Increase in Endogenous Glucose Production With SGLT2 Inhibition Is Unchanged by Renal Denervation and Correlates Strongly With the Increase in Urinary Glucose Excretion

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OBJECTIVE

Sodium–glucose cotransporter 2 (SGLT2) inhibition causes an increase in endogenous glucose production (EGP). However, the mechanisms are unclear. We studied the effect of SGLT2 inhibitors on EGP in subjects with type 2 diabetes (T2D) and without diabetes (non-DM) in kidney transplant recipients with renal denervation.

RESEARCH DESIGN AND METHODS

Fourteen subjects who received a renal transplant (six with T2D [A1C 7.2 ± 0.1%] and eight non-DM [A1C 5.6 ± 0.1%) underwent measurement of EGP with [3-^{3}H]glucose infusion following dapagliflozin (DAPA) 10 mg or placebo. Plasma glucose, insulin, C-peptide, glucagon, and titrated glucose-specific activity were measured.

RESULTS

Following placebo in T2D, fasting plasma glucose (FPG) (143 ± 14 to 124 ± 10 mg/dL; $P = 0.02$) and fasting plasma insulin (12 ± 2 to 10 ± 1.1 μU/mL; $P < 0.05$) decreased; plasma glucagon was unchanged, and EGP declined. After DAPA in T2D, FPG (143 ± 15 to 112 ± 9 mg/dL; $P = 0.01$) and fasting plasma insulin (14 ± 3 to 11 ± 2 μU/mL; $P = 0.02$) decreased, and plasma glucagon increased (all $P < 0.05$ vs. placebo). EGP was unchanged from baseline (2.21 ± 0.19 vs. 1.96 ± 0.14 mg/kg/min) in T2D ($P < 0.001$ vs. placebo). In non-DM following DAPA, FPG and fasting plasma insulin decreased, and plasma glucagon was unchanged. EGP was unchanged from baseline (1.85 ± 0.10 to 1.78 ± 0.10 mg/kg/min) after DAPA, whereas EGP declined significantly with placebo. When the increase in EGP production following DAPA versus placebo was plotted against the difference in urinary glucose excretion (UGE) for all patients, a strong correlation ($r = 0.824$; $P < 0.001$) was observed.

CONCLUSIONS

Renal denervation in patients who received a kidney transplant failed to block the DAPA-mediated stimulation of EGP in both individuals with T2D and non-DM subjects. The DAPA-stimulated rise in EGP is strongly related to the increase in UGE, blunting the decline in FPG.

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In individuals with type 2 diabetes (T2D), an increased basal rate of endogenous glucose production (EGP) and impaired suppression of EGP following a meal are characteristic pathophysiologic abnormalities that contribute to fasting and postprandial hyperglycemia, respectively (1–9). Thus, understanding the factors that regulate EGP is key to understanding the maintenance of normal glucose homeostasis and development of hyperglycemia in patients with T2D. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) lower the plasma glucose directly by inducing glucosuria and indirectly by ameliorating glucotoxicity, resulting in improved insulin sensitivity and β-cell function (10–12). We (10,12) and others (13) have demonstrated that the glucosuria produced by SGLT2i stimulates EGP and that the increase in EGP offsets by ~50% the amount of glucose lost in the urine. This observation suggests the presence of a renohepatic axis that is activated to prevent an excessive decline in plasma glucose concentration and resultant hypoglycemia. In contrast, the increase in EGP in individuals with T2D is paradoxical in that it occurs while the plasma glucose concentration is within the hyperglycemic range and, as stated above, quantitatively offsets by ~50% the amount of glucose lost in the urine (10), thereby attenuating the glucose-lowering effect of SGLT2i. Elucidating the mechanisms that mediate the rise in EGP in response to SGLT2i-induced glucosuria will provide a better understanding of glucose homeostasis and may allow the development of strategies to prevent the increase in EGP and enhance the efficacy of SGLT2i.

The rise in EGP following SGLT2i is associated with an increase in plasma glucagon concentration and progressive decline in plasma insulin concentration (10,13). Although SGLT2 transporter receptors have been demonstrated on α-cells (14), there are no SGLT2 transporters on β-cells (14). Moreover, the rise in plasma glucagon occurs well after the initial rise in EGP (10). The rapid onset (30–60 min) of rise in EGP following SGLT2i ingestion suggests the presence of a neural arc in which activation of the renal sympathetic nerves sends a signal to the brain, which in turn leads to *1*) increased hepatic glucose production, *2*) stimulation of glucagon secretion, *3*) inhibition of insulin secretion, or *4*) some combination of the three. The aim of this study is to examine the effect of SGLT2 inhibition on EGP and sympathetic nervous system activation in subjects with diabetes and without diabetes after kidney transplantation (i.e., renal denervation) in order to elucidate the possible role of a neural arc mediating the SGLT2i-induced stimulation of EGP.

