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Review

Reproductive actions of prolactin mediated through short and long receptor isoforms

Y. Sangeeta Devi [a,*,1], Julia Halperin [b,*,1]

[a] Department of Obstetrics, Gynecology and Reproductive Biology, College of Human Medicine, Michigan State University, Grand Rapids, MI-49503, USA
[b] Centro de Estudios Biomédicos, Biotecnológicos, Ambientales y Diagnóstico (CEBBAD), Universidad Maimónides, Hidalgo 775 6to piso, C1405BCK Ciudad Autónoma de Buenos Aires, Argentina and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Rivadavia 1917, Ciudad Autónoma de Buenos Aires, Argentina

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ABSTRACT

Prolactin (PRL) is a polypeptide hormone with a wide range of physiological functions, and is critical for female reproduction. PRL exerts its action by binding to membrane bound receptor isoforms broadly classified as the long form and the short form receptors. Both receptor isoforms are highly expressed in the ovary as well as in the uterus. Although signaling through the long form is believed to be more predominant, it remains unclear whether activation of this isoform alone is sufficient to support reproductive functions or whether both types of receptor are required. The generation of transgenic mice selectively expressing either the short or the long form of PRL receptor has provided insight into the differential signaling mechanisms and physiological functions of these receptors. This review describes the essential finding that both long and short receptor isoforms are crucial for ovarian functions and female fertility, and highlights novel mechanisms of action for these receptors.

Contents

Abbreviations: PRL, prolactin; PRLR, prolactin receptor; GH, growth hormone; PL, placental lactogen; dPRL, decidual prolactin; 20α-HSD, 20alpha-hydroxysteroid dehydrogenase; α2M, alpha 2-macroglobulin; PRAP, prolactin receptor associated protein; HSD17B-7, 17β hydroxysteroid dehydrogenase; JAK2, janus Kinase 2; STAT, signal transducer and activator of transcription; MAPK, mitogen activated protein kinase; IGFBP1, insulin-like growth factor binding protein 1; VEGF, vascular endothelial growth factor; FRET, fluorescence resonance energy transfer; DUPD1, dual specificity phosphatase and pro isomerase domain containing 1; GALT, galactose-1-phosphate uridylyltransferase.

* Corresponding authors. Addresses: 333 Bostwick Ave NE, Room – 4023, Grand Rapids, MI-49503, USA. Tel.: +1 616 234 0988; fax: +1 616 234 0990 (Y. Sangeeta Devi), CEBBAD-Universidad Maimónides, Hidalgo 775-C1405BCK, C.A.B.A., Argentina. Tel.: +54 11 49051100x1217 (J. Halperin).
E-mail addresses: Sangeeta@hc.msu.edu (Y. Sangeeta Devi), halperin.julia@maimonides.edu (J. Halperin).
[1] Equal contribution.

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1. Prolaction – synthesis and regulation

Prolactin (PRL) is a polypeptide hormone belonging to the PRL/GH/PL family (group I of the helix bundle protein hormones), that includes PRL-like and PRL-related proteins, with which PRL shares structure similarities and sequence homology, as well as overlapping biological properties (Bole-Feysot et al., 1998; Soares, 2004). PRL was originally identified by Stricker and Grueter (1928) as the pituitary factor responsible for milk secretion in rabbits, and almost 70 years later, its cDNA was cloned and characterized by Gabou and colleagues (1996). Today, its presence has been well documented in human (Truong et al., 1984), rat (Gubbins et al., 1979), mouse (Harigaya et al., 1986), guinea pig (Alam et al., 2010), goat (Le Provost et al., 1994), chicken (Harvey et al., 1978), and rainbow trout (Mercier et al., 1989). It is encoded by a six-exon gene, which is located in chromosome 6 in humans (Owerbach et al., 1981; Horseman and Yu-Lee, 1994); chromosome 17 in rats (Rat Genome Sequencing Project Consortium, 2004), and chromosome 13 in mice (Dai et al., 1998). PRL is synthesized as a prohormone containing a signal peptide. The mature protein contains 197–199 amino acid residues depending on the species, with a total molecular mass of approximately 23 kDa (Shome and Parlow, 1977; Bole-Feysot et al., 1998).

PRL is mainly synthesized and secreted by the lactotrope cells of the anterior lobe of the pituitary gland, and released into the blood mainstream enabling transit to different target tissues where it binds to its membrane receptor (PRLR) and acts as a classic endocrine hormone modulator. In addition, several extra-pituitary tissues produce PRL in a cell-specific manner and exert a local autocrine/paracrine response (Review in Ben-Jonathan et al., 1996, 2008). The extra-pituitary sites include the decidua (Gibori et al., 1974; Jayatilak et al., 1985; Prigent-Tessier et al., 1999), breast (Fields et al., 1993; Kurtz et al., 1993; Steinmetz et al., 1993), prostate (Nevalainen et al., 1997; Li et al., 2004), brain (Grattan and Kokay, 2008), skin (Craven et al., 2001; Foitzik et al., 2003, 2006), fat (Hugo et al., 2006) and immune cells (Jurcovicová et al., 1993; Gala and Shevach, 1994). In fact, pioneering investigations on production of PRL by decidua in humans and rodents have established a powerful tool that continues to be used today as one of the main markers of decidualization of stromal cells (Maslar and Riddick, 1979; Jayatilak et al., 1985).

