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Impact of Luminal Regulation of Hepatic Enzymes of Energy Metabolism in the Obese and Obese-Diabetic (T2DM) Corpulent Rat

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ABSTRACT

The global prevalence of obesity+T2DM is approaching endemic proportions throughout much of Industrialized society, creating a challenge to health care resources, with no easy resolution on the horizon. This study aims to determine the effect of delayed carbohydrate (sucrose) digestion in type 2 diabetes mellites on the activity of glycemic and lipogenic enzyme parameters that directly or indirectly impact on carbohydrate and lipid metabolism and energy deposition. Groups (n=6-8/group, mean BW 264 ± 5g vs 263 ± 4g) of young adult male obese T2DM (diabetic) SHR/Ntul//-cp rats were fed a nutritionally complete USDA-formulated diet containing 54% sucrose (Control, CON) or the same diet with 150 mg of the luminal α-glucosidase inhibitor miglitol (MIG) for up to 8 weeks. Standardized analytical procedures established in our laboratory were utilized to quantify the findings. All animals demonstrated profound (4+) glycosuria by 8-10 weeks of age to confirm T2DM. Body Weight Gain (BWG), relative adiposity and glycosuria were elevated in CON animals. Measures of Oral Glucose Tolerance (OGT, 2.50 g glucose/kg BW, via gavage), AUC for glucose and insulin response to OGT and glycated hemoglobin (HbA1c) were elevated in controls and decreased by ~20% after MIG treatment. Hepatic Glucokinase (GK), and lipogenic NADPH-generating enzymes malic enzyme (ME) and glucose-6-phophate dehydrogenase (G6PD) were elevated in the CON and all decreased following MIG treatment. MIG was without effect on percent adiposity in lean rats of both strains or in the obese, non-diabetic LA/Ntul//-cp rats, but adiposity was decreased by ~10% in the obese-T2DM diabetic rats, consistent with the impact on lipogenic enzymes in T2DM. In conclusion, these observations indicate that luminal modulation of carbohydrate digestion can be an effective, cost-effective clinical strategy to improve the magnitude of the elevated glycemic and lipogenic enzymes and their subsequent impact on developing adiposity in the T2DM-prone obese+SHR/Ntul//-cp genetic rat strain, and may be an effective adjunct in clinical management of obesity, hyperlipidemia and T2DM as it occurs in man and animals.

Keywords

Miglitol, Obesity, Diabetes, T2DM, Hemoglobin A1C, Glucokinase, G6PD, Malic Enzyme.

Introduction

The prevalence of obesity T2DM and it's multiple comorbidities has approached epidemic proportions in much of industrialized society, with little amelioration in sight [1-5]. Excess caloric intake particularly in the form of carbohydrates and fats in addition to a changing lifestyle in recent decades have been presumed to be significant contributing factors.[4,5] Starchy food selections, including the common staples of potatoes, pasta, sugar sweeteners, and other complex carbohydrate foods undergo rapid digestion into simple carbohydrate moieties including glucose and fructose in the lumen of the upper echelons of the small intestine. Once in the peripheral circulation, the glucose moieties undergo insulin-dependent uptake into most tissues [6,7]. The efficiency of luminal management of carbohydrate digestion into simple sugars contributes significantly to post-luminal insulinogenic actions, including substrate absorption, distribution and metabolism in peripheral tissues, facilitated via indirect impacts of plasma insulin on certain enzymatic processes [6,7]. Insulin actions impact genomic aspects of genetic expression on key aspects of protein synthesis, degradation, and the efficiency of substrate metabolism

