Researchers show that A3 adenosine receptor can activate 'off signals' for pain

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In a study published in the April issue of the *Journal of Neuroscience*, Saint Louis University scientists led by professor of pharmacological and physiological sciences Daniela Salvemini, Ph.D., discovered that drugs targeting the A3 adenosine receptor can "turn off" pain signals in the spinal cord to provide relief from chronic pain.

Pain is the most common reason that people seek medical attention, but the available treatments—most commonly non-steroidal anti-inflammatory drugs (NSAIDs) and opioids—are not always successful at relieving pain in patients with chronic pain. For this reason, Salvemini and colleagues teamed up with researchers from the National Institutes of Health, the University of Arizona and two institutes in Quebec, Canada, to investigate a new target for treating chronic pain: the A3 adenosine receptor or A3AR.

In earlier studies, Salvemini's laboratory demonstrated that two drugs which target the A3AR—IB-MECA and MRS5698—were effective in treating several models of chronic pain, including painful chemotherapy-induced neuropathy, metastatic cancer pain, and nerve injury. More recently, the group sought to uncover the mechanism of A3AR pain relief.

"Chronic pain can result from the loss of regulatory mechanisms in the nervous system pathway that transmits pain," Salvemini said. "Adenosine acts as a regulatory signaling molecule in other areas of the nervous system, so we hypothesized that A3AR might also play a role in regulating pain signals during pain processing."

Indeed, Salvemini and colleagues found that A3AR drugs not only relieved pain, but did so by activating an inhibitory transmitter system known as the gamma amino-butyric acid (GABA) system. In areas of the spinal cord and brain dedicated to pain processing, A3AR activation promoted GABA signaling by preventing the breakdown and removal of GABA from neuronal synapses.

"In chronic pain, GABA signaling is often lost or diminished. Our A3AR drugs were able to restore GABA signaling in areas that process pain and 'turn off' the signals that maintain the pain state," Salvemini said.

With A3AR drugs demonstrating good safety profiles in clinical trials as anti-inflammatory and anti-cancer agents, Salvemini and colleagues are enthusiastic about the potential of these new drugs to treat chronic pain in patients.

"Several lead molecules for prospective clinical use have been identified through our collaboration with Dr. Kenneth Jacobson at the National Institutes of Health and we are very excited about the potential for translational therapeutic impact," Salvemini said.

The lab will continue to investigate the intricate mechanisms underlying A3AR pain relief with the hope of providing better palliative care to individuals suffering from unnecessary chronic pain .

Provided by Saint Louis University