INTRODUCTION

It is now clear that actions of progesterone (P₄) in the nervous system go beyond its well-studied roles in regulating gonadotropin-releasing hormone (GnRH) release and feminine sexual behaviors (Chabbert-Buffeta et al., 2000; Mani and Blaustein, 2012). P₄ also modulates such diverse processes as neuroprotection and neurogenesis (Bali et al., 2012) and neuroinflammation (Giatti et al., 2013). Therefore, it is not surprising that, in addition to the classical progesterin receptor (PR), P₄ exerts effects through multiple non-classical receptors.

Two groups of putative non-classical signaling molecules have emerged as likely mediators of P₄ actions in the nervous system. One group consists of membrane P₄ receptors (mPRs) that belong to the progestin and adipoQ receptor (PAQR) family. Five of these molecules, mPRα, mPRβ, mPRγ, mPRδ, and mPRε, are found in the brain (Thomas and Pang, 2012; Pang et al., 2013). These receptors contain seven-trans-membrane domains and are thought to be unique G protein-coupled receptors that act through cAMP (Thomas and Pang, 2012). Of these receptors, mPRα, mPRδ, and mPRγ decrease cellular accumulation of cAMP, while mPRδ and mPRε increase accumulation (Karteris et al., 2006; Pang et al., 2013). There is evidence that mPRs are not always found in the plasma membrane or coupled to G proteins (Ashley et al., 2006; Krietsch et al., 2006; Smith et al., 2008). Thus, it has been suggested that they may function as alkaline ceramidases, enzymes that deacylate ceramides to produce lipid second messengers (Villa et al., 2009; Moussatche and Lyons, 2012). However, there is yet little data from mammalian cells to support this idea.

Members of a second group of molecules are structurally similar in that each contains a highly conserved cytochrome b5-heme/steroid-binding domain (Kimura et al., 2012). This group includes progesterone receptor membrane component 1 (PGRMC1; also known as 25DX (Selmin et al., 1996)), PGRMC2, neudesin, and neuferricin. Results of our recent mapping studies show that members of the PGRMC1/S2R family, but not mPRs, are quite abundant in forebrain structures important for neuroendocrine regulation and other non-genomic effects of P₄. Herein we describe the structures, neuroanatomical localization, and signaling mechanisms of these molecules. We also discuss possible roles for Pgrmc1/S2R in gonadotropin release, feminine sexual behaviors, fluid balance and neuroprotection, as well as catamenial epilepsy.

Keywords: PGR, PGRMC1, 25DX, PAQR, MPR

LOCALIZATION OF P₄ SIGNALING MOLECULES IN SPECIFIC NUCLEI OF THE BRAIN

Although mPRs and PGRMC1-related molecules are found in the brain, most early studies did not compare the distributions...
of these molecules using techniques that provide detailed neuroanatomical information. Such information gives important clues to the functions regulated by the various receptors. Therefore, we used in situ hybridization (ISH) to map genes encoding PR, mPRα, mPRβ and PGRMC1, as well as its binding partners PGRMC2 and SERPINE1 mRNA binding protein 1 (SERBP1), throughout the rat forebrain (Intlekofer and Petersen, 2011).

Somewhat surprisingly, neither mPRα nor mPRβ is expressed specifically in neuroendocrine or other nuclei that mediate P₄ functions (Intlekofer and Petersen, 2011). Moreover, for very high mPRβ mRNA levels in the nucleus of the oculomotor cranial nerve, mPRα and mPRβ expression is generally homogeneous and relatively low throughout the forebrain. In contrast, mRNAs encoding PGRMC1, PGRMC2 and SERBP1 are found in discrete neuroendocrine nuclei and in hippocampal, cortical and cerebellar regions that control functions modulated by P₄ (Intlekofer and Petersen, 2011). More recently, we mapped expression of mPRδ and mPRε mRNAs in the rat forebrain and found no specific signal for either of these mRNAs (Moura-Conlon and Petersen, unpublished data).

