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Effect of Carbohydrate Type on Brain Composition and Senescence in Aging, Hyperinsulinemia-prone OBESE LA/Ntul//-*cp* Rats

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

To determine if phenotype and the carbohydrate type resulted in alterations in brain composition in the obese phenotype of the congenic LA/Ntul//-*cp* rat, groups (n= 8 rats/group) of male littermate lean and obese rats were fed standardized isocaloric diets containing 54% (w/w) cornstarch (ST diet) or 54% (w/w) sucrose (SUC diet) from 1 until 10.5 ± 0.5 months of age. The obese phenotype of his strain develops early onset chronic hyperinsulinemia without NIDDM associated with hypertrophic-hyperplastic obesity during early postweaning growth. Brain tissues were dissected, and representative aliquots subjected to total fat, protein, and DNA analysis. Body weights of obese >> lean and were greater when fed the SUC than the ST diet in both phenotypes. Brain mass of lean > obese, and diet was associated with modestly lower brain weights in rats fed the SUC than the ST diet. Brain total Protein and DNA content of lean rats were > obese rats and were modestly Lower in SUC than ST fed rats in both phenotypes, but the percent of lipid content was proportional

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to brain mass. Total body fat mass of obese was significantly greater than occurred in lean littermates and was only modestly greater in SUC than ST fed rats in both phenotypes. These results indicate that brain growth and cellular development is impaired in the aging, hyperinsulinemia-prone obese phenotype of this strain, were further impaired when fed SUC than ST diets, and the decreased brain parameters were likely associated with development of a chronic neuronal inflammatory syndrome common to excessive fat accretion and obesity, resulting in premature brain senescence.

Keywords: Obesity; brain development; hyperinsulinemia; senescence; DNA; starch; sucrose; rat.

1. INTRODUCTION

Since the revision of the traditional food groups pyramid several decades ago, much of the dietary lipid previously present has been replaced with carbohydrate sources, often in the form of sucrose in order to retain a satisfactory magnitude and delivery of palatability considerations for many commercially processed foods. The consumption of simple vs complex carbohydrate (CHO) sources exerts significant differences on glycemic parameters in man and animals, with the simple CHO of sucrose resulting in a greater magnitude of hyperinsulinemia (HI) and glucose intolerance (IGT) in obesity than in non-obese subjects. Inflammatory cytokines originating from adipose tissue have been reported to contribute to DNA damage in tissues, impede cellular replication, and accelerate neural cell senescence. In the present study carbohydrate rich diets containing cornstarch or sucrose were fed to congenic lean and obese, non-diabetic rats until late adulthood at 10.5 months of age, resulting in decreases in brain DNA, protein, and total brain mass, with the greatest decreases observed in the hyperinsulinemia prone, sucrose fed obese animals, while brain mass and composition was normal in lean littermates consuming the same dietary regimen.

The prevalence of obesity is now a serious concern among Westernized societies, where it is rapidly approaching epidemic proportions [1]. Moreover, the prevalence of obesity and overweight conditions now represents one of the most challenging issues facing the delivery of health care, in large part due to its close association with comorbidities of hypertension and non-insulin dependent diabetes [1]. “In addition, chronic obesity and nutritional factors have been linked to DNA damage in multiple tissues and premature dementia including Alzheimer’s disease in addition to impaired neurodevelopmental changes that often occur in aging” [2-5]. “The syndrome of insulin resistance, glucose intolerance, and chronic inflammation typically accompanies progressive adiposity in man and animals, often contributing to increased comorbidities and decreased life span even when the obesity occurs without the pathophysiologic impacts of untreated hypertension or diabetes” [4,5]. “The pathophysiologic mechanisms contributing to chronic insulin resistance have been attributed to multiple factors including overnutrition and dietary macronutrient imbalances, disordered glucocorticoid metabolism and actions. Excess glucocorticoid actions also contribute to impaired cellular translocation of insulin-dependent GLUT4 transporters and immune dysfunctions” [6-8]. “Macrophage infiltration of adipose tissue contributes to disordered immune functions and is one of the earmarks of the dysfunction in obesity-mediated immune syndromes” [9,10]. “Because adipose tissue tends to attract macrophages, they can set the immunologic stage that may progress to secretion of inflammatory cytokines IL-6 and others, that may now circulate systemically and impinge on numerous central and peripheral tissues, where they may initiate pathophysiologic sequela including vascular lesions and likely microglial contributions to premature apoptosis of neuronal cells [9-12]. The neuronal changes in obesity plus Alzheimer’s syndrome include cognitive deficits and shrinkage of brain volume and neuronal cellularity” [13]. Thus, the purpose of the current study was to determine the effects of high- vs low glycemic diets on key parameters of brain composition in older, congenic lean and obese male rats with longstanding hyperinsulinemia, and to associate the carbohydrate diets with changes in brain composition.

