EFFECTS OF RAPESEED-DERIVED CHYMASE INHIBITORS ON BLOOD PRESSSURE & RENAL HAEMODYNAMICS & EXCRETION IN GENETICALLY DETERMINED HYPERTENSION

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INTRODUCTION

Chymase is known as a tissue angiotensin II-generating enzyme engaged in the control of the cardiovascular system. Since the ACE-independent pathway of angiotensin II (Ang II) synthesis is known to be active in pathological conditions, chymase inhibitors could be useful in prevention of cardiovascular diseases. It was found previously that the peptides isolated from rapeseed (fragments derived from seed storage proteins: VWIS, RIY, VW and IY) effectively reduced blood pressure in spontaneously hypertensive rats (SHR), however the exact mechanism of their action has not been fully elucidated. We hypothesize that their effectiveness is based on the inhibition of non-ACE conversion of angiotensin I to Ang II. It was proposed that chymase inhibitors could be applied to inhibit the local (tissue) renin-angiotensin systems (RAS) and possibly prevent the development of cardiovascular diseases.

METHODS

We examined the effects of rapeseed-derived peptides (two out of four above-mentioned: Valine-Tryptophan-Isoleucine-Serine, **VWIS** and Arginine-Isoleucine-Tyrosine, **RIY**), with proved *in vitro* anti-chymase activity (Fig. 1) on blood pressure, renal haemodynamics and excretion in anaesthetised (sodium thiopental, 100 mg/kg i.p.), surgically prepared SHR. Male SHRs in the early (age: 7-weeks) and established stage of hypertension (16 weeks) were used. In acute experiments the peptides, at 7.5 mg/kg/h, or their solvent (0.9% NaCl) were infused intravenously (1 ml/h for 1 h). Mean arterial pressure (**MAP**), intrarenal haemodynamic parameters (laser-Doppler fluxes), including cortical blood flow (**CBF**) as well as outer- and inner medullary blood flow (**OMBF, IMBF**) were recorded throughout experiments. Perfusion of the whole kidney (**RBF**) and of the hind limb (**IBF**) was measured using non-cannulating probes (Transonic system) placed on the left renal and the right iliac arteries, respectively. Timed urine collections were made and blood was sampled to determine renal excretion, glomerular filtration rate (GFR, inulin clearance), and plasma parameters.

