Inflammation controlled differently in brain and other tissues, study finds

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A team led by scientists from The Scripps Research Institute has identified a new metabolic pathway for controlling brain inflammation, suggesting strategies for treating it.

The new report, which appears in the October 20, 2011 edition of Science Express, focuses on the type of inflammation normally treatable with non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen.

The study shows this type of inflammation is controlled by different enzymes in different parts of the body.

"Our findings open up the possibility of anti-inflammatory drugs that are more tissue-specific and don't have NSAIDs' side effects," said the study's senior author Benjamin F. Cravatt, chair of the Department of Chemical Physiology and member of the Skaggs Institute for Chemical Biology and the Dorris Neuroscience Center at Scripps Research.

A Serendipitous Discovery

The serendipitous discovery originated with an attempt by Cravatt and his colleagues to develop a new kind of pain-relieving drug targeting an enzyme known as monoacylglycerol lipase (MAGL). This enzyme normally breaks down a natural pain-relieving neurotransmitter known as 2-AG, a "cannabinoid" molecule whose actions are mimicked by certain compounds within marijuana. To reduce the rate of 2-AG breakdown, allowing 2-AG levels to rise and provide more pain relief, the Cravatt lab developed a powerful and selective MAGL-inhibiting compound, which the scientists described in 2009 and are still investigating as a possible pain drug.

In the course of this research, the scientists tested their MAGL inhibitor on mice and also engineered mice that genetically lack MAGL. "We noticed that the brains of the MAGL-inhibited mice showed reduced levels of arachidonic acid, a key precursor molecule for inflammatory lipids," said Daniel Nomura, a former member of the Cravatt lab who is currently assistant professor in the Department of Nutritional Science & Toxicology at the University of California, Berkeley. Nomura is the paper's co-corresponding author with Cravatt, and co-first author with Bradley E. Morrison of Scripps Research.

Arachidonic acid had been thought to originate similarly throughout the body, from a process involving fat molecules and phospholipase A2 enzymes. To their surprise, the researchers found that in the brain, arachidonic acid production is controlled chiefly by MAGL.

In effect, the enzyme takes pleasure-associated 2-AG, which is found in high concentrations in the brain, and turns it into arachidonic acid-the precursor for pain- and inflammation-causing prostaglandin molecules. The researchers showed that blocking the activity of MAGL, or genetically eliminating it, shrinks the pool of arachidonic acid and prostaglandins in mouse brains, effectively limiting the possibility of brain inflammation.

Providing a Protective Effect

To further test this effect, the researchers set up two standard models of brain inflammation in lab mice. In one, they tried to induce inflammation with lipopolysaccharide, a highly pro-inflammatory molecule found in bacteria. In the other, they used the toxin MPTP, which induces brain inflammation and preferentially kills the same muscle-regulating neurons lost in Parkinson's disease.

"In both models, reducing MAGL - genetically or with our MAGL-inhibitor - provided the animals with protection from neuroinflammation," said Nomura, who is continuing to research the system at UC Berkeley.

NSAIDs such as ibuprofen are already used to reduce the inflammation that originates from arachidonic acid. They work by inhibiting the cyclo-oxygenase enzymes that convert arachidonic acid into prostaglandins. But NSAIDs also inhibit cyclo-oxygenase enzymes that protect the lining of the gastrointestinal tract. They thus can cause gastrointestinal bleeding, among other adverse side effects. That greatly limits their potential usefulness. In the brain, where MAGL is the major controller of arachidonic acid levels, blocking the enzyme could be a better strategy. Alzheimer's disease, Parkinson's disease, multiple sclerosis, and traumatic brain injury all involve harmful but potentially treatable brain inflammation.

"In principle, with a MAGL inhibitor we could avoid the gastrointestinal toxicity that's associated with NSAIDs while still maintaining the anti-inflammatory effect," said Nomura.

Unexpected Elements

The new findings also are important from a basic science perspective because they advance the understanding of prostaglandin-mediated inflammation. Phospholipase A2 enzymes have long been considered the dominant producers of arachidonic acid, and thus a major element in prostaglandin-mediated inflammation throughout the body.

Nomura, Cravatt, and their colleagues confirmed in their experiments that phospholipase A2 enzymes play a major role in arachidonic acid production in the gut and spleen. However, in the brain, the MAGL enzyme was the principal regulator, with phospholipase A2 enzymes making a more limited contribution. MAGL also regulated arachidonic acid and prostaglandins in liver and lungs.

"Biological pathways that we think we understand sometimes turn out to have these unexpected, tissue- or context-specific elements, which is why it's so important to follow up on clues such as the ones we found," Cravatt said.

More information: "Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation" *Science Express*, October 20, 2011.

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