PARICALCITOL MODULATES CIRCULATING ACE2 ACTIVITY IN TYPE 1 DIABETIC MICE

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INTRODUCTION AND OBJECTIVES

• Diabetic nephropathy (DN) progression can be slowed down by reducing albuminuria. Drugs targeting the Renin Angiotensin System (RAS) have been shown to be in part effective to reduce the protein excretion[1,2,3]. More recently, experimental studies suggest that the active form of vitamin D [1,25(OH)2D3] is a negative endocrine regulator of RAS by supressing renin expression[4].

• The main interest in our group is the modulation of RAS studying the role of ACE2 in DN. Previously we showed increased circulating ACE2 activity in non-obese diabetic mice (NOD)[5].

• The aim of the study was to test the renoprotective effect of Paricalcitol and its association with ACE2 enzyme activity in the experimental type 1 diabetes model, NOD strain. This study also tested the effect of the combination of Paricalcitol and the direct renin inhibitor, Aliskiren.

METHODS

ANIMALS: Females NOD mice were included in the study when two consecutive measurement of blood glucose were higher than 250mg/dL. Age-matched control animals were from the NOR strain. Animals were treated for 21 days.

DOSAGES: Paricalcitol was administered three times a week at 0.4µg/kg i.p. (NOD+PARI_0.4). Aliskiren was s.c. administered by miniosmotic pumps at rate of 25mg/kg/day (NOD+ALSK).

TECHNIQUES: Albumin/Creatinine ratio was measured from the urinary spot (Exocell). At day of sacrifice, plasma was obtained to measure ACE2 enzyme activity by modification of previously published methods [6,7,8] and renin activity using a commercial kit (SensoLyte® 520, Anaspec). Renal cortex homogenates were used to detect ACE2 enzyme activity in tissue, as previously published [6,7,8].

RESULTS

	Blood Glucose t=21d (mg/dL)	Age t=21d (weeks)	KW vs BW t=21d (%)	HW vs BW t=21d (%)	ACR t=21d (µgAlb/mgCrea)
NOR CONT (n=10)	156.5 7.1*	21.4 1.0	0.9 0.03*	0.43 0.02	14.7 3.7*
NOD DB (n=10)	582.3 11.6	20.0 0.7	1.61 0.05	0.40 0.02	1520.8 923.6
NOD+PARI_0.4 (n=10)	525.3 32.8	19.8 0.6	1.51 0.04	0.36 0.01$	711.3 284.4
NOD+ALSK (n=10)	582.4 9.3	21.0 0.6	1.51 0.05	0.39 0.02	312.2 106.5
NOD+PARI+ALSK (n=10)	538.5 23.7	19.2 0.8	1.62 0.05	0.40 0.03	390.9 164.2

*p<0.05 vs. NOD groups

$p<0.05 vs. NOD pe

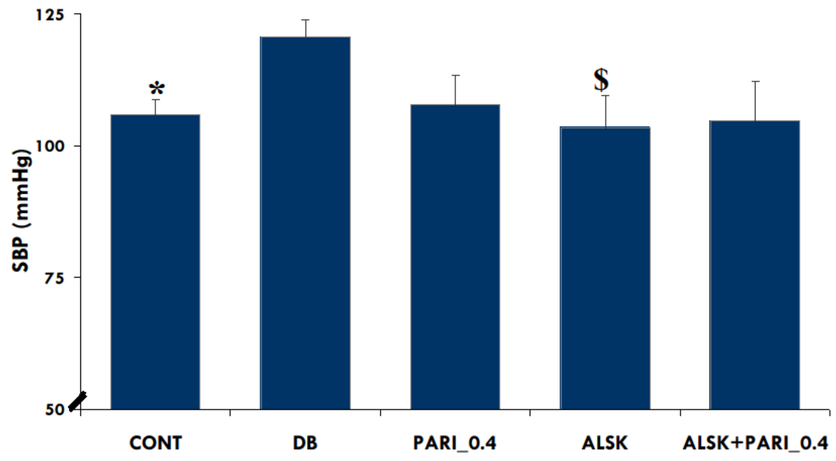
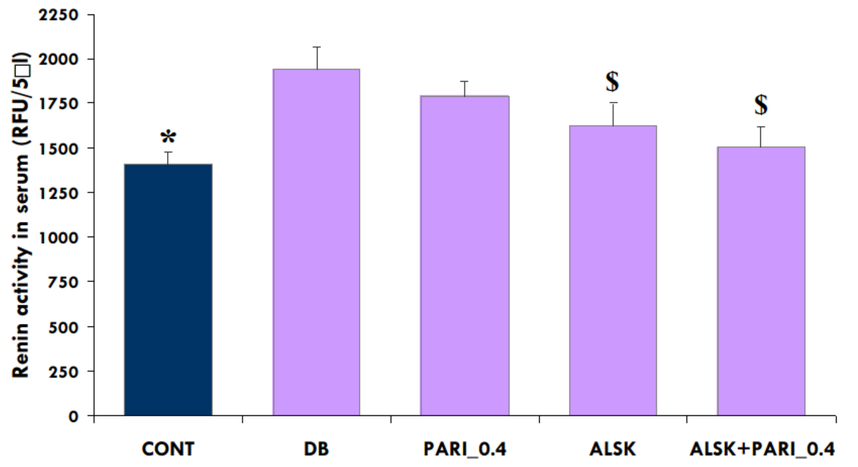


Figure 1. Sistolic Blood Pressure (SBP) was increased in diabetic NOD mice (*). Only Aliskiren treatment significantly reduced the values ($).

