Molecular and Cellular Endocrinology 434 (2016) 166–175

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Membrane progesterone receptors in reproduction and cancer

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ARTICLE INFO

Article history:
Received 2 March 2016
Received in revised form
15 June 2016
Accepted 27 June 2016
Available online 28 June 2016

Keywords:
Progesterone
Membrane progesterone receptors
Reproduction
Cancer
Reproductive diseases

ABSTRACT

Progesterone is a sexual steroid hormone that has a critical role in reproductive processes in males and females of several species, including humans. Furthermore, progesterone has been associated with pathological diseases such as breast, gynecological and brain cancer, regulating cell proliferation, apoptosis, and metastasis. In the past, progesterone actions were thought to be only mediated by its intracellular receptor (PR). However, recent evidence has demonstrated that membrane progesterone receptors (mPRs) mediate most of the non-classical progesterone actions. The role of the different mPRs subtypes in progesterone effects in reproduction and cancer is an emerging and exciting research area. Here we review studies to date regarding mPRs role in reproduction and cancer and discuss their functions and clinical relevance, suggesting mPRs as putative pharmacological targets and disease markers in cancer and diseases associated with reproduction.

Contents

1. Introduction

Progesterone is a steroid hormone that is mainly synthesized and secreted by ovaries, placenta, adrenal glands, and testis. It can also be *de novo* synthesized from cholesterol or from circulating pregnenolone in the brain, spinal cord and peripheral nerves (Genazzani et al., 2000).

Progesterone participates in the regulation of different reproductive processes in females such as ovulation, embryo implantation, pregnancy, mammary gland development, sexual differentiation and sexual behavior in several vertebrate species (Brinton et al., 2008; Guerra-Araiza et al., 2009; Macias and Hinck, 2012; Mesiano et al., 2011). It has also been demonstrated that progesterone is involved in the development and function of sperm (Baldi et al., 2009). Furthermore, progesterone has multiple non-reproductive functions such as neuroprotection and neurogenesis,

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http://dx.doi.org/10.1016/j.mce.2016.06.027
0303-7207/

immune system regulation and stimulation of respiration (Díaz et al., 2009; González-Arenas and Agramonte-Hevia, 2012; Nava-Castro et al., 2012). Importantly, progesterone plays a central role as critical regulator in breast, gynecological and brain cancer (Camacho-Arroyo et al., 2000; Diep et al., 2015; Obr and Edwards, 2012; Piña-Medina et al., 2016).

The mechanisms of action of progesterone can be classified as classical (genomic) and non-classical (non-genomic), with the possibility that both occur in the same cell at the same time (Faivre et al., 2005; Lösel et al., 2005). The first mechanism comprises the long-term effects that are modulated by the intracellular progesterone receptor (PR), a ligand-dependent transcription factor that dimerizes and binds to specific progesterone response elements (PREs) within the promoter of progesterone target genes to regulate transcription (Hernández-Hernández and Camacho-Arroyo, 2013; Scarpin et al., 2009). The second mechanism occurs in membrane and cytoplasm by generating short-term or rapid effects (in the lapse of seconds or minutes) such as ion channel activation, regulation of second messengers concentration and activation of kinases (Lösel and Wehling, 2003). The non-classical progesterone effects can be mediated by hormone interaction with PR (Leonhardt et al., 2003), ion channels (Lishko et al., 2011), neurotransmitter receptors (Henderson, 2007), growth factor receptors (Cheskis, 2004) and with specific receptors localized in the plasma membrane (Tubbs and Thomas, 2008).

The participation of specific membrane receptors involved in the non-classical progesterone actions has been demonstrated by the use of progesterone coupled to bovine serum albumin (BSA) that cannot pass into the cell (Peluso et al., 2002) and by binding studies (Dosiou et al., 2008). Furthermore, the fact that progesterone actions have been observed in cells not expressing PR has confirmed the involvement of other possible receptors in progesterone actions (Dosiou et al., 2008). For a long time, the identity of these receptors was uncertain, however, experimental evidence from recent years has demonstrated that two types of membrane proteins unrelated to PR can mediate progesterone effects: the membrane progesterone receptors (mPRs) and the progesterone receptor membrane components (PGRMCs).

In 2003, Thomas and collaborators first described a new class of progesterone receptor on the membrane of fish oocytes, named mPRα (Zhu et al., 2003b). Subsequently, two similar receptors were also identified in different vertebrates including humans and were called mPRβ and mPRγ (Zhu et al., 2003a); recently, the identity of two other mPR subtypes called mPRδ and mPRε were also confirmed in humans (Pang et al., 2013).

