Introduction

The idea that oxytocin can control luteinizing hormone (LH) is not new, and has always been intriguingly controversial. This paper will discuss some of the reasons for the confusion and consider the emerging evidence that indicates an important role in regulating gonadotrophins for oxytocin. Both prior and subsequent to the definition of the classical hypothalamic-releasing factors the possibility that the hormones from the posterior lobe of the pituitary gland had roles as additional regulators in anterior pituitary gland hormone secretion was also investigated (Martini & Morpurgo 1955, Benson & Folley 1957, McCann 1957). The anatomical proximity of the two lobes of the pituitary gland and the reports of evidence for direct portal communication between them (Baertschi 1980) pointed to the potential for interactions. In addition, nerve fibres from the hypothalamus were observed to terminate on the hypophysial portal vessels (Silverman 1976, Zimmerman & Antunes 1976). For at least four decades the particular possibility that oxytocin is involved in LH regulation has been postulated (Shibusawa et al. 1955). Other related peptides, particularly arginine vasopressin and arginine vasotocin, have also been the subjects of investigations but discussion of these is not included in this short review. Although there have been regular reports concluding a positive gonadotrophin response to oxytocin (Martini et al. 1959, Melin 1971, Robinson et al. 1985), not all experiments studying the proposition were able to substantiate it (Giuliana et al. 1961, Salisbury et al. 1980, Lumpkin et al. 1983). A combination of the unearthing of the spectacular potency of gonadotrophin-releasing hormone (GnRH) and the lack of a consistently observed effect by oxytocin temporarily removed oxytocin from serious consideration as a regulator of gonadotrophins (Wathes 1984).

Production of a surge of LH in pro-oestrus is essential to the process of ovulation and thus to continuation of the species. In recent years, evidence has accumulated that the mechanisms modulating LH include an important contribution from oxytocin. Most observations on the relationship between oxytocin and gonadotrophins have been made on rats or humans; other experimental animals have not received the same attention in this area. Various experimental models have been employed in adducing a vital role for oxytocin.

Characteristics of the gonadotrophin response to oxytocin

Inferences made from in vivo experiments in which oxytocin is raised in (pseudo-) physiological conditions should be viewed with caution because there will be other, interfering factors. Nevertheless, there are reports of observations which link oxytocin to LH, such as a positive correlation between oxytocin and LH in suckling sows on day 10 post-partum (Rojkittikhun et al. 1993), and mastectomized cows which were attempting to suckle having a bigger percentage increase of oxytocin associated with higher maximum LH concentrations (Stevenson et al. 1994). Earlier studies, too, had reported observations of stimuli which elicit oxytocin inducing an increase in gonadotrophin activity (Kovacs et al. 1955).

Dispersed cells in culture have been used widely in recent investigations of secretory activity by peptides. An LH response to oxytocin, in a dose-dependent manner, was observed in pituitary cells from female rats (Evans et al. 1989a). The time-course of LH secretion was relatively slow, increased LH release being detectable at 3 h and more substantial amounts at 5 h. Thus oxytocin might be one of a group of physiologically important peptides which manifest some of their activity only after protracted incubation with target cells (Moore et al. 1988, Mayerhofer et al. 1993). The use of shorter incubation times than appropriate for oxytocin might explain some studies concluding that oxytocin does not have LH-releasing activity (Lumpkin et al. 1983). Similarly, a short infusion time was unable to induce a gonadotrophin rise in vivo (Chiodera et al. 1984).

