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Renin-Angiotensin system inhibitors as antihypertrophic agents

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According to the classical description the renin-angiotensin system (RAS) is involved in cardiovascular regulation by producing active angiotensin, a peptide with important vassopressor activity. Drugs inhibiting this system at different levels (such as the angiotensin-converting enzyme inhibitors (ACE) and the selective antagonists of the angiotensin II-1 (AT1) receptor), are generally used for the treatment of hypertension. Advances in research have shown that the biology of RAS is more complex. It has become clear that a number of tissular renin-angiotensin systems exist in a variety of organs such as the heart [1], vasculature [2], testis [3], brain [4] adrenal glands, kidney etc. exerting specific and localized effects [5, 6].

The tissular RAS may be involved in the regulation of cellular growth [7, 8]. In a previous study we have argued a possible role of RAS in the control of the compensatory kidney hypertrophy development (in the rat) [9]. Our present goal was to determine whether the angiotensin-converting enzyme inhibitors ramipril and enalapril and the selective angiotensin II-1 (AT1) receptor antagonist losartan have an antihypertrophic effect.

Therefore we have introduced an experimental model for the investigation of kidney hypertrophy developed after ablation of the opposite kidney. The experiments were made on white Sprague-Dowley rats (males and females) having access to a standard lab feeding (160 to 240 g weigh).

We have investigated the kidney mass obtained by extirpation made with the occasion of unilateral nephrectomy (control group, $n = 11$) and the kidney mass of the restant kidney 7 days after the unilateral nephrectomy (the group with compensatory kidney hypertrophy, $n = 11$). After the unilateral nephrectomy one special group of animals was treated with losartan (1 mg/kg body weigh, $n = 16$), the second group was treated with enalapril (25 mg/kg body weigh $n = 18$) and the third group with ramipril (5 mg/kg body weigh, $n = 9$). The experimental surgery was done using nembutal (35 mg/kg body weigh i.p.) for anesthesia. The harvested kidneys were weight. For statistical analysis the Student's t-test was used.

Our results (Fig.) show that the growth related to compensatory kidney hypertrophy after 7 days was $33.4 \pm 9.46\%$ (mean $\pm$ s.d.) under losartan treatment this growth was only $16.06 \pm 6.63\%$, under enalapril $13.46 \pm 5.2\%$, and under ramipril $8.51 \pm 3.12\%$. The treatment induced significant changes of the hypertrophy levels ($p < 0.01$) in all cases.

It is obvious that the compensatory growth can be reduced using angiotensin-converting enzyme inhibitors (ramipril and enalapril) and a selective antagonist of the angiotensin II-1 (AT1) receptor (losartan). The antihypertrophic effect of ramipril and enalapril can be explained by their action on the RAS (they decrease the angiotensin II level) but also by their action on the bradykinin system (they increase the level of bradykinins) [10]. On the other hand, losartan acts only on the RAS and the antihypertrophic effect is maintained.

We can conclude that the renin-angiotensin system is involved in compensatory kidney hypertrophy. We can control the compensatory growth of the kidney using angiotensin-converting enzyme inhibitors (ramipril and enalapril) or the selective antagonist of the angiotensin II-1 (AT1) receptor (losartan). The mechanism of action is under study; free oxygen radicals may be involved [11].

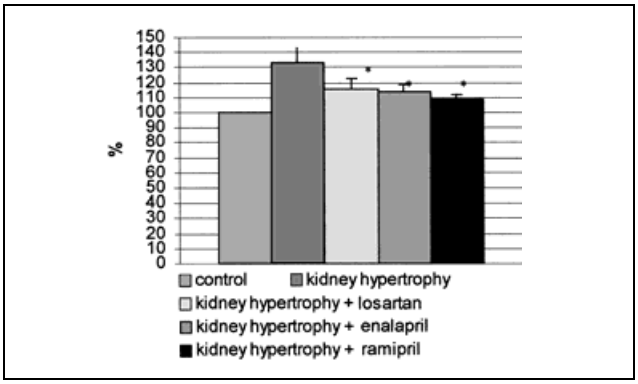

Fig.: The influence of losartan, enalapril and ramipril on the development of the compensatory kidney hypertrophy at the rat, *$p < 0.01$

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Received Febuary 28, 2000
Accepted April 8, 2000

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