Inhibition of apical sodium-dependent bile acid transporter as a novel treatment for diabetes

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Chen L, Yao X, Young A, McNulty J, Anderson D, Liu Y, Nystrom C, Croom D, Ross S, Collins J, Rajpal D, Hamlet K, Smith C, Gedulin B. Inhibition of apical sodium-dependent bile acid transporter as a novel treatment for diabetes. Am J Physiol Endocrinol Metab 302: E68–E76, 2012. First published September 20, 2011; doi:10.1152/ajpendo.00323.2011.—Bile acids are recognized as metabolic modulators. The present study was aimed at evaluating the effects of a potent Asbt inhibitor (264W94), which blocks intestinal absorption of bile acids, on glucose homeostasis in Zucker Diabetic Fatty (ZDF) rats. Oral administration of 264W94 for two wk increased fecal bile acid concentrations and elevated non-fasting plasma total Glp-1. Treatment of 264W94 significantly increased HbA1c and glucose, and prevented the drop of insulin levels typical of ZDF rats in a dose-dependent manner. An oral glucose tolerance test revealed up to sevenfold increase in plasma total Glp-1 and three-fold increase in insulin in 264W94 treated ZDF rats at doses sufficient to achieve glycemic control. Tissue mRNA analysis indicated a decrease in farnesoid X receptor (Fxr) activation in small intestines and the liver but co-administration of a Fxr agonist (GW4064) did not attenuate 264W94 induced glucose lowering effects. In summary, our results demonstrate that inhibition of Asbt increases bile acids in the distal intestine, promotes Glp-1 release and may offer a new therapeutic strategy for type 2 diabetes mellitus.

glucagon-like peptide 1; enteroendocrine

TYPE 2 DIABETES MELLITUS (T2DM, diagnosed and undiagnosed) is a major global health issue with its prevalence in the United States being currently estimated at 8.3% of the population (8). Both type 1 and type 2 diabetes are independent risk factors for cardiovascular diseases such as coronary heart disease. The $180 billion annual burden of care (8) derives mainly from the ensuing two- to fourfold elevation of cardiovascular risk (14, 16). Therefore, new modes of antidiabetic therapy, including an increase in intracellular thyroid hormone-activated energy expenditure in brown fat (40) and stimulation of glucagon-like peptide-1 (Glp-1) secretion in STC-1 cells, a murine enteroendocrine cell model (17). Although the pharmacological basis is unresolved, delivery of bile salts to the lumen of the distal bowel (colon and/or rectum) stimulates secretion of Glp-1 and peptide YY (PYY) secretion in both animal models (11, 28) and humans (1, 2), in the latter case resulting in insulin-stimulating and glucose-lowering responses at least equal to those reported with exogenous Glp-1 receptor agonists.

The implication of bile acids in metabolic control is suggested by recent reports that bile acid sequestrants (BAS) significantly reduce both blood glucose and LDL in T2DM patients (5, 35). BAS resins, by binding to bile acids in the intestinal tract to decrease reabsorption, were intended to deplete the bile acid pool at the expense of sterols, resulting in the observed cholesterol lowering. The unanticipated improvement in glycemic control and β-cell function, which we also observed in Zucker diabetic fatty (ZDF) rats, appeared to be associated with stimulated secretion of Glp-1 and not with the Fxr-Shp-Lxr pathway (9).

The apical sodium-dependent bile acid transporter (Asbt), also named the ileal bile acid transporter (Ibat; Slc10a2), is expressed predominantly in the distal ileum. Asbt plays an important role in the sodium-dependent reabsorption of bile acids from the lumen of the small intestine, which is critical for the enterohepatic recirculation and overall lipid homeostasis. Normally, 90–95% of secreted bile acids are reabsorbed, and only 0.2–0.6 g are lost daily, to be replaced by equivalent hepatic synthesis from the sterol pool (24). With a biological rationale as stated above for sequestrants, supported by cholesterol-lowering efficacy in patients with ileal bypass surgery (6), and because they could be restricted to the gut lumen (avoiding systemic exposure), inhibitors of Asbt from at least nine chemical classes were developed ~15 years ago by at least seven companies as LDL cholesterol-lowering agents (19). One of these, 264W94, inhibited ileal uptake by up to 97% (in vitro IC50 = 0.41 μM) (32). However, the connection between bile salts and glycemic control was not known at the time, and no Asbt inhibitor was tested as an antidiabetic agent. To test the hypothesis that

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increasing free bile acids in the distal intestine might improve glucose metabolism, we evaluated the effects of 264W94 on glucose homeostasis in ZDF rats and explored potential underlying mechanisms.

