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Isomaltulose Enhances GLP-1 and PYY Secretion to a Mixed Meal in People With or Without Type 2 Diabetes as Compared to Saccharose

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Scope: Secretion of the gut hormones glucagon-like peptide (GLP-1) and peptide YY (PYY) are induced by nutrients reaching the lower small intestine which regulate insulin and glucagon release, inhibit appetite, and may improve β-cell regeneration. The aim is to test the effect of a slowly digested isomaltulose (ISO) compared to the rapidly digested saccharose (SAC) as a snack given 1 h before a standardized mixed meal test (MMT) on GLP-1, PYY, glucose-dependent insulinotropic peptide (GIP), and metabolic responses in participants with or without type 2 diabetes (T2DM).

Methods and results: Fifteen healthy volunteers and 15 patients with T2DM consumed either 50 g ISO or SAC 1 h preload of MMT on nonconsecutive days. Clinical parameters and incretin hormones are measured throughout the whole course of MMT. Administration of 50 g ISO as compared to SAC induced a significant increase in GLP-1, GIP, and PYY responses over 2 h after intake of a typical lunch in healthy controls. Patients with T2DM showed reduced overall responses of GLP-1 and delayed insulin release compared to controls while ISO significantly enhanced the GIP and almost tripled the PYY response compared to SAC.

Conclusion: A snack containing ISO markedly enhances the release of the metabolically advantageous gut hormones PYY and GLP-1 and enhances GIP release in response to a subsequent complex meal.

1. Introduction

The gut-derived incretins glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP-1) regulate insulin and glucagon release in response to nutrient intake. Their beneficial effects are well-established in the treatment of type 2 diabetes (T2DM).[1] Moreover, GLP-1 receptor agonists and GIP/GLP-1 co-agonists have become an important treatment option in T2DM,[2,3] and obesity.[4]

The peptide YY (PYY) is co-produced and co-secreted with GLP-1 by L-cells in the distal small intestine and also in the colon.[5] Upon release, PYY[1–36] is converted by dipeptidyl peptidase-4 (DPP-4) and generates PYY.[3–36] The more distal small intestinal L-cells appear to secrete the majority of PYY compared to more proximal L-cells.[6,7] Short-chain fatty acids (SCFA) are the most potent inducers of PYY gene expression and secretion which involve inhibition of histone deacetylases, and to a minor extent, activation of fatty acid receptor 2

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(FFAR2) in human cell lines but not in mice.[8] PYY inhibited appetite and reduced body-weight gain in obese subjects by acting on the gut-brain axis and was investigated for the treatment of obesity[9,10] although controversial data have been published.[11] PYY also activates neuropeptide Y1 receptors (NPYR1) which are present in beta-cells.[12] The deletion of PYY-producing cells impaired beta-cell regeneration and proliferation suggesting an important role of PYY in the maintenance of intact islets.[13] Recent studies also provided evidence that PYY-receptors on islet cells promote transdifferentiation of alpha- and beta-cells.[14] The endogenous release of GLP-1, and PYY is mediated by a variety of stimuli including bile acids, fat, protein, and short-chain fatty acids resulting from the degradation of fibers including resistant starch and slowly cleavable carbohydrates.[15] In addition, glucose increases the release of GLP-1 if it reaches the small intestinal L-cells.[7]

The disaccharide isomaltulose (ISO) is characterized by a slow, yet full hydrolysis in the small intestine which contributes to its low-glycemic properties (16–18). Saccharose (SAC) has a 1,2-glycosidic bond which is rapidly cleaved by intestinal α-glucosidase enzymes while ISO with an α-1,6 linkage is more resistant toward enzymatic breakdown. Previous studies showed that ISO significantly enhanced GLP-1 and PYY-secretion compared to SAC in humans, while the release of GIP was reduced.[19–21] However, it is unknown whether ISO increases PYY release when consumed with a meal as might be expected upon stimulation of the more distal L-cells.

This study is aiming to investigate whether ISO increases the release of PYY in addition to GLP-1 when consumed as a snack before a standardized mixed meal as compared to SAC. Moreover, we compared controls with T2DM patients who may have impaired responses of incretins.[6] We therefore recruited patients with T2DM and healthy participants as controls.

2. Experimental Section

2.1. Ethics

The protocol and all amendments of this prospective, randomized, double-blind, controlled nutritional intervention study were approved by the Ethics Committee of the Charité Universitätsmedizin, Berlin, and conducted in accordance with the Declaration of Helsinki. It was carried out in the Department of Clinical Nutrition at the German Institute of Nutrition (DIfE). The trial was registered at Clinical Trials.gov (No. NCT03806920).

Table 1. Baseline clinical characteristics and fasting circulating concentrations for all participants.

