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SERVICES FOR SCIENCE AND EDUCATION

Effects of Delayed Carbohydrate Digestion on Energy Intake, Adiposity and Weight Gain in Congenic Lean and Obese-Diabetic Rats

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ABSTRACT

The burgeoning prevalence of obesity and overweight conditions including NIDDM and dysregulation of energy balance are rapidly approaching epidemic proportions in much of Western society and imposing a significant burden on available health care resources. Once diagnosed, treatment is typically a life-long effort to attenuate the continued progression of pathophysiologic sequela of the disorders. Since the predominate proportion of macronutrient energy source in most Western diets is often carbohydrate, typically more than 50% by weight at ~4 kcals/gram, efforts to modulate the impact of dietary CHO on parameters of adiposity and weight gain were investigated. This study determined the effects of delayed carbohydrate digestion on energy intake and consequent weight gain groups of young adults, obese-NIDDM rats that were fed a USDA-formulated, hyperinsulinemic diet consisting of 54% sucrose plus essential fats, proteins, micronutrients and fiber for up to 8 weeks, or the same diet containing 150 mg/kg of (1,5 dideoxy-1,5-[(2-hydroxyethyl) imino]-D glucitol; generic miglitol). Measures of daily energy intake and weight gain were determined at weekly intervals. Adiposity was determined by dissecting major fat depots at the end of the study and determining adipose tissue mass and cellularity. Miglitol resulted in 20% less energy intake and weight gain, and corresponding decreases in adiposity after 8 weeks of study. The results of this study indicate that delayed carbohydrate digestion via the α-glucosidase inhibitor miglitol or other similar agents may be a useful adjunct in the regulation of food intake and in attenuating weight gain in man and animals in addition to their well-established effects as an adjunct in the treatment of impaired glycemic responses in obesity and NIDDM.

Keywords: Obesity, diabetes, appetite, satiety, α-glucosidase, rat.

INTRODUCTION

The increase in the prevalence and magnitude of overweight and obese conditions and their inadvertent pathophysiologic sequala have imposed a significant challenge to the economy and availability of adequate resources to fully remedy the therapeutic remedies in recent decades.[1] In addition to the rising costs of pharmacologic and other measures, the economic loss to the workplace must also be addressed, as chronic disorders including NIDDM and others often interfere with full industrial and individual job performance and productivity.[2,3] The treatment regimens typically involve long-term adjustments in diet, lifestyle, and therapeutics, and may continue for much of the remaining years for individuals who are so affected.[2] The majority of the current pharmaceuticals approved for weight loss appear to bring about their effects via one or more elements of appetite control intended to reduce daily caloric intake, and are typically applied in concert with recommendations for more healthful food choices.[2] Weight loss pharmaceuticals although generally considered safe when taken as prescribed, are ultimately metabolized into less active products via hepatic or renal metabolism, and as such, may trigger adverse endocrinologic or metabolic responses in some individuals.[3,4] Thus, agents that can evade luminal absorption and systemic distribution while still bring about decreases in daily caloric intake are of interest in considering therapeutic options. [5-7]

