

SCAVENGING OF FREE HEMOGLOBIN DOWNREGULATES TOLL-LIKE RECEPTOR 4 AND DOWN-STREAM MEDIATORS OF INFLAMMATION AFTER INTRAVENTRICULAR HEMORRHAGE IN PRETERM RABBIT PUPS

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Background: Intraventricular hemorrhage (IVH) causes release of free hemoglobin and heme. Heme has been shown to initiate inflammation by activating toll-like receptor-4 (TLR-4). Inflammation following IVH has been shown to induce periventricular brain damage following IVH. Local treatment with a scavenger of free hemoglobin and heme, alpha-1-microglobulin, (A1M), might block inflammation and oxidative stress at an early up-stream level.

Objective: Evaluate if IVH in the immature brain causes an up-regulation of TLR-4 and if treatment with A1M can modify regulation of TLR-4 and heme-oxygenase(HO)-1 and down-stream mediators of inflammation.

Methods: IVH was induced in preterm rabbit pups and verified by high- resolution ultrasound (HR-US). A1M or artificial cerebrospinal fluid (aCSF) was administered to the intraventricular space. Levels of mRNA for TLR-4, COX-I, COX-2, heme oxygenase(HO)-1, TNFa and IL-1b were quantified by RT-PCR in periventricular tissue at 24h and 72h.

Results: Levels of TLR-4, HO-1, COX-1, COX-2 and IL-1b were upregulated in periventricular brain tissue at 72h in the IVH+aCSF group as compared to controls (all $p < 0.05$) but not at 24h. The IVH+A1M group had lower levels of TLR-4, HO-1, COX-1, COX-2 and IL-1b at 72h as compared to the IVH+aCSF group (all $p < 0.05$) and did not differ from controls.

Conclusions: IVH causes an upregulation of TLR-4. Scavenging of free hemoglobin and heme with A1M efficiently decreases upregulation of TLR-4 as well as that of down-stream key mediators of inflammation. This may be a novel treatment strategy to reduce brain damage in preterm infants with IVH.