RESEARCH DESIGN AND METHODS

Materials. GW4064 (23) and 264W94 (32) were synthesized by medicinal chemistry groups at GlaxoSmithKline.

Animal preparation. In the first study (study 1), male ZDF (ZDF/GmiCrl-fa/fa) were purchased from Charles River (Raleigh, NC) and housed under controlled conditions (12:12-h light-dark cycle, 24°C, and 50% relative humidity) with free access to rodent food (Purina 5008; Harlan Teklad, Indianapolis, IN). All rats arrived at 7 wk of age (±3 days). After a 1-wk acclimation period, rats were anesthetized with isoflurane (Abbott Laboratories), and tail vein blood samples were collected at 9 AM without fasting. Blood glucose levels were measured using a glucometer (Bayer, Leverkusen, Germany). To ensure balanced treatment groups, ZDF rats were assigned to six treatment groups based on baseline glucose: vehicle (0.5% hydroxypropyl methylcellulose (HPMC), 0.1% Tween 80) and five doses of 264W94 (0.001, 0.01, 0.1, 1, and 10 mg/kg). All treatments were given via oral gavage twice a day, and animals were followed for 2 wk with blood samples collected from tail vein at the end of each week at 9 AM without fasting. Three groups of the animals (vehicle and 0.1 and 10 mg/kg) were cannulated (jugular vein) at the beginning of the third week, and an oral glucose tolerance test (OGTT) was conducted at the end of the third week. Fecal samples were collected for 24 h during the second week of treatment.

In a separate study (study 2), 8-wk-old male ZDF rats were assigned to vehicle or 264W94 (1 mg/kg bid) groups based on baseline glucose and treated for 5 wk. A group of age-matched Zucker lean control rats was also included in the study. At the end of the study, intestinal (0.5-1 cm sections from the middle of duodenum, jejunum, ileum, ascending colon, and descending colon) and liver tissues were collected at 10 AM without fasting, and the mRNA expression of certain selected genes was determined using RT-qPCR.

In a third study (study 3), 8-wk-old male ZDF rats were assigned to four groups based on baseline glucose: vehicle, 264W94 (1 mg/kg bid), GW4064 (an Fxr agonist; 30 mg/kg bid) (23) and 264W94 + GW4064 (1 mg/kg and 30 mg/kg bid, respectively). Animals were treated for 2 days, and steady-state blood glucose was measured using glucometers at 9 AM without fasting.

Principles of laboratory animal care were followed. All procedures performed were in compliance with the Animal Welfare Act and US Department of Agriculture regulations and were approved by the GlaxoSmithKline Animal Care and Use Committee.

OGTT. Rats were fasted overnight (16 h) prior to OGTTs. Dextrose at 2 g/kg body wt was orally administered via gavage. Blood samples were collected via jugular vein cannulation immediately before and 5, 10, 20, 30, 60, 90, and 120 min after the administration of dextrose. Blood glucose levels were measured using glucometers (Bayer, Leverkusen, Germany), and plasma samples were collected for further analysis.

Measurement of clinical chemistry parameters. Plasma glucose, nonesterified fatty acids (NEFA), bile acids, and bile acids in fecal extraction were measured using the Olympus AU640 clinical chemistry analyzer (Beckman Coulter, Irving, TX). Glucose test reagents were manufactured by Beckman Coulter. NEFA reagents were manufactured by Wako and bile acids reagents by Trinity Biotech. Hb A1c was measured by the Primus Affinity Ultra2 HPLC System using Primus Affinity Assay reagents (Primus Diagnostics, Kansas City, MO). Insulin was assayed using the Meso Scale Discovery (MSD) Mouse/Rat Insulin assay kit. Total Glp-1 was assayed by the MSD Total Glp-1 assay kit. Both assays were analyzed on an MSD Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD). Plasma proinsulin was determined by ELISA (ALPCO, Salem, NH).

Fecal extraction. Fecal samples were air-dried for 5 days and extracted in methanol-KOH (300 mM) at 60°C for 24 h. Fecal extract was then mixed with 150 mM MgSO4 (1:1). After centrifugation, the supernatant was saved and submitted for bile acid and NEFA measurement as described above.

