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Activation of Progestin Receptors in Female Reproductive Behavior: Interactions with Neurotransmitters

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Abstract

The steroid hormone, progesterone (P), modulates neuroendocrine functions in the central nervous system resulting in alterations in physiology and reproductive behavior in female mammals. A wide body of evidence indicates that these neural effects of P are predominantly mediated via their intracellular progestin receptors (PRs) functioning as "ligand-dependent" transcription factors in the steroid-sensitive neurons regulating genes and genomic networks. In addition to P, intracellular PRs can be activated by neurotransmitters, growth factors and cyclic nucleotides in a ligand-independent manner via crosstalk and convergence of pathways. Furthermore, recent studies indicate that rapid signaling events associated with membrane PRs and/or extra-nuclear, cytoplasmic PRs converge with classical PR activated pathways in neuroendocrine regulation of female reproductive behavior. The molecular mechanisms, by which multiple signaling pathways converge on PRs to modulate PR-dependent female reproductive behavior, are discussed in this review.

Keywords

progesterone; progestin receptors; dopamine; signaling; cross talk; reproduction; behavior; brain; neurotransmitter; ligand-independent activation

1. Introduction

It has been recognized since the early 19th century that progesterone (P) is one of the most biologically active "progestins" of ovarian origin, which plays a major role in the reproduction of mammalian species. It was originally discovered as the mammalian pregnancy hormone, essential in the initiation and maintenance of pregnancy. In the decades following this discovery, the coordinating role of P in multiple interdependent reproductive functions, such as ovulation, mammary gland development and reproductive behavior has also been understood [40,171,210,211]. In recent years, the non-reproductive functions of P have been expanded to include its effects on the central nervous system, i.e., neuroprotection, myelination, inflammation, cognition and mood [40,44,67,171,236]. These findings have stimulated extensive investigations into the molecular mechanisms by which P exerts its broad range of effects on the brain and behavior.

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In this article, we will briefly review the current state of knowledge of the structural and functional aspects of progestin receptors (PRs), and discuss their functional role in the central nervous system. We will also discuss the neurotransmitter-PR interactions in the modulation of this behavioral response in rodents, and summarize our current knowledge of the cellular and molecular mechanisms involved in this regulation. The focus of this review is on PR-dependent effects on female reproductive behavior in rodent species. For further information on P effects on non-rodent species, the reader is directed to several excellent publications [14,15,17,160,80,174].

2. Mechanisms of Progesterone Action

2.1 Classical mechanism

Progestins, including P, exert their biological effects primarily by binding to PRs [240]. Upon binding, PRs undergo conformational change, leading to their nuclear translocation, dimerization and DNA binding [171,203–205,259]. When bound directly or indirectly to deoxyribonucleic acid (DNA), PRs interact with basal transcriptional machinery, assisted by coactivator molecules, to initiate chromatin remodeling and transcription of genes [114,135, 153,177]. Phosphorylation of both PRs and their coactivators is thought to play a crucial role in the activation of PRs [229–230].

2.1.1 PR: Structural organization and function—PRs have a modular protein structure consisting of distinct functional domains, capable of binding the ligand at the carboxyl (C)-terminal end (ligand binding domain; LBD), and a highly conserved DNA-binding domain (DBD), which is required for the transcriptional activity (Fig. 1A). The amino-terminal (N) region contains a transactivation function (AF1), which modulates the level and promoter specificity of target gene, by interacting with components of the core transcriptional complex and coregulator proteins [13]. A second activation function (AF2) is present in the LBD region, which contains sequences for dimerization, heat shock protein association, intermolecular silencing and intramolecular repression, in addition to P-binding function [114,259]. A unique third activation function (AF3) is present in the N-terminal segment of human PR (B isoform), which can function autonomously or synergize with, the downstream activation functions (AF1 and AF2) to enhance their activity [128].

In the absence of ligand, the inactive PRs are associated with a large complex of chaperone proteins in the cytoplasm of target cells [242]. Upon hormone binding, PRs dissociate from the chaperone proteins, dimerize, translocate to the nucleus and bind directly to progesterone-responsive elements (PRE) located in the regulatory regions of target gene DNA, or indirectly through tethering interactions with other transcription factors, i.e., Activator protein 1(AP1), Specificity protein 1(SP1), Signal transducers and activators of transcription proteins (STATs) [20,68,79]. Activated DNA-bound PRs, stimulate the rate of formation and/or stabilization of a preinitiation complex consisting of general transcription factors (GTFs), at enhancer-controlled promoters [132,139,149]. Whether the preinitiation complex is preformed or recruited sequentially, the rate of assembly of the complexes induced by PRs, in association with their coregulators, ultimately defines the transcriptionally permissive or non-permissive environment at the hormone-regulated promoters.

To date, ~300 nuclear receptor coregulators (coactivators and corepressors) have been biochemically and functionally identified [148]. Many of the coactivators have an L-X-X-L-L motif that permits the interaction of the coactivator with the receptor. In addition, coactivators also have other functional motifs, such as ribonucleic acid (RNA)-interacting domains, i.e., Lin11, Isl-1 and Mec-3 (LIM) domain and bromo domain, that interaction with transcriptional factors such as steroid receptor RNA activator [SRA; 147], small SRA binding protein (SLIRP) [116], and protein p53 [191]. Coactivators possess unique intrinsic enzyme activities including

acetyl transferase, ubiquitin ligase, methyl transferase, small ubiquitin-like modifier (SUMO) ligase, phosphokinase, phosphatase, hydrolase, ribosylase, isomerase, helicase, and pseudouridylate synthetase activities [119,130], which are required for nuclear receptor-mediated gene transcription [227]. The substrates of the enzymes associated with these coactivators involve histones and other coactivators present in the coactivator complex. The enzyme modulation properties of the coactivators afford a high level of regulatory flexibility in the control of PR-mediated gene expression. An excellent description of the coactivators involved in PR regulation can be found in other relevant publications [148,154,254]

2.1.2 Phosphorylation of PRs—PRs are phosphoproteins that undergo phosphorylation-dephosphorylation events and provide multi-functionality to P action. Phosphorylation events occur primarily on the serine residues within the N-terminus, and to a lesser extent throughout the PR. A total of 14 serine sites that are phosphorylated basally (in the absence of P), or in response to activation by P or various protein kinases, have been identified both *in vitro* and *in vivo* [117,146]. Among these 14 residues, basal level phosphorylation has been identified on four serine residues (81, 162, 190 and 400). P-dependent phosphorylation has been demonstrated to occur on 3 serine residues within 60 min of treatment, (102, 294, 345). Other serine residues on PR are phosphorylated by specific protein kinases including mitogen-activated kinase (MAPK; on serine 294), casein kinase II (CKII; on serine 81) and cyclin-dependent kinase 2 (cdk2; on serines 25, 162, 190, 213, 400, 554, 676). While the role of PR phosphorylation is not fully understood, it is thought to influence the regulation of both P-dependent and -independent PR nuclear localization, receptor turnover, and coregulator interactions that occur during transcriptional regulation [195].

2.1.3 Multiple forms of PRs—Multiple PR isoforms are produced from a single gene, consisting of 8 exons [Fig. 1B], as a result of transcription from different translational sites [61,133,141]. PR-B is the full-length protein consisting of 933 amino acids (101–120 kDa), while PR-A (79–94 kDa) lacks 165 amino acids in the N-terminus, called the B-upstream sequence (BUS). This region encodes AF3 that is specific to the PR-B protein [96], which allows the binding of a subset of coactivators exclusively to PR-B, and not to PR-A. PR-A and PR-B proteins can dimerize as three species A: A and B: B homodimers and A: B heterodimers, which interact with PRE and bind to DNA, as well as GTFs, to regulate gene expression. Thus, PR-A and PR-B contain all the critical components for PR function, including the LBD, DBD and 2 of the three AF domains. The differential structure of the PR isoforms confers distinct tissue-specific responses to P through post-translational modifications, dimerization, and recruitment of cofactor proteins. This contributes to the differential transactivation properties of each isoform, leading to the regulation of distinct subsets of P-dependent target genes. Consistent with the distinct tissue- and promoter-specific activities of PR-A and PR-B *in vitro*, each individual isoform has been found to modulate distinct subset of reproductive functions by regulating diverse subset of target genes, as seen in their phenotypic response to P in the uterus, the ovary and the mammary gland [62,63,192,193].

