Role of store-operated calcium channels and mitochondria in the inhibition of human coronary smooth muscle cell migration and proliferation by NSAIDs

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Abnormal vascular smooth muscle cell (VSMC) proliferation contributes to occlusive an proliferative disorders of vessel wall. Salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit VSMC proliferation by an unknown mechanism unrelated to anti-inflammatory activity. In search for this mechanism, we have studied the effects of salicylate and other NSAIDs on subcellular Ca2+ homeostasis and Ca2+ dependent cell proliferation in human coronary vascular smooth muscle cell (hcVSMCs). We found that hcVSMCs displayed both store-operated Ca2+-entry (SOCE and voltage-operated Ca2+-entry (VOCE)). Interestingly, the ratio of SOCE to VOCE and cell proliferation decreased with increased pass number, possibly due to the differentiation towards a contractile phenotype. Inhibition of SOCE by specific Ca2+-release-activated Ca2+ (CRAC/Orai) channels antagonists prevented hcVSMC proliferation. We also found that NSAIDs inhibited SOCE and thereby Ca2+-dependent proliferation and migration. In search for the action mechanism we found that NSAIDs prevented mitochondrial Ca2+ uptake in hcVSMCs, thus facilitating the Ca2+-dependent inactivation of store-operated Ca2+ entry. We conclude that NSAIDs inhibit human coronary vascular smooth cell migration and proliferation by enabling the Ca2+-dependent inactivation of store-operated Ca2+ entry regulated by mitochondria. This work has been funded by grants CSI12A08 from Junta de Castilla y León and BFU2009-08967 from Ministerio de Ciencia e Innovación.