

## PROTECTIVE EFFECTS OF AT1-RECEPTOR BLOCKER AND CA ANTAGONIST COMBINATION ON RENAL FUNCTION IN SALT LOADED SPONTANEOUSLY HYPERTENSIVE RATS

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### Abstract

Salt sensitive hypertension is known to be a contributing factor for the progression of kidney disease. This study was undertaken to investigate the role of excessive dietary salt on renal function and to evaluate the effect of valsartan and amlodipin given as a combination therapy on blood pressure and parameters specific to the renal function in salt loaded SHR rats. 48 male SHR rats at age of 20 weeks and body weight ranging between 270–350 g were used. SHR rats were divided into 3 groups: control group of rats -SHRC (n = 16) given tap water *ad libitum* and two salt treated groups in which tap water was replaced with a solution of NaCl (1%) from age of 8 weeks given *ad libitum*: SHRVAL+AMLO group (n = 16) where investigated drugs were administered at a dose of 10 mg/kg/ b.w. (valsartan) and 5 mg/kg/ b.w. (amlodipin) by gavage and SHR NaCl group (n = 16) that received saline in the same volume and the same time intervals as the SHRVAL+AMLO group. For a period of 12 weeks we have investigated the effect of the VAL+AMLO drug combination on systolic blood pressure (SBP), body weight and renal function tests. Salt loading with 1% solution in the SHR NaCl group has led to significant increase of blood pressure, proteinuria and decrease in creatinine clearance. Combined treatment with AT1-receptor blocker and calcium antagonist has managed to control blood pressure and ameliorated renal damage.

**Key words:** Salt loading, SHR rats, renal function, valsartan, amlodipin.

### Introduction

Salt sensitive hypertension is known to be a contributing factor for the progression of kidney disease as well as for cardiovascular diseases [1, 2]. Increased dietary salt intake beyond elevating the arterial pressure promotes kidney damage through non pressure related effects [3]. Antihypertensive drugs particular those that target the rennin-angiotensin system are able to blunt the progression of renal disease in hypertension [4–6]. As one of therapeutic strategies a combination of angiotensin II

receptor blocker (ARB) and calcium antagonist (CA) is mentioned. ARB and CA lower blood pressure by reducing peripheral resistance with calcium influx blockage and reduction of Ang II vasodilatation as complementary mechanisms. This complementary mechanism suggests that a combining therapy would lead to an optimal control of the blood pressure and slower progression of hypertension with potentiating of the protective effect of the kidneys as a hypertension target organ.

The spontaneously hypertensive rats (SHR) are considered a suitable model of essential hypertension as the natural progression of hypertension and organ damage including the kidneys are similar to man [7, 8]. As in humans, kidney damage and the progressive decline in glomerular filtration rate (GFR) occur at a much later stage in SHR [9]. SHR rats are also considered to be a salt-sensitive animal model [10, 11]. Salt sensitivity in SHR is more pronounced if salt loading is started at younger period (8 weeks old) leading to increased arterial blood pressure and development of structural and functional changes [12].

Goal of this study is to investigate the role of excessive dietary salt on renal function and to evaluate the effect of valsartan (ARB) and amlodipin (CA) given as a combination therapy on the blood pressure and parameters specific to the renal function in salt loaded SHR rats.

### Materials and methods

In this study 48 male SHR rats were used. These animals were 5 generation of rats originating from Charles River Laboratories Inc. bred at the animalia of the Institute of Preclinical and Clinical Pharmacology and Toxicology, Med. Fac. SK.

In order to minimize the effects of the inter-individual differences, all animals were at age of 20 weeks and body weight ranging between 270–350 g. Rats were fed with standard rats chow and housed in cages in groups of 5–6 in a temperature controlled environment (~22°C) and 12h light/dark cycle. The experimental protocol met the national guidelines on proper care and use of animals in laboratory research.

SHR rats were divided into 3 groups: control group of rats -SHRC (n = 16) that were given tap water *ad libitum* for the complete course of the study and two salt treated groups in which from age of 8 weeks tap water was replaced with a solution of NaCl (1%) given *ad libitum*: SHRVAL+AMLO group (n = 16) in which investigated drugs were administered at a dose of 10 mg/kg/ b.w. (valsartan) and 5 mg/kg/ b.w. (amlodipin) by gavage and SHRNAI group (n = 16) that received saline in the same volume and the same time intervals as the group of animals receiving the tested drugs.

