

Does Insulin Resistance Contribute to Neuroinflammation, Cognitive Decline and Brain Senescence in Obesity?

Orien L Tulp*

Professor, Colleges of Medicine and Graduate Studies, University of Science Arts and Technology, Montserrat, British West Indies, MSR1110 and the Einstein Medical Institute, North Palm Beach, Florida, USA.

*Correspondence:

Orien L Tulp, Professor, Colleges of Medicine and Graduate Studies, University of Science Arts and Technology, Montserrat, British West Indies, MSR1110 and the Einstein Medical Institute, North Palm Beach, Florida, USA.

Received: 30 Jul 2023; Accepted: 02 Sep 2023; Published: 10 Sep 2023

Citation: Tulp OL. Does Insulin Resistance Contribute to Neuroinflammation, Cognitive Decline and Brain Senescence in Obesity?. Int J Psychiatr Res 2023; 6(5): 1-7.

ABSTRACT

The burgeoning prevalence of obesity and overweight conditions from the age of adolescence and throughout the lifespan has reached epidemic proportions in industrialized nations throughout the globe. The development of insulin resistance is one of the most common observations in obesity and is associated with a systemic hypoxia in adipose tissue and a chronic inflammatory state. The insulin resistance affects multiple elements of substrate oxidation and oxidative free radical generation in both somatic and neural tissues and with cytokine-linked chronic inflammation likely originating in adipose tissue depots. In studies with aging congenic lean and obese rats chronic hyperinsulinemia and brain shrinkage has now been reported, albeit it in the absence of Type 2 diabetes (NIDDM), hypertension (HTN) or other comorbidities, thereby suggesting that aspects of disordered substrate metabolism including insulin resistance as commonly observed in obesity may be a key contributory factor in the development of a neuroinflammatory linked brain shrinkage with accompanying decreases in brain mass, protein and DNA content, and which were further compromised when fed an isocaloric high vs. a low glycemic insulinogenic diet containing sucrose vs. cornstarch respectively. These results suggest that chronic insulin resistance of obesity secondary at least in part to dietary factors represents a likely independent risk factor in the progression of neuroinflammation, DNA damage, brain shrinkage and neural senescence in this strain of obese rats.

Keywords

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

Introduction

Brain shrinkage is a common observation in generalized dementia and Alzheimer's disease, where it often impacts the health, wellbeing and cognitive abilities of older individuals as they experience their 'golden' years and late stages of life [1-3]. An increasing incidence of long-standing obesity is also a common observation in industrialized societies, and in recent decades the onset and prevalence of the overfat conditions has been noted to have an earlier onset often earlier during the childhood or adolescent years than previous [4]. Moreover, the prevalence of

obesity has increased since the recommendations of lower-fat, higher carbohydrate diets were implemented as an attempt to curb an increasing prevalence of cardiovascular disorders linked to saturated fats in the diet [5,6]. Carbohydrates typically exert a higher glycemic response than other macronutrient sources, promote insulin release, and an insulin mediated shift in oxidative metabolism toward lipid deposition [7,8]. Adiposity promotes the development of insulin resistance resulting in impaired glucose uptake and becomes prominent in muscle and adipose tissue in addition to neuronal tissues including the brain [7-9]. Moreover, the excess adiposity once established often remains present throughout adulthood and continuing for much of the remainder of one's lifespan, and thus can become a contributing factor in the progression of numerous additional comorbidities including non-insulin dependent diabetes (NIDDM), hypertension (HTN),

cardiovascular disorders (CD), and other often chronic conditions that can impact longevity potential and on the quality of life, including the progression of various intensities of cognitive decline in later years [9].