Tissue gene expression. All tissue samples were collected as described above and immediately frozen in liquid nitrogen and then stored at −80°C. Total RNA was isolated using an RNasey Mini Kit (Qiagen). The RNase Free DNase Set (Qiagen) was used to remove DNA contamination. Cleaned total RNA was reverse transcribed using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA). Quantitative PCR was performed and analyzed using a 384 format, ABI 7900HT Sequence Detection System (Applied Biosystems) with gene-specific primers and probes that were reported previously (9). The expression level was normalized for a group of housekeeping genes.

Data analysis. All studies described above were analyzed as described in this paragraph. Values are given as means ± SE. The data were analyzed in JMP 7.0.0 (SAS Institute, Cary, NC) using one-way ANOVA with prespecified contrasts to compare each group to the appropriate control group. P values < 0.05 were considered to indicate a significant difference between treatment groups. Dose responses were fitted to four-parameter logistic functions (GraphPad Prism v. 5.04, San Diego, CA).

RESULTS

Changes in fecal bile acid excretion and plasma bile acid concentrations. Oral administration of 264W94 dose-dependently increased bile acids in the feces. Fecal bile acid concentrations were elevated up to 6.5-fold with an ED50 of 0.15 mg/kg compared with vehicle-treated rats (Fig. 1A). Fecal NEFA also slightly increased in 264W94-treated rats (Fig. 1B). In contrast, plasma bile acid concentrations were decreased dose-dependently in 264W94-treated rats (Fig. 1C).

Effects of 264W94 on glycemic control in ZDF rats. All groups of ZDF rats had comparable levels of plasma glucose, insulin, and blood Hb A1c prior to the start of treatment (Fig. 2, A, C, and E). The average baselines plasma glucose and Hb A1c in ZDF rats were 327 ± 13 mg/dl and 4.8 ± 0.04%. As illustrated in Fig. 2A, during the 2-wk study, the vehicle-treated rats showed a marked progressive hyperglycemia with plasma glucose and Hb A1c reaching 522 ± 28 mg/kg and 7.2 ± 0.2%, respectively. In contrast, plasma glucose in 264W94-treated rats was reduced dose-dependently compared with the vehicle-treated group. The efficacious doses of 264W94 (0.1 mg/kg and above) reduced plasma glucose concentrations below the baseline level (Fig. 2, A and B). Hb A1c measured at the end of 2-wk treatment showed a dose-dependent decrease compared with vehicle-treated group (Fig. 2, C and D). Baseline insulin (Fig. 2E) and proinsulin (data not shown) concentrations were similar across the treatment groups. The vehicle-treated rats showed a marked decrease in plasma insulin levels. Although the plasma concentration of proinsulin (data not shown) did not change in vehicle-treated animals, the proinsulin/insulin ratio increased (Fig. 2F), indicating β-cell dysfunction over the course of the study. Treatment of 264W94 prevented the decline of insulin dose-dependently without an increase in proinsulin levels.

To explore potential mechanisms of Asbt inhibition-induced glycemic control, steady-state nonfasting plasma total Glp-1 was measured at the beginning and on day 7 and day 14 of study 1. As shown in Fig. 2, G and H, treatment with 264W94...
resulted in an elevation of plasma total Glp-1 in a dose-dependent manner. Plasma total Glp-1 increased up to 50% at the doses of 1 and 10 mg/kg compared with the vehicle group. At 0.1 mg/kg, 264W94 significantly decreased blood glucose and Hb A1c in ZDF rats (Fig. 2, A and B) but had minimal effects on steady-state nonfasting plasma total Glp-1 (Fig. 2, G and H). To explore whether 264W94 at 0.1 mg/kg could improve postprandial dynamic Glp-1, an OGTT was performed at the end of study 1.

Responses of plasma glucose, insulin, and total glp-1 during OGTT. To further investigate dynamic mechanisms for Asbt inhibition-induced improvement of glucose homeostasis, we performed an OGTT in three treatment groups: vehicle and 0.1 and 10 mg/kg of 264W94 after 3 wk of treatment. Both 264W94-treated groups showed significantly lower fasting blood glucose than the vehicle group (Fig. 3A). The 264W94-treated rats also showed a trend of reduced postprandial glucose excursion (Fig. 3, A and B). Glucose-stimulated insulin and total Glp-1 secretion was significantly enhanced with 264W94 treatment at both 0.1 and 10 mg/kg doses (Fig. 3, C–F).

