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Neural progestin receptors and female sexual behavior

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Abstract

The steroid hormone, progesterone, modulates neuroendocrine functions in the central nervous system resulting in integration of reproduction and reproductive behaviors in female mammals. Although it is widely recognized that progesterone's effects on female sex behavior are mediated by the classical neural progestin receptors (PRs) functioning as "ligand-dependent" transcription factors to regulate genes and genomic networks, additional mechanisms of PR activation also contribute to the behavioral response. Cellular and molecular evidence indicates that PRs can be activated in a ligand-independent manner by neurotransmitters, growth factors, cyclic nucleotides, progestin metabolites and mating stimuli. The rapid responses of progesterone may be mediated by a variety of PR types, including membrane-associated PRs or extra-nuclear PRs. Furthermore, these rapid, non-classical progesterone actions involving cytoplasmic kinase signaling and/or extra-nuclear PRs also converge with classical PR-mediated, transcription dependent pathway to regulate reproductive behaviors. In this review, we summarize some of the history of the study of the role of PRs in reproductive behaviors, and update the status of PR-mediated mechanisms involved in the facilitation of female sex behavior. We present an integrative model of PR activation via crosstalk and convergence of multiple signaling pathways.

Keywords

Progesterone; Progestin Receptors; Dopamine; Non-classical; Signaling; Cross-talk

Introduction

The dominant, model system for studying the cellular mechanisms of progesterone action in the brain remains the estradiol (E_2)/progesterone (P) induction of female sexual behavior in guinea pigs, rats and mice. In the 1930s, a series of experiments performed by W.C. Young and his collaborators demonstrated that female sexual behavior in both rats and guinea pigs required the sequential exposure to E2 followed a day or two later with P [1–4]. These findings were subsequently corroborated in mice [5]. To understand the importance of this work, which provided the model used by many research groups, it is necessary to bear in mind that these studies preceded the availability of chemical tools for assaying blood levels of steroid hormones. The findings that P was essential were not widely accepted [6], because sexual behavior is expressed during the estrous cycle prior to ovulation. However, P was believed to be secreted only by the corpus luteum, a structure that is formed at the time of ovulation. This work predicted the discovery of P secretion from the ovaries *prior* to

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ovulation, which was confirmed three decades later by gas chromatography [7, 8] followed by radioimmunoassay [9, 10].

Early hypotheses of P's cellular mechanisms suggested that P acted by a non-receptor-mediated mechanism. It was originally believed that for Pto act as quickly as it had been shown to facilitate female sexual behavior after intravenous injection in rats (<10 minutes: [11]; < 30 minutes:[12]; 30 minutes [13, 14], the hormone probably acted *via* a mechanism distinct from that of E_2[15], probably by a general membrane stabilization mechanism.

Progesterone action in brain

Although earlier signs from studies using *in vivo* uptake, *in vitro* binding and autoradiographic technique susing radioactively labeled progestins indicated that neural progestin receptors (PRs), which are similar to the previously characterized neural estrogen receptors (ERs), exist in some brain areas [16–22], studies of the physiological and behavioral relevance of the receptors began in earnest with the work of MacLusky and McEwen in 1978 [23]. Using a novel*in vitro* binding assay for brain PRs, these investigators demonstrated that PRs, physicochemically similar to those in peripheral reproductive tissues, were induced by E_2 in some brain areas of rats (pooled hypothalamus-preoptic area-septum), and independent of E_2 in other areas, including the cerebral cortex and amygdala.

Shortly after the characterization of these receptors in rats, a close relationship was reported between E_2-induced PRs in the pooled hypothalamus-preoptic area-septum, midbrain and hypothalamus and P-facilitated behavioral responsiveness in rats and guinea pigs [24–29]. To summarize, when PRs in guinea pig or rat brain are elevated by E_2, animals respond to P; when they are depressed by prior P treatment, they are less responsive (sequential inhibition/refractoriness). This suggested that PRs are essential for mediating both the facilitatory and inhibitory effects of P on female sexual behavior in guinea pigs and rats. Behavioral refractoriness to P is thought to involve degradation of PRs by 26S proteosome activity within the hypothalamus and preoptic areas (POA)[30].

