Ovarian Prolactin Receptors and Their Placental Ligands

Daniel I.H. Linzer and Brian J. Arey

Prolactin (PRL), which is closely related to growth hormone (GH), has a diverse array of physiological effects, including, for example, the regulation of reproduction, mammary development and lactation, metabolism, immune response, osmotic balance, and mating and maternal behavior. These effects of PRL are initiated by binding of the hormone to a cell-surface receptor that is a member of the cytokine receptor superfamily (1). At least three factors contribute to the complexity of PRL action: (i) the expression of multiple forms of the PRL receptor (PRL-R), (ii) the presence and action of these receptors in distinct cell backgrounds, and (iii) the synthesis of several different receptor ligands.

In the mouse at least 4 forms of the PRL-R are synthesized, 3 proteins with relatively short cytoplasmic domains and 1 with a long cytoplasmic region (2, 3). In contrast, only 1 short and 1 long receptor form have been identified in other species (1). The ability of the long receptor form to transduce PRL binding into an intracellular signaling cascade has been demonstrated in model cell systems (4), but the roles of the short receptor forms are unknown. Possibly, these short receptor forms may connect to different signaling pathways or they may target bound hormone to distinct intracellular fates.

As a reproductive hormone, PRL has direct effects on both the primary reproductive organs (ovary and testis) and the secondary organs, such as the mammary glands. Within the ovary PRL-R expression has been detected by immunocytochemistry, radioligand binding, and in situ hybridization in multiple cell types, including granulosa, luteal, thecal, and interstitial cells (3, 5–10). These cellular targets of PRL in the ovary are components of various structures, including small preantral follicles, mature preovulatory follicles, and corpora lutea.

The effects of PRL on these different cell types are numerous (Fig. 4.1). In granulosa and luteal cells, PRL acts to increase progesterone
production by increasing cholesterol uptake and the amount of progesterone synthetic enzymes and by decreasing progesterone-modifying enzymes (11–18). Under most conditions PRL inhibits androgen synthesis in thecal cells and estradiol production in granulosa and luteal cells, although PRL can also stimulate estradiol secretion during pregnancy (19–25). In addition to regulating hormone synthesis, PRL also affects the levels of hormone receptors, typically acting to increase and maintain luteinizing hormone receptor (LH-R) numbers on granulosa and luteal cells, but PRL has also been reported to cause a decrease in LH-R levels (15, 26–32). Finally, PRL influences the synthesis of proteins involved in proteolysis and tissue remodeling, including plasminogen activator and α2 macroglobulin, that in turn can influence ovulation and corpus luteum formation (33, 34).

The expression of 4 distinct receptor forms in the mouse liver and ovary (3) suggests that each of these forms may have a specific role in PRL physiology. For example, even though all 4 mRNAs are coexpressed in most cell types in the mouse ovary, we have found that 1 of the short receptor forms—designated PRL-Rs2—is uniquely expressed in the granulosa cells of atretic follicles at early to midpregnancy (3). Similarly, we have observed distinct expression patterns of the long and 1 short PRL-R mRNA in the rat ovary (10). On proestrus morning, both of these mRNAs are expressed at similar levels in the granulosa cells of