

Nociceptive-Like responses mediated by Transient Receptor Potential Melastatin-3 (TRPM3), in *Hydra vulgaris*.

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Mammals feel noxious stimuli through a heterogeneous group of primary somatosensory neuron, termed nociceptors, which express specific membrane receptors such as the Transient Receptor Potential (TRP) family. Here, we show that the freshwater coelenterate *Hydra vulgaris*, the most primitive organism possessing a nervous system, expresses TRPM3, a nociceptive calcium channel involved in the detection of noxious heat in mammals. Furthermore, we detected that TRPM3 is activated by both heat shock and specific agonist (i.e., pregnenolone sulfate), by inducing the modulation of the heat shock protein 70 (HSP70) and the nitric oxide synthase (NOS), two genes activated by TRP-mediated heat painful stimuli in mammals. We also showed these effects are inhibited by a TRPM3 antagonist (i.e., mefenamic acid). Interestingly, the TRPM3 agonist and heat shock induce the expression of nuclear transcription erythroid 2-related factor (Nrf2) and superoxide dismutase (SOD), known as markers of oxidative stress. This gene expression was also inhibited by the TRPM3 antagonist. As a whole, our findings demonstrate that of the most important oxidative/nociceptive-like pathway is conserved at the primordial level of the animal kingdom.