Changes in intestinal and hepatic gene expression. To further explore potential mechanisms for 264W94-mediated antidiabetic effects, in a separate study (study 2), we examined the expression of a group of genes in the liver and intestines of ZDF rats following treatment with 264W94 for 5 wk. Consistent glucose-lowering effects were observed through the entire study duration in 264W94-treated ZDF rats (data not shown). Treatment with 264W94 had no significant effects on Fxr expression in the intestines (Fig. 4A). Hepatic Fxr mRNA was lower in ZDF rats than in lean controls and was upregulated by the treatment of 264W94 (Fig. 4A). However, hepatic small heterodimer partner (Shp) expression was reduced in 264W94-treated rats (Fig. 4B). The expression of Shp mRNA was also decreased in duodenum, jejunum, and ileum but was slightly increased in the ascending colon with 264W94 treatment (Fig. 4B). ZDF rats had reduced mRNA levels of Tgr5 in duodenum and jejunum compared with the lean controls, and 264W94 tended to further reduce the expression of Tgr5 in the small intestines but slightly increased Tgr5 mRNA levels in the large intestines (Fig. 4C). Expression of preglucagon was increased in jejunum but decreased in the distal colon with 264W94 treatment (Fig. 4D). Although not statistically significant, treatment with 264W94 lowered the expression of two major gluconeogenic enzymes, G6pc and phosphoenolpyruvate carboxykinase (Pepck) (Fig. 4, E and F) in the liver but not the intestines. The expression of fibroblast growth factor (Fgf)15 was mainly restricted to the ileum. ZDF rats had significantly lower Fgf15 expression in the ileum compared with the lean controls, and 264W94 had no effect. Although Fgf15 mRNA was barely detectable in the ascending colon of ZDF and Zucker lean control rats, 264W94 slightly but significantly increased Fgf15 expression in the first part of the colon (Fig. 4G).

Assessment of the role of Fxr in the antidiabetic efficacy of 264W94. The decreased expression of Shp in the small intestine and the liver of 264W94-treated rats suggested reduced Fxr activity. We explored whether the reduction of Fxr activity contributed to 264W94-induced glycemic control by coadministration of GW4064, a potent Fxr agonist (study 3). Treatment of 264W94 (1 mg/kg) lowered blood glucose in all treated rats within 2 days, and that effect was not attenuated by adding GW4064 (30 mg/kg) as a cotreatment (Fig. 5).

DISCUSSION
The present study is the first to report an antidiabetic effect of a potent inhibitor of ileal bile acid transport (ASBTi). The progressive dysglycemia characteristic of ZDF rats, as reflected by nonfasting plasma glucose and Hb A1c measurements, was dose-dependently arrested and partly normalized with chronic oral administration of 264W94.

In contrast to the characteristic (13) progressive insulin decline in vehicle-treated ZDF rats, suggestive of B-cell failure, the effects of 264W94 on glycemic control were associated with dose-dependent preservation of plasma insulin concentration. Similarly, elevated proinsulin/insulin ratios [indicative of reduced insulin-secretory capacity, relative to demand (31)] were dose-dependently normalized with 264W94. In addition, treatment with 264W94 also dose-dependently elevated nonfasting plasma total Glp-1 concentrations. Our preliminary data suggested that it was not a direct effect of the compound on enteroendocrine L cells, because Asbt was not expressed in GLUTag and STC-1 cells and 264W94 (up to 10
mg/kg) did not induce Glp-1 release in fasted rats (unpublished data).

Dose-dependent effects on nonfasting concentrations of plasma glucose, insulin, and Glp-1 with 2-wk chronic 264W94 administration were mirrored during an oral glucose challenge. Reductions in post-challenge glucose profiles were associated with dose-dependent increases in insulin and total Glp-1 profile. These findings suggest a mechanistic association between

