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REVIEW ARTICLE

New Insight into Progesterone-dependent Signalization

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Abstract:

Background:

Various effects of steroid hormone activity cannot easily be explained by the action of classical nuclear receptors and genomic signal transduction pathways. These activities are manifested principally as rapid processes, lasting from seconds to minutes, resulting in changes in ion transduction, calcium intracellular concentration, and level of the second messengers, which cannot be realized through the genomic pathway. Hence, it has been proposed that other kinds of mediators should be involved in steroid-induced processes, namely receptors located on the cell surface. The search for their chemical nature and role is of utmost importance. Current state of knowledge confirms their relation to GPCRs. Moreover, it seems that almost every nuclear receptor specific for steroid hormone family has its membrane-bound equivalent.

Objective:

In this review, we summarize current state of knowledge about nuclear and membrane receptors for progesterone, and describe their potential functions alone, as well as in cooperation with other receptors.

Conclusion:

In the light of common expression, both in species and organs, membrane receptors could play a role that is at least comparable to nuclear receptors. Further exploration of membrane receptor-dependent signaling pathways could give a new insight in the treatment of many endocrine and oncological pathologies.

Keywords: Progesterone, Nuclear progesterone receptors, Membrane progesterone receptors, PGRMC1, Classical and non-classical signaling pathways.

1. INTRODUCTION

Progesterone (P4) is a 21-carbon steroid belonging to the family of pogestagens. It is synhesized in the corpus luteum, placenta, brain and adrenal gland. The nuclear progesterone receptor (nPR) with a gene located on chromosome 11 (11q13) is considered as a main target for P4. Its expression fluctuates in the ovary and endometrial layer of uterus during either physiologic and pathologic states [1 - 3]. The role of nuclear receptors for progesterone and other steroids, as well as molecular pathway mediated by them are widely recognized and achieved a significant position in the clinical practice [1, 2]. However there still exist some effects controlled by steroid hormones, which could not be easily explained with the activity of classical, genomic pathway. These effects apear in the course of shorter period of time and take place in different cells and tissues. Thus, it has been suggested that P4 could act through extragenomic, non-classical pathways with crucial role of membrane receptors [2]. Besides PR, also other steroid hormone receptors can be

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localized in cell membrane. A number of non-genomic pathways dependent on membrane receptors, with characteristic rapid effects, *i.e.* the influence of estrogens on neurons, testosterone on macrophages and prostate cells, as well as the activity of glucocorticosteroids, aldosterone, triiodothyronine, thyroxine, retinoids and calcitriol, have been described [4 - 7]. Membrane receptors seem to be specific variants of nuclear receptors and are formed through alternative splicing or post-translational modification [8].

2. GENOMIC PATHWAY

Classical receptors for P4 belong to the superfamily of nuclear receptors, which comprises also receptors for other steroids, thyroid hormones, retinoic acid and vitamin D, as well as the so-called 'small receptors', for instance the farnesoid X receptor (FXR), which binds bile acids, or the peroxisome proliferator activated receptor (PPAR), responsible for carbohydrate-lipid homeostasis [4, 9]. Proper ligands for many of these receptors were not recognized, hence they were called the 'orphan receptors' [4]. Currently, they are known to act as ligand-dependent transcriptional factors which regulate numerous physiologic processes through binding with specific hormone response element (HRE) sequences of the target genes [10, 11].

Two basic receptor isoforms are nPRA and nPRB, encoded by the same gene but characterized by distinct initiation sites of translation [9, 10, 12]. The primary structure of the nPR receptor is composed of domains with different conservativeness. The N-end is necessary for full transcriptional activity and is responsible for various, promoter-dependent properties of cell-specific nPR isoforms. Among functional domains, the DNA-binding domain (DBD; C region), less conservative ligand-binding domain (LBD; E region), and domains constitutively activating transcription (A/B region), can be distinguished [9, 10]. There are also two autonomous domains which activate transcription in the receptor structure: constitutive-activation domain AF-1 on the N-end, and AF-2 that is highly-conserved, ligand-dependent and localized on the C-end [13]. The AF-1 structure is not conserved and little is known about its coactivators. The activity of AF-2 depends on transcriptional factor belonging to the family of p160 proteins. Additionally, nPRB contains an AF-3 domain in its chain (which is absent in nPRA) and probably inhibits, both its ID (inhibitory domain) and transcriptional activity [9, 14]. Also, nPR contains a short, proline-rich motif (amino acids 421-428), which mediates an interaction between the cytoplasmic domain of the receptor and the SH3 membrane domain (Src Homology 3 – domain of SRC tyrosine kinase) after binding with P4 [15].