RESEARCH DESIGN AND METHODS

Fourteen subjects post–renal transplant (six with T2D and eight without T2D [non-DM]) participated in the study. The patient characteristics are shown in Table 1. All transplant subjects had their native kidneys in place. Subjects were in general good health as determined by history, physical examination, screening laboratory tests, and electrocardiogram.

Only subjects with stable body weight (± 3 lb) over the preceding 3 months and who did not participate in excessively heavy exercise were included. Subjects had to be at least 3 months post–renal transplantation, have no evidence of rejection, and be on a stable dose of prednisone (≤5 mg/day), tacrolimus, and mycophenolate mofetil. Subjects with diabetes could be drug naive ($n = 3$) or treated with metformin with or without dipeptidyl peptidase 4 inhibitor ($n = 3$). Subjects with evidence of proliferative diabetic retinopathy, estimated glomerular filtration rate <45 mL/min/1.73 m^2 (calculated by MDRD), or albumin-to-creatinine ratio >300 mg/g were excluded. Individuals taking a β-blocker or any medication known to affect sympathetic/parasympathetic activity were excluded.

Recruitment was done at the Texas Diabetes Institute in collaboration with the Transplant Clinic at UT Health San Antonio. After screening, eligible subjects received two measurements of EGP on separate days. Subjects reported to the Texas Diabetes Institute at 6:00 A.M. after a 10-h overnight fast. At 6:00 A.M. a catheter was placed into an anticubital vein, and subjects received an infusion of [3-^{3}H]glucose (prime = 25 μCi × fasting plasma glucose [FPG]/100; continuous = 0.25 μCi/min) for 3 h (6:00–9:00 A.M.). After the 3-h tracer equilibration period, subjects received one of the following medications in random order: *1*) placebo or *2*) dapagliflozin (DAPA) 10 mg. Plasma glucose, insulin, C-peptide, glucagon, catecholamine concentrations, and tritiated glucose-specific activity were measured at −30, −20, −10, −5, and 0 min and every 20 min for an additional 5 h after drug administration. Urinary glucose excretion (UGE) was measured from −180 to 0 min (6:00–9:00 A.M.) and from 0 to 300 min (9:00 A.M. to 2:00 P.M.). Subjects were fed and discharged after each procedure. All antidiabetic medications were held the morning of the study.

Analytical Techniques

Plasma glucose was measured by glucose oxidase reaction (Analox Instruments, Stourbridge, U.K.). Plasma insulin (IBL America, Minneapolis, MN) and C-peptide (MP Biomedicals, Santa Ana, CA) concentrations were measured by immunoradiometric assay. Glucagon concentration was measured by radioimmunoassay (MilliporeSigma, St. Charles, MO) and epinephrine/norepinephrine by ELISA (ALPCO, Salem, NH). Plasma [3-^{3}H]glucose–specific activity was determined on deproteinized barium/zinc plasma samples.

Table 1—Clinical and metabolic characteristics of the study participants

Parameter	T2D	Non-DM	*P* value
n	6	8	
Age (years)	55 ± 2.8	51 ± 5.1	NS
Sex (male/female), *n*	0/6	5/3	0.016
Weight (kg)	79 ± 4.7	84 ± 4.0	NS
BMI (kg/m^2)	32 ± 1.6	31 ± 3.1	NS
A1C (%)	7.2 ± 0.1	5.6 ± 0.1	<0.0001
FPG (mg/dL)	127 ± 14	84 ± 2.5	0.004
Plasma creatinine (mg/dL)	0.93 ± 0.10	1.18 ± 0.12	NS
eGFR (mL/min/1.73 m^2)	91.0 ± 11.8	85.4 ± 4.6	NS
Diabetes duration (years)	9.0 ± 4.3	NA	
Transplant duration (years)	3.0 ± 1.8	1.3 ± 0.2	NS

Data are mean ± SEM unless otherwise indicated. eGFR, estimated glomerular filtration rate (according to the Cockcroft-Gault equation); NA, not applicable.

Calculations and Statistical Analysis

Under steady-state postabsorptive conditions, the basal rate of EGP equals the [3-^{3}H]glucose infusion rate divided by steady-state plasma tritiated glucose-specific activity. After drug administration, non–steady-state conditions prevail for [3-^{3}H]glucose–specific activity, and the rate of glucose appearance was calculated with the Steele equation (15).