A third isoform PR-C (60 kDa), resulting from an in-frame initiation of translation at Methionine-595, located within the DBD, was identified in T47D human breast cancer cells. This isoform (338 amino acids; 595–933) contains a large N-terminal truncation that lacks AF3, AF1, and the first zinc finger of DBD [266–267]. While PR-C cannot function as a transcription factor independently, it can interact with the other two isoforms to modulate their transcriptional activity [267]. Several novel truncated isoforms and splice variants have also been identified *in vitro* [234,124,125,274], the functional relevance of which currently remain unknown. Expression analysis studies suggest that the latter were incapable of yielding translation products *in vitro* [233].

2.2 Non-classical mechanism

The classical view that PRs mediate P effects, acting as transcriptional factors to facilitate target gene expression, has undergone substantial modifications to incorporate recent discoveries of extra-nuclear, non-classical mechanisms of P regulation. These rapid signaling mechanisms are mediated by cytoplasmic protein kinase cascades [42,145,146,169,172] and are coupled to novel transmembrane G-protein coupled receptors [279], ion channels, adapter proteins and putative membrane receptors [42,117,235].

Rapid and transient activation of extranuclear PRs, independent of PR transcriptional activity, mediated by MAPK, has been demonstrated in mammalian cells *in vitro* [43,186]. P signaling, mediated by G protein βγ subunits, has been shown to activate the downstream MAPK cascade during meiotic progression in xenopus oocytes, demonstrating a biologically important role for G proteins in non-classical signaling [28,88,89,157]. Both an increase and a decrease in rapid Ca^{2+} influx by P has also been reported [115,179]. In addition, Boonyaratanakornkit *et al* [42,43] have demonstrated direct interactions between PRs and c-Src proteins, mediated by polyproline (PXXPXR) domains of PR, which lead to subsequent activation of downstream signaling kinases. Furthermore, a putative common-docking domain, which directly interacts with MEK1, a component of the MAPK cascade, has been reported in the N-terminal BUS of PR-B [117].

Recent evidence suggests the involvement of two types of novel membrane proteins unrelated to classical PRs, progesterone membrane receptor component 1 (PGMRC1; Mw~22 kDa) and progesterone membrane receptors (mPRs; Mw~40 kDa), in P signaling in several reproductive tissues and in the brain. PGMRC1, originally isolated from porcine liver membranes [84,85, 95,185], has also been identified in the rat (25-Dx, [203]) and in the human (Hpr6.6, [155]). PGMRC1 is thought to activate P450 proteins functioning as a component of multi-protein P-binding complex [223]. The mPRs, initially discovered in teleost ovaries, are G-protein coupled receptors (GPCRs) that belong to the seven-transmembrane progesterone adiponectin Q receptor (PAQR) family and comprise of at least three subtypes, α, β and γ. mPRs identified in the seatrout are localized to the plasma membrane, bind P with high affinity (Kd~5 nM), and have been shown to be involved in P-mediated induction of meiotic maturation [278, 279] and sperm motility [260]. mPRα receptors down-regulate adenylyl cyclase activity [257] by direct coupling to G proteins and activating pertussis-sensitive inhibitory proteins ($G_{i/o}$). Down-regulation of adenylyl cyclase activity has also been observed in the human breast cancer and myometrial cells, *in vitro* [131]. Zebrafish mPRs, when expressed in classical PR-deficient mammalian breast cancer cells, mediate a rapid and transient P-mediated activation of MAPK, and inhibition of 3′-5′-cyclic adenosine monophosphate (cAMP) production. In the human myometrial cells, mPR activation leads not only to a decline in cAMP levels, but also to the transactivation of classical PR-B. Transactivation of PR-B, not only involves G_i protein coupling, but also decreased steroid receptor coactivator-2 (SRC-2) levels, suggesting a crosstalk between the membrane and nuclear PRs at the transcriptional level [131].

2.3 Ligand-independent activation of PRs

Although, the conventional model of P action assumes that PRs mediate P effects *(ligand-dependent activation)*, a number of studies in the past couple of decades have shown that PRs can be activated by factors other than their cognate ligands (*ligand-independent activation)* (Fig. 2). Denner *et al* reported that P-dependent, PR-mediated transcription could be mimicked, in the absence of P, by 8-bromo-cAMP *in vitro* [68–70]. Protein kinase A (PKA) inhibitors blocked PR activation, suggesting that PR-mediated transcription could be modulated by phosphorylation of PR or other proteins in the transcription complex [70,229–230]. These observations were soon followed by the studies of Power *et al*, who reported ligand-independent activation of PRs by neurotransmitter dopamine (DA) *in vitro* [214–215].

Subsequently, epidermal growth factor (EGF), heregulin, phorbol myristate acetate and insulin growth factors have also been shown to activate PRs, by increasing the phosphorylation of PRs *in vitro* [84–85,212,276].

While the precise mechanism of ligand-independent activation of PRs has remained elusive, several studies suggest the involvement of PR phosphorylation in this mechanism. For example, growth factor-initiated signaling pathways (EGF and heregulin) have been reported to enhance phosphorylation of PRs on distinct sites (see 2.2.1). MAPK-dependent signaling has been demonstrated to enhance PR phosphorylation on Ser294 [217–218]. This enhanced phosphorylation has been shown to result in the rapid nuclear translocation of unliganded PRs and nuclear export of liganded PRs, suggesting that MAPK signaling could regulate PR nuclear sequestration, by altering nucleo-cytoplasmic shuttling [144,217–218]. Studies indicate that PR sequestration in the nucleus serves to protect the inactive and active PRs from degradation by the 26S proteosome pathway [217–218]. It is also tempting to speculate that distinct sets of genes could be activated by phosphorylated liganded PRs and unliganded phosphorylated PRs, via classical and non-classical mechanisms respectively [217–218].

A synergistic effect of P-dependent- and –independent activation of PRs has been reported in the upregulation of growth regulatory genes (cyclins D1 and E) in breast cancer cells *in vitro* [146,217]. Cdk2, activated by P, indirectly facilitates PR function, by increasing the recruitment of SRC-1 to liganded PR. In addition, activated Cdk2 also mediates transcriptional activation of PR by phosphorylating PR Ser400 in a ligand-independent manner [212]. In contrast to the direct effects of Cdk2 on PR phosphorylation, cAMP-dependent activation of PR does not involve direct phosphorylation of PR, but affects phosphorylation of SRC-1, to bring about the functional cooperation of SRC-1 and CREB-binding protein [13,229–230]. A detailed discussion of the studies on PR phosphorylation, using *in vitro* models, can be found in several excellent reviews [117,145,146].

3. Cellular function of P in brain and behavior

3.1 P in female reproductive behavior

In gonadally intact female rodents, the sequential release of ovarian estradiol (E_2) and P, integrates the appearance of feminine reproductive behavior (heat, behavioral estrus) with ovulation [19,41,66]. In ovariectomized rats, guinea pigs, hamsters and mice, this behavior can be restored by timed sequential administration of E_2 followed by P, or by high doses of E_2 alone [18,34,39,152,210,211,275]. Such a sequential treatment with E_2 and P maximizes the *probability* that the female will display “lordosis” response, a primary reflexive component of female reproductive behavior, upon mounting by a con-specific male [87,210–211]. The sequential hormonal regimen also allows lower doses of each of the hormones to be used [59,269], that results in a more predictable onset and termination of the period of sexual behavior [19,41] and lordosis duration [262].

Sequential release of E_2 and P, are also thought to be necessary for the display of species-typical proceptive or paracopulatory behaviors [19,37,39,40]. These paracopulatory behaviors, exhibited by estrous females in the presence of a sexually active male, include hopping, darting, ear wiggling, approach towards and withdrawal from the male, and production of ultrasonic vocalizations [19,173,270]. While E_2, by itself, is capable of inducing proceptive behaviors in female rats [81,104], in most instances, adrenal P is essential for the display of proceptive behaviors [104,251]. Paracopulatory behaviors have also been observed in ovariectomized and adrenalectomized E_2-primed female rats [37,40], and in DA- facilitation of reproductive behaviors in ovariectomized E_2-primed female rats and mice [Mani and Reyna, unpublished observations], suggesting that these behaviors may not be totally dependent on P. For further

discussion on the receptive and proceptive behaviors, the reader is referred to other excellent reviews [37,40].