In recent studies by Hu and Selvin, younger age of onset of Type 2 diabetes (NIDDM) onset has been found to be linked to increased dementia risk [10]. Longstanding NIDDM with elevations in hemoglobin A1c greater than 7% are a common characteristic finding in cases of undertreated NIDDM and hyperinsulinemia and have also recently been identified as a contributing factor in cognitive decline, but reports documenting radiographic evidence of brain shrinkage with insulin resistance and NIDDM per se are inconsistent and sparse at best [2-4]. Once clinically established however, the diagnosis of dementia and brain shrinkage tend to become more progressive over time, with little prospect of recovery [1-3]. The therapeutic regimens for treating dementia and brain shrinkage typically focus on ameliorative, palliative approaches, including end of life care as the disorder progresses to late stages of cognitive impairment [2]. Thus, identification of potentially preventative factors that may be causative or contribute to the neurologic deficits is a high priority currently impacting millions of adults in their senior years. A common denominator of obesity and NIDDM is chronic hyperinsulinemia, leading to the development of insulin resistance and other endocrinopathies, including chronic elevations in plasma insulin concentrations, disordered glucocorticoid actions, and a state of relative hypoxia and systemic inflammation linked to the obese state [10-16]. Investigation of obesity as an independent variable in human subjects would likely rely heavily on a population of so called 'healthy obese' subjects, somewhat of a contradiction in clinical medicine. Therefore, search for a suitable animal model may prove to be more productive to determine if insulin resistance and its direct metabolic sequelae might be significant co-contributors to the neuronal declines that occur in NIDDM, obesity, and progression of dementia conditions.

Williamson et al. reported the issue of insulin resistance in the brain, where it is presumed to impact on processes of neuronal glucose uptake and oxidation as it does in other somatic tissues [8]. Jaing et al. demonstrated that systemic inflammation contributes to impaired neurodevelopment, and Shimizu et al. and Huang et al. reported complimentary evidence of systemic inflammation on neuroinflammation including DNA damage in metabolic disease stigmata that were associated with insulin resistance [7,9-13]. Once the neural DNA becomes fatally damaged, further neuronal repair or DNA replication processes become largely implausible, and neuronal senescence may follow. As the magnitude of the neuronally compromised state advances, neuronal senescence would be anticipated to progress to the point of brain shrinkage, and is the likely endpoint in the progressive stages of dementia and Alzheimer's disease [8-10,13,16-18]. The lipogenic and antilipolytic effects of insulin in mammalian tissues are well established, and may be further enhanced in the presence of a high glycemic index, insulinogenic diets containing refined

carbohydrate sources including sucrose vs isocaloric ingestion of complex carbohydrate sources such as cornstarch. In the obese phenotype of the LA/Ntvl//*-cp* rat strain, carbohydrate rich diets enhances excess weight gain, the impact of the chronic hyperinsulinemia facilitates the onset of adipocyte hyperplasia and hypertrophy soon after weaning [19-21].

Adipose tissue is a common location for macrophage infiltration, where they may bring about the secretion of Type I and Type II cytokines that are proinflammatory (Type 1) vs anti-inflammatory (Type 2) in nature [22,23]. The Type 2 immune responses releases the cytokines IL-4, IL-5, and IL-13, which contribute to immunoprotective processes. In contrast, type 1 macrophage responses release the cytokines IL-6 and others that initiate inflammatory responses that in the most dire of scenarios can precipitate life threatening events [23]. 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 [23]. 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 [17,24].

The LA/Ntvl//*-cp* rat is a congenic animal model, where the obese phenotype becomes epigenetically expressed via an autosomal recessive trait, and results in one quarter of the offspring of breeding pairs that are heterozygous for the obese (*-cp*) trait develop early onset obesity soon after weaning [18,24,25]. The origin of the obese trait was derived from the Koletsky rat, back crossed with a longevity-prone NIH strain of the Lister/Albany rat to become the LA/N-*cp* and later designated as the LA/Ntvl//*-cp* rat strain in our colony. The congenic designation was established by the NIH Division of small animal genetic after 12 cycles of backcrossing which preserved the *-cp* trait as the only residual from the Koletsky origin [25]. A unique characteristic of the new strain is the absence of NIDDM, HTN or other potential comorbidities in this rat model, indicating the obesity likely exists as an independent variable in characterizing metabolic sequelae links to obesity. The obese phenotype develop impaired glucose tolerance with insulin resistance, plasma lipid aberrations, an impaired capacity for nonshivering thermogenesis, disordered thyroidal actions, and a shortened lifespan compared to their lean littermates [18,27]. Like most obese rodent strains, the obese phenotype of this strain seems incapable of reproduction, likely secondary to endocrinologic or physiologic functions [18].

