they have made major inroads in the industrialization and manufacture of foods and beverages for public consumption, often with an onset during the earlier formative years of a child's development. Since the acquisition of taste preferences including sweetness often typically occurs early in life, especially the early postweaning growth and development stages of early childhood, greater attention might be directed toward their inclusion in the manufacture of frequently consumed items commercially projected toward children and adolescents.[3] Moreover, once those early preferences are imprinted in the CNS during early life stages, they can influence food and taste preferences later in life, extending well into adulthood.[2] Sucrose and fructose in the form of high fructose corn syrup, while often considered as 'natural sweeteners' since they may be found in nature, may now be found in substantially greater proportions in beverages and liquid foods that may often be consumed during episodes of bottle feeding and early feeding practices.[2] Industrialization of the commercial food supply has contributed to the substitution of manufactured products for more wholesome and nutritious feeding practices common to previous generations and contributed to parents trend to turn away from traditional home sourced practices of infant nutrition to more convenient items albeit with a greater glycemic index and more immediate gratification and satiety.[3,4,5] The contributions of excess sugary foods on aspects of dental health has long been recognized, but the more serious impact on cardiovascular health only recently confirmed via large scale dietary preferences investigation.[3] In addition, unhealthy dietary practices have been reported to inactivate the anti-aging sirtuin 1 (Sirt1) that plays an instrumental role in the molecular regulation of epigenetic processes that promote dysfunction in the immune system, mitochondrial apoptosis, diabetes, fatty liver disorders and other comorbidities.[4,5] The effects on Sirt1 contributions to metabolism are particularly critical. Sirt1 is a nuclear receptor NAD (+) dependent class III deacetylase (HDAC) protein that facilitates transcription factors linked to epigenetic expression and is deemed especially important development of insulin resistance and inflammation.[4] Overnutrition is associated with down regulation and repression of Sirt1 activities.[4] Thus, as a result of the rapid expansion of carbohydrate-based sweeteners, HFCS in the commercial food production industries has resulted in up to a 5-fold or greater increase in daily consumption of fructose and other monosaccharide sugars in Westernized society, with detrimental impact on Sirt1 and anti-aging genes.[4,5] This increase in ingestion of caloric sweeteners likely contributes to potential pathophysiologic sequela including dysregulation of energy balance, insulin resistance, alterations in thyroidal actions, and their collective associated comorbidities. In addition, the increase in refined carbohydrates adds to a greater burden of maintaining nutritional wellness in a more sedentary population than was experienced in previous generations. In addition, the onset of

overweight conditions, including observation of early atheromatous lesions once thought to have an onset around middle age, have now been documented in younger adults and preadolescents.[1-4,7-9]

While acute inflammation is an essential component of normal physiological defense mechanisms, prolonged or excessive inflammation can contribute to illness and disease.[5,6] Systemic, chronic low-grade inflammation is a common observation in visceral central obesity and overweight conditions. Indeed, unresolved systemic and adipose tissue generated inflammation drives further complications of obesity-related cardiovascular disease, type 2 diabetes mellitus, and other comorbidities. The global prevalence of obesity is currently increasing at epidemic proportions, impacting a third or more of the population of many communities.[7-9.] Obese and overweight states are linked to systemic low-grade inflammation, which cumulatively contribute to the progression of cardiovascular disease and neuroinflammation and their pathophysiologic consequences in man and animals.[10-12] While brain senescence may and often does occur independently of obesity, the chronic insulinemia associated with obesity and overweight states contributes to neuroinflammation including the CNS.[12] The mechanisms contributing to chronic insulin resistance have been attributed to multiple factors, including overnutrition, poor dietary selections, chronic hyperphagia, sedentary lifestyle, genetic predisposition, and other dietary macronutrient imbalances.[1, 4-7] Learned and acquired taste preferences originating in early childhood may also be contributory to dietary indiscretions later in life. In addition, disordered glucocorticoid metabolism and actions, impaired cellular translocation and availability of insulin-dependent GLUT4 transporters, and immune dysfunctions all likely further contribute to insulin resistance and its pathophysiologic sequela.[13-16] In addition, the contributions of insulin resistance in neuronal tissues also likely contributes to the phenomena recently termed Type 3 diabetes (T3DM) where neuronal tissues, particularly those in the brain, fail to respond to the metabolic effects of insulin, necessary for numerous basic tasks including learning, memory and other executive functions, further contributing to cognitive decline.[17]