The LH response to oxytocin is enhanced by an oestrogenic environment. When oestradiol was added to cells cultured in steroid-deficient media, LH release was markedly increased (Evans et al. 1992). On the other hand, the extra addition of progesterone or testosterone to the incubation mixture suppressed the effect of oestradiol. Oestrogen has also been recognised for some time as increasing oxytocin receptors in diverse tissues (De Kloet et al. 1986, Maggi et al. 1988, Chadio & Antoni 1989, Bale...
& Dorsa 1995) and increasing oxytocin receptor gene expression (Bale & Dorsa 1995). These observations suggest that certain in vivo experimental models for investigating oxytocin will be less productive than others if the endocrinological state is not suitable. A number of in vivo studies of females in a state with low oestrogen or high progesterone or studies of males did not observe an effect of oxytocin on LH (Ditlove & Faiman 1970, Vaughan et al. 1979; who also reported a suppressive effect on post-castration follicle-stimulating hormone rise), Dawood et al. 1980, Amico et al. 1989). However advancement of the LH surge was observed in women (Fig. 1) by administering oxytocin at a stage of the menstrual cycle with elevated oestrogen and allowing for delayed effects (Hull et al. 1995). A few observations of oxytocin modifying gonadotrophins in male systems have been reported (Shibusawa et al. 1955, Legros & Franchimont 1968, Melin 1971) although their significance is uncertain.

The source of oxytocin

Oxytocin is delivered to the anterior pituitary gland via the hypothalamo-pituitary portal blood vessels at a concentration approximately an order of magnitude higher than in the peripheral circulation (Gibbs 1984, Horn et al. 1985). These are concentrations which are able to stimulate LH release in vitro (Evans et al. 1992). Fibres that terminate in the external median eminence (Silverman 1976, Zimmerman & Antunes 1976) directly release oxytocin into hypophysial portal vessels, and are distinct from those terminating in the posterior pituitary gland (Horn et al. 1985, Verbalis et al. 1986). There is also a variety of evidence indicating that a second means of oxytocin reaching the anterior pituitary gland is by pre-terminal release from magnocellular neurones in passage to the posterior lobe (Holmes et al. 1986, Buma & Nieuwenhuys 1988, Antoni et al. 1990). It seems that little if any oxytocin is transported by the short portal vessels from the posterior lobe (Horn et al. 1985). Oxytocin is, also, synthesised locally in the anterior pituitary gland (Morel et al. 1988).

Cyclical patterns of oxytocin in the oestrous cycle

The concentrations of oxytocin which are found in the portal blood system are higher at pro-oestrus than at other times in the cycle (Sarkar & Gibbs 1984, Sarkar et al. 1992). Additionally, oxytocin in peripheral plasma is highest at this time (Windle & Forsling 1993), although it is unlikely, because of the relatively low concentrations, that the circulation is an important means of delivering oxytocin to the anterior pituitary gland. In humans, too, there are measurably higher levels of oxytocin in venous blood at mid-cycle (Amico et al. 1981, Mitchell et al. 1981, Kumaresan et al. 1983, Shukovski et al. 1989).

The role of oxytocin in non-pregnant females has been debated for some time. It is plausible that at this time (periovulation) the main role of hypothalamic oxytocin is control of gonadotrophins of the anterior pituitary gland, peripheral oxytocin being an example of redundant peptide production, in this case overflow from oxytocin synthesised and released from the hypothalamic nuclei in response to signals related to the anterior pituitary-ovarian axis.

Oxytocin has been found to vary also in several other endocrine compartments during the ovulatory cycle. In the hypothalamus, oxytocin in the supraoptic nucleus (SON) and paraventricular nucleus increases between pro-oestrus–oestrus and metoestrus–dioestrus (Greer et al. 1986, Windle & Forsling 1993) consistent with release to the adenohypophysis during pro-oestrus. On the other hand, oxytocin mRNA levels in the SON increase between metoestrus and oestrus (Van Tol et al. 1988), implying stimulation of synthesis over that period. In the neurohypophysis, oxytocin levels are highest at pro-oestrus (suggesting little prior stimulation of release) and lower levels are subsequently present at oestrus (Crowley et al. 1978, Windle & Forsling 1993). In addition, cyclical alterations of oxytocin in the cerebrospinal fluid (low at

![Figure 1](https://example.com/figure1.png)

Figure 1 When preovulatory women were infused with oxytocin for 2 h the time from the start of the infusion to the onset of the mid-cycle LH surge was less than in the group of women who were infused with saline. Reproduced by permission from Oxford University Press from Hull et al. (1995) Human Reproduction 10 2266–2269.
pro-oestrus) have been observed (Miaskowski et al. 1987).
It has been reported that oestradiol, a hormone which has
increased concentrations at pro-oestrus, induces oxytocin
gene expression in vitro (Burbach et al. 1990).

