ISSN: 2994-9637

Volume 4 Issue 1
www.escientificlibrary.com

ES Journal of Public Health

Does Carbohydrate and Insulin Resistance of Obesity Contribute to the Senescence of Brain Atrophy in Aging? Here is What the Lab Rats May Be Telling Us about Carbohydrates

DOI: 10.59152/ESJPH/1017

Editorial

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Received: June 06, 2023; **Accepted:** June 16, 2023; **Published:** June 26, 2023

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Abstract

Since the dietary guidelines were adjusted several decades ago in an effort to improve cardiovascular health by promoting diets containing fewer calories from fats, the consumption of carbohydrate calories including those from refined carbohydrate sources have increased proportionately in much of industrialized society. Refined carbohydrates including sucrose are rapidly digested by brush border glucosidases and have a higher glycemic index and stimulate greater insulinogenic responses than calories obtained from complex carbohydrate sources and tend to contribute to greater body fat accretion over time. High carbohydrate diets promote greater elevations in insulin secretion and can lead to insulin resistance and its multiple pathophysiologic sequelae including increases in body fat accretion, obesity, non-insulin dependent diabetes (NIDDM) chronic inflammation, and other comorbidities that can compromise health and longevity including neurologic demise. In the obese phenotype of the aging congenic, chronically insulin resistant non- diabetic LA/Ntul//-*cp* rat, measures of brain composition and cellularity as determined by brain mass and DNA content were significantly decreased and were further compromised when fed a high glycemic index, insulinogenic diet where the starch was replaced with isocaloric quantities of sucrose. These observations are consistent with the chronic insulin and amylin resistance linked to high carbohydrate diets in the obese phenotype as a contributing factor in the progression of senescence and brain atrophy and suggest that the factors of obesity and insulin resistance, compounded by the glycemic index of the diet were key factors in the neurologic demise and premature death in the obese phenotype of this strain.

Keywords

Obesity, Aging, Brain composition, Hyperinsulinemia, Neuroinflammation, Neurosenescence, DNA, Cognitive Decline, Carbohydrate, Sucrose, Rat.

Introduction

The luminal absorption of dietary carbohydrate occurs with virtually 100% efficiency in the upper segments of the small intestine and occurs more rapidly with the digestion of high glycemic index simple carbohydrate sources such as sucrose vs lower glycemic index complex carbohydrate sources including cornstarch [1-5]. The brush border extensions lining the absorptive lumen of the small intestine are normally populated with a healthy abundance of sucrase and glucosidase enzymes, which have the enzymatic capacity to degrade disaccharides and complex carbohydrate polymers into absorbable monosaccharide moieties often within minutes of their presentation as

they progress downward through the gut. The rates and efficiency of their digestion is delayed only by the presence of gums, fibers and other inhibitory factors that may impede their direct interaction with their enzymatic digestive facilitators. Once the monosaccharide moieties are generated however, luminal absorption occurs rapidly resulting in the post prandial and insulinogenic phase of the glycemic response. The rise in the plasma glucose concentration after a fixed dose of a carbohydrate is the basis for the glycemic index, and the index varies based on the rate of digestion and absorption of the ingested carbohydrate source, with free glucose and sucrose being among the highest ranked glycemic responses of the various carbohydrate sources [5]. Moreover, the higher glycemic index of sucrose vs complex carbohydrates elicits greater increases in insulin responses with its attendant pathophysiologic sequelae including an increased propensity toward developing adiposity, insulin resistance and the chronic inflammation commonly associated with obesity when sucrose is consumed in abundance. In addition, factors of age and comorbidities including glucose intolerance also contribute to differences in the characteristics of the glycemic responses observed among different individuals [6].