At the time of the characterization of neural PRs, it was widely held that unoccupied steroid hormone receptors were localized in the cytoplasm of cells, and the binding of ligand caused translocation to the cell nucleus where these occupied receptors could be measured by binding assays. It was subsequently reported that many steroid receptors, including unoccupied receptors, reside in the cell nucleus [31, 32]. The development of an assay for what were then called "nuclear PRs," but should more appropriately be referred to as "occupied PRs", led to the observation that the animal's behavioral response to P was dependent on the level of hypothalamic, occupied PRs [13, 33–36].

Autoradiographic techniques provided better anatomical resolution than *in vitro* ligand binding techniques, albeit with low sensitivity. [^{3}H]Progestin binding was detected in parts of the POA, including its suprachiasmatic and periventricular aspect, as well as the ventromedial nucleus of the hypothalamus (VMN) and arcuate nucleus in rats [37, 38] and guinea pigs[21, 22].

The punch microdissection technique provided reasonable anatomical resolution as well as good sensitivity [39, 40]. With this technique, the regions with the highest abundance of E_2-induced PRs were the arcuate nucleus, the VMN, periventricular POA, the periventricular hypothalamus(PVN), the suprachiasmatic preoptic area (SC-POA), and the medial preoptic area (MPOA). Each of these areas also has a high concentration of ERs [41], and the list includes areas important in the regulation of female sexual behavior.

The advent of immunocytochemical techniques for PRs [42, 43] provided greater precision in the localization of the progestin-responsive cells. Consistent with the earlier findings that a subset of PRs was E_2-induced, in virtually all cells in which PR-immunoreactivity (-ir) is dependent onE_2, also have ERs [44, 45].E_2-induced PRs were seen in a variety of brain areas in guinea pigs related to reproduction and reproductive behavior, including the bed nucleus of stria terminalis, periventricular preoptic regions, medial preoptic nucleus, MPOA, ventrolateral nucleus of the hypothalamus (homologous with the VMN in rats), lateral hypothalamus, premammillary nucleus, arcuate nucleus [43, 46, 47], and the midbrain central gray and tegmentum[46]. Other PR-containing areas include the peripeduncular region, parabrachial nucleus of guinea pigs[46]and the hippocampus of rats [48, 49].It is important to note that many of the PR-ir cells in the ventrolateral area of the hypothalamus in guinea pigs [43, 50] and in the VMH in other species that we have examined (Blaustein, unpublished observations) lie outside of the Nissl-defined nuclei. In guinea pigs, they extend upwards in a crescent in proximity to the fornix.

A recent comprehensive analysis of the localization of PR mRNA by *in situ* hybridization (ISH) in E_2-treated, ovariectomized rats found the highest levels of PRs in some of the neural areas that are believed to be involved in reproduction or reproductive behaviors, including medial nucleus of the amygdala, anteroventral periventricular nucleus, arcuate nucleus, MPOA, median preoptic nucleus, anterior hypothalamic area, VMN, periaqueductal gray [51]. Numerous other areas not directly involved in reproduction have high levels, including CA3 pyramidal layer of the hippocampus, zonaincerta, interpeduncular nucleus, and nucleus of the oculomotor cranial nerve, and many other areas have moderate levels of PR mRNA (the reader is referred to Table 1 of reference: [51] for a comprehensive analysis).