Characteristics	Control	T2DM	p value
male:female	9:6	8:7	0.84
Age [years]	59 ± 10	70 ± 7	0.06
BMI [kg m^{-2}]	32.3 ± 4.1	30.0 ± 3.6	0.96
waist-to-hip ratio	0.96 ± 0.07	0.96 ± 0.08	0.31
Fat mass [%]	38.9 ± 7.2	37.3 ± 6.4	0.47
Fat-free mass [%]	61.1 ± 7.2	62.7 ± 6.2	0.55
HbA1c [%]	5.6 ± 0.14	6.9 ± 0.28	<0.01**
HOMA-IR	2.9 ± 0.22	4.7 ± 0.48	<0.001***
Fasting glucose [mmol L^{-1}]	5.8 ± 0.49	8.0 ± 1.6	<0.001***
Fasting insulin [pmol L^{-1}]	60.9 ± 23.0	72.0 ± 43.1	0.43
Fasting C-peptide [pmol L^{-1}]	2.0 ± 0.36	2.3 ± 0.97	0.007**
Fasting GLP-1 [pg m^{-1}]	2.1 ± 2.2	1.2 ± 0.88	0.38
Fasting GIP [pg mL^{-1}]	80.1 ± 41.4	66.9 ± 41.0	0.09
Fasting PYY [pg mL^{-1}]	80.9 ± 5.5	97.5 ± 7.4	0.08

HbA1c, glycated haemoglobin A1c; BMI: body mass index; HOMA-IR: homeostatic model assessment of insulin resistance; GIP: glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; PYY: peptide YY. Data are described as mean values ± SD, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

2.2. Study Design and Participants

Fifteen healthy volunteers and 15 orally treated patients with T2DM were recruited in this study. Oral glucose tolerance tests (OGTT) administering 75 g of glucose were performed to confirm normal glucose tolerance for controls. The characteristics of all subjects for two groups are presented in **Table 1**. Patients with insulin therapy or other medications which might affect glucose metabolism, malignant diseases, serious cardiovascular disease, heart attack or stroke less than 6 months ago, or serious diabetic complications were excluded in this study. Patients with T2DM were required to discontinue oral-antidiabetic medications one week before participation. All participants provided written informed consent prior to the study.

The study design is presented in **Figure 1** and the CONSORT flow diagram is shown in Figure S1, all subjects received the first mixed meal test (MMT-1) at 8:00 in the morning followed by the second mixed meal test (MMT-2) at 12:00 with 1 h preload at 11:00 of either 50 g ISO (isomaltulose/Palatinose, BENEO, GmbH, Mannheim, Germany) or SAC (saccharose/sucrose, Sudzucker, Mannheim, Germany) in the form of a citrus drink (500 mL). The drinks were comparable in appearance, taste, and sweetness, and were provided as encoded (blinded) portions. Visits were conducted on non-consecutive days. The compositions of both MTTs are presented in **Table 2**. On each clinical investigation day, a catheter was placed in a forearm vein wrapped in a heating pad for sampling of arterialized blood. Blood samples were drawn twice at fasting state (-15 and 0 min) and then 15, 30, 60, 90, 120, 180, 195, 210 and 240 min after MMT-1, following

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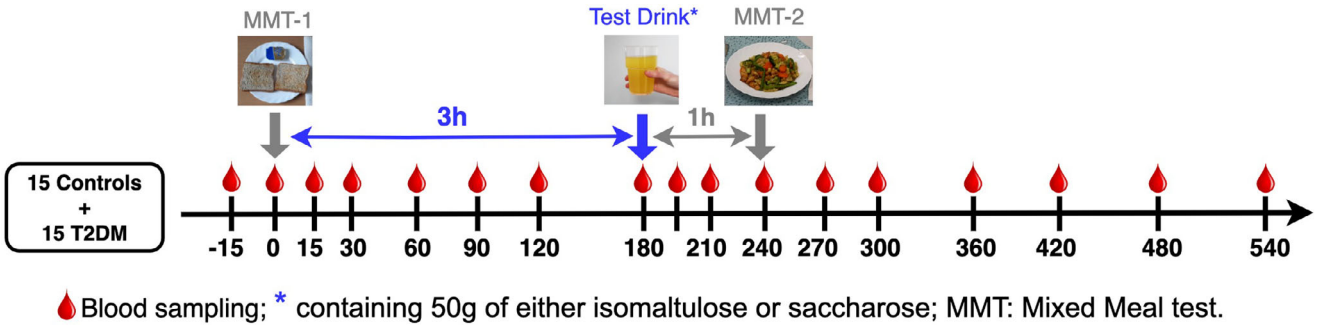

Figure 1. The overview of study design.

by 15, 30, 60, 90, 120, 180, 195, 210, 240 and 300 after either 50 g ISO or SAC preload in order to capture time-course changes of hormones (Figure 1). The blood was collected into prechilled EDTA tubes containing DPP-4 inhibitor (2.5 mM, Merck Millipore) for measurements of GIP, GLP-1, and PYY and into EDTA tubes for analyzing insulin, C-peptide as well as routine clinical parameters. Immediately after the blood collection, serum samples were clotting for 10 min at room temperature while plasma samples containing EDTA or/and DPP-4i were centrifuged immediately for 10 min at 4°C. The supernatant was collected after centrifuging and stored at −80°C for further analysis.