The aspects of posttranslational modifications in ligand-dependent or ligand–independent manner, are crucial for nPR stability, localization and acivity [16]. They affect also glucocorticoid receptor (GR) complex formation and interaction with other agents or recruitment of cofactors [16, 17]. These modifications could be tissue-specific [18] and involve phosphorylation, ubiquitination, methylation and so called SUMOylation (addition of small ubiquitin-related modifier – SUMO-peptides). What resembles the process of ubiquitination is a similarity of SUMO proteins to ubiquitin. The difference is that unlike ubiquitination, the process of posttranslational SUMOylation does not result in a degradation of target cells. It rather influences protein stabilization, localization, nuclear translocation, and particularly transcriptional activity. PR SUMOylation significantly suppresses transcriptional activity and *vice versa*, lack of SUMOylation induces PR transformation, especially nPRA, into a strong transcriptional activator [16]. Addition of SUMO peptides to lysine residues decreases GR transcriptional activity by corepressors recruitment, *e.g.* DAXX protein (death-domain associated protein). Furthermore, it cannot be excluded that SUMOylation induces a genome-wide chromatin occupancy redistribution of GR [17].

It seems that nPRA is vital for feminine reproductive functions and fertility, while nPRB determines proper development of the mammary gland in response to P4 [17, 19, 20]. It has been stated that female mice revealed a number of disorders, *e.g.* different sexual behavior, improper gonadotropin secretion, anovulatory cycles, deregulated uterine function, and invalid proliferation of the ductal or acinar cells in mammary glands after silencing genes for both nPR isoforms. The nPR receptor is also essential for the regulation of thymus involution during pregnancy and for augmented, P4-dependent, regulation of endothelial and smooth muscle cells proliferation in response to vessel detriment in the cardiovascular system [21].

The proportion of subtypes B/A of the nPR receptor varies in P4 target tissues and reveals interspecies differences. In chick oviduct, the number of both subtypes is more or less equal. In the human and mice myometrium nPRA is predominant, while in rabbit uterus the B isoform is the only one which is expressed [22]. In humans, the level of expression of both isoforms is different in the course of the menstrual cycle and in various types of cells. In the endometrium, their expression undergoes specific fluctuations: it increases during the follicular phase and decreases after the ovulation [22, 23]. Estrogens induce mRNA and protein expression of both nPRs, especially of nPRB in chick

oviduct, rat uterus and human endometrial cells. This activity increases the B/A ratio in favor of isoform B. In turn, nPR isoforms are down-regulated in the presence of their specific ligand – P4 [22, 23]. Diverse distribution of nPR isoforms in humans could implicate crucial clinical consequences. The nPRB/nPRA ratio determines the response of the tissue to P4 agonists or antagonists [22]. Disturbed isoform balance or overexpression of one of them could contribute to the development of carcinomas in mammary glands, ovary and endometrium, or correlate with tumor progression into more aggressive forms [24].

Inactive nPR is associated with chaperone proteins (HSP) in the cytoplasm [25]. Steroid hormones enter the interior of the cell both, passively by transmembrane diffusion or with participation of transporters [4]. Subsequently, they bind to intracellular receptors. Then, the receptors undergo conformational changes, chaperon proteins dissociate and the DNA-binding domain gains higher affinity [4, 25]. The steroid-receptor complex migrates to the nucleus and the DNA-binding domain is exposed. In the cell nucleus, the receptor dimerizes and joins its matching coactivators: SRC and CBP (CREBP Binding Protein), and then interacts with HRE. The final effect of signal transduction is the initiation of transcription and subsequently translation [9, 25]. This process involves the cell genome and it has been described as the classical, genomic pathway. The completion of this process requires a significantly prolonged period of time in comparison to shorter non-classical, extragenomic pathways. The genomic pathway is sensitive to transcription or translation inhibitors, like actinomycin D and cycloheximide, respectively [4].