In humans, the neuronal changes in obesity plus Alzheimer's syndrome include shrinkage of brain volume and subjective cognitive deficits that accompany the increased insulin resistance, adiposity and brain shrinkage in aging.[7,10,12,17] The pathophysiologic mechanisms contributing to chronic insulin resistance have been attributed to multiple factors, including overnutrition, poor dietary selections, chronic hyperphagia, sedentary lifestyle, genetic predisposition, and other dietary macronutrient imbalances.[4] In addition, disordered glucocorticoid metabolism and actions, impaired cellular translocation of insulin-dependent GLUT4 transporters, and immune dysfunctions also common in obesity all further contribute to insulin resistance and its pathophysiologic sequela.[15,16] GLUT4 glucose transporters are formed in the endoplasmic reticulum of somatic cells, including skeletal muscle and adipose tissue, the major locations where insulin resistance is typically manifested. Once formed, the GLUT4 transporters migrate to the plasma membranes of tissues where they play an essential role in facilitating cellular glucose uptake and subsequent glucose oxidation, storage, and mitochondrial energy balance.[15,16]

Summary of Experimental Methods

The LA/Ntul//-*cp* rat is a unique, congenic animal model, where the obesity trait is expressed as an autosomal epigenetic recessive trait (the -*cp* trait) originally obtained from the Koletsky rat and backcrossed into a longevity-prone Lister/Albany (LA/N) strain at the NIH by Hansen to attain a congenic status. In this strain, the only known surviving trait from the donor strain was the recessive -*cp* trait as reported previously.[18] In the present studies reviewed, groups of lean and obese rats (n=6 rats/experimental or control group) were fed a USDA formulated nutritionally complete diets containing 54% carbohydrate as cooked cornstarch (ST) or sucrose (SUC), 20% protein (equal parts casein + lactalbumin), 16% mixed fats plus essential vitamins mineral and fiber from weaning until 10.5 months of age also as described elsewhere[13,14] At the end of the study animals were sacrificed by decapitation, brain tissues were removed and weighed *in toto*, and analyzed for total lipid, protein and DNA content. Bloods were collected and glucose were determined with a hand-held glucose monitor and plasma insulin determination performed by radioimmunoassay and insulin resistance work product determined by multiplying body weights by plasma insulin concentrations as a function of whole-body insulin resistance and relative insulin resistance determined by dividing work product by plasma glucose concentrations as described previously.[14,25,28] Measures of thyroid parameters were determined via radioimmunoassay, and hormone a=receptor affinity determined in liver homogenates over a broad range of triiodothyronine (T3) concentrations.[19] Data were analyzed by standard statistical procedures.[20]

Results

This report is believed to be among the first observations to review evidence of decreases in essential metabolic and brain parameters in aging and obesity in association with

decreased brain mass and composition.[13,14] While brain protein content is linked to memory and other cellular and physiologic functions, while brain total DNA content is linked to neuronal cellularity without reference to any specific neuronal cell type or cognitive capacity. The effects of carbohydrate type and obese phenotypes on final body weights are depicted in Figure 1, and indicate that the final body weights of obese were significantly greater than in their lean littermates, and that rats consuming the sucrose laden diet weighted more than those consuming the isoenergetic cornstarch-based diet in both phenotypes. The effects of diet and phenotype on glycemic parameters are depicted in Figure 2A and 2B. Fasting plasma glucose concentrations are presented in the left panel of the figure 2A and indicate that fasting glucose concentrations of obese rats tended to be greater than in their lean littermates, and although considered euglycemic for rats, were modestly greater in both phenotypes when consuming the sucrose laden diet. Plasma fasting insulin concentrations are indicated in the right panel of Figure 2A and indicate that fasting insulin concentrations of obese rats were significantly greater than occurred in their lean littermates, and the sucrose diet resulted in still greater elevations in plasma inulin in the obese, but not in the lean animals. In addition, the insulin to glucose ratios depicted in the far-left panel of Figure 2B indicates that the insulin to glucose ratios observed in the obese phenotype were markedly elevated, consistent with insulin resistance in those animals, with the greatest magnitude of insulin resistance in the obese sucrose fed animals. The insulin work product, computed by multiplying plasma insulin concentration time body weight are depicted in the center panel, and are also consistent with significant insulin resistance in the obese phenotype, and became further increased when fed the sucrose laden diet. The magnitude of the insulin resistance facto is depicted in the right panel of Figure 2B, and also confirms significant insulin resistance in the obese but not the lean phenotype. In addition, the magnitude of insulin resistance was even greater in obese animals that were fed the sucrose laden diet. Thus, all obese animals developed insulin resistance, but not T2DM regardless of the dietary carbohydrate type in this study.