Site of interaction in the pituitary

The effects of oxytocin on LH release which were observed
in vitro on pituitary cells could conceivably have occurred
by cross-reaction via GnRH receptors. However, the
addition of a GnRH receptor antagonist to incubation
media inhibited the LH response to a GnRH agonist
analogue but not to oxytocin, indicating that a receptor
other than GnRH mediated the effect (Evans et al. 1989a).
On the other hand, stimulation of LH by oxytocin was
inhibited by a series of neurohypophysial hormone antag-
onists. Additionally, the selective oxytocin agonist,
Thr4Gly7-oxytocin, stimulated LH release from pituitary
cells in culture (Evans & Catt 1989). Thus the LH response
to the nonapeptide has been shown to be via specific
oxytocin receptors in the anterior pituitary gland.

Although oxytocin receptors have been characterised in
the anterior pituitary gland their cellular localisation is still
being debated. A gonadotrophin site has not yet been
established. A complexity in these studies is that possibly
down-regulation of oxytocin receptors occurs but substanc-
tial hormone response is retained; the number of oxytocin
receptors apparently not being necessarily related to pro-
lactin secretory capability (Chadio & Antoni 1989). The
possibility that there is more than one subtype of oxytocin
receptor and gonadotrophs contain a type different from
lactotrophs has been suggested (Breton et al. 1995), per-
haps explaining an observation that oxytocin receptor
mRNA is localised to lactotrophs but not gonadotrophs.
A possibility proposing no oxytocin receptors on gonado-
trophs under all circumstances envisages that the oxytocin
effect on LH is paracrine (Samson et al. 1992). How-
ever, whether a functional oxytocin receptor–mediated
mechanism is invariably present (and so available for
experimental characterisation) and the possibility of
separate subpopulations of oxytocin receptor– and GnRH
receptor–containing cells are aspects yet to be resolved.
The conditions of investigation may be particularly
influential on the results obtained.

In contrast, oxytocin receptors on gonadotrophs would
seem the most likely explanation of an immediate response
to oxytocin, reflected by an early intracellular calcium
response to oxytocin in gonadotrophs (Kirillova 1995), and
a rapid component of the LH response in perifusion
experiments (Evans et al. 1989b). Possibly both endocrine
and paracrine processes operate; receptors to a particular
peptide are not necessarily confined to one cell type
(Rawlings et al. 1995). It is possible that other components
of the endocrinological complex bring one or other of the
processes into dominance. There are parallels in other
pituitary systems in which both effects function in certain

In vivo administration

An effect of oxytocin on LH has been demonstrated in in
vivo models also. Oxytocin administered to pro-oestrous
rats caused advancement of the LH surge and earlier
ovulation (Robinson & Evans 1990). Of particular import-
ance are the observations that antagonists to oxytocin
inhibit the peak of LH at pro-oestrus (Johnston & Negro-
Vilar 1988, Robinson & Evans 1990). These results
indicate that oxytocin is vital to endogenous production of
the LH surge. Peptides, including oxytocin, seem to be
one group of potential contributors to features of physio-
logical LH regulation which are not accounted for by
simple GnRH stimulation alone (Fink 1988, Leiva & de la

There have also been observations indicating that
oxytocin can influence LH release by an activity sited in
the hypothalamus. Release of LH after i.c.v. oxytocin in
marmosets has been reported (O’Byrne et al. 1990). It has
been proposed, on the basis of studies with oxytocin and
GnRH antagonists, that central oxytocin stimulates
GnRH neurones in rats (Johnston et al. 1992). Oxytocin
antibody administered i.c.v. inhibited the pro-oestrous LH
surge, peripheral administration was less successful and the
observations were interpreted to mean that the protein
needed to cross the blood–brain barrier to reach a central
source of oxytocin participating in LH control (Johnston
et al. 1990). However, another study observed no effect of
antiseran to oxytocin administered i.c.v. to ovariectomised
rats under conditions where adrenocorticotrophin and
growth hormone were altered (Franci et al. 1993). In
connection with postulated central actions it has been
observed, albeit in vitro, that oxytocin inhibits
GnRH release from the median eminence of male rats
(Gambacciani et al. 1986).