The pharmacologic and natural classes of luminal glucosidase inhibitors represent a therapeutic category where their primary mechanism of action is on the surface of the brush border in the small intestine, where virtually 100% of the digested carbohydrate undergoes luminal absorption and subsequent systemic distribution.[5-9] In addition, little if any of the ingested administered agent is typically absorbed from the luminal epithelium. The class of agents includes both pharmaceutical grade and natural products, often from which the pharmaceutical may have been developed from.[5] Thus the purpose of the present study was to investigate the effects of (1,5 dideoxy-1,5-[(2-hydroxyethyl) imino]-D glucitol; generic miglitol) on parameters of food and energy intake and weight gain in a congenic animal model that is highly predisposed to development of early onset obesity and NIDDM, in a strictly controlled dietary and environmentally controlled environment, where the only variable was the inclusion of the α-glucosidase inhibitor in a therapeutically effective dosage range.[5-9,] The SHR/Ntul//-*cp* rat model was developed in the small animal genetics unit by Hansen at the NIH by incorporating the -*cp* trait from the Koletsky rat into a longevity-prone NIH (N) strain of unknown origin.[10,11] This was followed by crossing the N-*cp* strain with the spontaneously hypertensive and diabetes prone SHR rat and completing 12 or more cycles of backcrossing sufficient to establish a congenic status while preserving the SHR and -*cp* traits. The hypertensive trait was preserved only in the lean phenotype while the T2DM developed soon after weaning in the obese phenotype, and the newly developed SHR/N-*cp* strain preserved the albino coat characteristic of the donor SHR strain. Both phenotypes exhibit a significantly decreased lifespan due to complications of T2DM compared to their longevity-prone NIH (N) heritage.[10] The independent contributions of the obesity and T2DM traits may be assessed in the nondiabetic LA/Ntul-*cp* vs the SHR/Ntul//-*cp* strains.[7,10,11]

MATERIALS AND METHODS

Groups of congenic lean and obese male SHR/Ntul//-*cp* rats (n= 8 rats/group) housed under standard laboratory conditions of temperature (21-22 degrees C/ 50% RH) on a reverse light

cycle (dark 0800-2000 daily) in adjacent hanging steel cages with individual occupancy. Animals were fed Purina Chow and house water *ad libitum* from weaning to 8 weeks of age, at which time early stages of obesity and T2DM were clearly established and glycosuria and T2DM confirmed. When 8 weeks of age, rats were switched to a semi-purified control diet developed at the Carbohydrate Nutrition Laboratories of the USDA that contained 54% carbohydrate as sucrose, 20% protein as equal parts casein and lactalbumin, 5.9 % cellulose, 16% fats as equal parts beef tallow, lard, corn oil, and hydrogenated coconut oil, 3.1% AIN vitamin salt mix, and 1% Teklad vitamin fortification mix (Control diet).[12] The energy content of the diet was computed to provide 48.2 % of calories from CHO, 33.3 % of calories from fats, and 18.5% of calories from protein respectively, and provided 4.4 kcal/gram as described elsewhere.[12] The semi-purified diet was fed *ad libitum* for up to 8 weeks. In addition, additional quantities of the control diet were fortified with 150 mg of the α-glucosidase inhibitor (1,5 dideoxy-1,5-[(2-hydroxyethyl)-imino]-D glucitol; generic = miglitol) per kg diet (equal to ~ 2.5 mg of miglitol/rat/day) and was fed to the α-glucosidase inhibitor treatment group for up to 8 weeks duration. Measures of individual food intake were measured over a 2-day duration in metabolic cages after a 24-48 hr. acclimatization to the cages.[7] Body weights were monitored periodically throughout as an indicator of wellness. At the end of the study, rats were fasted overnight and blood obtained in heparinized tubes for plasma glucose and insulin determination. Data were analyzed via standard statistical procedures including application of Pages 'L' test for trend analysis where statistical significance via the 't' test was suggestive but not confirmatory.[13,14] The study was approved by the Institutional Animal care and Use Committee.

RESULTS

The effects of miglitol on body weight in lean and obese rats is depicted in Figures 1 and 12 below. As depicted in Figure 1, Miglitol was without significant effect on final body weight or weight gain compared to their lean control animals. In contrast, in Figure 2 the effect of miglitol resulted in moderate decreases in final body weight and in net weight gain over the course of the study regimen that were significant at the $p = < 0.05$ level. . The effects of Miglitol on daily food intake are depicted in Figures 3 and 4 and indicate that miglitol resulted in significant decreases in the daily food intake in both lean and obese T2DM phenotypes, and that the decreases in daily energy intake had an onset within the first week of observation and were sustained throughout the duration of study. The overall decrease in energy intake with the miglitol regimen averaged 20% in both phenotypes (Figure 5,6). The net caloric intake with miglitol was decreased, but the efficiency of weight gain, computed as the kcals consumed divided by the grams gained over the course of the study was impacted in the lean but not the obese animals with the miglitol regimen.

