mPR-Mediated Signaling with Other Steroid Signaling Pathways

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Progesterone (PRG) is a key cyclical reproductive hormone that has a significant impact on female organs in vertebrates. It is mainly produced by the corpus luteum of the ovaries, but can also be generated from other sources such as the adrenal cortex, Leydig cells of the testes and neuronal and glial cells. PRG has wide-ranging physiological effects, including impacts on metabolic systems, central nervous systems and reproductive systems in both genders. It was first purified as an ovarian steroid with hormonal function for pregnancy, and is known to play a role in pro-gestational proliferation during pregnancy.

Keywords: progesterone (PRG) ; CmPn signaling network ; CmP signaling network ; CCM signaling complex (CSC) ; classic nuclear progesterone receptors (nPRs)

1. mPRs and PGRMC Can Form Their Own Complexes

mPRs and PGRMC1 are two newly identified sub-classes of PRG receptors that are widely expressed in various cells and tissues [1] and have been suspected to form a PRG membrane receptor complex to exert their PRG actions [2]. One study showed that ectopically expressed PGRMC1 in an nPR(−) breast cancer cell line (MDA-MB-231) can induce upregulation of both PGRMC1 and mPRα proteins on the cell membrane while also increasing PRG levels bound to mPRα in cell membranes. This observation was confirmed in several nPR(−) breast cancer cell lines [3]. Similarly, loss of PGRMC1 leads to decreased protein expression levels of mPRα in PGRMC1-knockout zebrafish [4], further supporting the existence of the aforementioned PGRMC1/2-mPRα complex, as well as the complex's influence on the levels of mPRα expression.

2. mPR-Mediated Signaling and *Ionotropic Neuronal Receptor* $GABA_AR$ Coupled with Their Common Ligands

It has been well defined that PRG and its metabolic derivatives (such as 3α, 5α-THPROG, allopregnanolone, pregnenolone, etc.) are neurosteroids that can influence the generation of action potentials through their interactions with neuronal membrane receptors [5][6][7][8][9]. One of the major targets of neurosteroids is the GABA-A receptor [5][9]. Neurosteroids can either positively or negatively regulate GABA-A receptor signaling, depending on the chemical properties of the specific neurosteroid [9][10][11][12]. Recent studies have supported the idea that neurosteroids act as agonists of mPR, and have a neuroprotective effect on neuronal cells [13][14][15]. This was confirmed by a recent study, which found that neurosteroids can only activate mPR-specific signaling in brain ECs that lack nPR and do not have GABA-A receptors [16]. These results indicate the important impacts of PRG-mPR actions on neuronal development, biogenesis and major functions [17][18].

3. Reciprocal Hormonal Regulation of mPRs and G-Protein Coupled Receptors

Previous reports suggest that mPRs are G-Protein Coupled Receptors (GPCRs), or are at least associated with G proteins to exert their cellular functions, such that mPRα, β and γ (PAQR7, 8, 5) are coupled with inhibitory G (Gi) proteins while both mPRφ and ε (PAQR6, 9) are coupled with stimulatory G (Gs) proteins [18][19][20][21][22][23][24]. However, later evidence suggests that mPRs belong to the adipoQ family (PAQRs) [19][25] instead of the GPCR class [26][27][28]. Interestingly, it was found that G protein-coupled estrogen receptor 1 (GPER) can coordinate with mPRs in a reciprocal fashion of hormonal regulation. In this hormonal feedback regulatory loop, PRG will increase expression of mPRs but decrease expression of GPER, in order to regulate the maturation of oocytes [29][30].

4. Crosstalk and Reciprocal Regulation between nPRs and mPRs

PRG is capable of exerting its cellular effects through either its classic, non-classic or combined responses through binding to either classic nPRs, non-classic mPRs or both simultaneously, warranting both pathways equally important status in PRG-mediated signaling. Both nPRs and mPRs can be coupled with other steroid signaling pathways [30][31][32][33][34][35][36][37], and evidence indicates the existence of the coupled mPR-nPR signaling cascade in nPR(+) cells [30][38][39][40][41]. Despite its significance, the relationship between classic and non-classic PRG receptors has been largely unexplored. It was reported that activation of mPRs can result in activation of nPRs, leading to a proposed model where steroid hormone-dependent mPRs contribute to later actions of nPR [42]. Recent evidence shows that CCM signaling complexes (CSC), consisting of CCM1, CCM2 and CCM3 proteins [43][44][45], can couple both nPR and mPR signaling cascades to bridge crosstalk among nPRs, mPRs and their shared ligands (such as PRG and MIF) to form the CSC-mPR-PRG-nPR (CmPn) signaling network in nPR(+) cells or the CSC-mPR-PRG (CmP) signaling network in nPR(−) cells [16][46][47][48][49]. This demonstrates that a common core mechanism exists, regardless of nPR(+/−) cell type. Chronic disruption of this intricate balance within the CmPn/CmP signaling networks, such as patients under HRT or females taking prolonged hormonal contraceptives, could result in perturbation of this signaling network with potential pathological consequences [16][49][50]. In human myometrial cells with high expression of nPR-B isoform, mPRα (PAQR7)-mediated signaling was found to be able to modulate nPR-B signaling to maintain the biogenesis of the myometrium [38][51]. This supporting evidence suggests that PRG signaling in nPR(−) cell lines might be mediated solely through mPRs (PAQRs) [39], a finding that was validated by recent data on the novel CSC-mPRs-PRG (CmP) signaling network in nPR(−) breast cancer cells [52]. Furthermore, with nPR(−) cells utilizing the CmP signaling network in most tissues and organs [16][49], the CSC is able to stabilize mPRs under mPR-specific PRG actions, indicating a more essential role of the CSC on the stability of mPRs (PAQRs) in nPR(−) cells. The CSC can control the signaling pathways initiated by PRG receptors in breast cancer T47D cells [nPR(+)/mPR(+) and glucocorticoid receptor (−)]. The CSCs are able to link classic (nPR) and non-classic (mPR) signaling mechanisms, creating intercommunication between the two. Similarly, the actions of PRGs specific to mPRs have a reciprocal positive impact on protein expression in the CSC, which is comparable to the cellular compartments of other steroid receptors. Under PRG stimulation, the stability of CSCs is regulated through two main signaling pathways: firstly, by the detrimental effects of PRG or its antagonist, mifepristone, which act through both types of PRG receptors; and secondly by the positive impact of nPR signaling. This highlights mPRs as a novel type of PRG receptor that functions similarly to traditional nPRs [53]. The discovery highlights the significance of the balance between classic and non-classic PRG signaling in determining the function of the CSC. It also recognizes the CSC as a crucial mediator of cross-communication between nPRs and mPRs in cells that possess nPR. This observation is further strengthened by earlier findings that PRG can act on both nPRs and mPRs at the same time, and activating mPR signaling can enhance the hormone-activated nPR-2 isoform [38]. In summary, the intricate interplay between the CSC-mPRs-PRG-nPRs (CmPn) signaling network in T47D cells that have nPR can be understood as a universal mechanism present within the CmPn signaling network under steroidal influence, which have been validated in different nPR(−) breast cancer cells and nPR(−) ECs [16][46][47][50][52][53].

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