The protective effect of sodium butyrate on complement-mediated synapse degradation in a rat model of neonatal hypoxia-ischemia

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One of the most important causes of neonatal morbidity and mortality is perinatal asphyxia. The inflammatory response, including the activation of the complement system, is one of the essential pathogenic factors in hypoxic-ischemic brain injury (HI). The complement system, when over-activated, stimulates cells to release inflammatory factors and is involved in the degradation of synaptic connections after hypoxia-ischemia. On the other hand, complement is also involved in recovery processes. Sodium butyrate (SB), an inhibitor of histone deacetylase (HDACi), has been shown to provide a reduction in inflammation by decreasing the expression of pro-inflammatory markers.

The main objective of this study was to examine the influence of SB treatment on complement activation and elimination of synapses after HI.

Neonatal HI was induced in 7-days-old Wistar rats by permanent unilateral ligation of the common carotid artery, followed by 60-minute hypoxia (7.6% O2). SB (300 mg/kg, b.w.) was administered in a 5-day regimen, with the first injection administered immediately after the onset of HI.

In our study, we observed reduced levels of the presynaptic proteins synapsin I and synaptophysin, as well as the postsynaptic protein PSD-95 in the damaged hemisphere, suggesting a loss of synaptic proteins after neonatal HI. In transmission electron microscopy, we observed damage to synaptic structures in the cerebral cortex after HI. On the other hand, we noticed an increase in the level of synaptic proteins, improved the ultrastructure, and reduced the degradation of the synapses after SB treatment. Neonatal hypoxia-ischemia induced mRNA expression of the complement proteins C1q, C3, C5, C9, and their receptors C3aR and C5aR. Depending on the time after the induction of hypoxic-ischemic damage, the effect of SB was different. Furthermore, we have shown that the complement proteins (C3 and C5) were co-localized with the PSD-95 protein in the brain tissue after HI.

Our study showed that complement activity after experimental hypoxic-ischemic brain injury may be modulated by sodium butyrate, which demonstrates a neuroprotective effect.