ROLE OF OXYTOCIN AND OXYTOCIN RECEPTORS IN THE SYNTHESIS OF PROSTAGLANDIN F2α IN RUMINANTS

Şevket ARIKAN* Taner PAMUKCU*

Geliş Tarihi: 14.01.2000

Summary: In recent years, considerable progress has been made in our understanding of the role of oxytocin receptor in the synthesis of prostaglandin F2α (PGF2α) and cyclic regression of the corpus luteum. In non-pregnant ruminants, PGF2α is released in a pulsatile manner from the uterus late in the oestrous cycle to cause regression of the corpus luteum. Specific oxytocin receptors are present on the endometrial cells of uterus. Binding of luteal oxytocin to the receptor stimulates the conversion of arachidonic acid to PGF2α, which has the ability to release oxytocin from the corpus luteum, and oxytocin, in turn, has the ability to release PGF2α from the uterine endometrium. This positive feedback between luteal oxytocin and uterine PGF2α ultimately causes the regression of the corpus luteum. Concentration of oxytocin receptors in uterine tissues increase several days before oestrus, peaks at oestrus, and declines thereafter. If pregnancy occurs, both secretion of luteal oxytocin and development of endometrial oxytocin receptors are suppressed. Inhibition of oxytocin secretion and suppression of receptor development may serve to save corpus luteum for pregnancy.

Key Words: Oxytocin, receptor, prostaglandin, corpus luteum, uterus, ruminant.

Prostaglandin F2α Sentezinde Oksitosin ve Oksitosin Receptörlerinin Ruminantlardaki Rolü


Anahtar Sözcükler: Oksitosin, reseptör, prostaglandin, korpus luteum, uterus, ruminant.

INTRODUCTION

Oxytocin is a polypeptide hormone produced by the hypothalamus and released from the posterior pituitary known as neurohypophysis. It is also produced by the corpus luteum of ruminants. An oxytocic activity in the luteal tissue was first noticed by Ott and Scott in 1910. After injection of corpus luteum extract into a cannulated goat mammary gland, they found a subsequent increase in milk secretion. This result was ignored until first radioimmunoassay measurement of oxytocin in luteal extract obtained from ovine corpus luteum by Wathes and Swann in 1982. Until this date the role of oxytocin in reproductive physiology was partly established, but the effect was thought to be caused by hypothalamic oxytocin. Since then, many studies have been performed to understand mechanism by which
Luteal oxytocin participates in reproductive physiology.

Considerable evidence now exists indicating that pulsatile release of oxytocin from the ovary initiates a chain of events, which leads to demise of the corpus luteum at the end of the oestrous cycle. In ewes, the pulse interval for uterine oxytocin secretion at the time of the luteolysis is 2.5±0.19 pulses per 12 hours. Furthermore, the presence of specific receptors for oxytocin in the ewe and bovine uterus is well established. However, receptor concentration is fluctuated throughout oestrous cycle. The concentration of endometrial oxytocin receptors rises towards the end of luteal phase and remains maximum during luteolysis, then declines in the early luteal phase (Table 1).

Receptor formation appears to be regulated by oestrogen and progesterone. Follicular oestradiol induces endometrial oxytocin receptors which lead uterine secretion of PGF2α in a pulsatile manner. In ewes, 5 pulses of PGF2α within 24 h are necessary to cause luteal regression.

Table 1. Endometrial oxytocin receptor concentrations (fmol/mg protein) throughout the oestrous cycle of ewes.

<table>
<thead>
<tr>
<th>Days of cycle</th>
<th>Oxytocin receptors</th>
<th>No of ewes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>455.7±29</td>
<td>4</td>
<td>(13)</td>
</tr>
<tr>
<td>4</td>
<td>55.9±32</td>
<td>3</td>
<td>(13)</td>
</tr>
<tr>
<td>10</td>
<td>15.7±1.6</td>
<td>4</td>
<td>(9)</td>
</tr>
<tr>
<td>15</td>
<td>248.6±67</td>
<td>6</td>
<td>(14)</td>
</tr>
<tr>
<td>17</td>
<td>539.5±96</td>
<td>12</td>
<td>(15)</td>
</tr>
</tbody>
</table>

Oxytocin administration causes PGF2α secretion in the cow and sheep. This response increases as the luteal phase progresses and is maximal at the time of luteolysis. Furthermore, oxytocin administered during the early luteal phase induces a shortening of the bovine oestrous cycle, but this does not occur if this is given in the mid-luteal phase. In addition to oxytocin, administration of PGF2α causes the release of oxytocin from the corpora lutea of sheep. Active and passive immunisation of ewes against oxytocin is prolonged the luteal phase of the oestrous cycle. Therefore, the secretion of oxytocin from corpus luteum and expression of oxytocin receptors in the uterine endometrium are considered to be important in controlling the episodic patterns of PGF2α in both ewes and cows.

LUTEAL OXYTOCIN

The quantity of oxytocin produced in the corpus luteum varies throughout the oestrous cycle both in cow and ewe. The cyclic variation in the bovine ovarian oxytocin is shown in Table 2. The oxytocin concentration in the corpus luteum reaches its peak in the mid-luteal phase and then it falls as luteal regression begins. Both incubation of luteal cells in vitro and immunohistochemical studies have shown that the hormone resides in the large luteal cells.

