## The role of store-operated calcium channels in endothelin-1-mediated vasoconstriction of rat mesenteric arteries

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Cellular calcium is an essential regulator of vascular tone, which underscores the therapeutic potential of its regulation in the management of cardiovascular disease. Recent clinical and pharmacological evidence has indicated that the transient (T-type) calcium channels may be important in mediating endothelin-1 (ET-1) vasoconstriction. Using functional vascular myography, this study aimed to identify: (1) the efficacy of selective T-type calcium channel blockade (NNC 55-0396, 10μM) compared to conventional L-type calcium channel blockade (verapamil, 10μM); and (2) the contribution of intracellular inositol-1,4,5-trisphosphate-mediated calcium release and store-operated calcium entry to the activation of voltage-dependent calcium channels in ET-1-mediated vasoconstriction in isolated rat mesenteric arteries. Results indicated that the T-type calcium channel blocker, NNC 55-0396 is more effective than L-type calcium channel blocker, verapamil, in attenuating contractile responses in the context of $K^+$-mediated depolarisation (n=5) but not ET-1-mediated vasoconstriction (n=20). Inhibition of intracellular inositol-1,4,5-trisphosphate-mediated calcium release using the $IP_3$ receptor and store-operated calcium channel inhibitor, 2-aminoethyl diphenylborinate (100μM) further attenuated the force ($p<0.05$; n=4). Following complete depletion of intracellular calcium using the sarco-endoplasmic reticulum calcium ATPase inhibitor, cyclopiazonic acid (10μM), ET-1-mediated contractile responses were almost completely abolished ($p<0.05$; n=4). Combining calcium channels blockers with protein kinase C inhibitor, GF-109203X (5μM) also resulted in significant attenuation of ET-1-mediated vasoconstriction. In conclusion, extracellular, $IP_3$-mediated and store-operated calcium channels, as well as PKC pathways are involved in ET-1-mediated vasoconstriction in the microvasculature. These data highlighted the importance of understanding the molecular mechanisms underlying the plethora of calcium entry pathways, as well as providing potential therapeutic targets to combat the detrimental effects of vasoconstriction for the management of cardiovascular disease.