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Modulation of Choroid Plexus Immuno-Secretory Function to Restore Cerebrospinal Fluid Homeostasis in Post-Infectious Hydrocephalus

Jason K. Karimy M.S.; Jinwei Zhang; Mohammad Mansuri Ph.D.; Xu Zhou Ph.D.; Juihui Zhang MD; Volodymyr Gerzanich MD, PhD; J. Marc Simard MD; Ruslan Medzhitov Ph.D.; Kristopher Thomas Kahle MD PhD

Introduction

Hydrocephalus is often a fatal disease in developing countries due to a lack of access to neurosurgical care. Recent data1 has challenged dogma by showing intraventricular hemorrhage (IVH) triggers inflammation-dependent CSF hypersecretion from the choroid plexus (CP) to cause acute post-hemorrhagic hydrocephalus (PHH), and this can be prevented by FDA-approved drugs targeting Toll-like receptor-4 (TLR4) or SPAK kinase. Like PHH, post-infectious hydrocephalus (PIH) exhibits non-obstructive ventriculomegaly, CP inflammation, and a positive response to endoscopic choroid plexus cauterization. LPS, the canonical TLR4 ligand, is a component of many PIH-causing bacteria. We hypothesized that PHH/PIH share a common pathogenic mechanism of TLR4-SPAK-dependent CSF hypersecretion.

Methods

We developed a novel rat model of PIH via the continuous intracerebroventricular infusion of LPS. In vivo CSF secretion measurements and MRI imaging evaluated the impact of LPS on CSF dynamics. RNAseq and LC-MS/MS phospho-proteomics assessed changes in the CPe transcriptome/phospho-proteome in response to IVH and LPS. Immunoblotting evaluated LPS-induced changes in the functional expression of specific TLR4- and SPAK-kinase-associated molecules in the CPe.

Results

ICV-LPS infusion triggered a striking increase in CSF secretion (~3.5-fold; $p<0.01$) and ventriculomegaly (>300%; $p<0.01$). IVH and LPS induced a shared signature of TLR4-dependent signal transduction mediators and SPAK-regulated ion transporters in the CPe. LPS stimulated the activating phosphorylation of TLR4-NF-kB-mediated SPAK-NKCC1 ion-transport pathways to a greater extent than even IVH (>450%; $p<0.01$).[1]

Conclusions

IVH metabolites and bacteria-derived LPS similarly promote TLR4-NF-kB-dependent CSF hypersecretion and acute hydrocephalus via up-regulation of a SPAK-regulated network of ion transporters in the inflamed CP. Instead of being classified as “secondary” forms of hydrocephalus, PHH/PIH may be better termed “inflammatory hydrocephalus” to highlight disease mechanisms and therapeutic vulnerabilities. Non-surgical modulation of CP immuno-secretory function with repurposed FDA approved drugs targeting TLR4 or SPAK could create a breakthrough for health systems with resource limitations.

Learning Objectives

By the conclusion of this session, participants should be able to 1) Describe the importance of elucidating the molecular mechanisms underlying PIH and PHH; 2) Discuss in small groups the role of CSF hypersecretion as a contributing factor in the formation of PIH and PHH; 3) Identify potentially effective treatment targets in the inflammation-dependent signaling cascade involved in PIH and PHH that could be exploited in resource-limited countries.

References

1.Karimy, J.K., et al. Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nature Medicine (2017).

2.McAllister, J.P., 2nd, et al. An update on research priorities in hydrocephalus: overview of the third National Institutes of Health-sponsored symposium "Opportunities for Hydrocephalus Research: Pathways to Better Outcomes". Journal of neurosurgery 123, 1427-1438 (2015).

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