Activation of NRB2 mediates neuronal release of high mobility group box protein 1 (HMGB1): a novel link to cerebral edema?

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Acute neuronal necrosis clinically correlates with the development of cerebral edema, an important cause of patient mortality following traumatic brain injury (TBI). Given the established link between over-stimulation of NMDA-type glutamate receptors (NMDA-R) and neuronal excitotoxicity, we hypothesized that glutamatergic signaling may promote the development of brain edema. To test this hypothesis, we explored whether selective inhibition of individual NR2 subunits of the NMDA-R would reduce acute brain injury after a moderate TBI in mice. Selective inhibition of NR2B containing NMDA-R using Ro25-6981 (6 mg/kg), significantly attenuated cerebral edema at 24h post-TBI, as compared to placebo-treated mice, and reduced neuronal cell death. In contrast, selective inhibition of NR2A containing NMDA-R with NVP-AAM077 (5 mg/kg) did not significantly influence neuronal viability or TBI-induced brain swelling. Neuronal cell death within the pericontusional cortex was paralleled by a concomitant decrease in immunoreactivity for high mobility group box protein 1 (HMGB1), a predominantly neuronal nuclear protein that is released into the parenchyma to activate toll-like receptor 4 (TLR4)-dependent inflammatory response after a necrotic injury. As was observed with NR2B antagonism, inhibition of the HMGB1 activity using glycyrrhice acid (600 mg/kg) reduced the development of cerebral edema following TBI in mice. Cellular edema, which is characterized by glial swelling, is regarded as the major cause of brain swelling following TBI. Thus, functional studies to establish whether neuronally-derived HMGB1 affects astrocytes were performed. Consistent with a detrimental role in brain edema, treatment of cultured murine astrocytes with lipopolysaccharide, a specific TLR4 agonist, or HMGB1 increased the expression of aquaporin-4 (AQP4), a water channel implicated in TBI-induced cellular edema. Similarly, conditioned media from NMDA-treated neuronal cultures also stimulated AQP4 expression in cultured glia and this effect was prevented by co-treatment with glycyrrhice acid (200 μM). Together, these studies support an important mechanistic role for neuronal NR2B activation in the development of cerebral edema following TBI.