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Progesterone signaling mechanisms in brain and behavior

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Steroid hormone, progesterone, modulates neuroendocrine functions in the central nervous system resulting in alterations in physiology and behavior. These neuronal effects are mediated primarily by intracellular progestin receptors (PRs) in the steroid-sensitive neurons, resulting in transcription-dependent genomic actions (classical mechanism). In addition to progesterone, intracellular PRs can also be activated in a "ligand-independent" manner by neurotransmitters, peptide growth factors, cyclic nucleotides, and neurosteroids. Recent studies indicate that rapid, non-classical progesterone actions involving cytoplasmic kinase signaling and/or extranuclear PRs can result in both transcription-independent and transcription-dependent actions. Cross-talk between extranuclear and classical intracellular signaling pathways promotes progesterone-dependent behavior in mammals. This review focuses on the mechanisms by which progesterone-initiated signaling mechanisms converge with PRs in the brain to modulate reproductive behavior in female rodents.

Keywords: progesterone, progestin receptors, dopamine, non-classical, signaling, cross-talk

INTRODUCTION

Ovarian steroid hormones, estradiol (E_2) and progesterone (P) regulate cellular functions in the central nervous system resulting in alterations in reproductive physiology and behaviors in various species (Young, 1969; Pfaff, 1980; Blaustein and Olster, 1989; Meisel et al., 1990; Pfaff et al., 1994; Blaustein and Mani, 2007; Mani and Portillo, 2010). In addition to reproduction, P plays a role on other biological functions including aggression, maternal behavior, learning and memory, mood, and sexual differentiation (Fraile et al., 1987; Meisel et al., 1990; Flood et al., 1992; Vallee et al., 1997; Wagner et al., 1998; Numan et al., 1999; Bloch et al., 2000; Wagner, 2006; Dreher et al., 2007). While P-initiated mechanisms contributing to these physiological effects are actively being investigated, a wide body of literature exists on P action in reproductive behavior in female rodents. Reproductive behavior can be manipulated in a predictable fashion by sequential treatment of E_2 and P to an ovariectomized female rodent (Young, 1969; Pfaff, 1980; Feder, 1984). This behavior can be measured with a high degree of validity and reliability, and has remained the model of choice for investigations of mechanisms of P action in the brain.

NEURAL PROGESTIN RECEPTORS AND CLASSICAL MECHANISM OF PROGESTERONE ACTION

Although diverse cellular mechanisms have been ascribed to the P action in the brain, the primary mechanism involves its interaction with E_2-induced, intracellular progestin receptors (PRs), which function as transcriptional factors, regulating the expression of genes and genomic neural networks to initiate, and/or sustain physiological response (Blaustein and Olster, 1989; Pfaff et al., 1994). PRs undergo significant conformational change upon binding by progesterone, leading to their nuclear translocation, dimerization, and DNA binding (Tsai and O'Malley, 1994; O'Malley et al., 1995; Mani and O'Malley, 2002). When bound to DNA, PRs interact with basal transcriptional machinery, assisted by coactivator molecules to initiate chromatin remodeling (Horwitz et al., 1996; Katzenellenbogen et al., 1996; McKenna et al., 1999). Phosphorylation of the coactivators also plays a crucial role in the activation of steroid receptors (Rowan et al., 2000b).

This classical, genomic P action mediated by PRs has a delayed onset and is a protracted process. Temporal and functional correlation studies support this delayed action paradigm and suggest that PRs function as transcriptional mediators to regulate target gene transcription and affect the neural networks involved in the control of female reproductive behavior (Pfaff et al., 1994, 2002). The time course of activation and termination of 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 (Dempsey et al., 1936; Blaustein and Feder, 1980; Parsons et al., 1980; Rubin and Barfield, 1983; Brown et al., 1987). Studies using PR antagonists, protein and RNA synthesis inhibitors, antisense oligonucleotides to PR, and mutant mice with targeted deletion of PR gene have highlighted the involvement of PR-mediated genomic mechanism in the mediation of P-facilitated reproductive behavior (Whalen, 1974; Rainbow et al., 1982; Meisel and Pfaff, 1984, 1985; Pollio et al., 1993; Mani et al., 1994c, 1996; Ogawa et al., 1994).

