Peroxisome proliferation activation receptor alpha modulation of Ca2+-regulated exocytosis via arachidonic acid in guinea-pig antral mucous cells


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Abstract

Indomethacin (IDM, 10 microm), not aspirin (ASA; 10 microm), enhanced the Ca(2+)-regulated exocytosis stimulated by 1 microm acetylcholine (ACh) in guinea-pig antral mucous cells. Indomethacin inhibits prostaglandin G/H (PGG/H) and 15R-hydroperoxy-eicosatetraenoic acid (15R-HPETE) production from arachidonic acid (AA), while ASA inhibits PGG/H production but accelerates 15R-HPETE production. This suggests that IDM accumulates AA. Arachidonic acid (2 microm) enhanced Ca(2+)-regulated exocytosis in antral mucous cells to a similar extent to IDM. Moreover, a stable analogue of AA, arachidonyltrifluoromethyl ketone (AACOCF(3)), also enhanced Ca(2+)-regulated exocytosis, indicating that AA, not products from AA, enhances Ca(2+)-regulated exocytosis. We hypothesized that AA activates peroxisome proliferation activation receptor alpha (PPARalpha), because AA is a natural ligand for PPARalpha. A PPARalpha agonist (WY14643; 1 microm) enhanced Ca(2+)-regulated exocytosis, and a PPARalpha blocker (MK886; 50 microm) abolished the enhancement of Ca(2+)-regulated exocytosis induced by AA, IDM, AACOCF(3) and WY14643. Western blotting and immunohistochemical examinations demonstrated that PPARalpha exists in antral mucous cells. Moreover, MK886 decreased the frequency of Ca(2+)-regulated exocytosis activated by 1 microm ACh or 2 microm thapsigargin alone by 25-30%. Thus, ACh stimulates AA accumulation via an [Ca(2+)](i) increase, which activates PPARalpha, leading to enhancement of Ca(2+)-regulated exocytosis in antral mucous cells. A novel autocrine mechanism mediated via PPARalpha enhances Ca(2+)-regulated exocytosis in guinea-pig antral mucous cells.