For a period of 12 weeks we have investigated the effect of the VAL+AMLO drug combination on systolic blood pressure (SBP), body weight and renal function tests. SBP was measured by a plethysmographic method (IITC Life Science MRBP Blood Pressure System, California, USA) on the rats tail. Body weight was measured every second week of treatment. Renal functional tests were performed periodically (every 4 weeks) after urine was collected in metabolic cages in 24 hour intervals for determination of the following parameters: diuresis (24 hour urine), pH analysis, proteinuria and urine creatinine. Urine pH was measured by using test strips (Combina 10 M, Human GmbH, Germany), urine protein in 24-hour urine samples were determined turbidimetrically (Biochemical analyser ChemWell Awareness Technology) with sulfosalicylic acid according to the method of Meulemans et al [13].

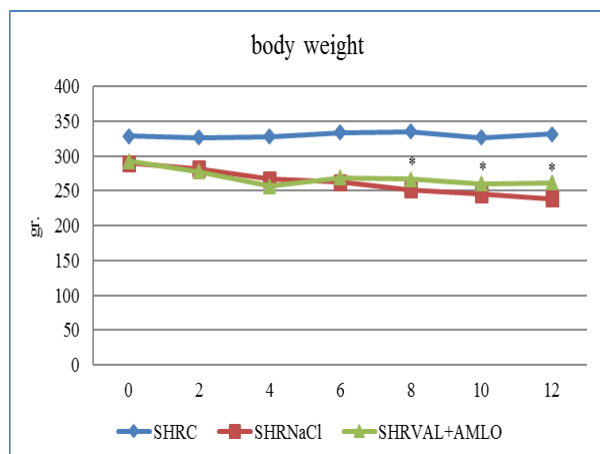
Creatinine clearance was used as a specific sensitive marker for detection of altered renal function of the animals. In order to determine the serum levels of creatinine, blood was taken by venipuncture from the orbital sinus of the rats. Blood samples of 400 µl were taken for serum separation (200 µl). Serum and urine creatinine were determined photometrically according to the method of Bartels et al [14]. Creatinine clearance (CrCl) was calculated from the creatinine concentration in the collected urine sample, urine flow rate and the plasma concentration of creatinine.

Statistical analysis: Data were expressed as mean ± SD. Student's unpaired and paired t-test and one way analysis of variance ANOVA were used as appropriate. P values < 0.05 were considered as statistically significant.

### Results

**Body weight:** For the investigative period, compared to the control group a decrease of body weight was noticed in the SHR NaCl group as well as in the SHRVAL+AMLO group (p < 0.001). The decrease of body weight in the SHR NaCl group of rats was gradual for the whole treatment period and by week 12 was significantly lower compared to baseline values (17.4%). In the SHRVAL+AMLO group a marked decrease of body weight was noticed starting from week 2 to week 4 (12.36%). Since

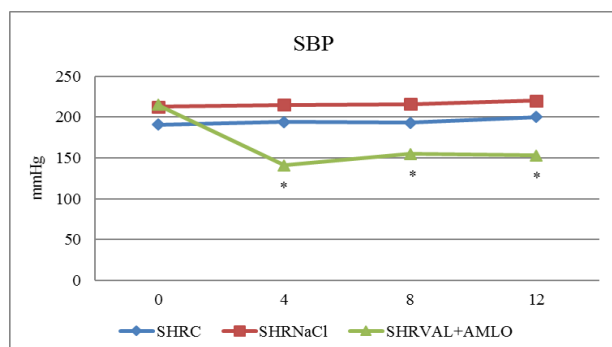
decrease of body weight was followed by a decrease of blood pressure, from week 4 a dose adjustment was made to 5 mg/kg/ valsartan + 2.5 mg/kg/amlodipine. This dose was given till the end of the study. Body weight in the SHRVAL+AMLO group by week 8 till week 12 was significantly higher compared to SHR NaCL group ( $p < 0.01$ ) (Figure 1).