3. NON-CLASSICAL PATHWAY

A number of steroid effects cannot be simply explained by functioning of the classical, genomic mechanism. Steroids were discovered to initiate rapid intracellular processes, unusual for nuclear signaling [26, 27]. They result in changes of ion channel conductivity, concentration of intracellular calcium, and second messengers (like cyclic nucleotides), as well as modifications in the activity of Erk 1 and 2 kinases [26, 27]. The wide spectrum of cells and tissues, where rapid, non-genomic effects appear, supports the fact that it is rather a universal process, and not a rare phenomenon [4]. The non-genomic signaling could be relevant for proper development and function of the tissues and organs [28].

Three different mechanisms of non-genomic (non-classical) pathway have been suggested: (1) 'the side-effect' of the classical pathway (especially P4 and estrogens); (2) non-specific, direct effects at the level of cell membrane (principally in relation to glucocorticoids, because they are present at high concentrations), and (3) *via* non-classical receptors [4]. Newly recognized receptor proteins not associated with previously described receptors, nuclear steroid receptors, receptors for other ligands exhibiting similarity to steroids, and GABAa and oxytocin receptors which have the ability to bind progestagens, have all been suggested as the components of this non-classical pathway [26]. It seems that signaling initiated on the cell surface by binding hormones to specific membrane receptors is the most probable among these three mechanisms [29]. Nonetheless, some aspects of progestagen activity remain unexplained [26]. The biological activity which is mediated by membrane receptors could be both, rapid like sperm motility, and slightly slower like oocyte maturation in fish or amphibians [26, 30].

Non-classical, rapid signal transduction of P4 signaling is suggested in many cells and tissues: spermatozoa, oocytes, corpora lutea, Leydig cells, as well as in uterine myometrium, hepatocytes, brain, and neoplastic cells of breast carcinoma [26, 31]. It has been demonstrated, that the acrosome reaction is induced with mediation of membrane receptors [32]. In some fishes (*Genyonemus lineatus* and *Cynoscion regalis*), decreased mPRα expression correlated with impaired sperm motility (asthenozoospermia) [26]. More evidence has been delivered from studies concerning membrane receptors expression in female mice and rats. Mice with nPR gene knock-out demonstrated fertility perturbations. In rat ovaries, nPR has not been expressed in granulosa and corpora lutea cells, despite the fact that at the same time P4 demonstrated its suppressor activity regarding the apoptosis of granulosa cells and its autocrine activity in luteal cells [15, 33].

Further evidence for rapid membrane signaling is the steroid hormone activity in the central nervous system (CNS), where the hormones dynamically induce neuronal excitability changes, neuroendocrine reactions and behavioral effects [34]. Stimulation of the membrane receptor-dependent GnRH secretion in ventral tegmental area, affecting sexual receptivity in rodents, is among these reactions. In rats, this phenomenon appears 10 minutes after i.v. P4 infusion (20-400 μg). It seems to be independent of nPR presence in ventromedial hypothalamus as there is no evidence of nuclear receptor presence in this localization. Possibly, that activity could be implemented through GABAa/benzodiazepines receptor [4, 26, 34, 35]. Not merely P4 *per se*, but also its metabolites seem to participate in the extragenomic signal transduction. For instance, 5α-pregnan-3,20-dion and 3α-hydroksy-4-pregnan-20-one bind to

membrane fractions of the neoplastic cells in breast carcinoma and porcine hepatocytes [4]. Other P4 metabolites, like 3α-hydroksy-5α-dihydroprogesterone, or deoxycorticosterone metabolites, like 3α,5α-tetrahydrodeoxycorticosterone, could modulate the function of the GABA receptor and act in the same subcellular localization as barbiturates [4, 34].

Modulated function of the immunological system in humans constitutes an another aspect arising from the analysis of P4 activity spectrum. Some kind of diversity in the immunological response can be observed in pregnancy, in the luteal phase of the menstrual cycle, or in the course of some diseases, especially those related to autoaggression. The significance of membrane receptors in these issues is associated with the presence of membrane receptors: mPRα and mPRβ on the leukocytes of the peripheral blood and T lymphocytes in the reproductive age, as well as on immortalized cells of human T lymphocyte line (Jurkat cells), with simultaneous exclusion of nPR presence [26, 36]. It has been proven that mPRα expression on CD8^{+} T lymphocytes increases approximately two-fold in the luteal phase of menstrual cycle, but not on CD4^{+}, what promotes humoral immune response [26].

