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Impact of an Intermittent Complex Carbohydrate Regimen on Insulin Resistance and Adiposity in Congenic, Lean and Obese LA/Ntul//-cp Rats

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Abstract: Chronic nutritionally induced increases in insulin resistance contribute to the progression of cardiometabolic disorders in man and animals. To determine the impact on adiposity, complex carbohydrate in the form of Polycose® was fed ad libitum intermittently to congenic lean and obese LA/Ntul//-cp rats as a 25% (w/v) dietary carbohydrate supplement in drinking water in addition to stock Purina chow and house water from 3 until 12 months of age. Final Body weights of chow-fed obese rats were 2.2-fold greater than their lean littermates, and Polycose® supplemental feeding was associated with 17% and 19% increases in final body weight in both lean and obese phenotypes respectively. The combined mass of the primary white adipose tissue (WAT) depots was 8.6-fold greater in the obese than in their similarly fed lean littermates, and the Polycose® regimen was associated with a 2.7-fold increase in the dorsal WAT depots and a 1.5-fold increase in the retroperitoneal and inguinal WAT depots in the obese phenotype. The Polycose®-associated increases in adiposity were consistent with the result of adipocyte hypertrophy and hyperplasia in both phenotypes. Interscapular brown adipose tissue (IBAT) mass of obese >> lean, and Polycose® was associated with a 1.9-fold increase in IBAT mass in the lean phenotype but was without further increases in the obese phenotype. Baseline- and insulin-stimulated in vitro glucose oxidation in diaphragm occurred normally in the lean phenotype but was impaired by over 50% in the obese phenotype, consistent with a decrease in insulin sensitivity and impaired oxidative metabolism in the obese animals. Measures of these observations confirm the marked adiposity of the obese phenotype of this strain, and suggest that long -term complex-CHO supplementations may contribute to an enhancement in the capacity for energy expenditure via non-shivering thermogenesis in IBAT in the lean phenotype, thereby partially buffering the against a propensity for overly excessive fat accretion, but that the capacity for IBAT-mediated NST and mechanisms of lipid accretion and energetic efficiency in the obese phenotype may be impaired thereby further enhancing their propensity for fat accretion and the development of obesity via a combination of depot-specific lipid accretion via hyperplasia and hypertrophy of adipocytes in both abdominal and subcutaneous depots.

Keywords: Complex carbohydrate overnutrition, Polycose®, adiposity, diaphragm, insulin sensitivity, congenic rats

INTRODUCTION

Complex forms of carbohydrate contribute an important role in the wholesome nutrition of most if not all of the world's populations, and current dietary recommendations of major health, wellness and medical organizations continue to include the majority of carbohydrates from complex carbohydrate sources while positioning simple carbohydrates

in the periphery of the food pyramid [1-8]. Chemically, Polycose® is a partially hydrolyzed form of cornstarch with a molecular mass of approximately 1000 Daltons, and is devoid of protein, fats, and micronutrients, and is virtually devoid most monomolecular forms of carbohydrates.(7) The decrease in net osmolality effectively reduces the luminal osmolarity by an average of 80% which facilitates physiologically controlled digestion of shorter chain glucose polymers including maltopolysaccharides, maltooligosaccharides, and maltose with only 1-2 % of the carbohydrate remaining as free glucose, and a decrease in orosensitive perception of sweetness in humans.[7] The complex glucose polymer is indicated as a complimentary energy source in both endurance sports and as a healthful nutritional energy supplement in debilitated subjects. Polycose® is primarily intended to help meet the nutritional needs and energy requirement of debilitated subjects. The complex carbohydrate source also confers some apparent secondary metabolic benefits in areas of athletic endurance, where it may contribute to a modified insulinogenic response and enhance glycogen loading. [7,8] In addition, Polycose® has been suggested as a diagnostic assessment measure for detection of gestational diabetes. [9-12]. Although Polycose® exerts only a mild sweetness taste in humans, it appears to be substantially more palatable in rodents. [13-16] Polycose® differs from other simpler carbohydrate energy sources such as sucrose by its lower intraluminal osmotic pressure (0.2 that of glucose) and by its ease of enzymatic luminal digestion and rapid absorption of the resulting molecular carbohydrate moieties. In addition, its rapid luminal post-enzymatic digestion and absorption and its ease of oxidative metabolism primarily via glycolytic pathways in intermediary metabolism, thereby resulting in glucose residues as the only monomolecular carbohydrate moiety present following the luminal digestion processes via an abundance of conveniently located α-glucosidases in the luminal environment.[17,18] Because of its physicochemical nature as a complex carbohydrate, intestinal digestion and subsequent luminal absorption may be modestly slower than occurs for molecular glucose moieties, thereby resulting in a more prolonged glycemic and insulinogenic response than occurs for other simpler, lower molecular weight carbohydrate sources such a glucose or sucrose [7,17,18). In addition, secondary metabolic effects have been observed in improvements and partial normalization in the activity of hepatic glycolytic and lipogenic enzymes. [20,21]