When crossed with the diabetogenic SHR/Ntvl//*-cp* strain, which shares the same trait for obesity, the F1 LA/tul//*-cp* x SHR/Ntvl//*-cp* offspring demonstrated an attenuation of the diabetic stigmata and improved survival over the parental obese SHR/Ntvl//*-cp* animals [28]. Thus, the LA/Ntvl//*-cp* rat strain represents a unique model in which to investigate the independent effects of obesity and its primary metabolic sequelae including chronic insulin resistance on parameters of brain shrinkage and senescence [18,19]. In both diabetic and non-diabetic strains of corpulent rat, longevity of the obese phenotypes was significantly decreased, with the greatest decrease in the obese-NIDDM SHR/Ntvl//*-cp* strain, where the obese phenotype seldom survived beyond 12-15 months of age, indicative of the NIDDM comorbidity exerting still greater and additive impact on decreased potential for longevity [18].

A recent study reported the observation of decreased brain mass, associated with proportionate decreases in brain lipid, protein and DNA content in the aging obese phenotype of the LA/Ntvl//*-cp* strain of rats, while similarly reared and fed lean littermates did not demonstrate stigmata of reduced brain mass or DNA content [28]. In addition, when isocaloric diets containing cornstarch or sucrose were fed for the duration of the 10 month study, the sucrose fed rats had a modestly greater carcass fat content, a greater magnitude of plasma insulin concentrations, and a modestly larger lean body mass consistent with the added muscular load-bearing impact of the obesity [13]. The decreasing brain mass was further impacted by insulinogenic sucrose diet in the obese phenotype, with proportionate further decreases in absolute brain protein and DNA content. Thus, while a causal mechanism for the brain shrinkage could not be confirmed, these observations represent an association only. However, the proportionate causative links between hyperinsulinemia and insulin resistance and neuronal DNA and neurocellular demise remain unclear based on other studies when taken into consideration with respect to the current findings in this strain of rats, and are suggestive that the factors of both obesity and insulin resistance may contribute independent influences in the progression of the pathophysiologic process of neuroinflammation and neurodegeneration in the CNS and other tissues.

Methods

The congenic LA/Ntvl//*-cp* rat was derived from a Koletsky x LA/N cross and backcrossed 12 or more cycles to attain a congenic status, where the only difference between the lean and obese phenotypes is the epigenetic expression of the obese phenotype by the age of weaning [24-26]. Groups of lean and obese male LA/Ntvl//*-cp* rats were reared and maintained in a stock Purina chow (#5012) diet *ad libitum* from weaning thereafter under standard laboratory conditions to determine optimal longevity in this strain. Additional subgroups were switched to a diet containing 54% carbohydrate as cornstarch, 20% protein, 16% fat plus essential vitamins, minerals and fiber diet from weaning until 10.5 months of age [27]. At the end of the study brain tissues were collected and subjected to measures of brain weights, total lipid, total protein and total DNA content via established analytical procedures described

elsewhere [13,28]. Data depicting serum glucose, insulin and insulin to glucose ratios were extracted from multiple publications, and data were analyzed via standard statistical procedures as described previously [13,16,18,25,27].

Results and Discussion

The mean range for longevity in 600 normally fed LA/Ntvl//*-cp* rats is depicted in Table 1 and indicates that the lean phenotype of both male and female rats typically outlive their obese littermates by approximately one third of their normal expected lifespan. Over 600 animals were weighed at periodic intervals, until the number of rats remaining were too few in number to represent a typical lifespan, as an occasional animal might survive for a very short time longer than indicated in the Figure 1. During the final one or two months the rats of both phenotypes began to lose weight, and necropsy studies indicated that abdominal and subcutaneous fat depots were substantially diminished upon their eventual demise [19,28].

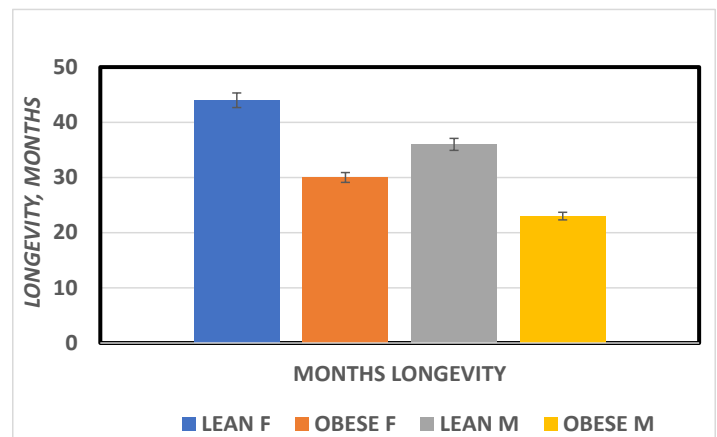


Figure 1: Effect of Sex and Phenotype on Longevity of Lean and Obese Rats.

