PW4-1

Hypothermia after hypoxia is neuroprotective possibly via upregulation of cold shock proteins RBM3 and CIRP

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Introduction: Ischemic insults during cardiac arrest or resuscitation can lead to a hypoxic state in the brain tissue and cause neurological sequelae. Therapeutic hypothermia is known to be an effective cytoprotectant, possibly improving the neurological outcome of these patients. Two RNA-binding proteins, the cold-inducible RNA-binding protein (CIRP) and the RNA-binding motif protein 3 (RBM3) have been observed to be upregulated during hypothermia. This observation prompted us to hypothesize a possible participation of CIRP and RBM3 in the hypothermia-induced neuroprotection.
Methods: The SK-N-SH neuroblastoma cell were exposed to either mild or severe hypoxia (8% or 0% oxygen) for 24hrs and afterwards kept at 33,5°C for 72h. LDH-assay for cell death, western-blot for quantification of the expression of the cold shock proteins RBM3 and CIRP were performed.
Mild and severe hypoxia for 24hrs increased the LDH-release in neurons, when incubated at 37°C afterwards, compared to a normoxic control group. Mild hypothermia for 24hrs, 48hrs or 72hrs could reduce the LDH-release significantly at all time points in both cells exposed to 8% and 0% hypoxia for 24hrs. These results support the theory of hypothermia function as a cytoprotectant after a hypoxic insult.
RBM3 is significantly upregulated by mild hypothermia in a time-dose-dependent manner in SK-N-SH cells at all time points, that were exposed to mild or severe hypoxia for 24hrs before. RBM3 is furthermore significantly upregulated in SK-N-SH cells that were not exposed to hypoxia, but incubated at 33,5°C for 24hrs and 48hrs. CIRP is upregulated by hypothermia in SK-N-SH cells, that were exposed to mild or severe hypoxia for 24hrs before. CIRP is furthermore upregulated in SK-N-SH cells that were not exposed to hypoxia, but incubated at 33,5°C for 48hrs.
Conclusion: Mild hypothermia after hypoxia reduces neuronal cell death .RBM3 and CIRP upregulation in response to hypothermia could be one possible mechanism for hypothermia-induced neuroprotection.