In the congenic LA/Ntul//-*cp* rodent strain, early onset obesity occurs as the result of an autosomal recessive trait originally derived from the Koletsky rat and transmitted to an unknown strain of Lister-Albany/NIH (LA/N) rats, known for their healthful longevity traits. [22,23] The incorporation of the corpulent (-*cp*) trait resulted in the development of early onset hypertrophic-hyperplastic obesity in 25% of the offspring by 8-10 weeks of age. [24-29] The obese phenotypes exhibit an impaired capacity for non-shivering thermogenesis [NST) in concert with dysregulation of both thyroidal and sympathetic entities. In addition, preobese animals also demonstrate an impaired, energy conserving process of protein turnover by 6 weeks of age, and which process further contributes to energy conservation and likely persists thereafter throughout their projected lifespan likely secondary to due to continuation of insulin resistance common to the obese phenotype. [24,25, 27, 29, 30] In the studies cited, the rates of protein synthesis and degradation in both skeletal and cardiac muscle were reported to be decreased by an average of 50% in the obese phenotype, consistent with hyperinsulinemia-induced suppression of protein turnover during preadolescent growth, and an insulin-induced prolongation of the half-life of affected proteins without apparent evidence of linear and muscular developmental growth deficits in lean tissues.[27] The dysregulation in hormonal contributors to energy metabolism, lipid

accretion and atherogenesis in the obese phenotype implicate insensitivity to circulating insulin in peripheral tissues, in addition to disordered parameters of thyroidal and autonomic hormones. [23,31-40] The magnitude of obesity in the obese phenotype becomes maximal by about 6-10 months of age and remains stable for many months thereafter. [20,31,37,40] The obesity is associated with impaired glucose tolerance [24,31,34], atypical anomalies in endocrinologic parameters[23,28,34,35] and an impaired capacity for thermogenic energy expenditure in response to dietary and environmental stimuli, in addition to atherogenic characteristics.[20,28,30, 39-41] The purpose of the present study was to determine the effects of chronic consumption of a complex CHO dietary supplement on parameters of adiposity in a congenic animal model that is highly predisposed to hyperinsulinemia and early onset obesity [22-24] The studies to follow were performed in animals obtained from the 12th backcross of original breeding stock obtained from the Veterinary Resources Branch, National Institutes of Health, Bethesda, MD, USA, and maintained thereafter as a closed VAF-SPF colony in our laboratory for many years. The Drexel University Colony was assigned the LA/Ntul//-*cp* designation by Greenhouse to distinguish this sub-colony from others of earlier or later sub-cross designations.[42]

MATERIALS AND METHODS

Groups of lean and obese normally reared male littermate LA/Ntul//-*cp* rats were obtained from the former Drexel University Colony at three months of age and randomly placed by phenotype into initial experimental groups. Animals were maintained (n=20-24 rats of each phenotype) under normal housing conditions until 3 months of age to allow for environmental and physiological acclimatation and to allow for potential inadvertent premature mortality prior to the completion of the study. Rats were maintained individually in hanging stainless cages, with a reverse light cycle (dark 0800-2000 hr) and 50% Relative Humidity (RH) and with free access to food (Purina Chow #5012) and house water throughout the study. When animals were 3 months of age, subgroups of animals (N=8 rats/subgroup) from each phenotype were administered the glucose polymer Polycose® as a 25% (W/V) solution in addition to the Purina ration and house water for 4-5 days of each week, with normal feeding during the interim periods of 2-3 days/week. Animals were monitored daily, and body weights obtained periodically. When animals were 12 months of age, rats were humanely sacrificed by decapitation after an overnight fast, and liver, IBAT, and principle adipose tissue fat pads (Epididymal, Retroperitoneal, Dorsal , and Inguinal Subcutaneous, and Interscapular brown adipose tissue [IBAT]) dissected in their entirety and weighed to the nearest 0.1 mg. Measures of baseline and insulin-stimulated glucose oxidation were determine in quarter diaphragm sections after a one hour incubation in a shaking water bath (30 shakes/minute, 37°C) in a pH 7.2 KRB bicarbonate buffer and glucose oxidation ± Insulin (100 μU/ml, Glucose at 10 mM) to CO2 determined. Data were analyzed via standard statistical procedures including analysis of variance and Student Newman Keuls analysis to detect the presence of mutually exclusive subgroups. [43] The effects of progressive development of hyperinsulinemia and insulin resistance in normally fed and reared lean and obese phenotype from previous investigations are included for reference, as the original specimens were lost due to a weekend power failure in the laboratory, but are deemed equivalent to those predicted in the animals of the present investigation. [27,40]