A role for steroid receptor coactivators (SRCs) in PR-mediated female reproductive behaviors has also been reported. Using antisense oligonucleotides for SRC-1 and cAMP response element binding protein (CBP), Molenda et al. (2002) and Molenda-Figueira et al. (2006) demonstrated the requirement of both the coactivators in P-facilitation of female reproductive behavior. Apostolakis et al. (2002) have demonstrated a role for SRC-2 in the PR-mediated female reproductive behavior. Interestingly, a strong

association between PRs and coactivators, SRC-1 and SRC-2, has been demonstrated using pull down assays (Molenda-Figueira et al., 2008; Yore et al., 2010). In addition to the hypothalamus, coactivators are also expressed in various regions of the brain, including the hippocampus, amygdala, and dentate gyrus (Ogawa et al., 2001; Yore et al., 2010).

Multiple PR isoforms have been reported in various P-sensitive tissues and are a result of transcription from different translational sites from a single PR gene (Conneely et al., 1989; Kastner et al., 1990; Kraus et al., 1993). Two major isoforms, PR-A and PR-B, have been reported in the rat brain. PR-B is a full-length protein consisting of 933 amino acids, while PR-A lacks 165 amino acids in the N-terminus. The isoforms have differential expression patterns and are regulated in a region-specific manner in the brain (Mani et al., 2006; Mani, 2008). Studies in mice in which PR-A and PR-B have been mutated have established a critical role for PR-A isoform in the P-facilitation of female reproductive behavior in female mice (Mani et al., 2006). The studies also suggested that PR-A isoform was necessary, but not sufficient, to mediate the full magnitude of the behavioral response in the absence of PR-B isoform (Mani et al., 2006). Interestingly, using antisense oligonucleotides to PR isoforms, Guerra-Araiza et al. (2009) report that PR-B was sufficient for P-facilitation of lordosis response in female rats. Furthermore, 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 E^2-primed female rats (Guerra-Araiza et al., 2009). These reports suggest the critical importance of PR in general, and PR-B isoform in specific, in P metabolite-facilitated female receptive behavior in rats.

Progesterone also plays a role in the termination of sexual behavior during estrous cycle (Sodersten and Hansen, 1977, 1979; Sodersten and Eneroth, 1981) and pregnancy (Baum et al., 1979). Rats, hamsters, guinea pigs, and mice, become refractory to reproductive behavior, upon further stimulation by the administration of P or by E_2 and P (Dempsey et al., 1936; Goy et al., 1966; Carter et al., 1976; Blaustein and Wade, 1977; Morin, 1977; Baum et al., 1979; Fadem et al., 1979; Blaustein, 1982a; Fabre-Nys and Gelez, 2007). This effect is generally referred to as postestrous-refractoriness (Morin, 1977) or sequential inhibition (Blaustein and Wade, 1977; Blaustein and Feder, 1979b) of P, is believed to limit the duration of behavioral estrus and is thought to occur due to P-dependent down-regulation of PRs (Blaustein and Wade, 1977; Blaustein and Feder, 1979b; Blaustein, 1982a). The hyposensitivity to P during this period could be attributable to the inadequate accumulation of occupied nuclear PRs, in response to P (Blaustein and Feder, 1979a, 1980). Administration of high pharmacological dose of P, not only re-instated P responsiveness, but also resulted in an increase in P-occupied hypothalamic PRs (Blaustein, 1982b). 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 (Gonzalez-Flores et al., 2004, 2008; Etgen et al., 2006; Gomez-Camarillo et al., 2011).

