17β-Estradiol and Progesterone Regulate Multiple Progestin Signaling Molecules in the Anteroventral Periventricular Nucleus, Ventromedial Nucleus and Sexually Dimorphic Nucleus of the Preoptic Area in Female Rats

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Abstract

Recent work identified novel progestin signaling molecules, including progesterone receptor membrane component 1 (Pgrmc1), Pgrmc2, serpine mRNA binding protein 1 (Serbp1), progestin and adiponectin receptors 7 (Paqr7) and Paqr8. These molecules mediate rapid progesterone (P₄) effects in non-neural tissue and we recently mapped their expression in the brain. Many rapid effects of P₄ require 17β-estradiol (E₂) and P₄ priming; therefore, we examined the effects of ovarian hormones on the expression of these non-classical progestin signaling molecules. We focused specifically on the anteroventral periventricular nucleus (AVPV), the sexually dimorphic nucleus of the preoptic area (SDN-POA) and the ventrolateral portion of the ventromedial nucleus (VMNvl). These brain nuclei are important for female reproduction. Ovariectomized adult female rats were implanted with capsules containing sesame oil or E₂, and injected 48 hours later with sesame oil or P₄. Brains were collected eight hours later and RNA was isolated from the AVPV, SDN-POA and VMNvl. We assessed the effects of ovarian hormones on mRNA levels using quantitative polymerase chain reaction (QPCR). In the AVPV, Serbp1 mRNA levels were increased by P₄ in the presence of E₂, and Paqr8 was downregulated by P₄ alone. In the SDN-POA, combined E₂ and P₄ increased Pgrmc1 and Serbp1 mRNA levels, and E₂ alone increased Paqr8 mRNA levels. Finally, in the VMNvl, P₄ increased mRNA levels encoding Pgrmc1, Pgrmc2 and Serbp1, and the combination of E₂ and P₄ increased Pgrmc1 and Serbp1 mRNA levels. Paqr7 was not regulated by E₂ or P₄ in any brain region examined. In summary, we showed that ovarian hormones regulate novel progestin signaling molecules in brain regions important for the neuroendocrine control of reproduction.

Keywords

Estradiol; progesterone; neuroendocrine; non-classical signaling; receptor
INTRODUCTION

Progesterone (P₄) signaling in the female brain regulates several facets of reproduction including the neural control of ovulation and the expression of feminine sex behaviors. The molecular mechanisms underlying these P₄ actions have been primarily attributed to activation of the progestin receptor (Pgr), a ligand-dependent transcription factor. This classical model of steroid hormone action has been revised to include rapid non-genomic effects of Pgr activation on diverse signaling systems, such as MAPK and c-Src pathways (Richer et al., 1998, Boonyaratanakornkit et al., 2001). However, this model may still be incomplete because many cells that lack Pgr retain rapid P₄-elicited responses (Ehring et al., 1998, Bar et al., 2000, Frye et al., 2006). These findings may be explained by recent discoveries of novel progestin signaling molecules that mediate diverse responses to P₄ in non-neural tissues (Falkenstein et al., 1999, Zhu et al., 2003b, Peluso et al., 2004).

We recently mapped the expression of several of these progestin signaling molecules in the rat forebrain (Intlekofer and Petersen, in press). Genes encoding progesterone receptor membrane component 1 (Pgrmc1), Pgrmc2 and serpine mRNA binding protein 1 (Serbp1) were particularly abundant in neuroendocrine nuclei important for female reproduction. We confirmed and extended findings on the distribution pattern of Pgrmc1 (Krebs et al., 2000, Sakamoto et al., 2004, Meffre et al., 2005), and showed that the pattern overlaps closely with that of its binding partner, Serbp1, and Pgrmc1 homologue, Pgrmc2. Few studies have examined the role of these molecules in neural function, but Pgrmc1 and Serbp1 have been implicated in the rapid effects of P₄ observed in ovarian cells and sperm (Correia et al., 2007, Peluso et al., 2009). While Pgrmc2 has not been studied in the context of rapid P₄ signaling, it may mediate P₄ actions in the ovary (Nilsson et al., 2006). Together these findings suggest that Pgrmc1, Pgrmc2 and Serbp1 may mediate non-classical P₄ signaling in the brain as in other tissues.