and energy deposition as glycogen and lipid [7]. The onset of duodenal luminal uptake of glucose typically occurs within minutes of luminal presentation and digestive activity in the brush border region of the small intestine, where the glucosidase and sucrase enzymes are located within the brush border microvillar extensions [3]. Numerous dietary constituents can influence the efficiency of luminal digestion and absorption of monosaccharides, including gums, fibers, minerals, and a plethora of naturally occurring phytochemical components of food that may impede the efficiency of brush border enzymatic actions [6-9]. Naturally occurring stereospecific inhibitors of starch digestion include a broad family of glucosidase and sucrase inhibitors that act at the level of the luminal brush border to delay enzymatic activity that contributes to the luminal digestion of starches and sugars [7]. Pharmaceutical agents that are modelled after the natural products can also impact the efficiency and activity of the luminal digestive enzymes, effectively delaying the rate of luminal carbohydrate digestion into absorbable monosaccharides and lowering blood glucose concentrations [8,9]. As the luminal generation of monosaccharides become decreased, the hormonal result includes an attenuation of insulin release and subsequent alterations in the processes of glucose uptake in peripheral tissues [3,10]. The downstream endocrinological responses impart numerous changes in glucose uptake and disposal in peripheral tissues, ultimately potentially improving insulin sensitivity and substrate distribution. Because the prevalence of obesity and overweight conditions is approaching extraordinary, epidemic proportions throughout much of industrialized society, more effective clinical strategies are deemed necessary to more effectively address the metabolic and pathophysiologic sequalae that coexist as contributors to the disorders [3,10]. The common denominator of the above conditions is a variable magnitude of insulin resistance, which as noted above, indirectly impacts expression of multiple insulin-linked enzymes of energy metabolism and storage as glycogen or lipid constituents [4-7]. Chronic elevations in blood glucose concentrations and glycated hemoglobin are a secondary consequence of the insulin resistance in T2DM [11-13]. The glycation of hemoglobin occurs as a non-enzymatic process, in proportion to the average plasma glucose concentrations over the lifetime of the erythrocyte and serve as a recognized diagnostic marker of plasma glucose control in diabetes [11,12]. Physiologically, the glycation process moves the blood oxygenation curve to the left, thereby impairing oxygen release to myoglobin, hence impacting multiple oxygen-dependent cellular processes in proportion to the magnitude of the glycation. Thus, agents that can reduce the extent of glycation such as photonic therapy, in addition to agents than can decrease the excursions in blood glucose, can exert a favorable impact on oxygen dependent healthful processes that contribute to tissue viability [11,12].

The concurrent increase in the prevalence of Type 2 diabetes mellites (T2DM) is now among the most common comorbidities of overweight and obese conditions and now impacts up to 1/6 or more of the populations of many communities [1,2,10,14]. Moreover, the economic costs of these stigmata due to lost achievement in the workplace and to the subsequent health and financial issues that necessarily follow their clinical diagnosis are becoming a major burden on available health care resources in many jurisdictions [1,2,8]. Since once an overweight or obese condition has been diagnosed, with or without confirmation of T2DM as a comorbidity, clinical patient management typically continues throughout the remainder of the individual's lifespan [6,13]. The lifelong impact typically occurs at great annual global expenditures on healthcare and thus can impact the community-wide economy in addition to individual's quality of life and their available healthcare resources going forward [1].

The Congenic Corpulent Rat Model

The development of the corpulent rat strains enabled new insights into the genomic and physiological mechanisms that contribute to the development of obesity and T2DM [15-20]. The congenic LA/Ntul//-*cp* and SHR/Ntul//-*cp* rat models were developed by Hansen in the small animal genetics laboratory at the NIH. The autosomal recessive obesity -*cp* trait originated from the Koletsky rat and was bred into a longevity-prone NIH (N) strain of unknown origin, followed by 12 cycles of backcrossing cycles to attain a congenic status in the newly established LA/N-*cp* and SHR/N-*cp* strains, where only prevailing trait of the new strains was the expression of the obesity trait [15-18]. The -*cp* trait was then bred and backcrossed into the spontaneously hypertensive rat (SHR) in a similar manner to finalize the SHR/N-*cp* strain, producing an obesity+T2DM-prone strain. The further addition of the [//tul-*cp*] identifier in the nomenclature was later assigned by the NIH to clarify the current distinctive sub-colonies of these strains that may have evolved from different backcrosses or sub-colonies reared elsewhere. The obese phenotypes of both strains exhibit a significantly decreased lifespan due to complications of obesity and T2DM respectively when compared to their longevity-prone NIH (N) heritage. The eptgenetic factors which differentiate the non-diabetic LA/Ntul//-*cp* from its T2DM cousin, the SHR/Ntul//-*cp* strain remain unclear, but are presumed to be secondary to sirtuins or other as yet unidentified physiological factors [19,20]. Thus, the purpose of the present study was to characterize the expression of glycolytic and lipogenic enzymes of energy metabolism in the lean and obese+T2DM phenotypes in the T2DM-prone SHR/Ntul//-*cp* strain when reared under identical, standardized conditions of diet and environment.

