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Breakthroughs and Views

Desensitization to gonadotropic hormones: a model system for the regulation of a G-protein-coupled receptor with 7-transmembrane spanning regions

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Abstract

Gonadotropic hormone, luteinizing hormone, and follicle-stimulating hormone exert their effect via activation of G-coupled receptors, which activate the hormone sensitive adenylyl cyclase, protein kinase A, and cyclic AMP responsive elements. This activation leads to specific de novo synthesis of steroidogenic factors and steroidogenic enzymes. In normal cells and following activation of this signaling pathway, desensitization period will be followed. This down-regulation, which was studied in detail for the last three decays, was found to take place at various steps of these signal transduction pathways as well as at different kinetics. A common and diverse feature of the mechanism of desensitization in other G-coupled-7-transmembrane receptor system is also discussed.

Keywords: Desensitization; Gonadotropin; G-coupled receptor; Steroidogenesis

Several important signal transduction mechanisms are operated by binding to G-coupled-7-transmembrane receptors, with common features, but also diverse ones, such as gonadotropic receptors to luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) receptor, and the β-adrenergic receptor to catecholamines [1–5], which differ markedly in their extracellular and intracellular domains [5–7]. Also possible sites for tyrosine or serine–threonine phosphorylation can be diverse [5,8–10]. In the gonadotropin responsive cells; i.e., Leydig and Sertoli cells in the male and follicular theca, and granulosa cells in the female, both the hormones and the receptors are glycoproteins [11–14], which activate the hormone sensitive adenylate cyclase (AC) via Gs protein leading to formation of cAMP, activation of PKA and CRE [10], and modulation of gene expression associated with enhanced steroidogenesis ([9,15] and Fig. 1). In this signal pathway, two transcription factors, SF1/Ad4BP and DAX-1, are also involved [10,15–17]. The first one in a positive manner in stimulation of steroidogenesis [18] and the latter in a negative manner [10,15,16]. However, whether the cAMP cascade regulates them is not entirely clear. The first obligatory step in steroid hormone biosynthesis is the up-regulation of the steroidogenic acute regulatory protein (StAR) followed by synthesis of the steroidogenic enzymes such as the cytochrome P450 side chain cleavage (P450scc) enzyme system and aromatase [19–21].

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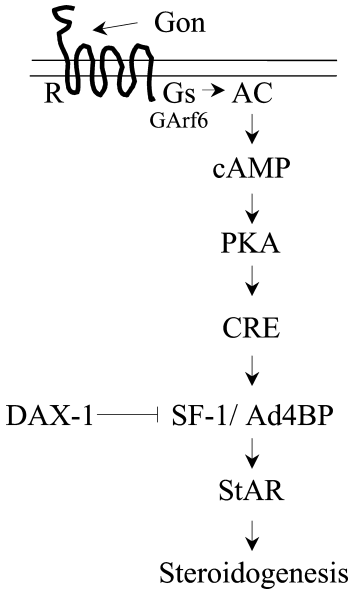

Fig. 1. A signaling pathway of gonadotropin-induced steroidogenesis in gonadal cells. Gon, gonadotropic hormone; LH, luteinizing hormone; CG, chorionic gonadotropin; and FSH, follicle-stimulating hormone. R, G-protein coupled receptor receptor with 7-transmembrane spanning regions (LH/CG receptor and FSH receptor). Gs, heterodimeric Gs; GArf6, small G protein Arf6; PKA, protein kinase A; CRE, cyclic AMP responsive element; DAX-1, dosage sensitive sex reversal adrenal gene 1; SF-1/Ad4BP, steroidogenic factor 1; StAR, steroidogenesis acute regulating protein. Steroidogenesis, biosynthesis of steroidogenic hormones catalyzed by the steroidogenic enzymes, the first step in the cascade is cytochrome P450 side chain cleavage (P450scc) enzyme metabolizing cholesterol to pregnenolone.

Desensitization

The cyclic nature of steroid biosynthesis in the female is mainly due to cyclic release of gonadotropic hormones from the anterior pituitary, in response to gonadotropic releasing hormone (GnRH) secretion from the hypothalamus [22]. GnRH secretion leads to the sequential release of FSH and LH during the estrus [23]/menstrual cycle [24]. However, desensitization to gonadotropic hormone stimulation is also evident in the gonadal cells, and more data are accumulated suggesting that desensitization of LH response can occur at different levels of the intracellular signaling pathway (Fig. 2 and [25,26]).

Internalization

It was found in 1978 that following binding of gonadotropins to their receptors on the cell surface internalization of the hormone–receptor complexes into endosomes occurs and finally the hormone–receptor complexes are degraded in the lysosomes ([27,28] and Fig. 2). Moreover, it was also demonstrated that internalization of the receptor molecules either by prolonged stimulation with gonadotropic hormones or induced aggregation of the hormone–receptor complexes by applying specific antibodies to the bound hormone will enhance the internalization [28]. The molecular mechanism, which triggers the clustering of the receptors, is not clear. It seems that the mechanism of internalization can occur only as a long-term mechanism of desensitization, since it was demonstrated that in cultured granulosa cells following stimulation by gonadotropins, there is a rise of intracellular levels of the cyclic nucleotide up to 20 min followed by a decline in the intracellular levels of the cyclic nucleotide and, therefore, alternative mechanism of desensitization was suggested [29].