Other P₄ signaling molecules include progestin and adiponectin receptor 7 (Paqr7) and Paqr8, G-protein-like receptors that bind P₄ and regulate cAMP levels in several fish species (Zhu et al., 2003a, Zhu et al., 2003b, Hanna et al., 2006). Although controversy surrounds their role in mammalian cells (Fernandes et al., 2008), mRNAs encoding Paqr7 and Paqr8 have been detected in mammalian reproductive tissues (Zhu et al., 2003a). Our recent work showed that Paqr7 and Paqr8 gene expression is present in the hypothalamus (Intlekofer and Petersen, in press), though expression appears lower compared with that of Pgrmc1, Pgrmc2 and Serbp1. Other evidence suggests that Paqr7 and Paqr8 mediate P₄ signaling and couple to inhibitory G-proteins in immortalized gonadotropin-releasing hormone (GnRH) neurons (Sleiter et al., 2009). Despite these significant advances, neither the regulation nor the functions of Paqr7 and Paqr8 in the brain are known.

In the female rodent, many of the rapid P₄ signaling events require 17β-estradiol (E₂) activation of estrogen receptor 1 (Esr1) (Edwards, 2005). This is partially due to E₂ induction of Pgr (Kastner et al., 1990), a nuclear transcription factor that also activates rapid intracellular kinase cascades (Leonhardt et al., 2003). In regions of high Esr1 expression, such E₂-induced effects result in greater P₄-sensitivity. For example, in the preoptic area (POA) and ventromedial nucleus (VMN) of the hypothalamus, E₂ exposure lowers cell signaling activation thresholds for P₄, resulting in greater P₄-sensitivity (Balasubramanian et al., 2008). In view of our recent findings that Pgrmc1, Pgrmc2, Serbp1, Paqr7 and Paqr8 are found in regions that contain Esr1 and Pgr, it is possible that E₂ and/or P₄ regulation of these molecules may be important in non-classical P₄ signaling. This idea is supported by findings that Pgrmc1 expression is regulated by P₄ in E₂-primed rats (Krebs et al., 2000), uterine levels of Pgrmc2 mRNA vary across the estrus cycle (Zhang et al., 2008) and Paqr7 and Paqr8 ovarian expression is regulated by E₂ (Karteris et al., 2006). It is unclear whether
Pgrmc1 is regulated by steroids in brain regions other than the VMN, and no studies have tested the effects of ovarian steroids on Pgrmc2, Serbp1, Paqr7 and Paqr8 in the brain. To address these issues, we examined the effects of E$_2$, P$_4$ and the combination of E$_2$ and P$_4$ (E$_2$+P$_4$) on levels of mRNA encoding Pgrmc1, Pgrmc2, Serbp1, Paqr7 and Paqr8. We focused specifically on the anteroventral periventricular nucleus (AVPV), the sexually dimorphic nucleus of the POA (SDN-POA) and the ventrolateral portion of the VMN (VMNvl). These nuclei have abundant expression of Esr1 and Pgr, are sexually dimorphic and are important for female reproduction (Dugger et al., 2007, Sakuma, 2009). In addition, we recently found expression of Pgrmc1, Pgrmc2, Serbp1, Paqr7 and Paqr8 in these nuclei (Intlekofer and Petersen, in press). We now report that ovarian steroid hormones regulate these putative progesterin signaling molecules, and do so in a region-specific manner.

**EXPERIMENTAL PROCEDURES**

**Animals**

All protocols and post-operative care were approved by the Institutional Animal Care and Use Committee of the University of Massachusetts, and animals were housed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Twenty-eight adult female Sprague-Dawley rats (200–250 g, Harlan, Madison, WI) were housed individually on a 14:10 light:dark cycle with food and water provided ad libitum. Animals were anesthetized with isoflurane and bilateral ovariectomies were performed through very small (5-mm) flank incisions that minimized tissue trauma. They were observed for respiratory distress and bleeding for 6 h postoperatively and examined again at 12, 24 and 48 h to ensure that they were freely moving and had no significant weight loss. One week later (Day 0), animals were implanted s.c. with Silastic capsules (Dow Corning, Midland, MI; 1.57 mm, o.d., 3.8 mm; 30 mm length) containing either sesame oil vehicle or E$_2$ (150 μg/ml 17β-estradiol in sesame oil) as described previously (Petersen and LaFlamme, 1997). At 0900 H on Day 2, animals were injected s.c. with either sesame oil vehicle or 50 mg P$_4$. Eight hours later, animals were anesthetized with CO$_2$ and brains were rapidly frozen on powdered dry ice, wrapped in Parafilm (American Can Co., Greenwich, CT) and stored at −80 °C.