“Nutritional factors are well established contributors to growth and development of both somatic and neuronal tissues throughout the lifespan” [14]. “Malnutrition and undernutrition during early growth stages are often followed by impaired developmental parameters including

reduced stature, typically proportional to the magnitude of the nutritional depravation or physiologic insult. Brain development can also be impacted by early nutritional factors, and in the most dire examples with reduced brain development and decreased brain DNA content" [14]. "In epigenetic forms of rodent obesity, however, pre- and early postnatal nutrition contributions are presumed to be comparable to similarly reared lean littermates since they typically share the same genetic origins, lactation, equivalent access to solid food and nutritional experiences by age of weaning and thereafter, especially when reared as littermates under standardized laboratory conditions" [15,16]. "Therefor, any growth or developmental deficits in a congenic animal model are unlikely to be associated with frank inadequacies in nutritional deficits, but may be associated with the hyperphagia and resulting metabolic sequela that normally accompany the epigenetic expression and development of hyperinsulinemia and disordered metabolic parameters typically followed by progressive increases in adiposity and obesity by adolescence and early adulthood" [14].

"The obese stigmata occur in the LA/Ntul//-cp (corpulent) rat via epigenetic expression of the obese characteristics as the result of an autosomal recessive trait, resulting in 25 % of the offspring of heterozygous breeding pairs demonstrating the stigmata of obesity by 5 to 6 weeks of age" [15-19]. "As the obesity phenotype develops, rats demonstrate progressive increases in hyperphagia, elevations in plasma insulin, amylin, hypertriglyceridemia and impaired glycemic responses to a glucose tolerance within a few early during postweaning life" [15,16,20,21]. "The obese littermates develop impaired glycemic responses typical of insulin resistance, but have remained non-diabetic throughout their lifespan" [15,20]. "Thus, the primary aspect of metabolism that remains in the obese phenotype is the chronic, lifelong hyperinsulinemia and hyperamylinemia and the pathophysiologic sequela which typically result from those factors" [15,16,21].

2. METHODS

In the present study, the animals were housed in littermate pairs in plexiglass cages lined with pine shavings and maintained under standard laboratory conditions (22°C and 50% RH). The only known difference between the congenic lean and obese phenotypes was the epigenetic expression of the *-cp* trait for obesity. The -cp trait originated in the Koletsky rat [18] followed by backcrossing into the longevity-prone NIH LA/N background strain for 12 or more cycles by Hansen, thereby establishing the criterion to satisfy a congenic designation at the NIH [17,19]. "Rats were maintained on Purina chow (#5012) and free access to house water from weaning until six weeks of age rats when they were switched to isocaloric nutritionally adequate diets containing 54% carbohydrate as cooked cornstarch as a low glycemic index diet or isocaloric 54% sucrose in place of the cornstarch for a high glycemic, insulinogenic diet. Additional dietary components included 20 % mixed protein, 16% mixed fat plus essential vitamins, minerals and fiber, *ad libitum*. This diet has previously been described by Michaelis et al. [20]. At 10.5 months of age animals were sacrificed by rapid decapitation with a small animal guillotine after a brief fast and cervical blood was obtained for later analysis". "The brain tissues were dissected and weighed to the nearest mg. and 50-75 mg tissue aliquots of representative samples taken for proximate analysis. The residual carcasses including the remaining brain tissues were frozen at -20C, homogenized with equal parts distilled water to form a homogenous slurry in a Waring blender at high speed, lyophilized and subjected to gravimetric analysis for determination of protein and lipid content" [22,23]. "The analysis for proximate analysis of brain and residual carcass lipid content was obtained with the methods of Dole and Meinertz and protein content determined via the classic methodology described by Lowry as described previously" [22,23]. "The brain DNA analysis was determined in delipidated samples by the method of Burton" [24]. The data were analyzed by standard statistical procedures [25,26]. The study was approved by the Institutional Animal Care and Use Committee.

