Commentary

The Long and Short of the Prolactin Receptor: The Corpus Luteum Needs Them Both!¹

Carlos Stocco²

Department of Physiology and Biophysics, College of Medicine, University of Illinois at Chicago, Chicago, Illinois

It is well known that prolactin is essential for the formation and maintenance of the corpus luteum in rodents. Prolactin secretion induced by mating transforms the corpus luteum of the cycle, a structure of limited functionality, into the corpus luteum of pregnancy, an endocrine gland that remains active throughout gestation, secreting sufficient progesterone to maintain uterine function [1]. What remains controversial is how prolactin interacts with the various types of cells that form the corpus luteum, leading to the initiation of luteal survival and developmental programs. This controversy was fueled by the finding that two major forms of the prolactin receptor are expressed from the same gene. Splicing of the initial transcript of this gene produces a long and a short form of the receptor. These forms, while identical in their extracellular structure, differ in their intracellular domain length and sequence [2]. The contribution of each form of the prolactin receptor to the regulation of the corpus luteum has puzzled researchers for decades. Nevertheless, because long form receptor signaling is required for corpus luteum function [3] and because overexpression of the short form of the receptor cannot prevent the luteal failure induced by deletion of the prolactin receptor gene [4, 5], activation of the long form was thought to mediate the luteotropic effect of prolactin. Until now, this hypothesis has remained untested.

In this month's *Biology of Reproduction*, Le et al. [6] address this issue by expressing the long form of the receptor in prolactin receptor knockout mice, either ubiquitously or specifically in the corpus luteum. Strikingly, the expression of the long form in either manner is not enough to sustain luteal function. As seen in the full knockout, long form knock-in females ovulate normally but are infertile, although progesterone administration rescues pregnancy, suggestive of inadequate luteal function. This is intriguing because the functionality of the reintroduced receptor was demonstrated by the phosphorylation of STAT5, one of the main mediators of prolactin action in luteal cells [7]. The long form receptor also rescues estrogen receptor- α and luteinizing hormone receptor expression, two well-known targets of prolactin [8]; their expression is abolished in the prolactin receptor knockout mice. Moreover, CDKN1B (p27^{kip}) and CEBPB (C/EBP β), two factors induced during luteinization [9, 10], are expressed in long form knock-in animals treated with hCG. Thus, although follicular cells respond to prolactin and luteinizing hormone, luteinization

does not proceed normally, serum progesterone never rises, and extensive apoptosis occurs in the corpus luteum, even in the presence of the long form of the receptor.

Unexpectedly, in vitro granulosa cells expressing only the long form of the receptor produce progesterone as efficiently as wild-type cells. This paradoxical finding led the authors to seek mechanisms that may explain the lack of in vivo luteinization. They show that there is defective neovascularization, based on diminished expression of VEGFA and abnormal collagen IV distribution. This interesting observation not only confirms the crucial role of angiogenesis in the formation of the corpus luteum [11] but also suggests that the short form of the prolactin receptor is required for this process. This potential angiogenic effect of the short form may target luteal cells and/or the endothelial cells that eventually form luteal blood vessels. The latter represents an exciting alternative, implying coordinated actions of prolactin in luteal and endothelial cells to support corpus luteum formation. In this scheme, the long form of the receptor mediates the effect of prolactin in luteal cells, whereas the short form acts on endothelial cells to stimulate angiogenesis.

In the corpus luteum of rodents, the highest proliferative activity of endothelial cells takes place during the second day of pregnancy [12], at the time when this gland regresses in both prolactin receptor knockout and long form knock-in mice. Moreover, prolactin stimulates the proliferation of luteal endothelial cells [12], whereas the expression of angiogenic genes decreases in the absence of prolactin signaling [13]. The study by Le et al. [6] suggests that the short form of the receptor mediates this effect of prolactin and directly controls the development of the vascular supply in the growing corpus luteum. The enrichment of the short form in endothelial cells of the bovine corpus luteum further supports this conclusion [14]. Angiogenesis is critical in the development of cancer; hence, further analyses of how the short form of the prolactin receptor regulates angiogenesis will be useful.

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²Correspondence: E-mail: costocco@uic.edu

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