**Tissue preparation**

Coronal cryosections that contained the AVPV, SDN-POA and VMNvl were acquired using a Leica CM3000 cryostat (Nussloch, Germany). These sections were taken from the rostral AVPV (bregma -0.02 mm), SDN-POA (bregma -0.4 mm) and VMNvl (bregma -0.20 mm) (Swanson, 1998). We obtained tissue punches from these sections using a 1.0-mm diameter Harris Uni-Core tissue needle (Ted Pella Inc., Redding, CA) from a single 300-μm section as illustrated in Fig. 1, and used this tissue for quantitative polymerase chain reaction (QPCR).

**RNA preparation and QPCR**

RNA was isolated from tissue punches using the RNeasy kit (Qiagen, Valencia, CA) and reverse transcribed with the QuantiTect Reverse Transcription Kit (Qiagen), using manufacturer’s protocol. QPCR was performed in a Stratagene Mx3000P thermocycler (Agilent Technologies, Wilmington, DE) programmed as follows: 95 °C, 10 min; 40 cycles of 95 °C for 15 sec; and 60 °C for 60 sec. Reactions contained reagents from QuantiTect SYBR Green Kit, following manufacturer’s protocol (Roche Diagnostics, Indianapolis, IN). Specific primer sets were obtained from Integrated DNA Technologies (Coralville, Iowa), and sequences are listed in Table 1. The efficiency of each primer set was validated over a range of cDNA concentrations and samples with no cDNA were included as negative controls.
controls. Primer specificity was verified using melting curve analyses and confirmation of a single fluorescence peak in each QPCR reaction. Melting curve analyses were performed by heating samples to 95 °C for two min, 55 °C for 15 sec, and recording fluorescence measurements during incremental increases of 0.5 °C for 80 cycles. Primer specificity was also validated using 2% agarose gel electrophoresis to verify single products following the QPCR reaction. Fluorescence measurements were detected using MxPro QPCR analysis software (Agilent Technologies). We verified that levels of mRNA encoding β-actin did not differ among treatments; therefore, we used it as an internal control (primers as indicated in Table 1). The ΔΔCt method was used to analyze the data (Livak and Schmittgen, 2001).

Statistics

All data are expressed as mean ± SEM. Effects of E₂, P₄ and E₂+P₄ on mRNA levels were detected using a one-way ANOVA, followed by pair-wise comparisons using t-tests with Bonferroni correction.

RESULTS

QPCR reaction specificity

First, melting curve analyses verified a single peak of fluorescence, and the size of each product was confirmed by gel electrophoresis. In addition, the PCR amplification efficiency calculated from the standard curve was between 96–100% for all primer sets used. Consistent with our previous in situ hybridization findings (Intlekofer and Petersen, in press), QPCR verified that the genes of interest were expressed in the AVPV, SDN-POA and VMNvl.

Esr1 and Pgr mRNA levels

In ovariectomized adult rats, exposure to E₂ reduced Esr1 mRNA levels in the AVPV, SDN-POA and VMNvl (Fig. 2a, b and c, respectively). P₄ administration significantly decreased Esr1 mRNA levels in the AVPV (Fig. 2a), but not in the SDN-POA (Fig. 2b) or VMNvl (Fig. 2c). In all three areas examined, E₂+P₄ reduced levels of mRNAs encoding Esr1 (Fig. 2a, b and c). E₂ markedly increased levels of mRNA encoding Pgr in all brain regions examined (Fig. 2d, e and f), and in the AVPV and SDN-POA, E₂+P₄ increased Pgr mRNA levels.