2.3. Biomarkers

Blood glucose concentrations were measured with a glucometer (Optium Xceed; Abbott Laboratories, Illinois); clinical routine parameters were measured with ABX Pentra 400 (HORIBA). Total as well as percentage fat mass and fat free mass were determined using Air Displacement Plethymography (BOD POD, Body Composition System; Life Measurement Instruments, Concord, CA). Plasma GLP-1 and GIP were detected by an electrochemiluminescent method (Meso Scale Discovery, Gaithersburg, MD); plasma PYY was measured using ELISA (Millipore, Billerica, MA, USA); insulin and C-peptide were measured by ELISA immunoassay (Mercodia, Uppsala, Sweden).

2.4. Calculations and Statistical Analysis

Mean fasting concentrations (glucose, insulin) were calculated as the mean of the two fasting samples. HOMA-IR was calculated based on fasting insulin and fasting glucose as described before.[22] Incremental area under time-concentration curves (iAUC) were calculated by the trapezoidal rule. MMT1: iAUC (0-180) 3 h after MMT1; MMT2: iAUC (180–540), i.e., up to 6 h after ISO or SAC preload (given at t = 180) and the test meal (consumed at t = 240 min).

The distribution of variables was evaluated by Shapiro–Wilk test. For the analysis of the difference between different time-points, the repeated measure ANOVA (rmANOVA) was performed using the Greenhouse–Geisser correction if sphericity was not given. Comparisons between the interventions were performed using paired *t*-test or Wilcoxon test depending on distribution. To compare the patient groups either Mann–Whitney *U* test or student's unpaired t-test was used depending on the distribution of data. Results are described as Mean ± SD in tables, statistical significance is defined as $p < 0.05$. All statistical calculations were performed using SPSS 28.0 (SPSS Inc, Chicago, IL, USA). The graphs were generated by GraphPad prism 9 (California, USA) and R Studio 4.2 (Germany).

Table 2. Nutrient composition of mixed meal tests and test drinks (ISO and SAC).

	Quantity [g]	Energy [kcal]	CH [g]	F [g]	P [g]	Fiber [g]
Dinner on the evening before						
Chicken meal (Frosta)	500	520	62.0	14.0	32.5	7.5
MMT-1 – breakfast fixed component						
Toast whole grain (REWE)	50	128	24.0	2.0	4.0	1.5
Butter (Meggle)	17	126	0.0	14.0	0.1	0.0
Total	67	254	24.0	16.0	4.1	1.5
MMT-2 – lunch fixed component						
"Spätzl'e"meal (Frosta)	500	530	65.0	14.0	33.0	9.0
Olive oil (Henry Lamotte)	15	133	0.0	15.0	0.0	0.0
Total	515	663	65.0	29.0	33.0	9.0
Test Drink – served 3h after breakfast						
Citrus drink (BENEO)	400	202.5	50.0	0.0	0.0	0.0

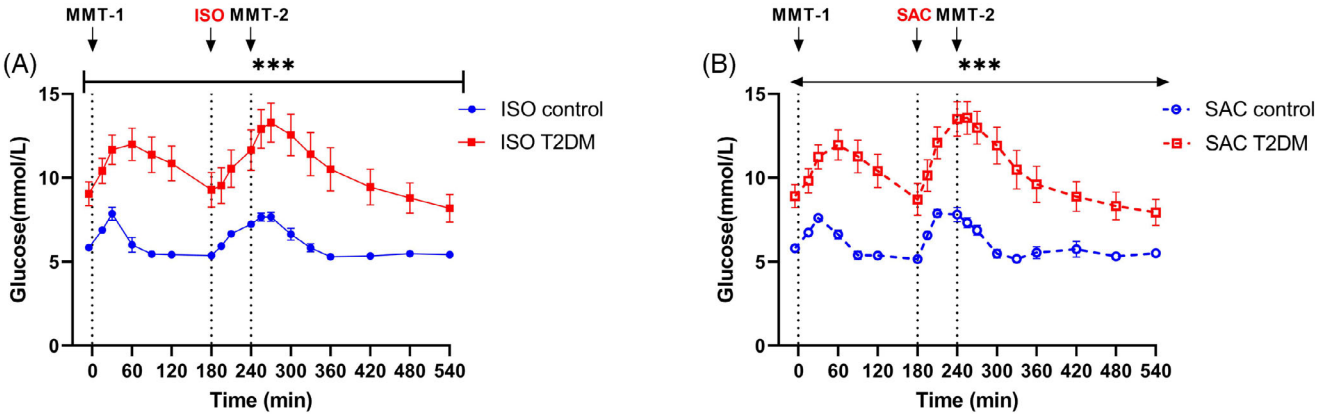

Figure 2. Glucose responses to MTTs with ISO (solid line) and SAC (dotted line) preload in controls (blue) and patients with T2DM (red). Data are described as Mean ± SEM, *** There was significant difference betwe6en two groups before and after both ISO/SAC preload at all time-points ($p < 0.001$).

