Purification and Drug Targeting of Family B G Protein-Coupled Receptors

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Transmembrane G protein-coupled receptors (GPCRs) belong to the largest gene family of the human genome and are important drug targets. Among these receptors are family B GPCRs with a characteristic N-terminal ligand-binding domain. They are responsible for sensing peptide hormones, of which the molecular mechanism is still largely unexplored due to the difficulty in purifying functional receptors for biophysical studies. To tackle this, we developed a method using nanodiscs to purify a family B GPCR, parathyroid hormone 1 receptor (PTH1R) that regulates calcium homeostasis and is a drug target for osteoporosis. Using the purified receptor, we observed for the first time that PTH1R activation by the PTH(1-34) ligand is enhanced by 20 time with 15 mM calcium. This result is important in bone physiology because the activation of PTH1R triggers bone resorption resulting in calcium release up to 20-40 mM. The result can also help understand the effect of PTH(1-34) as the only drug on market targeting PTH1R for osteoporosis. Moreover, we modified PTH(1-34) with a triblock design of peptide–linker–lipid. This triblock design enhances the activity of the PTH(1-14) peptide by 100 times mainly due to lipid insertion for higher local concentrations. The linker moiety, either poly(glycine-serine) or polyethylene glycol, provides flexibility for optimal ligand-receptor interactions. The lipid moiety enables the formation of micelle-like nanostructures that hinder proteolytic degradation, thus prolonging the life time. We conclude that the triblock design can be a general strategy in improving efficiency of peptide drugs targeting family B GPCRs.