Carbenoxolone and 18β-Glycyrrhetinic Acid Inhibit IP_3-Mediated Endothelial Cell Calcium Signalling and Depolarise Mitochondria

Charlotte Buckley[1], Xun Zhang[1], Calum Wilson[1], and John McCarron[1]

[1]University of Strathclyde

July 1, 2020

Abstract

Background and Purpose Coordinated endothelial control of cardiovascular function is proposed to occur by endothelial cell communication via gap junctions and connexins. To study intercellular communication, the pharmacological agents carbenoxolone (CBX) and 18β glycyrrhetinic acid (18βGA) are used widely as connexin inhibitors and gap junction blockers. **Experimental Approach** We investigated the effects of CBX and 18βGA on IP_3-evoked intercellular Ca^{2+} waves in the endothelium of intact mesenteric resistance arteries. **Key Results** Acetylcholine (ACh)-evoked IP_3-mediated Ca^{2+} release and propagated waves were inhibited by CBX (100μM) and 18βGA (40μM). Unexpectedly, the Ca^{2+} signals were inhibited uniformly in all cells, suggesting that CBX and 18βGA reduced Ca^{2+} release. Localised photolysis of caged IP_3 (cIP_3) was used to provide precise spatiotemporal control of site of cell activation. Local cIP_3 photolysis generated reproducible Ca^{2+} increases and Ca^{2+} waves that propagated across cells distant to the photolysis site. CBX and 18βGA each blocked Ca^{2+} waves in a time dependent manner by inhibiting the initiating IP_3-evoked Ca^{2+} release event rather than block of gap junctions. This effect was reversed on drug washout, and was unaffected by small or intermediate K^+-channel blockers. Furthermore, CBX and 18βGA each rapidly and reversibly collapsed the mitochondrial membrane potential. **Conclusion and Implications** CBX and 18βGA inhibit IP_3-mediated Ca^{2+} release and depolarise the mitochondrial membrane potential. These results suggest that CBX and 18βGA block cell-cell communication by acting at sites that are unrelated to gap junctions.

Hosted file

`Buckley et al.pdf` available at https://authorea.com/users/338545/articles/465047-carbenoxolone-and-18%CE%B2-glycyrrhetinic-acid-inhibit-ip3-mediated-endothelial-cell-calcium-signalling-and-depolarise-mitochondria