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CPU0213, a novel endothelin receptor antagonist, suppresses the upregulation of matrix metalloproteinases and connexin 43 in hyperthyroid myocardium

Xiao-Yun Tang*, Qing Liu*, De-Zai Dai, Yin Dai

Research Division of Pharmacology, China Pharmaceutical University, Nanjing, 210009, China

Correspondence: De-Zai Dai, e-mail: dezaidai@vip.sina.com

Abstract:
It has been verified that endothelin-1 (ET-1) activates matrix metalloproteinase (MMP) in the process of myocardial remodeling. Sustained high thyroid hormone level gives rise to left ventricular hypertrophy, in which the ET-1 system is probably involved. We attempted to study the effects of CPU0213, a novel endothelin receptor antagonist, on myocardial remodeling induced by high dose L-thyroxin. Adult male Sprague-Dawley rats were treated with L-thyroxin (0.4 mg/kg/d, *sc*) for 10 days to induce left ventricular hypertrophy. A subset of rats was given CPU0213 from day 6 to 10. Alterations in MMP, tissue inhibitor of metalloproteinase (TIMP), and connexin 43 were measured by reverse transcription polymerase chain reaction (RT-PCR), zymography, and Western blot assays. L-thyroxin treatment resulted in increased mRNA expression and MMP-2 and MMP-9 activities, along with decreased TIMP-1 and TIMP-2 mRNA expression. CPU0213 suppressed the increased activity of MMP, and prevented the downregulation of TIMP expression. The expression of connexin 43 was upregulated at both mRNA and protein levels after L-thyroxin treatment, which was attenuated by CPU0213. In addition, L-thyroxin caused upregulation of mRNA expression of preproET-1 (ppET-1) and endothelin converting enzyme (ECE). These results suggest that the ET receptors mediate high dose L-thyroxin induced myocardial remodeling by changing MMP, TIMP activities and connexin 43.

Key words:
L-thyroxin, MMPs, connexin 43, endothelin receptor antagonist, CPU0213