In addition to its facilitatory effects on female reproductive behavior in female rats, P also plays a role in the termination of sexual behavior during estrous cycle [244–246] and pregnancy [16]. Following exposure to P, rats, hamsters, guinea pigs and mice, become refractory to further stimulation of reproductive behavior, by the administration of P or by E_2 and P [29–31,49,66,[74],105,190,280–281]. This effect generally referred to as postestrous-refractoriness [190], sequential inhibition [30–31], or biphasic effect [280–281] of P, is believed to limit the duration of behavioral estrus to the periovulatory phase of the estrous cycle period, and is thought to occur as a result of P-dependent down-regulation of PRs [29–31].

Studies demonstrating the temporal concordance of E_2-induced PRs with the expression of lordosis, suggest that P plays a significant role in the facilitation of female reproductive behavior [37 and references therein]. Both, nuclear receptor-mediated (classical or genomic)-, and extra-nuclear (membrane-initiated, non-classical or non-genomic)- mechanisms, have been identified in the PR activation of female reproductive behavior. In addition, others and we have also demonstrated ligand-independent activation of PRs, by neurotransmitter DA, in the facilitation of lordosis. Studies in the recent years suggest that these mechanisms are not mutually exclusive, but interact with each other to achieve the behavioral end-point. A detailed discussion on this topic is dealt with in sections 4.0 and 5.0.

3.2 Classical nuclear PR-dependent mechanisms in female reproductive behavior

3.2.1 Spatial and temporal correlation between PR induction and reproductive behavior—Although, diverse cellular mechanisms have been ascribed to P action in the brain, the primary mechanism (although not exclusive) involves its interaction with E_2-induced nuclear PRs, which function as transcriptional factors, regulating the expression of genes and genomic neural networks, to initiate and/or sustain physiological response [40,210–211]. The time course of activation and termination of female sexual behavior parallels E_2-induced increase and decline in PRs in the ventrolateral region of the ventromedial hypothalamus (VMH) and the preoptic area (POA) of the brain [33,46,66,206,231]. Studies using PR antagonists [45,75,163,231], protein and RNA synthesis inhibitors [183,184,220], antisense oligonucleotides to PR [162,200,213], and mutant mice with targeted deletion of PR gene (Fig. 3a), have provided substantial proof of involvement of PR-mediated genomic mechanism in mediation of P-facilitated female reproductive behavior [158,165]. For an extensive discussion of these studies, the reader is referred to several excellent reviews [38,39,171,210,211].

A temporal correlation between declining PRs and female reproductive behavior has been reported during the refractory period in guinea pigs [31,32,41]. During this period, the animals were hyposensitive to P and had low concentration of unoccupied hypothalamic PRs. Treatment with physiological levels of P, however, resulted in low levels of occupied nuclear PRs, suggesting that the hyposensitivity and the resulting heat termination could be attributable to the inadequate accumulation of occupied nuclear PRs, in response to P [33–34]. Interestingly, the animals regained P responsiveness upon administration of a high pharmacological dose of P. A large increase in P-occupied hypothalamic PRs accompanied the P responsiveness [29]. Furthermore, pharmacological agents that prevent degradation of the PRs by inhibiting 26S proteosome activity, not only stabilized the concentration of PRs within the hypothalamus and POA, but also prevented the P-induced refractoriness in female rats, confirming that the behavioral refractoriness is causally related to the down-regulation of PRs [78,99,102]. Detailed discussion and the interpretation of these studies can be found in several excellent articles [39,40,254].

3.2.2 PRs, Coactivators and Behavior—Following reports of the expression of several members of SRC family in the brain [51–55,254 and references therein], several studies have examined the role of nuclear receptor coactivators in the PR-mediated female reproductive behaviors. Investigations into the role of the coactivators in P-facilitation of female reproductive behavior, using antisense oligonucleotides for SRC-1 and CBP, indicate the requirement of both the coactivators [187–189,255–256]. Studies by Apostolakis *et al* [5] have extended the role of coactivators to include SRC-2 in the PR-mediated female reproductive behavior. Coactivators are also expressed in other regions of the brain, including the hippocampus and dentate gyrus [199], and have also been demonstrated to be involved in sexual differentiation and male sex behavior [51–55]. For a detailed discussion on the location and the role of coactivators in the brain the reader is directed to other publication [254].

3.2.3 PRs: non-inducible by Estrogens—Using the high affinity progestin, ^{3}H-R5020 as a radioligand, two anatomically distinct classes of progestin binding sites were identified in the rat [159] and in the guinea pig [32]. In contrast to the E_2-induced PRs present in the hypothalamus, POA and pituitary of the female rat [160], guinea pig [33] and the rabbit [60], another class of PRs, insensitive to E_2-priming, was identified. These PRs were widely distributed in the cortex, hippocampus, amygdala, caudate-putamen and cerebellum [134]. Significant concentrations of PRs, non-inducible by E_2, were also found in areas that contain inducible PRs [207]. However, it should be noted that neural P implants in areas like the midbrain reticular formation [228], habenula [252] and tegmentum [156,252], some of which lack E_2-induced PRs, also facilitate the expression of lordosis in E_2-primed rats. While it is believed that these areas are components of the lordosis circuitry, it is not definitively known how the various regions are interconnected, or how they respond to hormones (in the absence of steroid receptors), to facilitate reproductive behavior. It is tempting to postulate that some of these effects could be mediated by non-genomic mechanisms of the steroid hormones, or interactions with neurotransmitters, neuropeptides or other sensory-motor components of the behavior. It is also possible that these non E_2-inducible PRs could be mediating P effects that are not dependent upon prior exposure to E_2: for example, alterations of cortical electroencephalograph patterns [6]. Whether P effects on negative changes in mood and anxiety seen during the late luteal phase of the menstrual cycle (when levels of P are high) in women could be mediated by the non E_2-inducible PRs, remain to be examined [118].

3.2.4 PR isoforms in brain and behavior—As discussed in section 2.1.2, multiple forms of PR have been reported to date. However, with the exception of PR-A and PR-B isoforms, none of the other isoforms have been identified in the brain. In the rat brain, differential expression patterns and region- and hormone-specific regulation of the individual isoforms during development and in adulthood have been documented [48,110–112,249]. A detailed discussion on the spatiotemporal expression of neural PR isoforms and their region-specific regulation in the brain can be found in other reviews [170–171].

The development of mutant mice in which the expression of PR-A (PRAKO $^{-/-}$) and PR-B (PRBKO $^{-/-}$) isoforms have been selectively ablated, has facilitated the direct analyses of the individual contributions of PR isoforms in mediating neuronal responses to P [192–193]. Studies using the mutant mice, generated by the introduction of point mutations into the PR gene at the ATG codons encoding Methionine 1 (M1A) and Methionine 166 (M166A), have established a critical role for PR-A isoform in the P-facilitation of female receptive behavior in female mice. Ablation of PR-A significantly inhibited P-facilitated receptive behavior in PRAKO$^{-/-}$ mice, while the ablation of PR-B resulted in a decrease in the magnitude of lordosis response to P, compared to their wild type littermates [168]. This reduction of female receptive behavior in PRBKO$^{-/-}$ was not significant, suggesting that PR-A was necessary, but not sufficient, to mediate the full magnitude of the behavioral response in the PRBKO$^{-/-}$ mice (Fig. 3b).

