Ibuprofen restores learning ability in rats with liver failure

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Cognitive impairment is one of the neurological effects in patients with hepatic encephalopathy (abnormal brain function due to severe liver disease). For the first time, a new study showed that treatment with an anti-inflammatory improves cognitive function in rats induced with chronic liver failure.

The results of this study appear in the August 2007 issue of Hepatology, the official journal of the American Association for the Study of Liver Diseases (AASLD). Published by John Wiley & Sons, Inc., Hepatology is available online via Wiley InterScience at http://www.interscience.wiley.com/journal/hepatology.

Previous studies suggested that high ammonia levels and inflammation may cooperate in the brain alterations seen in hepatic encephalopathy. Led by Vicente Felipo, of the Centro de Investigación Príncipe Felipe in Valencia, Spain, the current study examined whether alterations associated with inflammation are involved in learning impairment in rats who had chronic liver failure due to insertion of a porta-caval shunt (PCS). The PCS rats showed a decreased ability to learn a Y maze, but after administration of ibuprofen, their ability to learn the maze was completely restored. The results also showed that these results were due to ibuprofen's ability to restore the function of a pathway in the brain known as the glutamate-NO-cGMP pathway. In addition, the researchers found that ibuprofen normalized the activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX), two enzymes that play a role in inflammation in the cerebral cortex. They also found that

ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) that can potentially be toxic to the kidneys, did not significantly affect sodium or urea levels, although it caused a slight increase in creatinine levels.

It has been suggested that inflammation exacerbates the neuropsychological alterations caused by hyperammonemia (high ammonia levels). The researchers found that the PCS rats showed both high ammonia levels and inflammation, but reducing the inflammation improved their learning ability, even though ammonia levels remained high. “The data showed here point to the possible therapeutic utility of decreasing inflammation in the treatment of minimal or overt hepatic encephalopathy,” the researchers state.

Although the mechanisms by which anti-inflammatory agents improve cognitive function are not clear, the study provides some initial insight. The results showed that ibuprofen did not normalize levels of IL-6, a type of pro-inflammatory cell in the immune system, suggesting that IL-6 does not contribute to cognitive impairment. However, it did reduce COX activity, which supports the idea that COX activity is involved in learning impairment in hepatic encephalopathy. In addition, the study showed that decreased formation of cGMP by the glutamate-NO-cGMP pathway is responsible for decreased learning ability.

“The data presented here, using ibuprofen as an experimental tool to decrease inflammation, clearly show that decreasing inflammation completely restores the ability to learn the Y maze task in a rat model of hepatic encephalopathy,” the authors conclude. “This supports the idea that reducing inflammation would improve cognitive function in patients with hepatic encephalopathy. It would be convenient to look for procedures to decrease inflammation without having the possible secondary effects of NSAIDS, maybe new specific inhibitors of COX with no or less secondary effects could have beneficial effects.”

Source: John Wiley & Sons, Inc.