Thyroidal parameters are presented in Figure 3A and 3B, extrapolated from previous reports, and indicate that key thyroidal parameters were decreased in the obese phenotype of this strain. Plasma T3 concentrations are depicted in the left panel, and indicate that plasma T3 concentrations were reduced an average of 20% in the obese phenotype. In the next panel, the half-life of T4, was increased an average of 50% in the obese phenotype, indicative of decreases in the capacity for peripheral conversion of T4 to T3 via outer ring deiodinase activity, thereby generating the physiologically active form of the hormone. The right two panels reflect the *in vitro* T3 receptor affinity in liver homogenates at both physiologic and supraphysiologic concentrations, and indicates that receptor affinity in obese animals of a similar age were consistently decreased in the obese phenotype, consistent with a state of subclinical hypothyroidism. The role of insulin resistance in the impaired thyroidal actions is unclear, but the metabolic impact of the two disordered hormonal states remains associated and likely interrelated.

The brain parameters are depicted in Figure 4A and 4B. The results indicate that total brain mass, protein, and DNA content of obese rats became significantly decreased at 10.5 months of age in the obese phenotype. In addition, brain mass was further decreased in animals consuming the high glycemic index, sucrose laden diet, with corresponding decreases in the DNA content in sucrose fed, hyperinsulinemia obese animals. While the basis for the additive effect of the refined carbohydrate is unclear, the only major variable between the two diets is the glycemic index of the two diet formulations, and the greater magnitude of insulin resistance in the obese phenotype after consuming the sucrose-laden diet. In Figure 4A, the effects of diet and phenotype on brain mass and lipid content are presented, and indicate that brain mass was significantly decreased in the obese phenotype, and that the sucrose diet was associated with modestly greater decrease in brain mass in the obese phenotype. Brain lipid content is indicated in the right panel of Figure 4A, and indicates that brain lipid content is decreased proportionately to the decrease in brain mass in the obese phenotype. Brain protein and DNA content are indicated in Figure 4B, and indicate that net protein content in the obese phenotype is decreased compared to their lean, similarly fed littermates, and was further decreased in animals consuming the high sucrose diet. The effect of diet and phenotype on brain DNA content are depicted in the right panel of Figure 4B, and indicate that the DNA content of brains from the obese phenotype was significantly decreased compared to their lean littermates, and became further decreased in animals that consumed the sucrose-laden diet. The decreases in brain protein and DNA content are consistent with decreased neuronal cellularity in the obese, insulin resistant animals, with further decreases in the sucrose-laden, higher glycemic index diet. In the studies by Yi et al, the fiber to nutrient ratios indicated differential effects, while in the present study, the fiber to nutrient ratios were similar in both dietary formulations.

