2002 Mihara Prize Awardee's Summary

# DELAYED NEURONAL DEATH FOLLOWING CEREBRAL ISCHEMIA

Takaaki Kirino, M.D., Ph.D.
Department of Neurosurgery, Faculty of Medicine, The University of Tokyo

It has been well known that the CA1 sector of the hippocampus is extremely vulnerable to cerebral ischemia or severe epileptic seizure. The vulnerability of CA1 neurons accounts for the cause of temporal lobe epilepsy since it is believed to arise from Ammon's horn sclerosis due to the loss of CA1 neurons. On the other hand, since the hippocampus is the structure that functions in memory processing, the susceptibility of CA1 neurons is related to loss of short-term memory due to cerebral ischemia. Following a brief forebrain (or global) ischemia for 5-10 minutes, most of CA1 neurons are selectively destroyed. If the duration of ischemia is prolonged, ischemic damage expand to the striatum and cerebral cortex. The brain lacks a tolerance to ischemic brain injury and is the most vulnerable organ to the state of energy failure that is caused by ischemia, anoxia, or hypoglycemia. The hippocampus is the most vulnerable among those vulnerable structures in the brain.

When the hippocampal CA1 region is subjected to a very brief ischemia (around 5 minutes), most of CA1 neurons are killed. The process of cell damage, however, is extremely slow and delayed. This characteristic of cell death process led to the nomenclature, "delayed neuronal death". It takes for several days until overt morphological change of cell damage comes out. This delayed progression is seen not only in rodent but also in much larger animals including humans. The process of delayed neuronal death has attracted wide attention among researchers of cerebral ischemia because the death process takes place selectively in neurons and glial cells and vascular endothelia remain intact. It also attracted interest because the cell death process is very slow. During this delayed cell destruction, the membrane potential recovers, and energy metabolism and glucose metabolism are restored to normal. CA1 neurons die as if they once recover completely and then they are killed 3-4 days following ischemia. These characteristics prompted further investigations to solve the enigma of selective vulnerability of neurons to ischemia.

Using delayed neuronal death as a model system, there appeared several facts that could govern the fate of the brain following ischemic insults. One is that extracellular glutamate and intracellular free calcium are the determinants of ischemic brain injury. However, this is yet to be proved and still remains hypothetical. Another is that, once the brain is subjected to sublethal ischemia, it could acquire a transient tolerance to subsequent ischemia. This property of the brain is common with general cellular response, but may be deeply related to survival and death of CA1 neurons. The third finding is that CA1 neurons can regenerate at least in young adult rats following brief ischemia. This regeneration takes place by activation of endogenous neural progenitor cells. As a model system, delayed neuronal death in the hippocampal CA1 sector is reliable and reproducible. It will hopefully contribute to the discovery of new

treatment strategy for ischemic brain injury in humans.

REFERENCES


1. Kirino T: Delayed neuronal death in the gerbil hippocampus following ischemia. *Brain Res* 239,57-69 (1982).
2. Kirino T, Sano K: Selective vulnerability in the gerbil hippocampus following transient ischemia. *Acta Neuropathol (Berl)* 62,201-208 (1984).
3. Kirino T, Sano K: Fine structural nature of delayed neuronal death following ischemia in the gerbil hippocampus. *Acta Neuropathol (Berl)* 62,209-218 (1984).
4. Kirino T, Tamura A, Sano K: Delayed neuronal death in the rat hippocampus following transient forebrain ischemia. *Acta Neuropathol (Berl)* 64,139-147 (1984).
5. Kirino T, Tamura A, Sano K: Chronic maintenance of presynaptic terminals in gliotic hippocampus following ischemia. *Brain Res* 510,17-25 (1990).
6. Kirino T, Tsujita Y, Tamura A: Induced tolerance to ischemia in gerbil hippocampal neurons. *J Cereb Blood Flow Metab* 11,299-307 (1991).
7. Kirino T, Robinson HPC, Miwa A, Tamura A, Kawai N: Disturbance of membrane function preceding ischemic delayed neuronal death in the gerbil hippocampus. *J Cereb Blood Flow Metab* 12,408-417 (1992).
8. Nakagomi T, Kirino T, Kanemitsu H, Tsujita Y, Tamura A: Early recovery of protein synthesis following ischemia in hippocampal neurons with induced tolerance in the gerbil. *Acta Neuropathol (Berl)* 86,10-15 (1993).
9. Morimoto T, Ide T, Ihara Y, Tamura A, Kirino T: Transient ischemia depletes free ubiquitin in the gerbil hippocampal CA1 neurons. *Am J Pathol* 148,249-257 (1996).
10. Morikawa E, Mori H, Kiyama Y, Mishina M, Asano T, Kirino T: Attenuation of focal ischemic brain injury in mice deficient in the epsilon1 (NR2A) subunit of NMDA receptor. *J Neurosci* 18,9727-9732 (1998).
11. Ide T, Takada K, Qiu JH, Saito N, Kawahara N, Asai A, Kirino T: Ubiquitin stress response in postischemic hippocampal neurons under nontolerant and tolerant conditions. *J Cereb Blood Flow Metab* 19,750-756 (1999).
12. Qiu JH, Asai A, Chi S, Saito N, Hamada H, Kirino T: Proteasome inhibitors induce cytochrome c-caspase-3-like protease- mediated apoptosis in cultured cortical neurons. *J Neurosci* 20,259-265 (2000).
13. Asai A, Tanahashi N, Qiu JH, Saito N, Chi S, Kawahara N, Tanaka K, Kirino T: Selective proteasomal dysfunction in the hippocampal CA1 region after transient forebrain ischemia. *J Cereb Blood Flow Metab* 22,705-710 (2002).
14. Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, Tamura A, Kirino T, Nakafuku M: Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 110,429-441 (2002).
15. Kirino T: Ischemic tolerance. (Review) *J Cereb Blood Flow Metab* 22,1283-1296 (2002).