Effects of chymostatin, a chymase inhibitor, on blood pressure and kidney haemodynamics in different models of hypertension in the rat

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Background

Chymase:

- ❑ is known to form angiotensin II in cardiovascular and renal tissues independently of angiotensin-converting enzyme (ACE);
- ❑ its expression is elevated in pathological conditions;
- ❑ its inhibitors could have beneficial effects in the treatment of hypertension (HT);

Aim of the study

How blockade of chymase activity by chymostatin affects blood pressure and renal haemodynamic in different models of experimental hypertension?

Materials and methods

- ❑ **Acute experiments with ♂ rats:**

1. **Groups I & II**: Unilateral-nephrectomized rats maintained on high sodium diet + chymostatin (**UNX HS+Ch,** n=5) or its solvent (**UNX HS+C,** n=8) infusion
   - ➢ Right-side nephrectomy was performed in Sprague–Dawley rats two weeks before the final acute experiments; during this time rats were maintained on a high sodium (HS, 4% Na w/w) diet.
2. **Groups III & IV**: Two-kidney, one-clip Goldblatt hypertensive rats + chymostatin (**2K1C+Ch,** n=9) or its solvent (**2K1C+C,** n=6) infusion
   - ➢ In Sprague-Dawley rats, a silver clip (0.2 mm in internal diameter) was placed on a right kidney artery, 28 days prior to acute experiment.
3. **Groups V & VI**: Spontaneously hypertensive rats (SHR) in the development stage (age: 7 weeks) of hypertension + chymostatin (**SHR 7+Ch**, n=8) or its solvent (**SHR 7+C**, n=9) infusion
4. **Groups VII & VIII**: Spontaneously hypertensive rats (SHR) in the established stage (age: 16 weeks) of hypertension + chymostatin (**SHR 16+Ch**, n=8) or its solvent (**SHR 16+C**, n=9) infusion

- ❑ **Anaestesia:** sodium thiopenthal, 100 mg/Kg BW i.p.
- ❑ **Surgery and measurements:**
  - ➢ mean arterial pressure (MAP) and heart rate (HR), via a femoral artery cannula using pressure transducer (Stoelting);
  - ➢ renal blood flow (RBF), by noncannulating flow probe (1 mm in diameter) placed on left renal artery (Transonic TS420 flowmeter);
  - ➢ Renal regional blood perfusion: determined by laser-Doppler (Periflux 4001) probes placed on the kidney surface or inserted into respective zones of the medulla:
    CBF – cortical-, OMBF and IMBF - outer- and inner-medullary blood flow;
- ❑ **Chymostatin (Ch)/ solvent (C) dosage:**

  2 mg/kg/h infused i.v. during 1 hour (dissolved in 0.05% dimethyl sulfoxide (DMSO) with PBS and 0,9% sodium chloride - the final concentration of DMSO was 0,05%) was infused, bracketed by control and recovery measurement periods.