Figure 1. Projected longevity of lean and obese rats. Data are extracted from periodic weights of 600 rats taken over their lifespan. Tulp, OL, *ILAR J.* 32(3), 32-39, 1990. Rats were fed Purina Rodent Chow #5012 *ad libitum* from weaning.¹⁹ F = female; M = male rats.

Biometric and carcass composition data re depicted in Table 1 and indicate that obese animals at 10.5 months of age were 2.5 to 3-fold heavier than their lean littermates in both male and female rats, despite having received the same diets and environmental conditions throughout. A vanishing few rat of both sexes of each phenotype and sex survived slightly longer than the maximal longevity as indicated but the number of rats so survived was not significant, with no animals of either phenotype or gender surviving beyond 48 months (female) or 33 months (male). With larger numbers or dietary restriction particularly at the older ages modestly greater survival might have been noted as has modest caloric restriction been observed to prolong survival in other studies [19]. Dietary carbohydrate type impacts on the

insulinogenic response, with sucrose typically generating a greater insulinogenic response than starch based diets. When rats of both sexes and phenotypes were fed an isocaloric sucrose rich diet, sucrose fed rats gained more weight and accumulated modestly greater amounts of carcass fat than when fed a starch diet of the same overall macro- and micro-nutrient content, with the greatest carcass fat content observed in the rats receiving the high glycemic index sucrose diet.

Carcass protein content is a recognized marker of lean body mass and the data in Table 1 indicates that the sucrose fed rats accumulated modestly greater amounts of carcass muscle protein, likely indicative of the greater weight bearing impact of the greater body mass due to the greater fat accretion impact on weight bearing muscles among the obese animals. The carcass protein content of the obese phenotype was significantly greater than occurred in their lean littermates and also tended to be modestly greater when fed the more highly insulinemic sucrose diet, resulting in still greater fat accretion, and suggestive of a contribution of the chronic hyperinsulinemia status on energy conserving parameters of protein metabolism.

Table 1: Biometrics and carcass composition characteristics of aging lean and obese male rats at 10.5 months of age.

Group / Parameter	BW, gm	Lipid gm/Carcass	Protein gm, Carcass
Lean Control	315±10	25±1.3	64± 21
Lean Sucrose	405±13	90±4.5	73± 30
Obese Control	780±24	350±10.5	78±2.2
Obese Sucrose	840±30	384±11.1	84±2.5
ANOVA: Phenotype	<0.001	<0.001	<0.05
Diet	<0.05	<0.05	n.s.

Data are mean ± 1 SEM, n=6-8 rats/group, taken at the time of sacrifice.

The glycemic measures in lean and obese rats taken at sacrifice are depicted in Figure 2, obtained after a brief (2hr) period of food restriction prior to sacrifice. The plasma glucose concentrations tended to be greater in the obese than the lean phenotype in both

sexes but remained within the upper limits of the euglycemic range, consistent with other measures of glycemia in this strain after a longer duration of fasting [19,27,28]. Plasma insulin concentrations were significantly greater in the obese than the lean phenotype in both male and female rats, however, and were further increased in the obese but not the lean animals when fed the sucrose diet. Measures of the insulin to glucose ratio depicted in the far right panel of Figure 2 reflect a measure of the magnitude of insulin resistance developed in the obese phenotype. The glycemic parameters were elevated in the obese phenotype fed either carbohydrate diet, with the greatest increase in the obese animals consuming the more highly insulinemic sucrose diet.

Figure 2. Effect of diet and phenotype on glycemic parameters in aging lean and obese LA/Ntvl/-cp rats. Data are mean ± 1 SEM, n= 6-8 rats/group. Bloods obtained after a brief 2-4 hour fast. Phenotype p = <0.01 for insulin and insulin:glucose ratios and p = < 0.05 for diet in obese phenotype for insulin and insulin:glucose ratio.