3. Results

Fifteen controls (age 59.4 ± 10.1 years) and 15 subjects with T2DM (age 70.2 ± 6.7 years) completed the study. Baseline characteristics of each group are shown Table 1. Fasting glucose, HbA1c, and C-peptide were significantly higher in T2DM patients than controls.

3.1. Blood Glucose, Insulin Responses

3.1.1. Blood Glucose

In control subjects, SAC preload caused a rapid and 50% greater increase in glucose compared to ISO ($p < 0.01$) (**Figure** 2A, Table S1), reaching its peak at 210 min and then steadily declining. ISO had a less steep rise and decreased continuously after 270 min and formed a plateau until the end of MMT-2 (Figure 2A and B, Table S1, supporting information).

In T2DM subjects, the basal glucose levels were elevated significantly and there was a more extended increase in glucose in response to both sugars in the first 60 min. After SAC preload, glucose rose continuously and reached a maximum at 240 min and decreased thereafter, while ISO showed a similar response as in controls. SAC showed a significant increase in glucose in the first 30 min in controls but not in T2DM subjects (Figure S2A and S2B, Table S1, supporting information). There were no remarkable differences were found for iAUC MMT1 (0-180 min) as well as iAUC MMT-2 (180-540 min) within both groups after both ISO/SAC preload (Figure S2C and S2D).

3.1.2. Insulin

MMT-1 stimulated insulin release to reach the peak value at 30 min in controls and then returned to baseline in both tests as expected (**Figure** 3A and B, Table S2, supporting information). The SAC preload increased insulin significantly stronger than ISO. MMT-2 led to a further significant stimulation of insulin release with both sugars and was prolonged by 15 min with ISO compared to SAC. After that, the SAC curve initially dropped faster towards the end. These results are reflected in a significant and more than 2-fold higher absolute insulin concentration for MMT-2 compared to ISO (Figure S3A, Table S2).

In T2DM, both MMT-1 and MMT-2 with SAC/ISO preload resulted in a lower and delayed insulin release compared to controls (Figure 3A and B). After 60 min, the insulin concentration reached the peak and dropped constantly until 180 min. Compared to ISO, SAC induced a relatively steeper and faster increase of insulin release from 180 to 240 min (Figure S3B, Table S2). After MMT-2, the further increase in insulin release was more rapid with SAC than with ISO (Figure S3B, Table S2). Both ISO and SAC preload induced significantly more insulin release in T2DM compared to controls ($p = 0.047$ and $p = 0.011$, respectively) (Figure 3C and D).

3.2. Incretin Hormones Responses (GLP-1, GIP, and PYY)

3.2.1. GLP-1

The concentration of GLP-1 increased rapidly approximately 2.5-fold after MMT-1 in the first 15 – 30 min in both groups, followed by a decrease until 60 min with a plateau to 180 min (**Figure** 4A). As expected, MMT-1 showed no differences between the tests and also revealed no differences between controls and T2DM patients (Figure 4C, Table S3 and S4C, supporting information). The preload with ISO at 180 min produced significantly greater increases of GLP-1 than SAC at 255 min in both groups (Figure S4A, supporting information). Unfortunately, the blood samples from 180 – 240 min did not contain DPP-4 inhibitors and did not yield reliable incretin values. However, GLP-1 remained at much higher levels in both groups after ISO compared to SAC in the MMT-2 (Figure S4A and S4B, supporting information). Calculation of the iAUC GLP-1 (180 – 540 min) confirmed a significantly greater release of GLP-1 after ISO versus SAC throughout MMT-2 only in controls ($p < 0.01$) (Figure S4D). The GLP-1 responses to MMT-2 with both ISO and SAC preload were significantly more pronounced in controls than in diabetes patients ($p = 0.047$ and $p = 0.021$, respectively) (Figure 4C and D).