Neufericin is a recently discovered extracellular heme-binding protein that facilitates neurogenesis in cultured progenitor cells (Kimura et al., 2010). In preliminary in situ hybridization studies, we failed to detect neufericin mRNA in the rat forebrain. In contrast, the distribution pattern of neudesin gene expression is strikingly similar to that of pr in the rat forebrain, particularly in regions containing the anteroventral periventricular, arcuate, and the ventromedial nuclei [compare Figure 1 and (Simerly et al., 1996; Shughrue et al., 1997)]. This 171-amino acid secreted protein is expressed in neural, but not glial cells (Kimura et al., 2005). Similarly, it promotes differentiation of neurons and inhibits differentiation of astrocytes (Kimura et al., 2006). Neudesin exerts these effects through protein kinase and phosphatidylinositol-3 kinase pathways (Kimura et al., 2006), and its cytochrome b₅-like heme/steroid-binding domain is also required (Kimura et al., 2008). The role of neudesin in the regulation of adult neural functions is unclear, but the striking similarity of the neudesin and PR mRNA distribution patterns (Figure 1) suggests the possibility that neudesin may act in concert with PR to regulate neuroendocrine functions.

Our neuroanatomical findings indicate that pgrmc1 is the most abundant putative membrane P₄ receptor gene expressed in neuroendocrine regions; therefore, this review focuses on possible roles of PGRMC1 in regulating some of these functions. For a more detailed review of all the putative non-classical P₄ signaling molecules, see (Petersen et al., 2013).

STRUCTURES OF PGRMC1 AND PGRMC2

PGRMC1 has been partially purified from liver membranes (Meyer et al., 1996), spontaneously immortalized rat granulosa cells (Peluso et al., 2008), and human granulosa/luteal cells (Peluso et al., 2009). Results of studies using these preparations suggests that PGRMC1 binds P₄ with high affinity [kₐ estimates of 10, 11, and 35 nM (Meyer et al., 1996; Peluso et al., 2008, 2009)]. However, the idea that PGRMC1 alone binds P₄ is not universally accepted (Rohe et al., 2009). For example, Min et al. found that GST-tagged rat inner zone antigen [found to be identical to PGRMC1; see (Cahill, 2007)] expressed in E. coli did not bind P₄ in pull-down assays (Min et al., 2005).

It is possible that there are other P₄-binding proteins in the partially purified preparations wherein binding has been detected (Meyer et al., 1996; Peluso et al., 2008, 2009), but studies in rat granulosa cells suggest that PGRMC1 accounts for the specific P₄ binding. Peluso and colleagues showed that partially purified GFP-PGRMC1 fusion protein binds P₄ with nM affinity and deletions in various parts of the PGRMC1 molecule reduce P₄ binding (Peluso et al., 2008). SERBP1 (also called plasminogen activator inhibitor 1 RNA binding protein; PAIRBP1) is important for PGRMC1 functions (Peluso et al., 2013), but the P₄ binding site on PGRMC1 and the site for SERBP1 interaction differ (Peluso et al., 2008). In addition, depletion of SERBP1 increases, rather than decreases, P₄ binding in spontaneously immortalized granulosa cells (Peluso et al., 2013). Finally, perhaps the most compelling evidence that PGRMC1 binds P₄ comes from work showing that knockdown of PGRMC1 by 60% reduces P₄ binding by the same percentage (Peluso et al., 2008).

Few studies have examined binding of steroids other than P₄ to PGRMC1. Early work characterizing PGRMC1 showed that P₄, but not dexamethasone, aldosterone or β-estradiol bind specifically to partially purified PGRMC1 in microsomal or solubilized membrane fractions from porcine liver (Meyer et al., 1996). In the same studies, it was found that corticosterone and testosterone bind with affinities ~25% that of P₄, and cortisol with a relative affinity of 4%. Thus, PGRMC1 appears to preferentially bind P₄.

