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Uncovering lithium's mode of action

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Though it has been prescribed for over 50 years to treat bipolar disorder, there are still many questions regarding exactly how lithium works. However, in a study appearing in this month's *Journal of Lipid Research*, researchers have provided solid evidence that lithium reduces brain inflammation by adjusting the metabolism of the health-protective omega-3-fatty acid called DHA.

Inflammation in the brain, like other parts of the body, is an important process to help the brain combat infection or injury. However, excess or unwanted inflammation can damage sensitive brain cells, which can contribute to psychiatric conditions like bipolar disorder or degenerative diseases like Alzheimers.

It's believed that lithium helps treat bipolar disorder by reducing brain inflammation during the manic phase, thus alleviating some of the symptoms. Exactly how lithium operates, though, has been debated.

Mireille Basselin and colleagues at the National Institute of Aging and University of Colorado, Denver, took a detailed approach to this question by using mass spectrometry analysis to analyze the chemical composition of brain samples of both control and lithium-treated rats stressed by brain inflammation.

They found that in agreement with some other studies, rats given a six-week lithium treatment had reduced levels of arachidonic acid and its products, which can contribute to inflammation.

In addition, they also demonstrated, for the first time, that lithium treatment increased levels of a metabolite called 17-OH-DHA in response to inflammation. 17-OH-DHA is formed from the omega-3 fatty acid DHA (docosahexaenoic acid) and is the precursor to a wide range of anti-inflammatory compounds known as docosanoids. Other anti-inflammatory drugs, like aspirin, are known to also enhance docosanoids in their mode of action.

Basselin and colleagues noted that the concentration of DHA did not increase, which suggests that lithium may increase 17-OH-DHA levels by affecting the enzyme that converts DHA to 17-OH-DHA.

By reducing both pro-inflammatory AA products, and increasing anti-inflammatory DHA products, lithium exerts a double-protective effect which may explain why it works well in bipolar treatment. Now that its mechanism is a little better understood, it may lead to additional uses for this chemical.

More information: "Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation" by Mireille Basselin, Hyung-Wook Kim, Mei Chen, Kaizong Ma, Stanley I. Rapoport, Robert C. Murphy and Santiago E. Farias. www.jlr.org/cgi/content/full/51/5/1049

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