The experimental evidence supporting a direct role for hyperinsulinemia as the sole cause of insulin resistance remains equivocal however, as amylin, an islet beta-cell peptide that is co-secreted with insulin also in response to nutrient stimuli, also causes insulin resistance when infused into intact animals or when applied to isolated skeletal muscles and has been shown to be elevated in hyperinsulinemic obese rats [7]. In addition, hyperamylinemiaemia is also is associated with disordered gastric emptying due to amylin resistance in the musculature of the antrum of the stomach. In addition, elevations in glucocorticoid activity also contribute to insulin resistance by interfering with the biosynthesis and intracellular translocation of the insulin dependent GLUT4 glucose transporters thereby further impeding the process of glucose uptake and metabolic actions in insulin dependent tissues including skeletal muscle, adipose tissue and brain and where insulin resistance has been reported to occur [7-10]. Thus, systemic insulin resistance is implicated in multiple pathophysiologic processes at the cellular and organ levels in the obese phenotype of the LA/Ntul//-*cp* rat and is a likely contributing factor in the long term progressive metabolic and neuropathophysiological sequelae of obesity in this congenic animal strain [11].

In addition to impaired glucose uptake in peripheral tissues in the presence of insulin resistance, chronic hyperinsulinemia has also been linked to neuroinflammation and DNA damage, and is a contributing factor in the pathophysiologic processes that participate in the progression of brain senescence of Alzheimer's disease and the brain atrophy of aging [8-16]. Chronic elevations in hemoglobin A1c, characteristic of hyperinsulinemia and NIDDM have also been associated with Alzheimer's disease and dementia [14]. In a recent study, it was reported that brain atrophy was reported in aging obese hyperinsulinemia-prone LA/Ntul//-*cp* rats, characterized by significant decreases in brain mass, brain protein and brain DNA content, compared to their non-obese but similarly fed and reared lean littermates.[16] In the present review, we report that brain mass is further decreased in both mass and DNA cellularity when the starch diet was exchanged with an isocaloric sucrose based diet of equivalent nutritional value, producing a greater magnitude of insulin work product of insulin resistance in the obese phenotype, thereby establishing factors of both obese phenotype and glycemic index of the diet as contributing factors in the progression of brain atrophy in this strain of rat. Obesity decreased the observed lifespan in this strain by approximately 30% in both male and female rats when fed typical chow diets [11].

Overview of methods

The LA/Ntul//-cp rat is a congenic animal model, where the obesity trait is expressed as an autosomal epigenetic recessive trait (the -*cp* trait) originally obtained from the Koletsy rat and backcrossed into the longevity- prone LA/N strain at the NIH by Hansen to attain a congenic status, where the only known surviving trait from the donor strain was the recessive -*cp* trait as previously reported [11,17]. In the present studies groups of lean and obese rats were fed nutritionally complete diets containing 54% carbohydrate as cooked cornstarch (CON) 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 [18] 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. Data were analyzed by standard statistical procedures [16]. This study was approved by the Institutional Animal Care and Use Committee.

Results

The typical longevity of LA/Ntul//-*cp* rats as reared in our colony is depicted in Figure 1. Animals were fed Purina rodent chow #5012 during mating, pregnancy and weaning and offspring were maintained on the same diets and house water thereafter at 22 °C and 50% RH on a conventional light cycle. As depicted, obese females tended to survive longer than obese males, and lean females survived longer

than lean males under the stated conditions. Note that not all animals of each sex and phenotype survived as noted, and a very few survived a few weeks longer than the means indicated. A total of 600 rats are indicated in the numbers reported with about 60% of them represented by the lean phenotypes.

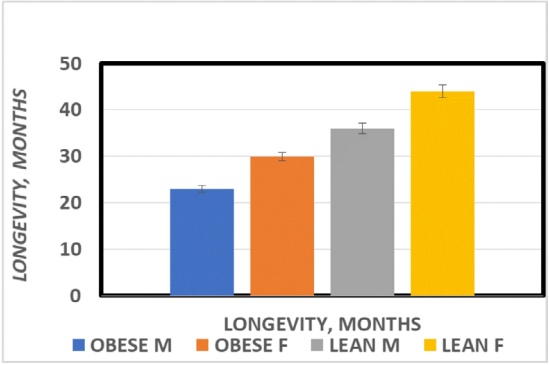

Figure 1: Effect of phenotpe and sex on average longevity.

