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Title Astrocytes death is enhanced by caspase-11 upregulation in an in vitro ischemia model.

Text Since neuronal death is bound to astrocytes death in some pathologic conditions, the research of the pathways leading to astrocyte death has gained interest. We have shown that one of these pathways involves the endoplasmic reticulum (ER) -stress response and CHOP upregulation. Although CHOP is a known mediator of the apoptosis caused by ER-stress, its downstream effectors have not been found yet. To continue with that work we have studied the contribution of caspase-11 to the astrocyte apoptosis induced by ischemia and drug treatments involving CHOP upregulation. Caspase-11 plays a crucial role in both inflammation and apoptosis through the activation of caspase-1, required for the maturation of inflammatory cytokines, and caspase-3 respectively. We have used primary cultures of rat astrocytes and oxygen and glucose deprivation (OGD) as an in vitro model of brain ischemia. We have analyzed the expression of caspase-11 mRNA by quantitative RT-PCR demonstrating that this caspase is significantly upregulated by OGD. Moreover, ER stress inducers thapsigargin and tunicamycin as well as CHOP overexpression were also very efficient in activating caspase-11. mRNA upregulation was followed by a significant increase of caspase-11 peptide as showed by western-blot and immunocytochemistry. Caspase-11 transcriptional activation was also shown by measuring luciferase activity of astrocytes transfected with a fragment of the caspase-11 promotor driving the luciferase reporter gene. The effects of caspase-11 on astrocyte survival to ischemia were analyzed by means of specific siRNA. Caspase-11 suppression induced a significant protection to astrocytes subjected to OGD, indicating that this caspase could play a critical role in the astrocyte apoptosis induced by ischemia and other ER-stress inducers. Supported by grants BFU-2006-14256 from the Ministry for Education and Science and PCI 08-0101-8639 (JCCM). N. F. is a fellow from JCCM.

Theme C - Disorders of the nervous system
Ischemia - Cellular and molecular mechanisms