3. RESULTS

The results of final body weight determinations over the lifespan of male and female rats are depicted in Fig. 1A. These data indicate that by 10.5 months of age, the obese phenotype in both sexes of rats weighed more than twice the weights of their lean littermates, despite having been reared identically with respect to both diet and environment, and with equal *ad libitum* access to the nutritionally sound diet [20]. In addition, the body weights of rats of both phenotypes fed the SUC diet weighed more than their ST fed littermate counterparts. In Fig. 1B,

the carcass fat content of male rats is depicted and indicates that the total fat content of the obese was markedly greater than occurred in their lean counterparts, and that the SUC diet was associated with modestly greater fat content than when fed the ST diet in both lean and obese phenotypes. Carcass protein content is depicted in Fig. 1C and indicates that the protein content of obese rats was greater than in their lean counterparts, with little additional increase with the SU diet.

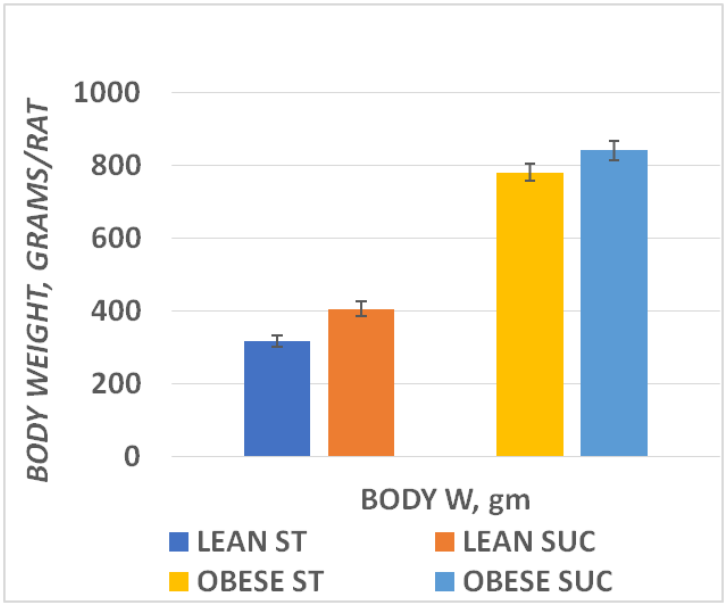

Fig. 1A. Effect of diet and phenotype on body weights of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.01 for phenotype and for diet in lean but not obese (p=<0.10)

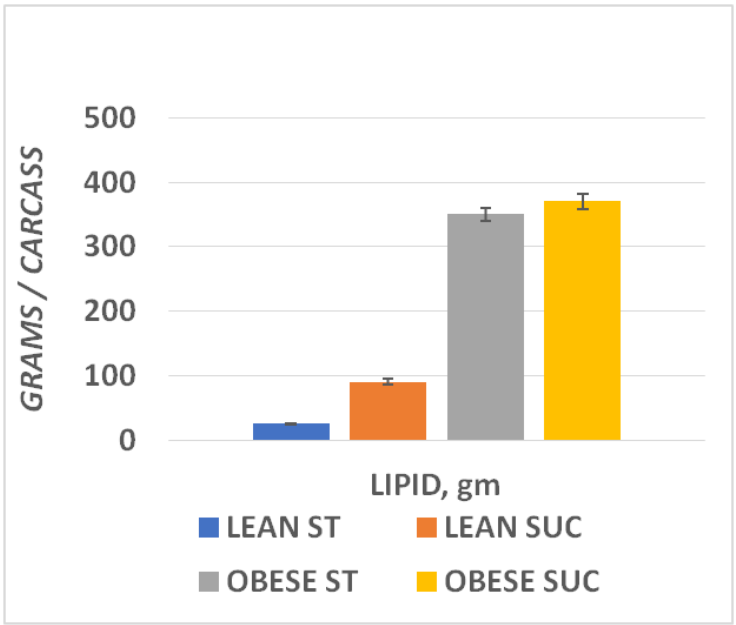

Fig. 1B. Effect of diet and phenotype on carcass fat content of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.05 for phenotype and for diet in lean but not obese (p=<0.10)