In contrast to these observations in mice, studies in rats indicated that antisense oligonucleotides to PR-B isoform significantly inhibited P-facilitated female receptivity [cf. 113], suggesting that PR-B was sufficient in mediating lordosis response in female rats. It is reasonable to assume that these conflicting observations of the requirement of PR-A in mice and PR-B in rats could reflect species-specific differences. However, deletion of PR (PR-A + PR-B), whether by targeted deletion (in mice [168]) or by the administration of a combination of PR-A + PR-B antisense oligonucleotides (in rats [113]), resulted in the inhibition of P-facilitated lordosis response, indicating similarities in PR requirement between the two species. This interesting conundrum needs further evaluation. Furthermore, intracerebroventricular (icv) administration of antisense oligonucleotides to PR-B or PR-A+PR-B combination inhibited not only P-, but also its ring A reduced metabolite (5α-pregnan-3, 20-dione (5α-DHP)-, and 5β, 3β-pregnan-20-one (5β, 3β-Pgl)- facilitated lordosis in EB -primed female rats [113]. Similar to the observations in response to P, the latter reports suggest the critical importance of PR in general, and PR-B isoform in specific, in P metabolite-facilitated female receptive behavior in rats. Further discussion on the role of P metabolites in female reproductive behavior can be found in section 3.3 below.

3.3 Membrane-initiated, non-classical actions of P

While genomic effects have been assumed to be the primary pathway for hormone action in the brain, there are numerous reports of short-latency effects of P suggesting the involvement of “non-classical” effects via putative cell surface receptors and other mechanisms coupled to second messenger signaling cascades. Rapid effects of P have been demonstrated in the release of gonadotropin releasing hormone (GnRH) [211], DA and acetylcholine [182] and excitatory amino acids [243], changes in neuronal activity [120,136–137] and on facilitation of lordosis response in estrogen-primed female rats [142,152,181]. These rapid effects of P are not blocked by protein synthesis inhibitors, are mediated by their binding to putative cell surface membrane receptors [221–222], receptors that gate ion channels [94,176], and are also coupled to certain second messenger systems [137,147,235].

In addition to P, several of its ring-A reduced metabolites, 5α-DHP and5β, 3β-Pgl, have been shown to facilitate lordosis response in ovariectomized, E_2-primed female rats [23,24,91,92, 98,225]. This facilitation appears to involve the activation of MAPK pathway, since MAPK inhibitors decreased the display of proceptive and receptive responses in female rats [99–100,103]. The behaviors were also inhibited by the administration of PR antagonist RU486, indicating functional interactions between the rapid, membrane-mediated pathways and nuclear PRs [102]. Such interactions between membrane-initiated P effects and intracellular PRs have been observed in the facilitation of sexual behavior in female hamsters, suggesting that both classical and non-classical mechanisms act in concert rather than independently [64–65].

Other studies have reported the involvement of cytoplasmic kinases, PKA, protein kinase C (PKC), Calcium and calmodulin kinase II (CaMKII) and protein kinase G (PKG) in mediating the rapid P effects in the VMH and POA in the female rat [11–12,22,56–[57],[101],140,208,209, 235]. Since the initiation of these non-classical effects occurs rapidly (in seconds or minutes) and is triggered at the membrane surface, the classical model of nuclear PR-mediation is inadequate to account for these effects. Numerous studies have identified crosstalk between various kinase-initiated pathways (by neurotransmitters, nucleotides and neuropeptides) and nuclear PRs in the brain, suggesting that both classical and non-classical mechanisms act in concert rather than independently. These interactions in the facilitation of female reproductive behavior will be discussed in section 4.0.

In a recent report, Sleiter *et al* [241] demonstrated the presence of mPRα and mPRβ message in the medial basal hypothalamus and their involvement in the negative feedback effects of P

on GnRH secretion. Using the PR knockout mice and their wild type littermates *in vivo* and GT1-7 cells *in vitro*, the authors reported that P effects on cAMP inhibition (via G_i) were independent of classical nuclear PR isoforms, PR-A and PR-B, making a case for the involvement of mPRs in GnRH secretion. Whether mPRα and mPRβ play a role in P-facilitation of female reproductive behavior and could be involved in the crosstalk with nuclear PRs remains to be determined.

4. Neurotransmitters in Female Reproductive behavior

Facilitation of female reproductive behavior appears to include pathways other than those involving rapid non-genomic and slower genomic pathways activated by P. Steroid hormones have been shown to influence female reproductive behaviors by alteration in neurotransmitter biosynthesis and release [198], allosteric modulation of membrane receptors [73,219], changes in neurotransmitter receptor densities, and interactions with G-protein coupling and subsequent intracellular signaling pathways in the hypothalamus and POA [76–77]. This steroid hormone-neurotransmitter interaction is not unidirectional. Not only do steroids affect neurotransmission, but changes in neurotransmission can also alter steroid activity. It has been recognized that in addition to steroid hormones, several neurotransmitters and neuropeptides influence female reproductive behavior in rodents. While the effects of acetylcholine, norepinephrine, serotonin (acting via 5-HT_2, receptor subtype), DA (acting via receptor subtype D_1) and the neuropeptides GnRH, TRH, prolactin, oxytocin, substance P, and $GABA_A$ are considered facilitatory, serotonin (acting receptor subtype 5-HT_{1A}), DA (acting through receptor subtype D_2), opioids, CRF, α-MSH, ACTH, β-endorphin, neuropeptide Y, cholecystokinin and glutamate are considered inhibitory on sexual behavior [26,76,93,210, 250,258].

Neuroanatomical studies have demonstrated the colocalization of neurotransmitters and neuropeptides in PR-containing neurons [210]. Dopamine-β-hydroxylase- and tyrosine hydroxylase- immunoreactive neurons have been reported to be present in close proximity with, and synapsing upon, PR-containing immunoreactive neurons in the POA and hypothalamus in guinea pig [35,253], rat and monkey [126–127]. Autoradiographic studies in the rat brain demonstrate the presence of E_2-concentrating neurons in the hypothalamus and POA that also have afferent input from catecholaminergic neurons [123]. Similarly, estrogen receptor immunoreactive neurons have been found to establish synaptic contact with dopamine-β-hydroxylase immunoreactive neurons in the hypothalamus of the guinea pig [253]. Although these studies do not definitively prove that genomic mechanism could be involved in neurotransmitter-related regulation of PRs involves, the feasibility cannot be ruled out.

A number of second messenger molecules, including cAMP, 3′-5′-cyclic guanosine monophosphate (cGMP) and nitric oxide (NO) can also substitute for P in the facilitation of reproductive behavior in female rats [56–57,103]. NO has been demonstrated to be a mediator of GnRH release and a facilitator of female reproductive behavior [164]. It has also been shown to be a signal transducer in the facilitatory effects of norepinephrine (mediated by α1-adrenoceptor), dibutyryl-cAMP (db-cAMP), GnRH, prostaglandin E_2 (PGE_2), ring-A metabolites of P, or vaginocervical stimulation (VCS)[58,101–103]. The involvement of PKG in the facilitation of lordosis by db-cAMP and PGE_2, but not by GnRH, has also been reported [103]. Furthermore, MAPK inhibitor also blocked db-cAMP-, PGE_2-, or GnRH-facilitated lordosis. These studies suggest the involvement of multiple signal transduction pathways in female reproductive behavior. The messenger molecules and their activated pathways that have been reported to interact with PRs, in the facilitation of rodent female reproductive behavior, are listed in Table 1. The crosstalk between these signaling pathways and PRs will be discussed further in section 4.2.

4.1 Neurotransmitter and PR interactions in female reproductive behavior

As described in section 2.3, ligand-independent activation of PRs by DA was first described *in vitro* [214]. Following these observations, the physiological relevance of ligand-independent activation of PRs was demonstrated in DA-facilitated female reproductive behavior in rats and mice [163,165]. Icv administration of apomorphine, a DA receptor stimulant, or the D_1 agonist, SKF 38393 (SKF), mimicked P effects in the facilitation of lordosis response in female rats [163]. The facilitatory effect of SKF was found to be specific to the D_1 receptor subtype confirming and extending an earlier report in which DA agonists, infused into the hypothalamus and POA facilitated lordosis response in female rats [90]. The effect of SKF on lordosis response was blocked by the administration of PR antagonists, D_1 receptor antagonist or antisense oligonucleotides to PR mRNA [163], demonstrating the requirement of intracellular PRs in DA-facilitation of female reproductive behavior. Furthermore, PR knockout mice were unable to exhibit SKF-facilitated female reproductive behavior, while their wild type littermates responded to SKF [165]. These studies provided definitive evidence for the obligatory role of PRs as transcriptional mediators in DA-facilitation of female reproductive behavior.

