PAIN

Resolvins show promise for treating inflammatory pain

Resolvins, a recently discovered family of endogenous omega-3 fatty-acid-derived mediators with potent immunoregulatory effects, could be novel analgesics for the treatment of inflammatory pain.

The term 'resolvins' was coined to denote that these resolution phase interaction products stimulate the resolution of inflammation, an active process that returns inflamed tissues to a normal state following the acute inflammatory response. New research shows that these compounds also have the potential to attenuate inflammatory pain.

In mice, resolvins were shown to modulate pain by regulating both peripheral and spinal sensitization and hyperalgesia. These findings may well be of particular importance given the well-known limitations of agents commonly used to treat inflammatory pain such as opioids and cyclo-oxygenase (COX) inhibitors.

The study that produced these findings was a joint effort between two laboratories in the Department of Anesthesiology, Perioperative and Pain Medicine of Brigham & Women's Hospital and Harvard Medical School. Lead investigators Ru-Rong Ji, Associate Director of the Pain Research Center, and Charles Serhan, Director of the Center for Experimental Therapeutics and Reperfusion Injury, hope this is the first of many such collaborations.

"Dr Serhan's lab discovered these lipid mediators and has demonstrated the dual anti-inflammatory and proresolution role of resolvins," explains Ji, "and my lab has been working on inflammatory pain mechanisms for many years, so it made perfect sense for these two labs in the same department to collaborate to test the effects of resolvins in mouse models of inflammatory pain."

The investigators used mouse models of acute, mid-term and persistent inflammatory pain induced by formalin, carrageenan and complete Freund's adjuvant, respectively. To determine the peripheral and central actions of resolvins on pain in these models, the synthetic

resolvins RvE1 and RvD1 were injected peripherally, into the foot pad, or centrally, into the spinal cord.

Investigations of the peripheral role of resolvins demonstrated that they can attenuate inflammatory pain through anti-inflammatory actions including reducing edema, neutrophil infiltration, and proinflammatory cytokine expression. Centrally, resolvins were shown to further attenuate inflammatory pain by blocking synaptic plasticity in the spinal cord.

Notably, resolvins were shown to effectively reduce pain at very low doses, 1–10 ng, which are much lower than those required for morphine and COX2 inhibitors. In addition, resolvins did not affect basal pain thresholds, suggesting that they have a 'normalizing' effect on pain.

Exploring the potential mechanisms of resolvins-induced inhibition of inflammatory pain, the researchers showed that spinal administration of RvE1 reduced heat hyperalgesia and spontaneous pain by blocking capsaicin receptor (TRPV1) and tumor necrosis factor (TNF) signaling in dorsal root ganglion neurons and spinal presynaptic terminals. In addition, they demonstrated that pretreatment with RvE1 reduces another feature of inflammatory pain, mechanical allodynia.

In electrophysiological studies, RvE1 was shown to block TRPV1-induced and TNF-induced excitatory postsynaptic current increases and TNF-evoked N-methyl-D-aspartic acid receptor (NMDA-R) hyperactivity in spinal dorsal horn neurons. The investigators suggest that RvE1 might resolve inflammatory pain by inhibition of the extracellular signal-regulated kinase (ERK) signaling pathway, which mediates glutamate release in presynaptic terminals in response to stimulation by TNF and TRPV1 activation and also mediates NMDA-R activation in postsynaptic dorsal horn neurons, a mechanism involved in central sensitization.

The researchers plan to extend their study of resolvins to other models of chronic pain, such as neuropathic pain models after nerve injury.

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Original article Xu, Z.-Z. *et al.* Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. *Nat. Med.* 16, 592–597 (2010)

Further reading Yacoubian, S. & Serhan, C. N. New endogenous anti-inflammatory and proresolving lipid mediators: implications for rheumatic diseases. *Nat. Clin. Pract. Rheumatol.* 3, 570–579 (2007)