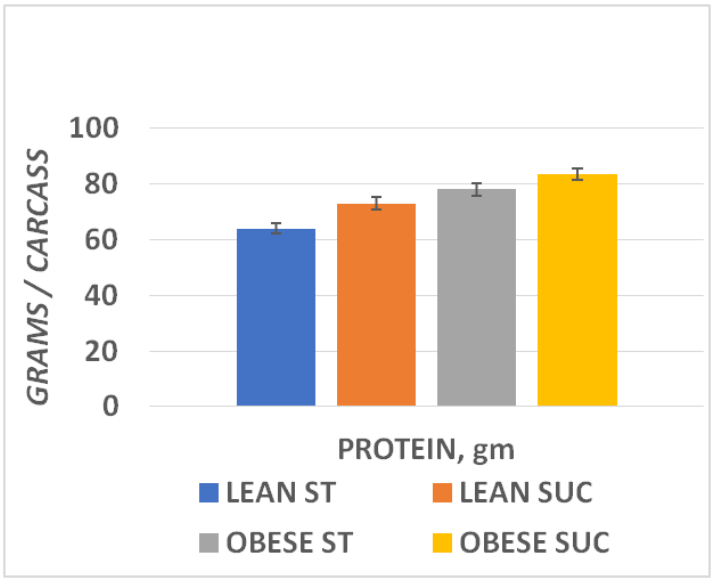

Fig. 1C. Effect of diet and phenotype on carcass protein content of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.01 for phenotype and p+<0.05 for diet in lean but diet trend effects for obese (p= n.s.)

Fig. 2 depicts the brain wet weights and the brain wet weight to final body weight ratios. These data clearly indicates that the brain weights of the obese rats weighed significantly less than their lean littermates at 10.5 months of age (p<0.05). In addition, the ratio of brain weight to body weight was also decreased in the obese phenotype. The effects of the higher glycemic index sucrose diet tended to result is yet smaller absolute brain weights when fed the SUC vs. the ST diet and resulted in a further moderate trend toward decreases in the brain weight to body weight ratios that were mostly secondary to the greater fatness in the sucrose fed obese phenotype. There appears to be a mild diet trend effect on final brain weights, with ST fed animals of both phenotypes trending to weigh slightly more than was recorded for their ST fed littermates. In addition, the ratio of brain weight to final body weight of obese animals is depicted in Fig. 3 and indicates that brain weights were also significantly less than were observed in their similarly reared lean littermates (p=<0.01).