Studies on the involvement of the PR isoforms on ligand independent activation by DA have revealed an interesting dichotomy. Using PR isoform-specific knockout mice Mani et al [168] demonstrated that both PR-A and PR-B isoforms are essential for the expression of the full complement of SKF-facilitated female reproductive behavior. The studies also demonstrated that the effects of cyclic nucleotide, 8-bromo-cAMP (8-br-cAMP), were primarily mediated by PR-A [168]. $PRAKO^{-/-}$ mice failed to display 8-br-cAMP-facilitated lordosis while $PRBKO^{-/-}$ mice displayed reduced levels, suggesting that SKF and 8bBr-cAMP are perhaps recruiting distinct intracellular signaling pathways to activate distinct PR isoforms and downstream genes (Fig. 3b). It is possible that SKF-and 8-br-cAMP- activation of murine PRs could involve altered phosphorylation of distinct coactivators, diverse sets of coactivators, dissimilar phosphorylation sites on the PRs and/or coactivators, in the multicomponent steroid receptor complexes that serve as a sensor(s) for modulatory signals.

Studies using antisense oligonucleotides to DA receptor subtypes indicate that DA-facilitated, PR-mediated behavioral effects occur via D_1B (D5) subtype, and not the D_1A subtype (167). *In situ* hybridization and immunohistochemical studies confirm the coexpression of D_1A/D_1B and PRs in the medial POA, lateral ventromedial nucleus of the hypothalamus and the arcuate nucleus of female rats [36,154]. Collectively, the data suggest crosstalk between the P- and DA-initiated pathways in the mediation of female reproductive behavior in rats and mice. As will be discussed in section 4.2, rapid membrane-initiated signaling cascades can also interact with the genomic pathways at the level of intracellular PRs to enhance or initiate facilitation of female reproductive behavior.

Ligand-independent mechanism activation of PRs has also been observed in other behaviors. Behaviorally relevant stimulus, such as the VCS, has been shown to activate neural PRs in the absence of P [9–10]. PR antagonists have been reported to inhibit GnRH- and PGE_2- facilitated reproductive behavior in female rats [25]. PR antagonist RU486 [2], also inhibited δ opioid agonist, [D-Pen2, D-Pen5]-enkephalin (DPDPE),-facilitation of lordosis in EB-primed female rats [1]. The involvement of PRs in the α1-adrenergic receptor-facilitated female reproductive behavior has also been reported [58]. Thus, indirect activation of PRs, by each of these compounds, appears to be a common mechanism mediating female reproductive behavior in rats and mice. Furthermore, the mechanisms by which many of these neurotransmitters and neuropeptides activate PRs appear to involve second messenger cascades as discussed below in sections 4.2 and 5.0.

In addition to the female reproductive behavior, ligand-independent activation of PRs has also been observed in other physiological processes. Ligand-independent activation of PR has been demonstrated in GnRH self-priming and preovulatory gonadotropin surges [4,50,150,221–222,261]. Antisense oligonucleotides to PR inhibited GnRH surges in female rats, suggesting the requirement of PR in GnRH regulation [50]. Oleson *et al* have demonstrated a role for ligand-independent activation of estrogen receptors (ERs) by DA agonist during development, and in juvenile play behavior [201–202], suggesting that ligand-independent activation is not exclusive to PRs and female reproductive behavior.

4.2 Intracellular signaling pathways in female reproductive behavior

A variety of compounds that activate several second and third messenger systems and stimulate protein kinases within the neurons, also facilitate female reproductive behavior in EB-primed rats. These compounds include adenosine and guanosine nucleotides, which can substitute for P, and cause an elevation in their second messengers, cAMP and cGMP respectively [21,56, 151,269]. GnRH- and PGE_2-permissive effects over female receptivity also involve an increase in levels of cAMP and PKA activity [223]. Recently, Gonzalez-Flores *et al* [103] have reported the involvement of downstream kinase, MAPK, in the facilitation of female reproductive behavior in ovariectomized, EB-primed female rats, not only by P, but also by GnRH, PGE_2 or di-bromo-cAMP. MAPK inhibitor, PD98059, was able to effectively inhibit the facilitation of reproductive behavior, induced by these compounds [100,103]. The involvement of MAPK pathway has also been shown in δ opioid-facilitation of lordosis [2]. Interestingly, not only does MAPK activated pathway facilitate lordosis, but it also subsequently promotes termination of behavioral estrous by targeting the PR for degradation by the 26S proteasome [47,99].

Phosphodiesterase inhibitors that increase cAMP, by interfering with the hydrolysis of cAMP, have been shown to potentiate the effects of sub-threshold doses of GnRH and P in the facilitation of lordosis [22]. Studies on cGMP effects on lordosis have identified a role for protein kinase G (PKG) in the signaling cascade. In addition, the cGMP-mediated response also required the presence of nuclear PRs, suggesting the existence of cross-talk between the two pathways [56–57]. Inhibitors to PKG were effective in reducing the lordosis response induced by P and its ring-A reduced progestins in ovariectomized, EB-primed female rats [100] or by VCS [101]. Studies on P-mediated signal transduction pathways also indicate rapid elevations in hypothalamic cAMP levels and PKA activity, by P, in EB-primed rats and mice [166]. Inhibitors of PKA reduced not only P-, but also GnRH- and PGE_2-facilitated female reproductive behavior, in EB-primed rats [166,223]. Signaling cascades mediating the P- and DA agonist-facilitated female reproductive behavior have also been shown to include a third messenger, DARPP-32 (dopamine and cAMP regulated phosphoprotein-32), the absence of which rendered both rats and mice incapable of expressing P- or SKF-facilitated lordosis response [166].

There is no doubt that the expression of female reproductive behavior involves substantial interplay between the rapid membrane-initiated extra-nuclear mechanisms, the slower genomic actions of P, and ligand-independent mechanisms that modulate signaling kinases (Fig. 4). However, a larger question that remains unanswered is the mechanism by which these pathways are coordinated to bring about transcriptional regulation of PRs, at the genomic level. It is reasonable to speculate that P-stimulated, rapid non-classical activation of cytoplasmic signaling pathways, can regulate gene expression independent of PRE binding [42,43,82,83, 216], by increasing the phosphorylation of CREB (Ca^{2+}/cAMP response element binding protein) or other transcription factors, i.e., ATF-1, enabling them to become transcriptional regulators [7]. In several regions of the rat brain lacking the classical PRs, E_2 causes a rapid increase in p–CREB with no concomitant increases in protein or mRNA levels [109,277]. P,

on the other hand, appears to have a bimodal effect on the phosphorylation of CREB, bringing about a rapid decrease followed by an increase [109]. These rapid effects on CREB phosphorylation also appear to be nuclear receptor-mediated, since PR antagonists block the hormonal effects on CREB phosphorylation, suggesting a cross talk between the two signaling pathways.

It is possible that protein kinases can also have effects on ion channels [180]. P has been shown to induce transcription of immediate early genes (IEGs) containing CRE-sequences such as *c-fos* and *c-jun* [178]. These genes encode the transcription factors, Fos and Jun that can form hetero- or homodimers and regulate downstream gene expression, by acting on target AP-1 DNA recognition sequences near promoter elements. AP-1 elements can substitute for hormone response elements in the steroid regulation of gene transcription [143]. Evidence from *in vitro* experiments indicates that ER and PR can also mediate transcription of genes controlled by an AP-1 enhancer element [262,265]. Furthermore, it has also been demonstrated that the two distinct classes of transcription factors, steroid hormone receptors and AP-1 complexes, interact to modulate each other's activity [3,238]. In addition, PR coregulators could also integrate steroid hormone signaling through CBP [161,258,271]. Functional cooperation between MAPK cascade-mediated phosphorylation of coactivator SRC-1 and CBP has been demonstrated in the activation nuclear PRs *in vitro* [229–230]. Thus, second messenger systems can potentially modulate gene expression via multiple transcription factors or coactivators, providing an alternative pathway to the genome [248,263,264]. The molecular mechanisms recruited by PRs to differentiate between various stimuli to activate female reproductive behavior remain to be determined.