RESULTS

The final body weights of lean and obese rats are depicted in Figure 1 and indicate that the final body weights of obese control rats at 12 months of age averaged 2.2-fold greater than their lean control littermates fed the stock chow diet. In addition, intermittent supplementation of their diet with the partially hydrolyzed cornstarch as Polycose® resulted in a 17% greater final body weight in the lean phenotype, and a 19% greater final body weight in the obese phenotype. The differences in final body weight between the phenotypes was highly significant ($p < 0.01$) and the effect of the Polycose® supplement was also significant ($p = < 0.05$) in both phenotypes.

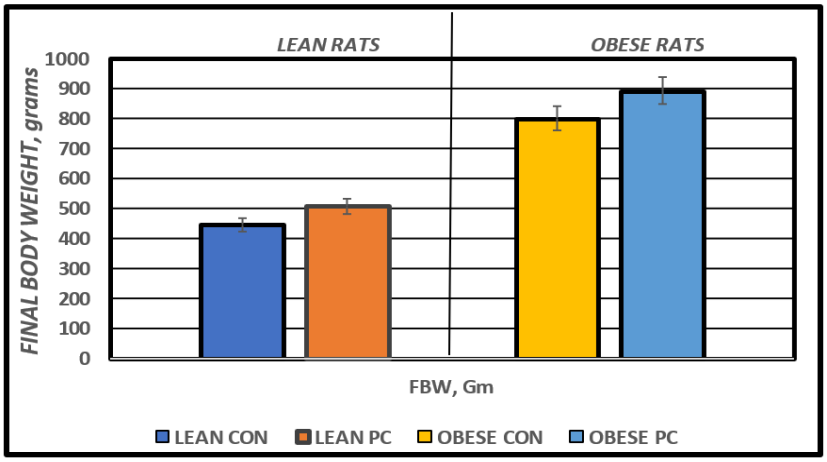


Figure 1: Final Body Weights of Lean and Obese LA/Ntul//-*cp* Rats, n = 8 rats/group. CON = control; PC = Polycose®p = < 0.05 for control vs. Polycose® in both phenotypes; p = < 0.001 Lean vs Obese phenotype.

The adiposity of the lean and obese phenotypes is depicted in Figures 2 and 3 below and indicates that the combined fat pad mass of the obese phenotype was markedly (7.1-fold) greater than occurred in the lean phenotype. In addition, the effect of intermittent feeding of the Polycose® regimen resulted in a further increase in fat pad mass in both phenotypes, equal to an increase of 2.3-fold in the lean phenotype, and a 1.6-fold increase in the obese phenotype. In Figure 3, the relative adiposity of the obese phenotype was markedly (4-fold) greater than occurred in their lean littermates. In addition, Polycose® regimen expressed as a ratio of the fat pad mass to final body weight of animals is depicted, and indicates that the Polycose® regimen resulted in a 2-fold increase in relative adiposity in the lean phenotype, and a further 1.6-fold increase among the obese phenotype, suggesting that the feeding of excess complex carbohydrate resulted in excess weigh gain in both phenotypes, although the absolute increment in cumulative fat pad mass and relative adiposity was greatest in the obese phenotype.

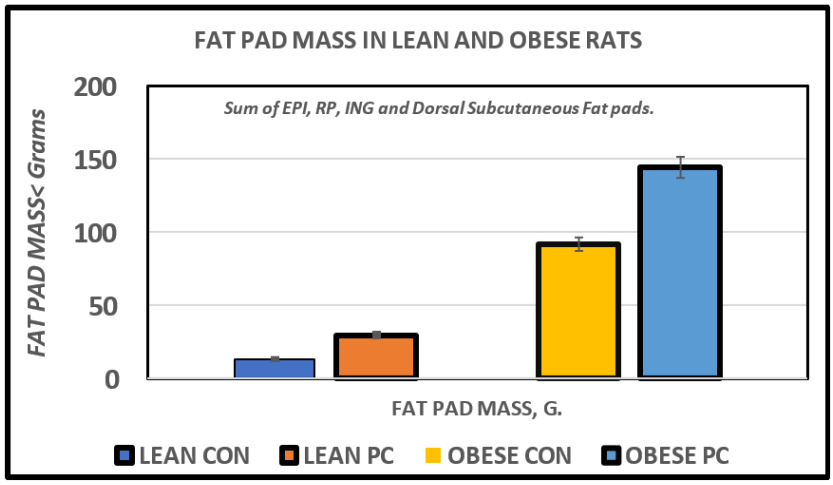


Figure 2: Arithmetic Sum of Epididymal, Retroperitoneal, and Dorsal subcutaneous fat pads. N = 8 rats/group. CON = control; PC = Polycose® p = <0.001 for phenotype, and p = < 0.05 for PC in lean, < 0.01 in obese.