Measures of brain composition of lean and obese rats are summarized in Table 2 and show that the brain weight per rat of lean animals was significantly greater than the brain mass of their similarly fed and reared obese littermates. In addition, animals of both phenotypes were found to have modestly lower brain mass when fed the sucrose vs the starch diets throughout the 9.5 months of the respective dietary regimens. The brain lipid content is shown in data column 3 and indicates that total brain lipid content of lean animals was significantly greater than in their obese littermates, and that the sucrose diet resulted in a modestly further downward trend in net lipid content and is proportional to the relative brain mass in the lean and obese animals. The protein content of the lean and obese animals is shown in column 4 as similar to the other measures of brain composition, brain protein content of lean rats was greater than in their obese littermates feed the same diets and tended to be less in sucrose fed obese but not in sucrose fed lean rats. Finally, of greatest significance, brain DNA content is shown in column 5 of Table 2 and reflect the effects of

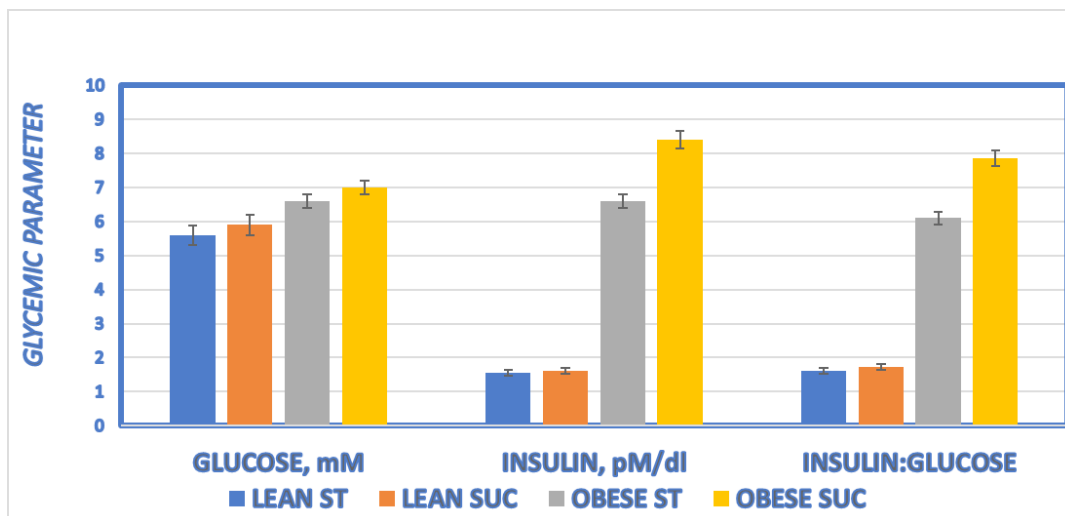


Figure 2: Effect of Cho Type on Glycemic Parameters in Lean and Obese Rats.

phenotype and dietary carbohydrate source on net DNA content. Brain DNA content of obese rats was significantly less than in their lean littermates, and the sucrose diet was linked to a trend toward greater deficits in brain DNA in both phenotypes when fed the sucrose than the starch diet. It is likely that with a greater number of animals in the experimental groups, or a longer duration of study, the sucrose associated declines in brain DNA may have achieved a greater level of statistical significance. None the less the obesity and insulin resistance in the obese phenotype resulted in less brain mass and proportional decreases in brain composition while preserving lean body mass in the obese phenotype.

Table 2: Brain composition of aging lean and obese rats at 10.5 months of age.

Group / Parameter	Brain weight	Lipid Content	Protein Content	DNA content
Lean Control	1.70±0.05	1.309±0.040	0.385±0.012	0.62±0.02
Lean Sucrose	1.60±0.05	1.215±0.036	0.378±0.011	0.55±0.01
Obese Control	1.31±0.04	1.052±0.032	0.245±0.054	0.35±0.01
Obese Sucrose	1.22±0.03	0.987±0.030	0.230±0.030	0.30±0.01
ANOVA	Phenotype p=	<0.05	<0.05	<0.05
	Dietp=<0.05	N.S.	N.S.	<0.10*

Table 2. Data are mean ± 1 SEM, n=6-8 rats / group. * p = < 0.05 by Pages L test for trend analysis as cited previously [14].