5. Dopamine signaling pathway convergence with PRs

Protein phosphorylation is common to the pathways and molecular mechanisms through which neurotransmitters and steroid hormones produce their biological effects. The regulatory mechanisms governing a variety of cellular processes in target cells are dependent not only on the state of intracellular phosphorylation of the receptor, but also on the dynamic balance between cellular protein kinases and phosphatases. This has also been found to be true to PRs, where the equilibrium between transcriptionally active and inactive forms of the receptor is under the regulation of kinases and phosphatases [70,239].

In the mammalian brain, a tissue having an abundance of kinases and phosphatases, protein kinases and protein phosphatases play an important role in phosphorylation of signaling molecules involved in signal transduction mechanisms [194,239]. Neuronal phosphoproteins are components of the signal transduction pathway, initiated by neurotransmitters and cyclic nucleotides [106–108], and can be phosphorylated/dephosphorylated in response to extracellular stimuli. Signal transduction cascades initiated by P and SKF significantly increase hypothalamic intracellular cAMP levels and PKA activities, resulting in enhanced phosphorylation of the neuronal phosphoprotein DARPP-32 on Threonine 34 (Thr^{34}) [166, 260–261]. Phosphorylation of DARPP-32 on Thr^{34} by PKA converts it into a potent inhibitor of serine/threonine protein phosphatase1 (PP1) [121–122,261]. PP1 has broad substrate specificity and controls the state of phosphorylation and activity of numerous physiologically important substrates, including transcription factors, ion pumps, voltage-gated ion channels and neurotransmitter receptors [108,122]. Thus compounds that increase or decrease phospho-Thr^{34} of DARPP-32 inhibit or activate PP1 respectively, thereby increasing or decreasing the state of phosphorylation and activity of large array of downstream physiological effectors [108]. PR and/or its coregulators could be the potential substrate proteins indirectly activated by DARPP-32 (Fig. 5).

A critical requirement of DARPP-32 in the P-and SKF-facilitation of sexual receptivity has been demonstrated in rats and mice [166]. Antisense oligonucleotides to DARPP-32, but not sense oligonucleotides, administered icv into the third cerebral ventricle, inhibited SKF- and P-facilitated sexual receptivity in EB-primed female rats [166]. EB-primed female mice carrying a null mutation for the gene encoding DARPP-32 exhibited significantly lower levels of P- or SKF-facilitated sexual receptivity compared to their wild type littermates. Similar to DA effects in the neostriatum, SKF, as well as P, significantly increased hypothalamic cAMP levels and PKA activities, and enhanced phosphorylation of DARPP-32 on Thr^{34} [166]. SKF-induced increases were inhibited by the D_1 receptor subclass DA antagonist, SCH 23390, indicating that the increases were due to the effects of SKF, initiated at its membrane receptor [166]. P-induced increases, however, were not inhibited by SCH 23390, suggesting that the observed increases were due to the direct effects of P and not secondary to modulation of DA receptors by P [166]. Rp-cAMPS, a compound that blocks cAMP signal transduction cascade by inhibiting PKA, inhibited SKF-and P-facilitated sexual receptivity in EB-primed female rats [166]. These observations indicate that DARPP-32 activation is an obligatory step in the regulation of sexual receptivity. It is likely that the mechanisms include both modulation of DARPP-32, making it an efficient inhibitor of PP1 [108,121] and/or DARPP-32's indirect effects on phosphorylation (activation) of PRs and/or PR-associated coactivators [229–230].

DARPP-32, a 205 amino acid protein is highly conserved in mammals. Studies on DARPP-32 regulation in dopaminoceptive neurons have identified multiple phosphorylation sites on DARPP-32 at Threonine75 (Thr^{75}), Serine102 (Ser^{102}) and Serine 137(Ser^{137}), in addition to Thr^{34} [64]. This multi-site phosphorylation involves enzyme-directed and substrate-directed complex feedback loops and amplifies the effects of DARPP-32, by converting it into a better substrate for phosphorylation at Thr^{34}, by PKA, contributing to its inhibitory effects on the downstream PP1 cascade [108]. A detailed discussion on the regulation of these feedback loops can be found in several publications [172,27,97,138,196,197,260]. While the involvement of the Thr^{34}/Thr^{375} feedback loop on DA-mediated DARPP-32 regulation has been extensively studied in the neostriatum and nucleus accumbens, its role in P- and SKF-regulation of PR-sensitive areas of the hypothalamus is unknown. Interestingly, Casein kinase enzymes I and II, known to phosphorylate DARPP-32 on Ser^{137} and Ser^{102} respectively [71,72,97], also regulate PR phosphorylation [276]. Thus, phosphorylation of serine residues on DARPP-32 could also be critical for P- and SKF-facilitated signals in female reproductive behavior. It is reasonable to speculate that such an intricate regulation of DARPP-32 at the multiple sites could provide a mechanism by which signal amplification is achieved to selectively alter P- and SKF- effects on behavior and physiology.

Interestingly, DARPP-32 also has a critical integrative role mediating the actions of various biogenic amines (DA and serotonin), aminoacids (glutamate and GABA), neuromodulators (adenosine and NO) neuropeptides (opioids, cholecystokinin and neurotensin), steroids (E_2 and P), therapeutic agents (antipsychotics, antidepressants), and drugs of abuse (ethanol, caffeine, cocaine and amphetamine) [247]. Whether DARPP-32 could be involved in all or any of the modulatory effects of neurotransmitters and neuropeptides, on female reproductive behavior in rodents, remains to be examined.

Summary and Conclusions

It is becoming abundantly clear that the integration of the ligand-dependent and ligand-independent mechanisms of PR activation is essential for neuroendocrine regulation of female reproductive behaviors. In addition, multiple intra- and intercellular mechanisms coexist and share signaling components to ensure that the female is in behavioral estrus at the right time. While the functional role of multiple signaling pathways can be explained by their ability to relay, amplify and integrate signals from a variety of extracellular stimuli, the molecular

mechanisms by which this synchronization occurs remains unclear. It will be critical to understand how neuronal kinases and phosphatases, activated by neurotransmitters, regulate the equilibrium between transcriptionally active and inactive states of PRs and their coregulators, in regulating female reproductive behavior. Furthermore, the molecular mechanisms by which this equilibrium could be fine-tuned by neuronal phosphoproteins, such as DARPP-32, functioning perhaps as signal amplifier remain to be established. Future studies will likely reveal further insights into the mechanisms by which the multiple signals converge and reinforce, neuronal responses to environmental and behavioral events, to alter steroid hormone effects on female reproductive behavior.

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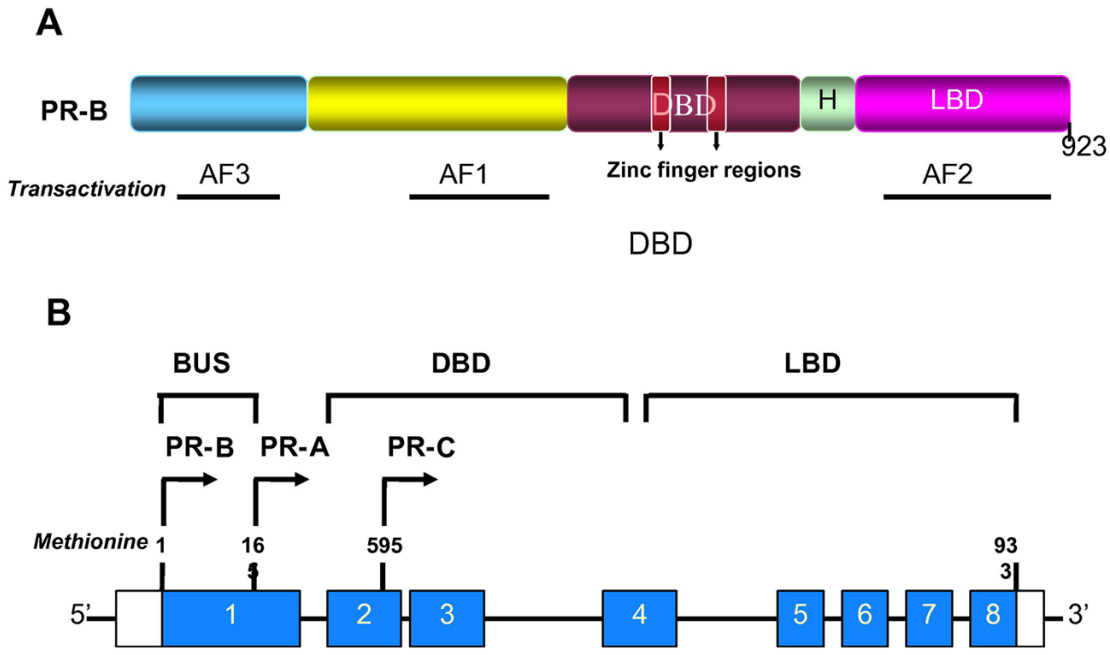

Fig. 1.