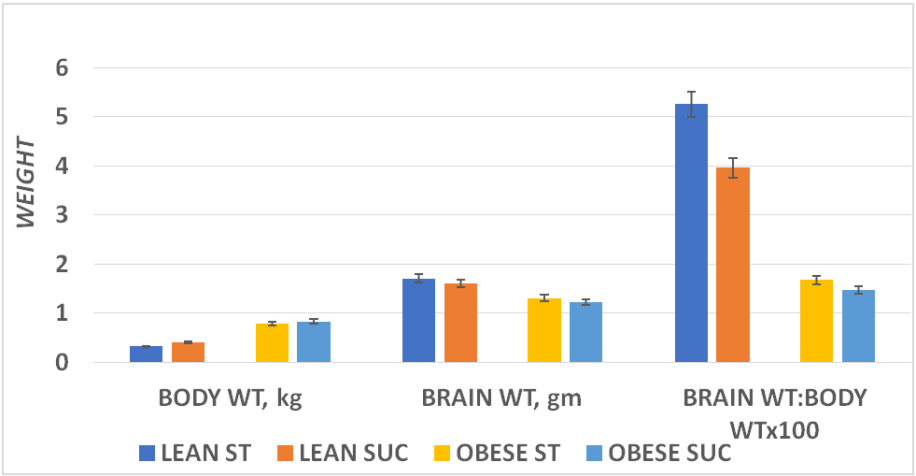

Fig. 2. Effect of diet and phenotype on brain weights and brain weights: body weights of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.05 for phenotype. Diet resulted in a significant trend toward lower brain weight in sucrose then in starch fed rats by Pages 'L' test for trend analysis [26]

The total protein and DNA content of brain tissues are depicted in Fig. 3. These data indicate that measures of the total protein and DNA content computed per brain were both decreased in the obese phenotype compared to their lean littermates. (p=<0.05 for both total protein and DNA). The effects of diet are depicted to the right of each set of bars, and while suggestive of a further decrease in protein and DNA content in the SUC fed animals, only the brain DNA content of the sucrose-fed obese animals were found to be highly suggestive of a significant negative trend by Pages L test for trend analysis. Thus, the decreases in brain content when fed both diets are generally proportional to the decreased brain weights observed in this study.

Brain tissues typically contain approximately 75 to 80 % lipid. The lipid content of lean and obese rats is depicted in Figs. 4A and 4B respectively and indicate that although the amount of lipid per brain was less in the obese phenotype, when expressed as a W/W percentage the brain lipid contents were similar in both phenotypes. This observation is suggestive therefor of a proportional decrease in overall brain composition rather than a decrease in any specific chemical constituent. Thus, although the brain mass and lipid weights were proportionately lower in the obese than the lean phenotype, the results appear entirely consistent with and correspond to the smaller brain mass observed in those animals. When the net brain mass is compared to final body weight, the proportion of brain tissue lipid to total body weigh was significantly less in the obese than the lean phenotype, likely reflecting the substantially greater adiposity and body fat accretion that occurred in the obese phenotype.

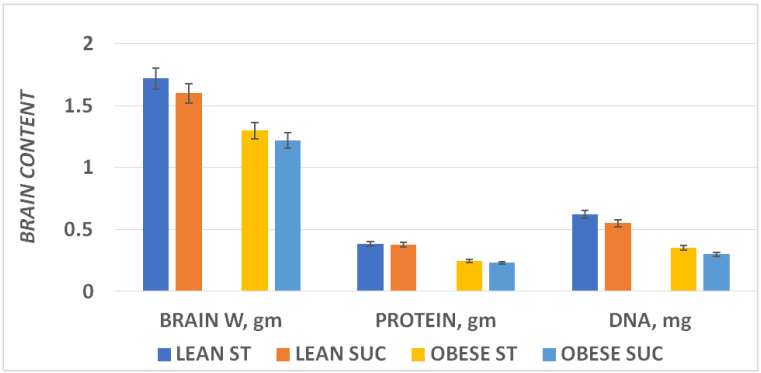

Fig. 3. Effect of diet and phenotype on brain protein and DNA content of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.05 for phenotype. Diet resulted in a significant trend toward lower brain weight in sucrose then in starch fed obese rats by Pages 'L' test for trend analysis

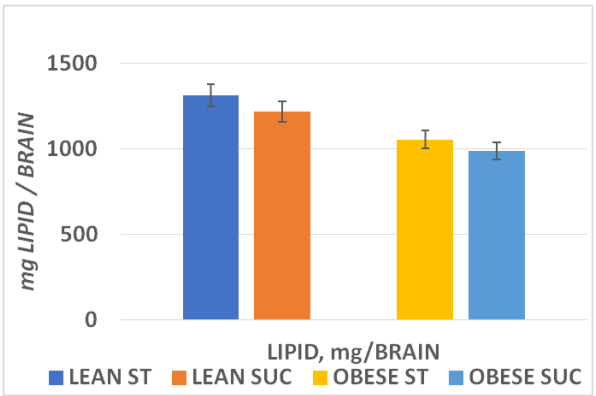

Fig. 4A. Effect of diet and phenotype on brain lipid content of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = < 0.05 for phenotype. A Diet effects on total lipid content trend (sucrose < starch) were not significant when computed as mg of lipid weight by Pages 'L' test for trend analysis [26]