Pituitary PRL exhibits a tonic secretion, mainly under the control of hypothalamic inhibitory factors, with dopamine being the best established modulator (reviewed in Ben-Jonathan, 1985; Freeman et al., 2000; Grattan and Kokay, 2008). Dopamine inhibits PRL release by binding to the D2 receptor, an adenylyl cyclase-linked dopamine receptor, on the pituitary lactotroph cells. It has been reported that PRL affects its own secretion by affecting the dopaminergic neurons via a short loop negative feedback (Milenkovic et al., 1990). Using either PRLR knockout or PRLR transgenic models, we and others have shown that disruption of normal PRLR expression causes a significant rise of PRL serum levels, suggesting that PRL/PRLR signaling down-regulates PRL synthesis and/or secretion at the hypothalamic and/or pituitary level (Binart et al., 2000 and Halperin et al., 2008). PRL secretion is pulsatile and is paced by a circadian rhythm. The lowest levels are observed in the morning about 2–3 h after waking up and the highest during sleep (Linkowski et al., 1998). On the other hand, the mechanism of PRL secretion in extra-pituitary sites is not fully understood but appears to be cell type specific and is not necessarily dependent on dopaminergic system (Gellersen et al., 1994; Ben-Jonathan et al., 2008). Ben-Jonathan and colleagues have recently shown expression of functional dopamine receptors in adipocytes that inhibit PRL expression and release after dopamine treatment (Borcherding et al., 2011). However, in other sites such as decidua, secretion of PRL is not dependent on dopamine but rather on transcriptional control, much like other cytokines (Ben-Jonathan et al., 2008).

Transcriptional regulation of pituitary and extra-pituitary PRL expression are under the control of two independent promoter regions: a proximal promoter region modulates pituitary PRL expression (Berwaer et al., 1991), whereas a distal upstream region directs extra-pituitary expression (Berwaer et al., 1994; Featherstone et al., 2012). The proximal promoter region contains multiple binding sites for Pit-1 transcription factor, a member of the POU homeodomain protein. Pit-1 is necessary for transcription of pituitary PRL and mediates its effect by interacting with nuclear hormone receptors and other coregulators (Featherstone et al., 2012; Ben-Jonathan et al., 2008). As for the extra-pituitary PRL, its expression is proposed to be independent of Pit-1 (Gellersen et al., 1994; Ben-Jonathan et al., 1996). However, recent data suggests that Pit-1 may be involved in the expression of PRL in human breast cell lines and tumors (Ben-Batalla et al., 2010). It is not clear whether this mechanism of regulation is unique to cancer cells or represents a common mechanism in other extra-pituitary PRL producing sites. Nonetheless, the diverse expression profile of the PRL gene in extra-pituitary sites suggests a complex system of regulation enabling cell-specific expression and response to differential regulatory mediators. In the case of the decidua, decidual PRL (dPRL) is synthesized and secreted by the human endometrium around day 23 of the normal menstrual cycle and depends primarily on levels of progesterone and estradiol (Lockwood and Schatz, 1996). In a fertile cycle, the capacity for dPRL production increases rapidly as implantation progresses. Together with IGFBP1, dPRL is the most dramatically induced gene in the human endometrium during pregnancy. The transcription factor C/EBPβ mediates cAMP induction of dPRL by forming a nucleoprotein complex that binds the proximal dPRL promoter region upon PKA activation in human endometrial stromal cells (Pohnke et al., 1999). Other reports have demonstrated that overexpression of Foxo1A induces a significant increase in dPRL promoter activity by cooperating with C/EBPβ (Christian et al., 2002 and Buzzio et al., 2006) and with HoxA-11 (Lynch et al., 2009), both studies performed in human endometrial stromal cells. Apart from serving as a useful marker of decidualization in endometrial stromal cells, dPRL has also been shown to play an important role in the maintenance of pregnancy, the findings of which are further emphasized in PRL and PRLR knockout mice (Binart et al., 2000; Bao et al., 2007).

2. PRL receptor isoforms

Prolactin receptor (PRLR) is a member of the class 1 cytokine receptor superfamily that lacks intrinsic tyrosine kinase activity (Walker, 2005), and is encoded by a gene located in chromosome 5, 15, or 2 for human (Boutin et al., 1989), mouse (Davis and Linzer, 1989), and rat (Jayatilak and Gibori, 1986; Boutin et al., 1988), respectively. This membrane-anchored protein is composed of an extracellular ligand-binding domain, a single pass transmembrane chain and an intracellular domain responsible for the signal transduction. PRLR was first cloned and characterized in rodents (Boutin et al., 1988; Kelly et al., 1989; Davis and Linzer, 1989, 1990), and almost simultaneously described in human (Boutin et al., 1989), rabbit (Edery et al., 1989), and later in bovine (Scott et al., 1992), chicken (Zhou et al., 1996), frog (Yamamoto et al., 2000), and rainbow trout (Prunet et al., 2000). Although it codes for a single gene product, alternative splicing of its primary transcript or post-translational cleavage can generate multiple variants of the receptor. These various PRLR isoforms share a common extracellular and transmembrane domain, but differ in the length and composition