Schematic representation of structure and functional organization of progestin receptor (A) and isoforms (B). (A) Progestin receptors (PRs) have a highly conserved DNA binding domain (DBD) and a ligand-binding domain (LBD) connected by a variable Hinge region (H). The N-terminal region contains a transactivation function -1 (AF1). The LBD region contains the AF2 domain. The third activation function domain, AF3 (BUS), is present in the N-terminal segment, and is unique to PR-B. (B) Schematic representation of PR isoforms and splice variants. Nuclear PR gene is composed of 8 exons with 3100-bp coding region and 5′- and 3′-untranslated regions. PR-B and PR-A isoforms are transcribed from two alternate transcription initiation sites. PR-C isoform results from an in-frame initiation of translation and lacks exon 1.

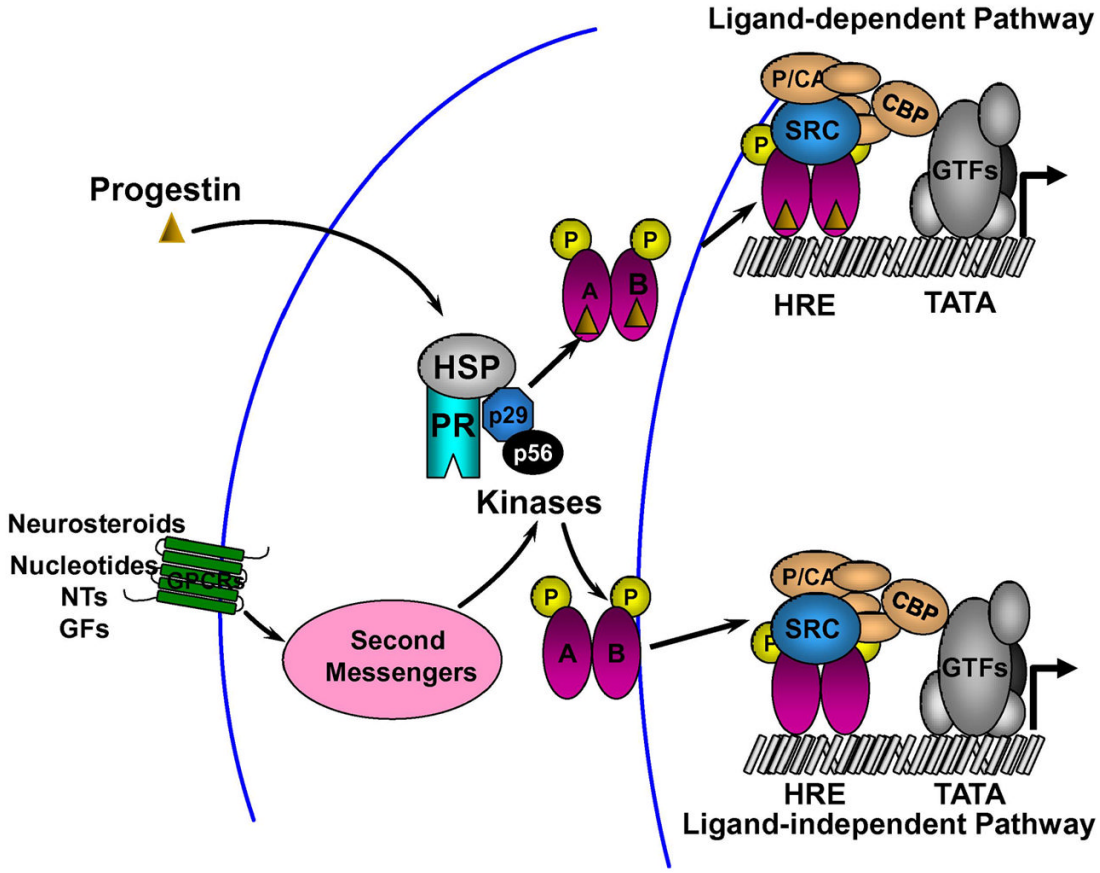

Fig. 2.

Mechanisms of PR activation. Unliganded PR is present as an inactive complex associated with heat shock proteins (HSP) and chaperone proteins (p29, p56) in the cytoplasm. In the classical ligand dependent pathway of activation (LDA), progesterone and other progestins bind to the PR to induce conformational change, dissociation of HSPs and chaperone proteins. PRs undergo dimerization and bind to the hormone response element (HRE) in the target DNA. Ligand-induced conformational change facilitates the recruitment of cofactors and other general transcription factors (GTFs) to the promoter, producing a transcriptionally active complex that can direct gene transcription. Compounds such as cyclic nucleotides, neurotransmitters (NTs), growth factors (GFs) and neurosteroids can activate second messengers and protein kinase pathways to activate PR and/or coactivators in a ligand-independent manner.

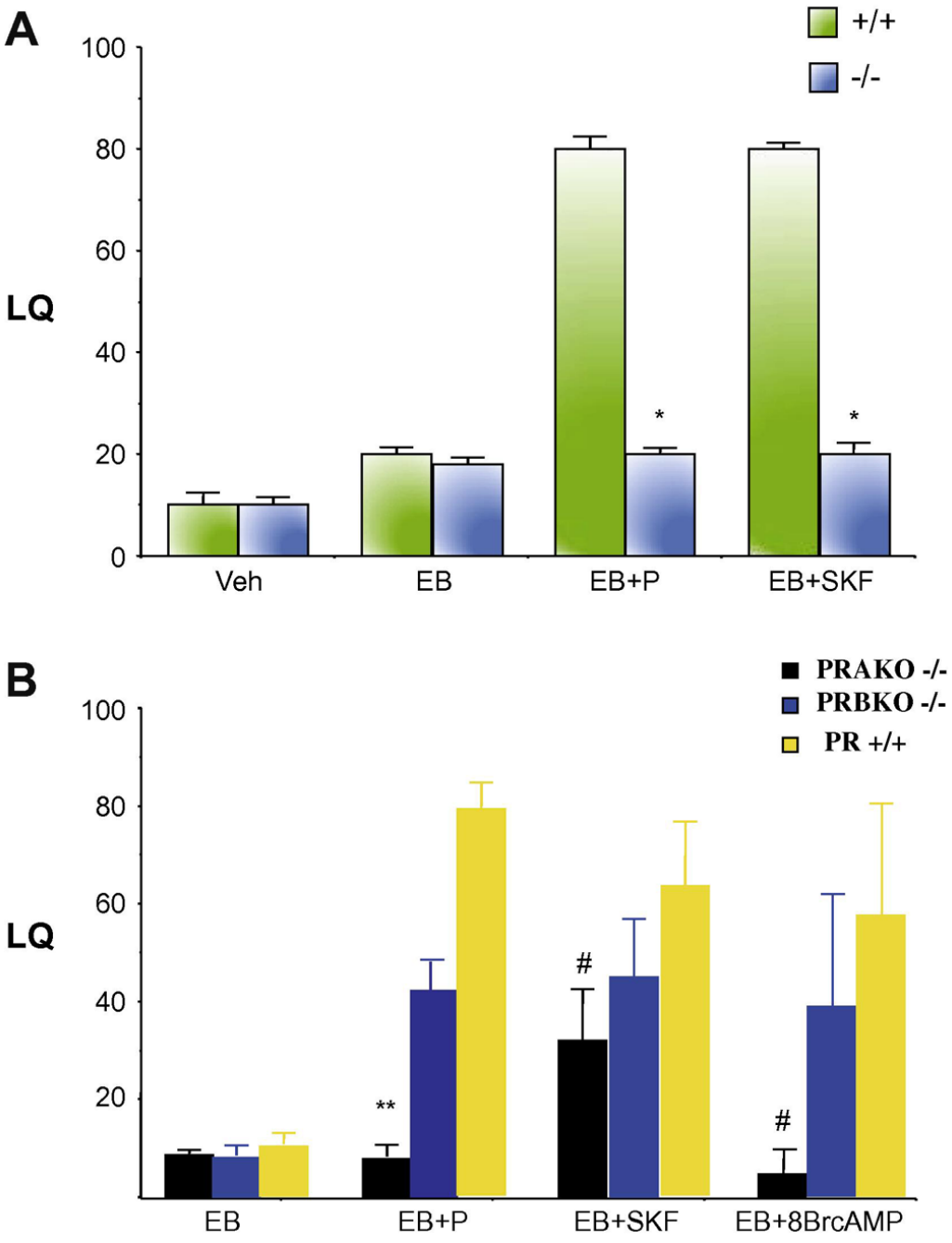

Fig. 3.