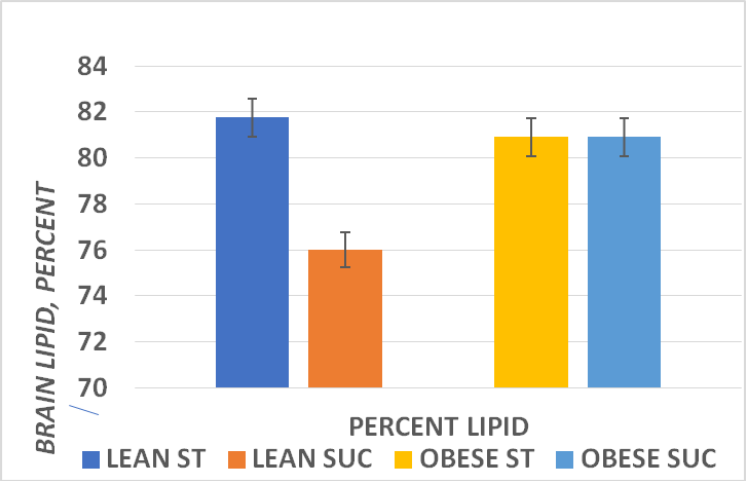

Fig. 4B. Effect of diet and phenotype on percent brain lipid content of rats. Data are mean ± 1 SEM, n=8 rats/treatment group. P = n.s. for phenotype and diet. A Diet effect on percent lipid content trend (sucrose < starch) was significant in lean but not obese rats when computed as percent of lipid weight by Pages 'L' test for trend analysis

4. DISCUSSION

The results of this study indicate that the total brain weight and absolute lipid, protein and DNA content were decreased in the obese phenotype when measured at 10.5 months of age, despite having been reared since birth with biological littermates via the same nutritional and environmental conditions when fed either a low glycemic index starch (ST) vs a sucrose higher glycemic index (SUC) diet. "The sucrose diet resulted in significantly greater fat accretion and greater final body weights than the starch-fed animals in both phenotypes, consistent with a greater magnitude of insulin stimulated lipogenesis. Although the study did not directly monitor daily caloric intake, numerous previous reports have demonstrated hyperphagia and hyperinsulinemia to occur throughout much if not all of the lifespan in the obese phenotype of this strain. In addition, the typical duration of the lifespan of the obese phenotype is reduced by about one third compared to their similarly reared and housed lean littermates [15,20,27-29]. Previously, Michaelis et al reported that the chronic hyperinsulinemia of sucrose-fed obese rats remained greater than occurred in starch fed rats of this strain" [20]. "In nutritional studies, brain size and cellularity have been shown to be decreased under conditions of severe malnutrition, as well as in humans that develop Alzheimer's disease. Only limited reports have suggested obesity as an isolated contributor to premature brain shrinkage or brain dysfunction to date. In the present study, the decreases in brain DNA content are consistent with decreased neuronal cellularity, and presumably decreased cognitive functions are likely to accompany the decrease in brain cellularity. Although the animals were not subjected to cognitive evaluation, the decreased brain size and cellularity or the insulinogenic diets while suggestive could not be directly correlated with cognitive decline. The findings do however permit an assumption of decreased overall cognitive potential, and one where the presence of inflammatory cytokines and hyperinsulinemia common to obesity may be considered as contributing factors in the neurologic decline. Of interest, the isocaloric substitution of sucrose for starch in the diets resulted in a trend effect toward further decreases in DNA and protein content, and thus it seems likely that with a larger number of animals per treatment group or a longer duration of the dietary treatment regimen that the diet induced results may have been more pronounced. Because the brain measurements were only undertaken at age 10.5 months, the chronologic timeline of the progression of neurologic decline or more profound effects of a high glycemic diet could not be firmly established. Unlike other dietary-induced forms of obesity, when animals were returned to the normal diet weight loss occurred. In the obese phenotype in this epigenetic strain however, has been found to be remarkably refractory to significant weight loss, or a return to the bodily habitus of their lean littermates following dietary normalization or nutritional interventions" [27,28]. "To date, only excess daily

T3 but not T4 administration has demonstrated significant increases in plasma T3, VO2 and in weight loss in the obese phenotype, with adrenalectomy resulting in partial but incomplete recovery" [27-30].