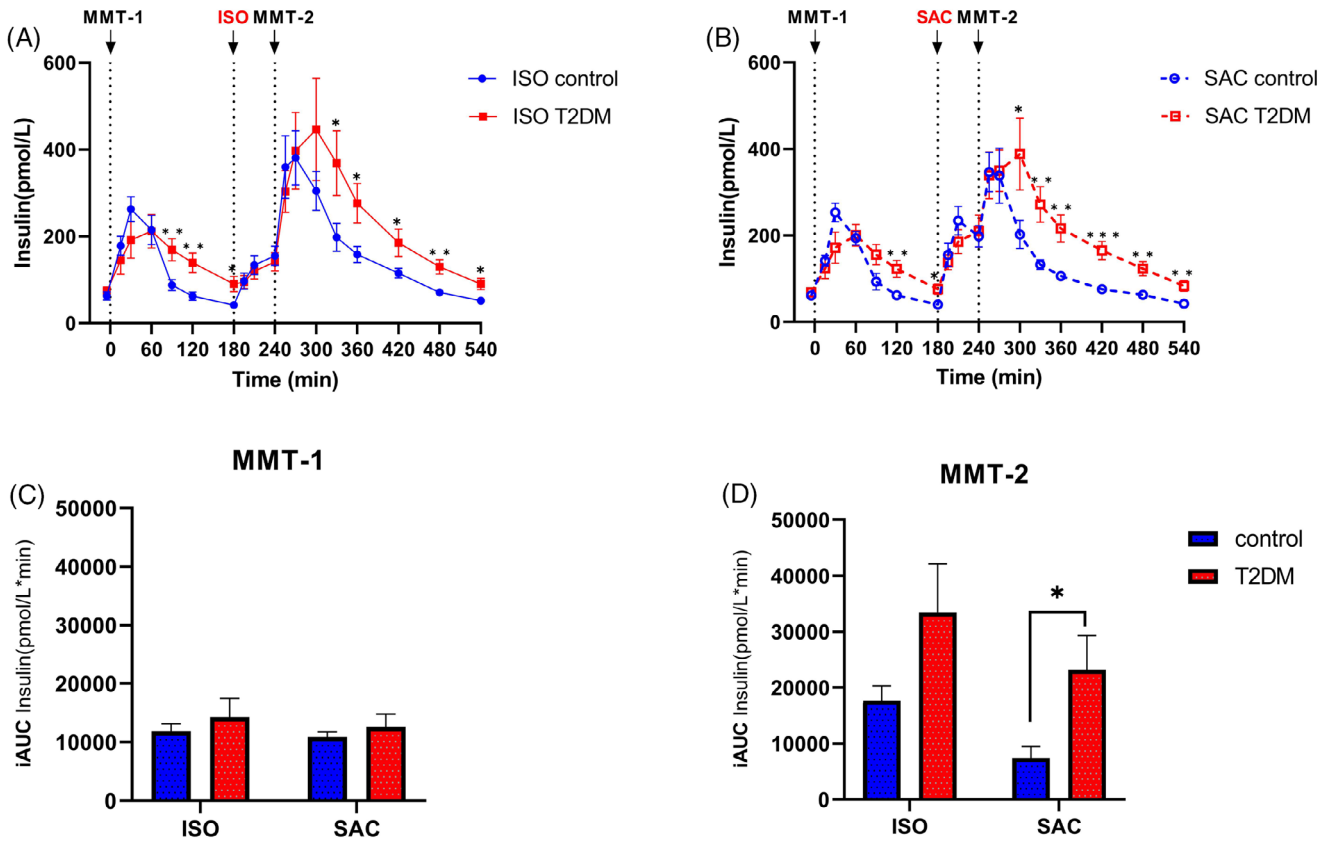

Figure 3. Insulin responses to MTTs with ISO (solid line, A) and SAC (dotted line, B) preload, and iAUC insulin to MMT-1 (0-180 min, C) and ISO/SAC preload with MMT-2 (180-540 min, D) in controls (blue) and patients with T2D (red). Data are described as Mean ± SEM, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

3.2.2. GIP

MMT-1 induced a rapid increase of GIP secretion peaking at 30 min in both groups followed by decrease until 180 min (**Figure** 5A and B, Table S4, supporting information). The SAC intake at 180 min produced only slightly greater increases of GIP than ISO in controls while T2DM patients showed a large difference with minimal stimulation of GIP after ISO and a pronounced rise after SAC. MMT-2 then induced a similar maximal increase of GIP in both groups. However, the increase of GIP was delayed in T2DM patients compared to sucrose (Figure S5B, supporting information) and both groups showed a prolonged rise (Figure S5A and B, Table S4, supporting information). The overall response of GIP was significantly greater with ISO compared to SAC in MMT-2 in both groups from iAUC (180 – 540 min) (Figure S5A–S5D). However, there was no significant difference ($p = 0.76$) of the whole GIP responses which was calculated with iAUC GIP (180-540 min) in T2DM than in controls (Figure 5C and D).

3.2.3. PYY

PYY did not increase after MMT-1 in both groups. The intake of ISO or SAC at 180 min did not result in immediate responses of PYY (**Figure** 6A and B). However, there was a significant and more extended increase in PYY after the intake of MMT-2 with ISO versus SAC preload in both controls and patients with T2DM (Figure S6A and S6B, Table S5). This was confirmed by significantly greater iAUCs after ISO versus SAC in both groups ($p = 0.021$ and $p = 0.004$, respectively) (Figure S6C and S6D, supporting information). Levels of PYY were numerically higher in patients with T2DM than in controls ($p > 0.05$) which was independent from the sugar intake and observed in MMT-1 (Figure 6C and D).

4. Discussion

An enhanced release of GLP-1 and delayed release of GIP has been observed with the slowly digested ISO compared to the rapidly digested SAC[16,17,19–21]. The meta-analysis by Calanna and coworkers[23] described reduced responses of GLP-1 in meal tests in subgroups depending on HbA1c and age and had an I^2 of 79% indicating significant heterogeneity. In this study we extend previous data to the enhanced release of PYY induced by ISO in both control and T2DM subjects.