The effect of miglitol on final mass of principal adipose tissue depots in depicted in Figures 7 and 8, for the lean and obese-T2DM rats respectively, and show that in the lean phenotype, there was a trend toward lower weights in the epididymal and retroperitoneal depots and on the sum of 4 depots reported as Total AT, while the dorsal and closely located IBAT depots were unaffected by the miglitol regimen. In obese rats (Figure 8) the effects of miglitol were associated with decreased mass in the retroperitoneal fat pad weight and in total AT combined mass, while the IBAT, epididymal and dorsal depots were not significantly impacted. Thus, the effects of miglitol-imposed delay in carbohydrate digestion impacted both

energy intake and further weight gain in the obese phenotype, while the effects on the lean phenotype were modest in comparison. The net difference in weight gain in the obese phenotype averaged 30 grams, while in the lean phenotype the net difference was less than 5 grams. The difference in the adipose tissue depots appear to have been the primary benefactors of the decreases in energy intake with the miglitol regimen.

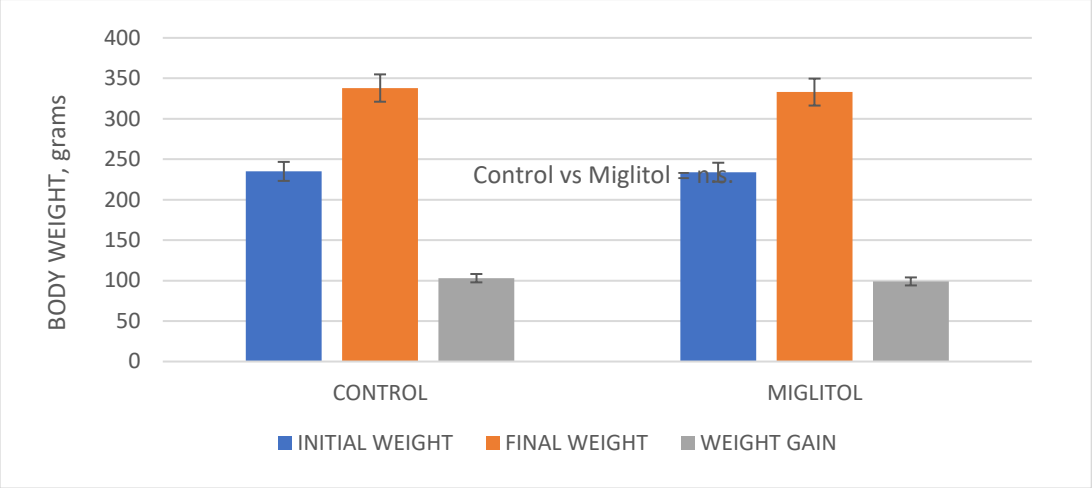

Figure 1: Effect of miglitol on the body weights of lean rats. Data are mean ± 1 SEM, n= 8 rats/group.

