Implication of calpain-mediated beta-secretase up-regulation for neurodegeneration in the postischemic basal ganglia

H. B. Liang, Y. Minabe, T. Yamashima
Department of Restorative Neurosurgery and Psychiatry, Kanazawa University, Japan

Brain hypoperfusion may be related to the development of Alzheimer's disease (AD), which was shown in some neocortex studies. However, the basal ganglia such as putamen, caudate nucleus and thalamus have received less attention. Although some brain imaging studies revealed diminished volumes of these structures in the various neurodegenerative diseases including AD, it still remains unknown how brain ischemia affects basal ganglia. In the present study, we focused on the implication of brain ischemia to elucidate the pathogenesis of sporadic AD, using the monkey experimental paradigm. As hallmarks of neurodegeneration induced by cerebral hypoperfusion, microtubule-associated protein 2 (MAP2) and glial fibrillary acidic protein (GFAP) were studied by immunohistochemistry in the monkey brain undergoing 20min whole brain ischemia followed by reperfusion. This showed that immunoreactivity of MAP2 was decreased while that of GFAP was increased in the basal ganglia and thalamus. Cerebral ischemia/reperfusion also induced amyloid precursor protein (APP) processing due to μ-calpain activation, which was represented by both up-regulations of β-Site APP-cleaving enzyme 1 (BACE1) and C-terminal fragment of 99 amino acid (β-CTF) protein levels. Moreover, decreases of the cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) were seen in postischemic basal ganglia and thalamus. These results suggest that brain ischemia plays an important role in the development of neurodegeneration in the basal ganglia. The μ-calpain-induced overexpression of BACE1 in the postischemic basal ganglia of monkeys, may suggest implication of brain ischemia for the development of AD.