NON-CLASSICAL MECHANISMS OF PROGESTERONE ACTION

While genomic effects characterized by a delayed onset have traditionally been assumed to be the primary pathway for progesterone action in the brain, recent studies suggest the involvement of "non-classical" mechanisms of progesterone action. These non-classical short-latency effects of progesterone widely affect cell functioning, through modulation of putative cell surface receptors, ion channels, and mechanisms coupled to cytoplasmic second messenger signaling cascades, independent of gene transcription (Schumacher et al., 1999; Beyer et al., 2003; Leonhardt et al., 2003; Boonyaratanakornkit et al., 2008). Extranuclear rapid and transient activation has been demonstrated to involve mitogen-activated protein kinase (MAPK), independent of PR transcriptional activity in mammalian cells *in vitro* (Migliaccio et al., 1998; Boonyaratanakornkit et al., 2001). P signaling mediated by G protein βγ subunits have 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 (Blackmore, 1998; Ferrell and Machleder, 1998; Ferrell, 1999; Lutz et al., 2000). Rapid effects of steroid hormones have also been demonstrated on the release of LHRH (Ramirez et al., 1990), dopamine and acetylcholine (Meiri, 1986), release of excitatory amino acids (Smith et al., 1987), and changes in neuronal activity (Kelly et al., 1977a,b; Havens and Rose, 1988). In addition to P, several of its ring-A reduced metabolites have been shown to facilitate lordosis response in ovariectomized, E_2-primed female rats via activation of MAPK pathway (Gonzalez-Flores et al., 2004, 2009). Others and we have reported the involvement of at least four extranuclear kinase systems, protein kinase A (PKA), protein kinase C (PKC), calcium and calmodulin kinase II (CaMKII), and protein kinase G (PKG) in the rapid P effects in the VMH and POA of the female rat (Beyer and Gonzalez-Mariscal, 1986; Petitti and Etgen, 1989, 1990; Schumacher et al., 1990; Kow et al., 1994; Chu and Etgen, 1997; Chu et al., 1999; Gonzalez-Flores et al., 2006; Balasubramanian et al., 2008a,b). 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.

MEMBRANE RECEPTORS UNRELATED TO CLASSICAL PRs

Recent evidence suggest the involvement of two types of novel membrane proteins unrelated to classical PRs, progesterone membrane receptor component 1 (PGMRC1) and progesterone membrane receptors (mPRs), in P signaling in several reproductive tissues and in the brain. PGMRC1, unrelated to the classical PR, was originally isolated from porcine liver membranes (Falkenstein et al., 1996, 1998; Meyer et al., 1996; Gerdes et al., 1998). Expression of 25-Dx, a homologous protein in rat (Selmin et al., 1996) was shown to be upregulated by E_2 and down regulated by P in the VMH of female rat (Krebs et al., 2000). The functional role of this protein and its downstream signaling pathway remains to be established.

The mPRs (Mw ∼40 kDa), initially discovered in teleost ovaries, are G protein coupled receptors (GPCRs) that belong to the seven-transmembrane adiponectin Q receptor (PAQR) family, and comprise of at least three subtypes, α, β, and γ.The mPRs localize to the plasma membrane, bind progesterone with high affinity

(K_d ~5 nM) and are involved in progesterone-mediated induction of sea trout meiotic maturation (Zhu et al., 2003a,b) and sperm motility (Tubbs and Thomas, 2008). mPRs are directly coupled to G proteins and activate pertussis-sensitive inhibitory proteins ($G_{i/o}$), to down-regulate adenylyl cyclase activity (Thomas et al., 2007). Human analogs of the mPRs, when expressed in human breast cancer cells, which lack classical PRs, mediate a rapid and transient P-mediated activation of MAPK, and inhibition of cAMP production. Endogenous mPRα and mPRβ in human myometrium was also shown to mediate inhibition of cAMP and to increase myosin light chain phosphorylation resulting in myometrial contraction (Karteris et al., 2006). Progestin upregulation of mPR has been reported to potentiate classical PR-B transactivation by a mechanism involving G_i proteins and a reduction in SRC-2 coactivator levels, suggesting a cross-talk between the membrane and nuclear PRs (Karteris et al., 2006). Sleiter et al. (2009) have reported the presence of mPRα and mPRβ message in the medial basal hypothalamus and their involvement in the negative feedback effects of P on gonadotropin releasing hormone (GnRH) secretion. Using the PR knockout mice and GT1-7 cells, the authors demonstrated that these mPR-mediated P effects inhibit cAMP accumulation (via G_i) and are independent of the classical nuclear PR isoforms, PR-A and PR-B.