Polycose® regimen expressed as a ratio of the fat pad mass to final body weight of animals is depicted in Figure 3, and indicates that the Polycose® regimen resulted in a 2-fold increase in relative adiposity in the lean phenotype, and a further 1.6-fold increase among the obese phenotype, suggesting that the feeding of excess complex carbohydrate resulted in excess weigh gain in both phenotypes, although the absolute increment in cumulative fat pad mass and relative adiposity was greatest in the obese phenotype.

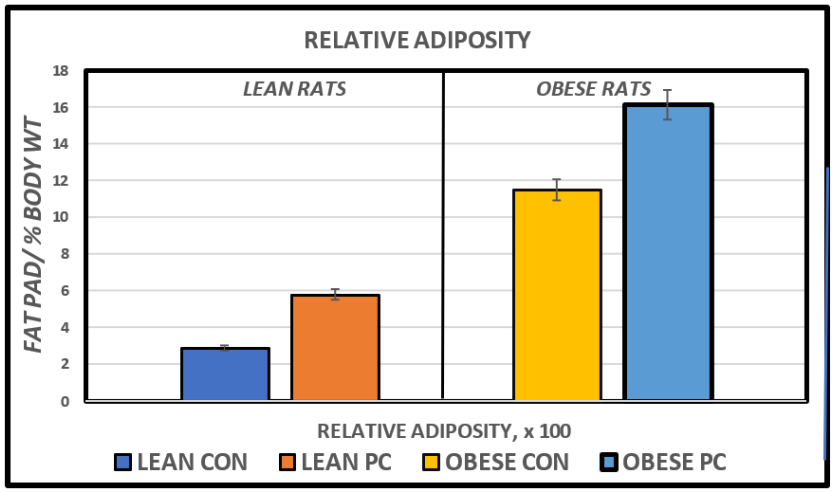


Figure 3: Effect of Polycose® on Relative adiposity of lean and obese rats. N = 8 rats/group. CON = control; PC = Polycose®p = < 0.05 for diet in both phenotypes; p = < 0.01 for phenotype (Lean vs. obese)

The effects of the Chow vs. the Polycose® regimen on IBAT mass in lean and obese animals are depicted in Figure 4 and indicates that IBAT mass of obese phenotype was 3.6-fold greater than occurred in their lean littermates fed the normal chow regimen. In addition, the Polycose® regimen resulted in a near doubling of IBAT mass (1.9-fold) in the

lean phenotype, while is was without further effect on IBAT mass in the obese phenotype. When IBAT mass was expressed as a function of final body weight, the Polycose® regimen resulted in a 1.7-fold increase in the lean phenotype, but was modestly decreased [by almost 20%] in the obese phenotype, an artifactual reflection of the greater final body weights recorded in the obese+ Polycose® regimen group.

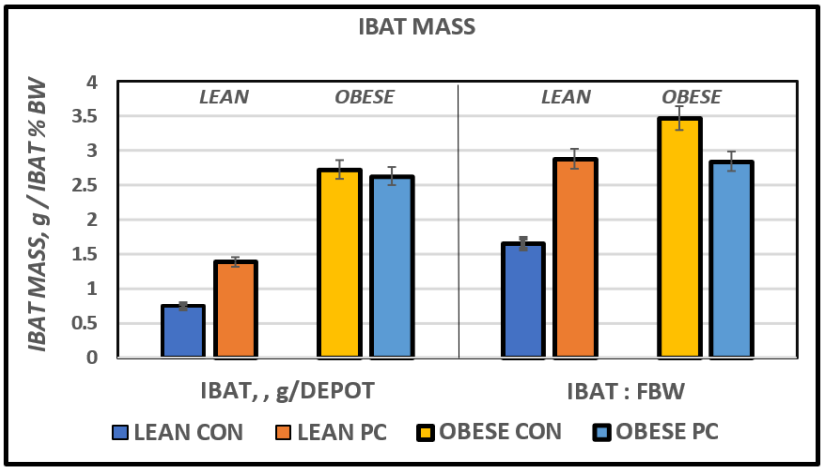


Figure 4: Effect of the Polycose® regimen on IBAT mass of lean and obese rats. N = 8 rats/group. CON = control; PC = Polycose®. p = < 0.01 for phenotype (lean vs obese); p = < 0.05 for diet in lean phenotype, p = n.s. for obese phenotype.