Changes in the rate of EGP after placebo versus DAPA were compared with paired *t* test. Statistical significance was set at $P < 0.05$.

Study Approval

The study protocol was approved by the Institutional Review Board of The University of Texas Health Science Center at San Antonio. All subjects gave their written informed voluntary consent prior to participation.

RESULTS

Table 1 summarizes the clinical characteristics of study participants.

Effect of DAPA on EGP

In the T2D group treated with placebo (Fig. 1*A*), EGP decreased progressively over the 5-h study period from 2.03 ± 0.20 to 1.55 ± 0.09 mg/kg/min ($P = 0.03$). Following DAPA administration in the T2D group, EGP did not change significantly from baseline (2.2 ± 0.19 to 1.96 ± 0.14 mg/kg/min; P = NS). In the non-DM group treated with placebo, there was a small but significant decline in EGP over the 5-h study period (1.92 ± 0.10 to 1.68 ± 0.10 mg/kg/min; $P < 0.05$) (Fig. 1*D*). Following DAPA administration in the non-DM group, EGP did not change significantly (1.85 ± 0.10 to 1.78 ± 0.09 mg/kg/min; P = NS vs. baseline) (Fig. 1*B*).

Effect of DAPA on Plasma Glucose, Insulin, Glucagon, and Catecholamine Concentrations

In the T2D group treated with placebo, the plasma glucose concentration declined from 143 ± 14 to 124 ± 10 mg/dL ($P < 0.05$). Following DAPA, the decline in plasma glucose (143 ± 15 vs. 112 ± 9 mg/dL) was significantly greater than with placebo ($P < 0.05$). In the non-DM group treated with placebo, the plasma glucose decreased slightly from 95 ± 3 to 92 ± 2 mg/dL during the last 30 min (P = NS). In the non-DM group treated with DAPA, the decline in plasma glucose (96 ± 3 to 90 ± 1 mg/dL; $P < 0.05$) was significantly greater than with placebo ($P < 0.05$).

The plasma insulin concentration dropped slightly but significantly in both the groups with and without diabetes following DAPA ($P < 0.05$), whereas following placebo, there was a significant decrease in insulin only in the group with diabetes. Plasma C-peptide levels tended to parallel the change in plasma insulin concentration in both groups (Table 2).

The plasma glucagon concentration in the T2D group tended to rise after DAPA versus placebo (45 ± 13 to 54 ± 14 pg/mL; $P = 0.10$). In the non-DM group, there was no significant change in the plasma glucagon concentration after DAPA or placebo.

There was no significant change in plasma norepinephrine concentration in either the group with T2D or the non-DM group following either DAPA or placebo treatment (Table 2). In the T2D group, plasma epinephrine concentration increased similarly but did not reach significance following both DAPA and placebo (Table 2). In the non-DM group, there was no change in plasma epinephrine concentration following either DAPA or placebo.

CONCLUSIONS

The current study is the first to examine the effect of renal denervation on the SGLT2i-induced stimulation of EGP. Our hypothesis was that the increase in EGP following SGLT2i administration was related to activation of the sympathetic nervous system secondary to stimulation of the renal nerves. To test this hypothesis, we administered DAPA to subjects with diabetes and without diabetes who had received a renal transplant for at least 1 year, showed no sign of rejection, and were receiving ≤5 mg of prednisone per day. As shown in Fig. 1*A*, the fasting-related decline in EGP in patients with diabetes following placebo administration was completely negated following DAPA administration. EGP declined by 0.48 mg/kg/min following placebo or 7.4 g over the 5-h study period. In contrast, there was no change in EGP in DAPA-treated subjects. Thus, there was a net accumulation of 8.2 g of glucose following DAPA administration. Over the same time period, the amount of glucose excreted in the urine (above baseline) following DAPA was 11.4 g. Thus, the DAPA-induced rise in UGE was offset by 71.6%. Further, it is noteworthy that activation of EGP was observed within the first 30 min after DAPA administration and occurred when the plasma glucose concentration was >140 mg/dL.

