EFFECTS OF HIGH SALT LOAD ON RENAL HEMODYNAMICS AND FUNCTION IN NORMOTENSION AND HYPERTENSION: ROLE OF Alpha$_1$-ADRENOCEPTOR

ABSTRACT

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Hypertension is a major cause of coronary heart disease, renal failure and stroke. Sodium plays an important pathophysiological role in the development of hypertension. The renal adrenergic system contributes to the hypertensive effect of sodium loading. The aim of this study was to investigate whether elevated dietary sodium intake had any effect on the mean arterial blood pressure (MAP) and renal cortical vascular reactivity to adrenergic stimuli in terms of its relation to α_1-adrenergic mechanism. Further this study aimed to identify the contribution of α_1-adrenoreceptor subtypes in the regulation of renal cortical hemodynamic and renal tubular functions in both normotensive WKY (Wistar Kyoto rat) and SHR (spontaneously hypertensive rats) subjected to high sodium load. Both SHR and WKY rats were kept on normal (WKYNNa & SHRNNa) and high sodium diet (WKYHNa & SHRHNa) for six weeks and the metabolic data collected. The animals were housed individually in custom-built stainless steel metabolic cages; baseline data were determined followed by experimental data collection for six consecutive weeks. Weekly blood and urine samples were collected, and body weight, 24-h water intake and 24-h urine output were measured. The rats were subjected to acute renal hemodynamic and functional studies at the end of the 6-

weeks period of metabolic data collection. In the renal hemodynamic study, changes in the renal cortical perfusion (RCP) of the animals caused by close renal arterial administration of noradrenaline (NA), phenylephrine (PE), and methoxamine (ME) were determined in the absence and presence of 5-MeU, chloroethylclonidine (CEC) and BMY7378. Renal tubular functional parameters namely glomerular filtration rate (GFR), urine flow rate (UFR), absolute and fractional sodium excretion ($U_{Na}V$ & FE_{Na}) upon infusion of PE in the absence and presence of 5-MeU, CEC and BMY7378 were assessed as a measure of inulin clearance. Data, mean ± s.e.m., were analyzed with one and two way analysis of variance followed by Bonferroni post hoc with the significance level of 5%. Results showed that MAP in SHRHNa and WKYHNa diet and in the control SHRNNa and WKYNNa diet were not statistically significantly different. There was significant ($p<0.05$) increase in the water intake, urine output, urine sodium of WKYHNa and SHRHNa compared to control groups. Statistically significant ($p<0.05$) increase in the body weight observed only in the WKYHNa verses WKYNNa. Plasma sodium remains unchanged in both SHRHNa and WKYHNa diet as compared to the control. Both SHRHNa and WKYHNa groups expressed significantly enhanced renal cortical vascular sensitivity to NA, PE, and ME compared to control SHRNNa & WKYNNa. Renal vasoconstrictor response to NA, PE and ME was significantly ($p<0.05$ for all) attenuated by 5-MeU and BMY7378 in SHR and WKY on normal and high sodium diet. On the one hand, CEC accentuated ($p<0.05$) the renal vasoconstrictor response to NA, PE and ME in SHRNNa and WKYNNa. On the other hand in SHRHNa and WKYHNa groups, renal cortical vasoconstriction to NA, PE and ME was inhibited (all $p<0.05$) by CEC. SHRHNa and WKYHNa showed exaggerated increase in the diuresis and natriuresis. Irrespective of dietary sodium intake, PE infusion led to

significant ($p<0.05$) antidiuresis and antinatriuresis in WKY and SHR. This antidiuretic and antinatriuretic response to PE was significantly ($p<0.05$) inhibited by 5-MeU and BMY7378 in WKYNNa diet, while 5-MeU significantly ($p<0.05$) attenuated the antidiuretic and antinatriuretic response to PE in SHRHNa. There were no significant changes observed in the RCP, RAP (renal arterial pressure) and GFR during renal tubular functional experiments. Thus it is concluded that, augmented α_1-adrenergic responses to adrenergic stimuli contribute to salt-related increase in renal vascular sensitivity in SHRHNa and WKYHNa. Irrespective of dietary sodium intake α_{1A} and α_{1D}-adrenoceptors are the functional subtypes involved in mediating the adrenergically induced renal cortical vasoconstriction in SHR and WKY rats. On the other hand α_{1B}-adrenoceptors are the functional subtype involved in mediating the adrenergically induced renal cortical vasoconstriction in WKYHNa and SHRHNa. Furthermore, α_1-adrenoceptors are involved in the mediation of antinatriuresis and antidiuresis in SHR and WKY rats on normal and high sodium diet. In addition, it is proposed that α_{1A} and α_{1D}-adrenoceptors are the functional subtypes involved in mediating the adrenergically induced antidiuresis and antinatriuresis in WKYNNa. On the other hand α_{1A}-adrenoceptors mediate the antidiuresis and antinatriuresis in SHRHNa diet.