RENOPROTECTIVE EFFECT OF SGLT2 INHIBITOR DAPAGLIFLOZIN IN TYPE 1 DIABETES

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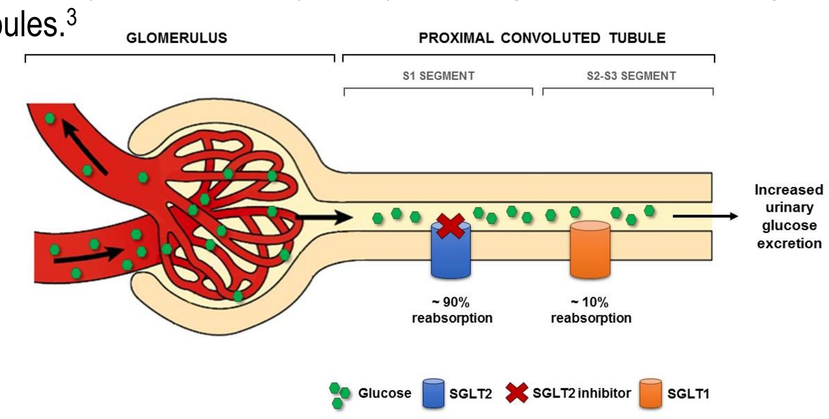
INTRODUCTION

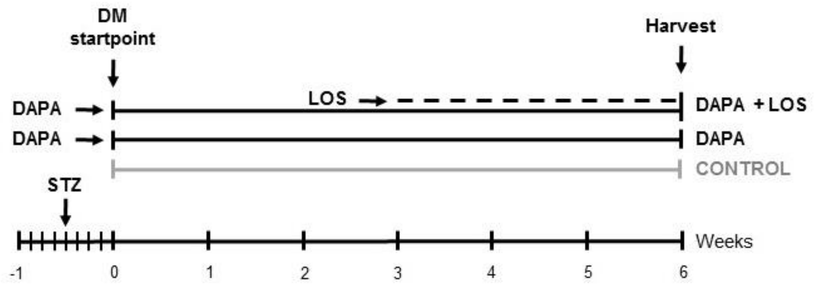
Blood glucose control is vital in diabetic (DM) patients to attenuate the progression of metabolic dysfunction and to reduce the secondary consequences including nephropathy (DNP).[1,2] Sodium-glucose co-transporter 2 (SGLT2) blockers have recently been approved as new antidiabetics in type 2 DM.[4] They act by inhibiting SGLT2 mediated glucose reabsorption in proximal tubules.[3]



There is an unmet need for approved oral therapies for type 1 diabetes mellitus (T1DM). Here we investigated the effect of highly selective SGLT2 inhibitor dapagliflozin (DAPA) in the prevention of diabetic nephropathy (DNP) in T1DM in monotherapy and in combination with ARB losartan (LOS).

METHODS

- Animal model: T1DM was induced by streptozotocin (STZ; 65 mg/bwkg, *ip.*) in adult, male Wistar rats.
- Treatment: Following the onset of T1DM for six weeks animals were treated *per os* with DAPA either in monotherapy (D+DAPA, 1 mg/bwkg/day) or in combination with LOS (D+DAPA+LOS, DAPA: 1 mg/bwkg/day; LOS: 20 mg/bwkg/day - only in the last three weeks). *(Protocol is summarized in the Fig. below)*
- Blood glucose level, body weight, blood pressure were monitored, metabolic and renal parameters were measured, histological evaluation of glomerular and tubulo-interstitial damage characteristic to DNP was performed.



RESULTS – METABOLIC PARAMETERS

DAPA improves metabolic parameters

Metabolic Parameters	Control	Diabetes (D)	D+DAPA	D+DAPA+LOS
MAP (mmHg)	90.6±2.43	85.9±2.23	73.9±2.78*	79.0±6.24
Heart rate (bmp)	398±4.87	317±5.65***	353±5.68***§	362±5.86**§§§
Changes in body weight (g)	187±18.3	55.2±12.9***	118±11.3**§	91.9±10.9***
Non-fasting blood glucose (mmol/L)	6.52±0.23	34.4±0.16***	17.7±1.99***§§§	18.1±2.18***§§§
Fructosamine (µmol/L)	142±1.69	274±5.57***	206±12.1***§§§	217±9.81***§§
Total Cholesterol (mmol/L)	1.98±0.06	2.70±0.17**	1.96±0.13§§	2.46±0.17
Triglycerides (mmol/L)	1.39±0.24	2.84±0.51**	1.08±0.20§§§	0.91±0.74§§§
LDL-C (mmol/L)	0.44±0.06	0.84±0.05***	0.51±0.05§§	0.80±0.05***
GOT (U/L)	127±7.15	347±69.5**	191±8.99§	214±31.3§
GPT (U/L)	42.8±3.08	166±33.6***	84.6±5.76§§	65.2±4.06§§§

Table 1. Blood pressure, heart rate, changes in body weight and metabolic parameters of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. MAP: mean arterial pressure, LDL-C: low-density lipoprotein cholesterol, GOT: serum glutamate-oxaloacetate transaminase, GPT: serum glutamate-pyruvate transaminase. (All data are represented as mean±SEM. n=6-8/group. *p<0.05 *vs.* Control, **p<0.01 *vs.* Control, ***p<0.001 *vs.* Control, §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes, §§§p<0.001 *vs.* Diabetes.)