Fig. 2. Effects of 264W94 on plasma glucose, insulin, proinsulin, Hb A1c, and total glucagon-like peptide-1 (Glp-1). Male ZDF rats (n = 8) were administered vehicle or 264W94 (0.001, 0.01, 0.1, 1, and 10 mg/kg) twice a day for 2 wk. Plasma glucose (A), insulin (E), and total Glp-1 (G) and levels were monitored weekly. Blood Hb A1c (C) and plasma proinsulin (F) were measured before and at the end of 2 wk of treatment (C). The 2nd-wk dose response curves for glucose (B), Hb A1c (D), insulin (F), and total Glp-1 (H) were also presented. Data are expressed as means ± SE. *P < 0.05, **P < 0.01, ***P < 0.001 vs. vehicle group.
ASBTi-mediated stimulation of Glp 1, its recognized antidiabetic effects (including stimulation of insulin secretion) (3), and the antidiabetic effect observed in the present study. However, it is important to notice that the increase of plasma Glp-1 after 264W94 treatment was significantly smaller compared with pharmacological treatment with Glp-1 analogs/mimetics. This may suggest that nutrient-induced incretin release and its effect on glucose metabolism can act through certain local gastrointestinal mechanisms that are different from those of exogenous Glp-1 analogs/mimetics. In a recent study, Waget et al. demonstrated the local importance of endogenous incretins by inhibiting dipeptidyl peptidase IV only in the gastrointestinal system (39). The fact that at 0.1 mg/kg, an efficacious dose for glucose lowering, 264W94 only increased nutrient stimulated dynamic elevation but not the steady-state plasma Glp-1 also suggested that timing could be an important factor for the glucose-lowering effect of endogenous Glp-1. Although 264W94 was a systemically available compound, we were confident that the antidiabetic effect originated from its inhibition on Asbt within the intestine for the following reasons. First, 264W94 was at least 100-fold more potent for Asbt vs. the hepatic Na⁺-taurocholate cotransporting polypeptide (Ntcp, unpublished data). In addition, we also tested other luminal restricted Asbt inhibitors (~100% fecal recovery of compounds) and obtained essentially the same glucose-lowering efficacy as 264W94 (unpublished data). Asbt inhibitors block enterohepatic recirculation and deliver more free bile acids into the colon. An effect of bile acids on stimulating Glp 1 secretion is supported by several lines of evidence. In the 1980s, before the therapeutic significance of Glp-1 was understood, intraluminal application of bile acids into distal intestine stimulated the secretion of gut glucagon-like immunoreactive materials (enteroglucagon, corresponding to Glp-1) in dogs (25, 26) and healthy human subjects during colonoscopy (1). These findings were affirmed in isolated rabbit colon (4) and rat colon preparations (28). Recently, rectally administered taurocholate stimulated vigorous release of peptide YY and Glp 1 in T2D patients in association with increases in insulin and lowering of glucose that surpassed effects reported for injected Glp 1 agonists (2). In addition to direct stimulatory effects, our unpublished preliminary data also suggested that bile acids might potentiate nutrient-induced Glp-1 release, consistent with a recent report (30).

How bile acids induce Glp-1 release from enteroendocrine L cells is not clear. Katsuma et al. (17) have reported that bile acids stimulated Glp-1 secretion in a murine enteroendocrine cell line,
Fig. 4. Eight-week-old male ZDF rats were randomized on fed glucose and assigned to vehicle or 1 mg/kg bid 264W94 groups. A group of age-matched Zucker lean control rats was also included in the study. All animals were monitored for 5 wk. Treatment with 264W94 decreased serum glucose and blood Hb A1c through the study (data not shown). At the end of the study, intestinal and liver tissues were collected in the fed state, and mRNA expression of selected genes was determined using RT-qPCR. Expression level was normalized for a group of housekeeping genes. Data are expressed as means ± SE. *P < 0.05, **P < 0.01, ***P < 0.001 vs. ZDF vehicle group.
STC-1, via Tgr5 signaling. Using a synthetic bile acid-derived Tgr5 agonist, Thomas et al. (37) confirmed the Tgr5-dependent Glp-1 stimulatory effect both in vitro and in vivo. In a recent study, Parker et al. (27) demonstrated that Tgr5 is a molecular mechanism for bile acid-induced Glp-1 release in L cells. Chronic treatment of ZDF rats with 264W94 tended to decrease Tgr5 expression in jejunum but increase its expression level in the ascending colon. Yet, in OGTT of the present study, the fact that plasma Glp-1 increased within 5 min after glucose administration suggested an L cell-potentiating effect of bile acids. More studies are needed to demonstrate that Tgr5 agonism can both directly stimulate and modify nutrient-induced Glp-1 secretion from L cells or that additional bile acid-related mechanisms other than Tgr5 were involved in Asbt inhibition-mediated glucose-lowering efficacy. In addition to functionally stimulating Glp-1 release, inhibiting Asbt might also change the total number of L cells or the expression of proglucagon in enteroendocrine cells. While preliminary histology results did not suggest a clear increase in Glp-1-positive cells in the intestine (data not shown), mRNA analysis indicated an increase of proglucagon expression only in the jejunum. More studies are needed to determine the significance of that change.

