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Modulation of angiotensin II signalling by cannabinoid receptor 1 antagonism in human coronary artery smooth muscle cells

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The endocannabinoid system consists of at least two G-protein coupled receptors (GPCR), CB1 and CB2, and endogenous ligands such as anandamide (AEA) and 2-arachidonolyglycerol (2-AG). CB1 receptors are expressed in the brain but also in peripheral tissues. Several studies have demonstrated the possible importance of the peripheral endocannabinoid system, mainly in the pathogenesis of cardiovascular diseases. Angiotensin type 1 receptor (AT1R) is a GPCR that transduces the main physiological actions of the renin-angiotensin system in target cells. The major signaling events following agonist binding to this receptor are activation of phospholipase C via a Gαq protein, mobilization of calcium from intracellular stores, and activation of other signaling pathways such as the MAP kinase pathway that participates in the hypertrophic actions of Ang II. Following characterization of CB1 and AT1R in human coronary artery smooth muscle cells (hCASMC), this project investigated evidence for functional cross talk between AT1R and CB1. CB1 and AT1R expression was examined in hCASMC using RT-qPCR and Western blotting. Phosphorylation of MAP kinase was determined using Western blotting. CB1 and AT1R were expressed in a range of hCASMC cell sources, and functional MAP kinase activity was observed following application of agonists. Peak pERK1/2 occurred at 5 minutes following 100nM Ang II and at 10 to 15 minutes after 1µM AEA. Furthermore, a concentration-dependent increase in phosphorylation of ERK1/2 in response to Ang II or AEA was observed with pEC_{50} values of 8.64±0.41 and 8.17±0.32 respectively. We examined if the presence of CB1 contributed to the response of AT1R to Ang II stimulation by directly altering pERK activation. Pre-incubation with the CB1 antagonist, SR141716A (10µM), significantly reduced Ang II-induced pERK activity. In conclusion, CB1 and AT1R receptors are expressed and are functionally active in hCASMC and it is suggested that there is cross talk between the two GPCR pathways. Future work will include study of other MAPK pathways such as p38 and Junk pathway as well as effects on Ca^{2+}mobilization.