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TRP Ca^{2+}-PERMEABLE CHANNELS IN AIRWAY SMOOTH MUSCLE CELLS

Greg J Barritt

Department of Medical Biochemistry, School of Medicine, Flinders University, Adelaide, South Australia

Regardless of the triggering stimulus in asthma, contraction of the airway smooth muscle (ASM) is considered to be the final pathway leading to the manifestation of asthmatic symptoms. The various ion channels that modulate ASM contraction and relaxation are particularly attractive targets for therapy. Although voltage-operated Ca^{2+} channels (VOCCs) are the most extensively characterised Ca^{2+}-permeable channels in the plasma membrane of ASM cells, and are obvious pharmacological targets, blockers of VOCCs have not been successful in alleviating ASM contraction in asthma. A body of evidence indicates that store-operated Ca^{2+} channels (SOCs) and receptor-activated Ca^{2+}-permeable non-selective cation channels (RACCs) most likely predominantly mediate Ca^{2+} entry for ASM contraction. Cl^- and K^+ channels may modulate ASM contraction and relaxation by regulating plasma membrane potential. Many RACCs in ASM cells are likely composed of members of the mammalian transient receptor potential (TRP) protein family, which form voltage-independent channels with different degrees of Ca^{2+} selectivity. Studies with human and guinea pig ASM have provided evidence for the expression of mRNA encoding TRPC1, TRPC3, TRPC4, TRPC6, TRPV2 and TRPV4. Expression of TRPC1 is increased in proliferating ASM cells. Due to difficulties in often obtaining good antibodies to TRP proteins, there is limited direct evidence for expression of TRP proteins (*cf* mRNA) in ASM cells. Studies measuring Ca^{2+} entry and using various pharmacological inhibitors of TRP channels have provided evidence for functional TRPC6, TRPV4 (and TRPV1) in ASM cells. While TRPC1 and TRPC3 have been considered as candidates for Ca^{2+}-selective SOCs in mammalian cells, there is little convincing evidence for this possibility. (Recent work with other cell types suggests that the membrane-spanning protein CRACM1 and regulatory protein STIM1 constitute the core of the highly Ca^{2+}-selective SOCs.) Studies with TRPV4 provide evidence that this TRP protein acts as an osmolarity sensor in ASM cells. Changes in Ca^{2+} and Na^+ entry through TRP channels may contribute to hypercontractivity of ASM in asthma. TRP channels are important potential targets for pharmaceutical intervention.

S 9-2

REGULATION AND FUNCTION OF VASCULAR TRP CATION CHANNELS

Ryuji Inoue, Shinichi Takahashi, Yasuhiro Kawarabayashi, Yuki Nakamura, Akira Honda, Hai Lin and Akira Uehara

Department of Physiology, Graduate School of Medical Sciences, Fukuoka University, Fukuoka, Japan

Mammalian homologues of *Drosophila* transient receptor potential (TRP) protein constitutes a vast superfamily of non-voltage-gated Ca^{2+} entry channels activated by a variety of physiococchemical stimuli such as receptor agonists, chemicals, temperature, osmolarity, oxidative and mechanical stresses. Amongst them, eleven TRP isoforms including TRPC1, TRPC3-TRPC6, TRPV1, TRPV2, TRPV4, TRPM4, TRPM7, TRPP2 are abundantly expressed in vascular tissues. These vascular TRP isoforms are not only activated in response to various vasoactive agents released from autonomic and sensory nerves, vascular endothelium, endocrine organs and migrating inflammatory cells, but also by mechanical forces imposed on the vascular wall, participating in regulation of both vascular reactivity and remodeling. Recent evidence implicates TRPC1 in hypoxia-induced vasoconstriction and neointimal hyperplasia after vascular injury via store-depletion operated Ca^{2+} entry. TRPC6 likely contributes to receptor-operated and mechanosensitive Ca^{2+} mobilizations, being involved in vasoconstrictor and myogenic responses and pulmonary arterial proliferation and its associated disease (idiopathic pulmonary arterial hypertension). Considerable evidence has also been accumulated for the unique role of TRPV1 in blood flow/pressure regulation via sensory vasoactive neuropeptide release, which is associated with myogenic response in resistance artery and protection against the development of salt-sensitive hypertension. Other lines of evidence suggest that TRPV2 may act as arterial stretch-activated Ca^{2+} channels, TRPV4 as a mediator of endothelium-dependent hyperpolarization, TRPM7 as a pro-proliferative vascular Mg^{2+} entry channel and TRPP2 as a Ca^{2+} entry channel requisite for vascular integrity. The latest report has revealed sphingosin-1 phosphate -mediated activation of TRPC5, which seems be an essential process to initiate the migration of vascular smooth muscle cells. In addition, we will discuss about the mechanisms powerfully regulating these TRP isoforms, particularly TRPC6, with respect to its effective regulation by Ca^{2+}/calmodulin/calmodulin-dependent kinase II and 20-hydroxyeicosatetraenoic acid upon receptor-mediated and mechanical stimulation.