LIGAND-INDEPENDENT ACTIVATION OF PRs

Studies in the past decades have demonstrated that PRs can be activated by factors other than P (ligand-independent activation). A number of second messenger molecules, including 3′-5′-cyclic adenosine monophosphate (cAMP), 3′-5′-cyclic guanosine monophosphate (cGMP), nitric oxide (NO), and neurotransmitters have been shown to substitute for P in the facilitation of reproductive behavior in female rats (Mani et al., 1994a,b; Chu and Etgen, 1997; Gonzalez-Flores et al., 2009). Inhibition of MAPK signaling pathway results in reduction of P, dibutyryl-cAMP (db-cAMP)-, prostaglandin E_2 (PGE_2)-, or GnRH-facilitated female reproductive behavior in rats (Gonzalez-Flores et al., 2008). These studies suggest the involvement of multiple signal transduction pathways in female reproductive behavior.

Over the past several years, studies from our laboratory have demonstrated that in addition to P, the neurotransmitter dopamine (DA) can activate neural PRs to facilitate reproductive behavior (Mani et al., 1994a,b,c). Using PR antagonists, antisense oligonucleotides and null mutants for PRs, we demonstrated a critical requirement of classical PRs as transcriptional mediators in the cross-talk between P and DA-initiated pathways in the facilitation of female sexual receptive behavior (Mani et al., 1994a,b,c, 1996). Studies from our laboratory also demonstrated that the DA-initiated second messenger signaling cascade involves the activation of PKA and neuronal phosphoprotein, dopamine and 3′-5′cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein-32 (DARPP-32), leading to the alterations in the phosphorylation dynamics and activation of PRs and/or its coregulators in the hypothalamus (Mani et al., 1996, 2000, 2006; Mani, 2006). Interestingly, using PR-A and PR-B mutant mice Mani et al. (2006) demonstrated that both PR-A and PR-B isoforms are essential for the expression of the full complement of DA-facilitated female reproductive behavior.

Ligand-independent activation of PRs has also been observed in behaviorally relevant stimuli such as the vaginal–cervical stimulation (VCS; Auger et al., 1996, 1997). Administration of the progesterone antagonist RU38486 to estradiol-primed female rats blocked sexual receptive responses to mating stimuli by VCS or mounting by a male rat, suggesting that the somatosensory information provided by the either of the stimuli could be due to ligand-independent activation of PRs. Induction of the immediate early gene (IEG) "Fos" was reduced in PR-rich areas like the medial POA and ventromedial nucleus of the hypothalamus upon RU38486 treatment (Auger et al., 2000). Based on PR immunostaining studies, Auger et al. (2000) suggest that PRs could be activated differentially by progesterone-dependent or progesterone-independent mechanisms, possibly leading to different neuronal consequences.

While the precise mechanism of ligand-independent activation of PRs has remained elusive, several studies suggest the involvement of PR phosphorylation in this mechanism. PKA inhibitors inhibit PR activation, suggesting that PR-mediated transcription could be modulated by phosphorylation of PR or other proteins in the transcription complex (Denner et al., 1990a,b; Rowan et al., 2000a,b). Growth factor-initiated signaling pathways (EGF and heregulin) enhance phosphorylation of PRs on distinct amino acids (Hagan et al., 2011). Enhanced phosphorylation can result in rapid nuclear translocation of unliganded PRs and nuclear export of liganded PRs, suggesting that kinase signaling could regulate PR nuclear sequestration, by altering nucleo-cytoplasmic shuttling (Labriola et al., 2003; Qiu and Lange, 2003; Qiu et al., 2003). PR sequestration in the nucleus protects inactive and active PRs from degradation by the 26S proteosome pathway (Qiu and Lange, 2003; Qiu et al., 2003). Activated calcium-dependent kinase 2 (Cdk2) mediates transcriptional activation of PR by phosphorylating Ser400 moiety in the PR in a ligand-independent manner (Pierson-Mullany and Lange, 2004). Furthermore, cAMP-dependent activation of PR does not involve direct phosphorylation of PR, but involves phosphorylation of SRC-1, to bring about the functional cooperation of SRC-1 and CREB-binding protein (Bai and Weigel, 1995; Rowan et al., 2000a,b; Narayanan et al., 2005).

