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学 位 論 文 の 要 約
（研 究 成 果 の ま と め）

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学位論文名　　アンジオテンシン II ２型受容体による PPARγ 活性化を介した虚血性脳障害抑制作用

学位論文の要約

In addition to controlling blood pressure, the renin-angiotensin system (RAS) plays a crucial role in brain damage after ischemic stroke. Angiotensin (Ang) II, the major component of the RAS has many functions via binding to its type 1 (AT1) receptor and type 2 (AT2) receptor. Recently, it is suggested that stimulation of the AT2 receptor has a protective effect against ischemic brain injury. Compound 21 (C21) is a newly developed selective and potent nonpeptide direct AT2 receptor agonist, and expected to attenuate brain injury after ischemic stroke. It is well known that peroxisome proliferator-activated receptor-gamma (PPAR-γ) which is a nuclear transcription factor, plays an important role in diabetes and atherosclerosis development. Recently, PPAR-γ has been reported to exert neuroprotective role after ischemic stroke. We recently demonstrated that AT2 receptor stimulation by C21 inhibited vascular intimal proliferation with activation of PPAR-γ. It is accepted that the AT1 receptor blockers mediates its beneficial effects on multiple organ damage through both PPAR-γ pathway and AT2 receptor signaling activity. In the present study, we examined whether direct AT2 receptor stimulation by C21 inhibit ischemic brain injury via PPAR-γ activation. Eight-week-old male C57BL/6J mice were used, and brain ischemia was induced by middle cerebral artery (MCA) occlusion. Mice were administered C21 (intraperitoneally at 10 ug/kg/day) with or without GW9662 (in drinking water at 0.35 mg/kg/day), a PPAR-γ antagonist two weeks before MCA occlusion. Neurologic deficit, ischemic size, superoxide anion, superoxide dismutase (SOD) activity, expression of NADPH subunits and blood brain barrier (BBB) stabilization were assessed 24 hours after MCA occlusion. Cerebral blood flow (CBF) was measured in the core and periphery of the MCA territory before, immediately after, 1 hour and 24 hours after MCA occlusion. After MCA occlusion, ischemic area in brain section was observed in non-

treated mice. Treatment with C21 significantly decreased the neurologic deficit and ischemic area with increases in CBF, SOD activity and BBB stabilization genes compared with the non-treated group. Co-administration of GW9662 partially attenuated these protective effects of C21 on neurologic deficit and ischemic size by inhibiting the decreased superoxide anion production and the increased CBF, SOD activity and BBB stabilization genes, while GW9662 treatment alone had no significant effects on neurologic deficit and ischemic size. These results demonstrated that direct AT2 receptor stimulation by C21 has an inhibitory effect on stroke-induced brain injury at least due to activation of PPAR-γ.

All above data are involved the published paper.

Main Paper : Shan BS, Mogi M, Iwanami J, Bai HY, Kan-no H, Higaki A, Min LJ, and Horiuchi M: Attenuation of stroke damage by angiotensin II type 2 receptor stimulation via peroxisome proliferator-activated receptor-gamma activation. Hypertension Research 2018 DOI : 10.1038/s41440-018-0082-9