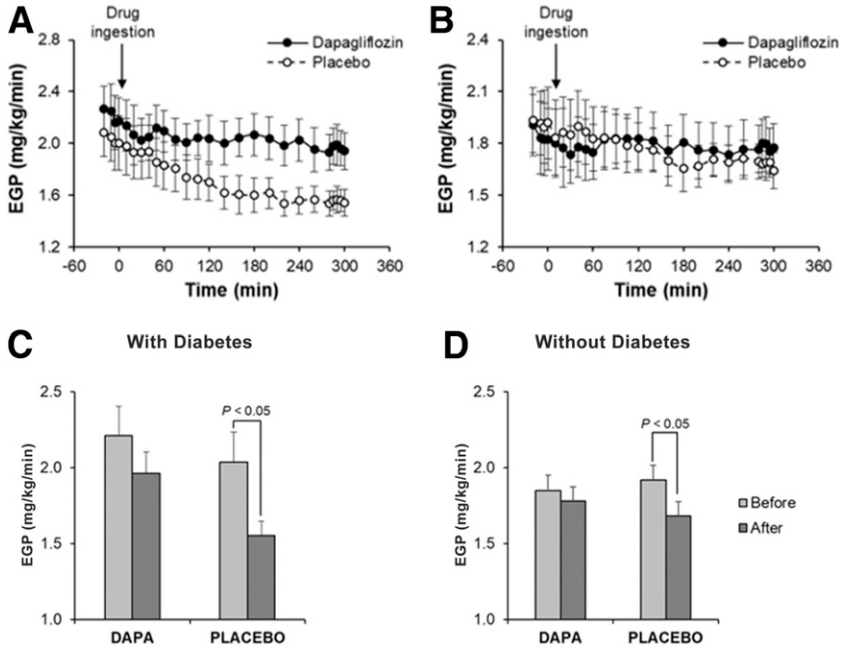

Figure 1—EGP after DAPA and placebo in subjects with diabetes (*A*) and without diabetes (*B*). Baseline EGP (Before) and EGP during the last 30 min (After) of the 5-h study and placebo in subjects with diabetes (*C*) and without diabetes (*D*) treated with DAPA and placebo.

Table 2—Effect of DAPA on plasma insulin, C-peptide, glucagon, epinephrine, and norepinephrine concentrations in subjects with diabetes (T2D) and without diabetes (non-DM)

	DAPA			Placebo		
	Baseline	End	*P* value	Baseline	End	*P* value
T2D						
Insulin (μU/mL)	14 ± 2.7	11 ± 1.9	0.024	12 ± 1.9	10 ± 1.4	0.047
C-peptide (ng/mL)	4.40 ± 0.47	3.67 ± 0.37	0.005	4.37 ± 0.52	3.71 ± 0.36	0.036
Glucagon (pg/mL)	45 ± 13	54 ± 14	0.095	42 ± 11	46 ± 11	0.456
Epinephrine (pg/mL)	6.8 ± 3.2	14 ± 6.1	0.389	4.8 ± 3.0	12 ± 4.8	0.071
Norepinephrine (pg/mL)	579 ± 156	712 ± 196	0.432	556 ± 169	639 ± 202	0.140
Non-DM						
Insulin (μU/mL)	10 ± 2.0	7.5 ± 1.1	0.043	9.1 ± 1.8	8.2 ± 1.6	0.128
C-peptide (ng/mL)	3.4 ± 0.4	2.8 ± 0.3	0.006	3.5 ± 0.4	3.1 ± 0.4	0.008
Glucagon (pg/mL)	49 ± 6.3	49 ± 6.6	0.985	47 ± 4.4	43 ± 4.6	0.137
Epinephrine (pg/mL)	35 ± 8.5	44 ± 13	0.225	40 ± 10	44 ± 10	0.091
Norepinephrine (pg/mL)	482 ± 81	471 ± 105	0.793	517 ± 98	564 ± 123	0.403

Data are mean ± SEM.

A similar scenario was observed in subjects without diabetes (Fig. 1*B*), although the magnitude of the difference in EGP between DAPA-treated versus placebo-treated subjects with diabetes was quantitatively much less. A better way to appreciate the stimulatory effect of DAPA on EGP is to view the lack of change in plasma glucose concentration despite the marked increase in UGE, which amounted to −11.5 g over the 5-h study period. This increase was precisely matched by the increase in EGP, resulting in no change in FPG. This explains why hypoglycemia is not observed with DAPA even when the drug is administered to subjects without diabetes.

When the difference of EGP production following DAPA versus placebo is plotted against the corresponding difference in UGE for all patients, a strong correlation ($r = 0.824$; $P < 0.001$) is observed. Thus, the higher the increase in UGE, the higher the rise in EGP (Fig. 2).