Summary of Materials and Methods

Groups of lean and obese SHR/Ntul//-*cp* rats were selected from the breeding colony at ~5 weeks of age (n=8 rats/treatment group) and maintained on stock Purina rodent chow and house water, *ad libitum*, until 7 weeks of age under AVMA guidelines and standardized conditions of housing. Conventional environmental conditions were (20-22°C, 50% RH; housed in plexiglass cages lined with ~1 inch of fresh pine shavings). Animals were then switched to a USDA-formulated control diet containing 54% carbohydrate as sucrose, 20% protein as equal parts lactalbumin and casein, 16 % fats as equal parts corn oil, beef tallow, lard and coconut oil, 5.9 % cellulose, 3.1 % AIN vitamin and mineral salt mix, and 1% Teklad vitamin mix, for the remainder of the study [21]. In addition, a second group of littermates of each phenotype were fed the same diet with the addition of miglitol

([1,5 dideoxy-1,5-[(2-hydroxyethyl) imino]-D glucitol; generic = miglitol) at a dosage of 150 mg/kg (0.015%) of diet as an admixture. This admixture was calculated to provide ~ 2.5 mg of miglitol per animal per day based on typical daily consumption of the control diet. Body weights were obtained periodically as an indicator of animal wellness. Urines were collected in a metabolic cage periodically beginning at 8 weeks of age for measures of glycosuria to confirm the onset and progression of diabetic status via a dipstick estimation for glycosuria. After 6 weeks of the miglitol diet, rats were subjected to an oral glucose tolerance (250 mg/kg BW via gavage administered slowly within a one-minute duration) and blood obtained periodically via tail bleeding over a 2-hour duration for measures of glucose (glucose oxidase method; based on methods originally described by Raabo and Terkildsen) and plasma insulin concentration via immunochemistry [22,23]. The area under the glucose and insulin curves was determined via the method of Sagakuchi et al. [24] Measures of Hemoglobin A1c were determined via spectrophotometry after microcolumn separation [25]. At the end of the study, rats were humanely sacrificed with a small animal guillotine via AVMA recommended protocol and principal fat pads including the dorsal, retroperitoneal, and epididymal fat pads were dissected in their entirety, weighed to the nearest 0.1 mg., and the sum of the 3 depots expressed as a percent of body weight as a measure of relative adiposity. The liver tissue was also dissected free in its entirety, weighed, and aliquots homogenized in a sucrose-EDTA phosphate buffer for measures of glucokinase, malic enzyme, and glucose-6-phosphate dehydrogenase activity and expressed as units/mg protein/liver [26-29]. Tissue protein was determined with the classic method of Lowry and Rosebrogh [29]. Data were analyzed via standard statistical procedures including student t test, ANOVA, and Pages L test for trend analysis as appropriate [30,31]. The study was approved by the Institutional Animal Care and Use Committee.

Results

The effects of Miglitol on weight gain in rats is depicted in Figure 1 and indicates that the net weight changes of all lean groups of both strains were not impacted by the miglitol diet. In addition, the effect of the miglitol diet on the obese phenotype of the LA/Ntul//-*cp* strain was similarly not significantly impacted by the miglitol diet. In contrast, the miglitol diet resulted in a significant decrease in net weight gain only in the obese+T2DM phenotype of the SHR/Ntul//-*cp* rat strain. The effects of strain, phenotype and miglitol on adiposity are depicted in Figure 2, and indicate that the effects of phenotype on adiposity were highly significant in both strains. The relative adiposity was quantified by the combined mass of the WAT mass of multiple WAT depots including the epididymal, retroperitoneal and dorsal fat pads as a proportion of final body weight. In addition, while the effects of the miglitol diet were not significant in the lean or obese phenotype of the LA/Ntul//-*cp* strain, the miglitol treatment resulted in a significant decrease in relative adiposity only in the obese phenotype of the T2DM-prone SHR/Ntul//-*cp* strain, suggestive of a unique T2DM-specific factor or factors operative in obese+T2DM animals.

