Sodium Depletion Enhances the Antiproteinuric Effect of ACE Inhibition in Established Experimental Nephrosis

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Dear Sir,

The beneficial effect of angiotensin-**I**-converting-enzyme inhibition (ACEi) to prevent both a rise in proteinuria as well as progression of renal function loss has been documented in different models of experimental nephrosis [1]. Extrapolation to the human situation however seems rather hazardous, since the majority of these animal studies started ACEi before or immediately after disease induction, whereas treatment in patients is only started at the time that renal disease is fully established. This difference in disease state when starting ACEi may have consequences for the interpretation of data; the level of proteinuria in the animal studies may be an indication of the amount of structural damage to glomeruli, whereas the antiproteinuric effect of ACEi in the human situation, according for instance to its reversibility, is probably due to a functional alteration. Only a few animal studies have, in analogy to the human situation, investigated the effect of ACEi in an established disease state. Some investigators found no effect of ACEi on proteinuria [2-4], while others found a significant decrease [5-7]. In man sodium depletion is necessary to obtain an optimal antiproteinuric effect of ACEi [8]. We hypothesized that differences in sodium intake and volume status between the above-mentioned animal studies could account for the conflicting results. We therefore studied the effect of differences in sodium intake on proteinuria and on

the antiproteinuric effect of ACEi in an experimental model of established adriamycin nephrosis.

Ten male Wistar rats, age 12 weeks, weighing 270 ± 12 g, were injected with adriamycin in a dose of 3 mg/kg i. v. to induce nephrosis. The study consisted of four periods during which 24-hour protein was measured twice weekly and blood pressure once weekly. Every period lasted until a stabilization of proteinuria and blood pressure was achieved. Statistical analysis was performed by non-parametric analysis of variance (Kruskal-Wallis) using the last, stable, values of each period. Significance was assumed at $p < 0.05$. During the first period all rats were fed a low-salt diet, containing 0.05% NaCl. Six weeks were allowed for proteinuria to develop and stabilize. In period 2, lasting 4 weeks, rats were matched for blood pressure and proteinuria and divided into two groups in order to study the effect of different sodium intake on these parameters. One group ($n = 5$) continued the low-salt diet, while the other group ($n = 5$) received

a 'high'-salt diet, containing 0.3% NaCl, which is comparable to standard chow. No significant changes occurred in blood pressure or proteinuria between the two groups (fig. 1). Both groups continued their diets throughout the rest of the study. In period 3, lasting 4 weeks, addition of lisinopril in the drinking water, in a dose of 2.5 mg/kg, lowered proteinuria and blood pressure significantly in both groups. The antiproteinuric effect in the low salt group ($-82.4 \pm 5.2\%$) appeared to be significantly greater compared to the high salt group ($-52.8 \pm 8.0\%$). The blood-pressure-lowering effect was also, albeit not significantly, enhanced in the low-salt group. The results show that the maximum antiproteinuric effect is achieved only several weeks after the start of treatment, similar to human data. This is also true for the blood pressure lowering effect, which seems to parallel the antiproteinuric effect. Withdrawal of the drug in period 4, lasting another four weeks, resulted in an increase of blood pressure and proteinuria to pre-treatment values in almost every individual rat. This reversibility in both groups suggests that the antiproteinuric effect of ACEi is based on a functional alteration, rather than due to long term effects on preventing glomerular damage. We conclude that differences in sodium-intake per se do not seem to affect proteinuria. The ACE-inhibitor lisinopril lowers proteinuria and blood pressure in male Wistar rats with established adriamycin nephrosis. Sodium depletion potentiates these effects. We hypothesize that the conflicting results of studies on antiproteinuric effects of ACEi in experimental established nephrosis might in part be due to differences in sodium-intake.

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Fig. 1. Time course of systolic blood pressure (SBP, upper part) and proteinuria (lower part) after adriamycin (ADM) injection. Solid line and symbols represent the low salt group, dashed line with open symbols represents the high salt group. Data are given as mean $\pm$ SEM. (* = $p < 0.05$; period 3 versus period 2 in same group. † = $p < 0.05$; low versus high salt group in same period).

200-
80 100 120 140 days after ADM injection

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