"The metabolic or physiologic differences in brain weight and composition are unclear in the present study but are highly suggestive of chronic hyperinsulinemia as contributing factors. Michaelis et al has previously reported impaired glucose tolerance and hyperinsulinemia in this strain from postweaning to 10 months of age" [20]. "Thus, the elevations in plasma insulin noted in this study have been reported to occur through much if not the entire lifespan of the obese phenotype of this strain. The metabolic factors which contribute to the impaired thermogenesis in the obese phenotype have been linked to hyperinsulinemia, which contributes to insulin inhibition metabolic actions of the thermogenic mitochondrial uncoupling protein UCP1 in brown adipose tissue (BAT)" [29-32]. "The BAT has been found to be a primary tissue in expressing nutritionally and environmental increases in thermogenesis, and when impaired due to metabolic aspects of insulin resistance in BAT and other peripheral tissues, results in impaired thermogenesis, metabolic efficiency, increased rates of lipogenesis, and excess body fat accretion in both visceral and subcutaneous adipose tissue depots, sites where inflammatory cytokines are expressed" [30-34].

White adipose tissue (WAT) In lean animals is enriched with Type 2 immune cells, which undergo cell to cell interaction to facilitate the generation of Type 2 cytokines. The Type 2 cytokines include IL-4, IL-5, and IL-13 and help to maintain a healthy and immunoprotected type 2 physiologic environment. In contrast however, as the development of obesity progresses and chronic hyperinsulinemia occurs, [9,10] the obese tissues may promote development of an inflammatory Type 1 immune response, including the generation of inflammatory cytokines IL-6 and others which when systemic may produce damaging effects on neuronal DNA and prevent neuronal replication and survival. The type 1 inflammatory response includes metabolically activated macrophages, T-cells, B cells and other cell types which release inflammatory cytokines, resulting in a chronic systemic inflammatory state. Thus, the activated macrophages and other immune cells can collectively induce a chronic Type 1 inflammatory environment that can promote neurologic demise. The inflammatory cytokines can now migrate systemically to virtually all somatic and neuronal tissues, where they may contribute to progressive cellular senescence. Dietary factors including excess fatty acids common to hypertriglyceridemia and obesity in concert with the low-grade hypoxia that occurs in WAT have also been shown to contribute to a chronic low-grade inflammation that can further induce the pathophysiologic sequela including premature apoptosis among neuronal tissues, similar to that which appears to occur in Alzheimer's disease [9,13]. The high sucrose insulinogenic diet likely contributes to an augmentation of the senescent responses in the obese phenotype.

Plasma glucocorticoid actions on substrate metabolism are generally counterregulatory to those of insulin and in the context of the present study merits some discussion. Dysregulation of glucocorticoid actions may follow several lines of evidence, including glucocorticoid effects on intracellular GLUT4 transporters, which when impaired contribute to development of insulin resistance. With respect to inflammation, glucocorticoids can induce both anti-inflammatory (Type 2) and inflammatory (Type 1) immune responses from macrophages and thus promote inflammatory responses [2,3,32-36]. The physiologic interrelationships between glucocorticoids and insulin mediated aspects of carbohydrate metabolism tend to be antagonistic, creating a somewhat vicious cycle that may only become further aggravated in the presence of a chronic hyperinsulinemia state. The greater the magnitude of insulin resistance the greater the impaired modulation of immune responses may occur [2,7,29]. The chronic dysregulation of glucocorticoid actions impede the biosynthetic expression, release, and cellular translocation of insulin dependent GLUT4 glucose transporters from the endoplasmic reticulum of somatic cells. The impaired GLUT4 expression and actions results in impaired or delayed cellular glucose uptake. The impairments in cellular glucose uptake may be followed by further increases in insulin release mechanisms to insulin dependent tissues including skeletal muscle, adipose tissue and brain, while promoting lipogenesis in liver and other receptive tissues [7,8]. Indeed a hallmark characteristic of genetically-obese rats if the progressive development of a fatty liver with advancing age, and which were visually apparent in all of the obese rats of the present study that were dissected [15-16,17]. Although glucocorticoids can induce cellular death and

