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Acute and Chronic Renal Tubular Response to SGLT2 Inhibitors in Diabetic Mice

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Objectives: Inhibition of sodium-glucose cotransporter 2 (SGLT2) in proximal renal tubules may induce glucosuria and sodium excretion to lower serum glucose in patients with type 2 diabetes mellitus.The design of this study was to explore changes in electrolyte and associated transporters.

Methods: C57BLKsJ-db/db mice were used as spontaneous type 2 diabetic animal model. Dapagliflozin, a SGLT2 inhibitor, was fed with 1 mg/kg. Serum and urine were collected after 6-hours and 24-hours and kidneys were extracted for quantification of protein amount by Western blotting.

Results: Fraction excretion of sodium, potassium, phosphate, calcium and magnesium were all decreased after 6 hours and increased after 24 hours.In proximal renal tubules, the insignificant changes of sodium-hydrogen exchangers 3, type 2a and 2c sodium-phosphate cotransporters were noted.The protein expression of sodium-chloride cotransporters in distal tubules and sodium-potassium-2 chloride cotransporters in thick ascending limbs were enhanced at 6 hour but decrease to baseline at 24 hour. The epithelial sodium channels increased at both 6 and 24-hour sampling.

Conclusions: Inhibition of SGLT2 may alter renal tubular sodium handling and the expression of Na-dependent cotransporters. The underlying mechanism needs further exploration and investigation.

Table 1 Urine and serum electrolyte change

Characteristic	db mice(n=3)	db+SGLT2 inhibitor 6 hr(n=3)	db+SGLT2 inhibitor 1day(n=3)
Blood			
GLU(mg/dL)	895.00±76.69	139.00±20.61***	532.33±90.74*
Creatinine(mg/dL)	0.60±0.08	0.40±0.00*	0.53±0.05
Na+	152.00±1.41	163.00±4.32*	157.33±2.49
K+	5.30±0.71	5.07±0.41	5.07±0.31
Cl-	103.67±1.70	107.33±4.11	111.33±2.36*
Ca2+	8.93±0.12	10.03±0.05***	10.23±1.23
P	8.87±0.92	20.53±0.66***	11.40±1.82
Mg+	3.93±0.26	5.33±0.25**	4.53±0.12
BUN	27.00±0.82	37.67±8.58	54.67±18.12
Uric Acid	2.57±1.17	3.83±0.87	2.33±0.42
Urine			
Creatinine(mg/dL)	25.60±2.78	12.08±1.39	13.77±1.52
Na^{+}/Creatinine	1.27±0.20	0.85±0.05*	1.85±0.64
K^{+}/Creatinine	1.33±0.10	0.97±0.15*	1.50±0.29
Cl^{-}/Creatinine	0.66±0.02	1.18±0.18*	1.03±0.11*
Ca^{2+}/Creatinine	0.07±0.01	0.03±0.01*	0.04±0.02
P/Creatinine	11.96±0.47	1.52±0.52***	5.37±1.46**
Mg^{+}/Creatinine	0.44±0.05	0.18±0.06**	0.43±0.28
UUN	2406.33±384.59	576.83±72.96**	918.00±156.85**
UUA	3.37±0.57	1.20±0.23**	1.33±0.17**
Osm	494.00±98.07	315.00±18.47	400.00±44.11

Table 1 :Urine and serum biochemistry data

Figure 1 NCC changes along with SGLT2 treatment

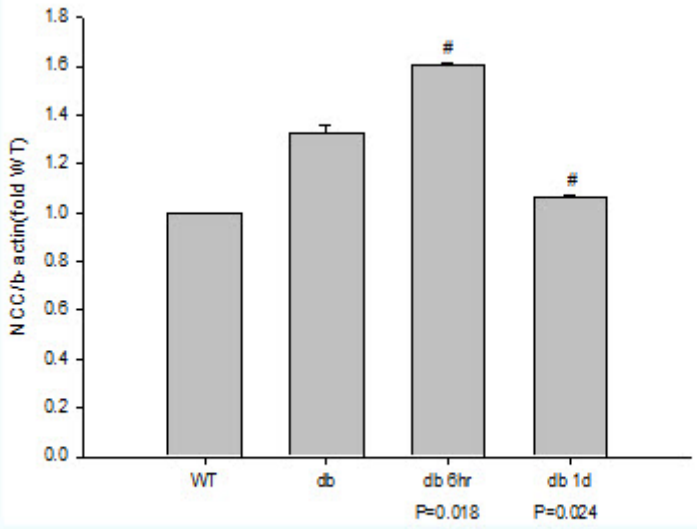

Figure 1 : NCC expression along with SGLT2 inhibitor treatment