Phosphorylation/dephosphorylation

Potential phosphorylation–dephosphorylation of the gonadotropic hormone receptors are multiple and those which are relevant to the coupling to Gs protein are located in the intracellular part of the receptor [8,30]. It was found that staurosporine, which blocks the activity of PKA, PKB, and PKC, can release granulosa cells from desensitization to gonadotropin stimulation. On the other hand, it was found that PKC activation was able to induce desensitization to LH stimulation. Therefore, it is suggested that phosphorylation–dephosphorylation can control activity of both the LH and FSH receptor [31–34]. In the β-adrenergic receptor system, arrestin participates in the phosphorylation of the receptor [35,36]. Moreover, desensitization of the β-adrenergic receptor was induced at least in part by agonist-induced phosphorylation and internalization of the receptor [37]. Recently, interaction of arrestin with the gonadotropic receptor was also revealed, but it is not completely clear how it might be involved in receptor desensitization [35,38,39].

G-protein and adenylyl cyclase

The coupling between the hormone and the receptor complex, and the adenylate cyclase is exerted via G-stimulatory protein (Gs), but evidence for its regulation on the level of the expression of G-protein was only recently revealed [40,41]. The gonadotropin appears to activate signaling cascades via two types of G proteins; heterotrimeric Gs and small G-protein Arf6 (Fig. 1). Arf6 activation releases docked β-arrestin necessary for receptor desensitization, providing a feedback mechanism for receptor self-regulation [42]. It should be noted that arrestin was found to be involved also in desensitization of the β-adrenergic receptor [35,43].

The regulation of the gonadotropin sensitive adenylyl cyclase by Gs protein was demonstrated: a mutant LH/CG receptor, which is a G-coupled receptor in young

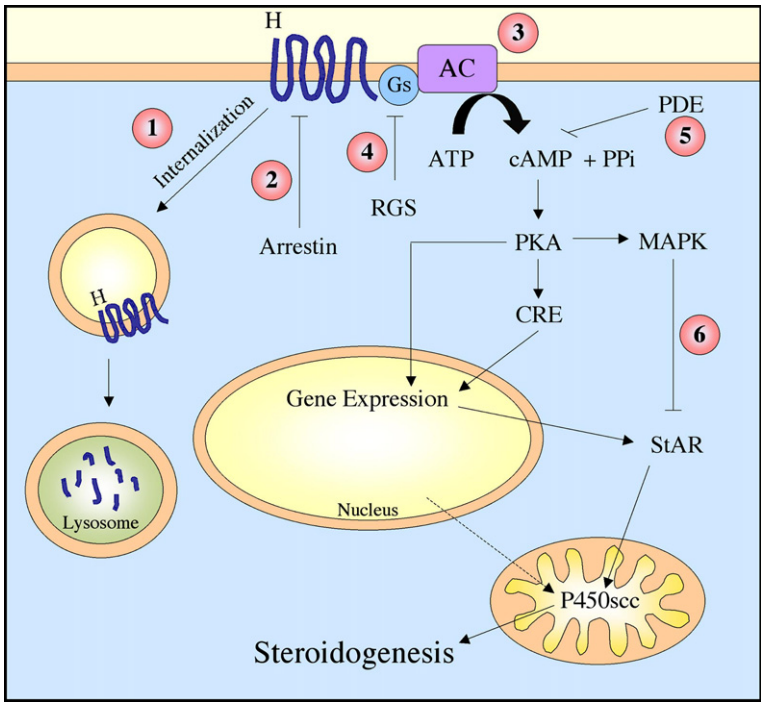

Fig. 2. A proposed model for desensitization to gonadotropic hormone in ovarian follicular cells (granulosa). Gonadotropins bind to a receptor of 7-transmembrane domain on granulosa cells and activate the hormone sensitive adenylyl cyclase, PKA, and expression of steroid factors and enzymes. There are several possible points in this cascade of events that can lead to desensitization to the hormone: (1) internalization of the hormone–receptor complex, (2) phosphorylation of the receptor molecule either through arrestin–kinase pathway or independently, (3) down-regulation of AC expression, (4) up-regulation of RGS proteins, (5) elevation of cAMP dependent phosphodiesterase, and (6) activation of MAPK, which down-regulate StAR expression and steroidogenesis.

boys suffering from testotoxicosis, shown to be constitutively active and unresponsive to hormone stimulation. This mutant receptor when transfected to other cells expressing the non-mutated LH/CG receptor causes attenuation of gonadotropin-dependent cAMP accumulation, probably by an activation of the phosphodiesterase (PDE) 4D3 [44]. Interestingly, co-expression of the mutated LH/CG receptor with human β2-adrenergic receptor causes also an attenuation of isoproterenol-stimulated cAMP formation, suggesting heterologous desensitization of the catecholamine receptor probably through Gs coupled mutated gonadotropin receptor. This demonstrates some common features and cross talk between two different G-coupled receptors [44].

