SUMMARY OF Ph.D. DISSERTATION

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Title

Study on thrombus formation and endothelial gene expression in diabetes mellitus

Abstract

High risk of developing thrombotic complications in diabetes mellitus has been elucidated by various clinical studies but mechanism of the pathogenesis has not yet been clearly understood. Hyperglycemia in diabetes mellitus induces abnormal blood rheology and vascular endothelial dysfunction, thereby thrombosis and atherosclerosis are caused and developed. Pathogenesis and development of thrombotic complications are secondary changes based on hyperglycemia, hence they need to be clarified from the viewpoint of hemodynamics. In this study, therefore, thrombus formation in diabetes mellitus was analyzed by means of *in-vivo* and *in-vitro* experiments from the viewpoint of hemodynamics. Firstly, thrombus formation in diabetic rats was investigated using photothrombosis model. As a result, time of thrombus formation significantly decreased in diabetic rats compared to that in normal rats, thus thrombus formation was accelerated in diabetic conditions. In addition, the thrombi consisted of platelets with endothelial cells were precisely observed by using electron microscopy. The result showed that interaction of platelets with endothelial cells was very important to accelerate thrombus formation in diabetes mellitus. The accelerated platelet aggregation in diabetes induces morbid thrombus formation in blood vessels, and is closely involved with thrmobotic complications. From the clinical viewpoint, platelet aggregation of diabetic patients was measured by a particle counting method using laser-light scattering. Platelet aggregation of diabetic patients significantly increased in comparison with the healthy controls. Secondly, a pulsatile perfusion system was developed to investigate patho-physiological function of endothelial cells on which arbitrary shear stress and transmural pressure can be exposed simultaneously or independently over wide range of physiological flow conditions. To evaluate hydrodynamic efficacy of the system, simple hydraulic load of pressure or complex load of pressure with shear stress was exposed respectively on the cultured endothelial cells. As the result, exposure of the complex load made tight connection of the cell-cell arrangement. By using the pulsatile perfusion system, effect of the complex load and hyperglycemia on gene expression was also investigated in respect to thrombus formation. Gene expression of intracellular adhesion molecules and chemokine enhanced more significantly under the complex load with hyperglycemia than those of single exposure of hyperglycemia or complex load stress. From the results, it can be concluded that hemodynamics is very important to the mechanisms of pathogenesis and development of thrombosis and atherosclerosis especially under diabetic conditions.