It has been also demonstrated that PR, as estrogen receptors, is present on β cells of islets of Langerhans, and seems to regulate the functions and the survival of β cells [37, 38]. P4 has been suggested to be the key hormone in the development of gestational diabetes, since it is known to be relevant for insulin secretion and pancreatic function [39]. The mechanism of P4 activity probably involves a decrease of GLUT4 expression and an impairment of glucose uptake by the skeletal muscles. Simultaneously, PR antagonist – RU486, decreases glucose serum concentration [30]. It should also be noted that P4 exhibits a suppressive influence on pancreatic cell proliferation, and the stage of malignancy of tumors derived from the endocrine part of pancreas negatively correlates with PR immunoreactivity.

In P4 signalization the family of membrane heptahelical receptors coupled with G-proteins probably play the key role [6]. Activation of G proteins results in cyclic nucleotide production, calcium transport, and rapid activation of kinase cascade [40]. Every impairment regarding this pathway could implicate disturbances on molecular level, like trouble in cell signaling, i.e. in MAPK and PI3 activation. Some factors, like point mutations of membrane receptor genes, can lead to the loss of phenylalanine, cysteine or tyrosine from the polypeptide chain, and impair proper receptor localization in cell membrane. Disturbances in proper cell signaling translate into clinical features. For instance, it seems that the development of aggressive forms of breast carcinoma or resistance to tamoxifen could stem from lack of palmitoylation or prolonged receptor existence in caveolae [40].

3.1. PAQR Family and mPR Receptor

The PAQR (Progesterone Adiponectin Q Receptor) family comprises highly conserved proteins with high amino acid homology, occurring in many organisms, from *Eubacteria* to *Eutheria* [15, 41]. Its members are identified in *Arabidopsis, Drosophila, Caenorhabditis elegans, Xenopus, Danio rerio, Fugu*, and birds [35, 42]. mPRs have their receptor equivalents in the PAQR family. mPR is an oligomeric protein complex with the molecular mass of about 40 kDa. It includes three mPR subtypes: α, β and γ. The proofs that PAQR family members are *bona fide* P4 receptors come from the studies on knockout animals with inoperative selected PAQR receptors. For example, in PRKO mice, a decrease in LH secretion by P4 was mediated by a membrane progesterone receptor [26, 43].

The core region containing seven transmembrane domains and four highly conserved metal-binding motifs is the common and dominant feature of proteins belonging to the PAQR family [42]. Three subfamilies have been distinguished within the PAQR family on the basis of phylogenetic analysis: receptors related to adiponectin, membrane receptors for progestins, and receptors associated with hemolysin III. Generally, 11 proteins typical for mammals (PAQR I-XI), as well as hemolysin III derived from *Bacillus cereus* (HLYIII), YOLOOLC and *Sacharomyces cerevisiae* proteins have been included [42, 44]. Adiponectin receptors: PAQR I, II, III, IV, YOLOO2C and other yeast proteins, transmembrane adiponectin receptors 1 and 2 (adipoRs) derived from *Eubacteria*, are all involved in lipid homeostasis regulation (especially fatty acids), as well as phosphate and zinc metabolism. PAQR I and II are involved in adipokine (adiponectin) binding [15, 42].

Human gene for mPRα consists of three exons separated by two introns, gene for mPRβ has two exons and one additional intron in comparison to mPRα, while the gene for mPRγ is composed of eight exons and seven introns [5, 44]. 5'-end is deprived of typical TATA sequence (TATA box); the proximal region is abundant in GC pairs. Some motifs regulating DNA synthesis, like AP2, NF-AT, CIEBP and AhR/Arnt, have been identified [5]. The transcripts for human mPR isoforms differ in molecular mass within the range of 2.8 to 5.8 kb [35]. In catfish, amino acid homology among mPR subtypes, i.e. between α and β, is 50%, whereas among γ and the remaining two is less than 30% [44].