Ligand-dependent and –independent activation of nuclear PRs in female reproductive behavior in mice. (a) Ovariectomized, wild type (+/+) and homozygous (−/−) PR mutant mice were primed with estradiol benzoate (EB), followed by intracerebroventricular administration of progesterone (P) or D_1 agonist, SKF38393 (SKF) 48 h later. Female receptive behavior in the presence of a male mouse was quantitated and represented as lordosis quotient (LQ). Statistically significant differences were seen in P- and SKF-facilitated lordosis responses of the −/− compared to their +/+ littermates (*P < 0.001). Adapted from Mani *et al* [165]. (b) Ligand dependent- and -independent induction of sexual receptivity in PR isoform-specific null mutant mice. Ovariectomized $PRAKO^{-/-}$, $PRBKO^{-/-}$ and $PR^{+/+}$ mice were primed with

EB for 48 h, followed by icv administration of progesterone (P), dopamine D_1 agonist SKF 81297 (SKF) or 8-Bromo-cAMP (8-Br-cAMP). P-facilitation of lordosis response was significantly lower in PRAKO$^{-/-}$ null mutants compared to the wild type animals (**$P < 0.05$). Statistically significant differences (#$P < 0.01$) were observed in SKF- and 8-Br-cAMP-treated animals compared with EB-treated controls. Adapted from Mani *et al* [168].

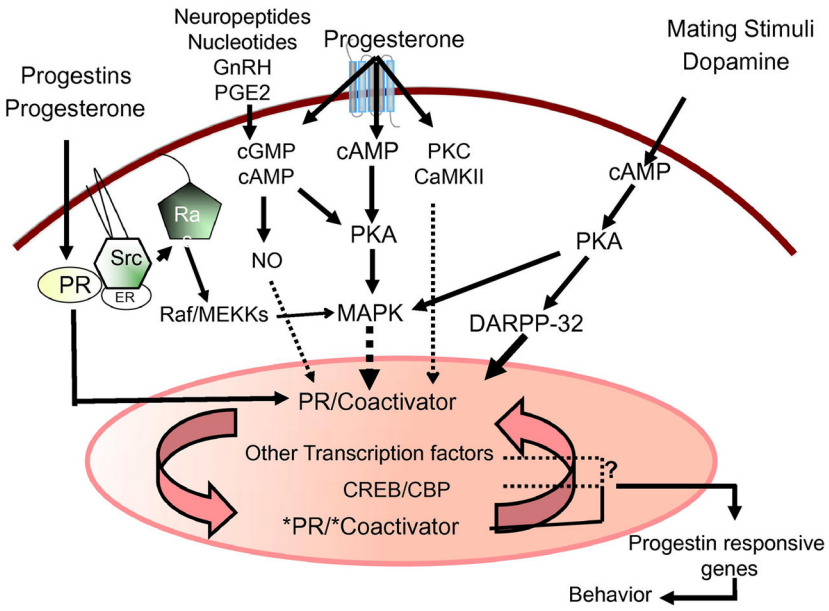

Fig. 4.

Crosstalk between intracellular signaling pathways in female reproductive behavior. The schematic representation of potential signaling pathways operating in the hypothalamus and preoptic areas. (1) Classical genomic mechanism of action by progesterone- and ring-A class of progestins, mediated by nuclear PRs, plays a predominant role. The ligands allosterically bind to their cognate nuclear receptors and activate PRs to promote interactions with coactivator proteins (2) Progesterone effects mediated by second messengers (cAMP, cGMP) and extra-nuclear signaling kinases (PKA, PKC, CaMKII), activates MAPK signal transduction cascade, leading to plausible phosphorylation of nuclear TFs, PRs/PR coactivators, CREB, and/or its associated protein CBP. (3) Progesterone and progestins, act via the Src kinase, to interact with extranuclear PRs and activate MAPK cascade. (4) Progesterone acting via the extra-nuclear PKA/MAPK/DARPP-32 pathway can cause a decrease in phosphatase activity and an increase in phosphorylation of PR and/or its coactivators. (5) Mating stimuli (VCS) and dopamine D_1 agonist can stimulate PKA activation. D_1 agonist-stimulated PKA-mediated pathway phosphorylates DARPP-32, which inhibits PP1, leading to the activation of CREB/PR/coactivators. VCS-stimulated PKA activation can also interact with MAPK cascade. (6) Neuropeptides, nucleotides, GnRH and PGE2 can act through various receptor- and/or second messengers (cAMP, cGMP, NO) and transmit signals to the nuclear PRs or other TFs. Interactions between the signal transduction pathways may serve as an amplification mechanism to converge on nuclear TFs and/or coactivators to regulate gene transcription and translation to facilitate female reproductive behavior.

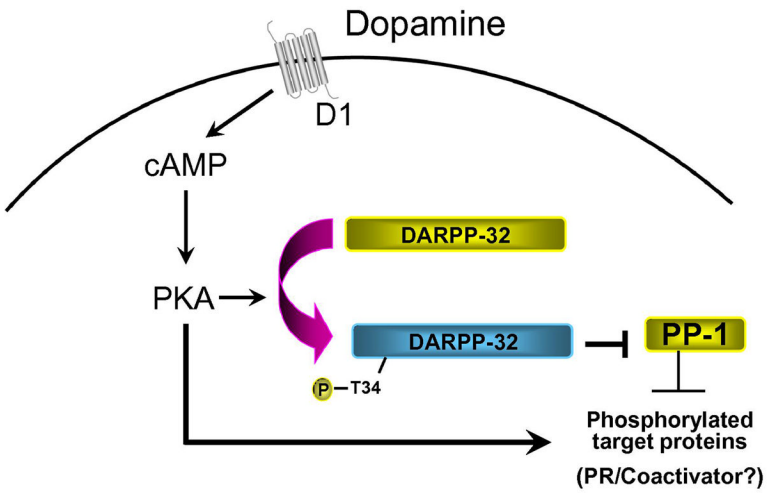

Fig. 5.

Mechanism of dopamine action in the hypothalamus. Dopamine acting via D_1 receptor subtype stimulates an increase in cAMP levels and PKA activity, leading to enhanced phosphorylation of the neuronal phosphoprotein DARPP-32 on Thr^{34}. Phosphorylation of DARPP-32 converts the phosphoprotein to a potent inhibitor of protein phosphatase 1 (PP-1). Phosphatase inhibition leads to increased kinase activity and increased phosphorylation of target proteins including PR and/or coactivators.

Table 1

Factors and pathways linking PR effects on reproductive behaviors

Factors	Pathway(s)	References
Progesterone	PKA/MAPK	[166,100]
Dopamine D1 agonist (SKF28293)	cAMP/PKA/DARP-32	[166]
δ opioids	MAPK	[2]
cAMP	PKA	[166
cGMP	NO	[56,57]
cGMP	PKG/MAPK	[100]
PGE2	PKA	[223]
GnRH	cAMP/PKA/MAPK	[25,103]
5α-pregnan-3, 20-dione (5α-DHP)	MAPK	[100]
5α, 3α-pregnanolone (5α, 3α-Pgl)	MAPK	[100]
Vaginocervical stimulation (VCS)	PKA/MAPK	[102]