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Multi-disciplinary study for the “neurovascular unit” – a putative therapeutic target for the brain ischemia

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Microvessels and neurons rapidly as well as simultaneously respond tothe ischemic injury.Indeed, the responses seem to be coordinated even under the brain ischemia. The ability of neurons to modulate cerebral blood flow in regions of activation results from neurovascular coupling. However, little is known about the microvessel-neuronrelationship. The participation of intervening glial cells implies the association of microvessels, glia, and neurons in a unique structure referred asthe 'neurovascular unit'.

This research project aims to explore and elucidate the pathophysiology of brain ischemia in acute as well as chronic stage through the view point of the 'neurovascular unit'. Moreover, for the future prospect of the regeneration of injured'neurovascular unit' under the brain ischemia is to be explored. The project will be achieved by several different disciplinary aspects.

1) Brain microcirculation

   The characteristic model of middle cerebral artery occlusion in Tie2-GFP mouse whose endothelial cells are labeled by auto-fluorescence is established. The electrical activity of the brain surface, regional cerebral blood flow as well as vessel diameter and the velocity of red blood corpuscle (RBC) in the capillary vessels in the brain parenchyma are measured. These parameters are examined also in the state of cortical spreading depression elicited by micro application of KCl onto the brain cortex. The laser speckled flowmetry and confocal laser microscope as well as two photon microscope are also utilized for observation and analysis of blood flow, and astroglialand/or neuron activity.

2) Astroglial function

   In order to analyze the mechanism of metabolic control of neurons and glial cells, the oxidative metabolite of fatty acid in the cultured these 2 components utilizing $^{14}CO_2$ delivered from [1-^{14}C]palmitic acid.To analyze the generation and utilization of keton bodies in the astroglia, acetoacetate and β-hydroxybutyrate are measured.

3) Function of endothelial cell

To realize the vascular regeneration model, the gliovascular complex is established by co-culture of endothelial cell, pericyte, and astroglia. The migration and adhesion of pericyte and astroglia are observed and analyzed in this model.

4) Neuron regeneration in the ischemia

The evidence of neuronal regeneration under the brain ischemia utilizing human iPS derived neuronal stem cells was demonstrated. To extrapolate this theory to the clinical level, as a first step, the possibility of regenerative mechanism of the 'neurovascular unit'is explored.

To overcome the burden of ischemic stroke, the new therapeutic concept, the 'neurovascular unit', should become one of the most substantial targets in the stoke research.