Form 1-5-2

Japan-US Brain Research Cooperation Program
The Dispatch of Joint Researcher Report in 2006 fiscal year

[field: ④ ]

1. Affiliation/ Title/ Name: Yukihiro Takayasu, Research Associate,
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2. The Project Title: Elucidation of the role of glutamate transporters
in ischemia-induced neuronal cell death

3. U.S. Investigator's Name, Title, and Affiliation: Prof. R. Suzanne Zukin
Department of Neuroscience,
Albert Einstein College of Medicine

4. The Term of Research: From 2006 /4 /18 to 2007 /1 /17 (9 months)

5. The Abstract, the Result and the Significance of Research (300 Words):

Glutamate is the major excitatory neurotransmitter in the CNS, while high glutamate exposure triggers neuronal cell death via the excessive activation of glutamate receptors, which is known as excitotoxicity. Excitotoxicity has been implicated as the mechanisms of neuronal injury resulting from acute insults such as ischemia, epilepsy, trauma, and chronic neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, etc. It is critical to keep extracellular glutamate concentrations very low for maintaining high signal-to-noise ratio and preventing from neurotoxicity.

Glutamate transporter proteins represent the only significant mechanism for removal of extracellular glutamate, and defective glutamate uptake has been suggested to be important in connection with these neurodegenerative diseases. Recently, Rothstein and colleagues have shown that β-lactam antibiotics increase the expression of glutamate transporters and protect neurons from excitotoxicity of *in vitro* and *in vivo* models of neurodegenerative diseases (*Nature* 433, 73-77, 2005).

One of the main research themes in the Zukin lab is the elucidation of the molecular and cellular mechanisms that underlie the neuronal death associated with stroke and epilepsy, and I started the investigation of neuroprotective effects of β-lactam antibiotics on *in vivo* animal models of global ischemia. At beginning, adult rats were subjected to global ischemia by 4 vessel occlusion (10 min) after 5-days treatment with β-lactam antibiotics (ceftriaxone 200 mg per kg, i.p., daily) and normal saline (9% NaCl as a control, i.p., daily), respectively. The number of pyramidal neurons in the hippocampal CA1 of antibiotics-treated animals was histologically compared with that of control animals at 7 days after the reperfusion. Furthermore, the antibiotics-induced changes in the expression of glutamate transporters and ischemia-induced accumulation of glutamate will be examined with western blot analysis and patch-clamp recording, respectively.

These results using *in vivo* models would provide a fundamental evidence for the new treatment of ischemia-induced neuronal injury with β-lactam antibiotics.

6. The Others (Practical Issues, Special Mention Matters): N/A