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Review / Revue

Towards a systems biology approach of G protein-coupled receptor signalling: Challenges and expectations

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Abstract

G protein-coupled receptors (GPCRs) control all the main physiological functions and are targeted by more than 50% of therapeutics. Our perception of GPCRs signalling has grown increasingly complex since it is now accepted that they activate large signalling networks which are integrating the information fluxes into appropriate biological responses. These concepts lead the way to the development of pathway-selective agonists (or antagonists) with fewer side effects. Systems biology approaches focused on GPCR-mediated signalling would help dealing with the huge complexity of these mechanisms therefore speeding-up the discovery of new drug classes. In this review, we present the various technical and conceptual possibilities allowing a systems approach of GPCR-mediated signalling. The main remaining limitations are also discussed. ***To cite this article: D. Heitzler et al., C. R. Biologies 332 (2009).***

Résumé

Vers une biologie systémique de la signalisation des récepteurs couplés aux protéines G : Défis et attentes. Les récepteurs couplés aux protéines G (RCPGs) contrôlent toutes les grandes fonctions physiologiques et sont la cible de plus de 50% des médicaments. Notre perception de la signalisation des RCPGs s'est considérablement complexifiée puisqu'il est maintenant admis qu'ils activent de larges réseaux de signalisation capables d'intégrer les flux d'information en des réponses biologiques appropriées. Ces concepts ouvrent la voie au développement d'agonistes (ou d'antagonistes) sélectifs de voies de signalisation qui présenteraient moins d'effets indésirables. Une démarche de biologie systémique appliquée à la signalisation des RCPGs aiderait à appréhender la complexité des mécanismes de signalisation et accélérerait ainsi l'émergence de nouvelles classes de médicaments. Dans cette revue, nous présentons les différentes possibilités techniques et conceptuelles permettant la mise en place d'une approche systémique de la signalisation des RCPGs. Les principaux défis auxquels nous restons confrontés sont également discutés. ***Pour citer cet article : D. Heitzler et al., C. R. Biologies 332 (2009).***

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1. Introduction

An impressive amount of detailed information has been gathered over the past decades on how external stimuli activate plasma membrane receptors, how they translate to the activation of linear downstream signalling cascades and eventually affect cell fate. Recently, the advent of highly sensitive proteomic methods has produced maps of protein interactions and led to the reconstruction of biochemical networks [1]. As a consequence, it is now widely accepted that signalling pathways are organized as coordinated communication networks in which multi-protein complexes process and integrate the signal fluxes. Now, the challenge in cell signalling is to understand the behaviour of these intertwined communication networks in order to decipher the cellular language [2]. G protein-coupled receptors (GPCR) represent the largest class of membrane receptors. They are capable of binding a wide diversity of molecules that regulate most physiological processes and are involved in a plethora of diseases. Noteworthy, GPCRs have long been preferential targets of therapeutic research and development and they currently account for up to 50% of marketed drugs [3].

2. The growing complexity of GPCR-induced signalling

Classically, upon ligand binding, GPCRs undergo a conformational change that leads to heterotrimeric G protein recruitment and activation, followed by the generation of diffusible second messengers such as cAMP (cyclic Adenosine Mono-Phosphate), calcium or phosphoinositides. However, it is increasingly recognized that GPCRs trigger multiple signalling pathways which lead to the formation of signalling networks [4] (Fig. 1). For instance, some GPCRs have the ability to couple to multiple G protein subtypes [5] and many GPCRs directly interact with non-G protein signalling effectors through specific protein–protein interaction domains [6]. But quite remarkably, outside of heterotrimeric G proteins, only two protein families are able to specifically interact with the majority of GPCRs in their activated conformation: G protein-coupled receptor kinases (GRKs) and β-arrestins [7]. Historically, GRKs and β-arrestins have been associated with the desensitization and internalization/recycling of most GPCRs [8]. However, recently, GPCRs have also been demonstrated to elicit signals, independently of heterotrimeric G protein coupling, through interaction with β-arrestins 1 and 2. Indeed, β-arrestins have been shown to act as multifunctional scaffolds and activators for a growing number of signalling proteins including ERK, p38, JNK, I-κB, Akt and RhoA [7,9–13]. Moreover, a recent proteomic study has reported as many as 337 protein interactions involving β-arrestins [14], strongly suggesting that they play a central role in the ability of GPCRs to activate very complex signalling networks. In addition, GRKs have also been reported to elicit signalling responses on their own right through protein/protein interactions [13]. Indeed, GRKs interact with a variety of proteins involved in signalling and trafficking such as Gαq, G$\beta\gamma$, PI3Kγ, clathrin, GIT (G protein-coupled receptor kinase-interacting protein) and caveolin [15]. Phosphorylation of Raf kinase inhibitor protein (RKIP) by PKC displaces it from Raf and increases its association with GRK2 [16]. In addition, the physical interaction between GRK2 and Akt leads to the inhibition of Akt activity [17]. Finally, GRK2 and MEK1 have been found in the same multimolecular complex and this interaction is correlated with an inhibition of MEK activity [18].

Adding to this complexity is the fact that GPCR-induced signals can be spatially and temporally encoded. Signalling networks actively modulate the transmitted signals: negative feedback allows pathways to adapt or desensitize to persistent stimuli whereas cross inhibition is used to avoid crosstalk between pathways [19,20]. In addition to transmit qualitative information (e.g. the presence or absence of a stimulus), signalling pathways must also convey quantitative information about the strength of the stimulus (i.e. ligand concentration). It has been recently shown that signalling pathways can take advantage of their non-linear nature to convert stimulus intensity into signal duration [21]. Modulation of signal duration increases the range of stimulus concentrations for which dose-dependent responses are possible as dose-dependent responses are still possible after apparent saturation of the receptors. Another well documented example of spatial and temporal encoding in GPCR-induced sig-