Another alternative pathway of possible regulation of Gs protein coupled to gonadotropin receptor was also suggested. Regulation of G-protein signaling (RGS) proteins was found to negate G-protein signaling [45,46]. Gene transcripts to RGS16 were found to be up-regulated by gonadotropins in human granulosa cells [47,48]. Since RGS16 is controlled specifically by gonadotropins it seems likely that RGS16 up-regulation may contribute to down-regulation of gonadotropin signaling during luteinizing of granulosa cells. In contrast, gene transcripts of RGS4 and 5 were down-regulated by gonadotropins [47]. This modulation may also contribute to the regulation of gonadotropic response to luteinizing signals in granulosa cells. Future experiments will be able to clarify, which member of the RGS proteins interacts with gonadotropin signaling and other signaling pathways via G-coupled-7-transmembrane receptors.

Adenylyl cyclase

Adenylate cyclase activity is an important step in signaling in many systems. However, it was not clear until recently how the expression of this key enzyme is modulated. It was recently found that adenylate cyclase 7 and 9 (ADCY7 and 9), and adenylate cyclase-associated protein 2 (CAP2) expression were down-regulated following one day of stimulation with gonadotropins [49–53]. This may suggest lower response to gonadotropins even when the receptor level remained high; e.g., in the corpus luteum. Interestingly, adenylate cyclase 3 was not modulated either by LH or FSH [47,54], suggesting that gonadotropins may affect only specific isoforms of ADCY. Interestingly, it was suggested that ADCY9 is involved in signaling in steroidogenic cells. This regulation is probably for a prolonged period of time, since it is controlled by modulation of gene expression.

Phosphodiesterase

The level of cAMP, which is a key second messenger, is determined both by its synthesis and degradation. It is well known that inhibition of PDE in the gonadal cells gives rise to intracellular cAMP enhancing the rate of steroid hormone biosynthesis [55]. The expression of genes coding for PDE 4D [56], cAMP specific (PDNHD) was found to be considerably up-regulated by LH, which may contribute to the attenuation of LH-dependent cAMP formation during granulosa cell luteinization.

Desensitization via activation of the MAPK cascade

It was discovered recently that MAPK cascade is activated by gonadotropins [57]. Most of this activation is exerted via the cAMP cascade, since most of this activation can be abolished by specific inhibitors of PKA, H89 and also by a plasmid coding for PKA inhibitors (PK1) [16,25,58,59]. However, a significant part of this activation is not blocked by both H89 and PK1 following FSH stimulation, suggesting that MAPK cascade may be activated directly via the interaction of the gonadotropin with its receptor [25]. The effect of the activation of MAPK and the phosphorylation of ERK1 and ERK2 [60] lead to suppression of the expression of StAR protein, which is an obligatory step in the induction of the biosynthesis of the steroidogenic hormones; i.e., progesterone and estrogen. The evidence for MAPK involvement in regulation of steroidogenesis emerged from recent experiments using specific inhibitors of ERK1 and ERK2 phosphorylation, which augment progesterone production via StAR expression in ovarian follicular cells (granulosa) [16,59]. This enhancement can occur within minutes and activation of MAPK cascade, i.e., phosphorylation of ERK1 and ERK2 can occur within 1 min as was checked recently in bovine theca follicular cell (K. Tajima and A. Amsterdam, unpublished). This cascade of events allows a rapid control of steroidogenesis not via internalization of the hormone–receptor complex and probably not via phosphorylation of the receptor molecule. An interesting example for desensitization to gonadotropin stimulation occurring in spite of elevation in the density of LH receptor could be found in lutenized granulosa cells [47]. In these cells, obtained from in vitro fertilization program, stimulation with LH increased the density of receptors on the cell surface, however, it was found by using DNA arrays that the expression of genes coding ADCY 3 and 7 was down-regulated and that of RGS16 was elevated, which may reduce the activation of Gs protein. Moreover, up-regulation of PDE was also observed in this particular system [47]. These observations may be relevant to desensitization of the intact corpus luteum to LH/CG stimulation [61].

Conclusions

Desensitization to G-coupled-7-transmembrane receptor can occur through the following mechanism:

1. Uncoupling of the receptor molecule to formation of the second messenger. For example, raising the activity of RGS proteins, which negates the activity of the Gs protein.
2. Down-regulation of the number of receptors by internalization.

These are common features for most of the G-coupled-7-transmembrane receptors. More specific mechanism can be found in downstream signals, such as attenuation of steroidogenesis by activation of the MAPK cascade, which is typical of steroidogenic follicular cells (Figs. 1 and 2). It seems that the alternative pathways of desensitization are important to assure that biologic response, and at least in normal physiological process, could also terminate in time.

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