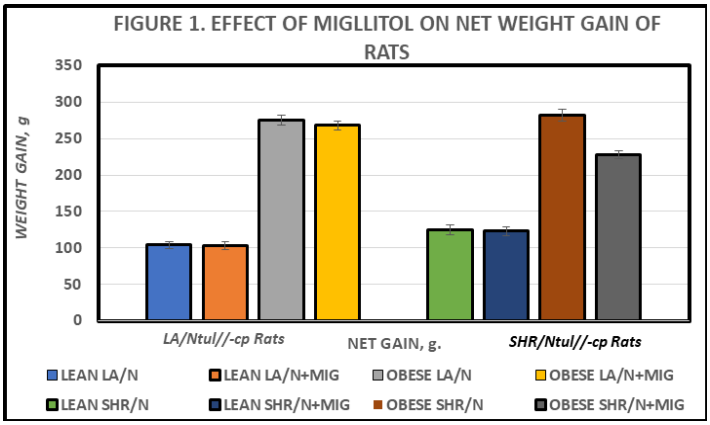

Figure 1: Effect of miglitol, strain and phenotype on final body weights of rats. Data are the mean ± 1 Standard Error of the Mean, n = 6-8 rats./group.

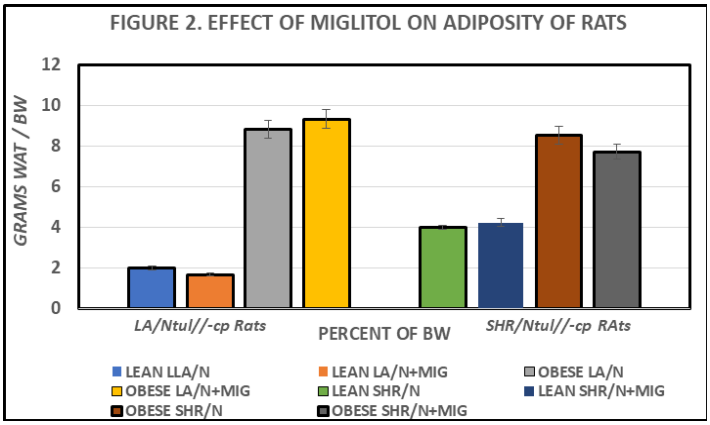

Figure 2: Effect strain, phenotype and miglitol on percent adiposity in lean, obese, and obese+T2DM rats. Data are mean ± 1 SEM, expressed as a percentage of the sum of epididymal, dorsal and retroperitoneal fat pads divided by final body weight; n = 6-8 rats/group.* = p = n.s.; p = < 0.05^{V} via trend analysis= significant trend via Pages L test for trend analysis. LA/N = :A/Ntul//-cp rats; SHR/N = SHR/Ntul//-cp rats.

The effects of miglitol, strain and phenotype on the mean efficiency of weight gain are depicted in Figure 3A, and indicate that The efficiency of weight gain in the obese phenotypes in both strains tended to be greater than occurred in their lean littermates. In addition, while miglitol tended to be associated with a modestly greater efficiency of weight gain in both phenotypes, the differences failed to achieve statistical significance. When factors of caloric intake in the obese T2DM SHR/N-cp strain were taken into consideration in Figure 3B, it was evident that food intake in the miglitol treated obese rats was decreased by an average of ~15%, proportionally similar to the decreases in adiposity and weight gain with the miglitol treatment in those animals. Indeed, when miglitol-treated Obese T2DM rats were compared to their untreated littermates, not only did they gain les weight over the course of the study, but the miglitol also was associated with a proportionate decrease in total caloric intake over the course of the study. As indicated in the right panel of Figure 3B, the overall efficiency of weight gain was similar in both T2DM-Obese SHR/Ntul//-*cp* groups.