\*  $p < 0.01$  SHRVAL+AMLO vs. SHRNAcl

Figure 1 – Effects of valsartan/amlodipin combination on body weight in salt loaded SHR rats in comparison to a control group for a investigative period of 12 weeks

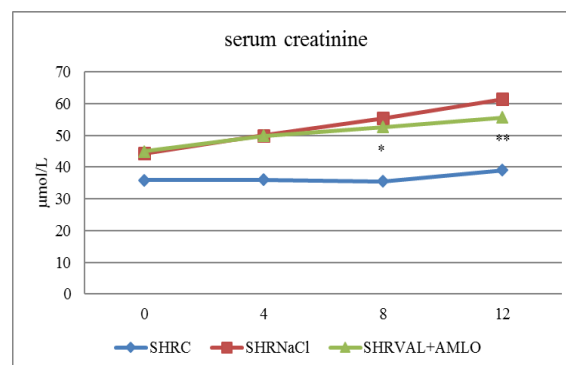
**Systolic blood pressure:** For the investigative period gradual increase of blood pressure was noticed in the SHR NaCL group. In the SHRVAL+AMLO group a significant decrease of blood pressure was noticed in the first 4 weeks of dosing (35%). For the period of 4–12 weeks with the adjusted dose the decrease of blood pressure was still statistically significant ( $p < 0.001$ ) between SHR NaCL and SHRVAL+AMLO group (Figure 2).



\*  $p < 0.001$  SHRVAL+AMLO vs. SHRNAcl

Figure 2 – Effects of valsartan/amlodipin combination on systolic blood pressure in salt loaded SHR rats in comparison to a control group for a investigative period of 12 weeks

**Serum Creatinine:** Compared to the control group of rats a significant increase of serum creatinine was noticed in the SHR NaCL group as well as in the SHRVAL+AMLO group ( $p < 0.001$ ). In the SHR NaCL group continuous increase of the serum creatinine was noticed. By week 12 creatinine was increased to  $61.45 \pm 6.12 \mu\text{mol/L}$  (38.65%) compared to baseline values. In the SHRVAL+AMLO group a decrease of serum creatinine compared to SHR NaCL group was noticed from week 8 as 16.9% ( $p < 0.05$ ) to 23% for week 12 ( $p < 0.01$ ) (Figure 3).



\* $p < 0.05$  \*\* $p < 0.01$  SHRVAL+AMLO vs. SHRNAcl

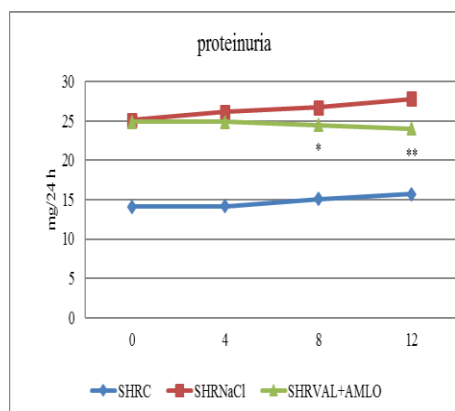
Figure 3 – Effects of valsartan/amlodipin combination on serum creatinine levels in salt loaded SHR rats in comparison to a control group for a investigative period of 12 weeks

**Diuresis:** For the investigative period, compared to the control group of rats a increase of diuresis was noticed in the SHR NaCL group as well as in the SHRVAL+AMLO group ( $p < 0.001$ ). In the SHR NaCL group by week 12 diuresis was increased to  $37.31 \pm 5.72 \text{ ml/24h}$  (9.96%) compared to baseline values. In the SHRVAL+AMLO group a significant ( $p < 0.001$ ) decrease of diuresis compared to SHR NaCL was noticed starting from week 4 as  $30.63 \pm 3.3 \text{ ml/24h}$  (22.45%) to  $24.38 \pm 3 \text{ ml/24h}$  (38.27%) for week 8 and  $22.63 \pm 2.9 \text{ ml/24h}$  (42.7%) for week 12.

**Urine pH:** Between the three investigated groups of animals there was no significant difference in urine pH.

**Proteinuria:** In the SHR NaCL group a significant ( $p < 0.001$ ) increase of the proteinuria compared to baseline values was noticed. Proteinuria was increased to  $26.17 \pm 1.97 \text{ mg/24h}$  for week 4 (4.22%),  $26.71 \pm 1.86 \text{ mg/24h}$  for week 8 (6.37%) and  $27.84 \pm 1.58 \text{ mg/24h}$  (10.87%) for week 12.

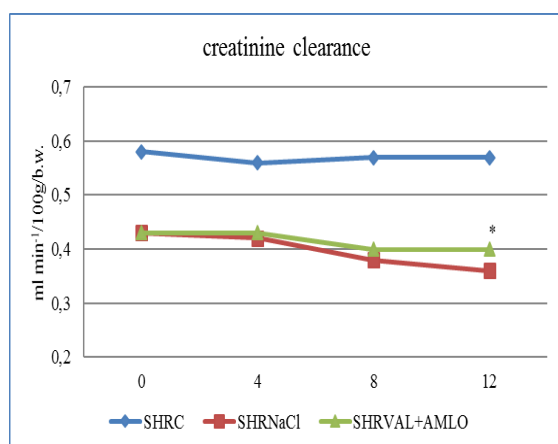
In the SHRVAL+AMLO group proteinuria increase was less pronounced than the SHR NaCl group -values ranging from week 4 as  $24.87 \pm 2.1$  mg/24h, week 8 as  $24.47 \pm 1.86$  mg/24h (1.6%  $p < 0.01$ ) and  $24.02 \pm 1.69$  mg/24h (3.41%  $p < 0.001$ ) for week 12 (Figure 4).