Figure 2. Renin Activity in serum was increased in NOD diabetic (DB) mice as compared to the non-diabetic control (*). Only animals given Aliskiren showed significant reductions in circulating Renin Activity ($).



ACE2 activity was measured in Serum (figure 3) and Renal cortex (figure 4) in study groups. Animals given Paricalcitol show a significant decrease in serum as compared to non-treated diabetic animals ($). However, renal cortex showed a different profile with no effects of Paricalcitol or Aliksiren in renal cortex ACE2 activity. Protein expression with Western Blot analysis (figure 5) in renal cortex showed similar results as cortical ACE2 activity.

figure 3

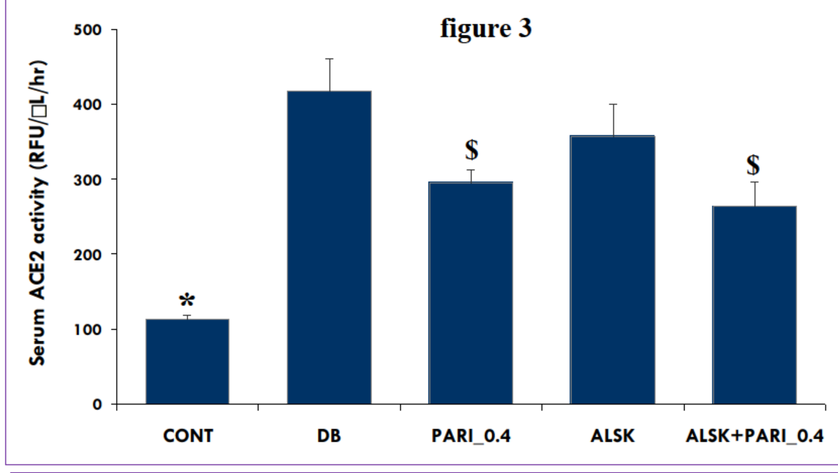


figure 4

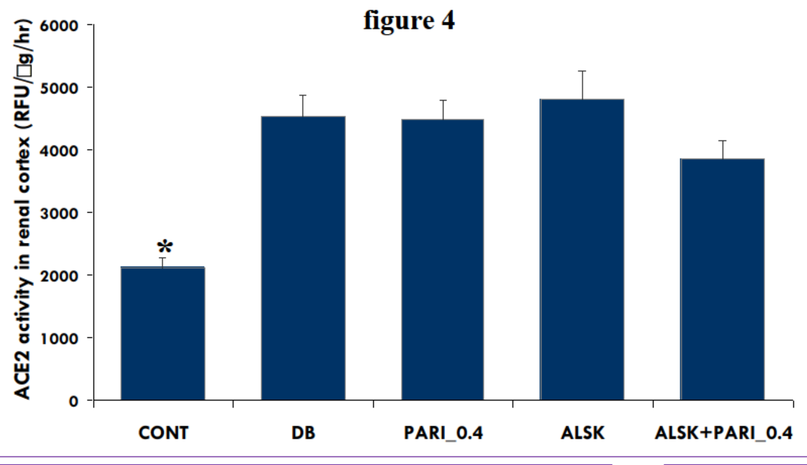
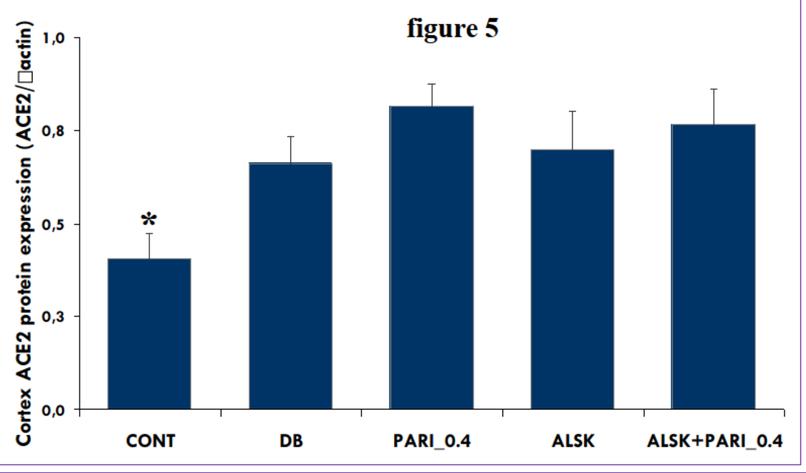


figure 5



CONCLUSIONS

• In the NOD diabetic mice, a type 1 diabetic model, Paricalcitol may modulate circulating ACE2 activity independently from the serum renin inhibition.

• In the early diabetic nephropathy stage, Paricalcitol treatment counterbalances the effect of diabetes on circulating ACE2 activity.

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