Fxr, a nuclear receptor for bile acids, is also highly expressed in the intestine, especially in the ileum and ascending colon. Treatment with 264W94 decreased Fxr activity (as measured by Shp expression) in the duodenum and the jejunum but might have increased Fxr activity in the ascending colon (as measured by Shp and Fgf15 expression). However, administration of GW4064, a potent Fxr agonist, directly into the proximal colon did not induce Glp-1 release (data not shown). Fgf19 is a member of the fibroblast growth factor (FGF) family, and Fgf15 is the rodent ortholog of human FGF19. Bile acids stimulate Fgf19/15 release from ileum by an Fxr-dependent transcription mechanism (34). Transgenic mice expressing human Fgf19 displayed increased metabolic rate and decreased adiposity (38) and exogenous Fgf19 increased metabolic rate and reversed dietary and leptin-deficient diabetes (15). Fgf15, predominantly expressed in rat ileum, was significantly downregulated in ZDF rats and was not increased by treatment with 264W94. Although there was a significant increase of Fgf15 mRNA in the ascending colon of 264W94 treated ZDF rats, the magnitude was very modest compared with the normal level in the ileum. We consider it improbable that antidiabetic effects of Asbt inhibition were mediated via circulating Fgf15 in the current study.

Although Fxr agonism may decrease serum glucose by reducing the expression of hepatic gluconeogenesis genes and hepatic lipogenesis in multiple animal models (7, 21, 36, 42), hepatic Fxr activity, as measured by expression of Shp, was decreased by 264W94 in the current study. A recent study by Prawitt et al. (29) demonstrated that Fxr deficiency improved glucose homeostasis and insulin sensitivity in a genetically obese mouse model, and that effect was independent of bile acid-mediated pathways. Since the reduced Fxr activity observed in our study was a consequence of decreased bile acid stimulation, it was unlikely that the hypoglycemic effect of Asbt inhibition could be explained by Fxr “deficiency”. Furthermore, an Fxr agonist, GW4064, did not affect the antidiabetic effect of Asbt inhibition.

Overall, further studies are needed to understand how Asbt inhibition improves glucose metabolism, which may include mechanisms within and out of the gastrointestinal tract and are Glp-1 dependent or Glp-1 independent (30). Our unpublished preliminary results also suggest that Asbt inhibition may affect plasma and fecal bile acid composition and release of gastrointestinal hormones, nutrient absorption (e.g., NEFA) and have potential effects on gut microbiota, all of which may have an impact on glucose metabolism (10, 41). Previously, we reported similar antidiabetic effects of a BAS, cholestyramine, in ZDF rats. Since both bile acid sequestration and Asbt inhibition increased the presence of the bile acids in the distal intestine, they might share similar mechanisms for their antidiabetic efficacy. In a recent paper, Shang et al. (33) reported that colesvelam (a BAS) had an effect on a glucose tolerance test but not SC-435, an Asbt inhibitor. In contrast to the present study, Shang et al. did not assess the effects of or dose dependency of SC-435 on increasing intraluminal (or fecal) bile salt concentrations. They surmise in their discussion that they may not have achieved sufficient luminal concentrations to evoke an effective L cell response. Another notable difference is that their animal model, a diet-induced obesity (F-DIO) rat, was not a true diabetic animal model. In addition, differences in dosing regimens (oral gavage vs. food supplement) might also have an impact on outcomes.

In summary, we describe inhibition of Asbt as a potential novel pharmaceutical approach for glycemic control in T2DM. This approach is possible with agents that remain within the gut lumen, thereby posing a reduced risk of systemic toxicity. Since inhibition of Asbt also reduces low-density lipoprotein cholesterol (LDL-C) (13), it may convey a dual benefit, controlling both hyperglycemic and hypercholesterolemic cardiovascular risk in T2DM patients.

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DISCLOSURES

AUTHOR CONTRIBUTIONS


REFERENCES


AUTHOR CONTRIBUTIONS


