Treating neonatal meningitis -- is nitric oxide a foe or a friend to bacteria?

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Current research suggests that nitric oxide may play a role in the pathogenesis of neonatal meningitis. The related report by Mittal et al, "Inhibition of inducible nitric oxide controls pathogen load and brain damage by enhancing phagocytosis of *Escherichia coli* K1 in neonatal meningitis," appears in the March 2010 issue of The *American Journal of Pathology*.

Bacterial meningitis, or inflammation of the membranes that cover the brain and spinal cord, is often fatal, even when treated with antibiotics. In neonates, mortality occurs in 25 to 35% of all patients, and long-term neurological and psychological effects are reported in up to 50% of survivors. One of the most common causes of neonatal meningitis is a serotype of Escherichia coli that expresses the capsular antigen K1, which is similar in structure to proteins expressed in the brain.

Nitric oxide plays a key role in the pathogenesis of meningitis; however, it remains unclear whether it plays a pro- or anti-microbial role. To determine the role of inducible nitric oxide synthase (iNOS), responsible for the production of nitric oxide, in meningitis, a group led by Dr. Nemani Prasadarao of the Childrens Hospital Los Angeles examined the effects of *E. coli* K1 infection in brains of neonatal mice. They found that *E. coli* K1 infection induced nitric oxide due to the activation of iNOS and that mice deficient in iNOS were resistant to *E. coli* infection. In addition, treatment with the iNOS-specific inhibitor aminoguanidine cleared the pathogen from circulation and prevented brain damage, likely via increased uptake and killing of bacteria by immune cells.

Therefore iNOS inhibition may provide a new therapeutic strategy for treating neonatal *E. coli*-induced meningitis.

Mittal et al conclude that "further understanding of the complex interactions between *E. coli* K1 and macrophages are important to the identification of novel interventional strategies that can improve the outcome of this deadly disease." Since these studies showed that the prevention of nitric oxide production by *E. coli* also suppressed the production of inflammatory cytokines, inhibition of nitric oxide might also be used as a therapeutic strategy for the prevention of sepsis. In future studies, Dr. Prasdarao and colleagues intend to "develop small molecule inhibitors that prevent the interaction of *E. coli* with its receptor on various cells and thereby reduce the production of nitric oxide."

More information: Mittal, R, Gonzalez-Gomez I, Goth KA, Prasadarao NV: Inhibition of inducible nitric oxide controls pathogen load and brain damage by enhancing phagocytosis of Escherichia coli K1 in neonatal meningitis. Am J Pathol 176:1292-1305

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