Data are the mean ±1 SEM of 600 rats of various ages obtained from our breeding colony as reported previously [11].

The brain mass and brain mass to body weight are depicted in Figure 2A and indicate that brain mass in the left panel was 25% greater in the lean than the obese phenotype. In addition, the brain mass was decreased by a further 6% in animals consuming the sucrose in both phenotypes. The reductions in brain mass to body weight were more pronounced due to the significantly greater fat accretion in the sucrose fed rats of each phenotype (90g SUC vs 25 g CON in lean phenotype vs 406 g SUC vs 350g CON in obese phenotype).

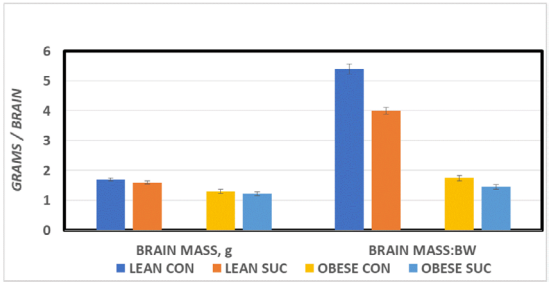

Figure 2A: Effect of Phenotype and diet on brain mass and composition: grams brain mass and ratio of brain mass to body weight. Data are mean ± 1 SEM, n-8 rats/group.

The effects of phenotype and dietary carbohydrate are depicted in Figure 2B and indicate that brain lipid content of the lean rats was significantly greater than in the obese phenotype with both diets, and there was a trend toward lower brain lipid when fed the more highly insulinogenic sucrose diet than the starch control diet in both phenotypes. Brain protein content I depicted in the central panel of Figure 2B and indicates that brain protein content was also decreased in the obese phenotype compared to their lean counterparts, the differences in diet were although suggestive of a modest trend were not significant in either phenotype, however. Brain DNA content is depicted in the right panel of Figure 2B and indicates that brain DNA content and thus brain cellularity was greater in the lean than the obese phenotype. In addition, the SUC diet was associated with further decreases in brain DNA content in both phenotypes, suggestive of an additive effect of dietary carbohydrate type on neurocellular demise likely due to the greater magnitude of insulin resistance and neuroinflammation.

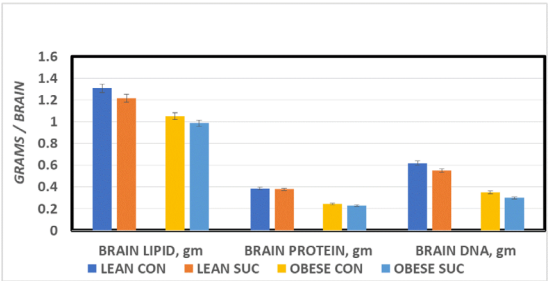

Figure 2B: Effect of Phenotype and diet on brain composition: brain lipid, protein, and DNA content. Data are mean ± 1 SEM, N=8 rats/group.

The effect of phenotype and insulin resistance work product is depicted in Figure 3. The insulin resistance work product is computed by multiplying the body weights of animals by the plasma inulin concentrations as an indicator of the whole-body magnitude of insulin resistance, including skeletal muscle, adipose tissue, and brain tissue, three of the most significant tissues with respect to the current topic of insulin resistance and brain atrophy. A qualitatively similar result was obtained if only the brain mass was multiplied by the plasma insulin concentrations.

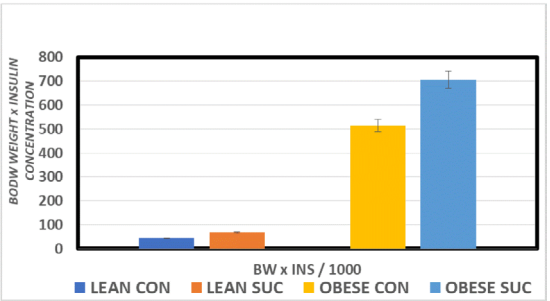

Figure 3: Effect of Phenotype and diet on work product coefficient of insulin resistance in lean and obese rats. Data are Mean ± 1 SEM, n= 8 rats/group, Body weight x plasma insulin concentration / 1000.