In general, both recombinant and wild receptor types display high affinity and specificity of P4 binding [26]. It is

possible to distinguish extracellular N-end and intracellular C-end in their structure [35]. mPR, especially mPRα, is directly coupled with G-proteins and typically activates pertussis toxin-sensitive inhibitory Gi protein, ultimately leading to adenylate cyclase down-regulation and decrease in cAMP concentration [26]. However, the analysis of the mPRβ signal path revealed that the receptor is not sensitive to pertussis and cholera toxins, what suggests that it activates another G-protein, insusceptible to the aforementioned toxins [45, 46].

mRNA for mPRs is widely distributed in both, reproductive and non-reproductive tissues of vertebrates, what indicates multipotent properties of membrane receptors [26]. Transcripts of mPRα have been identified in the ovaries (corpus luteum), testes, placenta, amnion, chorion, uterus (myometrium and endometrium), mammary gland, brain (hypothalamus, hypophysis), heart, intestines, liver, spleen, skeletal muscles, adrenal glands, and lungs [26, 35]. Transcripts of mPRβ have been identified in the brain, hypophysis, ovaries and testes, and mPRγ - in the abdominal aorta, and intestines [31, 35, 44]. A significant level of the expression of all three subtypes has been demonstrated only in kidneys [35]. Therefore, mPRs expression seems to be tissue-specific. Subunit α dominates in reproductive tissues, β in nervous tissue, and γ in the alimentary tract [42]. This is in contrast with the fact of tissue specificity of nuclear receptors, which tend to appear primarily in brain and gonads, and have potential abilities to form heterodimers, what is almost impossible in case of mPR in most human tissues [35]. Currently, the significance of such diverse distribution of three mPR subtypes is not clear. One of the possible explanations for different mRNA mPRβ localization in the nervous tissue is the fact that mPRβ is a subtype typical for tissues derived from ectoderm. On the other hand, mPRβ was obtained from mouse testes, which originate from the mesoderm. In turn, in *Cynoscion regalis*, subtype α has been found in the brain, what suggests that both, subtype β and α could be mediators of P4 activity initiated on the neuron surface in vertebrate brain. Thus, subtype α mediates not only rapid, non-genomic P4 action in reproductive tissues [35].

mPR isoforms differ among species in tissue distribution and the level of expression during the menstrual cycle, thus implying their diverse physiologic functions [26, 47]. mPRα, γ and PAQR IX expression in the endometrium depends on the phase of the ovarian cycle, and initiation of parturition is associated with significant reduction of mPR α and β concentration in the myometrium. mPRα and PAQR IX are significantly expressed in the placenta [42]. What is relevant, changes in mPRs distribution constitute not only morphological but also functional diversity. Therefore, modulation of mPRα expression has been demonstrated in both, physiologic (*e.g.* during the ovarian cycle), and pathologic processes (malignant proliferative processes, e.g. in human mammary gland). It underlines the relevant physiologic role of the receptor in a wide range of organs and tissues, and also during carcinogenesis [26].

3.2. PGRMC1 Receptor

PGRMC1 (Progesterone Receptor Membrane Component One) is the membrane protein with the molecular mass of approximately 26-28 kDa. It has been primarily isolated from porcine liver microsomes, and then identified in other tissues, like smooth muscle cells [12, 26, 41, 48 - 50]. In humans, the receptor was identified in 1996 and is known as Hpr6.6 (Human P4 receptor). In rats, it is called RDA 288, with the mass of about 60 kDa, and it has been obtained from hepatocytes and granulosa cells [26, 51]. In rat corpus luteum, RDA 288 acts against apoptosis.

PGRMC1 contains a single transmembrane domain and a potential internal cytochrome b5-like heme/steroid-binding sequence [26, 52, 53]. Both, PGRMC1 and the closely related PGRMC2 receptor, belong to the family of receptors associated with membranes (MAPR) [12, 26, 54]. Their homologues belonging to the MAPR genes family appear also in other *Eucaryota*, including nematodes, insects, yeast, and *Arabidopsis thaliana*. Another member of this family – neudesin, has been also identified in mammals [26]. PGRMC1 is localized principally in the epithelium, within cell membrane, cytosol and nucleus, and also in endoplasmic reticulum and Golgi apparatus [12, 55]. Its expression has been demonstrated in many organs, *i.e.* uterus, liver, kidneys, adrenal glands and brain. It has been also identified in tissues involved in drug metabolism [56 - 58].