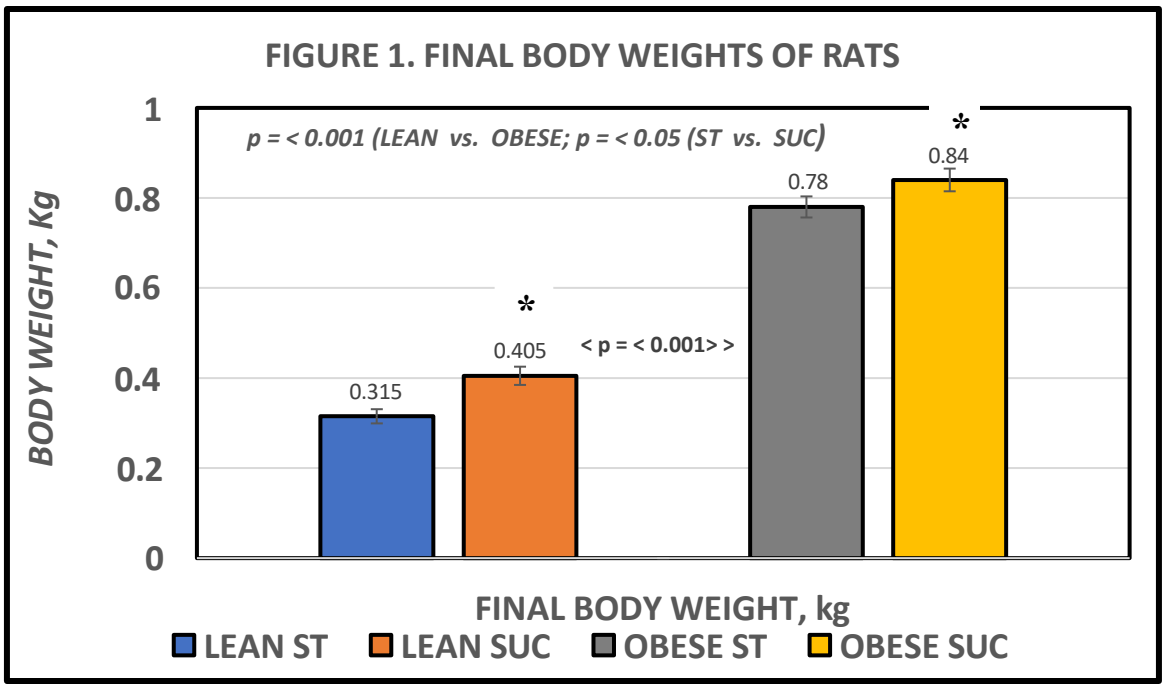

Figure 1. Body weights of lean and obese rats. Data are mean ± 1 SEM, n = 6-8 rats/group. P = < 0.05 9lean ST vs SUC; p = < 0.001 Obese vs Lean; Obese St vs SUC = trend by Pages L test for trend analysis.

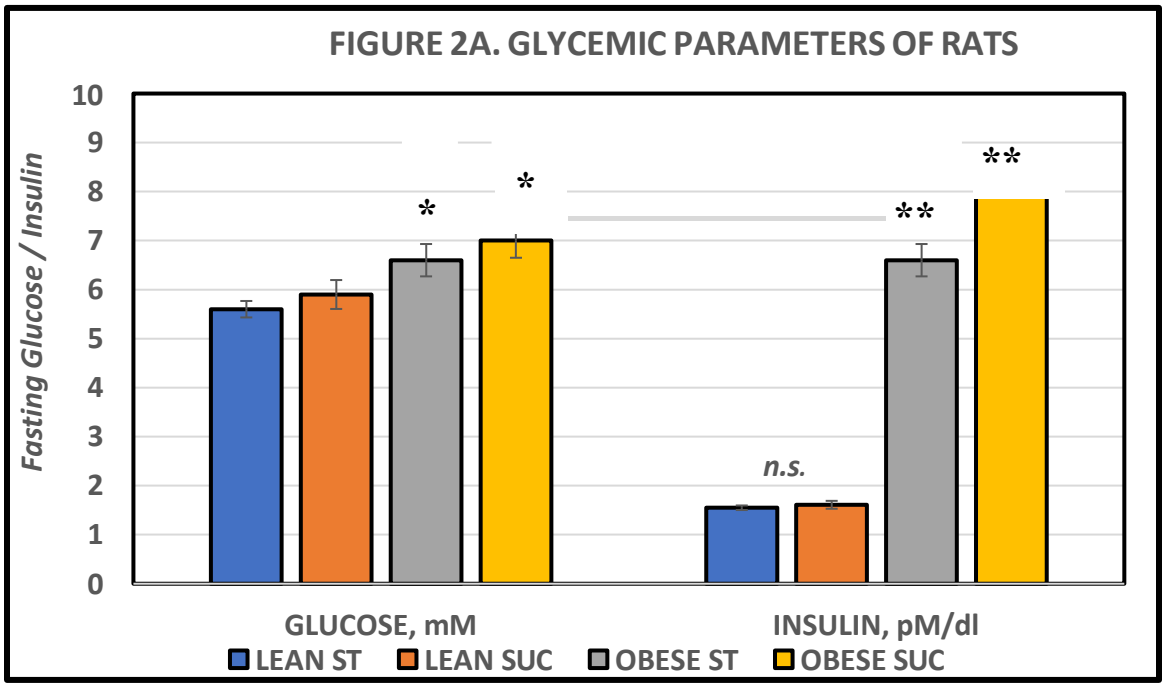

Figure 2A. Glycemic responses of lean and obese rats. Data are mean ± 1 SEM, n = 6 rats/group. p = < 0.01-0.05 (Leas vs obese, SUC / ST in obese phenotype.