The sucrose associated decrease in brain mass and brain DNA content in the lean and obese phenotype are depicted in Figure 3, computed as the difference in the Starch vs. the Sucrose associated parameter that was computed and subjected to trend line analysis. This data indicates that the sucrose resulted in similar negative effects on brain mass and DNA content in both phenotypes, both resulting in computation of an R² value of 1.0 and with similar downward slopes. Thus, this data demonstrates an insulinogenic influence at least partially independent of obesity on brain DNA content in the aging obese rat, since the absolute decline in both lean and obese phenotypes was of similar magnitude, independent of the expression of the obesity (-cp)trait.

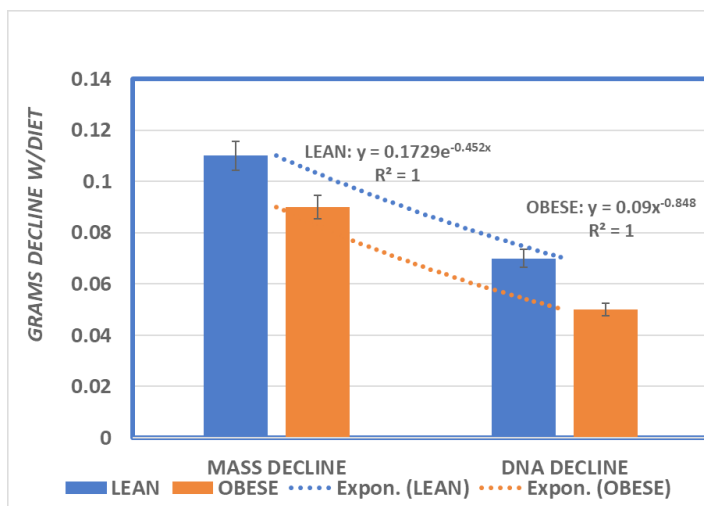


Figure 3: Effect of Phenotype and Diet on Decrease in Brain Mass and DNA Content.

Figure 3. Mean SUC associated weight decrease in brain mass and brain DNA content of lean and obese rats fed ST or SUC diets from 1 until 10-11 months of age, computed as the difference between the ST and SUC diet in both phenotypes. Data represent mean ± 1 SEM, n=6-8 rats / treatment group. The decreases in brain mass and DNA content were significant the obese phenotype compared to the lean phenotype and the effects of diet were significant by Pages L test for trend analysis. The R² values were computed via standard statistical analysis. The SUC associated decrease in brain DNA averaged 11.2% in lean vs, 14.3% in the obese phenotype (n.s.).

Discussion

The results of this brief review provide support for the impact of obesity as an independent comorbidity factor for decreases in longevity in addition to a compounding trend for diet-linked evidence of brain shrinkage associated with a progressive loss of cellular elements in the aging obese phenotype brain of a hyperinsulinemic-prone congenic rat model. The primary decreases in brain composition appeared to have occurred in the obese phenotype independent of diet and were linked to a further decreasing trend in both phenotypes when animals consumed a higher glycemic index, insulinogenic diet of equivalent caloric density for the same duration of their postweaning lifespan. All animals were studied before attaining 11 months of age, only a few months before the anticipation of their natural demise. Had the study been continued for a longer duration, it is likely that the number of obese animals continuing to survive among the obese sucrose fed phenotype would have become compromised and their complete data set lost. Obese male LA/Ntvl//cp rats may survive beyond 18 months of age under ideal conditions but seldom survive as long as their lean littermates. While brain shrinkage may not be directly linked to the cognitive deficits observed in dementia or Alzheimer's disease, there remains a strong association between decreasing brain volume and the cognitive deficits observed in those disorders.

In the study reported by Callisaya et al., elevations in hemoglobin A1C and plasma insulin typical of NIDDM were found to be associated with cognitive decline [1]. Insulin resistance is a common denominator in NIDDM, and the magnitude of insulin resistance typically becomes greater with the magnitude and duration of overweight and obesity. The comingling impact of the individual contributions of obesity, hyperinsulinemia and insulin resistance and other simultaneous comorbidities are difficult to separate however when they occur together as occurred in the reported clinical studies. In addition, the differential impact of excess adiposity and fat accretion in different adipose tissue depots remains unclear, however as lower body vs upper body vs visceral fat accretion linked obesity all contribute differentially to the pathophysiologic development of cardiovascular and other obesity-linked comorbidities. Thus, the obese phenotype of the LA/Ntvl//cp rat strain served as a suitable animal model to evaluate the impact of diet and obesity on brain shrinkage as the major comorbidities of NIDDM and hypertension are not known to occur in the obese phenotype of this congenic animal strain, while

the body fat distribution patterns in the obese phenotype displays a qualitatively similar pattern to that of syndrome X or metabolic syndrome in humans but in this animal model occurs without the glycemic derangements often observed in human clinical studies [18,26,27].