PGRMC1 displays moderately high affinity to P4. It constitutes the target also for other hormones, like glucocorticosteroids (corticosterone and cortisol) and 21-carbon steroids (testosterone). However, the affinity for P4 is about 2-10 times higher than for testosterone and glucocorticosteroids [26]. PGRMC1 is capable of binding various molecules, like heme (its main known function), cholesterol and its metabolites, cytochrome P450 proteins, and many others [26, 59]. Combined with the affinity to such functionally and morphologically different molecules, the relevant role of this receptor in the wide spectrum of processes, like steroid synthesis and metabolism, regulation of cholesterol conversion, axonal guidance, stress response, endocytosis, cellular homeostasis and influence on the reproductive behavior, has been indicated [15, 26, 50, 60]. Some drugs, for instance, haloperidol competes with endogenous P4 in

binding to PGRMC1, while P4 binding is inhibited by such drugs as fluphenazine or carbapentane citrate [26]. This makes the receptor and the associated proteins an attractive target of numerous, especially oncological therapies, firstly - due to high affinity to steroids and drugs, secondly - due to their activity promoting neoplastic cells survival. Hormonal regulation of PGRMC1 expression is tissue-specific.

Many of described activities and functions of PGRMC1 both, in reproductive system and other tissues and organs, like central nervous system are obtained from the studies on animals with PGRMC1 gene knockout [50, 58]. In the nervous system, PGRMC1 has been identified in hypothalamus, circumventricular organs, ependyma of the lateral ventricles and meninges, structures directly involved in the production of the cerebrospinal fluid, and osmoregulation. In rats, PGRMC1/25 D-x is expressed in cerebellum and displays age-dependence: moderate expression in young individuals, mainly in Purkinje cells and cells of the granular layer, and low expression in mature individuals, only in Purkinje cells. This expression appears to be sex-independent [26]. PGRMC1 displays pleiotropic activity. It affects Schwann cell proliferation, and myelinization, synaptogenesis, memory and cognitive processes, neuronal excitability, glial function, and progenitor cell proliferation [61 - 63]. Furthermore, PGRMC1 most likely mediates neuroprotective action of P4, thus its expression increases after brain injury and it induces synthesis of brain-derived neurotrophic factor (BDNF) in glial cells [63, 64]. It has been proven that P4 and its metabolites decrease cerebral edema, have beneficial influence on blood-brain barrier function and intracranial pressure, and shorten recuperation time after brain damage as far as restored cognitive and behavioral functions are concerned [63]. Also, neudesin exhibits neurotrophic activity. It binds with heme and directly stimulates MAP kinase and neuronal signalization and activity [53]. That activity is believed to be mediated by membrane receptors [63].

PGRMC and its homologues regulate cholesterol synthesis through cytochrome P450, Cyp51 (lanosterol demethylase) activation, what plays a key role in cardiovascular diseases. PGRMC1 participation is also suggested in metabolism of drugs, hormones and lipids. The aspect of regulation of cholesterol concentration is especially important here [26]. It is also known that P4 affects the signal transduction and subdomain localization of receptors *via* its influence on cholesterol trafficking. Since cholesterol-rich rafts are considered to be organization centers for cellular signal transduction, changes of cholesterol concentration or distribution may have profound effects on receptor-mediated signaling in general. This mechanism has been shown to underpin the inhibitory effects of P4 on OTR (oxytocin receptor) signaling, not competitive binding to the receptor itself [64].

In the process of regulation of cholesterol concentration, PGRMC1 creates complexes with proteins, *e.g.* Scap (SREBP-cleavage activating protein) and Insig1 (Insulin-induced gene) [26]. After their synthesis in the endoplasmic reticulum, transcriptional factors, which activate genes encoding enzymes necessary for lipid synthesis SREBPs (Sterol Regulatory Element-binding Protein), bind to the Scap protein [15]. In the case of sufficient cholesterol concentration, Insig-1 forms a complex with Scap, what facilitates retention of the Scap/SREBP protein complex in the endoplasmic reticulum. In turn, in case of cell deprivation of sterols, Scap regulates the transport of SREBPs from the endoplasmic reticulum to the Golgi apparatus, where the complex is subjected to proteolysis. This event enables SREBPs migration to the nucleus and leads to the transactivation of genes involved in cholesterol synthesis. The fact that PGRMC1 binds, both Insig-1 and Scap, confirms its localization in the endoplasmic reticulum and suggests that its function could be 'sterol detection' [15, 26, 53].

