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## Hydrocephalus-induced ischemia relating to VEGF-R2 and blood vessel density in hippocampus

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### Background

Chronic hydrocephalus (CH) is characterized by increased cerebrospinal fluid volume with or without increased intracranial pressure (ICP), and often associated with impaired cognition thought to be related to decreased cerebral blood flow and oxygen delivery. In hydrocephalus, increased ICP and vascular compression as the result of enlarged ventricles may be directly responsible. VEGF plays a critical role in angiogenesis, neuronal protection as it relates to ischemic/hypoxic events. Previously, using an experimental model of hydrocephalus, we have shown decreased cerebral blood flow, oxygen delivery and increased capillary density.

### Materials and methods

In a model of chronic obstructive hydrocephalus developed in our laboratory, we investigated the relationship between the duration and severity of CH and the density of VEGF+ neurons, glial, endothelial cells and blood vessels (BV) in ventral hippocampus: CA1, CA2-3, dentate gyrus (DG, granule cell layer) and hilar region. CH animals were divided into Short Term (ST, n = 5) and Long Term (LT, n = 5) and compared with Surgical Controls (SC, n = 5). The density of blood vessels and cellular VEGF-R2+ was estimated using stereological cell counting methods. Values were expressed as %VEGF-R2 + cells to the total number of cells in each region.

### Results

Overall, there was approximately six to eight fold increase in %VEGF-R2+ neurons, and approximately six-fold increase in %VEGFR-R2 glial and endothelial cells in the hippocampus of CH compared to SC. Specifically, %VEGFR-R2+ neurons were significantly greater in CH (50–75%) than SC (10–25%). Similarly, %VEGF-R2+glia were significantly higher in CH (57–62%), then SC (5–10%). BV density was found to be double in CH than SC. Overall, we did not find regional differences in VEGFR-2 cellular and BV density. %VEGFR-2+ cells was significantly correlated to BV density ( $p \leq 0.05$ ). Finally, VEGFR-2 and BV density was significantly correlated to changes in CSF ventricular volume, and not ICP.

### Conclusion

CH resulted in increased VEGFR-2 and BV density in hippocampus. Increased % VEGF-R2 of neurons and glia in CH indicates a stimulated VEGF response that may be related to mechanical injury and hypoxia seen with CH. Similar density distribution suggests similar neuroprotective mechanisms and/or vulnerability to CH-induced ischemia. However, VEGF also having adverse effects such as increasing vessel permeability may exacerbate the development of CH. Modulation of VEGF receptors may be important in our understanding of hypoxic conditions and its role in the pathophysiology of hydrocephalus.