THE ROLE OF *brain-derived neurotrophic factor (BDNF)* IN DIABETES-ASSOCIATED NEPHROPATHY AND COMORBID DEPRESSION

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Introduction

- Both **diabetes** (DM) and **depression** affect more than 350 million people worldwide *(WHO, 2013)*
- **Comorbid depression increases** the **mortality** and progression of diabetes-induced nephropathy *(Zhang, 2005)*
- **Renin-angiotensin-aldosterone system (RAAS) inhibitors** are the gold standard therapy in diabetic nephropathy (DNP) *(ADA, 2011)*
- BDNF and Sigma-1 receptor (S1R) expression decrease in depression *(Hashimoto, 2013)*
- The importance of **S1R-BDNF signaling pathway has been proved** in **depression** and BDNF was proposed as a biological link between DM and depression *(Hashimoto, 2013)*
- The **S1R-BDNF** pathway has **not** been investigated **in DNP** yet

Methods

- *In vivo* model: After 5 weeks of streptozotocin (65 mg/bwkg, *ip*. single dose) induced diabetes, male Wistar rats (n=8/group) were treated *po.* with enalapril (40 mg/bwkg/day) or ramipril (10 µg/bwkg/day), losartan (20 mg/bwkg/day), spironolactone (50 mg/bwkg/day) or eplerenone (50 mg/bwkg/day) and vehicle. Aged-matched healthy animals served as controls
- Evaluation of blood pressure, renal parameters and depression
- *In vitro* model: Human kidney-2 proximal tubular cells (HK-2) were cultured in normal (5 mM) and high glucose (HG, 35 mM) medium for 24 or 48 hours and HG groups were treated with enalapril (1 µM) or ramipril (10 µM), losartan (10 µM), spironolactone (200 nM) or eplerenone (10 µM). Untreated and mannitol treated cells were used as controls
- Measurement of BDNF and S1R protein levels by Western blot

Results

1. Blood pressure and metabolic parameters

Parameters	Control	Diabetes (D)	D+Enalapril	D+Ramipril	D+Losartan	D+Spironolactone	D+Eplerenone
MAP (mmHg)	73 11	69 17	65 6	72 7	74 14	77 20	72 12
Body Weight (g)	418 ± 34	267 ± 41*	291 ± 37.6	281 ± 27.6	263 ± 37.7	287 ± 39.3	284 ± 39.5
Kidney/ Body Weight x 100	0.7 ± 0.1	1.6 ± 0.3*	1.4 ± 0.2	1.3 ± 0.1§	1.3 ± 0.1§	1.3± 0.2§	1.3 ± 0.1§
Serum Glucose (mmol/L)	12.7 ± 1.8	41.6 ± 3.8*	35.3 ± 9.2	44.1 ± 5.6	43.8 ± 6.9	42.6 ± 3.4	34.8 ± 4.8
Serum Creatinine (µmol/L)	52 ± 13.5	70.5 ± 13.1*	66.3 ± 9	60.5 ± 5.1§	65.5 ± 5.8	63.5 ± 7.1	62.2 ± 5.6
Urea Nitrogen (µmol/L)	8.8 ± 0.7	26.2 ± 6.8*	17.5 ± 5.5§	19.3 ± 3.9§	18.1 ± 4.7§	19.7 ± 2.4§	20.2 ± 2.1§
GFR (mL/min/100g)	3.1 ± 0.1	1.5 ± 0.9*	2 ± 1	2 ± 0.5§	1.66 ± 1	1.8 ± 0.4§	2 ± 0.7§

Table 1: Mean arterial pressure (MAP) and renal parameters of control, diabetic (D) and treated diabetic animals. MAP was unchanged in diabetes and after RAAS blocker treatment. In diabetes decreased body weight, increased kidney/body weight ratio and declined renal function was observed. The various RAAS inhibitors improved renal function.
(*p<0.05 *vs*. Control; p<0.05 *vs.* D; n=8/group)

2. Analysis of depression

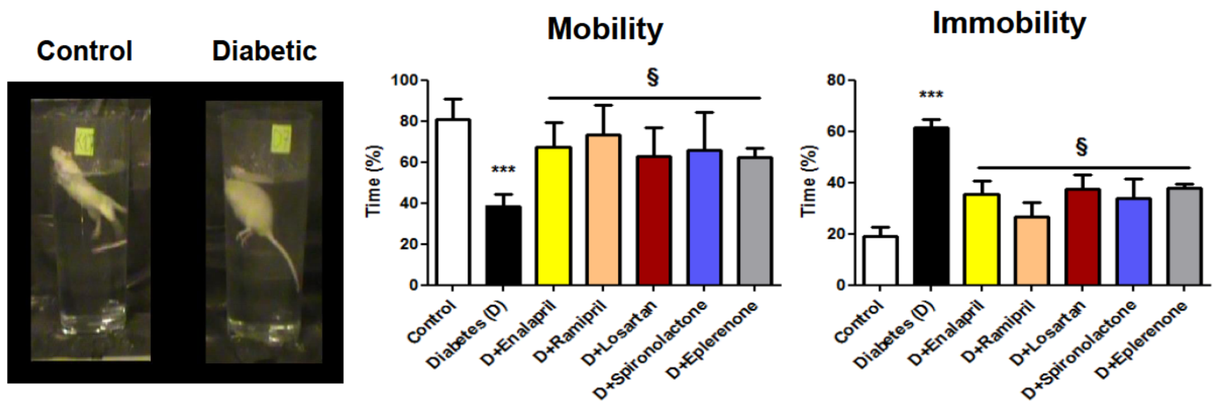

Figure 1: The Porsolt forced swim test was used to analyze depression. Mobility parameters (swimming, diving, struggling) and immobility parameters (floating) were measured. In diabetes the time of mobility phase decreased. Each RAAS inhibitor improved the depressive-like moving pattern, suggesting an antidepressant effect.
(***p<0.001 *vs*. Control; p<0.05 *vs.* D; n=8/group)