PGRMC1 is induced by different carcinogens, including dioxins. It is up-regulated in many types of malignant tumors, where it promotes cell survival and determines their resistance to damage and also affects tumor vascularization [52, 53, 65 - 69]. The PGRMC1 expression is augmented by chemotherapy, and also in mouse cells with short telomeres and impaired chromosomes. Thus, the hypothesis has been made that DNA damage is followed by an increase in the receptor expression, and it plays a role in neoplastic promotion. The protein receptor overexpression has been demonstrated in carcinoma of breast, colon, thyroid gland, lungs, cervix and ovary, what suggests its potential role as a marker for neoplasia [49, 52, 70]. In this process, binding PGRMC1 with EGFR could constitute a key point. Simultaneously, EGFR inhibitors, e.g. erlotinib/tarceva and tyrphostin/AG-1478 could be effective in antineoplastic therapy [66].

Significantly less is known about PGRMC2, although it seems that, similarly to PGRMC1, it is necessary for proper function of the reproductive system. It has been proven in macaques that during the secretory phase, mRNA and PGRMC2 protein are expressed in functional layer of endometrium, principally within the luminal and glandular epithelium, what corresponds with simultaneous lack of PGRMC1 and nPR in these locations. It suggests that P4 could participate in embryo implantation precisely due to PGRMC2 [43]. In turn, through PGRMC1 activation, P4 allows the maintenance of pregnancy, thus suppressing premature uterine contractile activity and affecting the vascular bed of the

placenta. Decreased expression of this membrane receptor seems to be one of the key factors necessary for the initiation of parturition [55, 71]. PGRMC1 with PGRMC2 are probably involved in the functioning of oviduct smooth muscles, and they form a proper environment conducive to conception and oocyte transport, what has been proven already in cows [12]. In males, both isoforms could mediate in the acrosome reaction induced by P4 [26, 72].

3.3. Non-classical Activity

Three mechanisms involved in the activation of non-classical pathway have been suggested. Many aspects still remain unresolved and only single pathways, through which progestagens could realize their actions, are being analyzed in different species. Mediation of G-proteins, including typical α subunit dissociation from subunits β and γ, is the common reference for these pathways. The first mechanism assumes that progestagens activate MAPK kinases, *e.g.* Akt/PI 3, probably through G-protein βγ subunits (it has been proven in case of mPRα and mPRβ in fish), what results in Erk1/2 phosphorylation, leading to changes in gene transcription [26, 73]. The second mechanism underlines the role of one of the MAPK – p38, in which mPRα activation in the myometrium leads to phosphorylation of myosin light chains [26]. The third path includes a suppression of adenylate cyclase activity. It is also mediated by progestagens/mPRα signalization and subunit α of the inhibitory Gi protein. As a result of cyclase inhibition, the concentration of cAMP decreases [36, 47, 74]. However, in the process of activation of this path, the stimulatory G-protein is also involved (Gs), which could lead to increased cAMP concentration (*e.g.* in spermatozoa of *Genyonemus lineatus*). In the course of non-genomic pathway induction through mPRα and mPRβ, transactivation of the nuclear receptor and expression of steroid receptor co-activator - SRC2 within the human myometrium becomes impaired [26].

4. HOW BOTH GENOMIC AND EXTRAGENOMIC PATHWAYS COULD AFFECT ONE ANOTHER?

In all likelihood, classical and non-classical pathways could functionally cross, and nuclear and membrane fractions of receptors could cooperate with one another. The first proof for 'cross-talk' between mPR and nPR is based on the fact that mPR activation through P4 leads to nPRB transactivation. Additionally, mPR activation results in decreased concentration of steroid receptor co-activator 2 [75]. The process of initiation of parturition is an example of a cooperation between membrane and nuclear fractions of P4 receptors. The decrease in progestagen concentration is crucial for labor initiation in numerous mammal species [75, 76]. However, a different mechanism, namely the decrease in P4 receptors expression, has been proposed in humans. Normally, PGRMC1 receptor synthesis increases in the course of pregnancy and decreases during parturition. Moreover, its inadequate decrease in the expression could lead to preterm delivery [55]. In case of nPR, and especially nPRB, the situation is similar: the expression of this receptor in primates also decreases. The nPRA isoform, which is up-regulated in the myometrium during labor and could suppress transcriptional activity of nPRB, is the potential mediator in this phenomenon.