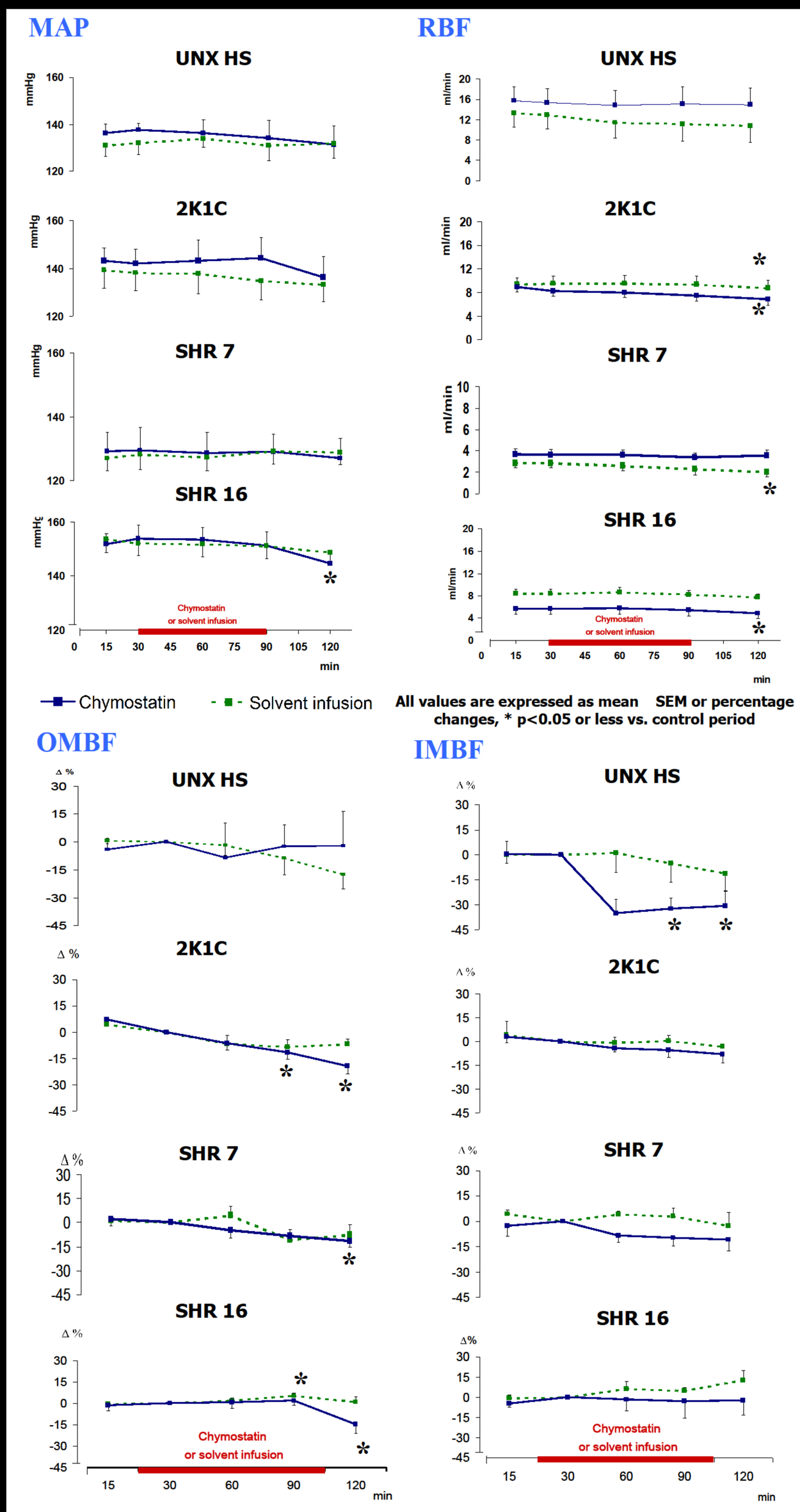
PART II Effects of chymase blocade:

❑Chymase inhibition caused a significant decrease in OMBF in all groups with one exception. In unilaterally nephrectomised rats on high sodium diet OMBF remained unchanged. Contrary, only these rats reacted by significant decrease in IMBF. CBF remained stable in all groups.

❑Haemodynamic effects of chymostatin infusion persisted until the end of experiment i.e. after discontinuation of the drug infusion.

❑It seems that in early stage of hypertension (7-weeks' SHR) the role of the **systemic RAS** remains crucial.

Results



All values are expressed as mean SEM or percentage changes, * p<0.05 or less vs. control period

Summary and conclusions

PART I Effects of chymase blocade:

❑ The degree of MAP reduction after chymostatin was found to depend on the model of HT; There was a slight decrease in MAP in each model of experimental HT, but only the 16-week SHR rats responded to chymase blockade with a significant decrease in blood pressure and RBF;

❑ The greatest MAP decrease was observed in SHR rats aged 16 weeks, which **suggests an important functional role of the ACE-independent pathway** of the tissue RAS system **in the established stage of genetically determined hypertension;**

❑ The decrease in MAP is probably responsible for the observed decrease in renal perfusion;

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