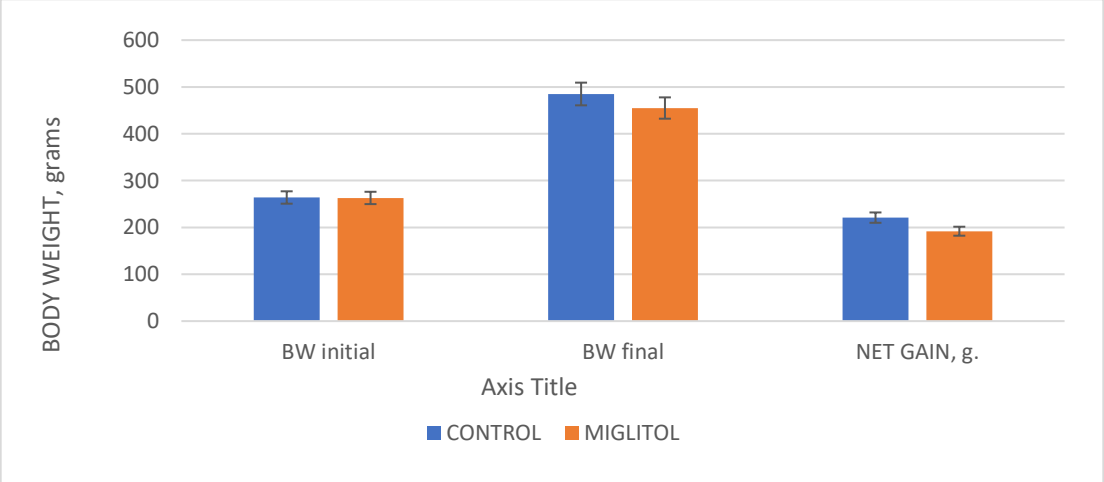

Figure 2: Effect of miglitol on body weights of obese rats. Data are mean ± 1 SEM, n= 8 rats/group.

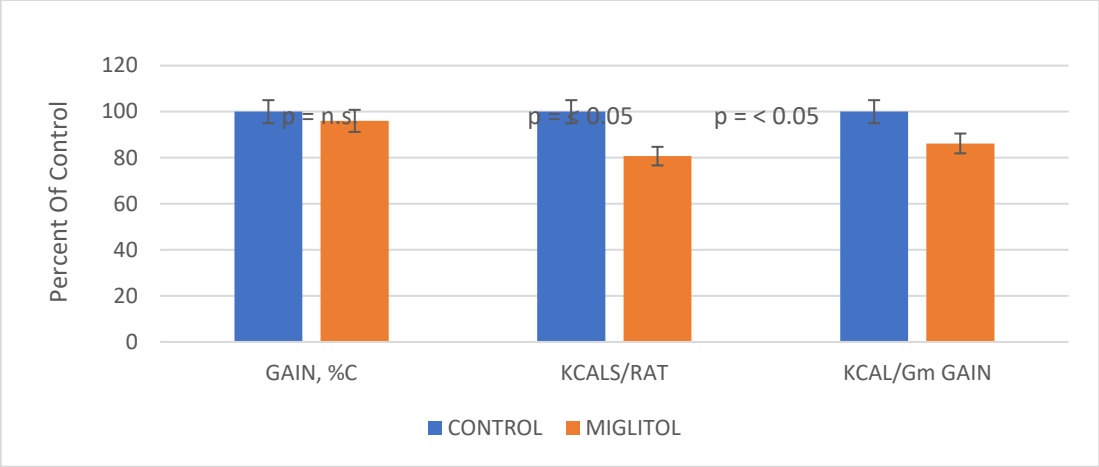

Figure 3: Effect of miglitol on body efficiency of weight gain in lean rats. Data are mean ± 1 SEM, n= 8 rats/group. P = < 0.05 by Students t Test.