Indirect effects

In addition to the effects of oxytocin alone on LH
secretion, oxytocin has been observed to synergistically
enhance GnRH-stimulated LH release. The effect was
observed both in vitro (Fig. 2) (Evans et al. 1995) and in vivo
(Evans & Tulloch 1995). Possibly one role of oxytocin is in
the early part of the LH surge, after oestrogenisation of
the pituitary, when GnRH levels are still low. By enhancing
the activity of these low amounts of GnRH, oxytocin
would enable an earlier, more efficient development of the
LH surge. Furthermore the studies on pituitary pieces
in vivo suggested that oxytocin would additionally be able
to increase LH release at a later stage of the surge when
GnRH self-priming was also occurring. The reports,
although not of studies performed concurrently, that the oxytocin peak appears before the GnRH rise in portal blood (Sarkar et al. 1976, Sarkar & Gibbs 1984), are consistent with the concept that oxytocin sensitises the pituitary prior to full GnRH stimulation. Studies in humans (Hull et al. 1995), as well as in rats (Robinson & Evans 1990), in which oxytocin was effective in altering the LH surge when administered prior to an established rise in gonadotrophin, are consistent with oxytocin having an effect on the early parts of the process.

Conclusions

The physiological connection between oxytocin and LH release has yet to be definitively established. Thus in experimental studies the site of action of oxytocin has been indicated to be the hypothalamus and the pituitary, the mechanisms of action are possibly endocrine and paracrine, and oxytocin is derived from both the hypothalamus and the anterior pituitary. Which of these components is more important physiologically at any given stage of LH control is still to be determined. The robust response of LH under suitable conditions, the modulation of oxytocin activity by steroids and the cyclic variation of oxytocin levels provides substantial circumstantial evidence that oxytocin has an integral function in gonadotrophin control and is responsive to stimuli associated with the ovulatory cycle. This proposal is greatly strengthened by observations that removing endogenous oxytocin activity with antagonists prevents development of the LH surge. The reason many previous studies did not observe an effect of oxytocin on gonadotrophins, leading to conclusions that oxytocin had no gonadotrophin-related activity, can be understood in the light of the more recently obtained information.

These studies have so far been applied to a limited number of species. Indications that oxytocin influences LH have been obtained in rats, humans, dogs (Shibusawa et al. 1955), horses (Alexander et al. 1995), mice (Robinson et al. 1985) and rabbits (Martini et al. 1959, Melin 1971). There does not appear to be any conclusive evidence that gonadotrophins in sheep and cows exhibit a similar physiological response to oxytocin, and there is no rise in peripheral oxytocin approaching the LH surge (Schams et al. 1982, Walters & Schallenberger 1984). It is of yet uncertain value to note that the role of oxytocin in luteal demise is most prominent in these latter species. There are possibly species-specific control mechanisms in the hypothalamo-pituitary axis (Clarke et al. 1993) although this matter awaits investigation.

It should not be surprising to biologists who have come to realise the complexities of biological systems that several components make up control processes. It would not be disconcerting at this time, when many peptides have been found localised in several sites, for a peptide traditionally associated with a well-established function (such as milk ejection) to be found also involved in another (such as LH control). More recent experiments have altered the old prevailing concept that gonadotrophin control is almost entirely performed by GnRH, modulated by steroids. Because oxytocin has demonstrable activity in gonadotrophin control in human females there may be potential for oxytocin to be utilised in modulating fertility of women, and so improving personal and societal well being.
References