Table 2. The cyclic variation in the bovine ovarian oxytocin.

<table>
<thead>
<tr>
<th>Days of cycle</th>
<th>Oxytocin</th>
<th>No of ewes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>38.00±26.0</td>
<td>7</td>
<td>(19)</td>
</tr>
<tr>
<td>5-10</td>
<td>1774±125</td>
<td>3</td>
<td>(20)</td>
</tr>
<tr>
<td>10</td>
<td>2000±139</td>
<td>12</td>
<td>(19)</td>
</tr>
<tr>
<td>8-13</td>
<td>1374±908</td>
<td>10</td>
<td>(16)</td>
</tr>
<tr>
<td>11-17</td>
<td>986.0±223</td>
<td>6</td>
<td>(16)</td>
</tr>
<tr>
<td>18-20</td>
<td>55.40±20.6</td>
<td>6</td>
<td>(16)</td>
</tr>
</tbody>
</table>

ROLE OF PROGESTERONE AND OESTROGEN IN THE CONTROL OF UTERINE OXYTOCIN RECEPTORS

Endometrial oxytocin receptors are influenced by circulating levels of steroid hormones. The rise in oxytocin receptor
concentration coincides closely with progesterone withdrawal and the preovulatory rise in oestrogen levels\textsuperscript{21}. Hixon and Flint\textsuperscript{22} showed that administration of a luteolytic dose of oestradiol leads an increase in the concentration of uterine oxytocin receptors before the onset of episodic PGF\textsubscript{2\alpha} secretion and luteolysis. Furthermore, a positive correlation between plasma oestradiol concentrations and uterine oxytocin receptors, and a negative correlation between plasma progesterone concentrations and oxytocin receptors are also reported\textsuperscript{23}.

Changes in uterine secretory responsiveness to oxytocin that occur during the oestrous cycle may arise due to ovarian steroids. Oestradiol from ovarian follicles and progesterone from corpus luteum have a controlling influence on the oxytocin receptor concentration and the uterine PGF\textsubscript{2\alpha} response to oxytocin\textsuperscript{24}. The increase in the concentration of oxytocin receptors around luteolysis coincides with a fall in the concentrations of progesterone in plasma in ewes\textsuperscript{21,25}. In ovariolectomized ewes, administration of progesterone initially decreases the receptor concentrations, but if treatment is continued progesterone loses its inhibitory effect after 10 to 14 days and receptors reappear\textsuperscript{24,26}. However, administration of progesterone during the first 3 days of the oestrous cycle results in the premature release of ovarian oxytocin and uterine PGF\textsubscript{2\alpha}\textsuperscript{27}. Administration of oestrogen alone to anoestrous animal increases the number of oxytocin receptors on the uterine endometrium and myometrium\textsuperscript{28}. However, administration of oestrogen and progesterone together initially depress endometrial oxytocin receptors in ovariolectomized ewes, but the presence of oestrogen after prolonged progesterone treatment or progesterone withdrawal enhances both the oxytocin receptors and the PGF\textsubscript{2\alpha} response to an oxytocin challenge\textsuperscript{29}. In the ovarian auto-transplanted ewe, administration of exogenous oestrogen provides a positive stimulus for the release of ovarian oxytocin and uterine PGF\textsubscript{2\alpha}\textsuperscript{30}. It is also suggested that chronic treatment of ewes with oestradiol during the cycle (for 20 days, beginning on day 4 of the cycle) can prolong the inter-oestrous interval by reducing uterine concentration of oxytocin receptors and hence oxytocin-induced secretion of prostaglandin\textsuperscript{31}.

### PROSTAGLANDIN F\textsubscript{2\alpha} SECRETION IN RESPONSE TO OXYTOCIN

Administration of oxytocin was first shown to stimulate endometrial PGF\textsubscript{2\alpha} secretion in anoestrous ewes by Sharma and Fitzpatrick\textsuperscript{32} and subsequently in cycling ewes by Roberts et al.\textsuperscript{25}. For much of the oestrous cycle, the uterus cannot secrete PGF\textsubscript{2\alpha} in response to oxytocin\textsuperscript{33}. Effects of progesterone withdrawal on uterine secretion of PGF\textsubscript{2\alpha} in response to oxytocin in ewes were investigated by Kaminski et al.\textsuperscript{34}. They demonstrated that the increase in uterine secretory responsiveness to oxytocin is dependent on oestradiol replacement in ovarioectomized ewes.