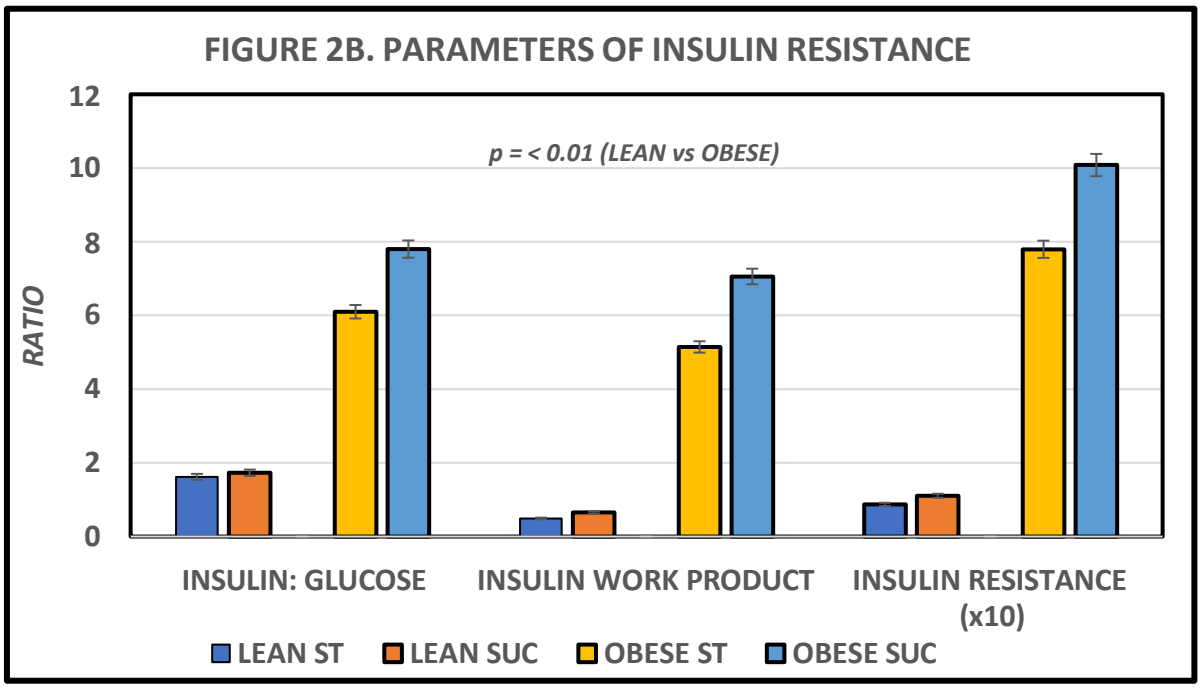

Figure 2B. Glycemic parameters of lean and obese rats. Insulin work product is computed by multiplying plasma insulin concentration time body weight; Insulin resistance factor determined by dividing insulin work product by plasma fasting glucose concentrations. Data are mean ± 1 SEM, n = 6 rats/group. * = p = < 0.05. Ref

