Cardiac and renal protective effects of 2,5-dimethylcelecoxib in angiotensin II-induced hypertension model mice

Misaki Yamamoto¹, Fumi Takahashi-Yanaga², Toshiyuki Sasaguri¹

¹*Dept Clin Pharmacol, Faculty Med Sci, Kyushu Univ,* ²*Dept Pharmacol, Faculty Med, Univ Occup Environ Health*

We previously reported that 2,5-dimethylcelecoxib (DMC), a celecoxib derivative that is unable to inhibit cyclooxygenase-2, prevented cardiac remodeling in different types of mouse heart failure models by suppressing the Wnt/ β -catenin signaling pathway.

The renin-angiotensin-aldosterone system plays a central role in the development of chronic heart failure and chronic kidney disease. Previous reports showed that angiotensin II (Ang II) caused podocyte injury and albuminuria by activating the canonical Wnt pathway.

In the present study, therefore, we investigated the effect of DMC on cardiac remodeling and kidney injury in hypertension model mice generated by Ang II infusion in the absence or presence of high-salt load.

DMC prevented cardiac remodeling and markedly reduced urinary albumin excretion without altering blood pressure in those mice. DMC also prevented podocyte injury, glomerulosclerosis and interstitial fibrosis in the kidney in mice loaded with Ang II and high-salt. Moreover DMC significantly improved the survival rate of mice loaded with Ang II and high-salt. DMC reduced the phosphorylation level of Akt and activated glycogen synthase kinase-3 (GSK-3), which led to the suppression of the canonical Wnt pathway in the heart and kidney.

These results suggested that DMC prevented cardiac remodeling and kidney injury by inhibiting Akt-mediated phosphorylation of GSK-3 and thereby inhibiting the canonical Wnt pathway in the hypertension model mice.