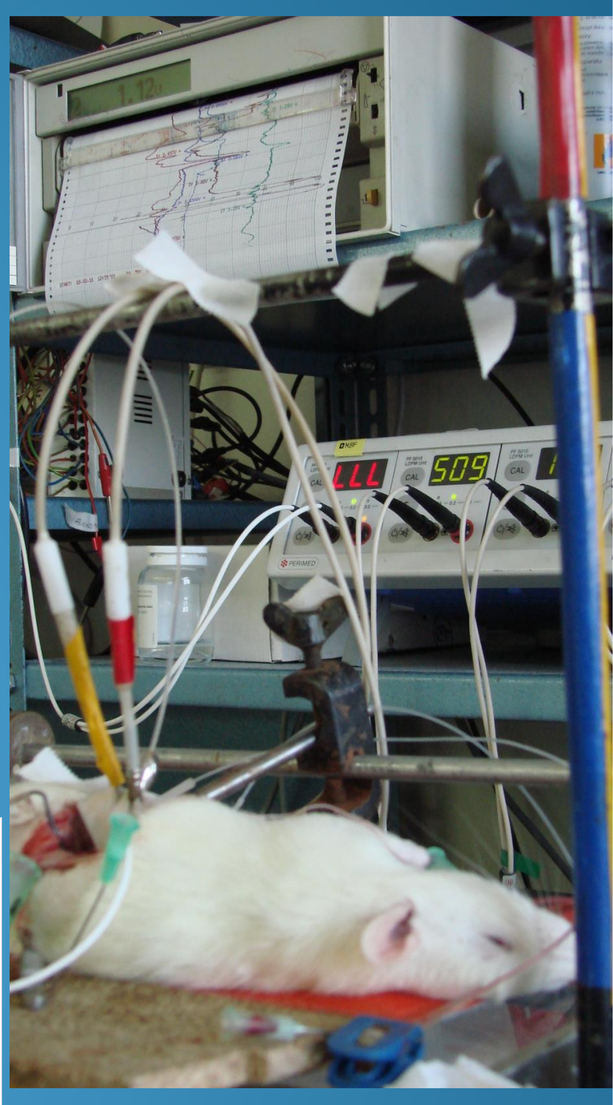
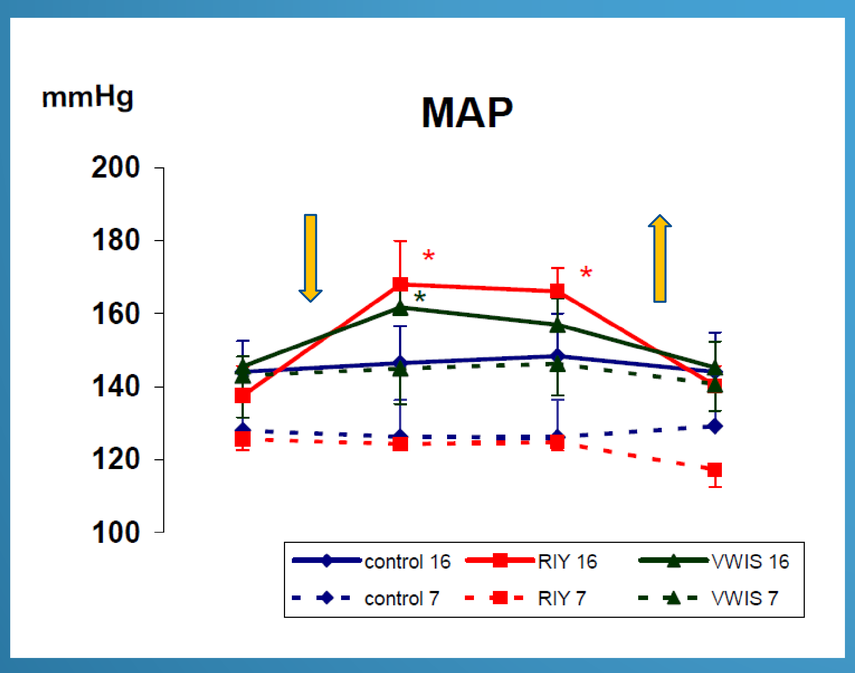