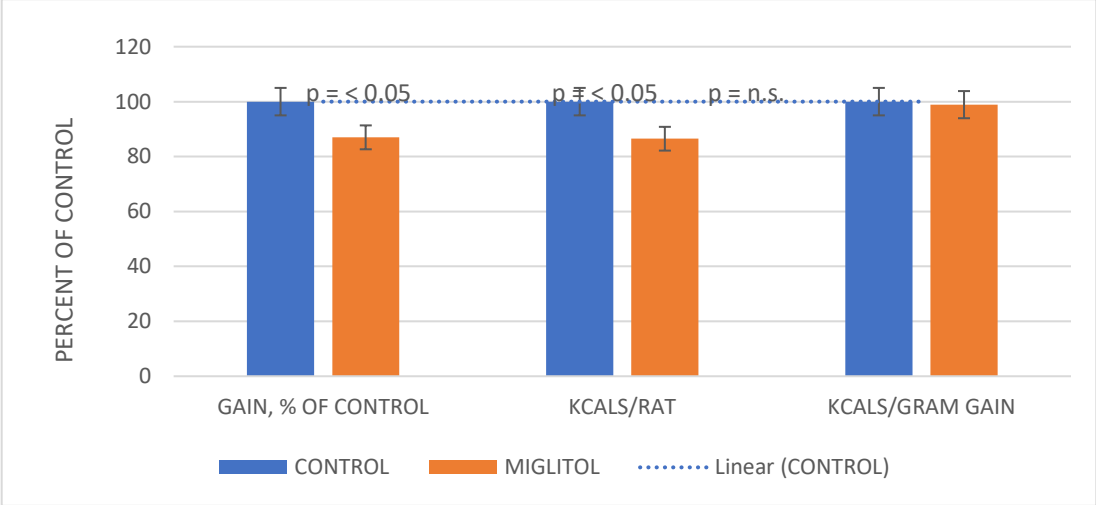

Figure 4: Effect of miglitol on body efficiency of weight gain in obese-T2DM rats. Data are mean ± 1 SEM, n= 8 rats/group. P = < 0.05 by Students t Test.

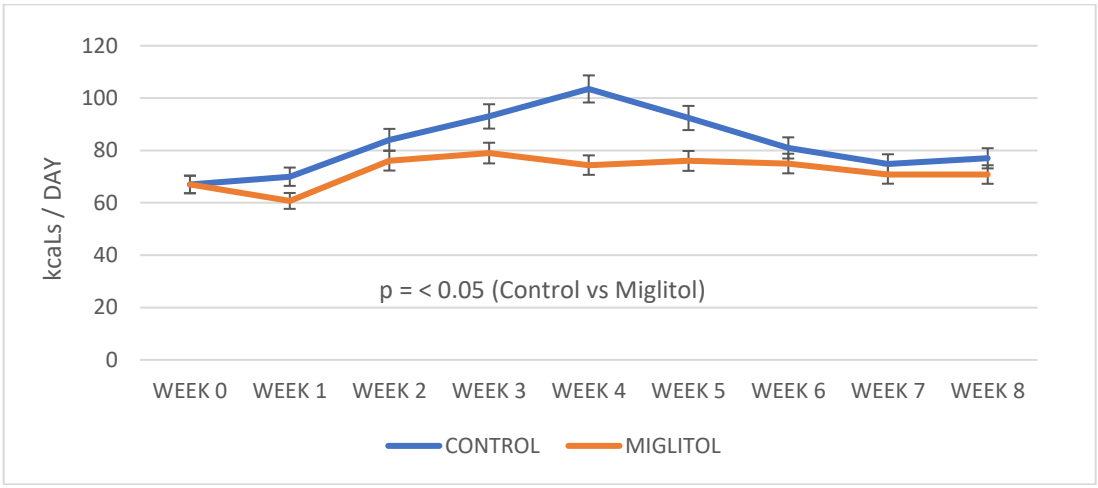

Figure 5: Effect of miglitol on daily energy intake in lean rats. Data are mean ± 1 SEM, n = 8 rats/group.

