TRPV1 in the airways

Maria G. Belvisi and Peter J. Barnes

Respiratory Pharmacology Group and Airway Disease Section, National Heart & Lung Institute, Imperial College, Dovehouse Street, London SW3 6LY, UK

Introduction

Sensory nerves in the airways regulate central and local reflex events such as bronchoconstriction, airway plasma leakage, mucus secretion and cough [1]. Sensory nerve activity may be enhanced during inflammation such that these protective reflexes become exacerbated and deleterious [1]. Sensory nerve reflexes are under the control of at least two different classes of sensory fibre: the myelinated, rapidly-adapting stretch receptors and non-myelinated, capsaicin-sensitive, C-fibres [2, 3]. In the airways, activation of rapidly-adapting stretch receptors and C-fibres elicits cough, bronchoconstriction and mucus secretion via an afferent central reflex pathway [1, 4–6]. Activation of C-fibres in the airways also mediates efferent excitatory non-adrenergic, non-cholinergic (e-NANC) responses such as bronchoconstriction, mucus secretion, plasma exudation and vasodilatation, via the peripheral release of neuropeptides, a phenomenon known as neurogenic inflammation [1] (Fig. 1). A characteristic feature of many nociceptive sensory fibres is their sensitivity to capsaicin [7, 8]. However, until recently the molecular mechanisms involved in activation of sensory nociceptive fibres were unknown. Pharmacological evidence for the presence of a capsaicin receptor in sensory nerves was provided by the use of two capsaicin analogues, resiniferatoxin (a potent agonist) and capsazepine (a selective antagonist). Firstly, specific binding sites for resiniferatoxin were demonstrated on dorsal root ganglion membranes [9] and, secondly, capsazepine has been found to inhibit numerous capsaicin-evoked neuronal responses [10, 11], including those in the airways [12]. The capsaicin receptor has recently been identified and has been named the type 1 vanilloid receptor (VR1; or TRPV1, for transient receptor potential vanilloid 1) [13].
The type 1 vanilloid receptor (TRPV1)

TRPV1 is a membrane-associated vanilloid receptor. It is a ligand-gated ion channel expressed selectively on the neuronal plasma membrane of nociceptive C-fibres and is required for the activation of sensory nerves by vanilloids such as capsaicin, the pungent extract from plants in the *Capsicum* family (hot chilli peppers) [14, 15]. TRPV1 also mediates the response to painful heat, extracellular acidosis, protons and tissue injury [15, 16]. The convergence of these stimuli on TRPV1 channels, which are highly expressed in the sensory neurons of dorsal root and trigeminal ganglia, underlies the common perceptual experience of pain due to these stimuli. TRPV1 is an outwardly rectifying, cation-selective ion channel with a preference for calcium ($P_{Ca}/P_{Na} \sim 10$) and magnesium ($P_{Mg}/P_{Na} \sim 5$) [14], which depends on a single aspartic acid residue in the pore region of the protein. TRPV1 is activated by...