学位論文抄録

Direct Renin Inhibition Ameliorates Cardiovascular Complications and Pancreatic Injury in Obese and Type 2 Diabetic Mice

（直接レニン抑制は肥満および2型糖尿病マウスにおける心血管合併症、膵臓障害を抑制する）

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Abstract of the Thesis

Background and Purpose It is still unclear about the effect of direct renin inhibition on type 2 diabetes and its complications. The present study was undertaken to examine the efficacy of aliskiren, a direct renin inhibitor, on cardiovascular injuries, glucose intolerance and pancreatic injury in obese and type 2 diabetic mice.

Methods Aliskiren (3, 6, 12 and 25 mg kg^{-1} day^{-1}) or hydralazine (80 mg kg^{-1} day^{-1}) were administrated to obese and type 2 diabetic db/db mice for 6 weeks. The protective effects were compared among these groups.

Results Sub-pressor (3 mg kg^{-1} day^{-1}) and hypotensive (6, 12 and 25 mg kg^{-1} day^{-1}) doses of aliskiren significantly attenuated cardiac fibrosis, macrophage infiltration and coronary remodelling, and improved vascular endothelial function in *db/db* mice. These protective effects of aliskiren were attributed to the attenuation of cardiac $p22^{phox}$-related NADPH oxidase-induced superoxide and the restoration of downregulation of vascular endothelial nitric oxide synthase. Aliskiren, at the maximum dose (25 mg kg^{-1} day^{-1}) partially reduced glucose intolerance in *db/db* mice. Furthermore, the maximum dose of aliskiren significantly attenuated the decreases of pancreatic islet insulin content and beta cell mass, and prevented pancreatic islet fibrosis in *db/db* mice. These beneficial effects of aliskiren on pancreatic injury were associated with the reduction of 8-hydroxy-2'-deoxyguanosine-positive cells and *Nox2* expression in pancreatic islets.

Conclusions This study provides the first evidence that direct renin inhibition with aliskiren protects against cardiovascular complications and pancreatic injury through the attenuation of oxidative stress in type 2 diabetic animal model. Furthermore, our data also indicate the potential beneficial effect of aliskiren on diabetes itself. Therefore, aliskiren may be a promising therapeutic agent for type 2 diabetes and its cardiovascular complications.