# **ORAL PRESENTATION**

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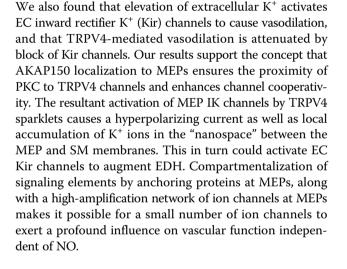
# Elementary Ca<sup>2+</sup> signals through endothelial TRPV4 channels regulate vascular function

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*From* 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications Erfurt, Germany. 28-30 June 2013

The endothelial cells (ECs) lining blood vessels are pivotal regulators of vascular tone. Endothelial-dependent vasodilation by classic agents such as acetylcholine (ACh) depends on an elevation of EC Ca<sup>2+</sup>, and can act through the generation of nitric oxide (NO). An elevation of EC Ca<sup>2+</sup> also activates small- and intermediate-conductance (SK and IK) potassium channels. This leads to endothelium-dependent hyperpolarization ("EDH"), which is spread through gap junctions in specialized EC projections to adjacent smooth muscle cells (SMCs) to cause vasodilation of small resistance arteries and arterioles, and this pathway is responsible for the majority of the ACh-induced dilation in resistance arteries [1]. We have recently reported the first measurements of elementary Ca<sup>2+</sup> influx events ("sparklets") through single TRPV4 (transient receptor potential vanilloid 4) channels in ECs of intact, small mesenteric arteries. Cooperative opening of as few as 3 TRPV4 channels per EC caused maximum vasodilation primarily through activation of EC IK channels [2]. This raises the fundamental question about how these sparse channels maintain the functional linkages necessary for efficient signaling. An architectural feature of ECs that is likely centrally important in this regard is the myoendothelial projection (MEP). These specialized projections through the internal elastic lamina (IEL) connect ECs with adjacent SMCs through gap junctions. The objective of this study was to elucidate the signaling network that enables efficient and effective endothelial-dependent vasodilation through the EDH pathway. Our results indicate that muscarinic receptor agonists activate TRPV4 sparklets exclusively at MEPs in a protein kinase  $C\alpha$  (PKC $\alpha$ ) and Akinase anchoring protein (AKAP150)-dependent manner.

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## Published: 29 August 2013

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## doi:10.1186/2050-6511-14-S1-O23

**Cite this article as:** Nelson *et al.*: **Elementary Ca<sup>2+</sup> signals through endothelial TRPV4 channels regulate vascular function**. *BMC Pharmacology and Toxicology* 2013 **14**(Suppl 1):O23.



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