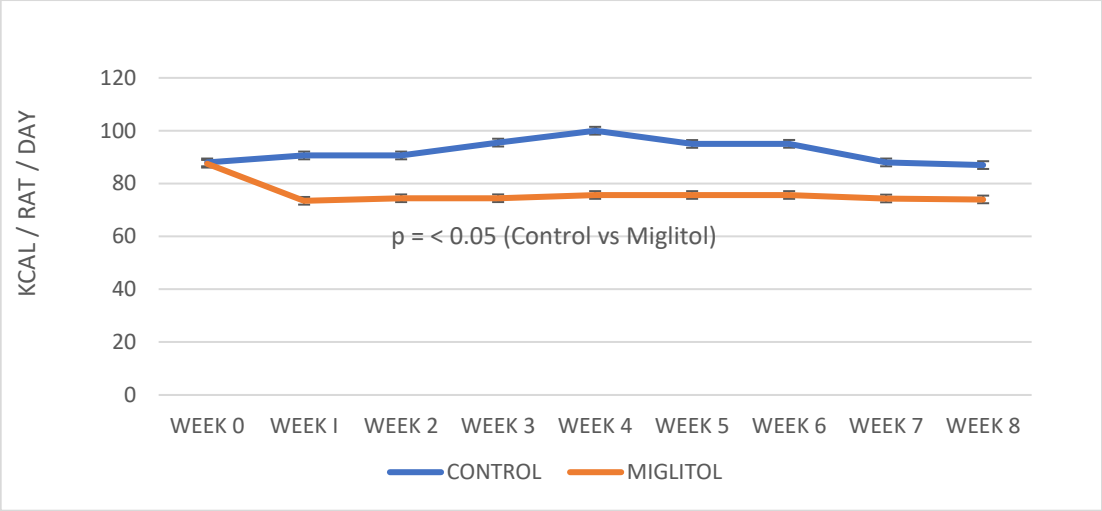

Figure 6: Effect of miglitol on daily energy intake in obese T2DM rats. Data are mean ± 1 SEM, n = 8 rats/group.

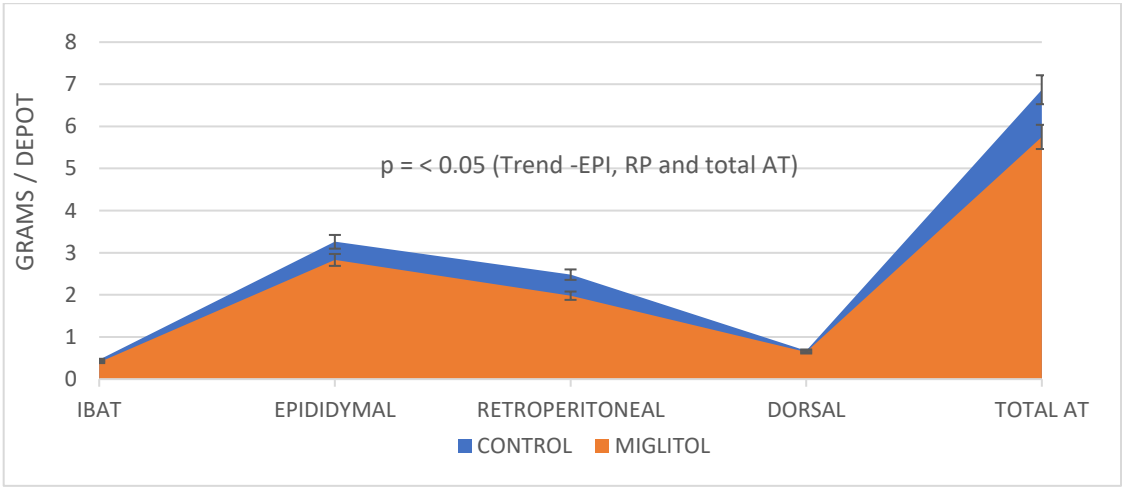

Figure 7: Effect of miglitol on adipose tissue depots in lean rats. Data are mean ± 1 SEM, n = 8 rats/group.

