

# Response of the Corpus Luteum to Luteinizing Hormone

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The response of steroidogenic tissues to tropic hormones is regulated in part by specific receptors in the target cells for the stimulatory hormone. As a result of hormone binding to receptor the enzyme adenylate cyclase is activated with a resultant increase in intracellular levels of cAMP. Enhanced protein kinase activity then leads to increased steroidogenesis via several possible mechanisms, including direct activation of components of steroidogenic enzyme systems via phosphorylation.

The initial effects of tropic hormones such as LH are dependent upon the number of receptors present on the surface of the target cell. Numerous factors influence the number of LH receptors in the corpus luteum. A model is presented for the mechanisms involved in the loss and renewal of LH receptors in the luteal cell. The life of the LH receptor on luteal cells appears to be a single binding of hormone. The hormone-receptor complex is then internalized by endocytosis and the hormone is degraded in lysosomes. After internalization the receptor is also degraded in lysosomes or recycled via the Golgi apparatus. New or recycled receptors for LH are incorporated into the limiting membrane of protein containing secretory granules. One of the actions of LH is enhancement of the exocytosis of these secretory granules with incorporation of the limiting membrane (and the LH receptors?) of the granule into the plasma membrane of the cell. These proposed mechanisms explain the increase in the number of receptors for LH seen immediately after stimulation of the luteal cell with massive doses of LH and also explain the "down-regulation" of LH receptors 24 hr after administration of LH.

The purpose of this communication is to describe some of the mechanisms involved in the regulation of ovarian progesterone secretion by luteinizing hormone (LH). Particular attention will be given to the function of receptors for LH and the mechanisms involved in the regulation of LH receptor numbers. Although this discussion will, in general, be limited to the ovarian luteal cell, it is known that most of the mechanisms to be discussed are also operable in the ovarian follicle, the testes and the adrenal gland. Therefore, the concepts to be presented appear to be general and are likely to be applicable to all steroid secreting glands.

In mammals, LH secreted by the anterior pituitary gland appears to be the primary factor which regulates the secretion of progesterone from the corpus luteum (1-5). Other endocrine factors are also important for regulation of the lifespan and

function of the corpus luteum including prolactin in rodents, prostaglandins in domestic animals and rodents and placental or embryonic hormones in most species.

The actions of LH at the level of the luteal cell appear to be mediated via a specific receptor for this hormone in the plasma membrane (5-7). Interaction of LH with its specific receptors results in activation of adenylate cyclase and results in elevated intracellular levels of cAMP (8). The elevated cAMP results in enhanced activity of protein kinase and increased steroidogenesis (7, 9). There is evidence that the activity of at least two of the enzymes in the steroidogenic pathway in luteal cells is influenced directly by protein kinase. The activities of cholesterol esterase, the enzyme responsible for cleavage of the ester form of cholesterol to allow its utilization as substrate for steroidogenesis (10), and of cholesterol side-chain cleavage complex (11), which is thought to be the rate-limiting enzyme complex in steroid-secreting cells, both appear to be increased as a result of increased protein kinase

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activity. The effects of LH on steroidogenesis have been reviewed recently (5, 8).

The effects of LH are mediated via a specific receptor in the plasma membrane of target cells. Therefore, the responsiveness of the target tissue is dependent upon the number of receptors present on the cell. Thus, the factors which regulate the numbers of these receptors become important in regulating target cell function. There are several endocrine mechanisms which influence the number of receptors for LH on the luteal cell. First, dramatic elevations of LH itself can have both a positive (up-regulation) and a negative (down-regulation) effect on the number of receptors in target tissues for LH. Following administration of 1 mg of ovine LH to sheep there is a significant increase in the number of receptors for LH within 10 min but by 12 to 24 hr the total number of receptors is decreased to 20-30% of that seen prior to the injection (12). Within 48 hr the number of receptors for LH had returned to preinjection levels. There was a high degree of correlation between the number of receptors occupied by LH at 10 min and the number lost by 24 hr. This observation suggests that loss of receptors for LH is coupled to binding of LH to the receptor.

The phenomenon of "down-regulation" of receptors for LH has also been demonstrated in rat luteal (13), follicular (14), and testicular (15) tissues. This phenomenon is more pronounced in studies using human chorionic gonadotropin (hCG) than when LH is employed due to the much longer life of hCG in the circulation (12). The biological significance of "down-regulation" of receptors for LH is unclear at the present time. In general, it appears to be a "pharmacologic" effect due to administration of massive quantities of exogenous hormone. The single exception may be the loss of LH receptors in follicular granulosa cells during luteinization, after the naturally occurring preovulatory LH surge (16, 17). However, this point is controversial, since Nimrod et al. (18) were unable to detect any significant loss of receptors for LH under physiological conditions.