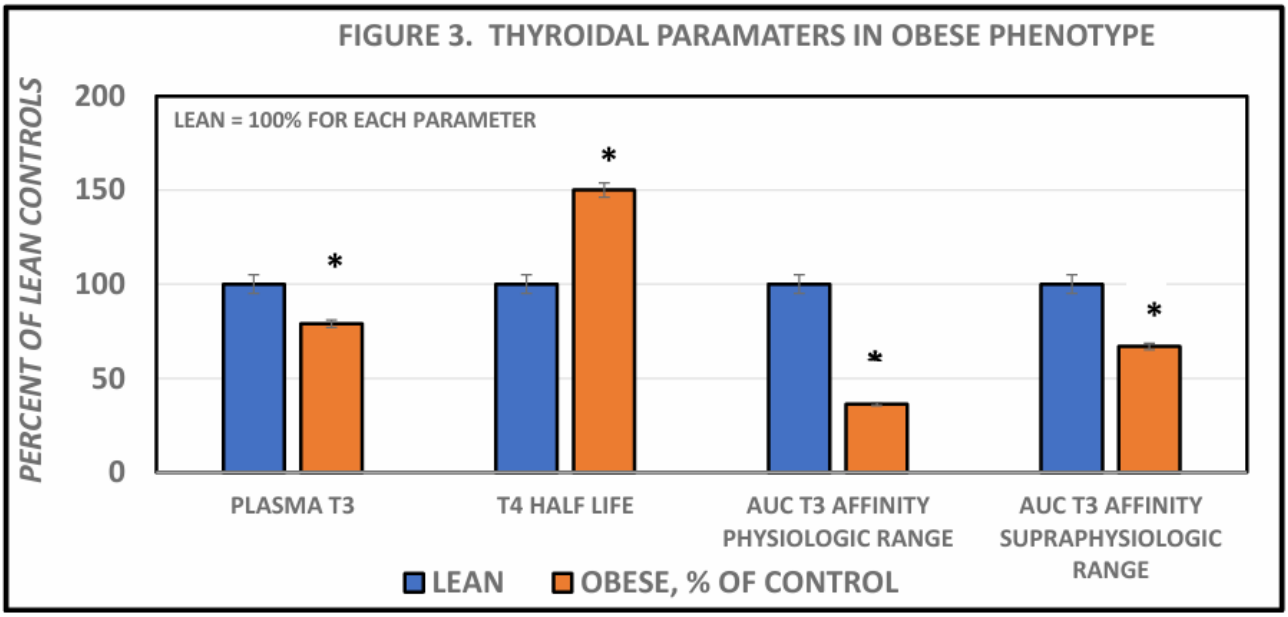

Figure 3. Thyroidal parameters in obese phenotype. Data are mean ± 1 SEM, n = 4-8 rats/group; data are expressed as percent of lean controls, at 4 months of age. *= p = < 0.05. Extrapolated; T3 Binding affinity obtained from liver homogenates; physiologic range of 0 to 10 nM; suprophysiologic range all concentration > 10 nM substrate concentrations. T4 half-life determined via infusion of 1 µCi of 131-I T4.

