How Can 5-HT_3 Receptor Antagonists Exert Analgesic Properties?

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See "Ondansetron pretreatment reduces pain on injection of propofol" by Zahedi H, Maleki A, Rostami G on pages 239-243 (1).

5-HT_3 receptors occur on various components of the pain modulation system. Expressed on peripheral nerve endings and autonomic afferents as well as in the monoaminergic descending inhibitory system and certain brain regions, 5-HT_3 receptors play an indispensable role in spinal pain transmission and endogenous pain suppression. Yet, their role in this context has not been defined lucidly, and studies have yielded fairly controversial results. The stimulation of spinal 5-HT_3 receptors in the dorsal horn has an antinociceptive effect in acute pain models, probably via release of GABA and consequent activation of the descending inhibitory system. This antinociceptive effect is reasonably abolished by the administration of 5-HT_3 receptor antagonists. In chronic pain, however, different situation reigns (2).

Ample evidence implicates the 5-HT_3 receptor subtype in pain and inflammation. The efficacy of 5-HT_3 antagonists in rheumatic diseases is now well-documented. In human monocytes, tropisetron inhibited lipopolysaccharides (LPS)-stimulated secretion of TNF-α and IL-1β (3). In human macrophage-like synovial cells, tropisetron completely blocked the serotonin-evoked over-expression of prostaglandin E2 (PGE2) (4). In pilot studies, local injection of tropisetron potently relieved inflammation and pain in RA, activated osteoarthritis (OA) and tendinopathies. In a double-blinded study, a single intra-articular injection of tropisetron yielded comparable clinical benefits to methylprednisolone in RA and OA which lasted for at least three weeks following its administration (5). By contrast, granisetron displayed an immediate, short-lasting alleviation in temporomandibular joint inflammatory arthritis. Of note, the effect was greater in patients with higher levels of circulating 5-HT indicating the crucial role of 5-HT_3 receptor subtype in antiphlogistic properties repeatedly reported with this class of drugs. The analgesic effect of 5-HT_3 antagonists emerges from their aptitude to inhibit the release of sensory neuropeptides which trigger the development of neurogenic inflammation. Neuropeptides such as substance P and neuropeptide Y, released from sensory afferent neurons, play significant roles in initiating and modulating inflammatory pain (6). Inhibition of the release of pro-inflammatory neuropeptides from sensory afferent nerves may result in attenuation of pain. Given their effects on various disease processes and a broad therapeutic window, 5-HT_3 receptor antagonists merit consideration for larger-scale clinical trials to closely scrutinize their potential efficacy in pain management.

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