\* $p < 0.01$  \*\* $p < 0.001$  SHRVAL+AMLO vs. SHRNaCl

Figure 4 – Effects of valsartan/amlodipin combination on urinary protein excretion in salt loaded SHR rats in comparison to a control group for a investigative period of 12 weeks

**Creatinine clearance:** Creatinine clearance was used as specific parameter to assess GFR. In the SHR NaCl group creatinine clearance gradually decreased in comparison to the control group and the baseline values (16%  $p < 0.05$ ). Treatment with the combination of valsartan and amlodipin prevented the decrease of creatinine clearance and by week 12 in the SHRVAL+AMLO group decrease of creatinine clearance was 6.9% ( $p < 0.001$ ) (Figure 5 and 6).



\*  $p < 0.001$  SHRVAL+AMLO vs. SHRNaCl

Figure 5 – Effects of valsartan/amlodipin combination on creatinine clearance in salt loaded SHR rats in comparison to a control group for a investigative period of 12 weeks

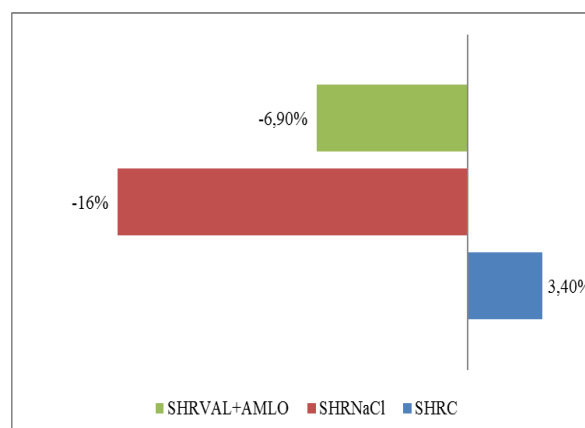


Figure 6 – Decrease/Increase of creatinine clearance (%) at the end of the study

## Discussion

Many epidemiological studies in humans have suggested a positive correlation between habitual salt intake and the prevalence of hypertension [15–18]. Although the relationship between salt intake and blood pressure can be clearly demonstrated by comparing populations with extremes in salt intake, this is less apparent when individuals are placed on diets with different contents of salt [19]. As one of possible explanation is that the increase of blood pressure to a large extent depends on genetic factors.

Variations of genetic susceptibility to salt can be investigated on experimental animals. Spontaneously hypertensive rats are often used animal model of human essential hypertension [7]. In SHR rat hypertension can be influenced from the interaction between genetic and environmental factors [20–22]. Since development of hypertension is genetically determent and blood pressure progressively rises after the 8th week of their lives reaching maximum of 170–210 mmHg the additional environmental influences such as excessive salt intake can modify the course and the severity of hypertension. Salt sensitivity in SHR is also influenced by age. Young rats (8 weeks old) have increased arterial pressure in response to salt loading inn contrast to adult rats (17 weeks) who are less sensitive [23]. In our study we have investigated the effects of salt loading as 1% solution of NaCl given from the period of 8 to 32 week of age.

Long-term salt loading in the SHR NaCl group has lead to 17.4% decrease of body weight and gradual increase of blood pressure.

Compared to the control group increase of blood pressure was significant ( $p < 0.001$ ) for the entire investigative period. Proteinuria and creatinine clearance were used as more specific parameters of renal function and glomerular filtration rate. A significant ( $p < 0.01$ ) increase of urine protein values was recorded in the period 4–8 week of the study. These values were additionally increased (10.87%  $p < 0.001$ ) for week 12. Creatinine clearance gradually decreased in comparison to baseline values (16%  $p < 0.05$ ) leading to a conclusion that in the SHR NaCl group a renal suffering in a form of chronic renal failure has started to develop. Several authors have investigated effects of salt loading in SHR rats in similar salt concentrations [24, 25] and reported results confirming SBP increase followed by aggravation of vascular changes (thickening of aortic media, narrowing of lumina and greater wall thickness in small intrarenal arterial vessels). Matavelli et al. have investigated the effects of different concentrations of salt in rats chow (4%, 6% and 8% of NaCl) starting from 8 weeks of age. Salt loading even in the 4% NaCl deteriorated renal function, renal and glomerular hemodynamic in SHR rats independent of arterial pressure. Proteinuria and albuminuria rised progressively in the second week of salt loading in the 6 and 8% group of rats [26].