PGRMC1 is relatively small [194 amino acids (Falkenstein et al., 1996)] with a molecular weight estimated between 25 and 28kDa (Meyer et al., 1996; Selmin et al., 1996; Raza et al., 2001; Peluso et al., 2009). However, higher molecular weight molecules can also be detected and likely represent dimers (Meyer et al., 1996), multimers (Losel et al., 2005), or molecules...
modified post-translationally through sumoylation or other pro-
cesses (Peluso et al., 2012). PGRMC1 contains an N-terminal extracellular domain, a transmembrane domain, and a cytoplas-
mic region with a heme-binding domain (Peluso et al., 2006; 
Cahill, 2007).

Consistent with evidence that PGRMCI and sigma-2 recep-
tors are the same protein (Xu et al., 2011), the two molecules have 
 similar steroid hormone-binding profiles with high affinity for P4 
(Meyer et al., 1996; Peluso et al., 2008). Moreover, sigma-2 ligand 
binding colocalizes with PGRMC1 expression in the endoplasmic 
reticulum (ER) and mitochondria (Xu et al., 2011). In addition, 
changes in PGRMC1 levels correlate with changes in sigma-2 lig-
and binding (Xu et al., 2011). Finally, sigma-2 receptors regulate 
intracellular calcium levels (Vilner and Bowen, 2000) and apopto-
sis (Vilner and Bowen, 1993; Vilner et al., 1995), as does PGRMC1 
(Viero et al., 2006; Peluso et al., 2008; Bashour and Wray, 2012; 
Lai et al., 2012).

PGRMC2 is structurally similar to PGRMC1 (Cahill, 2007; 
Wendler and Wehling, 2013), except in the N-terminus and trans-
membrane domain. This finding may explain why PGRMC2 does 
not bind P4 (Peluso, Pers. Commun.), because the P4 binding 
site of PGRMC1 is in the transmembrane domain [26]. In con-
trast, PGRMC1 and PGRMC2 both bind the same members of a 
group of heme-containing molecules, the cytochrome P450 pro-
teins (Albrecht et al., 2012), suggesting that the heme-binding 
sites function similarly in PGRMC1 and PGRMC2. It is notable 
that PGRMC2 expression widely overlaps that of PGRMC1 in 
brain nuclei (Intlekofer and Petersen, 2011). However, the role of 
PGRMC2 in P4 signaling in the nervous system or in other tissues 
remains unclear.

POSSIBLE ROLES FOR PGRMC1 IN REGULATING RAPID 
NEUROENDOCRINE RESPONSES

GONADOTROPIN RELEASE

Most studies examining PGRMC1 functions have focused on 
non-neural reproductive tissues such as the ovary (Kowalik and 
Kotwica, 2008; Peluso, 2011) and uterus (Zhang et al., 2008). 
Results of our neuroanatomical studies suggest that PGRMC1 
and its partners also regulate the neural structures that control 
reproductive functions. The region in which mRNAs encoding 
PGRMC1, PGRMC2 and SERBP1 are highest is the antero-
ventral periventricular nucleus (AVPV), a group of cells in which E2 
acts to induce luteinizing hormone (LH) surge release and ovu-
lution in rodents (Petersen et al., 2003). E2 triggers the LH surge 
mechanism, at least in part, by upregulating PR expression in the 
AVPV (Chappell and Levine, 2000) and by increasing synthesis of 
neurosteroids in the region (Micevych and Sinchak, 2008, 2011). 
The surge is then rapidly amplified by rising levels of circulat-
ing P4 (Levine, 1997). Based on the high levels of expression 
in the AVPV, it is possible that PGRMC1 may mediate one or both 
of these rapid effects of P4. Unfortunately, this idea is difficult to 
test because the LH surge does not occur in the absence of PR 
(Chappell et al., 1997, 1999).