Pgrmc1, Serbp1 and Pgrmc2 mRNA levels

In the AVPV, mRNA levels of Pgrmc1 were unaltered by treatment with E₂, P₄ or E₂+P₄ (Fig. 3a). Serbp1 and Pgrmc2 mRNA levels were both increased by E₂+P₄ in the AVPV (Fig. 3d and g). Within the SDN-POA, E₂+P₄ increased Pgrmc1 and Serbp1 levels (Fig. 3b and e) and decreased Pgrmc2 mRNA levels (Fig. 3h). In the VMNvl, P₄ increased Pgrmc1, Pgrmc2 and Serbp1 mRNA levels (Fig. 3c, f and i). Levels of mRNA encoding Pgrmc1 and its binding partner, Serbp1, were also increased by E₂+P₄ in the VMNvl (Fig. 3c and f).

Paqr7 and Paqr8 mRNA levels

Ovarian steroids did not regulate Paqr7 mRNA levels in any brain region examined (Fig. 4a, b and c). In contrast, Paqr8 mRNA levels were repressed by treatment with P₄ in the AVPV and increased by E₂+P₄ (Fig. 4d). Paqr8 mRNA levels were increased by E₂ in the AVPV and SDN-POA (Fig. 4e), but not altered in the VMNvl (Fig. 4f).
These results are the first to show that E$_2$ and P$_4$ regulate non-classical progestin signaling molecules in the AVPV, SDN-POA and VMNvl. Importantly, E$_2$+P$_4$ increased Serbp1 mRNA levels in all brain regions examined, but increased expression of its putative binding partners, Pgrmc1 and Pgrmc2, in a region-specific manner. These findings are consistent with the idea that Serbp1 availability is the key factor determining P$_4$ responsiveness of Pgrmc1 complexes (Peluso et al., 2004). Ovarian steroid regulation of Paqr8 also varied by brain region; however, the closely-related Paqr7 was not regulated in any region examined. Together these findings support the hypothesis that Pgrmc1, Pgrmc2, Serbp1 and Paqr8 mediate rapid P$_4$ signaling within neuroendocrine nuclei important for female reproduction.

Our findings that E$_2$ decreased Esr1 and increased Pgr in the AVPV and VMNvl are similar to results of previous studies (Lauber et al., 1990, Simerly and Young, 1991). We now report that the same pattern exists in the SDN-POA. Interestingly, in the VMNvl, P$_4$ abrogated the effects of E$_2$ on Pgr mRNA levels. Although this was not seen in other brain regions examined herein, P$_4$ blocks E$_2$ induction of Pgr in non-neural cells (Kraus and Katzenellenbogen, 1993).

We found that E$_2$+P$_4$ increased Pgrmc1 mRNA levels in the SDN-POA but not the AVPV; however, in both regions Serbp1 expression was increased, and this may be sufficient for rapid P$_4$ effects. This idea is supported by findings that P$_4$ responses mediated by the Pgrmc1/Serbp1 complex depend upon Serbp1 levels in non-neural cells (Peluso et al., 2005). Interestingly, E$_2$+P$_4$ increased Pgrmc2 mRNA levels in the AVPV, though no studies have tested whether Serbp1 binds Pgrmc2 to form a functional complex. These mechanisms are of particular interest as the AVPV is required for induction of the preovulatory luteinizing hormone surge (Wiegand et al., 1980, Ronnekleiv and Kelly, 1986, Petersen et al., 1995, Chappell and Levine, 2000). The AVPV and SDN-POA have dense projections to GnRH neurons (Simonian et al., 1999), and show abundant Pgrmc1, Pgrmc2, and Serbp1 mRNA levels (Intlekofer and Petersen, in press). Thus, further studies are warranted to determine whether these signaling molecules mediate rapid P$_4$ effects in the AVPV and SDN-POA.