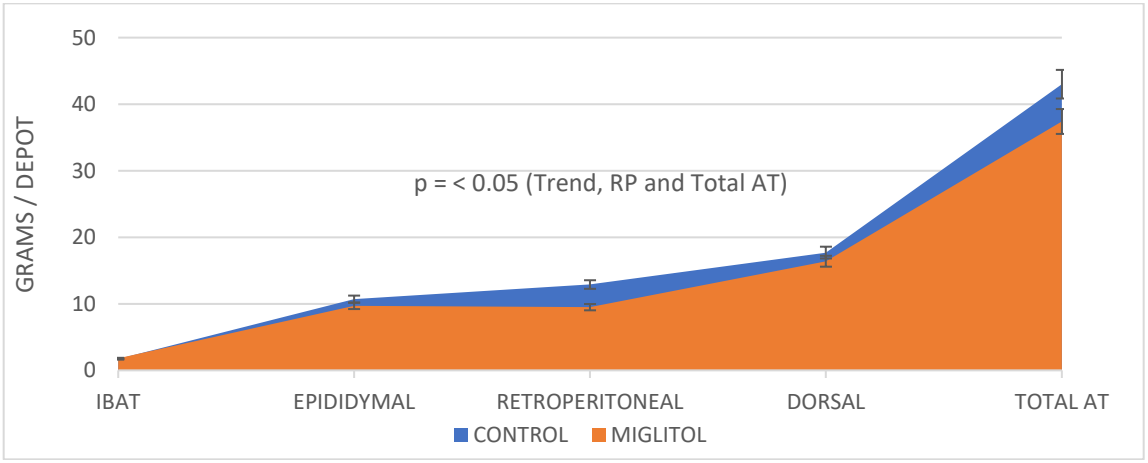

Figure 8: Effect of miglitol on adipose tissue depots in obese R2DM rats. Data are mean ± 1 SEM, n = 8 rats/group.

DISCUSSION

The ingestion of high glycemic index carbohydrate diets is associated with increases in the glycemic responses to a carbohydrate meal, including the glucose area under the excursions in plasma glucose concentrations and the resulting insulinogenic responses, which can contribute to the development of hyperinsulinemia in obesity and T2SM prone humans and animals. Insulin can impact numerous aspects of intermediary metabolism, including glucose uptake in peripheral tissues via GLUT4, and insulin dependent glucose transporter protein, glucose oxidation, glycogen and lipid biosynthesis, protein metabolism, and less advantageous, systemic inflammatory responses under prolonged states of hyperinsulinemia.[11,15] While increases in energy intake are not limited to carbohydrates, their broad applications to commercial food processing and palatability interests mandate consideration in the burgeoning prevalence of obesity and overweight conditions , including metabolic syndrome (MeTS) and T2DM. all of which have a common denominator of hyperinsulinemia and insulin resistance.[16,25] The associations of the triad of chronic overweight conditions, insulin resistance and cognitive decline in aging are now also approaching epidemic prevalence, and are attributed at least in part to a neuroapoptosis syndrome linked to systemic inflammation and neurodegeneration. In animal studies, chronic hyperinsulinemia was shown to be associated with significant decreases in brain protein and DNA content, and which was further exaggerated when sucrose-laden diets were fed. [11,17] In both human twin studies and in numerous animal models, a predisposition for expression of an obesity-prone phenotype has been reported. [11,17]

