＜シンポジウム 06―3＞脳血管障害治療の次のブレークスルーを目指して

The involvement of endoplasmic reticulum stress in pathogenesis after cerebral ischemia

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Endoplasmic reticulum (ER)-stress, which is caused by an accumulation of unfolded proteins in the ER lumen, is associated with stroke and with neurodegenerative diseases such as Parkinson's and Alzheimer diseases. However, there are a few reports regarding a role of ER stress on ischemia-induced neuronal damage. Therefore, we investigated the regional and time-dependent changes in ER stress-related markers after transient forebrain ischemia in gerbil and middle cerebral artery occlusion (MCAO) in mice.

We assessed the expression patterns of immunoglobulin heavy chain binding protein (BiP) /glucose-regulated protein (GRP) 78, activating transcription factor (ATF) -4, and C/EBP homology protein (CHOP) after transient forebrain ischemia in gerbils. Double-fluorescent staining involving CHOP immunohistochemistry and TUNEL method was performed to clarify the involvement of CHOP in cell death. Immunohistochemical and Western blot analyses of the hippocampal CA1 subfield showed that BiP expression was increased at 12 h, peaked at 3 days, then decreased. A transient increase was detected in CA3 at 1 day after ischemia, but BiP expression was unchanged in dentate gyrus and cortex. Signals for ATF-4 and CHOP were increased at 1 day and 3 days in CA1, and at 12 h in CA3. Co-localization of CHOP immunoreactivity and DNA fragmentation was detected by the TUNEL method at 3 days after ischemia in CA1, but not at 12 h in CA3.

ER stress-related markers in the striatum and the cortex were investigated after permanent MCAO in mice. Using ER stress-activated indicator (ERAI) transgenic mice, which show splicing of X-box protein 1 (XBP-1) mRNA as green fluorescence, we monitored the regional changes in fluorescence after MCAO. BiP mRNA was increased in the cortex at 6 h. In immunohistochemical and/or Western blot analysis, the expressions of ER stress-related markers (BiP, ATF-4, and CHOP) were increased in the infarct region, more strongly in the cortex than in the striatum. ERAI fluorescence was observed in the ischemic area starting from 6 h and 12 h, respectively, after MCAO, with the peaks at 1 day and the fluorescence co-localized with TTC-visible extension of brain infarction. These findings are consistent with ER stress playing a pivotal role in post-ischemic neuronal death in the gerbil hippocampal CA1 subfield and the mouse MCA territory.

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