A receptor-specific crosstalk between the prostanoid 3 and the Bombesin subtype 3 receptors

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Bombesin receptor subtype-3 (BRS-3) is a G protein-coupled receptor that is expressed in the central nervous system, peripheral tissues and in tumors. Our understanding of BRS-3's role in physiology/pathophysiology is limited because its natural ligand is unknown. In an attempt to identify this ligand, we screened toad skin extracts and identified prostaglandins as putative ligands. In BRS-3-transfected HEK cells we show that prostaglandins, PGE₂ being the most potent, fulfill the pharmacological criteria of affinity, selectivity and specificity to be considered as agonists to the BRS-3 receptor. However, PGE₂ is unable to activate BRS-3 in different cellular environments. We speculated that endogenous prostanoid receptors (EPs) might be the cause of this cellular selectivity, and found that EP₃ is the receptor primarily responsible for the differential PGE₂ effect. Consequently we reconstituted the HEK environment in CHO cells and found that BRS-3 and EP₃ interact to potentiate PGE₂ signaling. This potentiating effect is receptor specific, and occurs only when BRS-3 is paired to EP₃. Our study represents an example of functional cross-talk between two distantly related GPCRs and may be of clinical importance for BRS-3 targeted therapies.