While it is often assumed that decreases in brain mass, whether a result of early nutritional insult or neurologic decline at later stages of growth, development and maturity, is somehow linked to cognitive deficits, which may or may not be partially or wholly recoverable following remediation, the assumption remains somewhat speculative. Neurologic development particularly in the CNS follows chronologic patterns, much of which occurs early in life in mammalian species. In addition, all elements of the CNS and other component of the nervous system do not develop simultaneously, and depending on the neuroanatomic location within the neuron, some recovery and regrowth may occur if the nuclear DNA should retain its DNA repair mechanisms [28]. Neuroinflammation has been linked to insulin resistance and neuronal decline by damaging elements of the DNA and its base repair mechanisms, thereby precluding some if not all capacity for local neurologic regeneration and thus resulting in potential cognitive impairment as the stage of neurosenescence progresses. Discovery of restorative processes which may curtail continued neurodegeneration or enable partial or eventual recovery remain a challenge in the treatment and management of cognitive deficits associated with senescence [29,31-34].

Finally, the question remains unanswered: does a decrease in brain mass, DNA and protein content necessarily directly correlate with cognitive decline? And can a brain remain fully functioning in terms of cognitive and other neurologic functions if the mass and cellularity become diminished? Since no cognitive studies were undertaken in the current study that assumption remains to be confirmed and must await future studies. The obese state imposes an independent impact of impaired physiologic performance, due to factors linked to the excess body fat and disordered mobility secondary to the hobbling effect of obesity *per se*. While early nutritional insults may carry longer term neurologic deficits that may not fully recover if remediation is provided later in life due to chronologic effects on organ growth and development, the potential and individual capacity for neurologic recovery in later chronologic stages of growth and development including aging remain unclear, and likely dependent at least in part on the magnitude of the injury and the life stage during, which the insult occurred, with injury during earlier stages likely resulting in the most capacity for recovery. Most brain growth and development normally occurs prior to adolescence, while most brain shrinkage has been observed to occur late in life at an age where less opportunity for complete or partial recovery remains.

Acknowledgement

The author thanks the University of Science Arts and Technology, Montserrat for Institutional resources to complete this manuscript.

References

1. Callisaya ML, Beare R, Moran C, et al. Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: a longitudinal study. *Diabetologia*. 2019; 62: 448-458.
2. Cho S, Kim C-O, Cha B-s, et al. The effects of long-term cumulative HbA1c exposure on the development and onset time of dementia in the patients with type 2 diabetes mellitus: hospital based retrospective study (2005–2021). 2023.
3. Jason C D Nguyen, Simon Killcross A, Trisha A. Jenkins. Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci*. 2014; 8: 375.
4. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweights://doi.org/10.1016/j.diabetes.2023.110721>
5. Kelly T, Wang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (London)*. 2008; 32: 1431-1437.
6. Stampfer MJ, Willett WC. Rebuilding the food pyramid. In: *Scientific American Magazine*. 2006.
7. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Invest*. 2017; 127: 1-4.
8. Williamson R, McNeilly A, Sutherland C. Insulin resistance in the brain: an old-age or new-age problem. *Biochem Pharmacol*. 2012; 84: 737-745.
9. Kahn SE, Hull RI. Mechanism linking obesity to insulin resistance and type 2 diabetes. *Nature*: 2006; 444: 840-846.
10. Hu J, Selvin E. Younger age of Type 2 diabetes onset linked to dementia. *Diabetologia*. 2023.
11. Tulp OL. Does Insulin resistance contribute to the naturally occurring ‘unbrowning’ or beigeing of brown adipose tissue in obese and obese-diabetic rats? *Academia Biology*. 2023; 1: 001-004.
12. Shimizu I, Yoshida Y, Suda M, et al. DNA Damage Response and Metabolic Disease. *Cell Metab* 2014; 20: 967-977.
13. Jiang NM, Cowan M, Moonah SN, et al. The Impact of Systemic Inflammation on Neurodevelopment. *Trends Mol Med*. 2018; 24: 794-804.
14. Tulp OL. Effect of carbohydrate type on brain composition and senescence in aging, hyperinsulinemia-prone obese LA/Ntvl/-cp rats. *Asian J Med & Health*. 2023; 21: 80-91.
15. Carter SU, Oakmoto K. Effect of insulin and glucocorticoids on glucose transporters in rat adipocytes. *Am J Physiol*. 1987; 252: E441-E453.
16. Huang HJ, Young AA, Koda JE, et al. Hyperamylinemia, hyperinsulinemia, and insulin resistance in genetically obese LA/N-cp rats. *Hypertension*. 1992; 19: 101-109.
17. Huang C, Irwin MG, Wong GT, et al. Evidence of the impact of systemic inflammation on neuroinflammation from a non-bacterial endotoxin animal model. *J Neuroinflammation*. 2018; 15: 147.
18. Tulp OL. Does the epigenetic expression of obesity, insulin resistance and their metabolic sequelae contribute to brain senescence? *Int J Fam & Comm Med*. 2023; 7: 67-71.