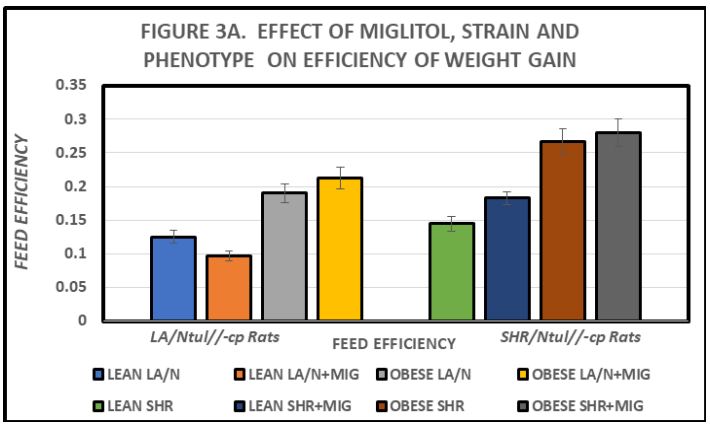

Figure 3A: Effect of miglitol on strain and phenotype of rats. Efficiency of weight gain is determined by grams gain/ grams food intake. Data are presented as the mean ± 1 SEM, n = 6 rats / group.

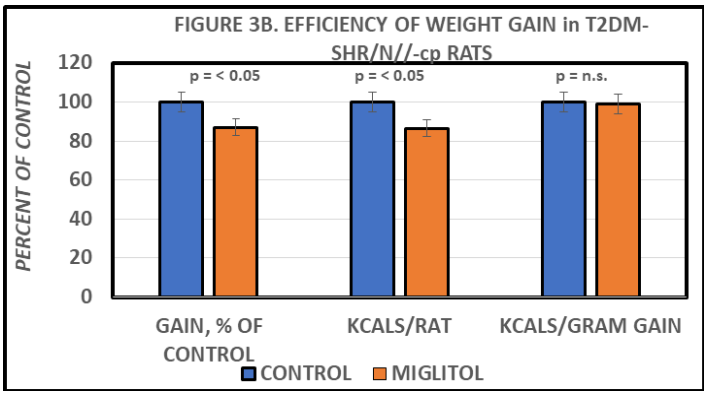

Figure 3B: Effects of miglitol on the mean efficiency of weight gain in T2DM-prone obese-SHR/Ntul//-cp rats. Data are presented where miglitol-treated obese-T2DM SHR/Ntul//-*cp* rats are expressed as a percent of the untreated obese+T2DM control rats. Data are presented as the mean ± 1 SEM, n = 6 rats / group.

The effects of miglitol and strain in obese and obese T2DM rats on the area under the OGT glucose curve for glucose and insulin are depicted in Figure 4A and 4B and indicate that the AUC for both glucose and insulin were greater in obese than in lean rats. In addition, miglitol was without significant effect in lean (Figure 4A) or obese (Figure 4B) LA/Ntul//-*cp* rats. In contrast, miglitol resulted in over 20% average decrease in both AUCglc (-22%) and AUCins (-24%) in the obese phenotype of the obese+T2DM SHR/Ntul//-cp rats. This observation is consistent with likely improvements in glucose uptake in peripheral tissues, indicative of a modest improvement in insulin sensitivity in those animals following 8 weeks of miglitol treatment. In addition, it suggests that the impaired glycemic responses in obesity *per se* may be expressed differentially in the obese, T2DM-prone SHR/Ntul//-*cp* rats, and implies that additional factors that contribute to the genomic expression of energy metabolism such as certain sirtuins may be impacted differentially in the two obesity-prone strains.

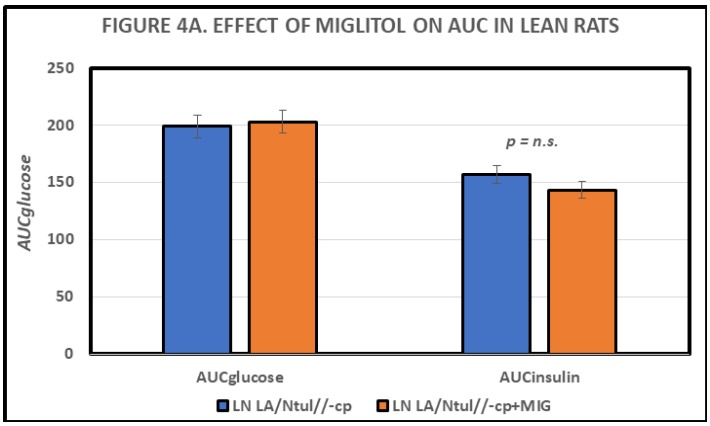

Figure 4A: Effects of miglitol on the mean area under the OGT curve for glucose and insulin in lean LA/Ntul//-*cp* rats. Data are presented as the mean ± 1 SEM, n = 6 rats / group.