Measures of baseline and insulin-stimulated *in vitro* glucose oxidation were determined in quarter diaphragms from lean and obese animals of each group as a possible indicator for evidence decreases in insulin sensitivity in obese and Polycose®-overfed obese animals. The diaphragm remains physiologically active throughout the lifespan of an animal, thereby reflecting the magnitude of insulin sensitivity vs. insulin insensitivity, in contrast to skeletal muscles where physiologic activity is often intermittent and the impact of insulin resistance greater depending on the physiologic activity of supporting muscle groups during intermittent periods of locomotor activity during wakeful and somnolent phases of activity. Lean animals are depicted in the left panel, and obese littermate animals in the right panel. These data indicate that baseline glucose oxidation rates were like controls when offered the Polycose® regimen, and both dietary regimens were associated with a 15% to 20% increase in the rate of glucose oxidation in the presence of insulin. In contrast, both basal- and insulin-stimulated glucose oxidation in obese rats were decreased by over 50% and became only modestly greater in animals when offered the Polycose® regimen. The greatest improvement was observed in the obese, Polycose® + insulin regimen, and implies potential impairments in mechanisms of mitochondrial substrate oxidation in the obese phenotype, consistent with evidence of mitochondrial dysfunction in various tissues in the obese phenotype of this and other obese rodent strains. [35,44-48] Regardless of the cellular mechanisms, obese animals gained greater increases in adiposity during the study than their similarly-fed lean littermates, consistent with the observation for differing propensities for weight gain and excess adiposity during episodes of excess caloric intake in human subjects and animal populations, and which has been attributed at least in part to thermogenic energy expenditure in BAT and other tissues, especially during episodes of excess carbohydrate intake.[6,46-53]

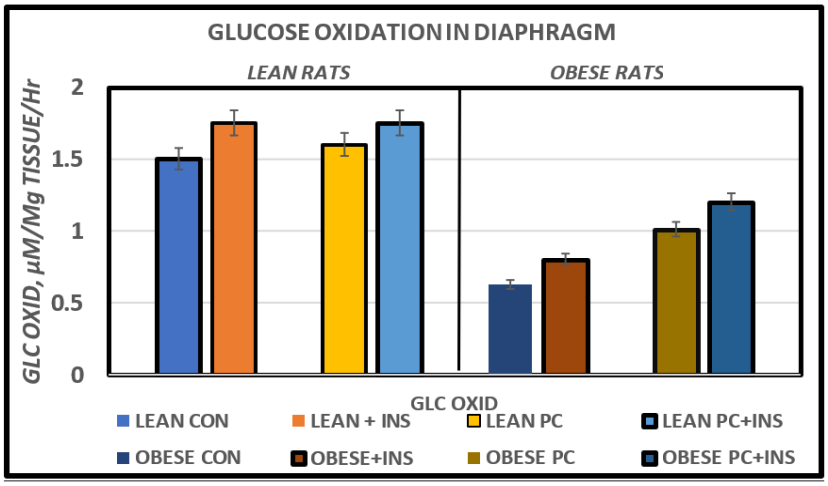


Figure 5: Effect of insulin and phenotype of glucose oxidation in lean rats. . CON = control; PC = Polycose®p = < 0.05 for phenotype; p = < 0.05 baseline vs. insulin vs in both phenotypes

The effects of the progressive development of insulin resistance in the obese phenotype is depicted in Figure 6 and indicates that while plasma glucose concentrations remained well within the euglycemic range throughout the projected age span in both phenotypes, plasma insulin concentrations and the insulin : glucose ratios, indicative of insulin resistance, were significantly greater in the obese phenotype at all ages studied. In addition, while plasma insulin concentrations remained unchanged in the lean animals at all ages measures, plasma insulin concentrations gradually decreased with advancing age in the obese phenotype, as daily energy intakes were also showing gradual decreases while Insulin : glucose ratios and energetic efficiency remained consistent with continued insulin resistance. [40]