P$_4$ and E$_2$+P$_4$ increased Pgrmc1 and Serbp1 mRNA levels in the VMNvl, a region in which P$_4$ facilitates lordosis (Pfaff and Sakuma, 1979, Pfaff et al., 1994, Frye and Vongher, 1999, Frye, 2001). These rapid P$_4$ effects are partially due to activation of cGMP-dependent protein kinase (DeBold and Frye, 1994, Lydon et al., 1995). This is especially interesting because Pgrmc1 is involved in P$_4$ induction of cGMP-dependent protein kinase (Peluso and Pappalardo, 2004), and the C-terminus of Pgrmc1 contains several putative kinase binding sites (Cahill, 2007). Other researchers examining the entire VMN also found that Pgrmc1 was regulated by ovarian steroids; however, in that study E$_2$ alone increased Pgrmc1 mRNA levels (Krebs et al., 2000). Factors that may explain these differences include dosage, duration of treatment, and region examined. Overall, these findings suggest a link between Pgrmc1/Serbp1 and the rapid facilitation of feminine sex behavior.

Our findings are the first to show that ovarian steroids regulate Paqr8 mRNA levels in the brain. Similar to studies in myometrial cells, we found that E$_2$ increased both Paqr8 and Pgr mRNA levels in the AVPV and SDN-POA. These results are interesting in light of evidence that Paqr8 cross-talks with Pgr through coupling to inhibitory G-proteins and decreasing Pgr transactivation (Karteris et al., 2006). In contrast to Paqr8, ovarian steroid exposure did not alter Paqr7 mRNA levels in any brain region examined. In other reproductive tissues, E$_2$ and P$_4$ also have variable effects on these signaling molecules (Cai and Stocco, 2005, Fernandes et al., 2005). Thus, despite their structural similarities, Paqr7 and Paqr8 may be regulated differently by ovarian steroids and may have functionally distinct roles.
Though reproductive functions coordinated by ovarian hormones have been studied extensively, the underlying molecular events are unclear. The present studies identified several steroid-inducible progestin signaling molecules that may mediate rapid P$_4$ actions in the neuroendocrine control of reproduction. The functional relevance and specific role(s) of these novel signaling molecules will be the topic of future research.

### Highlights

- Non-classical progesterone signaling molecules are regulated by ovarian steroids in the brain
- Rapid progestin signaling molecules are found in brain nuclei that regulate female reproduction
- Ovarian steroids regulate Pgrmc1, Pgrmc2, Serbp1, and Paqr8 in a brain nucleus-specific manner

### Acknowledgments

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### Abbreviations

- **AVPV**: anteroventral periventricular nucleus
- **E$_2$**: 17-$\beta$ estradiol
- **Esr1**: estrogen receptor 1
- **GnRH**: gonadotropin releasing hormone
- **P$_4$**: progesterone
- **Paqr7**: progestin and adipoQ receptor 7
- **Paqr8**: progestin and adipoQ receptor 8
- **Pgr**: progestin receptor
- **Pgrmc1**: progesterone receptor membrane component 1
- **Pgrmc2**: progesterone receptor membrane component 2
- **QPCR**: quantitative polymerase chain reaction
- **SDN-POA**: sexually dimorphic nucleus of the preoptic area
- **Serbp1**: serpine mRNA-binding protein 1
- **VMNvl**: ventrolateral portion of the ventromedial nucleus of the hypothalamus

### References


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Neuroscience. Author manuscript; available in PMC 2012 March 10.


