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ABSTRACTS

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Abstracts

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

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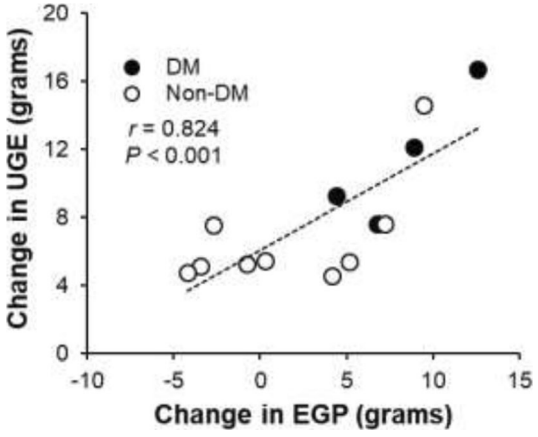
Background and aims: SGLT2 inhibition causes a "paradoxical" increase in endogenous glucose production (EGP), indicating the presence of a "reno-hepatic axis." We previously demonstrated that changes in plasma glucagon and insulin cannot explain the increase in EGP. We measured EGP after SGLT2 inhibition 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±0.1) and 8 non-T2D (A1c = 5.6±0.1) with normal renal function and no history of rejection (prednisone ≤ 5mg/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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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

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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. SGTL2i-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 (*slc5a1*) 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 perifusion (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 μM, a SGLT family-specific inhibitor), dapagliflozin (1-10 μM), empagliflozin (1-10 μM) and sotagliflozin (1 μM, 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 μM 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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