The present results also shed light on the role, or lack thereof, of changes in plasma glucagon and insulin on the SGLT2i-induced stimulation of EGP in individuals with diabetes. With regard to glucagon, the present results confirm our previous observation (10) that the rise in glucagon does not occur until 90 min after DAPA administration (Supplementary Fig. 1), whereas the increase in EGP is observed within 30 min. In addition to being delayed, the absolute increase was small and statistically significant. Further, in subjects without diabetes, there was absolutely no change in plasma glucagon concentration despite the marked stimulation of EGP, which maintained the FPG concentration constant at the basal level (Fig. 2). With regard to insulin (paralleled by C-peptide), the plasma level decreased similarly by 2–3 μU/mL following both DAPA and placebo in both subjects with diabetes and without diabetes, yet EGP increased only following DAPA administration.

The current study provides the first data on changes in plasma catecholamine concentration following SGLT2i administration. Baseline plasma norepinephrine levels were not significantly different in individuals with diabetes versus without diabetes and did not change following DAPA or placebo in both groups. Of interest, the plasma epinephrine concentration was significantly lower in subjects with diabetes versus without diabetes and increased significantly in subjects with diabetes following both DAPA and placebo. In subjects without diabetes, neither DAPA nor placebo administration caused any significant change in plasma epinephrine level.

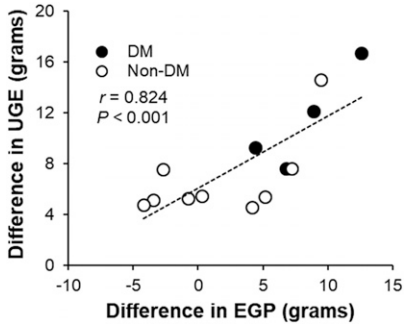

Figure 2—Correlation between the difference of total EGP above baseline vs. the difference of total UGE in all subjects. DM, with diabetes.

Although we failed to observe any mitigation of the rise in EGP following DAPA administration in patients who received a renal transplant, we cannot definitively exclude a role for the renal nerves because the native kidneys remained intact due in part to a small sample size. After transplantation, the native kidneys have been shown to continue to contribute to glomerular filtration (16,17). Thus, it is possible that in the native kidneys, the sympathetic nerves are activated and transmit a stimulus to the liver to produce glucose. In support, earlier animal studies have shown that the compensatory increase in hepatic and renal glucose production during insulin-induced hypoglycemia is reduced with β-adrenergic blockade (18,19). It also is possible that the increase in EGP production following DAPA was due to an increase in renal glucose production due to local activation of renal gluconeogenesis by glucosuria or other local effects of SGLT2 inhibition (20,21).

After DAPA administration, EGP increased within 30 min and remained elevated during the entire 5-h study period, behaving in the same way as in subjects with enervated kidneys (10,13). Due to the rapidity of increase in EGP after DAPA administration, it is possible that, at least to some degree, the sympathoadrenergic system is involved. Catecholamines are known to increase EGP and to blunt the action of insulin on the liver (18,22). In subjects with normal glucose tolerance, a combined epinephrine/insulin infusion has been shown to increase EGP fivefold compared insulin infusion alone (22). If catecholamines were elevated by SGLT2i (i.e., secondary to volume contraction or some other mechanism), this could explain the renal–hepatic axis. In our study, no significant difference in plasma norepinephrine levels was noted in either subjects with diabetes or without diabetes

treated with DAPA or placebo. However, a role for norepinephrine and activation of the sympathetic nervous system cannot be excluded because the majority of secreted norepinephrine is retaken up by nerve terminals. To examine this possibility would require a study with radiolabeled norepinephrine in subjects with diabetes following DAPA. Further, no increase in plasma epinephrine was observed in subjects with diabetes (or without diabetes) following DAPA administration, making epinephrine an unlikely candidate to explain the SGLT2i-induced rise in EGP. A limitation of the current study is the relatively small number of subjects, although the individual subject results were quite consistent. Further, the observation period was short, 300 min, and the study was not designed to look at chronic SGLT2i administration in subjects who received a renal transplant.

In conclusion, renal denervation in transplanted patients with diabetes and without diabetes did not blunt the increase in EGP following DAPA administration or alter the changes in plasma glucagon or insulin. The DAPA-stimulated rise in EGP is strongly related to the increase in UGE, blunting the decline in FPG.

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Author Contributions. C.S.-H., G.D., C.T., E.C., S.D.P., and R.D. contributed to the study concept and design, analysis and interpretation of data, drafting and revision of the manuscript, statistical analysis, and study supervision. C.S.-H., M.A., C.A., C.T., J.A., and R.P. contributed to the study recruitment, experiments, and data acquisition and analysis. A.G. and M.A.-G. contributed to the study concept and analysis. H.H. and X.C. contributed to acquisition and data analysis. R.D. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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