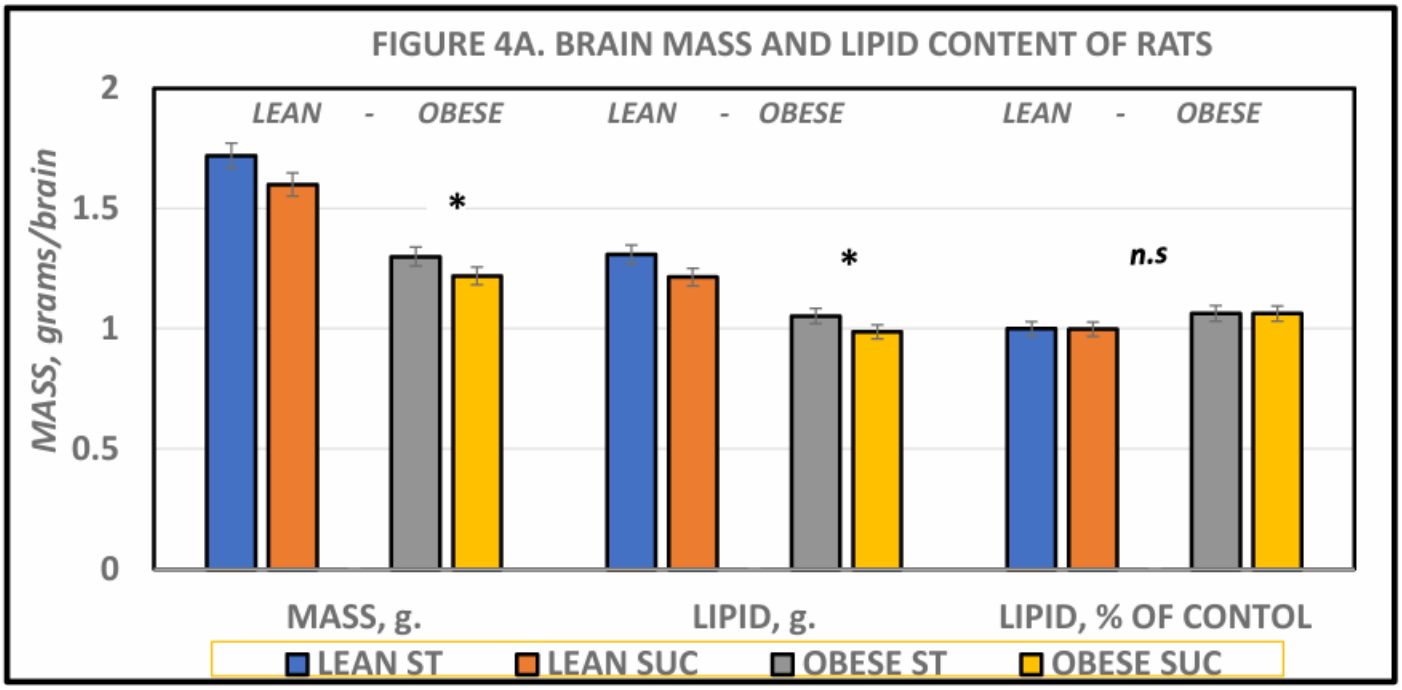

Figure 4A. Brain composition of rats. Data are mean ± 1 SEM, n = 6-8 rats/group. Mass: p = < 0.05 for mass and grams lipid; p = n.s. for lipid as percent of control. P = < 0.05 for St vs SU via Page's L test for trend analysis for mass and g. lipid content.

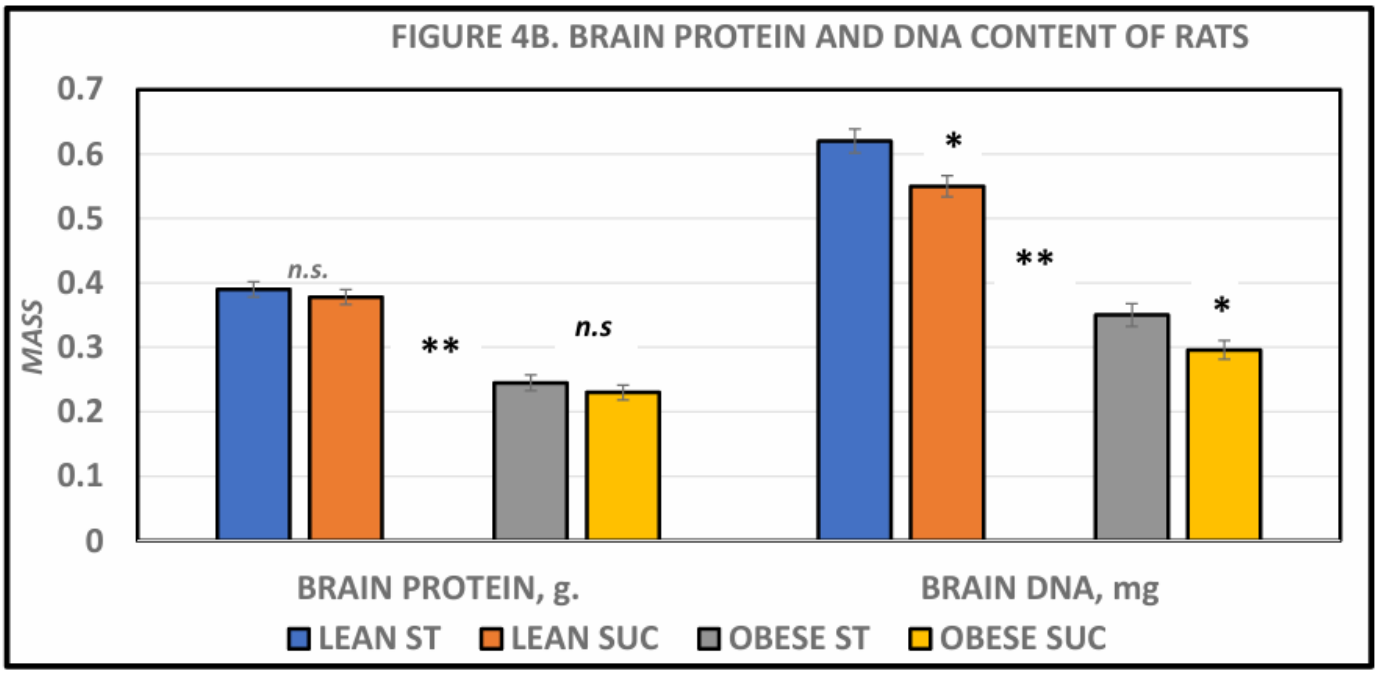

Figure 4B. Brain protein and DNA content of rats. Data are mean ± 1 SEM, n = 6-8 rats/group. **P = < 0.01 Lean vs Obese for brain protein and DNA; P = < 0.05 for DNA St vs SUC for both lean and obese.

