TLR-4-Regulated Cerebrospinal Fluid Hypersecretion in Post-Hemorrhagic Hydrocephalus

Jason K. Karimy M.S.; Jinwei Zhang; David B Kurland BA; Brianna Carusillo Theriault PhD; Daniel Duran MD; Charuta Gavankar Furey BA; Volodymyr Gerzanich MD, PhD; J. Marc Simard MD; Kristopher Thomas Kahle MD PhD

Introduction

Intraventricular hemorrhage (IVH) frequently causes post-hemorrhagic hydrocephalus (PHH) as a result of impaired cerebrospinal fluid (CSF) homeostasis.[1,2] The most common treatment for PHH is surgical CSF shunting, a procedure fraught with complications.[3,4] Historically, it is thought that PHH results from impaired reabsorption of CSF, however, little consideration has been given to the role of CSF hypersecretion. Recently, toll-like receptor-4 (TLR-4) has been implicated in the CNS by detecting “alarmins”,[5] including IVH-derived metabolites,[6] via recognition of damage-associated molecular patterns.[7,8] We speculate that IVH triggers TLR-4-dependent inflammation at the choroid plexus epithelia (CPE), leading to CSF hypersecretion contributing to the development of PHH.

Methods

In an established rat model of IVH,[9] we assessed the rate of CSF secretion, CPE inflammation and the effect of genetic and pharmacological intervention on the development of PHH. We developed and implemented a novel surgical method in rats to measure the rate of CSF secretion.[10] TLR-4 knockout rats,[11] antisense oligodeoxynucleotide-mediated gene knockdown,[12] and intracerebroventricular delivery of FDA-approved drugs were used to assess the role of specific inflammatory and ion transport targets on CSF secretion rate and ventriculomegaly following IVH. Immunoblot and immunohistochemistry were used to detect and quantify inflammatory markers.

Conclusions

These data uncover a previously unrecognized role for CSF hypersecretion in the pathogenesis of PHH, and reveal a novel TLR-4-dependent regulatory pathway of CSF secretion that can be targeted with repurposed, FDA-approved drugs for the non-surgical treatment of PHH.

Results

We show IVH triggers TLR4-NFkB-mediated inflammation at the CPE that is associated with a striking ~3-fold increase in CSF secretion sufficient to cause PHH. CSF hypersecretion is dependent on the NFkB-regulated kinase SPAK,[13-15] which interacts with and phosphorylates the bumetanide-sensitive NKCC1 at the CPE apical membrane. Genetic ablation of TLR-4 or SPAK, and pharmacology antagonizing TLR-4-NFkB signaling or the SPAK-NKCC1 complex normalizes CSF secretion rates and ventriculomegaly after IVH.

Learning Objectives

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

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