The PR is expressed in two isoforms, PR-A and PR-B, that are synthesized from alternate estrogen-inducible promoters on the same gene, as well as alternate transcription start codons (Fig.1; [52, 53]). Tools used in the experiments discussed thus far could not discriminate between these two isoforms, because they bind progestins with equal affinity and are identical with the exception of 164 amino acids on the amino-terminus of PR-B that is absent from PR-A [54]. Relatively little is known about the role of each isoform in brain. However, the two isoforms are expressed in the rat brain [55], and that the ratio of the two isoforms varies under different hormonal [56–59] and mating [60] conditions. Mani et al. [61] used PR isoform-specific knockout strains of mice to determine the relative contribution of each isoform to P-facilitated female sexual behavior. P-facilitated lordosis was completely eliminated in the PR-A null mutant mouse. PR-B null mutant mice showed a trend of suppression of P-facilitated sexual behavior. Collectively the data suggest that PR-A is essential for P-facilitated lordosis, and both isoforms are required for optimal facilitation by P.

Although PRs bind directly to hormone-response elements on the promoters of target genes, PRs, like other steroid hormone receptors, do not act alone. Rather, a complex of coregulators (coactivators that enhance gene expression and corepressor that repress it) interacts to fine-tune gene expression [62]. Since the characterization of the first steroid hormone receptor co-activator, steroid receptor co-activator-1 (SRC-1) in 1995 [63], over 300 coregulators have been discovered [62]. Very few of these coregulators have been studied within the context of ER or PR action in the brain; however, a decrease in SRC-1 expression by infusion of antisense oligonucleotides into the brain decreases the expression of E_2-induced PR-ir in the VMH and the expression of female sexual behavior [64]. SRC-1 and another co-activator, CREB binding protein (CBP) influence the activity of both, ERα and PR [65], in the hormonal regulation of female sexual behaviors. Furthermore, SRC-1 from either hypothalamus or hippocampus, interacts in pull-down assays with ligand-

occupied, ERα, ERβ, PR-A and PR-B in a receptor-specific and brain region-specific manner [66], perhaps helping to explain some of the diverse actions of steroid hormones on the brain. A related co-activator, SRC-2, from hypothalamus and hippocampus interacted with ligand-occupied ERα, PR-B in pull-down assays, but had very little interaction with ERβ and did not interact with PR-A [67].

In order for these coactivators to influence steroid receptor action directly and thereby influence reproductive behaviors, the co-activators must be co-expressed in cells containing steroid hormone receptors in brain areas involved in reproductive behaviors. SRC-1-ir is present in most cells containing estradiol-induced PRs in the VMN, MPOA, and arcuate nucleus, and many in the midbrain central gray [68]. Most cells containing E_2-induced PRs in these areas also express CBP-ir. SRC-2 is also highly expressed within these regions [67] and is expressed in many ERα-ir cells (many of which are likely to co-express PR-ir). Thus, co-activators confer another, complex level of fine-tuning of steroid hormone response systems. Response to P is dependent not only on the presence of sufficient levels of PRs in relevant cells, but also dependent upon, and fine-tuned by the co-expression of a variety of steroid receptor co-activators.

Like ER-ir[69], PR-ir is observed in both cell nuclear, and extranuclear, sites [43] within hypothalamic areas, suggesting extra-nuclear sites of action as well as the classical nuclear site. The notion that ERs and PRs were shunted to distal subcellular sites was supported by work showing that the microtubule inhibitor, colchicine, induced the appearance of ER-ir and PR-ir in some brain areas in which they were not typically seen [70]. These extranuclear receptors may represent receptors *en route* to membrane sites and may explain some of the reported membrane effects of P on sexual behavior [71].