INTEGRATION OF NON-CLASSICAL AND CLASSICAL MECHANISMS OF P ACTION

Classical PRs are not kinases, nor do they possess other known features of signaling molecules, leading to the questions on how they can interact with signaling molecules in a P-dependent manner and how this interaction can trigger a signaling cascade. The answers perhaps lie not only in mPR-mediated signaling, but also in the proline-rich PXXP motif located in the N-terminal domain of PRs. Studies have implicated c-sarcoma (Src) tyrosine kinase as a key molecule in mediating P-initiated rapid signaling (Thomas and Brugge, 1997). Unliganded and liganded classical PRs have been shown to participate in cytoplasmic or membrane-associated signaling complexes that activate Src/Ras/Raf/MAPK signaling pathway in mammalian cells by a direct interaction with the Src homology 3 (SH3) domain of Src tyrosine kinases through the PXXP motif. MAPK activation can lead to phosphorylation of PRs and/or transcriptional coactivators, which can activate transcription directly by binding to progesterone response elements.

Mutation of the nuclear localization signal of PR, which forces PR to the cytoplasm, enables P-dependent activation of c-Src and MAPK confirming that cytoplasmic localization was essential for c-Src-mediated signaling cascade (Boonyaratanakornkit et al., 2001).

Progesterone actions appear to involve integration of rapid membrane and slower genomic actions of P. Rapid non-classical activation of cytoplasmic signaling pathways by P can alter both transcription-independent and transcription-dependent actions (Boonyaratanakornkit et al., 2001; Faivre et al., 2005; Proietti et al., 2005; Faivre and Lange, 2007; Hagan et al., 2011). Rapid signaling can enhance transcription of the classical PRs through activation of signaling cascades that ultimately phosphorylate classical PRs *per se* (Denner et al., 1990b) and/or the phosphorylation of the coactivators (Denner et al., 1990b; Font de Mora and Brown, 2000; Rowan et al., 2000a,b; Xu et al., 2000). Interactions between membrane-initiated P effects and intracellular classical PRs have been observed in the facilitation of sexual behavior in female hamsters (DeBold and Frye, 1994a,b) suggesting that both classical and non-classical mechanisms act in concert rather than independently. Studies on activation of PRs by growth factors (Zhang et al., 1994; Etgen et al., 2006), neurotransmitters (Mani et al., 1994a,b, 1996, 2000; Chu et al., 1999) and peptide hormones (Chappell and Levine, 2000; Gonzalez-Flores et al., 2009) suggest that classical and non-classical mechanisms are not mutually exclusive and signals generated at the membranes enhance gene expression regulated by classical intracellular hormone receptors. Cytoplasmic second messenger systems have been shown to modulate gene expression via multiple transcription factors or transcription coactivators (Watters et al., 1997; Watters and Dorsa, 1998). 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 (Gu et al., 1996; Zhou et al., 1996). 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 (Gu et al., 1996). These rapid effects on CREB phosphorylation also appear to be nuclear receptor-mediated since anti-hormones to ER and PR block the hormonal effects on CREB phosphorylation suggesting a cross-talk between the distinct signaling pathways. P has been shown to induce transcription of IEGs containing CRE-sequences such as *c-fos* and *c-jun* (Meredith et al., 1997). These genes encode the transcription factors, Fos and Jun, that can form