19. Tulp, OL. Characteristics of thermogenesis, obesity, and longevity in the LA/N-cp rat. *ILAR J.* 1990; 32: 32-39.
20. Tulp OL, Awan AR, Einstein GP. Adrenalectomy improves glycemic parameters in congenic LA/Ntul//cp rats. *Endocrinology & Metabolism International Journal.* 2021; 9: 61-67.
21. Tulp OL, Einstein GP. Thermogenesis, aging, and obesity in the LA/Ntul//cp (corpulent) rat. *Adv Obes Weight Manag Control.* 2021; 11: 37-43.
22. Tulp OL, Carlin C. "Carbohydrate overnutrition induces increased adiposity in rats", *Obesity Update.* 1993; 1-2.
23. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003; 112: 1796-1808.
24. Christiansen T, Richelsen B, Bruun JM. Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associated with adiposity, and reduced after weight loss in morbid obese subjects. *Int J Obes (Lond).* 2005; 29: 146-150.
25. Greenhouse DD. New Models of Genetically Obese Rats for Studies in Diabetes, Heart Disease, and Complications of Obesity. *ILAR J.* 1990; 21: 1-5.
26. Tulp OL, Einstein GP. Review: Obesity and its associated inflammatory cytokines pose significant risk factors for COVID-19 outcomes. *Advances in Obesity, Weight Management and Control.* 2022; 12: 14-20.
27. Hansen CT. The development of the SHR/N- and LA/N-cp (Corpulent) Congenic Rat Strains. In: *New Models of Genetically Obese Rats for Studies in Diabetes, Heart Disease, and Complications of Obesity.* NIH publication, Division of Research Services, Veterinary Resources Branch, National Institutes of Health, Bethesda. 1988; 7-10.
28. Michaelis OE, Ellwood KC, Tulp OL, et al. Effect of feeding sucrose or starch diets on parameters of glucose tolerance in the LA/N-corpulent rat. *Nutr Res.* 1986; 6: 95-99.
29. Tulp OL. Effect of the obese phenotype on brain composition in congenic lean and obese LA/Ntul//cp rats. *J Psychol & Clin Psychiatry.* 2023; 14: 38-43.
30. Tulp OL, DeBolt SP, "Aging and Obesity in the Corpulent Rat", In: *Nestle Nutrition Series, Research and Practice in MNA and Aging.* 1999; 149-155.
31. Sadler TW. *Langman's Medical Embryology*, Lippincott Williams Pub 2011. ISBN: 1451113420 ISBN13: 9781451113426.
32. Kobara M, Toba H, Nakuta T. Chapter 2, In: *Aging, Oxidative Stress and Dietary Antioxidants.* 2 nd Ed: Caloric restriction, reactive oxygen species, and longevity.
33. McCay CM, Crowell MF, Maynard LA. The Effect of Retarded Growth upon the Length of Life Span and Upon the Ultimate Body Size. *The Journal of Nutrition.* 1935; 10: 63-79.
34. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nature Reviews Endocrinology.* 2018; 14: 591-604.