The effects pf diet and phenotype on brain atrophy are depicted in figure 4 and indicate that the sucrose diet resulted in modest decreases in both brain mass (Right panel) and DNA content (Left Panel) in both phenotypes. The absolute decreases while modest in absolute amount were significant when analyzed by Pages L test for trend

analysis, as all rats decreased in each parameter by some amount when compared to the control diets. Had the number of animals in each treatment group been greater or the duration of the dietary treatment been of longer duration it is likely that the results would likely have been of greater magnitude than were recorded in this study. Indeed, the differences in the work product of insulin resistance in the lean phenotype were minimal, while the differences in this parameter in the obese phenotype were significantly greater with the sucrose diet, indicative if a greater magnitude of insulin resistance and potential insulin resistance induced contributions to neuroinflammation in the sucrose fed obese animals.

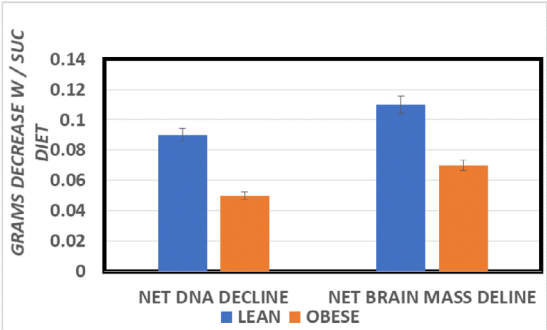

Figure 4: Effect of sucrose vs starch and phenotype on aging brain atrophy. Data are mean ± 1 SEM, n= 8 rats / group. Net decline equals the difference between starch and sucrose fed rats of each phenotype.

As depicted in Figure 1, the projected longevity of the obese phenotype is reduced by approximately one third in both phenotypes when maintained under ideal laboratory conditions throughout their lifespans. The animals in this colony were maintained as a SPF population with periodic necropsy for detection of possible infectious agents, in an isolated environment in the same animal room with the same animal handler throughout their lifespan, thus were never exposed to additional external environmental threats. These factors in addition to their LA/N background genetics, likely contributed to their generous gift of longevity.

Discussion and Conclusion

The results of this study indicate that the effects of isoenergetic substitution of sucrose for starch in the diet of lean and obese rats leads to a further decline in the brain mass and cellularity in the obese phenotype as they approach the projected late stage of their lifespan, while the damaging effects of the sucrose dietary impact on the lean phenotype were minimal at best. Although the sucrose diet resulted in a significant increase in fat accretion in the lean phenotype (90 vs 25 g fat/carcass) the sucrose diet failed to result in development of an obese state in those animals and the cumulative effects of the sucrose diet on the insulin work product in the lean phenotype were also minimal. In contrast, the sucrose diet resulted in the work product of insulin resistance and in still greater increases in net fat accretion in the obese phenotype (406 g fat in SUC vs 350 g fat in CON obese) indicating that the insulin resistance of the obese phenotype itself is a significant factor in the fat accretion but is likely further aggravated by the higher glycemic index and insulinogenic responses of the sucrose diet. In other studies, the lean phenotype of this strain has demonstrated a prominent capacity to elicit diet induced increases in thermogenesis, while the capacity for diet induced thermogenesis and caloric efficiency of weight gain in response to diet and environment in the obese phenotype is impaired and was deemed a likely contributor to the progressive expression of obesity in the obese phenotype while only contributing to lesser degrees of excess adipose weight gain in the lean phenotype [19]. Insulin resistance is a known factor in the inhibition of diet induced thermogenesis and in the disruption of mechanisms of energy balance and energy expenditure in the obese phenotype of this and of numerous obese rodent strains [20].

