Papers of the Week

Two Types of Novel Allosteric Modulators Activate β_2-AR Signaling, a G Protein-coupled Receptor Involved in Airway Smooth Muscle Relaxation and Asthma ♦

♦ See referenced article, *J. Biol. Chem.* 2014, **289,** 35668–35684

Development and Characterization of Pepducins as G_s-biased Allosteric Agonists

The β_2-adrenergic receptor (β_2AR) is a G protein-coupled receptor (GPCR) involved in hormonal signal transduction and plays a role in many physiological processes including cardiac muscle contraction and airway smooth muscle relaxation. β-Agonists, which stimulate the β_2AR, are commonly used as therapeutics in the treatment of asthma. However, desensitization of the receptor in response to β-agonists, which is largely mediated by GPCR kinases and β-arrestins, reduces agonist efficacy. An agonist that can stimulate G protein signaling through the β_2AR while bypassing GPCR kinases and β-arrestins may be useful in the treatment of asthma. In this Paper of the Week, a team led by Jeffrey Benovic at Thomas Jefferson University screened lipidated peptides from the intracellular loops of the β_2AR, known as pepducins, and discovered two types of biased activators of β_2AR signaling. One type was a receptor-dependent pepducin that stabilized a conformation of the β_2AR that was biased towards the G_s heterotrimeric G protein while a second group of pepducins directly activated G_s. The investigators say that these molecules "provide a valuable tool for the continued study of β_2AR function and may prove useful as next-generation asthma therapeutics."

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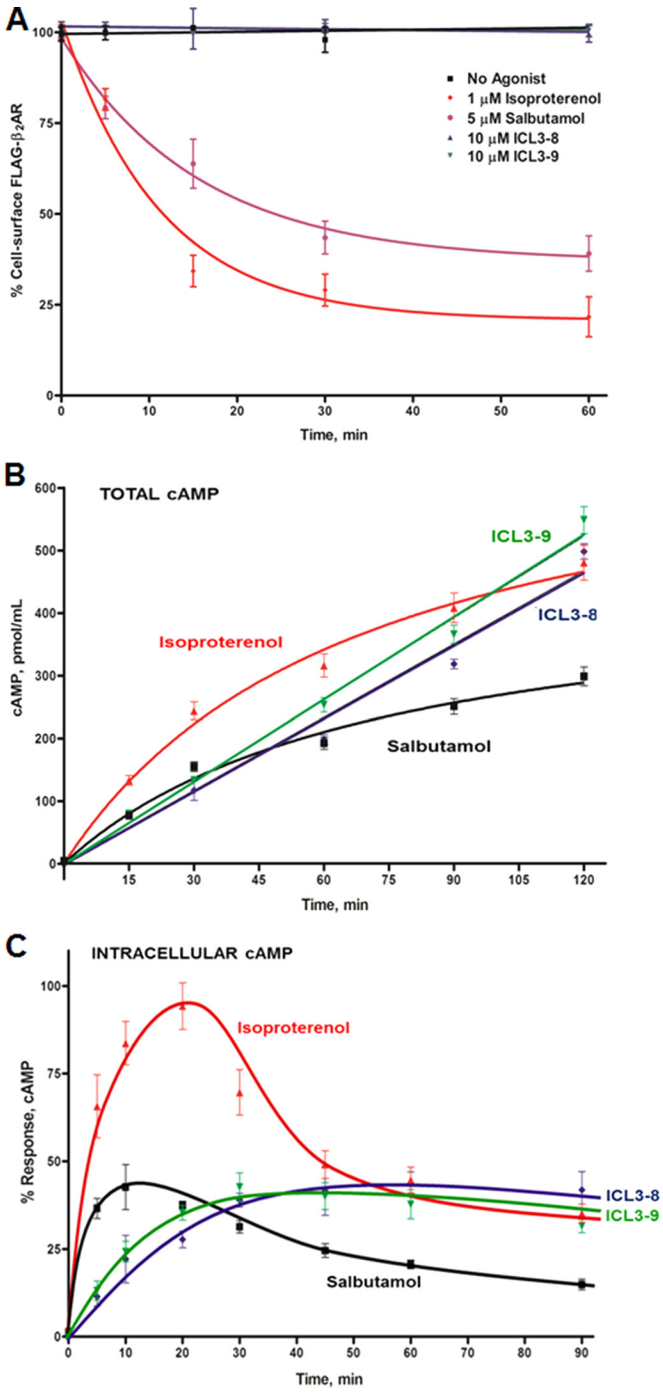

G_s-biased agonists do not promote β_2AR internalization or desensitization.