One possible way in which PGRMC1 might enhance LH 
surge release is by increasing neurosteroid synthesis in the AVPV. 
Local steroid production in the AVPV is important for the LH 
surge (Micevych and Sinchak, 2011) and PGRMC1 enhances the 
activity of cytochrome P450 (Cyp) enzymes involved in steroid 
synthesis (Hughes et al., 2007; Rohe et al., 2009; Ahmed et al., 
2012). For example, through its heme-binding site, PGRMC1 
binds to and enhances the activity of Cyp51, an enzyme necessary 
for the conversion of lanosterol to cholesterol (Craven et al., 2007; 
Hughes et al., 2007). This is a key finding because cholesterol does 
not appear to be synthesized in the brain (Bjorkhem and Meaney, 
2004). Similarly, PGRMC1 activates Cyp19 aromatase, an enzyme 
necessary for E2 synthesis (Ahmed et al., 2012), a hormone that 
acts in the AVPV to induce the LH surge (Petersen et al., 2003). 
It has not yet been determined whether PGRMC1 regulates the 
activity of other heme-dependent Cyp enzymes involved in P4 
synthesis or its metabolism to other neuroactive progestins such 
as allopregnanolone. However, it seems likely considering that 
PGRMC1 regulates nearly all Cyp enzymes tested to date (Ahmed 
et al., 2012). Thus, PGRMC1 may indirectly amplify the preovu-
latory LH surge by enhancing activity of enzymes involved in 
neurosteroid synthesis and metabolism.

It is also possible that PGRMC1 mediates rapid inhibitory 
effects of P4 on LH release. Both PGRMC1 and SERBP1 are detected in 
nearly all GnRH neurons of embryonic explants, (Bashour and Wray, 2012). Similarly, PGRMC1 is found in 
immortalized GnRH neurons, GT1-7 cells (Krebs et al., 2000). As 
on-neural cells (Peluso et al., 2002), P4 rapidly inhibits fluc-
tuations in intracellular calcium levels in GnRH neurons through 
mechanisms that do not involve GABA_A receptors (Bashour and Wray, 2012) as have been described previously in embry-
onic sensory neurons (Viero et al., 2006). Rather, a putative 
PGRMC1 antagonist blocks the inhibitory effect of P4 and, 
consistent with evidence that PGRMC1 signals through PKG 
(Peluso and Pappalardo, 2004; Peluso et al., 2007), PKG inhibitors 
block P4 inhibition of calcium flux in explant GnRH neurons 
(Bashour and Wray, 2012). Thus, PGRMC1 may be important 
for turning off the LH surge or limiting it to one day of the 
cycle.

PGRMC1 is also interesting in the context of sexual dif-
erentiation of brain nuclei, particularly of preoptic area and 
hypothalamic nuclei that develop through sex-specific and E2-
regulated apoptosis. Sexual differentiation of the AVPV occurs 
during the perinatal period when the developing testes, but not 
 ovaries, are active. In the male AVPV, testosterone is aromatized to 
E2 and this hormone triggers apoptosis (Arai et al., 1996; Forger, 
2009; Tsukahara, 2009) and dememinization of LH release mech-
аниsms. Importantly, PGRMC1 prevents apoptosis in non-neural 
tissue (Peluso et al., 2009) and we recently found that PGRMC1 
mRNA levels are lower in the neonatal AVPV of males than 
females (Figure 2). Moreover, the arylhydrocarbon receptor lig-
and, 2,3,7,8-tetrachlorodibenzo-p-dioxin, increases pgrmc1 gene 
expression (Selmin et al., 1996) and developmental exposure to 
TCDD blocks dememinization of LH release (Mably et al., 1992). 
Thus, indirect evidence suggests that PGRMC1 may prevent cell 
death in the developing AVPV.

