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CHARACTERIZATION OF PROTEIN SENSITIVE G PROTEIN-COUPLED RECEPTORS

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Characterization of Protein Sensitive G-Protein Coupled Receptors

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ABSTRACT

G protein-coupled receptors (GPCRs) are membrane-bound receptors that can stimulate an intracellular signaling pathway following activation by a ligand. According to the International Union of Basic and Clinical Pharmacology (IUPHAR) database, GPR4, GPR65, and GPR132 are Class A orphan GPCRs with protons reported as their putative endogenous ligand; however, these receptors are currently understudied. After confirming whether these receptors are pH-sensitive, the purpose of our study was to investigate the interactions between GPR4, GPR65, GPR132, and G protein subtypes ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$) upon stimulation with an acidic solution. Using bioluminescence resonance energy transfer (BRET), we studied the coupling between luciferase-tagged GPR receptors and fluorescent protein (Venus)-tagged G proteins in response to pH changes. Data indicated that all three receptors responded to pH changes. Upon extracellular response to pH changes, the receptors activate different G protein subtypes and thus, different signaling pathways: GPR4 activates $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$; GPR65 activates all four subtypes; and GPR132 activates $G\alpha_i$ and weakly activates $G\alpha_q$, and $G\alpha_{12}$. Identifying these receptors as true proton sensors leads the way in understanding the role they play in maintaining acid-base homeostasis and will be critical for the development of novel drugs combatting acid-base related disorders.

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