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Review article

Computational modeling approaches in gonadotropin signaling

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ABSTRACT

Follicle-stimulating hormone and LH play essential roles in animal reproduction. They exert their function through binding to their cognate receptors, which belong to the large family of G protein–coupled receptors. This recognition at the plasma membrane triggers a plethora of cellular events, whose processing and integration ultimately lead to an adapted biological response. Understanding the nature and the kinetics of these events is essential for innovative approaches in drug discovery. The study and manipulation of such complex systems requires the use of computational modeling approaches combined with robust *in vitro* functional assays for calibration and validation. Modeling brings a detailed understanding of the system and can also be used to understand why existing drugs do not work as well as expected, and how to design more efficient ones.

1. Introduction

Follicle-stimulating hormone and luteinizing hormone receptors (FSHR and LHR) play central roles in animal reproduction. These two receptors belonging to the family of G protein–coupled receptors (GPCRs) are able to transduce the signals mediated by the variations of FSH and LH blood concentrations in adapted cellular responses in gonads, mostly through the control of follicle development in the ovary and gametogenesis in the testis [1,2]. Binding of the hormone to its cognate receptor triggers cascades of biochemical reactions within the cell, which results in profound changes in gene transcription [3] and protein translation [4,5]. These signaling cascades mainly originate from the interaction of the activated receptors with Gαs on the one hand, and ß-arrestins on the other hand [6–8]. The precise balance between these two pathways is essential for the biological outcome of cell stimulation. As an example, the modification of this balance in the N680S single nucleotide polymorphism in the FSHR is thought to be responsible for the relative resistance of S/S women to FSH treatments [9].

G protein–coupled receptors being membrane receptors have a high specificity for their ligands and are often individually expressed in a reduced number of cell types. Moreover, they are involved in most cellular processes. Consequently, they are ideal drug targets, and about 40% of the marketed drugs target GPCRs [10]. Some of these drugs are balanced full agonists, meaning that they trigger the same signaling pathways than the natural agonists, with the same balance between G-dependent and ß-arrestin–dependent pathways. During the last decade, it has been shown that it was possible to find GPCR ligands, generally referred to as “biased”, which trigger only part of the natural ligand’s signaling repertoire. From the therapeutic point of view, such pharmacological profile is thought to be more efficient and safer because only the beneficial pathways (G proteins or ß-arrestins) are targeted. The most famous example of such use of GPCR-biased

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ligand is the ß-blocker carvedilol [11]. ß-blockers are extensively used in heart failure pathologies. By blocking the ß-adrenergic receptor, they reduce the catecholamine stimulation in heart and other organs. Contrarily to most ß-blockers which are full antagonists, carvedilol only blocks the G-dependent pathways, leading to therapeutic efficacy comparable to the one of other ß-blockers, and extends survival as compared with other molecules [12].

Although the events after ligand binding are referred to as signaling pathways, the term signaling networks better represents the complexity of these events and the tight interconnections between them. This complexity can be envisaged at different levels. (1) A large number of molecules participate to this network, and there are many regulation feedback loops within it. (2) The existence of homodimers and heterodimers has been reported for many GPCRs [13,14]. (3) The biological outcome depends on the duration of the stimulation and on the stimulation profile (short vs. long, continuous vs. pulsatile). (4) *In vivo*, the cell is submitted to multiple and coordinated stimulations, and the resulting signaling networks are interlocked. Those points are nicely illustrated by the strong interconnections between LH and FSH, which (1) share large portions of intracellular mechanisms triggered by their cognate receptors (Fig. 1), (2) whose receptors have been shown to heterodimerize [15], (3) have antagonistic cellular effects, (4) have very precise and coordinated secretion profiles (5), and of course are both involved in the control of reproduction.

The pharmacology of gonadotropin receptors is still very poor as only natural hormones are used, either extractive in animal reproduction or recombinant in human health. These last years have seen the appearance of many small molecules [16], either targeting the orthosteric site (as the natural ligand) or allosteric modulators (modulating the action of the natural ligand) of the FSHR and LHR [17]. However, optimizing the action of such pharmacological molecules requires the detailed knowledge of their action, which in turn depends on the precise knowledge of the signaling networks. Over the last decade, it has become increasingly evident that computational modeling is a tool of choice for such purpose.

2. Modeling the signaling network activation

Signaling networks trigger complex cellular responses such as proliferation, differentiation, and apoptosis, through the regulation of translation and transcription processes. Each of these responses results from precise activation/deactivation kinetic profiles of the molecules constituting the network. Therefore, it is of paramount importance to understand the major molecular mechanisms set off by the binding of a given ligand to the receptor, how this signal propagates throughout the signaling network, and how the different profiles are integrated in adapted cellular responses. The complexity of these networks in itself prohibits the direct measurement of all the kinetic profiles. Moreover, for many of these molecules, the appropriate experimental tools are not available. Building computational kinetic models of the network allows accessing these profiles by measuring only a small subset or readouts.

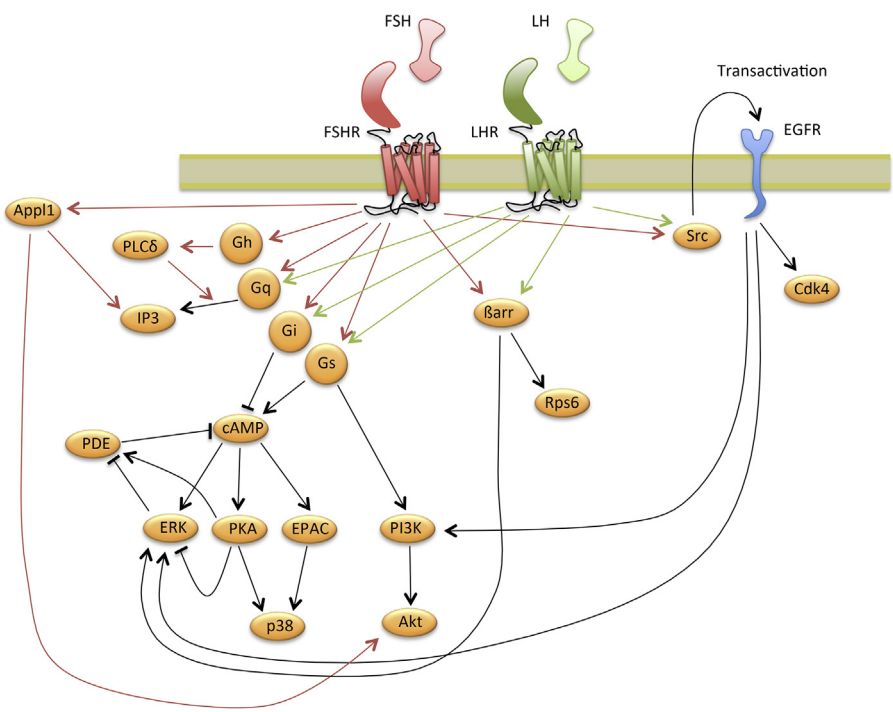

Fig. 1. Schematic view of the FHSR and LHR signaling networks. Red lines show regulations specific to FSH signaling, green lines show regulations specific to LH signaling, and black lines show regulations common to both receptors. Arrows symbolize activations; lines terminated by an orthogonal dash symbolize inhibitions. FHSR, follicle-stimulating hormone receptor; LHR, luteinizing hormone receptor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)