FEMININE SEXUAL BEHAVIORS

In addition to its effects on GnRH and LH release, P4 also 
rapidly enhances female mating behaviors through actions in 
brain regions that contain PGRMC1. Most of these brain regions

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also contain dopamine (DA) receptors and PGRMC1/sigma-2R agonists increase DA release (Garcés-Ramírez et al., 2011). For example, PGRMC1/sigma-2R mRNA levels are high in the medial preoptic area (Krebs et al., 2000; Intlekofer and Petersen, 2011), a region in which P4 increases DA release (Matuszewich et al., 2000). DA, in turn, acts through DA D2 receptors in the medial preoptic area to enhance feminine precopulatory behaviors (Graham and Pfau, 2010). In addition, DA input into the medial preoptic area comes primarily from the zona incerta (Wagner et al., 1995), a region that contains high levels of PGRMC1, PGRMC2, and SERBP1 mRNA. Levels are also high in the ventromedial hypothalamus (Krebs et al., 2000; Intlekofer and Petersen, 2011), a brain region in which both P4 and DA regulate lordosis through actions involving DA D1 and D5 receptors (Intlekofer and Petersen, 2011). This is not a well-studied brain structure from a neuroendocrine perspective, but the piriform cortex is central to the development and propagation of kindled seizures (Wahnschaffe et al., 1993; Loscher et al., 1995). Although no changes in kindled seizure threshold are observed during the estrous cycle of rats (Wahnschaffe and Loscher, 1992), many women with epilepsy experience seizures clustered around the time of the menstrual cycle when P4 levels are low (termed catamenial epilepsy) (Duncan et al., 1993; Herzog et al., 2004; Gilad et al., 2008; Reddy, 2009). P4 can significantly reduce the frequency of seizures in women with this disease (Reddy, 2009; Motta et al., 2013). Further studies are required to determine whether PGRMC1 plays a role in catamenial epilepsy and whether PGRMC1/sigma-2 ligands would be effective in treating this disease without the side effects of progestins.

**SUMMARY**

A large body of literature catalogues the many neural actions of P4 that may also mediate effects of P4 on non-reproductive functions. Two of the regions in which PGRMC1 was first detected are the supraoptic and paraventricular nuclei (Krebs et al., 2000; Meffre et al., 2005). These regions contain among the highest levels of PGRMC1, PGRMC2, and SERBP1 mRNA in the rat forebrain (Intlekofer and Petersen, 2011). PGRMC1 is also expressed in circumventricular organs, ependymal cells and meninges, and colocalizes with vasopressin in paraventricular and supraoptic nuclei; therefore, it has been proposed that PGRMC1 might be involved in water homeostasis in the brain (Meffre et al., 2005). Support for this idea comes from evidence that PGRMC1 expression increases in neurons and appears in astrocytes after traumatic brain injury that results in edema (Meffre et al., 2005). This finding has important clinical implications because P4 is now in clinical trials to evaluate its effectiveness on decreasing brain damage in stroke and traumatic brain injury (Stein, 2011). It remains to be determined whether P4 acts, at least in part, through PGRMC1 to exert its neuroprotective effects by controlling edema in the brain.

Finally, the piriform cortex is a part of the limbic system and both PGRMC1 and SERBP1 mRNA levels are very high in this region, while PR and mPR mRNAs are quite low or absent (Intlekofer and Petersen, 2011). This is not a well-studied brain structure from a neuroendocrine perspective, but the piriform cortex is central to the development and propagation of kindled seizures (Wahnschaffe et al., 1993; Loscher et al., 1995). Although no changes in kindled seizure threshold are observed during the estrous cycle of rats (Wahnschaffe and Loscher, 1992), many women with epilepsy experience seizures clustered around the time of the menstrual cycle when P4 levels are low (termed catamenial epilepsy) (Duncan et al., 1993; Herzog et al., 2004; Gilad et al., 2008; Reddy, 2009). P4 can significantly reduce the frequency of seizures in women with this disease (Reddy, 2009; Motta et al., 2013). Further studies are required to determine whether PGRMC1 plays a role in catamenial epilepsy and whether PGRMC1/sigma-2 ligands would be effective in treating this disease without the side effects of progestins.