Since mPRs discovery, the interest in elucidating their functions has increased, as they are differentially expressed in reproductive and neural tissues, as well as in immune cells (Dressing et al., 2011). Furthermore, the recent finding that mPRs are also expressed in different cancer cells lines and tissues has opened a new interesting field of study. In fact, mPRs have been related to key processes in cancer disease such as proliferation, apoptosis, and metastasis (Dressing et al., 2012; Vares et al., 2015; Zuo et al., 2010).

PGRMC family of progesterone receptors located in the cell membrane also participates in many physiological and pathological processes, such as estrous cycle, pregnancy, cell cycle progression in granulosa cells, breast, and ovarian cancer (Kowalik et al., 2013; Mueck et al., 2014; Peluso, 2011; Peluso et al., 2014). This review will focus on mPRs characteristics and their role in mediating progesterone actions in reproduction and cancer. In addition, clinical implications and future perspectives in mPRs research are discussed.

2. mPRs

mPRs belong to the progesterone and adipoQ receptor (PAQR) family, which is divided into three subgroups according to the structure and ligand specificity: related to adiponectin receptor (Class I), related to mPR (Class II) and related to hemolysin III (Class III) (Baida and Kuzmin, 1996; Lyons et al., 2004; Tang et al., 2005). According to this classification, PAQRs class II comprises five members present in vertebrates: PAQR7 (mPRα), PAQR8 (mPRβ), PAQR5 (mPRγ), PAQR6 (mPRδ) and PAQR9 (mPRε) (Smith et al., 2008).

In humans, mPRs are encoded by different genes located on distinct chromosomes (Tang et al., 2005) (Table 1). The length of mPR proteins varies between 330 and 377 amino acids (Table 1) and all of them contain a large proportion of α-helices in a central region encoded within the UPF0073 domain (Pfam database EMBL-EBI) (Finn et al., 2016; Tang et al., 2005). These receptors have hydrophobic properties and according to an *in silico* analysis, they contain three conserved regions that share the PAQR family: 1) the $Px_nGYRx_nEx_2Nx_3H$ motif that precedes the transmembrane domain 1 (TMD1); 2) the Sx_3Hx_nD motif that spans the end of TMD2 and the beginning of TMD3; 3), the $PEx_3PGx_nHQx_2H$ motif that spans the loop preceding TMD7 (Smith et al., 2008).

Nowadays, there is still some controversy regarding the structural and topological features of mPRs since their tridimensional structure has not been elucidated by experimental approaches due to their rapid degradation. By using bioinformatics, Thomas and colleagues reported that mPRs are formed by seven TMD and contain an extracellular amino-terminal domain and an intracellular carboxyl-terminal domain (Tang et al., 2005; Zhu et al., 2003a).

This model supported the idea that mPRs are similar to G-protein coupled receptors (GPCRs), which to date is the most widely accepted model. We have built a tridimensional model of mPRα, mPRβ and mPRγ by using the Phyre2 web portal (Fig. 1A, B and C, respectively) that constructs tridimensional models based on advanced remote homology detection methods (Kelley et al., 2015). Interestingly, when comparing the obtained tridimensional models for the three mPRs and searching for similarity among structures with the FATCAT web server (Ye and Godzik, 2004) and PyMOL software (The PyMOL Molecular Graphics System, Version 1.7.4.5 Schrödinger, LLC) it was observed that the three predicted structures are highly similar (Fig. 1D). This suggests that the tridimensional conformation of the modeled mPRs subtypes is conserved, however, further studies are required to elucidate their structure and confirm this finding.

mPRs were discovered in teleost ovaries (Zhu et al., 2003b) and subsequently identified in sheep, pig, mouse, rat and human (Aparicio et al., 2011; Dressing et al., 2011; Qiu et al., 2008; Thomas

Table 1
General characteristics of human mPRs.

Receptor	Alternative name	Locus	Gene length (bp)	Number of exons	Protein length (aa)	Protein weight (Da)
mPRα	PAQR VII	1p36.11	10,044	1	346	39,719
mPRβ	PAQR VIII	6p12.1	46,357	1	354	40,464
mPRγ	PAQR V	15q23	108,834	7	330	38,014
mPRδ	PAQR VI	1q22	4676	7	344	37,989
mPRε	PAQR IX	3q23	14,173	1	377	42,692