Discussion

The transition of the traditional wholesome food diet to manufactured commercial diets often containing excess proportions of refined carbohydrates, salt and preservatives in recent decades has been associated with acceleration of decline for markers of healthy longevity including cardiovascular, malignancies, SCD and other debilitating disorders.[1-3] The markers include increases in the magnitude of insulin resistance, with impacts in skeletal muscle, adipose tissue and neurologic tissues including the CNS and which impairments may become further deranged when consuming high glycemic index diets containing refined carbohydrates. Sucrose and HFCS are the major refined sweeteners in most households where typically they often occupy over 20% daily caloric intake of adults and children.[2] The incidence of SCD in developed counties, where the abundant consumption of refined carbohydrate sources is also commonplace, is virtually staggering, currently approaching over 10% of the population over age 45 with no definitive end in sight.[3-7] There are a dirth of human or animal studies to investigate the relationship of high glycemic index, fiber-deficient diets and neurodegeneration or animal forms of SCD.[1] However in an editorial, Tulp reviewed previously reported studies that reflected decreases in brain mass and cellularity based on protein and DNA composition in obese and hyperinsulinemia rats after consuming a high glycemic index diet throughout much of their projected lifespan.[13,14] In human studies, Yi et al recently reported the habitual consumption of high vs. low quality carbohydrates over a prolonged duration was associated with acceleration of epigenetic markers of decreased longevity in a large cross-sectional study, where the higher dietary fiber to refined carbohydrate ratio proved to be contributory to epigenetic markers that contribute to SCD and decreased longevity.[1] In those studies, the epigenetic markers were determined via DNA analysis after 20 years of consuming their dietary preferences and imply that nutritional and environmental factors contribute to the epigenetic expression of SCD, aging, and Sirt1 mediated antiaging traits.[1]

The obese phenotype of the LA/Ntul//-*cp* rat demonstrates characteristics of subclinical hypothyroidism in association with early onset obesity characterized by decreases in resting and catecholamine stimulated non shivering thermogenesis, decreases in baseline, cold stimulated, and nutritionally induced increased in plasma T3 concentrations, combined with decreased molecular binding affinity to hepatic thyroid hormone receptors.[21,22] The activation of thyroxine to metabolically active T3 is mediated at least in part by Sirt1.[23] On a molecular basis, the discovery of sirtuins including Sirtuin 1 (Sirt 1) has added additional insights into the molecular basis of aging and longevity, where it has been reported that overnutrition results in down regulation and decreased caloric intake upregulation of Sirt1 actions in peripheral tissues.[23] Among the additional numerous epigenetic traits now also attributed to modulation by Sirt1 actions are mitochondrial apoptosis, immune functions, appetite, diabetogenic expression, glucose homeostasis, hormonal activation and regulation of thyroid hormones, and other aspects of metabolism, human health and longevity when deranged.[24] Thus, the likelihood of nutritional status including dietary quality, fiber to caloric ratio, and epigenetic factors are significant factors in the expression and preservation of the multiple metabolic contributors to healthful antiaging traits and characteristics.

Conclusion

The role of Sirt 1, an NAD(+) dependent histone deacetylase protein is often referred to as an antiaging factor, and when impaired, has been proposed as a contributory entity in the progression of various chronic disorders including insulin resistance and systemic inflammation, common hallmarks of obesity and T2DM. Martins suggested that the down regulation of Sirt1 occurs following states of overnutrition, also impairs hepatic metabolic and biodetoxification processes, comorbidities of obesity, T2DM and major organ dysfunction.[3,4] In the present study, both the expression of obesity, and a high glycemic index, sucrose laden diet resulted in decreases in the absolute mass, protein and DNA content of brain tissues in late adulthood. The observations of differences in glycemic index in otherwise isoenergetic diets were suggestive of an increased potential for a contribution of the high sucrose diet in the deranged metabolic sequelae of insulin resistance as a likely pathophysiologic factor in the progression of brain shrinkage and presumed cognitive decline in the aging obese, hyper insulinemic rat. These results are analogous to clinical observations which may occur in senescence, dementia and Alzheimer's disease in aging human populations and implicate the glycemic index of the refined carbohydrate source as a contributory factor in the progression of accelerated aging, cognitive decline, and SCD in man and animals.

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Disclaimer (Artificial Intelligence)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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 no competing interests exist.

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