Ligand-independent action of progestin receptors

Although P-dependent activation of neural PRs remains the prevalent model in the regulation of female sexual behavior, alternate mechanisms by which PRs can be indirectly activated cannot be ignored. As early as in the 1970s, non-steroidal agents, gonadotropin releasing hormone (GnRH; [72]) and prostaglandins (PGE_2; [73]) were shown to influence female sexual behavior in rodents, independent of P. Subsequent studies demonstrated that a large number of peptide hormones (e.g., oxytocin, melanocyte stimulating hormone, prolactin, adenocorticotropic hormone), neurotransmitters (e.g., noradrenaline, dopamine, acetylcholine, gamma-aminobutyric acid)and cyclic nucleotides also facilitate female sexual behavior (reviewed in [74–76]).In this context, it is interesting to note that levels of hypothalamic GnRH, PGE_2, oxytocin and dopamine peak in estrous cycling rats concurrently with the rise in P levels, that is, at about the time that the animal exhibits sexual behavior [77–81].However, unlike P, these agents do not bind to PRs. Instead, they acton G-protein coupled membrane receptors to elevate hypothalamic levels of second messengers(cyclic AMP, cyclic GMP, calcium), suggesting that alternate pathways mediated by second messengers indirectly influence female sex behavior[74].We now know that such second messengers can substitute for P in the facilitation of female sex behavior[82]. These observations do not diminish the importance of classical mechanism through which P activated neural PRs mediate transcription-dependent genomic actions to influence sexual behavior. Indeed, studies using PR antagonists, protein and RNA synthesis inhibitors [83–86], antisense oligonucleotides to PR[87–89], and mutant mice with targeted deletion of PR gene[90] provide substantial proof that PR- mediated classical mechanism plays an important role in the facilitation of female sexual behavior.

Studies demonstrating that factors, other than its cognate ligands, can activate PRs have led to a better understanding of the mechanisms involved in the regulation of female sex

behavior. This mechanism termed “Ligand-independent activation” was first demonstrated in dopamine (DA) facilitation of sexual behavior. Although it was known that DA could substitute for P in the facilitation of female sexual behavior [91], the demonstration that this behavior involved ligand-independent activation of PRs by DA provided the molecular underpinnings for the observed effects and highlighted a great degree of cross-talk between P- and DA-initiated pathways [90, 92].

Using biochemical and molecular tools, Mani *et al.*[93] demonstrated that both P and DA initiate second messenger signaling cascades involving increases in 3’-5’-cyclic adenosine mono phosphate(cAMP) levels, activation of protein kinase A (PKA) and phosphorylation of neuronal phosphoprotein, dopamine and cAMP regulated phosphoprotein-32 (DARPP-32), leading to the alterations in phosphorylation dynamics and activation of PRs and/or its coregulators in the hypothalamus. Homozygous mice carrying a null mutation for DARPP-32 gene exhibited significantly reduced P- and DA-facilitated female sexual receptive behavior compared to their wild type littermates, reinforcing the obligatory role of DARPP-32 in PR-mediated ligand-independent activation mechanism[93]. While the observations indicate that DARPP-32 activation is an obligatory step in PR regulation of sexual receptivity, the subsequent sequence of events leading to the activation of PR have yet to be defined. It is likely that the mechanisms include, not only a direct phosphorylation and activation of PR, but also enhanced phosphorylation of a distinct, yet diverse, set of PR-associated coactivators leading to rapid efficient transcriptional activation [54, 94–97]. Furthermore, ligand-independent activation by DA requires the expression of both PR-A and PR-B isoforms, since both PR-A and PR-B mutant mice displayed reduced female sexual behavior [61].

Ligand-independent activation of PRs is also observed in other physiological processes associated with female sexual behavior. Mating related stimuli induced by copulatory attempts by a male rodent, or manually by the experimenter, activate PRs in the absence of P [98–101]. Since mating stimulation induces DA release[102–105]and immediate early gene response (Fos) in PR-containing neurons [106], it is possible that DA activates PRs via ligand-independent activation mechanism. Ligand-independent activation of PRs also appears to play a role in VCS-, GnRH-, PGE2-, δ opioid-, nitric oxide-, and α1 adrenergic receptor-facilitation of sexual behavior in rats, since PR antagonists inhibit the behavior [107–111]. Thus, ligand-independent activation of PRs by non-ligands, involving cross-talk with second messenger cascades, appears to be a common mechanism mediating female sex behavior in rats and mice and is discussed in the following sections.