RESULTS – HISTOLOGY

DAPA attenuates mesangial matrix expansion and tubulo-interstitial fibrosis

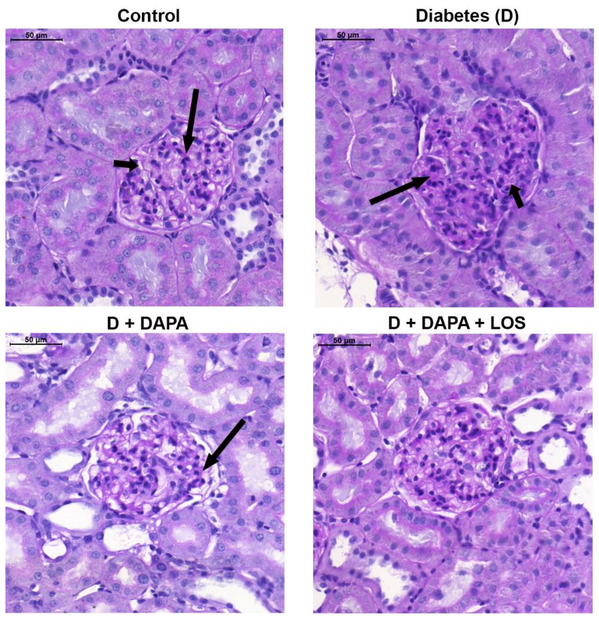
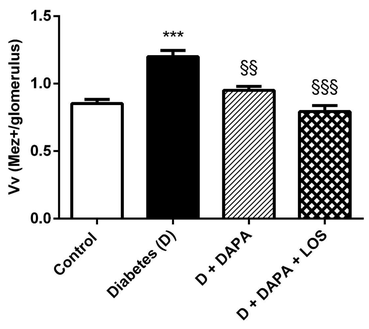


Figure 1. Histopathology of kidney sections of control, diabetic, and treated diabetic rats. Representative Periodic acid–Schiff stained kidney sections (x400 magnification; scale bar=50 µm) of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. (All data are represented as mean±SEM. n=6-8/group. ***p<0.001 *vs.* Control, §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes, §§§p<0.001 *vs.* Diabetes)



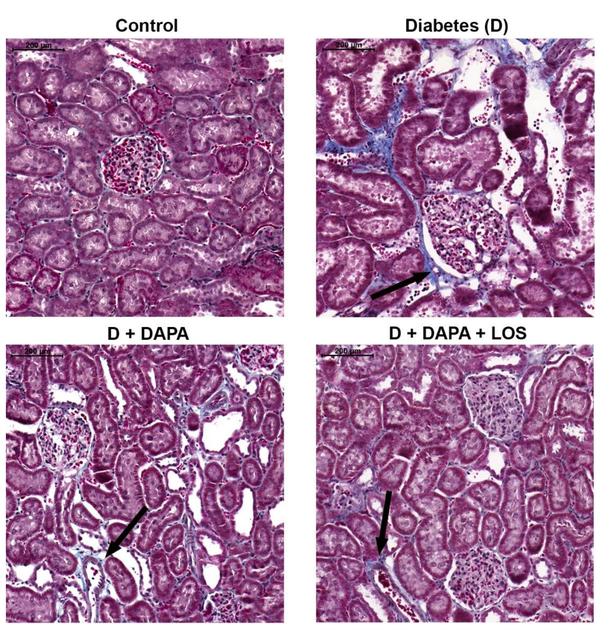
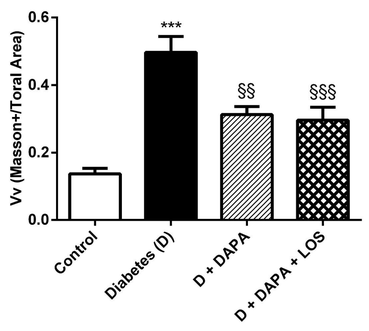


Figure 2. Histopathology of kidney sections of control, diabetic, and treated diabetic rats. Representative Masson trichrome-stained kidney sections (x200 magnification; scale bar=200 µm) of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. (All data are represented as mean±SEM. n=6-8/group. ***p<0.001 *vs.* Control, §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes, §§§p<0.001 *vs.* Diabetes)



