One of the biochemical consequences of cerebral ischemia is the activation of neuronal protein kinase C (PKC).1-4 This calcium-mediated cascade is probably triggered by ischemia-induced release of excitatory neurotransmitters such as glutamate.5,6 PKC translocation leading to a relative increase in membrane-bound and decrease in cytosolic PKC activity has been noted after cerebral ischemia.7 Studies showing that H-7, staurosporine, HA-1077, GM1 ganglioside, and other inhibitors of PKC or its translocation are neuroprotective8-10 raise the possibility that PKC activation may contribute to ischemic brain injury. Efforts to define the exact role of PKC in cerebral ischemia, however, have been clouded by recent conflicting observations. Dependent on the animal models, assay methods, and experimental conditions, cerebral ischemia may actually reduce PKC activity.11,12 Controversy regarding the function of PKC in cerebral ischemia is further compounded by the identification of several PKC isoforms12 and dissociation of PKC translocation from its enzyme activity.13 Specific function of each PKC isofrom has yet to be defined. Using spontaneously hypertensive stroke-prone rats (SHR-SP) as a stroke model, De Jong et al report reversed alterations of hippocampal PKCγ isoform and parvalbumin immunoreactivity. These immunohistochemical changes could be prevented by chronic treatment with nimodipine, which also prevented the development of stroke in these animals. The decrease in PKCγ immunoreactivity in CA1 pyramidal cells described in this study probably does not share the same mechanism of PKC activation in the ischemic brain reported elsewhere.12-14 The SHR-SP develop stroke upon aging. The primary vascular lesion is in the cerebral cortex, particularly the watershed regions, where anastomoses develop between two vascular tributaries. According to the authors’ own observations, no pathological changes were noted in the hippocampus. Since regional cerebral blood flow was not determined in this study, it is difficult to ascertain that the increase in PKCγ immunoreactivity was caused by ischemia in the hippocampus. Cerebral ischemia is known to induce the expression of stress genes, such as heat-shock protein and c-fos.15,16 The induction of these genes in the hippocampus can occur as a consequence of ischemia in a remote region. In a stroke model with ischemia confined to the cerebral cortex irrigated by the middle cerebral artery, no reduction of blood flow in the hippocampus was noted.16 In this stroke model, heat-shock protein, c-fos and jun B mRNA signals increased in the hippocampus after cortical ischemic insult.16,17 These findings suggest that ischemia-induced activation of neuronal pathways originating from the cerebral cortex may activate distant structures, such as the hippocampus.16 A similar scenario leading to PKC activation in the hippocampus conceivably may also occur after cortical infarction in SHR-SP.

The pattern of PKCγ and parvalbumin immunoreactivity in untreated animals is intriguing and may represent a probable counterregulatory mechanism served, respectively, by excitatory and inhibitory neurotransmitters. The authors contend that an increase in PKCγ immunoreactivity, reflecting enhanced CA1 pyramidal cell function, may be partially related to a reduced γ-aminobutyric acid (GABA)-ergic input. Limited findings from in vivo studies are consistent with the notion that GABA may play an opposing role to glutamate in cerebral ischemia.18,19 Further experiments are needed to confirm the authors’ hypothesis.

Chung Y. Hsu, MD, PhD, Guest Editor
Department of Neurology
Washington University School of Medicine
St Louis, Mo

References