Non-classical mechanisms of P action

P also exhibits short-latency effects *via* modulation of putative cell surface PR receptors, ion channels and mechanisms coupled to cytoplasmic second messenger signaling cascades, independent of gene transcription [75, 112, 113]. Since these non-classical effects occur rapidly (in seconds or minutes) and are triggered at the membrane surface, the classical model of nuclear PR-mediation is inadequate to explain these effects. The identification of two types of novel membrane proteins unrelated to classical PRs, membrane PRs (mPRs) and progesterone receptor membrane component 1 (PGRMC1), in the brain suggests the possibility of these proteins in mediating effects [51, 114–117]. mPRs, originally discovered in teleost ovaries, are G-protein coupled receptors, which belong to the seven trans-membrane adiponectin Q receptor (PAQR) family and comprise of at least three subtypes α, β and γ [118, 119]. PGRMC1 (25Dx), a single trans-membrane protein, was originally isolated from porcine liver membranes [120] and has been shown to be regulated by E_2 and P in the VMH of female rat [121].

Real time reverse transcriptase-polymerase chain reaction (RTPCR) and *ISH* studies indicate that both these membrane proteins are present in the rat brain. Sleiter*et al* have reported the presence of mPRα and mPRβ message in the medial basal hypothalamus [115]. mRNA levels of PRB, mPRα and mPRβ, but not of mPRγ and PGRMC1 levels, are elevated in the mediobasal hypothalamus on the afternoon of proestrus, around the time of pre-ovulatory peak of P in cycling rats, suggesting that P action could involve both rapid and classical genomic mechanisms around that period [117]). In contrast, neuroanatomical distribution studies using ISH demonstrated low and homogenous expression of mPRs in the hypothalamus and robust expression in the thalamic nuclei and cortex of estradiol-treated, ovariectomized female rat. In addition, PGRMC1, PGRMC2 and classical PR mRNAs were highly expressed and displayed extensive overlap in the preoptic and hypothalamic nuclei and their projection sites [51]. Furthermore, using realtime RTPCR, Intlekofer and Peterson [116] also demonstrated that P treatment resulted in a significant increase in PGRMC1 mRNA levels in the ventrolateral region of VMN and sexually dimorphic nucleus of the POA, the areas known to be involved in female sexual behavior. While the functional role of these putative membrane receptors remains to be determined, the findings suggest possible interactions of membrane PRs and classical PRs within the same neurons in mediating the effects of P.

In addition to the factors discussed above, ring-A reduced metabolites of P, 5α-dihydroprogesterone and allopregnanolone, facilitate lordosis response in ovariectomized, E_2-primed female rats [122–125]. Since ring-A reduced progestins have decreased affinity for the PRs, direct PR binding is probably not involved in this response. Furthermore, inhibition of this behavioral response by RU 38486, suggests that pathways antagonized by this compound could be involved in the facilitation of sexual behavior [111, 123, 126].Accumulating evidence suggests that several of these agents influence female sexual behavior, by activating extra-nuclear protein kinases A, C and (PKA, PKC, PKC), calcium and calmodulin kinase II (CaMKII) and mitogen activated protein kinase (MAPK) in the VMH and POA in the female rat [30, 74, 111, 127–137].

Integration of mechanisms

Studies till date have identified a high degree of cross-talk between various kinase-initiated pathways (by neurotransmitters, nucleotides and neuropeptides) and nuclear PRs in the brain, suggesting that integration of both rapid membrane and slower genomic actions is an essential component of female sexual behavior. A model depicting the interactions is shown in Figure 2. Classical actions of P, mediated by intracellular PRs functioning as transcription factors, remain the primary mechanism of P action in female sex behavior [65, 90].

