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PLASMA OXYTOCIN CONCENTRATIONS DURING THE MENSTRUAL CYCLE

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Concentrations of oxytocin have been measured in plasma samples obtained daily from 6 women throughout complete menstrual cycles. Measurements of menstrual blood loss and plasma levels of luteinizing hormone (LH), progesterone and 17β-oestradiol suggested that normal ovulatory cycles were studied. A significant elevation in the circulating concentration of oxytocin was found in association with peak levels of LH. It is suggested that oxytocin may have a role in the process of ovulation in the human female.

oxytocin; ovulation; menstrual cycle

INTRODUCTION

It is widely believed that oxytocin plays a significant part in the mechanisms associated with the milk ejection reflex and parturition. Recently, however, the possibility has been raised that oxytocin may have a role in the luteolytic process since, in sheep, immunization against oxytocin was found to prolong luteal function (Sheldrick et al., 1980). Moreover, oxytocin has previously been shown to have luteolytic activity in intact cows (Armstrong and Hansel, 1959). In addition to a role in luteolysis, oxytocin has also been suggested as playing a certain part in the mechanism of ovulation based on the finding, in rhesus monkeys, of a mid-cycle peak in circulating oxytocin levels (Falconer et al., 1980). This suggestion of a role for oxytocin in ovulation is consistent with the ability of exogenously administered oxytocin antiserum to inhibit ovulation in rabbits (Roca et al., 1978).

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The presumptive evidence of a role for oxytocin in cyclical ovarian activity has led us to investigate possible variations in plasma oxytocin concentrations during the human menstrual cycle. A preliminary report of part of this study has been published (Mitchell et al., 1980a).

PATIENTS AND METHODS

Six women volunteers gave their full and informed consent to participate in this study. The age of the women ranged between 20 and 45 yr and all had histories of regular menstrual periods. None of the women were taking hormonal contraceptives or any form of medication during the period of the study. Peripheral venous blood samples were taken daily from these women throughout a complete menstrual cycle. Blood was taken into heparinized tubes and plasma was subsequently separated and stored at −20°C. All sanitary pads and tampons were collected during the menstrual period preceding the study cycle and the period ending the cycle. The menstrual blood content was measured using the method of Hallberg and Nilsson (1964).

Immunoreactive LH was measured by a double antibody radioassay in the Supraregional Laboratory, Department of Medical Biochemistry, Welsh National School of Medicine, Cardiff. The reference preparation for LH was MRC 68/40. Progesterone and 17β-oestradiol were determined by methods described previously (Turnbull et al., 1974). Oxytocin was measured by a sensitive and specific radioimmunoassay technique which has been fully described and validated elsewhere (Mitchell et al., 1980b). Intra- and inter-assay coefficients of variation are 9.4 and 13.9%, respectively, and the assay has a lower limit of sensitivity of 0.8 pg/tube. Recovery of standards from human plasma (accuracy study) when subjected to linear regression analysis gives $y = 0.93x + 0.41$ ($r = 0.99$); y = amount added, x = amount recovered (allowing for endogenous concentrations) and r = correlation coefficient.

Statistical differences were assessed by the Wilcoxon signed rank test. Results are quoted as mean ± SEM.

RESULTS

Menstrual blood loss was 34 ± 10 ml at the end of the cycle prior to the study and 28 ± 7 ml at the end of the study cycle. These values are considered to be within the usual range and much less than the 80 ml or more generally regarded as a definition of menorrhagia (Nilsson and Rybö, 1971). Progesterone and 17β-oestradiol levels exhibited normal qualitative and quantitative trends (data not shown). The results of the oxytocin determinations on samples from individual subjects are expressed diagrammatically in Fig. 1 and have been related to the day of maximal LH concentrations. Although there is considerable individual variation a strong trend emerges for elevated levels of oxytocin over the days around the LH peak with a less consistent trend for raised levels leading up to menstruation. The data have been grouped into intervals of 2 days (Fig. 2), with each subject contributing

