Hitting thermo-TRPs and other targets: a more efficacious and safer strategy to treat pain?

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Thermosensitive transient receptor potential (thermo-TRP) channels, and TRPV1 (the 'capsaicin receptor'), TRPA1 (the 'mustard oil receptor') and TRPM8 (the 'menthol receptor') in particular, are deeply involved in pain transmission at the sensory, spinal and supraspinal neuron level as well as in inflammation. Their expression and cation channel activity (in terms of phosphorylation, sensitization and cation gating) is often increased during both inflammatory and chronic (e.g. neuropathic) pain states. Both TRPV1 agonists and antagonists have contraindications that have so far prevented their clinical development as systemic analgesic and anti-inflammatory agents. On the other hand, the recently elucidated 3D-structure of thermo-TRPs is such that many physical and chemical agents can allosterically modulate their activity and the subsequent gating of cations and the membrane potential of the sensory, spinal and supraspinal neurons that express these channels, thus modulating pain sensation too. Among the several chemicals that, for example, modulate TRPV1 activity, many also modulate the activity of other molecular targets involved in pain transmission. Hence, it is not so difficult to find both natural products and synthetic compounds that either activate/desensitize or antagonize TRPV1 channels, and at the same time modulate the activity of, e.g. opioid and cannabinoid receptors, endocannabinoid and adenosine inactivating proteins, prokineticin receptors, and others.
I will review how several natural and synthetic compounds appear to produce more efficacious and safer analgesic actions in animal models of inflammatory and neuropathic pain due to their capability of modulating the activity of one or more thermo-TRPs and at the same time some of these other proteins, and will discuss the potential future clinical development of these molecules for the treatment of pain.