Ca^{2+}-sensing receptor-$G_{q/11}$ protein signaling pathway is involved in nitric oxide release from human vascular endothelial cells

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Ca^{2+}-sensing receptor (CaSR) belongs to family C of G protein-coupled receptors and is activated by the endogenous agonists such as Ca^{2+}. Stimulation of CaSR expressed in vascular endothelial cells through the increase in extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$) is reported to induce vasorelaxation via the production of nitric oxide (NO). The purpose of the present study is to characterize the CaSR-mediated NO production in human vascular endothelial cells. In human endothelial EA.hy926 cells, the increase in $[Ca^{2+}]_o$ from 0.2 to 2 mM induced a concentration-dependent increase in intracellular Ca^{2+} concentration, which was significantly inhibited by NPS 2143 (a CaSR antagonist) and YM-254890 (a $G_{q/11}$ protein inhibitor). Stimulation with 2 mM Ca^{2+} for 4 h elicited an increase in the phosphorylation level of eNOS at Ser^{1177}, which was significantly depressed by NPS 2143, YM-254890, and removal of Ca^{2+} from the medium. Ca^{2+} (2 mM) induced an increase in NO production, which was inhibited by NPS 2143, YM-254890, removal of Ca^{2+} from the medium, and L-NAME (a competitive eNOS inhibitor). These results provide evidence that activation of CaSR with extracellular Ca^{2+} facilitates NO release from human vascular endothelial cells via a $G_{q/11}$ protein-eNOS-dependent pathway.