The rennin angiotensin aldosterone system (RAAS) is mentioned as one of possible mechanisms by which renal injury with salt loading happens. Salt loading suppresses rennin release from the renal juxtaglomerular apparatus leading to a reduction in systemically generated angiotensin II [27]. However, experimental studies have demonstrated a local participation of the RAAS in the kidneys suggesting that despite the systemic suppression during salt loading locally generated renal RAAS is stimulated [28–30]. Antihypertensive drugs particular those that target the rennin-angiotensin system are thought to able to control the progression of renal disease in hypertension [25, 32]. Valsartan and amlodipin lower blood pressure by reducing peripheral resistance with calcium influx blockage and reduction of Ang II vasoconstriction as complementary mechanisms. In this study a combination therapy of valsartan and amlodipin was used (starting

dose of 10 mg/kg/ b.w. valsartan and 5 mg/kg/ b. w. amlodipin).

Because of marked decrease of body weight in the SHRVAL+AMLO group followed by a decrease of blood pressure, from week 4 a dose adjustment was made to 5 mg/kg/ valsartan + 2.5 mg/kg/amlodipine. Combination therapy with the adjusted dose in the SHRVAL+AMLO group had lead to significant decrease of blood pressure ( $216 \pm 10.48$  vs.  $155 \pm 5.48$  week 12) followed with decrease of serum creatinine and proteinuria. Combination therapy also prevented the decrease of creatinine clearance.

### Conclusion

Salt loading with 1% solution in the SHR NaCl group has lead to significant renal damage. Combined treatment with angiotensin II receptor blocker and calcium antagonist has managed to control blood pressure, excessive urinary protein excretion and creatinine clearance.

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## Резиме

**ПРОТЕКТИВНИ ЕФЕКТИ  
НА КОМБИНАЦИЈАТА  
НА AT1 РЕЦЕПТОРЕН БЛОКАТОР  
И КАЛЦИУМ АНТАГОНИСТ  
ВРЗ РЕНАЛНАТА ФУНКЦИЈА  
КАЈ СПОНТАНО ХИПЕРТЕНЗИВНИ  
СТАОРЦИ ОПТОВАРЕНИ СО СОЛ**

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Познато е дека хипертензијата зависна од сол придонесува кон прогресија на бубрежните заболувања. Ова испитување беше преземено со цел да се одреди влијанието на екцесивното внесување сол врз бубрежната функција, како и да се одреди ефектот на валсартан и амлодипин дадени во комбинација врз крвниот притисок и параметрите специфични за бубрежната функ-

ција кај спонтано хипертензивни стаорци оптоварени со сол. Во испитувањето беа употребени вкупно 48 стаорци од машки пол на возраст од 20 недели и телесна тежина меѓу 270–350 грама. Стаорците беа поделени во три групи: контролна група SHRC (n = 16), кај која во текот на целото испитување беше давана вода *ad libitum*, и две групи стаорци кај кои на возраст од 8 недели водата беше заменета со раствор на NaCl (1%) *ad libitum*: група SHRVAL+AMLO (n = 16) кај која лековите беа аплицирани во доза од 10 mg/kg/ т.т. (valsartan) и 5 mg/kg/ т.т. (amlodipin) со интрагастрична сонда и SHRNaCl група (n = 16), која примаше физиолошки раствор во ист волумен и во ист временски интервал како групата SHRVAL+AMLO. Во период од 12 недели беше одредуван ефектот на комбинацијата на валсартан со амлодипин врз крвниот притисок, телесната тежина и параметри специфични за бубрежната функција. Оптоварувањето со сол како 1% раствор во групата SHRNaCl доведе до сигнификантно зголемување на крвниот притисок, појава на протеинурија и намалување на клиренсот на креатинин. Комбинираниот третман со AT1 рецепторен блокатор и калциум антагонист соодветно го контролираше крвниот притисок и ја подобри бубрежната функција.

**Клучни зборови:** оптоварување со сол, бубрежна функција, СХР-стаорци, валсартан, амлодипин.