The rate of luminal carbohydrate digestion via the brush border glucosidases of the small intestine is a key determinant of the net glycemic response generated by the meal.[5,6,9] The rate of the digestion occurs most rapidly in the upper third of the small intestine, where the density of the brush border glucosidases is also greatest, and results in virtually 100% of the ingested carbohydrate undergoing hydrolysis to yield simple monosaccharide moieties and subsequent transluminal absorption into the systemic circulation. The greater the mass of the carbohydrate meal, the greater will be the typical resulting excursions in the systemic circulation, and the greater the magnitude and duration of the insulinogenic response. .Thus, dietary factors that have the propensity to suppress or delay the digestive process are likely to bring about an attenuation in the insulinogenic response and subsequent glucose disposal in peripheral tissues and a decrease in the immediate magnitude of the insulin response. Since skeletal muscle, liver and adipose tissue are among three of the prime benefactors of circulating glucose moieties, dietary and pharmacologic agents that may improve the efficiency of substrate metabolism and storage in those tissues are of interest in combatting the maladies associated with obesity, T2DM and systemic inflammation that occur during the processes of dysregulated carbohydrate metabolism. Dietary fibers, gums, and resins tend to slow the digestive process by impeding on the carbohydrate access to the glucosidase receptor domains, while inhibitors of the glucosidase enzymatic activity including a broad range of α-glucosidase and sucrase inhibitors act as competitive inhibitors of the digestive enzymes. Competitive inhibition of glucosidases thereby delays the rate of digestive activity, prolonging the rate of luminal absorption, attenuating the insulinogenic response, and decreasing the glycation reactions between the luminal-generated monosaccharide moieties and plasma proteins including hemoglobin. Glycated proteins including hemoglobin A1c often

lose much of their intended physiological functionality, with physiological ramifications liked to their individualized functions.[24]

In the case of Hemoglobin A1c, glycation moves the oxygen saturation leftward, impeding essential oxygen release from hemoglobin and contribute to impaired immune and tissue oxidative functions, including aspects of protein metabolism, tissue regeneration and wound healing.[24] Thus, modulation of the glycemic and insulinogenic responses play an important role in broad aspects of metabolism in mammalian species. In the present study, the α-glucosidase competitive inhibitor miglitol resulted in an attenuation in the rate of ingestion and digestion of carbohydrate feeding, and functional alterations in the magnitude and duration of monosaccharide metabolism. While the luminal physiologic effects if any of the miglitol presence in the lumen of the small intestine may have brought about potential changes in the secretion or actions of appetite satiety factors is unclear, but the pharmacologic effects appear to have had an onset soon after the introduction of the miglitol diet, and persisted throughout the duration of the miglitol dietary regimen, and without apparent adverse side effects in the animals.[5-9]

Miglitol absorption from the intestine is minimal if any, thereby minimizing the potential for adverse side effects of metabolic origin. While voluntary reductions in daily caloric intake may bring about similar reductions in glycemic responses and subsequent increases in weight gain and adiposity, the effects of luminal inhibitors of luminal glucosidase activity may further amplify the effects of caloric restriction by not only decreasing net dietary energy intake, but also delaying luminal digestion and vascular absorption into the systemic circulation, and in further attenuation of the glycemic and insulinemic responses. Collectively, the combined impact of dietary and pharmacologic responses of α-glucosidase inhibition via miglitol resulted in favorable effects of developing adiposity and weight gain in T2DM rats, while the pharmacologic impact on the same parameters in their lean non- diabetic littermates was minimal and without evidence of toxicity in either phenotype. Indeed, numerous clinical trials have also reinforced the safety and efficacy of miglitol. [18-23]

SUMMARY AND CONCLUSION

The results of this study resulted in significant attenuations in caloric intake and subsequent increases in adiposity and weight gain when offered miglitol as an admixture to a high glycemic index diet. The effects on daily energy intake were similar in both lean and obese-T2DM rats, with an onset of action during the first week of administration, and which persisted throughout the duration of administration. The effects of the miglitol diet regimen resulted in significant decreases in net weight gain and in depot-specific decrease in AT mass in the obese phenotype while the effects on weight gain and adiposity were modest in the lean, non-diabetic phenotype. Moreover, no evidence of toxicity or untoward reactions of any sort were observed in either phenotype at the dosage provided. These results compliment the beneficial findings of other studies with luminal glucosidase inhibitors as an adjunct for the treatment of glycemic and lipid responses and provide further support for the inclusion of miglitol in the treatment of impaired carbohydrate metabolism and insulin resistant states associated with obesity and T2DM in man and animals.

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Use of AI

No use of AI was utilized in the generation of this manuscript or in the experimental studies presented.

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