



55th EASD Annual Meeting of the European Association for the Study of Diabetes

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Abstracts

Index of Oral Presentations

- OP 01 SGLT2 inhibitors: glucose and beyond
- OP 02 Looking ahead towards better treatments for type 1 diabetes
- OP 03 Addressing limitations of insulin therapy
- OP 04 Mechanisms of adaptation of insulin secretion
- OP 05 Monitoring risk and prognosis of peripheral diabetic neuropathy
- OP 06 Novel biomarkers of CVD in type 2 diabetes
- OP 07 Benefits of technologies in type 1 diabetes
- OP 08 Inflammation: new and old kids on the block
- OP 09 Semaglutide: ingested or injected
- OP 10 Looking into the future: predicting renal outcomes
- OP 11 Lost islets in type 2 diabetes
- OP 12 Prediction of vascular complications in type 1 diabetes
- OP 13 Nephropathy: mechanisms of renal injury and nephroprotection
- OP 14 New insights on early onset type 2 diabetes
- OP 15 Clinical aspects of hypoglycaemia
- OP 16 The many faces of metabolic surgery
- OP 17 Are we making progress in diabetic neuropathy?
- OP 18 The still mysterious alpha cells
- OP 19 Treating diabetes with peptides from the gut
- OP 20 Youth-onset type 1 diabetes: Are we making progress?
- OP 21 Cardiovascular disease in diabetes: causes and consequences
- OP 22 Determinants of exercise response
- OP 23 The diabetic brain: culprit or victim?
- OP 24 More and better beta cells for therapy
- OP 25 New horizons in incretin-based therapies
- OP 26 Gestational diabetes: novel biomarkers and consequences
- OP 27 Modulations of insulin secretion
- OP 28 What you eat is what you are
- OP 29 Spotlights on prediction and prevention of type 2 diabetes
- OP 30 NAFLD and diabetes: new horizons
- OP 31 Innovative insulin therapy
- OP 32 Novel biomarkers in diabetes, towards precision medicine
- OP 33 Heart failure: a novel complication of diabetes?
Human and animal studies
- OP 34 New light into the signalling pathway
- OP 35 Novel concepts paving the way for future treatments
- OP 36 Genetics of diabetes: the final countdown?
- OP 37 New modes of organ crosstalk
- OP 38 Continuous measurement of glucose: standard of care?
- OP 39 Insights on retinopathy from observational studies
- OP 40 Novel treatments in obesity: lean on me
- OP 41 Cardiovascular hotspots in diabetes
- OP 42 The inner life of the beta cell
- OP 43 Disease progression in type 2 diabetes
- OP 44 Exploring novel mechanisms of action of SGLT2 inhibitors
- OP 45 Integrating psychology into diabetes care
- OP 46 Holistic view on ageing
- OP 47 Type 2 diabetes across ethnicities
- OP 48 Not all beta cells are alike