The L-cell derived hormone PYY has been attributed with important health promoting effects. PYY was associated with an inhibition of appetite involving central mechanisms in several animal and human studies either alone or in cooperation with

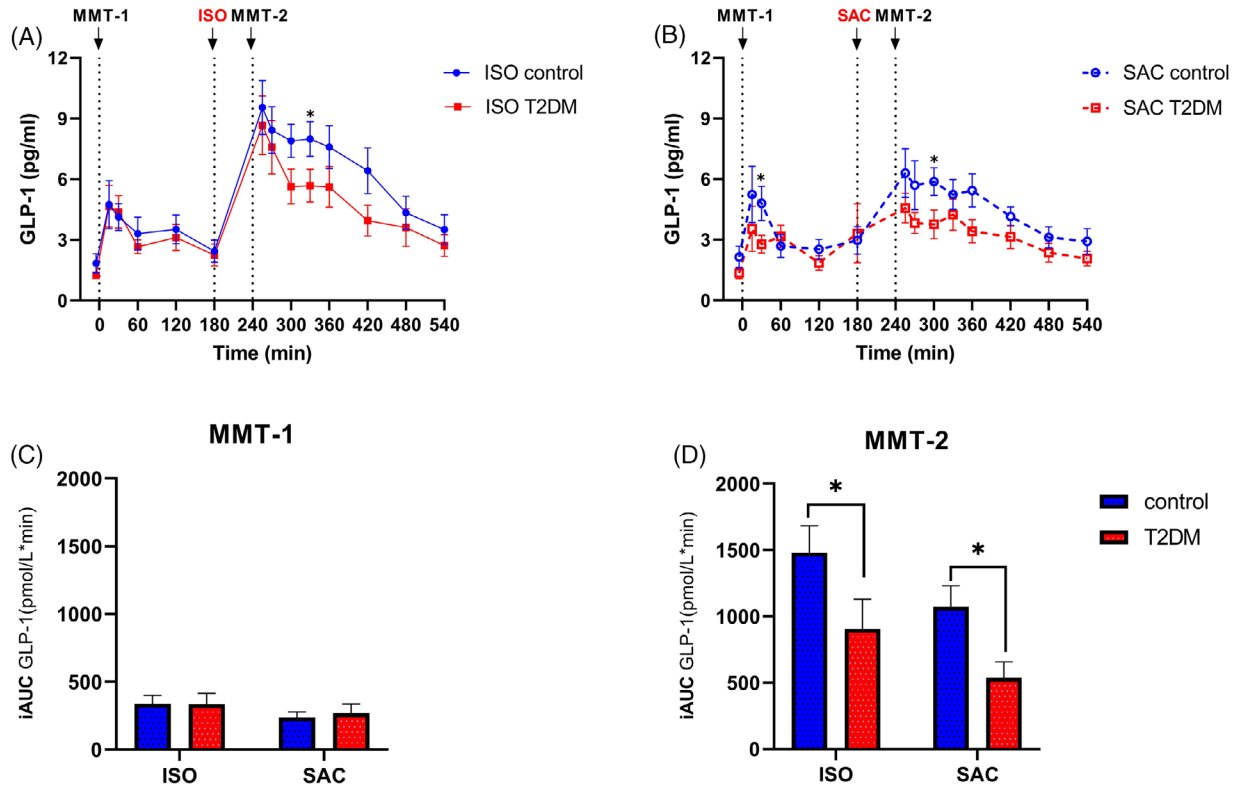

Figure 4. GLP-1 responses to MTTs with ISO (solid line, A) and SAC (dotted line, B) preload, and iAUC GLP-1 to MMT-1 (0-180 min, C) and ISO/SAC preload with MMT-2 (180-540 min, D) in controls (blue) and patients with T2DM (red). Data are described as Mean ± SEM, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