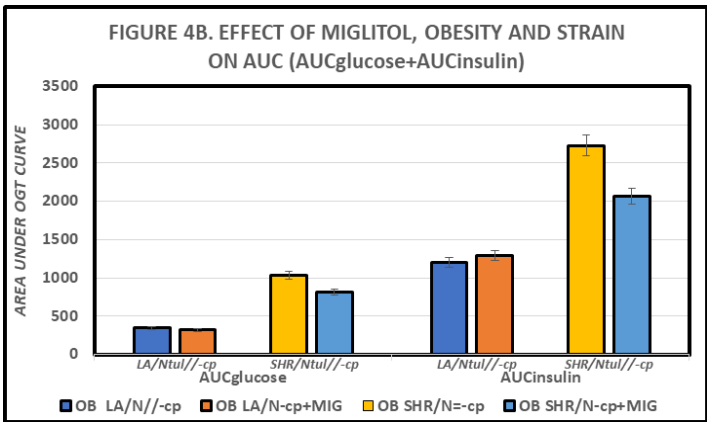

Figure 4B: Effects of miglitol on the mean area under the OGT curve for glucose (AUCglucose) and insulin (AUCinsulin) in obese LA/Ntul//-*cp* and obese T2DM-prone SHR/Ntul//-*cp* rats. Data are presented where miglitol-treated obese-T2DM SHR/Ntul//-*cp* rats are expressed as a percent of the untreated obese+T2DM control rats. Data are presented as the mean ± 1 SEM, n = 6 rats / group.

The effects of miglitol, strain and phenotype on parameters of glycemic parameters and hepatic enzymes of glycemic and lipogenic actions are presented in Table 1. These data indicate that fasting glucose and insulin concentrations were both elevated in the obese of both strains, and that miglitol was associated with modest decreases in both parameters in the obese animals. Measures of glycated hemoglobin concentration were similar in the lean animals of both strains and decreased modestly in lean non-T2DM LA/Ntul//-*cp* rats when given the miglitol diet. Glycated hemoglobin concentrations in the obese+T2DM SHR/Ntul//-*cp* rats were significantly elevated by approximately 90%. Miglitol was associated with an approximate 25% reduction in HbA1c, but the drug failed to return the glycated hemoglobin concentrations to those of non-diabetic rats of either strain. Hepatic insulin-linked enzyme activities of glycemic and lipogenic enzymes are shown in the left three columns of Table one, and indicate that the activities of all three enzymes measures were greater in the obese than in the lean phenotypes of both strains. In addition, miglitol did not impact on the activities of the liver enzymes in the lean phenotype

of either strain but was associated with a significant decrease in glucokinase and malic enzyme, and with a trend toward a decrease in glucose-6-phosphate dehydrogenase. Glucokinase plays an important role in signaling the pancreatic β-cells to release insulin, in addition to facilitating hepatic glycogen storage, while Malic enzyme and glucose-6-phosphate dehydrogenase are instrumental in the formation of NADPH required for de novo hepatic fatty acid biosynthesis in response to meals and metabolic substrate availability. Thus, the results of the lipogenic enzyme activity are consistent with the modest decrease in adiposity in the obese+T2DM phenotype of the SHR/Ntul//-*cp* rat strain.