Index of Poster Sessions

- PS 001 Twisting the helix
- PS 002 The attack from within: autoimmunity in diabetes
- PS 003 Monogenic diabetes: from MODY and beyond
- PS 004 Additional spotlights on cardiovascular disease
- PS 005 Diagnostic discussions in diabetes
- PS 006 Trends, prevalence and incidence
- PS 007 Biomarkers and diabetes: new and old
- PS 008 Genetics of diabetes: more to know?
- PS 009 Diabetes: new lessons from animals
- PS 010 Treatments for type 2 diabetes
- PS 011 Control, incidence and risk factors in type 1 diabetes
- PS 012 You are what you do: environment, lifestyle and diabetes
- PS 013 Infections and pancreatitis in diabetes
- PS 014 Islets in the stream: transplantation for a better journey
- PS 015 You ain't seen nothin' yet with stem cells,
the best is yet to come
- PS 016 Reaching to the stars for future type 1 diabetes treatment
- PS 017 Beta cells: be yourself and grow
- PS 018 The ins and outs of ions in islets
- PS 019 GLPR and other GPCRs: juggling with acronyms
- PS 020 Rise and fall of the beta cell
- PS 021 Tales of the injured beta cell
- PS 022 Inflamed islets in type 1 diabetes
- PS 023 The downfall of beta cells
- PS 024 The endocrine role of the gut: incretins and other hormones
- PS 025 Changing insulin sensitivity: a stairway to heaven?
- PS 026 Causes and consequences of insulin resistance
- PS 027 Insulin secretion and beta cell function
- PS 028 Incretins regulating incretins
- PS 029 Modulation of islet hormones
- PS 030 How to optimise exercise
- PS 031 Sugar on the run
- PS 032 A mixed bag of metabolism
- PS 033 The many roles of other hormones
- PS 034 Surgery: What we need to learn
- PS 035 The obesity battle
- PS 036 Diabetic complications of the mind
- PS 037 Diet, bugs and drugs
- PS 038 Hungry like the wolf: What's in it for the brain?
- PS 039 Metabolic adaptations and outcomes
- PS 040 Diabetic staging
- PS 041 From mice to men?
- PS 042 The many ways of improving metabolism
- PS 043 Adipose tissue: what, where and how?
- PS 044 Inflammation and beyond
- PS 045 Not all fats are the same...
- PS 046 Burning down the fat
- PS 047 SGLT2 inhibitors and the cardiorenal axis
- PS 048 Combating diabetes with diet
- PS 049 Food, food, food... nutritional interventions
- PS 050 All the roads leading from SGLT2 inhibitors

247

The increase in endogenous glucose production with SGLT2 inhibition is unchanged by renal denervation but highly correlates to urinary glucose excretion

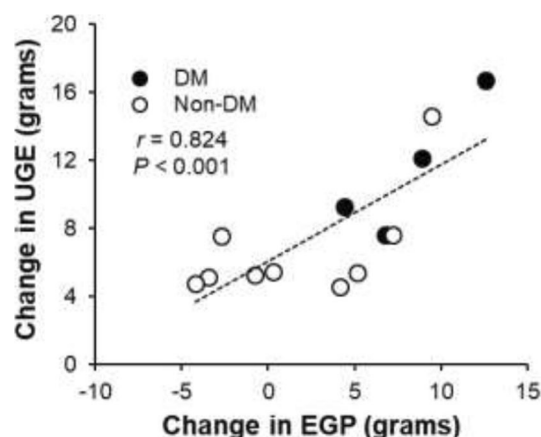
C. Solis-Herrera, M. Alatrach, C. Agyin, H. Honka, R.D. Patel, C. Triplitt, J.M. Adams, A. Gastaldelli, M. Abdul-Ghani, D. Tripathy, E. Cersosimo, R. DeFronzo;
Diabetes Division, University of Texas Health Science Center at San Antonio, USA.

Background and aims: SGLT2 inhibition causes a “paradoxical” increase in endogenous glucose production (EGP), indicating the presence of a “reno-hepatic axis.” We previously demonstrated that changes in plasma glucagon and insulin cannot explain the increase in EGP. We measured EGP after SGLT2 inhibition in renal transplant subjects with and without type 2 diabetes (T2D) to evaluate the role of renal nerves and sympathetic nervous system (SNS) in mediating this “reno-hepatic axis”.

Materials and methods: Six T2D ($A1c = 7.2 \pm 0.1$) and 8 non-T2D ($A1c = 5.6 \pm 0.1$) with normal renal function and no history of rejection (prednisone ≤ 5 mg/day) received two 6-hr measurements of EGP preceded by dapagliflozin (DAPA) or placebo.

Results: Following DAPA in T2D, FPG (143 ± 15 to 112 ± 9 mg/dl, $p=0.01$) and FPI (14 ± 3 to 11 ± 2 , $p=0.02$) decreased while glucagon increased (45 ± 13 to 54 ± 14 pg/mL, $p=0.09$) (all $p < 0.05$ vs placebo); plasma epinephrine and norepinephrine did not change from baseline. Following placebo, EGP decreased ($p < 0.01$) in both T2D and non-diabetics. In contrast, after DAPA EGP increased ($p < 0.01$) in both T2D (by 0.4 ± 0.1 mg/kg.min) and in non-T2D (by 0.1 ± 0.1 mg/kg.min) compared to placebo. The DAPA-induced increment in EGP production was highly correlated ($r = 0.824$, $p < 0.001$) with the increment in urinary glucose excretion in all subjects (Figure)

Conclusion: (1) Renal denervation in renal transplant patients failed to block the DAPA-mediated stimulation of EGP; (2) DAPA-stimulated rise in EGP is strongly related to the increase in urinary glucose excretion blunting the decline in fasting plasma glucose.



