Role of a RhoA/ROCK-dependent pathway on renal connexin43 regulation in the angiotensin ii-induced renal damage

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In various models of chronic kidney disease, the amount and localization of Cx43 in the nephron is known to increase, but the intracellular pathways that regulate these changes have not been identified. Therefore, we proposed that: ?In the model of renal damage induced by infusion of angiotensin II (AngII), a RhoA/ROCK-dependent pathway, is activated and regulates the abundance of renal Cx43". In rats, we evaluated: 1) the time-point where the renal damage induced by AngII is no longer reversible; and 2) the involvement of a RhoA/ROCK-dependent pathway and its relationship with the amount of Cx43 in this irreversible stage. Systolic blood pressure (SBP) and renal function (urinary protein/urinary creatinine: Uprot/UCrea) were evaluated as systemic and organ outcomes, respectively. In kidney tissue, we also evaluated: 1) oxidative stress (amount of thiobarbituric acid reactive species), 2) inflammation (immunoperoxidase detection of the inflammatory markers ED-1 and IL-1?), 3) fibrosis (immune detection of type III collagen; Col III) and 4) activity of RhoA/ROCK (amount of phosphorylated MYPT1; p-MYPT1). The ratio Uprot/UCrea, SBP, oxidative stress, inflammation, amount of Cx43 and p-MYPT1 remained high 2 weeks after suspending AngII treatment in rats treated for 4 weeks with AngII. These responses were not observed in rats treated with AngII for less than 4 weeks, in which all measurements returned spontaneously close to the control values after suspending AngII treatment. Rats treated with AngII for 6 weeks and co-treated for the last 4 weeks with Fasudil, an inhibitor of ROCK, showed high SBP but did not present renal damage or increased amount of renal Cx43. Therefore, renal damage induced by AngII correlates with the activation of RhoA/ROCK and the increase in Cx43 amounts and can be prevented by inhibitors of this pathway.

Cx43

Fasudil

Fibrosis

Hypertensive nephropathy

Inflammation

Oxidative stress

alpha tubulin

angiotensin II

CD68 antigen

collagen type 3

collagen type 4

connexin 43

creatinine

fasudil

interleukin 1beta

mypt1 protein

peptides and proteins

protein

Rho kinase

RhoA guanine nucleotide binding protein

thiobarbituric acid reactive substance

unclassified drug

1 (5 isoquinolinesulfonyl) 2 methylpiperazine

angiotensin II

connexin 43

creatinine

fasudil

GJA1 protein, mouse

Rho kinase

RhoA guanine nucleotide binding protein

RhoA protein, mouse

animal experiment

animal model

animal tissue

Article

clinical evaluation

clinical outcome

controlled study

correlation function

creatinine urine level

enzyme activation

enzyme activity

histopathology

immunoperoxidase staining

inflammation

kidney fibrosis

kidney function

kidney injury

kidney tissue

male

nonhuman

oxidative stress

protein phosphorylation

protein urine level

rat

regulatory mechanism

renal protection

signal transduction

systolic blood pressure

animal

disease model

gene expression regulation

kidney disease

metabolism

signal transduction

time factor

urine

1-(5-Isoquinolinesulfonyl)-2-Methylpiperazine

Angiotensin II

Animals

Connexin 43

Creatinine

Disease Models, Animal

Gene Expression Regulation

Kidney Diseases

Male

Oxidative Stress

Rats

rho-Associated Kinases

rhoA GTP-Binding Protein

Signal Transduction

Time Factors