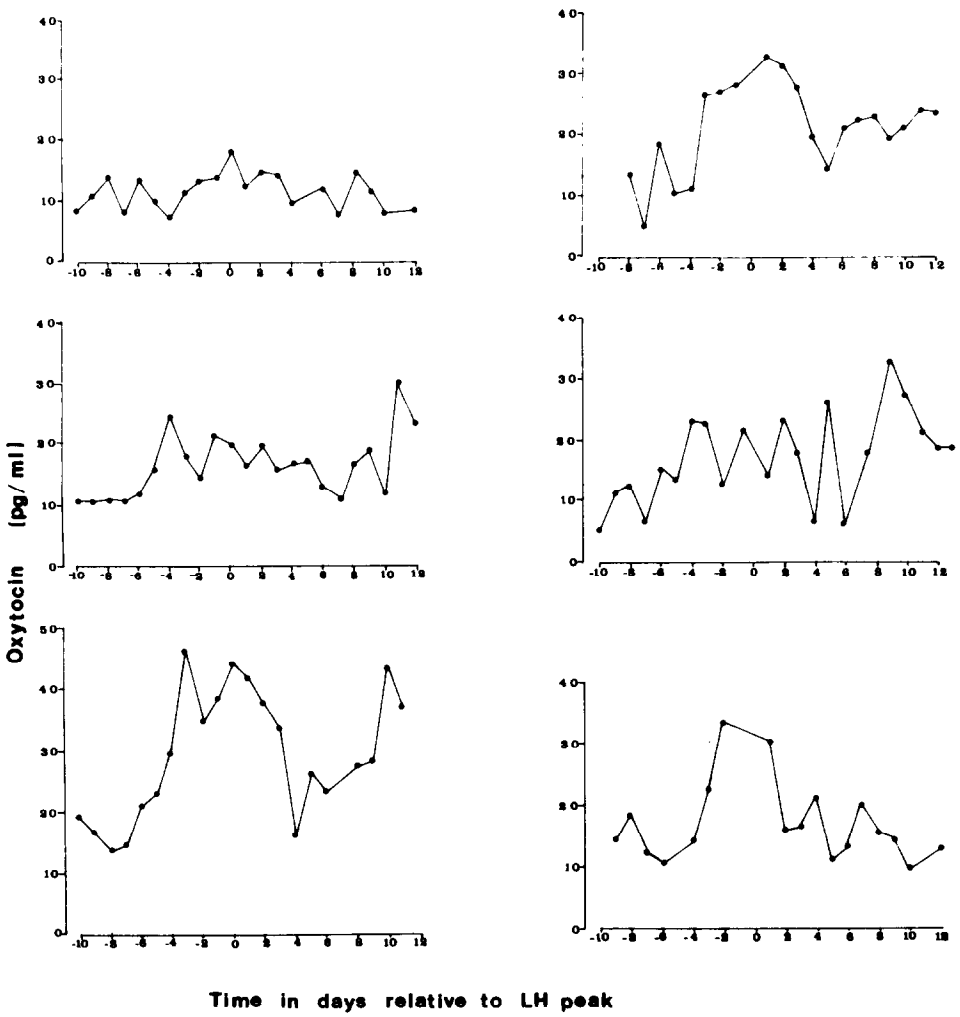

Fig. 1. Concentrations of oxytocin in the peripheral plasma of 6 spontaneously ovulating women throughout a menstrual cycle.

one value in each interval (mean taken where two results were available) to prevent bias. The grouping has allowed statistical analysis. Oxytocin concentrations were significantly higher ($P < 0.05$) at mid-cycle and 2—3 days before and after the LH peak than at 8—9 and 6—7 days before the LH peak. In order to clarify the temporal hormonal relationships during the menstrual cycle, plasma concentrations of progesterone, 17β-oestradiol and oxytocin in an individual subject have been plotted on the same time scale (Fig. 3). It can be seen that whereas 17β-oestradiol and oxytocin levels rise somewhat contemporaneously in the follicular phase of the cycle, in the luteal phase these hormones have diverse trends.

