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Target for new Rx class for inflammatory disorders discovered

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Research led by Charles Nichols, PhD, Associate Professor of Pharmacology at LSU Health Sciences Center New Orleans, describes a powerful new anti-inflammatory mechanism that could lead to the development of new oral medications for atherosclerosis and inflammatory bowel disorders (IBS). The findings are published in *PLOS ONE.*

One of the master inflammatory molecules in the body is Tumor Necrosis Factor-alpha (TNF-alpha). Infections and certain diseases lead to the production of this molecule, which then stimulates an immune response. Diseases like atherosclerosis, rheumatoid arthritis, and IBS are believed to have inflammation influenced by TNF-alpha as a primary component. Unfortunately, there are no convenient therapeutics to treat inflammation caused by TNF-alpha. Current therapies directed at blocking TNF-alpha inflammation are very expensive antibody treatments that are administered in the clinic.

The research team found that activation of serotonin 5-HT2A receptor proteins potently blocks TNF-alpha induced inflammation. The serotonin 5-HT2A receptor is the main target of classic hallucinogenic drugs like LSD, and the drug the researchers used to activate the receptor protein is itself a member of this class. In the study, the researchers activated serotonin 5-HT2A receptors, and then administered TNF-alpha to mice to produce an inflammatory response. In mice when 5-HT2A receptors were activated before TNF-alpha was administered, there was a near complete blockade of inflammation

compared to mice where the 5-HT2A receptors were not activated that had a full inflammatory response. The effects were most powerful in vascular tissues like the aorta, and the intestine. In the intestine, inflammation was blocked with an extremely low dose of the drug – 300 times lower than required for any behavioral effects of the drug.

"Our results potentially represent a breakthrough of a new first in class orally available small molecule-based therapeutic strategy to treat inflammatory diseases involving TNF-alpha," notes Charles Nichols, PhD, Associate Professor of Pharmacology at LSU Health Sciences Center New Orleans. "Although the serotonin 5-HT2A receptor is the primary target for certain drugs, including LSD, to mediate their behavioral effects, the dose of drug necessary for anti-inflammatory effects is orders of magnitude lower than intoxicating doses, and future therapies may target directly the relevant cellular processes activated by the 5-HT2A receptor rather than the receptor itself."

More information: dx.plos.org/10.1371/journal.pone.0075426

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