3. Western blot analysis of BDNF and S1R in the kidney

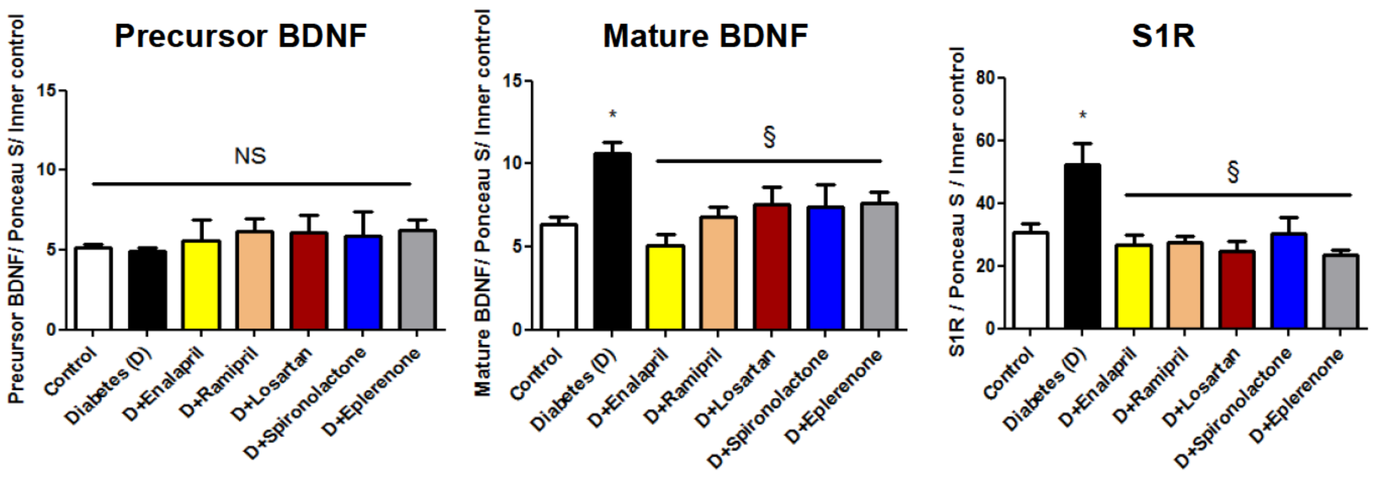

Figure 2: Both forms of BDNF were investigated: the expression of the precursor form was unchanged in all groups. Mature BDNF was higher in diabetic animals, but was decreased by all RAAS blockers. The level of S1R changed similarly to mature BDNF, S1R increased in diabetic animals but was decreased by RAAS inhibitors.
(*p<0.05 *vs*. Control; p<0.05 *vs.* D; NS: non-significant; n=8/group)

4. Western blot analysis of mature BDNF in HK-2 cells

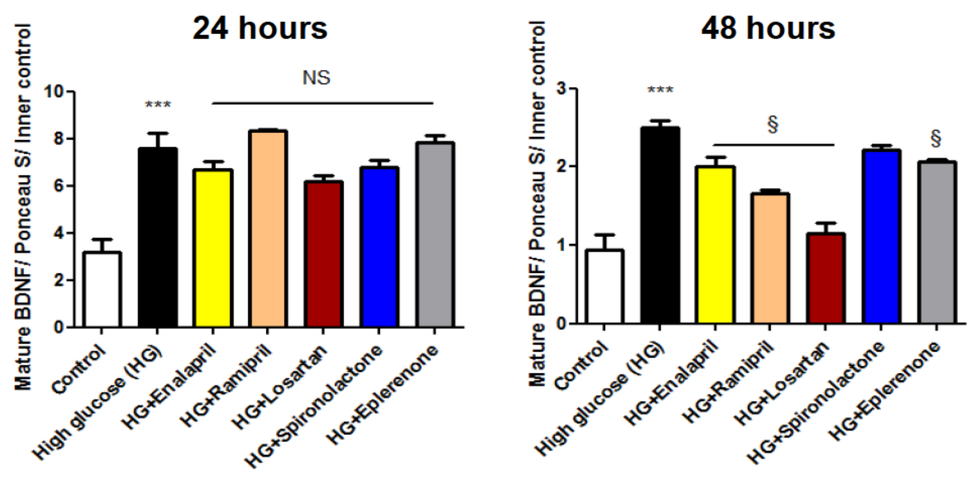

Figure 3: *In vitro* experiments confirmed that HK-2 can express BDNF and its expression is highly upregulated by glucose as soon as after 24 hours. RAAS inhibitors decreased mature BDNF levels after 48 hours.
(***p<0.001 *vs*. Control; p<0.05 *vs.* HG; NS: non-significant; n=6/group)

Summary

- RAAS blockers improved the depression-like behavior of diabetic animals
- Both forms of BDNF were expressed in the kidney and the level of mature BDNF and S1R increased in DM
- RAAS blockers decreased mature BDNF and S1R protein levels in the diabetic kidney
- Blood pressure remained unaltered both in diabetes and after RAAS inhibitor treatment
- In HK-2 cells mature BDNF was increased after glucose treatment, while was decreased by RAAS inhibitors

Conclusions

The RAAS-regulated common S1R–BDNF pathway may have a role in the co-development of DM–DNP and comorbid depression. This pathway could serve as a new therapeutic target for RAAS inhibitors.

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