THE ROLE OF TRANSIENT RECEPTOR POTENTIAL (TRP) CHANNELS IN INFLAMMATORY RESPIRATORY DISEASES

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Transient receptor potential (TRP) are an increasingly growing superfamily of ion channels that are expressed in and regulate the function of a large variety of cells. Some of these channels are highly expressed on specific subsets of primary sensory neurons that transmit nociceptive impulse and mediate neurogenic inflammatory responses. Sensory neurons expressing TRP channels are also present in the airways, where they regulate *via* the release of the sensory neuropeptides, tachykinins and calcitonin gene related peptide (CGRP), bronchomotor tone, arterial calibre, leakage of plasma proteins, seromucous gland secretion and other responses. TRP expressing neurons in the airways also contribute to the generation of reflex responses, including reflex bronchoconstriction and cough. TRPV1 is co-expressed with TRPA1 in a subset of neurons. In contrast the TRPM8, activated by menthol, is expressed in TRPV1-negative neurons. Additional TRP expressed by sensory neurons are TRPV4, TRPV3 and TRPV2. All these channels, being stimulated by different temperatures, are considered thermosensors, but it is apparent that their physiological and pathophysiological roles are multiple and beyond temperature sensation. TRPV1 is the best known of the TRPs expressed on primary sensory neurons. TRPV1 is activated by capsaicin, low extracellular pH and various lipids. Its activity is regulated by a large variety of intra and extracellular mediators and by a wide range of exogenous stimuli that may be relevant in airway inflammation, including nerve growth factor, kinins, alcohols and many others. The lowered threshold to capsaicin-induced cough, observed in patients with asthma, cough variant asthma and COPD suggests the hypothesis that different types of chronic airway inflammation promote a process that exaggerates TRPV1 mediated responses. Little attention has been paid to the study of TRPV2, TRPV3 and TRPV4, as well as of TRPM8, in airway sensory neurons. Previous evidence indirectly suggested that TRPA1, a channel activated by low temperature, cynnamaldehyde and mustard oil, could be the mediator of the neuronal effect produced by cigarette smoke (CS) in the airways. Plasma protein extravasation evoked by CS in the rodent airways was abolished by capsaicin desensitization (1), and inhibited by the non-selective TRP antagonist ruthenium red (2), but not by the TRPV1 antagonist capsazepine (2). These early observations could not be clarified until the cloning of the TRPA1 and the recent finding that it is stimulated by acrolein, a major component of CS. We recently demonstrated that acrolein and crotonaldehyde two major aldehydes contained in CS stimulate sensory neurons, thus causing neurogenic inflammation in guinea pigs.

1. Lundberg and Saria, Nature 1983, 302, 251
2. Geppetti et al, Br J Pharmacol, 1993, 108, 646
3. Bautista et al., Cell, 124, 1269