Non-classical activation of cytoplasmic signaling pathways, mediated by kinases, whether initiated by non-steroidal agents or by progestins, can affect both transcription-dependent and –independent actions [94, 138–141]. Interactions between membrane-initiated signaling pathways and intracellular classical PRs resulting in transcription-dependent actions have been demonstrated in the ligand-independent activation of PRs by various factors [82, 111, 123]. Transcription-independent response of PR has been reported to involve the interaction of membrane-initiated signaling cascade Src/Ras/Raf/MAPK with the Src homology3 (SH3) domain of Src tyrosine kinases through the PXXXP motif at the N-terminal domain of PRs [140]. Recently, Gonzalez-Flores [30] reported that a specific inhibitor of Src kinase family blocked P-facilitated sex behavior in E_2-primed rat. While this study suggests that Src kinase could be involved, its activation and its interactions with PRs in mediating transcription-independent actions remain unknown. The downstream mechanisms could involve gene expression via multiple transcription factors or transcription coactivators [142, 143].P has been shown to induce transcription of immediate early genes containing CRE-

sequences such as c-fos and c-jun[144] to regulate downstream gene expression, by acting on target AP-1 DNA recognition sequences near promoter elements. In addition, integration of the signaling pathways could occur at the level of steroid receptor coregulators through phosphorylation of coactivators [141].

Summary and conclusions

The original two-step classical model of PR activation has undergone substantial modifications and evolved into a highly complex integrative model involving multiple signaling pathways. Recent studies have provided insights into ligand-dependent and ligand-independent mechanisms of receptor activation and provided a blueprint for the integrative model for PR activation in the regulation of female sexual behavior. It is also becoming abundantly clear that multiple intra- and inter-cellular mechanisms share signaling components that potentially amplify and integrate signals from a variety of stimuli to achieve neuroendocrine integration required for complex behaviors like reproductive behaviors. 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 relevant areas of the brain that contribute to the regulation of female sexual behavior. Furthermore, the molecular mechanisms by which this equilibrium could be fine-tuned by second and third messengers functioning as signal amplifiers 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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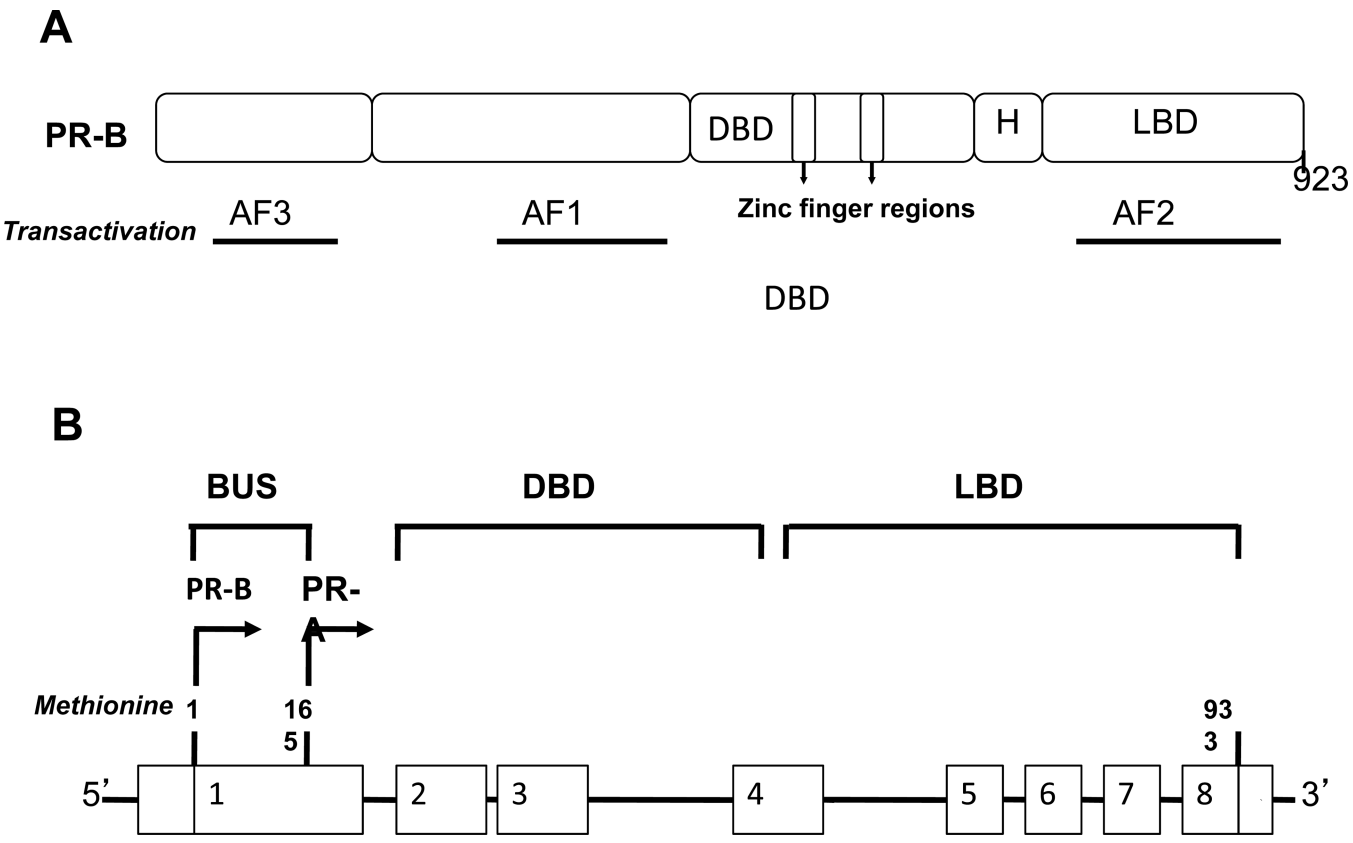

