No. 1632

The Mechanism of Salt-Sensitive Hypertension in Diabetic Nephropathy and Novel Antihypertensive Therapy Using Its Inhibitors

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Summary

Chronic kidney disease caused by diabetic nephropathy (DN) is characterized by proteinuria, Na retention and hypertension. In the setting of proteinuria, serine protease such as plasmin filtered through damaged glomeruli could activate the epithelial Na channel (ENaC) leading to hypertension, independently of aldosterone. In this study, we evaluated effects of a synthetic serine protease (SP) inhibitor (SPI), camostat mesilate which inhibits the plasmin activity, on salt-sensitive hypertension in a rat model of DN with high-salt (HS) diet. In addition, we studied protective effects of SPI against podocyte injury in vitro.

Five-week-old SHR and control WKY were divided into WKY, SHR, and SHR+SPI (Experiment 1), and 13-week-old SHR/ND mcr-cp (model rats for DN) were divided into normal chow (NS), HS (8.0% NaCl diet), and HS+SPI (Experiment 2). After systolic BP measurement and 24h urine collection were performed for 4 weeks, rats were sacrificed for histological examination. Urinary serine proteases were evaluated by zymography and immunoblotting.

In Experiment 1, although SHR displayed hypertension, either urinary protein excretion nor urinary serine proteases were not substantially increased. Accordingly, SPI did not prevent hypertension in SHR. In Experiment 2, HS diet induced severe hypertension, marked proteinuria and plasmin activation as well as prostasin excretion in urine in SHR/ND mcr-cp. These changes were significantly suppressed by the treatment with SPI. SPI increased urinary sodium/potassium ratio, indicating that SPI inhibited the ENaC activity. Furthermore, SPI mitigated glomerular injuries by suppressing apoptosis of podocytes.

In conclusion, SPI could exert significant antihypertensive and renoprotective effects in a rat model of DN with HS diet, suggesting that SP inhibition could be a new therapeutic strategy against salt-sensitive hypertension in DN.