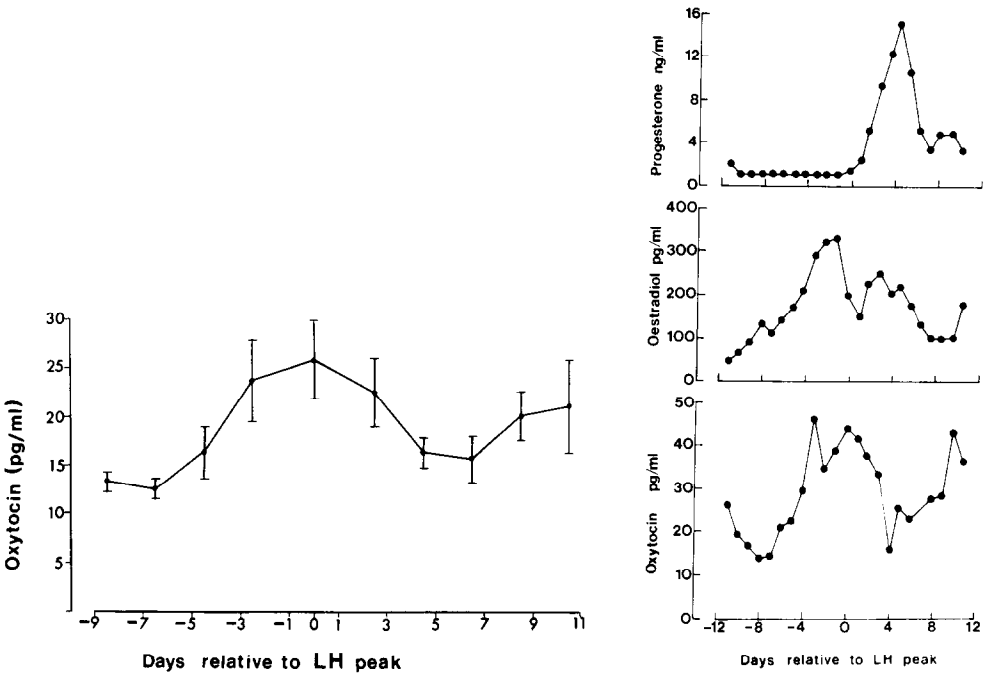

Fig. 2. Mean ± SEM concentrations of oxytocin in the peripheral plasma of 6 spontaneously ovulating women throughout a menstrual cycle. (For statistical differences between time periods see text.)

Fig. 3. Concentrations of progesterone, 17β-oestradiol and oxytocin in the peripheral plasma of a spontaneously ovulating woman throughout a menstrual cycle.

DISCUSSION

These results clearly demonstrate that, in spontaneously ovulating women, there is an approximate doubling of the circulating level of oxytocin associated with the time of ovulation. It is tempting to suggest that the elevated oxytocin concentrations play a part in the mechanism of ovulation. Although speculative, such a suggestion would be consistent with the inhibition of ovulation in rabbits produced by administration of oxytocin antiserum (Roca et al., 1978). Furthermore, a similar mid-cycle peak in plasma oxytocin levels has been described in rhesus monkeys (Falconer et al., 1980); these authors suggested that oxytocin may have a role in ovulation by inhibiting degradation of gonadotropin-releasing hormone (GRH) (Griffiths and Hooper, 1974) and hence providing more GRH for stimulation of LH (Robinson et al., 1976). Subsequently, LH may contribute to the further stimulation of oxytocin release since Swaab and Jongkind (1971) showed that gonadotropic hormones are capable of activating neurosecretory activity in rats.

Oxytocin is known to stimulate the release of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Sharma and Fitzpatrick, 1974; Mitchell et al., 1975; Roberts et al., 1975). Since $PGF_{2\alpha}$ is necessary for ovulation in some species (Lindner et al., 1980), it is possible that oxytocin may have its effect on ovulation via $PGF_{2\alpha}$ mediation.

The mechanisms controlling oxytocin secretion throughout the menstrual cycle are uncertain. It is known that oestrogen and progesterone will respectively potentiate and depress the release of oxytocin in response to vaginal stimulation in sheep and goats (Roberts and Share, 1969; Roberts, 1975). If these effects were reflected in basal secretion rates it could explain our finding of relatively parallel increases in 17β-oestradiol and oxytocin concentrations in the follicular phase of the cycle and the falling levels of oxytocin in the luteal phase despite rising 17β-oestradiol levels, perhaps due to progesterone suppression. The control of oxytocin action is probably closely related to the availability of specific high affinity binding sites. Oestrogen can increase the concentration of oxytocin binding sites whilst progesterone can suppress oxytocin binding to barely detectable levels (Soloff, 1975; Nissenson et al., 1978). During the human menstrual cycle, therefore, it is possible that maximal oxytocin-receptor concentrations would be seen shortly before ovulation concomitant with almost maximal circulating levels of oxytocin. Such a situation would be consistent with a role for oxytocin in the mechanism of ovulation.

The variable finding of a secondary rise in oxytocin levels associated with the time of luteolysis is intriguing. In sheep, there is a strong possibility that oxytocin forms a part of the luteolytic mechanisms probably via stimulation of $PGF_{2\alpha}$ secretion (Roberts et al., 1976). Present evidence suggests that in man, however, $PGF_{2\alpha}$ is not luteolytic, so that any effect of oxytocin would be either direct or through some other mediating factor.

In conclusion, we have demonstrated an association between ovulation in the human female and raised circulating levels of oxytocin. The hypothesis that oxytocin plays a significant part in the mechanism of ovulation has been put forward and may now be tested.

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