reduce cell survival in immune cells including T cells and B cells, the macrophages in most tissues fortunately tend to be relatively resistant to glucocorticoid-induced apoptosis, thereby allowing other essential glucocorticoid actions to continue. Overall glucocorticoids act to suppress systemic inflammation and are frequently prescribed to treat chronic inflammatory condition involving lymphocytes, but they are reportedly less effective in macrophage-mediated diseases such as chronic obstructive pulmonary disease (COPD) and the chronic inflammation and hypoxia of obesity. In those conditions, an elevated release of inflammatory cytokines may continue to occur differentially in different adipose tissue depots, with visceral adipose tissue depots ranking among the most prolific in the generation of inflammatory cytokines [33-38]. Regardless of the cellular processes implicated in this study, the brain size, absolute composition, and cellularity based on DNA content was reduced in the aging adult obese non-diabetic phenotype of the LA/Ntul//-*cp* rat and further impaired when fed a high glycemic index sucrose diet throughout much of their projected lifespan.

5. SUMMARY AND CONCLUSIONS

The brain mass and cellularity of the present study was decreased in the obese phenotype and was further impaired when fed an isocaloric high glycemic index sucrose diet in the hyperinsulinemia-prone obese phenotype of this strain. The chronic hyperinsulinemia was likely associated at least in part with a chronic inflammatory syndrome and cytokine expression. These characteristics are common to hyperinsulinemia adiposity and obesity, and the deleterious responses on brain protein and DNA content were further impaired when obese animals were fed the high glycemic, insulinogenic sucrose diet. Specifically, isocaloric substitution of the higher glycemic index sucrose diet resulted in a trend toward further decreases in brain DNA and protein content, but the trends were not highly significant by conventional statistical analysis. The results could not determine the chronology of development the decrease or confirm an etiologic or developmental origin in brain size or composition as the data reflect only a single time point taken during late adulthood, in animals that typically often only survive for 12 to 15 months due to pathophysiologic complications of their obesity. In contrast the lean littermates have been observed to survive for 2 to 3 years or longer under similar environmental conditions, with obese females exhibiting a lesser magnitude of hyperinsulinemia and glucose intolerance and surviving significantly longer than their male counterparts.

In the present study, the decreased brain mass was characterized by proportionate decreases in total lipid, brain protein and brain DNA content and were further impaired when fed the insulinogenic sucrose diet. These brain changes occurred in association with marked increases in body fat accretion, progressive increases in obesity and a decreased brain to body weight ratio in the epigenetic obese (-*cp/-cp*) phenotype of this congenic rat strain. It is proposed that the status of insulin resistance was a contributing factor in the brain senescence, as the brain parameters were further deranged in obese animals fed the insulinogenic sucrose diet. The decreases in brain size, cellularity and shrinkage were of similar magnitude to that which occurs in dementia and Alzheimer's Disease where chronic exposure to inflammatory cytokines may prevail and that tend to occur in aging humans. Because only a single time point was measured in the present study, the chronology through which the changes in brain composition occurred in the present study could not be determined but were similar to the decreases in brain mass and composition observed in obese animals fed a starch diet reported elsewhere [38]. Inflammatory cytokines of the macrophage-generated Type 1 category include IL-6 and others and have been reported to generate free radical damage to DNA and contribute to neuronal senescence via inhibition of cell replication, and thus remain an interesting causal speculation from the data obtained. Regardless of the biological physiological or epigenetic mechanisms involved, the brain mass and apparent cellularity was significantly decreased in the obese phenotype of this rodent strain, and the more highly refined high glycemic index sucrose diet tended to exaggerate the damaging impact on brain composition in the obese phenotypic of this strain.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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