The human oxytocin receptor has been cloned and shown to encode a 388-aminoacid polypeptide\textsuperscript{35}. Binding of oxytocin to its endometrial receptors activates a G protein\textsuperscript{35} which mobilises intercellular calcium and activates protein kinase C to catalyse the hydrolysis of phosphoinositide\textsuperscript{36,37}. This in turn activates the synthesis of arachidonic acid from which prostaglandins are derived. Thus, the administration of oxytocin into the peripheral circulation by jugular vein will only result in increases in plasma concentrations of PGF\textsubscript{2\alpha} metabolite, 13, 14-dihydro 15-keto-PGF\textsubscript{2\alpha}, in venous blood if endometrial oxytocin receptors are present. Hence, an indirect measure of uterine oxytocin receptor function can be obtained by determining the sensitivity to oxytocin by measuring the release of PGF\textsubscript{2\alpha} from uterus in response to parenteral injection of oxytocin.

Uterine oxytocin receptor concentrations are low between days 3 and 13 of the cycle, but rapidly increase between days 14 and 16 post oestrous and reach maximum level on the day of oestrous in sheep\textsuperscript{21,25}. The presence of receptors on uterine endometrium allows exogenous oxytocin to cause rapid secretion of endometrial PGF\textsubscript{2\alpha}. Thus, the peripheral injection of a bolus of oxytocin during the early and mid-luteal phase has no effect on plasma PGFM, Whereas treatment between days 14 and 16 result in an increase to reach maximum level on day of oestrous\textsuperscript{33}.\textsuperscript{21}
INHIBITION OF OXYTOCIN RECEPTORS IN EARLY PREGNANCY

Normal pregnancy depends on a process called early embryonic signalling. This process is termed maternal recognition of pregnancy. Failure in the embryonic signalling leads to loss of the pregnancy and return to oestrous cycle as a result of luteolysis of corpus luteum and loss of progesterone secretion. Therefore, it seems essential that, in ruminant, the formation of the uterine oxytocin receptors and the pulsatile release of PGF2α must be inhibited for the establishment of pregnancy. Uterine endometrial oxytocin receptors and plasma progesterone concentrations on day 18, in cyclic and pregnant cows are shown in Figure 3.

The expression of oxytocin receptor in the uterine endometrium plays an important role in the initiation of luteolysis. During early pregnancy, the conceptus secretes trophoblast interferon that inhibits oxytocin receptor up-regulation and luteolysis. In ewes, the endometrial receptors for oxytocin are present early in oestrous cycle (days 0-3) decline and remain low until day 13 and then increase to their highest numbers at oestrous.

The suppression of the oxytocin receptors in the late luteal phase is a major component of the maternal recognition of pregnancy in domestic ruminants. Both receptor binding and autoradiographical studies have shown that endometrial oxytocin receptors are considerably reduced in early pregnancy. During the early pregnancy, a specific class of trophoblast interferon is released by the developing blastocyst and this interferon inhibits the formation of uterine oxytocin receptors. Hence, in vivo oxytocin injection fails to induce PGF2α production between days 13 and 20 of pregnancy.

The response to oxytocin administration in pregnancy apparently reappears by day 24, at the time when the endogenous interferon production falls. Therefore, the ability of the trophoblast interferon to inhibit uterine secretory responsiveness may be a transient phenomenon. Nevertheless, levels of oxytocin receptor genes (mRNA) are also two-fold lower in the endometrium of day 15 cyclic ewes receiving intrauterine injections of recombinant ovine trophoblast interferon from day 11 to day 14 compared to control ewes. The concentration of oxytocin levels is decreased after 18 day of pregnancy. After this period luteal oxytocin secretion is absent. Hence, episodic secretion of PGF2α fails.

Table 3. Endometrial oxytocin receptor (fmol/mg protein) and plasma progesterone concentrations (ng/ml) on day 18, in cyclic and pregnant cows.

| Table 3. Sikkusun 18. gününde gebe ve gebe olmayan ineklerde, endometrium okisitosin receptors (fmol/mg protein) ve plasma progesteron (ng/ml) konsantrasyonu |
|---------------------------------|----------------------|------------------|
| Cycle  | Pregnant  |
| Oxytocin receptors | 563.4±117            | 18.1±4.6         |
| Progesterone        | 0.93±0.4              | 8.37±0.7         |
| No of cows         | 4                     | 6                |

CONCLUSIONS

In this review, the interaction among prostaglandin, oxytocin and oxytocin receptors at luteolysis and at the time of maternal recognition has been discussed. It has been suggested that a better understanding of these interactions could lead to advances in the control of cyclic activity and to decrease in early embryonic loss in ruminants. There is no doubt that real, authentic oxytocin, is present in the ruminant ovary and indeed, is synthesised there. It is now clear from work in ruminants that oxytocin and oxytocin receptors play a key role in reproductive processes. In the ruminants, the majority of luteal oxytocin is secreted during the early and mid-luteal phases at a time when receptors are not apparently present in the uterine endometrium. Thus, it seems that the endometrial response to oxytocin in vivo is regulated at the receptor level, rather than by circulating oxytocin concentrations. On the other hand, has to be stated that there is a lack of knowledge about relationship among oxytocin, oestrogen and progesterone receptors. Therefore, further studies are required to elucidate interrelationship between two steroid
hormones and between steroid and oxytocin receptors. Furthermore, additional studies regarding to oxytocin receptor gene (mRNA) might lead to a greater understanding of the mechanism of action of ovarian oxytocin in the future.

REFERENCES