Another suggested mechanism is that progestagens influence the myometrium through a non-classical pathway with the participation of mPR [77]. In early stages of pregnancy, nPRB predominates in the human myometrium and acts synergistically with mPR. nPRB transactivation is the result of subunit Gi activation. Simultaneously, circulating sex steroids up-regulate both, mPRα and mPRβ. In turn, mPR activation at the end of pregnancy leads to SRC2 down-regulation, what together with changed nPRB/nPRA balance leads to a decrease of nPRB transcriptional activity in the myometrium [75, 77]. As a result, mPR cannot activate nPRB. This cascade of reactions enables P4 to act preferentially for mPRs during parturition in order to suppress adenylate cyclase activity, leading to smooth muscle phosphorylation and subsequent contractions [78]. cAMP, the second messenger formed by adenylate cyclase from ATP, is the universal signal in the cross-talk between nuclear and membrane receptors. It subsequently activates PKA, leading to CREB phosphorylation [4]. This, in turn, activates MAPK pathway, resulting in SRC1 phosphorylation. The phosphorylated forms of pCREB and pSRC1 cooperate in steroid receptor activation. Other mediators, which regulate the cross-talk between steroid receptors, are proline, glutamine acid, leucine-rich protein 1, or paxillinproteins [1].

Classical nPR receptors could mediate P4 activity also through the non-genomic pathway. For instance, human nPRB contains poliproline motif in the amino acid domain, which interacts with SH3 domain of Src. In this way, cytoplasmic PR could mediate P4-induced rapid activation of c-Src and downstream Ras/Raf/ERK1/2, independently of its transcriptional activity. Activation of the MAPK pathway invariably leads to phosphorylation of the following transcriptional factors: c-Fos, c-Jun and nPR [74].

5. SUMMARY

Membrane receptors mediate a wide spectrum of processes in the body, *e.g.* acrosome reaction, oocytes maturation,

autocrine activity in the corpus luteum, steroid and cholesterol metabolism, cellular homeostasis, neuronal excitability, neuroendocrine effects, behavioral processes, and response to stress. The receptors are situated in many tissues and organs, displaying a predilection to specific localizations, what has a special significance in both, morphologic and physiologic aspects. The cooperation between nuclear and membrane fractions of P4 receptors plays a relevant role. Thus it seems safe to hypothesize that membrane receptors are necessary in a number of processes for specific fulfillment of the activity initiated by nuclear receptors. Taking into consideration a broad distribution and significance of non-classical pathways and membrane receptors, the aspect of receptor stimulation or inhibition could be useful in treating multiple pathologies, *e.g.* some forms of infertility [1, 46].

Plenty of aspects regarding membrane receptors and non-classical pathways are still uncovered or controversial. Despite a great number of PGRMC1 function aspects which have been described so far, some authors hypothesize that this receptor could play a role as an adaptor protein, accompanying mPR transport to the cell surface. What is relevant, the same hormone could induce different effects in various species through non-classical pathway, or the same result could be achieved by different steroids. Controversies regarding membrane pathway could stem just from this diversity and heterogeneity [8]. Both, visualization of levels on which nuclear and membrane fractions of the receptors could reciprocally work, and recognition of every cell and tissue where membrane receptors are expressed, might enable a new, innovative look at processes which, although known, remain elusive [79].

LIST OF ABBREVIATIONS

CNS	=	Central Nervous System
GR	=	Glucocorticoid Receptor
HRE	=	Hormone Response Element
HSP	=	Chaperone Proteins
PAQR	=	Progesterone Adiponectin Q Receptor
PGRMC1	=	Progesterone Receptor Membrane Component One
P4	=	Progesterone
PR	=	Progesterone Receptor
mPR	=	Membrane Progesterone Receptors
nPR	=	Nuclear Progesterone Receptors

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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