Figure 1.
Diagrams of brain sections containing the a) AVPV, b) SDN-POA and c) VMNvl modified from the atlas of Swanson (1998). Circles indicate regions from which tissue was excised for analysis. OC, optic chiasm; 3V, third ventricle; AC, anterior commissure.
Figure 2.
Levels of mRNAs encoding Esr1 and Pgr in ovariectomized rats treated with oil, E₂, P₄ or E₂+P₄. Esr1 mRNA levels in the AVPV (a), SDN-POA (b) and VMNvl (c), and Pgr mRNA levels in the AVPV (d), SDN-POA (e) and VMNvl (f) were determined by QPCR. Bars = means ± SEM. a Significantly different from oil-treated controls; b significantly different from E₂-treated animals; c significantly different from P₄-treated animals; values considered significantly different if p < 0.05 in post-hoc analyses. One-way ANOVA results: a) F(3,22)=4.72, p < 0.010; b) F(3,20)=11.81, p < 0.0002; c) F(3,20)=8.14, p < 0.001; d) F(3,20)=20.83, p < 0.0001; e) F(3,20)=17.14, p < 0.0001; f) F(3,20)=41.49, p < 0.0001.
Figure 3.
Levels of mRNAs encoding Pgrmc1, Pgrmc2 and Serbp1 in ovariectomized rats treated with oil, E2, P4 or E2+P4. Pgrmc1 mRNA levels in the AVPV (a), SDN-POA (b) and VMNvl (c), Pgrmc2 mRNA levels in the AVPV (d), SDN-POA (e) and VMNvl (f), and Serbp1 mRNA levels in the AVPV (g), SDN-POA (h) and VMNvl (i) were determined by QPCR. Bars = means ± SEM. a significantly different from oil-treated controls; b significantly different from E2-treated animals; c significantly different from P4-treated animals; values considered significantly different if p < 0.05 in post-hoc analyses. One-way ANOVA results: a) F(3,22)= 2.32, p < 0.103; b) F(3,20)= 8.56, p < 0.001; c) F(3,22)= 28.59, p < 0.0001; d) F(3,22)= 21.79, p < 0.0001; e) F(3,22)= 6.56, p < 0.002; f) F(3,22)= 21.13, p < 0.0001; g) F(3,22)= 4.65, p < 0.01; h) F(3,22)= 4.55, p < 0.01; i) F(3,22)= 6.16, p < 0.003.
Figure 4.
Levels of mRNAs encoding Paqr7 and Paqr8 in ovariectomized rats treated with oil, E2, P4 or E2+P4. Paqr7 mRNA levels in the AVPV (a), SDN-POA (b) and VMNvl (c), and Paqr8 mRNA levels in the AVPV (d), SDN-POA (e) and VMNvl (f) were determined by QPCR. Bars = means ± SEM. * significantly different from oil-treated controls; † significantly different from E2-treated animals; ‡ significantly different from P4-treated animals; values considered significantly different if p < 0.05 in post-hoc analyses. One-way ANOVA results: a) F(3,22)=0.65, p < 0.59; b) F(3,22)=0.037, p < 0.99; c) F(3,20)=3.67, p < 0.03; d) F(3,22)=10.39, p < 0.0002; e) F(3,22)=33.87, p < 0.0001; f) F(3,20)=1.35, p < 0.29.
### Table 1

**Primers Used in QPCR Studies**

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<th>NCBI Gene Name and Refseq ID#</th>
<th>Primer sequences 5′-3′</th>
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<th>Amplicon (bp)</th>
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<td><strong>Actb</strong>&lt;br&gt;NM_031144</td>
<td>GGGAAATCGTGCGTGACATT&lt;br&gt;GCGGCAATGGCCATCTC</td>
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<td>76</td>
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<tr>
<td><strong>Esr1</strong>&lt;br&gt;NM_012689</td>
<td>AGTGAAGCCTCAATGATGGG&lt;br&gt;ATCTCCAACCAGGCACACTC</td>
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<td>146</td>
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<tr>
<td><strong>Pgr</strong>&lt;br&gt;NM_022847</td>
<td>GGTGGAGGTCTGTACCAAGCAT&lt;br&gt;AGGCCTTCCAAGGAATTGT</td>
<td>2261–2280</td>
<td>214</td>
</tr>
<tr>
<td><strong>Pgrmc1</strong>&lt;br&gt;NM_021766</td>
<td>CTGCCGAACCTAAAGGCGATAC&lt;br&gt;TCCAGTCATTCAAGGTCTC</td>
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<td>247</td>
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<tr>
<td><strong>Pgrmc2</strong>&lt;br&gt;NM_001008374</td>
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<td>306–325</td>
<td>139</td>
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<tr>
<td><strong>Serbp1</strong>&lt;br&gt;NM_145086</td>
<td>GAAACACCCGAAGGTGAAGA&lt;br&gt;TTTTCATGTCCTACCAGCA</td>
<td>789–808&lt;br&gt;978–959</td>
<td>190</td>
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<tr>
<td><strong>Paqr7</strong>&lt;br&gt;NM_001034081</td>
<td>GTGCCAAGCATTCATAGTGTC&lt;br&gt;TGATAGTCCAGCGTCACAGC</td>
<td>661–680&lt;br&gt;890–871</td>
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<td><strong>Paqr8</strong>&lt;br&gt;NM_001014099</td>
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