**OTHER POTENTIAL NEURAL FUNCTIONS OF PGRMC1**

Results of our neuroanatomical studies suggest that PGRMC1 may also mediate effects of P4 on non-reproductive functions. For example, PGRMC1/sigma-2R agonists increase DA release (Garcés-Ramírez et al., 2011). For example, PGRMC1/sigma-2R mRNA levels are high in the medial preoptic area (Krebs et al., 2000; Intlekofer and Petersen, 2011), a region in which P4 increases DA release (Matuszewich et al., 2000). DA, in turn, acts through DA D2 receptors in the medial preoptic area to enhance feminine precopulatory behaviors (Graham and Pfau, 2010). In addition, DA input into the medial preoptic area comes primarily from the zona incerta (Wagner et al., 1995), a region that contains high levels of PGRMC1, PGRMC2, and SERBP1 mRNA. Levels are also high in the ventromedial hypothalamus (Krebs et al., 2000; Intlekofer and Petersen, 2011), a brain region in which both P4 and DA regulate lordosis through actions involving DA D1 and D5 receptors (Intlekofer and Petersen, 2011). This is not a well-studied brain structure from a neuroendocrine perspective, but the piriform cortex is central to the development and propagation of kindled seizures (Wahnschaffe et al., 1993; Loscher et al., 1995). Although no changes in kindled seizure threshold are observed during the estrous cycle of rats (Wahnschaffe and Loscher, 1992), many women with epilepsy experience seizures clustered around the time of the menstrual cycle when P4 levels are low (termed catamenial epilepsy) (Duncan et al., 1993; Herzog et al., 2004; Gilad et al., 2008; Reddy, 2009). P4 can significantly reduce the frequency of seizures in women with this disease (Reddy, 2009; Motta et al., 2013). Further studies are required to determine whether PGRMC1 plays a role in catamenial epilepsy and whether PGRMC1/sigma-2 ligands would be effective in treating this disease without the side effects of progestins.

**SUMMARY**

A large body of literature catalogues the many neural actions of P4 that may also mediate effects of P4 on non-reproductive functions. Two of the regions in which PGRMC1 was first detected are the supraoptic and paraventricular nuclei (Krebs et al., 2000; Meffre et al., 2005). These regions contain among the highest levels of PGRMC1, PGRMC2, and SERBP1 mRNA in the rat forebrain (Intlekofer and Petersen, 2011). PGRMC1 is also expressed in circumventricular organs, ependymal cells and meninges, and colocalizes with vasopressin in paraventricular and supraoptic nuclei; therefore, it has been proposed that PGRMC1 might be involved in water homeostasis in the brain (Meffre et al., 2005). Support for this idea comes from evidence that PGRMC1 expression increases in neurons and appears in astrocytes after traumatic brain injury that results in edema (Meffre et al., 2005). This finding has important clinical implications because P4 is now in clinical trials to evaluate its effectiveness on decreasing brain damage in stroke and traumatic brain injury (Stein, 2011). It remains to be determined whether P4 acts, at least in part, through PGRMC1 to exert its neuroprotective effects by controlling edema in the brain.
molecules in the brain. Based on our neuroanatomical findings that PGRMC1, PGRMC2, and SERBP1 are found in brain regions wherein P4 exerts rapid effects, it seems likely that these molecules are involved in diverse functions. These functions include the control of GnRH/LH release, feminine mating behaviors, fluid balance, and neuroprotection and seizure activity. The extensive overlap in patterns and levels of expression suggest that PGRMC1 and PR signaling pathways regulate the same cellular functions, but probably through different mechanisms. Considering the importance of these functions in physiology and disease, further study of PGRMC1, PGRMC2, and SERBP1 in the nervous system is warranted.

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