Fig. 2



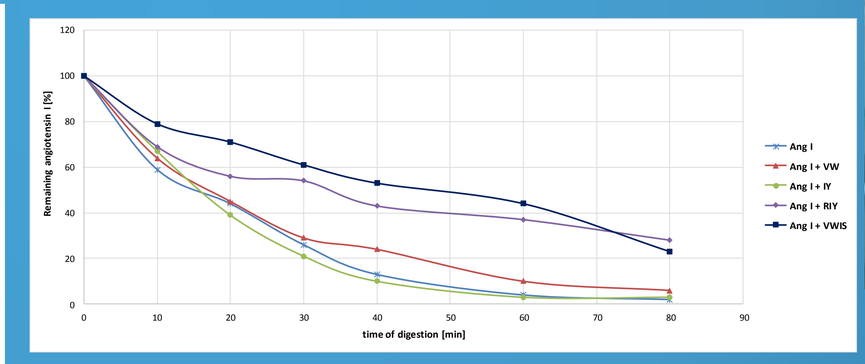
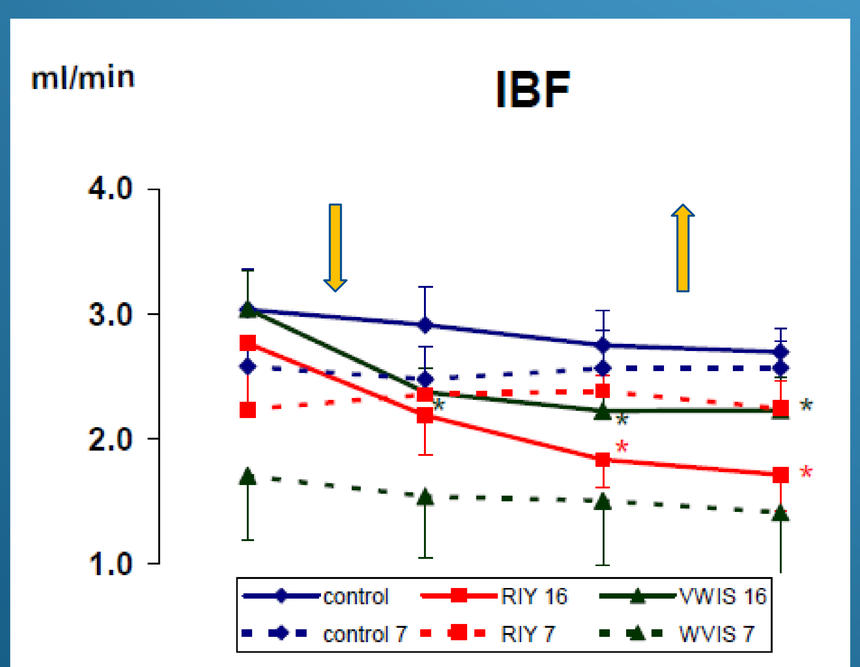
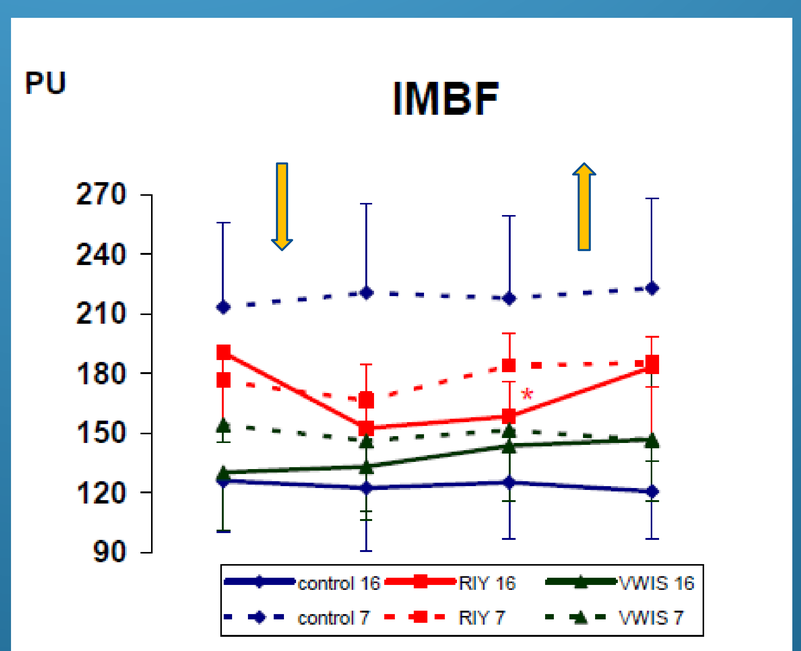


Fig. 1 Illustrates the digestion of Angiotensin I (Ang I) in human chymase solution. Ang I was incubated with the enzyme for different time periods in the absence or presence of the inhibitory peptides and the remaining Ang I amounts were determined by reversed-phase high performance liquid chromatography. These results were independently repeated in a second experiment (paired *t*-test, $p \leq 0.05$ for VWIS and RIY vs. other series).

Fig. 3





Changes in mean arterial blood pressure (MAP, Fig.2), iliac blood flow (IBF, Fig. 3) and inner medullary blood flow (IMBF, Fig. 4) in response to infusion (5.5 mg/kg; 1ml/h) of chymase inhibiting peptides (Valine-Tryptophan-Isoleucine-Serine, **VWIS** ; Arginine-Isoleucine-Tyrosine, **RIY**) or theirs' solvent (0.9%NaCl) in spontaneously hypertensive rats in early (SHR 7) and established (SHR 16) phase of disease.

Fig. 4

RESULTS & CONCLUSIONS

The changes in MAP and IBF after VWIS and RIY were found to depend on the stage of hypertension. The unexpected increase in blood pressure after chymase blockers observed in SHR 16 was prevented in pre-hypertensive rats. The decreasing tendency of MAP after RIY in 7-week old SHR could depend on the increasing tendency in renal medullary perfusion. It appears that in the early stage of hypertension the crucial pathogenetic role should be ascribed to systemic RAS, however, chronic studies are required to confirm this conclusion.

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