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248

SGLT2 is not expressed in pancreatic alpha and beta cells and its inhibition does not directly affect glucagon and insulin secretion in rodents and humans

P. Gilon¹, H. Chae¹, N. Antoine¹, B.-K. Lai¹, B. Singh¹, L. Ruiz¹, A. Wojtuszczyński², C. Broca², B. Stierstorfer³, H. Klein³, E. Mayoux³, M. Pieper³, M. Mark³, R. Augustin³;

¹Pole d'Endocrinologie, Diabète et Nutrition, Université Catholique de Louvain, Brussels, Belgium, ²Laboratory of Cellular Therapy for Diabetes, University Hospital of Montpellier, Montpellier, France, ³Department of CardioMetabolic Diseases Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany.

Background and aims: SGLT2 inhibitors (SGLT2i), such as dapagliflozin and empagliflozin, are effective glucose-lowering medications with a unique, insulin-independent mechanism that is to promote glycosuria. SGLT2i-induced glycosuria is associated with metabolic responses including increases in fatty acid mobilization, hepatic glucose and ketone body production, and circulating glucagon levels. These metabolic adaptations are considered causative for rare cases of euglycemic ketoacidosis reported for SGLT2i. One potential cause of euglycemic ketoacidosis is the SGLT2i-mediated increase in glucagonemia and drop in insulinemia. It has been suggested that direct inhibition of α -cell SGLT2 stimulates glucagon release. Here, we investigated the potential role of SGLT1 and SGLT2 in the control of glucagon and insulin secretion from rat, mouse and human islets.

Materials and methods: mRNA expression of SGLT1 (*scl5a1*) and SGLT2 (*scl5a2*) was assessed by qPCR in islets, FACS sorted α - and β -cells and control tissues. Immunodetection of SGLT2 was performed on pancreatic sections and isolated islet cells. Glucagon and insulin secretion experiments were performed in incubation (human and rat islets) or perfusion (human and mouse islets), or with the *in situ* perfused mouse pancreas.

Results: SGLT1 and SGLT2 mRNAs were highly expressed in the kidney but absent in rodent and human pancreatic islets and in FACS-sorted α - and β -cells. Immunodetection of SGLT2 revealed a strong expression of the protein in the kidney or recombinant SGLT2 HEK293 expressing cells, but no expression in sections from rat and human pancreas or in dispersed human islet cells. The potential role of SGLTs on glucagon secretion was assessed by several approaches. In all tissue preparations (islets or pancreas), a drop of the glucose concentration of the medium (from 7–15 mM to 0.5–2 mM) robustly stimulated glucagon secretion. By contrast, α -methyl-D-glucopyranoside (2 and 20 mM), a non-metabolizable glucose analogue, which is specifically transported by SGLT, did not affect glucagon secretion from mouse islets. Phlorizin (100 μ M, a SGLT family-specific inhibitor), dapagliflozin (1–10 μ M), empagliflozin (1–10 μ M) and sotagliflozin (1 μ M, a dual SGLT1/2i) had no effect on glucagon secretion when tested acutely at low or high glucose, and did not affect the glucagon secretory response to a drop of the glucose concentration in all tested models. Insulin secretion, measured in dynamic experiments, was unaffected by the different SGLTi, but stimulated by glucose. Overnight culture of human islets with 10 μ M dapagliflozin or empagliflozin in the presence of 5 or 15 mM glucose had no effect on glucagon mRNA expression.

Conclusion: Our data provide evidence that the increase in glucagonemia or drop in insulinemia induced by SGLT2i is not due to a direct, SGLT2-dependent effect on the pancreatic α - or β -cell, respectively.

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