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EDITORIAL

The *Toll* of Hyperammonemia on the Brain

Acute liver failure (ALF) is a devastating disease characterized by inflammation, immune activation, and hyperammonemia.[1] These processes predispose patients to the development of cerebral edema, which can have fatal consequences.[2] Therefore, defining the mechanisms by which hyperammonemia results in cerebral edema in ALF is important in order to discover newer therapeutic targets. The article by Vijay et al[3] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* elucidates the role of Toll-like receptor 9 (TLR9) as a mediator of cerebral edema in a model of hyperammonemia.

In recent years, the contribution of inflammatory processes to central nervous system (CNS) dysfunction has become increasingly apparent. While explicitly autoimmune CNS disorders such as multiple sclerosis have long been associated with inflammatory changes,[4] the pathophysiology of other CNS disorders, including neuropsychiatric disorders such as schizophrenia and autism[5] and mood disorders such as major depression,[6] have also implicated immune system dysfunction. These connections between the CNS and immune system reveal the vulnerability of the CNS to inflammatory changes associated with dysfunction of other organ systems. TLR3 and TLR4 ligands, for example, have been used in animals to model the gestational insults that contribute to neuropsychiatric disorders[7–9] and the sickness behavior produced by TLR3 ligands[10] is an explicit example of the effect of peripheral immune function on CNS performance. Given the striking inflammatory effects[11] and devastating CNS sequelae[12] associated with ALF, there remains an urgent need to investigate mechanisms by which immune changes associated with liver disease contribute to CNS-relevant phenotypes such as those resulting in brain edema, intracranial hypertension, and HE. Within these disorders, TLRs, given their crucial immune function[13] and implication in both CNS[14] and hepatic disease,[15] are an appealing target for investigation.

Although it had previously been established that TLR9 signaling is necessary for the progression of acetaminophen-induced liver injury[16] and therefore subsequent development of brain edema, the importance of the receptor for the earlier stages of this process had prevented understanding of its role for later stage disease. Here, the authors use a novel combination of ammonium acetate and *Tlr9*$^{-/-}$ mice to directly induce hyperammonemia while maintaining liver function, allowing direct evaluation of receptor knockout's effect on the subsequent development of brain edema. Further nuance is achieved by use of *Tlr9*$^{fl/fl}$ mice crossed with mice expressing Cre recombinase under the control of the *lysozyme* promoter, generating macrophage and neutrophil conditional knockouts of TLR9. With these tools, the authors are able to establish that absence of TLR9 within these cell populations is capable of preventing ammonium acetate-induced increases in brain water, proinflammatory cytokine production, and hepatocyte swelling. The TLR9 antagonist ODN2088 is similarly able to prevent these phenotypes. Interestingly, increases in plasma DNA following ammonium acetate administration are observed regardless of TLR9 status, suggesting that this alteration is upstream of the receptor. Despite the undoubtedly interesting findings in this article, further studies are needed using models of brain edema with concomitant liver failure, which are closer to the human disease process.[17]

These findings suggest TLR9 as a key mediator of the progression from hyperammonemia to brain edema and associated intracranial hypertension. This knowledge of TLR9's role in later stages of this process allows for further investigation into the therapeutic window for TLR9 antagonism and suggests a potential benefit even in cases where liver failure has progressed to hyperammonemia. This investigation of neuroimmune regulation of brain edema could set the basis for new therapeutic options for the prevention and treatment of this feared complication of acute liver failure.

JUSTIN M. SAUNDERS, BS
JAVIER GONZÁLEZ-MAESO, PhD
Department of Physiology and Biophysics
Virginia Commonwealth University and McGuire VA Medical Center
Richmond, Virginia

JASMOHAN S. BAJAJ, MD
Division of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University and McGuire VA Medical Center
Richmond, Virginia

References

1. Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013;369:2525–2534.
2. Larsen FS, Wendon J. Prevention and management of brain edema in patients with acute liver failure. Liver Transpl 2008;14(Suppl 2):S90–S96.
3. Manakkat Vijay GK, Hu C, Peng J, Garcia-Martinez I, Hoque R, Verghis RM, Ma Y, Mehal WZ, Shawcross DL, Wen L. Ammonia-induced brain edema requires macrophage and T cell expression of toll-like receptor 9. Cell Mol Gastroenterol Hepatol 2019;8:609–623.
4. Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 2006;52:61–76.

5. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science 2016;353:772–777.
6. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;16:22–34.
7. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 2013; 155:1451–1463.
8. Wischhof L, Irrsack E, Dietz F, Kock M. Maternal lipopolysaccharide treatment differentially affects 5-HT(2A) and mGlu2/3 receptor function in the adult male and female offspring. Neuropharmacology 2015; 97:275–288.
9. Holloway T, Moreno JL, Umali A, Rayannavar V, Hodes GE, Russo SJ, González-Maeso J. Prenatal stress induces schizophrenia-like alterations of 5-HT_{2A} and mGluR2 receptors in the adult offspring: Role of maternal immune system. J Neurosci 2013;33:1088–1098.
10. Cunningham C, Campion S, Teeling J, Felton L, Perry VH. The sickness behaviour and CNS inflammatory mediator profile induced by systemic challenge of mice with synthetic double-stranded RNA (poly I:C). Brain Behav Immun 2007;21:490–502.
11. Donnelly MC, Hayes PC, Simpson KJ. Role of inflammation and infection in the pathogenesis of human acute liver failure: clinical implications for monitoring and therapy. World J Gastroenterol 2016; 22:5958–5970.
12. Rabinstein AA. Treatment of brain edema in acute liver failure. Curr Treat Options Neurol 2010;12:129–141.
13. Cook DN, Pisetsky DS, Schwartz DA. Toll-like receptors in the pathogenesis of human disease. Nat Immunol 2004;5:975–979.
14. Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. Clin Sci (Lond) 2011;121:367–387.
15. Nakamoto N, Kanai T. Role of toll-like receptors in immune activation and tolerance in the liver. Front Immunol 2014;5:221.
16. Imaeda AB, Watanabe A, Sohail MA, Mahmood S, Mohamadnejad M, Sutterwala FS, Flavell RA, Mehal WZ. Acetaminophen-induced hepatotoxicity in mice is dependent on Tlr9 and the Nalp3 inflammasome. J Clin Invest 2009;119:305–314.
17. Butterworth RF, Norenberg MD, Felipo V, Ferenci P, Albrecht J, Blei AT. Members of the ISHEN Commission on Experimental Models of HE. Experimental models of hepatic encephalopathy: ISHEN guidelines. Liver Int 2009;29:783–788.

Correspondence
Address correspondence to Jasmohan S. Bajaj, MD, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23249. e-mail: jasmohan.bajaj@vcuhealth.org; fax: (804) 675-5816.

Conflicts of interest
The author discloses no conflicts.

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