Phosphorylation of NMDA 2B at S1303 in human glioma peritumoral tissue: implications for glioma epileptogenesis.


Abstract

OBJECT: Peritumoral seizures are an early symptom of a glioma. To gain a better understanding of the molecular mechanism underlying tumor-induced epileptogenesis, the authors studied modulation of the N-methyl-d-aspartate (NMDA) receptor in peritumoral tissue.

METHODS: To study the possible etiology of peritumoral seizures, NMDA receptor expression, posttranslational modification, and function were analyzed in an orthotopic mouse model of human gliomas and primary patient glioma tissue in which the peritumoral border (tumor-brain interface) was preserved in a tissue block during surgery.

RESULTS: The authors found that the NMDA receptor containing the 2B subunit (NR2B), a predominantly extrasynaptic receptor, is highly phosphorylated at S1013 in the neurons located in the periglioma area of the mouse brain. NR2B is also highly phosphorylated at S1013 in the neurons located in the peritumoral area from human brain tissue containing a glioma. The phosphorylation of the extrasynaptic NMDA receptor increases its permeability for Ca(2+) influx and subsequently mediates neuronal overexcitation and seizure activity.

CONCLUSIONS: These data suggest that overexcitation of the extrasynaptic NMDA receptors in the peritumoral neurons may contribute to the development of peritumoral seizures and that the phosphorylated NR2B may be a therapeutic target for blocking primary brain tumor-induced peritumoral seizures.

KEYWORDS: DAPI = 4',6-diamidino-2-phenylindole; EGFP = enhanced green fluorescent protein; FBS = fetal bovine serum; GBM = glioblastoma multiforme; GFAP = glial fibrillary acidic protein; Glu = glutamate; NMDA; NMDA = N-methyl-d-aspartate; NMDAR = NMDA receptor; NR2B; NR2B = NMDA receptor containing 2B subunit; NeuN = neuron-specific nuclear protein; PBS = phosphate-buffered saline; glioblastoma multiforme; pNR2B = phosphorylated NR2B; peritumoral seizures

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