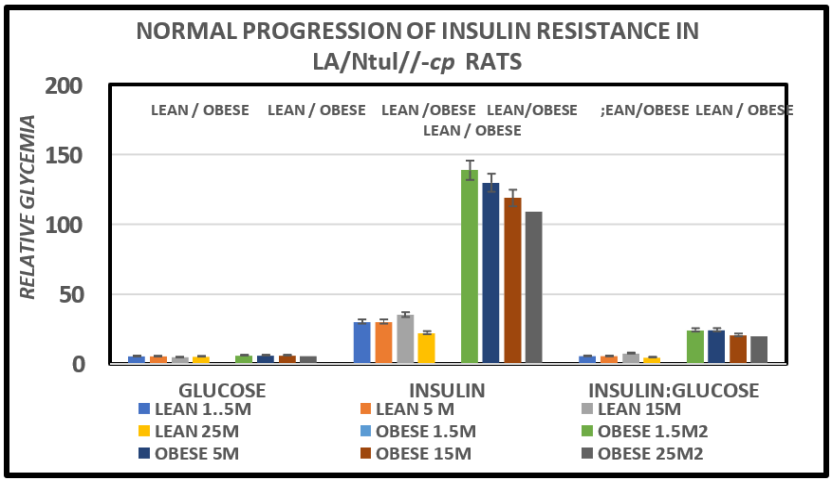


Figure 6: Normal progression of insulin resistance in normally fed and reared LA/Ntul//-cp rats. N = 6-8 rats/group. Extracted from reference 27 and 40. N = 6-8 rats/group. p = < p.05 for phenotypes at all ages studied (Obese >> lean). Glucose as mM; Insulin as µUnits/ml. LEAN = lean phenotype; Obese = obese phenotype. M = months age when studied.

DISCUSSION

The results of this study confirm the propensity for greater fat accretion in the obese phenotype of this strain, and indicates that carbohydrate supplementation with Polycose®, a highly palatable, commercial form of partially hydrolyzed cornstarch results in greater final body weight and fat accretion than occurred in both lean and obese phenotypes of this unique, congenic strain. Additionally, the greatest magnitude of fat accretion occurred in the obese phenotype, suggesting that those animals had an even greater propensity for development of excess adiposity and weight gain than their similarly fed lean littermates. Moreover, the greatest adiposity likely occurred in the .obese phenotype as a result in increased adipose tissue cellularity while in the lean phenotype, the increases in adiposity were of substantially lesser magnitude. Adipose tissue typically expands initially throughout postweaning and adolescence growth periods via hyperplasia, followed by hypertrophy in later life as the adipocytes take up some of the excess substrate, with apparent preferential deposition in deep abdominal retroperitoneal and subcutaneous depots until a maximum cellular lipid content is attained. [26] The biochemical or physiologic basis for the differences in adiposity in the two phenotypes could not be confirmed with certainty in the present study but are presumed to be at least in part due to a lesser metabolic capacity for thermogenic mechanisms of energy expenditure, and which have been widely reported to be linked to hormonal actions in BAT and other tissues in previous studies in this and other rodent strains. [23-25, 30,52-54] Brown adipose tissue deposits have long been known to occur in humans, where it is presumed to exert similar physiologic functions to those discovered in rodents and other mammalian species, leading to exploration of potential therapeutic applications for the treatment of obesity. [45,52,53,55,56] The observation and presumed metabolic function in energy balance of brown adipose tissue in humans during necropsy studies and suggested as an element in DIT has long been apparent. [62,63] Sims was among the first to concluded that dietary carbohydrate was most associated to the energy wasting phenomena, now also supported by numerous animal studies where carbohydrate has been demonstrated to enhance thermogenic activity, while insulin resistance has likewise been demonstrated to impede thermogenic activity in IBAT and skeletal muscle . [27,46-47,4952,54,55] Muscle tissues consume significant energy from ATP support of protein synthesis, while in the absence of insulin resistance, while in the presence of insulin resistance, rates of protein synthesis and $T_{1/2}$ of protein turnover *in vitro* were decreased by an average of 50%, representing a significant conservation in energy expenditure secondary to ATP conservation, and associated with corresponding increases in adipose cellularity in preobese, hyperinsulinemia animals from early in postweaning life. [26,27]