It is important to point out that the use of "pharmacologic" levels of LH or hCG to study the kinetics of loss and renewal of LH receptors is necessary in order to magnify the relatively minor changes in receptor numbers which occur with the levels of LH which circulate normally. The use of these and other procedures has allowed us to formulate a hypothetical model for the mechanisms which modulate the turnover of LH receptors in the luteal cell membrane (5). It appears that LH binds to its specific receptor which results in activation of the intracellular events leading to enhanced pro-

gesterone secretion (5, 8). The LH-receptor complex is then internalized via endocytosis (19-22) and the hormone is subsequently degraded in lysosomes (23, 24). The receptor is either degraded in the lysosome or recycled. New receptor, synthesized in the endoplasmic reticulum, or recycled receptor is then incorporated into the limiting membrane of protein containing secretory granules at the level of the Golgi apparatus. Under the stimulatory action of LH, or other secretagogues such as beta-agonists or prostaglandin E<sub>2</sub>, the release of these granules is stimulated via exocytosis with the limiting membrane of the secretory granule along with the receptors for LH being incorporated into the plasma membrane of the cell (5, 24). This model would predict that stimulation of the luteal cell with large quantities of LH would result in exocytosis of large numbers of secretory granules and increased numbers of LH receptors immediately following stimulation (i.e., 10-30 min). However, after granule numbers are depleted, synthesis of new granules would be required before the process could continue. During this period of granule synthesis, LH-receptor complexes would continue to be internalized resulting in a net loss of receptor (down-regulation) from the plasma membrane. Thus, what is predicted and the experimental data are in good agreement. There is also good evidence that exocytosis of granules is associated with the secretion of progesterone (25).

Other hormones also play a role in the regulation of ovarian receptors for LH. In rats, prolactin appears necessary for normal numbers of receptors for LH in the corpus luteum (26). This role is consistent with the known biological effects of prolactin on luteal function in this species. However, prolactin does not appear to influence luteal function in cattle (3, 27) or sheep (28, 29). Although receptors for prolactin have been demonstrated in porcine luteal tissue (30), the role of this hormone in regulation of luteal function in this species has not been defined clearly. There is also good evidence that estradiol-17 $\beta$  and follicle-stimulating hormone act synergistically to induce LH receptors in the maturing rat follicular granulosa cell (17).

Finally, there is considerable information which correlates the number of receptors for LH and biological function of the corpus luteum. In rats, receptors for LH appear first in granulosa cells of the maturing follicle (17, 31) and as the follicle matures and increases in size the number of receptors for LH increases dramatically (16, 32-34). Then, after the preovulatory surge of LH the number of granulosa cell receptors for LH decreases. A similar pattern of receptor development has been reported in sheep (35) and pigs (36).

After ovulation the number of luteal receptors for LH appears to decrease (16, 37), although this point is controversial (18). Once the corpus luteum begins to develop, secretion of progesterone is correlated highly with the number of receptors for LH in rats (38, 39), cows (40), sheep (41), and women (42). Since basal levels of LH do not change throughout the luteal phase of the reproductive cycle and since the average association constant of the LH receptor for LH does not change (41) the increased number of total receptors for LH results in an increase in the number of receptors occupied by endogenous hormone. Therefore, there is also an excellent correlation between the number of LH receptors occupied by endogenous hormone and serum levels of progesterone. This was to be expected based on our current understanding of the actions of LH.

As the corpus luteum regresses during the late luteal phase of the reproductive cycle, there is a dramatic decline in the number of receptors for LH and serum levels of progesterone (41). The loss of receptors for LH during luteolysis in rats appears to be mediated by prostaglandin  $F_2\alpha$  ( $PGF_2\alpha$ ) (43). However, administration of a luteolytic dose of  $PGF_2\alpha$  to ewes during the mid-luteal phase of the estrous cycle resulted in decreased levels of progesterone in serum several hours before a decline in the number of receptors for LH (44). Thus, it appeared that the reduced number of receptors for LH was a result of luteolysis and not the mechanism whereby  $PGF_2\alpha$  induced luteal regression.

This brief review has provided an overview of the factors involved in the regulation of LH receptors and progesterone secretion in the luteal cell. For an in-depth examination of the various aspects of these subjects three recent reviews are recommended (5, 7, 8).

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