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Review

Gαq signalling: The new and the old

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ABSTRACT

In the last few years the interactome of Gαq has expanded considerably, contributing to improve our understanding of the cellular and physiological events controlled by this G alpha subunit. The availability of high-resolution crystal structures has led the identification of an effector-binding region within the surface of Gαq that is able to recognise a variety of effector proteins. Consequently, it has been possible to ascribe different Gαq functions to specific cellular players and to identify important processes that are triggered independently of the canonical activation of phospholipase Cβ (PLCβ), the first identified Gαq effector. Novel effectors include p63RhoGEF, that provides a link between G protein-coupled receptors and RhoA activation, phosphatidylinositol 3-kinase (PI3K), implicated in the regulation of the Akt pathway, or the cold-activated TRPM8 channel, which is directly inhibited upon Gαq binding. Recently, the activation of ERK5 MAPK by Gq-coupled receptors has also been described as a novel PLCβ-independent signalling axis that relies upon the interaction between this G protein and two novel effectors (PKCζ and MEK5). Additionally, the association of Gαq with different regulatory proteins can modulate its effector coupling ability and, therefore, its signalling potential. Regulators include accessory proteins that facilitate effector activation or, alternatively, inhibitory proteins that downregulate effector binding or promote signal termination. Moreover, Gαq is known to interact with several components of the cytoskeleton as well as with important organisers of membrane microdomains, which suggests that efficient signalling complexes might be confined to specific subcellular environments. Overall, the complex interaction network of Gαq underlies an ever-expanding functional diversity that puts forward this G alpha subunit as a major player in the control of physiological functions and in the development of different pathological situations.

Contents

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1. Introduction

Many hormones, neurotransmitters and different stimuli with a paramount role in health and disease elicit specific cellular responses through cell surface receptors. Of the several families of membrane receptors, by far the largest, most versatile and most ubiquitous is that of the seven-transmembrane receptors (also referred to as G-protein-coupled receptors (GPCRs)) [1]. These proteins are a physical conduit for the transmission of chemical signals across the cell membrane and mediate the activation of intracellular G proteins (α, β and γ subunits) [2].

Agonist binding to the receptor involves an important rearrangement of intracellular helices 6 and 3 [3,4] which leads to the activation of Galpha subunits by sequentially promoting GDP dissociation, and GTP binding (Fig. 1). This leads to the dissociation of the G protein

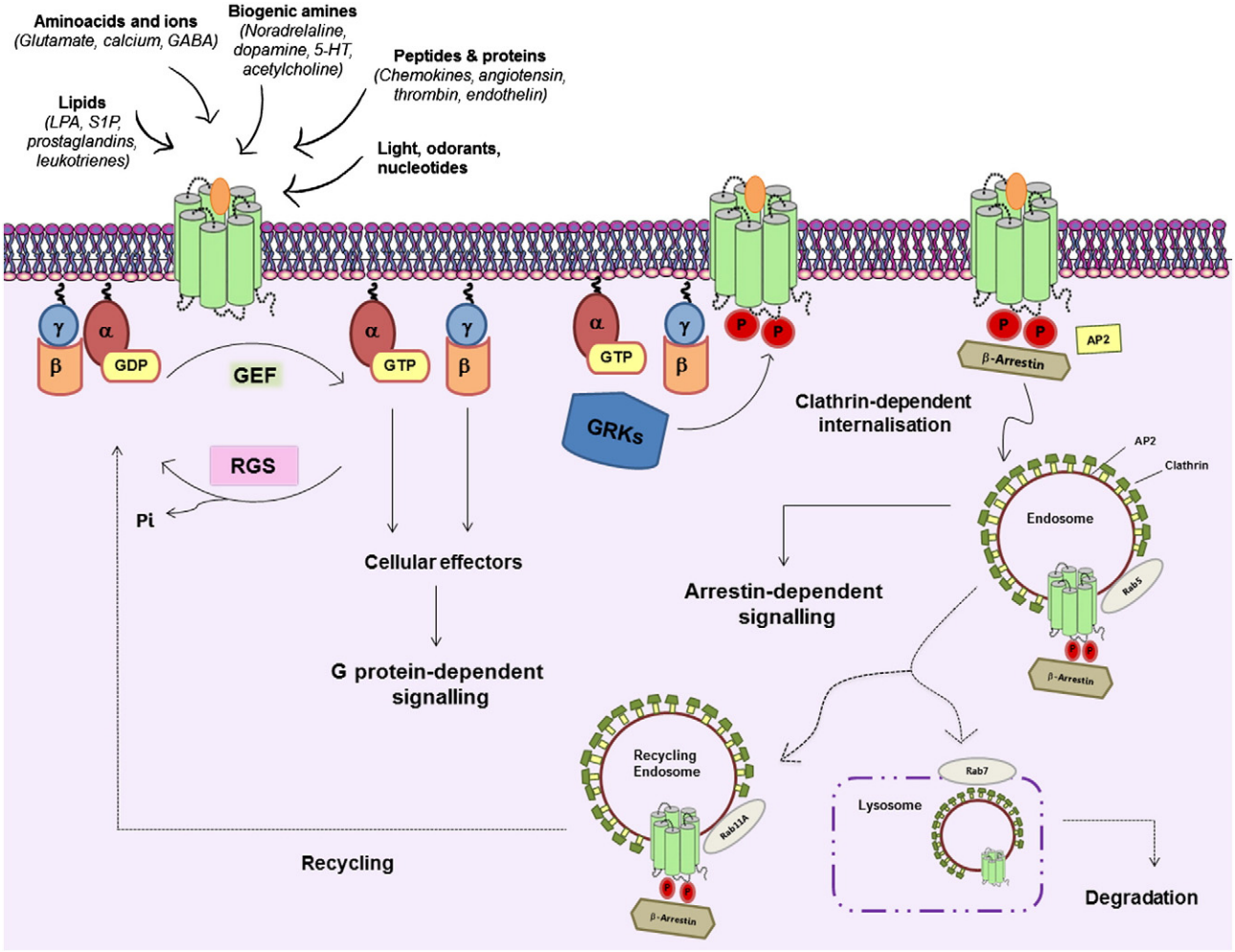

Fig. 1. GPCR activation and deactivation cycle. A huge diversity of ligands bind and activate GPCRs. In turn, receptors stimulate heterotrimeric G proteins by promoting GDP to GTP exchange in the Gα subunit and dissociation from the βγ dimer. Both Gα and βγ initiate signalling through different effector proteins. Activated GPCRs are phosphorylated by GRKs on the internal loops creating recognition sites for β-arrestins that, together with AP2, promote clathrin-mediated receptor internalisation into Rab5-containing vesicles. These can progress into Rab7-containing multivesicular bodies and degradation, or into Rab11A-containing vesicles to recycle receptors back to the plasma membrane [230]. Addionally, arrestins are also known to initiate diverse signals independently of G proteins.