Fig. 1.

Structure and functional organization of progestin receptor (A) and isoforms (B). (A). Progestin receptor (PR) has a conserved DNA-binding domain (DBD) and a ligand binding domain (LBD) connected by a hinge region (H). The N-terminal region contains a transactivation function 1 (AF1) and the LBD contains the AF2 domain. AF3, present in the N-terminal domain is unique to PR-B isoform. (B) Schematic representation of PR isoforms and splice variants. Classical PR gene is composed of 8 exons with 3100bp coding region and 5'- and 3'- untranslated regions. PR-B and PR-A isoforms are transcribed from two alternate transcription initiation sites.

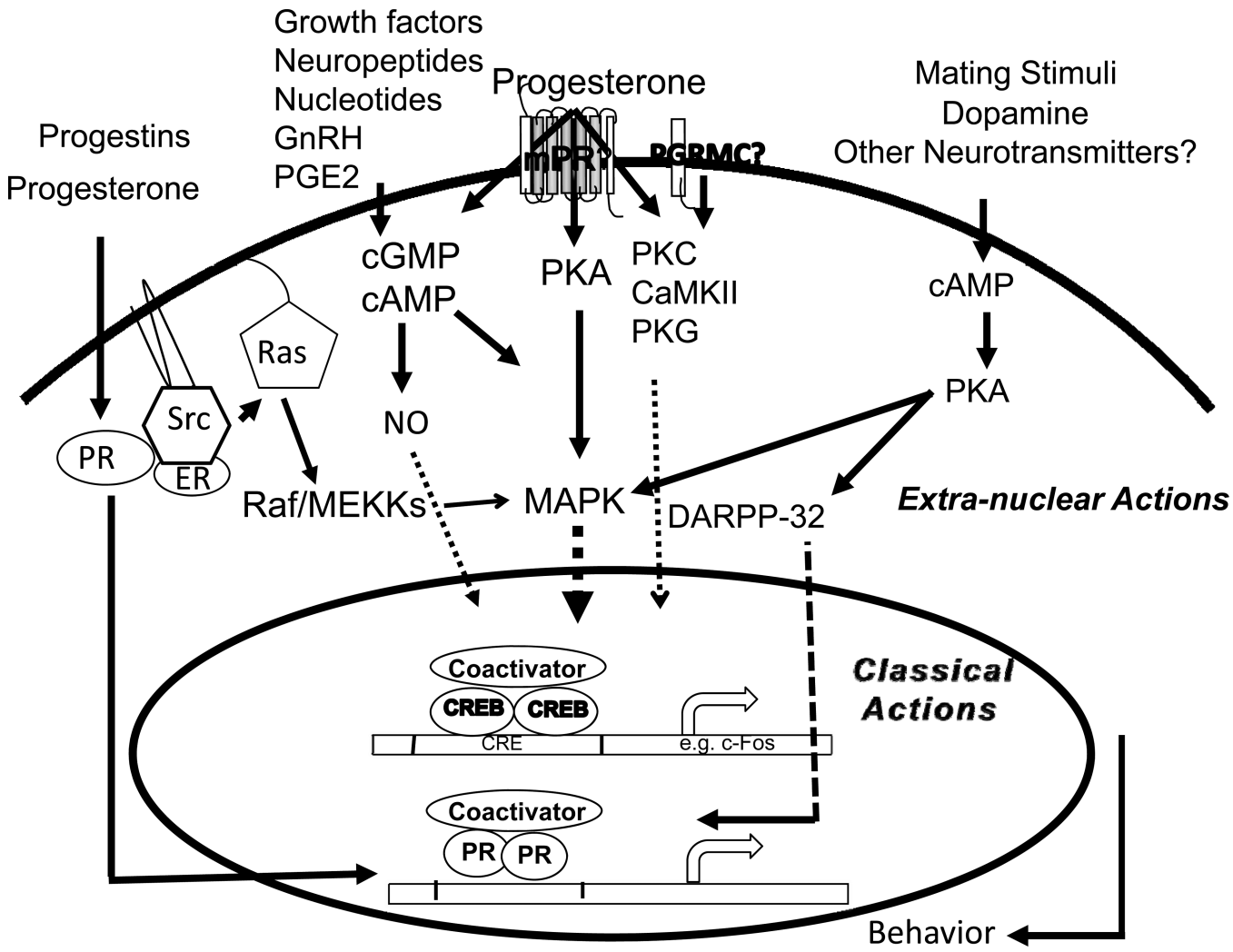

Fig. 2.

A schematic representation of the crosstalk between classical and non-classical mechanisms in female reproductive behavior. Classical mechanism of action by progesterone- and ring-A class of progestins, mediated by classical PRs, promotes interactions with coactivators and plays a predominant role. Progesterone effects mediated by second messengers (cAMP, cGMP) and extra-nuclear signaling kinases (PKA, PKC, PKG, CaMKII) activates MAPK signal transduction cascade, phosphorylation of nuclear transcription factors, PRs/ PR coactivators and CREB. Progesterone and progestins, can act via the Src kinase, interact with extra-nuclear PRs to activate MAPK cascade. 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. Mating stimuli (VCS), dopamine or other neurotransmitters can stimulate PKA activation, phosphorylates DARPP-32, leading to the activation of CREB/PR/coactivators. VCS-stimulated PKA activation can also interact with MAPK cascade. Neuropeptides, nucleotides, growth factors, GnRH and PGE2 can act through various receptor- and/or second messengers (cAMP, cGMP, NO) and transmit signals to the nuclear PRs or other transcription factors. Interactions between multiple pathways may serve as an amplification mechanism to converge on nuclear transcription factors and/or coactivators to regulate gene transcription and translation, to facilitate female sex behavior.