Polycose® consumption resulted in regional differences in fat accretion in the two phenotypes. In lean rats, Polycose® was associated with an approximate doubling of most fat depots, with the greatest expansion occurring in the abdominal retroperitoneal depots. Among obese rats, however, the total increase in adiposity was of much greater magnitude, with the greatest increase in the subcutaneous depots, consistent with a greater magnitude of insulin insensitivity. The physiologic basis for the phenotypic differences remains unclear from this investigation but may be at least in part a reflection of hormonally mediated differences in energy metabolism, including differences in physiologic sensitivity to insulin and an endocrinologic progression to greater insulin resistance common to obesity in man and animals. Insulin resistance impedes glucose uptake in skeletal muscle and adipose tissues, including thermogenically active brown adipose tissue.[45-48] Under such

physiologic conditions, insulin resistance may result in a more favorable substrate uptake in adipose tissues compared to muscle.[18,19,48] The marked hyperinsulinemia commonly observed in the obese phenotype is consistent with lipogenesis and fat accretion, as is the chronic subclinical hypothyroid state that has also been reported in this strain. [31-33] Additionally, the significant enhancement in the energy costs of protein synthesis in pre-obese rats likely also contribute to a greater caloric efficiency and lipid accretion in responsive muscle and adipose tissue depots. [26,27] These hormonal and metabolic factors would be conducive to an improved efficiency of conversion of non-fat substrates to lipid stores in the obese phenotype. In addition, the abdominal depots may already have been approaching maximal expansion in the obese phenotype, thus facilitating a metabolic shift toward excess substrate and metabolic energy partitioning of the excess energy retention into the subcutaneous depots.[27,28] The specific factors which result in increases in adipocyte proliferation and lipid filling are unclear but may be related to factors such as the pre-existent cell size constraints, hormonal status, hormone responsive lipoproprotein lipase activity, the rate of net lipid biosynthesis in liver and adipose tissue and other tissue depots, or other as yet unrecognized factors.

Brown adipose tissue has been shown to differential increase in mass and cellularity following experimental overnutrition in lean and in genetically obese rodent species, with the most dramatic increases in hyperplasia during the preadolescent stage of growth and development [23,24, 57,58], and is presumed to have exerted a similar impact in the obese phenotype of this strain. In the lean phenotype, increases in energy intake result in increases in non-shivering thermogenesis, in young and adolescent animals, mediated at least in part via thyroidal and sympathetic hormonal factors and substrate activation of brown adipose tissue first proposed by Rothwell and Stock, who proposed that this tissue may determine metabolic efficiency and resistance to obesity following studies in humans and animals. [32,39,45-48,52-54,59] Brown adipocyte proliferation in the IBAT depot may continue for several weeks or months, attaining a maximum cell number by late adolescence (~3 months of age). Once formed, the brown adipocytes would appear to remain present for an extended duration and contribute to an enhanced capacity for NST following dietary or pharmacologic stimulation [59], and where under ideal circumstances may provide a metabolic buffer to development of obesity.[53,54] The increase in IBAT development and IBAT-mediated thermogenesis would appear to be similar following cold exposure and overnutrition.[23,41,46,,53,54] Hyperphagia has long been recognized to be an original factor identified as leading to BAT hyperplasia of preadolescent lean and obese rats. [27,59] Pre-Obese rats demonstrate hyperphagia early in life, however, suggesting that hyperplasia of brown adipocytes may become more maximal at younger ages than occur in normally fed lean animals later in life. Brown adipose tissue later in life is quite likely chronologically limited to hypertrophy only due to exhaustion of brown adipocyte preadipocytes, in addition to hormonal factors. In the present study, IBAT mass increased significantly in the lean phenotype following carbohydrate overnutrition via an intermittent Polycose® feeding regimen, while the IBAT mass of the obese phenotype failed to undergo additional hypertrophy or hyperplasia, suggestive of an impaired signaling mechanism with regard to recruitment of diet induced thermogenesis in BAT in those animals. In the lean phenotype, the greater IBAT was likely linked to hyperphagia-associated increases in DIT while in the obese phenotype, dietary or environmental increases DIT may have been less marked or impaired as in other studies [24,29,59], and did not stimulate further hyperplastic growth

or embryologic development of the tissue mass, resulting in cellular hypertrophy only to account for the greater lipid mass.

