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BRAIN RESEARCH REVIEWS

Review

Roles of transient receptor potential channels in pain

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ABSTRACT

Pain perception begins with the activation of primary sensory nociceptors. Over the past decade, flourishing research has revealed that members of the Transient Receptor Potential (TRP) ion channel family are fundamental molecules that detect noxious stimuli and transduce a diverse range of physical and chemical energy into action potentials in somatosensory nociceptors. Here we highlight the roles of TRP vanilloid 1 (TRPV1), TRP melastatin 8 (TRPM8) and TRP ankyrin 1 (TRPA1) in the activation of nociceptors by heat and cold environmental stimuli, mechanical force, and by chemicals including exogenous plant and environmental compounds as well as endogenous inflammatory molecules. The contribution of these channels to pain and somatosensation is discussed at levels ranging from whole animal behavior to molecular modulation by intracellular signaling proteins. An emerging theme is that TRP channels are not simple ion channel transducers of one or two stimuli, but instead serve multidimensional roles in signaling sensory stimuli that are exceptionally diverse in modality and in their environmental milieu.

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Contents

1. Introduction

The Transient Receptor Potential (TRP) superfamily of ion channels comprises proteins with six transmembrane domains and cytoplasmic N- and C-termini. TRP proteins assemble as homo- or heterotetramers to form cation-permeable ion channels (Voets et al., 2005). Currently, 28 TRP channels have been discovered in mammals and based on their sequence homology, are classified into six subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP and TRPML (Montell, 2005). This review highlights recent discoveries describing the roles of TRPV1, TRPM8 and TRPA1 in transduction and sensitization in primary afferent somatosensory neurons. The first TRP channel discovered in mammalian sensory neurons was Transient Receptor Potential Vanilloid 1 (TRPV1). TRPV1 is the obligate receptor for capsaicin, the spicy ingredient in hot chili peppers, and also a key receptor for noxious physical heat (>42 °C; Caterina et al., 1997). TRPV1 is found on many small-medium-diameter nociceptive sensory neurons which are likely to have C fiber axons (Tominaga et al., 1998). The identification of TRPV1 was the major catalyst that launched the fields of somatosensory and pain transduction research to the molecular level, and discovery of additional TRP family members rapidly followed.

TRP melastatin 8 (TRPM8) was subsequently discovered in 2002 and found to be strongly activated by the cool-mimetic chemical menthol and by physical cooling (McKemy et al., 2002; Peier et al., 2002). TRPM8 is located in small- and medium-diameter sensory neurons within the trigeminal and dorsal root ganglia. Recently, three independent studies of TRPM8-null mice have firmly established that TRPM8 is a major cold and cooling transduction channel in mammalian sensory neurons (McKemy et al., 2002; Peier et al., 2002; Bautista et al., 2007; Dhaka et al., 2007; Colburn et al., 2007).

Transient Receptor Potential Ankyrin 1 (TRPA1) is the only member of the ankyrin subfamily found in mammals. Originally called ANKTM1, TRPA1 was identified by a homology search for ankyrin domains and six transmembrane