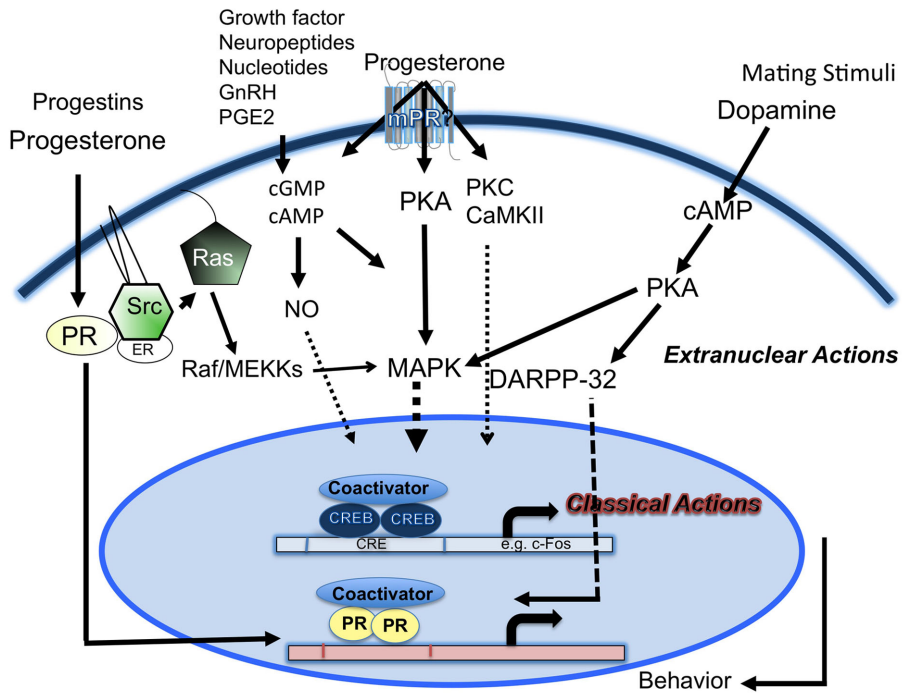

FIGURE 1 | A schematic representation of the cross-talk between extracellular and intracellular progesterone signaling pathways in female reproductive behavior. Classical mechanism of action by progesterone- and ring-A class of progestins, mediated by nuclear PRs, promotes interactions with coactivators, and plays a predominant role. Progesterone effects mediated by second messengers (cAMP, cGMP) and extranuclear signaling kinases (PKA, PKC, CaMKII), activates MAPK signal transduction cascade, phosphorylation of nuclear transcription factors (TFs), PRs/PR coactivators, and CREB. Progesterone and progestins, act via the Src kinase, interact with extranuclear PRs to activate MAPK cascade. Progesterone acting via the extranuclear 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) 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. Neuropeptides, nucleotides, GnRH, and PGE_2 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.

hetero- or homodimers and regulate downstream gene expression by acting on target AP-1 DNA recognition sequences near promoter elements. In addition, recent studies have also indicated that nuclear receptor coregulators could also integrate steroid hormone signaling through CBP (Torchia et al., 1997; Mahajan and Samuels, 2000; Xu et al., 2000). Functional cooperation between MAPK cascade-mediated phosphorylation of coactivator SRC-1 and CBP has been demonstrated in the activation nuclear PRs *in vitro* (Rowan et al., 2000a).

SUMMARY

Integration of the extranuclear and intranuclear steroid signaling mechanisms PR activation is essential for neuroendocrine regulation of female reproductive behaviors. The interplay between the non-classical and classical pathways activated by P could be a "reinforcing" mechanism to achieve neuroendocrine integration required for complex behaviors like reproductive behaviors. The amplification process involving extranuclear signaling perhaps absolves the necessity for voluminous classic PR expression in the early stages of P action. A model depicting the interactions is given in **Figure 1**. Classical genomic pathway mediated by intracellular PRs, functioning as transcription factors, induces conformational changes, nuclear translocation, dimerization, and binding to PREs in the promoters of target genes. Downstream cytoplasmic signaling cascades can mediate the non-classical mechanisms. Alternatively, a subpopulation of classic PRs localized in the cytoplasm can lead to the activation of the downstream kinase cascades. A biologic consequence of the cytoplasmic signaling cascades is to influence gene transcription.

Multiple intra- and intercellular signaling mechanisms 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 extranuclear signaling mechanisms regulate the equilibrium between transcriptionally active and inactive states of PRs and their coregulators, in regulating female reproductive behavior. 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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