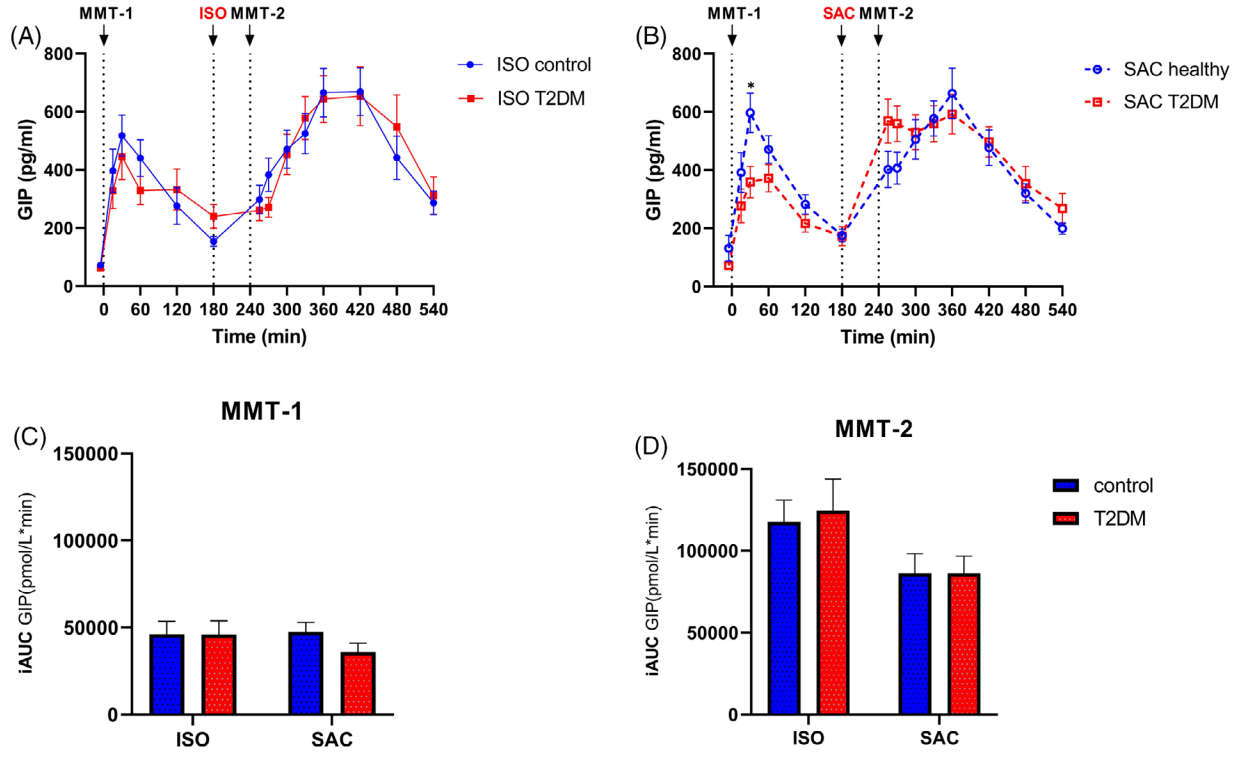

Figure 5. GIP-1 responses to MTTs with ISO (solid line, A) and SAC (dotted line, B) preload, and iAUC GLP-1 to MMT-1 (0-180 min, C) and ISO/SAC preload with MMT-2 (180-540 min, D) in controls (blue) and patients with T2DM (red). Data are described as Mean ± SEM, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