Several hormonal factors are known to be implicated in the activation of BAT thermogenesis. Thyroid hormones, particularly T3, in addition to fatty acids are necessary for permissive effects and may be implicated in the induction of uncoupling protein (UCP1) are known to be essential for the activation of BAT thermogenesis.[53-55] Corticosteroids are also essential in small concentrations and have recently been demonstrated to inhibit the expression of UCP1 [13] Insulin may also contribute to the lipid accumulation within the IBAT tissue via stimulation of glucose uptake, combined with activation of hormone-sensitive LPL, and when present in higher concentrations, may impede the activation of hormone-sensitive LPL and the consequent mobilization of fatty acids also required for activation of BAT thermogenic activity via decreasing receptor sensitivity to insulin. Norepinephrine has also been shown to markedly stimulate glucose uptake in isolated brown adipocytes, also contributing to metabolic fuel availability and usage in support of NST [46-49]. Obese animals of this strain have been shown to have marked hyperinsulinemia , in addition to decreases in the generation of T3 from T4 in BAT from an early age, and in decreases in the nuclear receptor affinity for the thyroid hormone [32,24,40,45-46,61] These derangements in insulin concentrations plus the impairment in thyroid hormone mediated processes are presumed to have a collectively negative impact on the expression of NST in the obese phenotype of this strain, and in all likelihood to have contributed to the pattern of lipid accretion observed in the brown, beige, and white adipose tissue depots in this congenic strain, and to contribute to the decreased thermogenesis activity observed in the brown adipose tissue.[62] Additionally, most skeletal muscle groups contribute to insulin resistance that is often greater than that which occurs in adipose tissue depots, due in part to their greater fat-free mass than occurs in adipose tissue. Diaphragm represents a somewhat unique skeletal muscle however, in that it obligatorily remains physiologically active throughout the lifespan in man and animals, in contrast to other skeletal muscles that are typically most active during episodic periods of physical exertion associated with locomotion and movement. During such activity, substrate uptake and mitochondrial respiration become increased, while in resting skeletal muscle substrate oxidation likely returns toward baseline activity, thereby conserving ATP-driven energy demands, but while diaphragm skeletal muscle remains active.[27,28] Thus, in the presence of insulin resistance, mitochondrial oxidation may become impaired, with decreases in relative energy expenditure, and favoring energy conservation in adipose tissue. [27,28,62].

CONCLUSIONS

The results of this study indicate that intermittent overnutrition with a complex carbohydrate supplement to normal feeding results in greater adiposity and final body weights in both lean and obese phenotypes of the congenic LA/Ntul//-*cp* rodent strain, with the greatest impact noted in the obese phenotype. Depot specific fat accretion was apparent with this regimen, with a prevalence of the abdominal depot ft accretion in the lean phenotype, and the subcutaneous depots in the obese phenotype, suggestive of phenotype differences in insulin sensitivity for lipid deposition in the different depots. Additionally, Measures of these observations confirm the marked adiposity of the obese phenotype of this strain, and suggest that long -term complex-CHO supplementations may enhance the

capacity for energy expenditure via non-shivering thermogenesis in IBAT in the lean phenotype, thereby partially buffering the against a propensity for overly excessive fat accretion, but that the capacity for IBAT-mediated NST and mechanisms of lipid accretion and caloric efficiency in the obese phenotype may be impaired thereby further enhancing their propensity for fat accretion and the development of obesity via a combination of depot-specific lipid accretion via hyperplasia and hypertrophy of adipocytes in both abdominal and subcutaneous depots. Polycose® is a widely available complex carbohydrate supplement devoid of other nutrients, and with favorable digestibility throughout the lifespan due to its low osmotic impact during luminal digestion. It is primarily intended to support energy requirements in athletics and elderly populations, but its long-term impact on adiposity has seldom been examined. Chronic consumption of excess energy intake above that needed for energy balance is a known contributor to fat accretion and can contribute to the increasing global prevalence of overweight and obese conditions and the healthcare implications of their common pathophysiologic sequela. The present studies were conducted in an otherwise healthy animal strain noted for longevity, and with an autosomal epigenetic trait for early onset obesity, while minimizing the rapid progression of common pathophysiologic stigmata of obesity commonly observed in humans. Moreover, the epigenetic differences in fat accretion between the lean and the obese phenotypes in reminiscent of the long-held concepts of luxusconsumption and dietary induced thermogenic energy expenditure, thereby offering a somewhat buffer against excess lipid accretion during periods of episodic carbohydrate overnutrition, but where not all subjects experience the same propensity for maintaining energy balance or not. In clinical studies, this was illustrated in the often cited Vermont Study of Obesity , were normally lean subjects with no family history of obesity or its common pathophysiologic sequela were offered up 10,000 calories a day for an extended duration, gained little excess weight, failed to develop obesity, and returned to their previous weight within a few weeks upon resumption of their normal diet. Such was the apparent case with the lean phenotype of this strain, while the obese phenotype demonstrated a marked propensity for increasing adiposity. From an early age. While specific determinations of VO2 were not included, the diet induced increases in IBAT mass were suggestive of increases in NST, while in the obese phenotype, the excess carbohydrate was without further impact beyond that of normally obese animals of this strain, and consistent with an insulin induced unbrowning of the IBAT tissue, and an impaired capacity for full expression of diet- and cold-induced thermogenesis.

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DISCLAIMER (ARTIFICIAL INTELLIGENCE)

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

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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