Discussion

The results of this study indicate that the luminal α-glucosidase inhibitor miglitol may result in differential improvements in fasting and carbohydrate-stimulated insulin responses on key glycemic and lipogenic enzymes of glucose and lipid metabolism, with corresponding improvement in parameters of lipogenesis and adiposity in obese and obese+T2DM phenotype of the corpulent rat strains. In contrast, the hormonal impact in both lean phenotypes on enzyme activity and adiposity were not significant and the responses measured remained within the normal range for most metabolic and enzymatic parameters in the lean phenotypes. The specific hepatic markers selected for measurement were intended to identify essential insulin-linked regulatory elements of carbohydrate and lipid metabolism. Glucokinase is essential for glycogen deposition and insulin signaling in the fed state. Malic enzyme and glucose 6 phosphate dehydrogenase activity are essential for the generation of NADPH required for de novo fatty acid biosynthesis in liver [22]. Sirtuins are silent information transfer factors that are linked to the genomic expression of multiple aspects of hormonal activation and energy metabolism and storage [32]. Their complimentary roles in lipid biosynthesis and energy metabolism are unclear, but the results of this study suggest that differential epigenetic expression of multiple factors including the possible contributions of glucocorticoids contribute to the expression of metabolic enzymes of energy metabolism and storage [32-34]. Since Miglitol reduced adiposity in obese+T2DM but not in Obese non-diabetic, this observation is suggestive of differential effects of the agent in T2DM or on diabetic obese or lean rats. This raises questions as to the likelihood of specific epigenetic markers noted above that may differentiate obesity from obesity associated with T2DM in this model may be potential targets for future development of pharmacologic agents that mat modulate their activity, thereby contributing to a resolution of the global burden of obesity and T2DM in man and animals.

Summary and Conclusions

The present study characterized the expression of key glycolytic and lipogenic enzymes of energy metabolism in the lean, obese and obese+T2DM phenotypes in the congenic LA/Ntul//-*cp* and T2DM-prone SHR/Ntul//-*cp* rat strains. In addition, the effects of the luminal α-glucosidase competitive inhibitor miglitol on glycemic responses were determined in lean animals and in additional obese and obese-diabetic (T2DM) animals. Miglitol has been demonstrated to decrease the rate of sucrose and starch digestion in the brush border lumen of the upper regions of the duodenum of mammalian species including mankind via competitive inhibition [5]. The uptake of glucose moieties typically occurs rapidly and with great efficiency in this region of the duodenum in mammals. The hydrolysis of carbohydrate residues into monosaccharide moieties normally occurs rapidly and is often considered to be the rate limiting stage in luminal glucose uptake, especially in the upper regions of the small intestine, where virtually all carbohydrate digestion normally occurs. Intestinal glucose uptake is normally virtually complete within the first hour post ingestion when in the absence of inhibiting factors. However, while glucose generation from complex carbohydrates in the presence of miglitol may be delayed, post-digestive luminal absorption Is typically virtually complete within one to two hours of meal ingestion. The high efficiency of luminal starch digestion and monosaccharide uptake thereby decreases the potential of symptoms of maldigestion of undigested residues during intestinal transit by the colonic microbiome. Miglitol differs from other members of the glucosidase inhibitor family in that like glucose, miglitol also undergoes virtually complete luminal absorption within two hours of ingestion, soon after the glucose moieties have also been absorbed. Luminal absorption of miglitol is typically

Table 1: Effect of miglitol on liver enzymes and glycemic parameters in lean and obese LA/Ntul//-*cp* rats. Rats.

GROUP	N	GK	ME	G6PD	GHB	FBS	INS
Lean LA/N	(6)	0.77 ± 0.10a	4.8 ± 0.08a	3.7 ± 0.4a	7.03 ± 0.81b	75 ± 5a	70 ± 7b
Lean LA/N+MIG	(6)	0.66 ± 0.11a	3.9 ± 0.4a	4.5 ± 0.7a	5.43 ± 0.37a	73 ± 6a	36 ± 4a
Obese LA/N	(6)	1.88 ± 0.22b	45.0 ± 6.2c	13.1 ± 1.0b	8.64 ± 1.26c	127 ± 107b	734 ± 28d
Obese LAN+MIG	(6)	1.75 ± 0.15b	38.1 ± 10.6c	14.3 ± 1.5b	7.33 ± 1.14b	88 ± 5a	435 ± 21c

Table 1B: Effect of miglitol on liver enzymes and glycemic parameters in lean and obese T2DM+SHR/Ntul//-cp rats.