RESULTS – RENAL PARAMETERS

DAPA improves renal parameters

Renal Parameters	Control	Diabetes (D)	D+DAPA	D+DAPA+LOS
Creatinine (µmol/L)	22.0±0.93	39.5±2.3**	25.1±0.93§§	26.1±1.9§§
BUN (mmol/L)	7.07±0.20	25.3±3.90**	10.5±1.63§§	15.8±0.73§§
Creatinine clearance (mL/min)	1.23±0.05	0.62±0.74**	1.09±0.08§§	0.96±0.13
FENa (%)	0.22±0.02	3.58±0.74**	0.5±0.08§§	0.45±0.08§§
Na (mmol/L)	141±0.56	131±1.48***	142±1.07§§§	143±1.23§§§
K (mmol/L)	6.38±0.22	7.42±0.24	5.80±0.29§§	6.71±0.33

Table 2. Renal parameters of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. BUN: blood urea nitrogen, FENa: fractional excretion of sodium, UN: undetermined. (All data are represented as mean±SEM. n=6-8/group. *p<0.05 *vs.* Control, **p<0.01 *vs.* Control, ***p<0.001 *vs.* Control, §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes, §§§p<0.001 *vs.* Diabetes.)

RESULTS – TUBULAR DAMAGE MARKERS

DAPA decreases early and sensitive markers of renal tubular damage

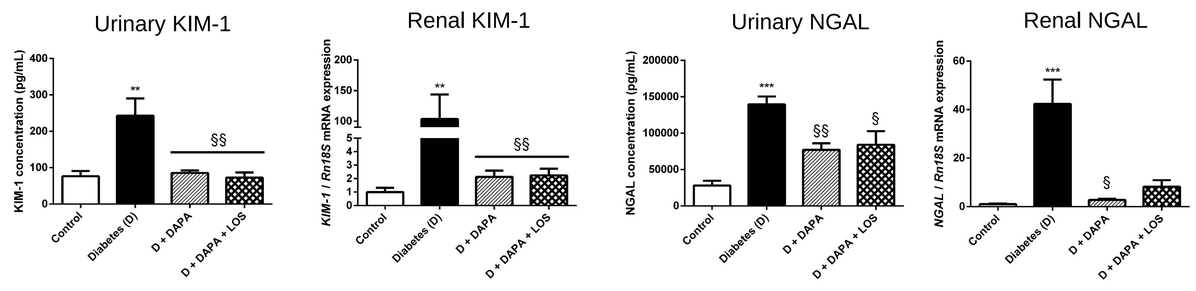


Figure 3. Urinary and kidney NGAL and KIM-1 levels of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. (All data are represented as mean±SEM. n=6-8/group. *p<0.05 *vs.* Control, **p<0.01 *vs.* Control, ***p<0.001 *vs.* Control, §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes)

RESULTS – PROFIBROTIC FACTORS

DAPA decreases profibrotic growth factor levels in the kidney

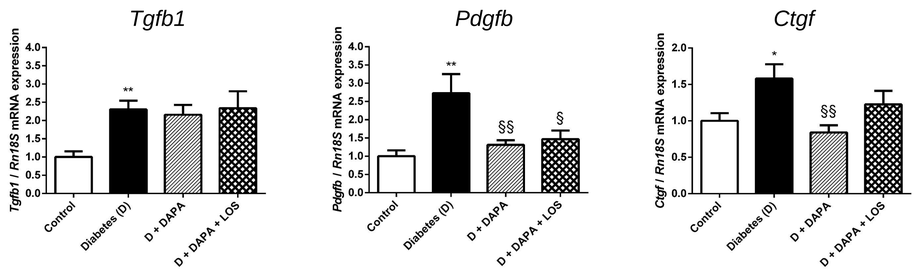


Figure 4. Kidney *Tgfb1, Pdgfb* and *Ctgf* levels of control, diabetic (D), dapagliflozin (DAPA) and DAPA+losartan (DAPA+LOS) treated diabetic rats. (All data are represented as mean±SEM. n=6-8/group. *p<0.05 *vs.* Control, **p<0.01 *vs.* Control; §p<0.05 *vs.* Diabetes, §§p<0.01 *vs.* Diabetes)

CONCLUSIONS

- DAPA improved metabolic and renal parameters and decreased the histological lesions in the kidney.
- The renoprotective effects of DAPA were equal to the gold standard therapy ARB losartan.
- These results support the effective and safe clinical application of DAPA in the prevention/treatment of T1DM and associated nephropathy.

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FUNDINGS: LP008/2016, NN OTKA-114607, OTKA-K116928, -K112629

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Diabetes -Basic science
Dora Balogh
DOI: 10.3252/pso.eu.54ERA.2017
ePosters supported by F. Hoffmann- La Roche Ltd.
54th ERA-EDTA CONGRESS Madrid, Spain June 3-6th 2017
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