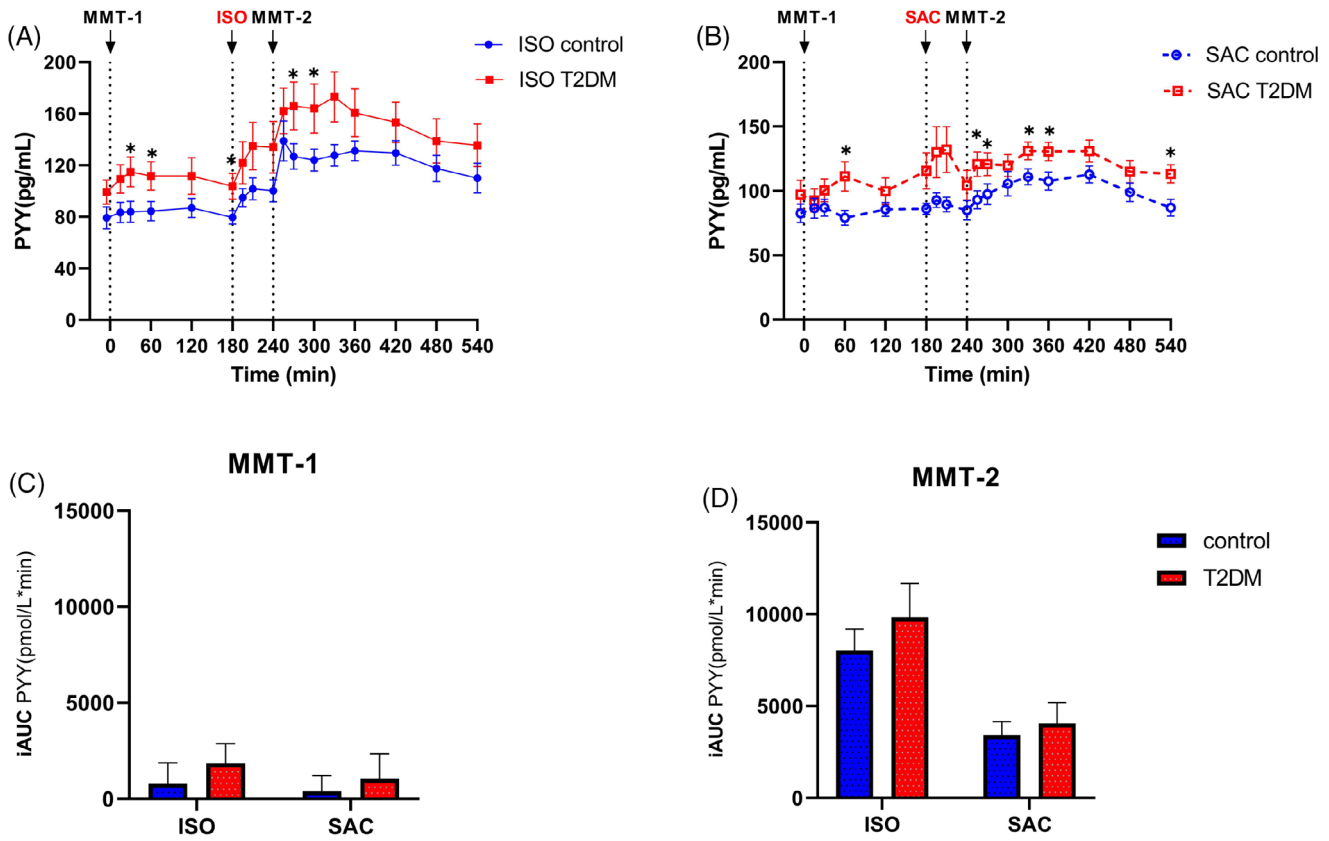

Figure 6. PYY responses to MTTs with ISO (solid line, A) and SAC (dotted line, B) preload, and iAUC PYY to MMT-1 (0-180 min, C) and ISO/SAC preload with MMT-2 (180-540 min, D) in controls (blue) and patients with T2DM (red). Data are described as Mean ± SEM, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

GLP-1.[9,24–26] Moreover, PYY was reported to improve beta-cell function and regeneration in animal models and humans.[12,27–29] This led to the development of foods being rich in short-chain fatty acid (SCFA) which particularly increase PYY and were shown to support weight loss in humans.[30–34] Our study adds ISO to foods promoting the release of PYY.

Our study also provides important information regarding the effect of ISO vs SAC in combination with complex meals which differ from those observed when supplied alone. First, the reduction of glucose due to the delayed uptake of ISO vs SAC is not apparent in complex meals in this study. Furthermore, ISO or SAC preload 1 h before a standardized meal does not lead to differences in glucose response to this standardized meal. The release of the incretin hormones GLP-1 and GIP was more strongly stimulated by ISO compared to SAC. This may explain the increased insulin secretion observed in T2DM patients and controls after ISO vs SAC. The increases of GLP-1 were greater in controls compared to T2DM after both ISO or SAC supporting a moderate impairment of GLP-1 responses in T2DM patients. Responses of GIP and PYY did not differ significantly between T2DM patients and healthy controls.

Regarding the mechanisms involved in the differential release of GIP, GLP-1 and PYY in response to nutrients both the location of the enteroendocrine cells and the nutrient receptors expressed on the cells in different locations of the intestine were shown to play a role.[7,29] The concept that ISO acts on more distally located enteroendocrine cells such as L-cells and bypasses the proximally located GIP producing K-cells was supported by comparing patients after bypass of the upper intestine by bariatric surgery with controls.[21] However, the increased release of GIP in the complex meal (MTT-2) indicates an interaction of the ISO preload with the subsequent GIP responses to the meal. Indeed, the increase of GIP after the ISO preload before the MTT-2 (180–240 min) was reduced compared to SAC as observed in previous tests with the isolated sugars. However, the subsequent stimulation of GIP by the MTT-2 containing fat, carbohydrates and protein, was significantly enhanced in both groups. Thus, a reduction of GIP is probably not achievable by using a 1 h preload with ISO prior to a complex meal.[17] The mechanisms involved remain unclear. GIP was shown to be colocalized with GLP-1 in a subpopulation of L-cells which may have been activated under these conditions.[7,29] With regard to nutrient stimuli involved, previous studies showed that glucose infusion activated duodenal L cells through Na^+ and Ca^{2+} channel activation in the human intestine or through glucose sodium-glucose cotransporter 1 (SGLT-1) in animal models and, thus increased plasma GLP-1 levels.[35,36] The fermentation of fiber to SCFA by gut microbiota was shown to provide a strong stimulus for the mRNA-synthesis and release of PYY and GLP-1 which involved the inhibition of HDACs.[8,33,37] In addition, free fatty acid receptors were shown to be involved in the release of all three intestinal hormones.[33] Although both GLP-1 and PYY are released from L-cells, the

kinetics of their release differed which is in line with a separate regulation of their release as reported previously.[38,39]

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

Stephan Theis is the employee of BENEO GmbH who revised the final version of the manuscript, with no intervention in the data analysis, statistical evaluation or final interpretation of the results of this study. The remaining authors have no conflicts of interest to declare.

Author Contributions

A.F.H.P. and M.K. conceptualized and designed this human intervention study. M.K. and O.P.R. performed the study and collected samples. S.R. and O.P.R. analyzed the data and performed laboratory analysis. J.D., D.S., and S.K. analyzed the data, generated tables and graphs and wrote parts of manuscript. D.T and AM ran the model to calculate insulin secretion rate (ISR) and revised the manuscript. A.F.H. P. conceived the studies, wrote the manuscript and supervised the studies. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data sets are available by request to the corresponding author.

Keywords

incretin hormones, isomaltulose, postprandial metabolism, saccharose, T2DM

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