GROUP	N	GK	ME	G6PD	GHB	FBS	INS
Lean SHR	(6)	0.89 ± 0.14a	6.1 ± 1.0a	4.6 ± 0.5a	6.57 ± 1.83b	N.D.	N.D.
Lean SHR+MIG	(6)	0.85 ± 0.08a	7.1 ± 1.0a	4.6 ± 0.7a	8.82 ± 1.11c	N.D.	N.D.
Obese SHR	(6)	2.45 ± 0.15c	30.1 ± 5.5c	17.0 ± 2.0b	12.5 ± 0.78e	155 ± 8c	986 ± 25d
Obese SHR+MIG	(6)	1.45 ± 0.25b	23.1 ± 2.9b	15.9 ± 3.2b	9.42 ± 0.77d	119 ± 8b	842 ± 23d_/785

Data are mean ± 1 SEM, n = 6 rats/group. GK = glucokinase; ME = malic enzyme; G6PD = glucose-6-phosphate dehydrogenase; GHB = Glycated hemoglobin, or HbA1c; FBS = fasting glucose concentration; INS = fasting plasma insulin concentration. Numbers with a different letter indicate a statistically different subgroup by Student Newman Keuls analysis. N.D. = not done.

followed by peripheral distribution and renal excretion without further metabolism, metabolic actions, or hepatic detoxification throughout the pharmacokinetic process. The decreased area under both the glucose and insulin curves following a carbohydrate challenge as occurred in miglitol treated diabetic rats is indicative of delayed carbohydrate digestion, resulting in gradual improvements in insulin sensitivity after several weeks of treatment. The effects of miglitol in lean animals in non-diabetic obese animals was less dramatic, however, indicative of likely differences in the normal rate of gastric emptying in non-diabetic animals of either phenotype.

Miglitol is one member of a family of naturally occurring luminal inhibitors of carbohydrate digestion that exert similar actions on luminal carbohydrate digestion. Because miglitol undergoes virtually complete luminal absorption within 2 hours of administration, further luminal effects have not been observed. In addition, because miglitol bypasses hepatic detoxication during its post ingestive absorption, neither have significant aberrations in hepatic, cardiovascular or renal excretion been observed in animals or in human trials. In the present study, miglitol was found to result in decreases in several insulin-linked enzymes of glycemic and lipogenic actions in obese-diabetic animals, and in a modest trend toward decreases in plasma lipid profiles and in decreased adiposity after only two months of treatment, while in non-diabetic animals of either phenotype, significant effects were not observed. In contrast, effects of miglitol were not observed in the lean phenotypes of either strain on the hepatic enzymes studies. Miglitol effects were observed in fasting glucose, insulin, and glycatd hemoglobin concentrations in both the non-diabetic and T2DM-obese animals however, suggestive of graded responses in the obese animals that corresponded somewhat directionally with the magnitude of the impaired OGT responses, and where the greatest response occurred in the obese+T2DM animals. Thus, the greatest magnitude of the phenotype effects of miglitol on adiposity were only noted in the T2DM-obese animals. The basis for the differential impact of miglitol is unclear but may be linked to accelerated gastric emptying in the T2DM animals, a common observation in diabetes, with possible differential effects on sirtuins, genomic mediators of epigenetic expression of hormonal actions on gene expression. If present, the impact of accelerated gastric emptying on luminal glucose uptake would be expected to result in an accelerated rise in the immediate post ingestive phase of glucose uptake of an OGT-linked glucose meal. With normal meal feeding, however the post-ingestive phase of glucose uptake would likely be delayed in the presence of miglitol, thereby accounting for the improvements in insulin linked enzymatic and glycemic improvements. The decreases in glycated hemoglobin are particularly important, as they provide confirmation of the improved chronic glycemic status with miglitol treatment. Glucosidase agents including miglitol exert their pharmacologic actions in the brush border region of the small intestine and are not known to be highly prone to deleterious, pathogenic or adverse toxicology actions. Adverse reactions have only rarely been reported in human treatment protocols with glucosidase inhibitors as monotherapy and may be suitable for those with milder forms of the glucose intolerance. In contrast, the favorable glycemic actions of glucosidase inhibitors may become additive when combined with other hypoglycemic agents. In the present study, therapeutic benefits resulted in improvements if glycated hemoglobin, and in the activity of several key insulin linked hepatic enzymes of glucose and lipid metabolism, and in modest decreases in adiposity in obese T2DM rats. While not specifically addressed in the present investigation, the results are consistent with modest improvements in insulin sensitivity, an important objective in the treatment of T2DM in man and animals.

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