The luminal brush border enzymes of the upper small intestine play a critical role in the glycemic index of ingested carbohydrate sources, particularly those residing in the duodenum where the ingested carbohydrates make their first contact with luminal absorbance mechanisms before entry into the circulation for uptake into peripheral tissues [1-3]. The more rapid entry of the acid chyme into the duodenum in the obese phenotype enables more carbohydrate residues from more frequent meals to make their appearance for neutralization and immediate digestion and absorption, thereby eliciting a greater and more prolonged magnitude of insulinogenic response than occurs in their lean littermates, where the ingestion and gastrointestinal functions occur along a more graded time frame, even in the presence of a sucrose-rich diet and where metabolic regulation mechanisms remains operative. The rate of luminal digestion of carbohydrates can be delayed or otherwise moderated in the presence of glucosidase inhibitory pharmacologic and nutritional agents including fructans and other agents capable of temporary, dose-related competitive or non-competitive inhibition of luminal carbohydrate digestive active activity or more permanent damage following intestinal parasitic infestations, either of which may alter the physiologic glycemic response to a carbohydrate load [3,5].

The peripheral responses to a glycemic response are dependent on both insulin and glucocorticoid interdependent actions, as the mechanism of insulin resistance has multiple elements, several of which contribute to the inflammatory responses of interest. Insulin and glucocorticoids are notoriously counter regulatory in nature, as untoward increases in one ultimately trigger increases in the other. As glucocorticoids increase they impede the biosynthesis, generation and

translocation of GLUT4 glucose transporters from the endoplasmic reticulum to the plasma membrane, where they are needed to facilitate the membrane transport of glucose across the plasma membrane to the cytosol, where glycolysis can occur, ultimately providing essential substrates for mitochondrial oxidation and energy generation [10,16,21]. The insulin responses also promote lipogenesis from both lipid and non-lipid substrates particularly in hepatic tissue, where they can efficiently be transported into adipose tissues with an optimal energetic efficiency of fatty acid and triglyceride deposition, thereby contributing to progressive adiposity [11].

The relative hypoxia of adipose tissue provides an ideal metabolic site for the uptake of macrophages and the generation and release of inflammatory cytokines IL-6 and others that can bring about systemic inflammatory responses including those that may elicit neuroinflammatory responses ultimately resulting in brain atrophy over time if left unchecked [9,12,13,15,22]. The common denominator of obesity is the presence of chronic insulin resistance, and may occur with or without NIDDM, and in either case lipogenesis may continue unabated in the presence of hyperinsulinemia and suppressed energy expenditure [10]. Adipose tissue is a common location for macrophage infiltration, where they may bring about the secretion of both Type I and Type II cytokines [23,24]. Type I cytokines release the cytokines IL-6 and others that initiate proinflammatory and inflammatory responses that in the most dire of scenarios can precipitate life threatening events, while Type II cytokines release the cytokines IL-4, IL-5, and IL-13, which contribute to immunoprotective processes [23-25]. The adipose tissue-based macrophages can also release a monocyte chemoattractant protein (MCP-1) which further augments the attraction of additional macrophages and thus the onset of a generation of events leading to the systemic release of the inflammatory cytokines IL-6 and others that may seek refuge in neuronal, respiratory, or other tissues of opportunity. Visceral adipose tissue, which often tends to increase in quantity with aging, rates among the most productive sources of the inflammatory cytokines and represents a significant comorbidity in adiposity and the obese state [25]. In addition to the above, the counter regulatory effects of disordered glucocorticoid actions common to obesity interfere with insulin dependent GLUT4 formation and intracellular translocation, increasing the magnitude of insulin resistance, and also contribute to the inflammatory process by suppressing the Type 2 macrophage responses, further aggravating the balance between inflammatory and anti-inflammatory cytokines in neural and somatic tissues [23-26]. Thus, the insulin resistance of the obese phenotype of the aging congenic LA/Ntul//-cp rats represents a unique model to investigate the effects of obesity independent of NIDDM on the development of brain atrophy of aging and its sequelae and the pathophysiologic sequelae that progress to its neurodevelopment in this model [11,20,27].

Acknowledgement

The author acknowledges the Institutional support of the University of Science Arts and Technology Montserrat for the resources for this research.

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