

Effects of naloxone or transient weaning on secretion of LH and prolactin in lactating sows

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Summary. Sows (N = 16) were infused intravenously for 8 h with saline or naloxone (200 mg/h) or their litters were transiently weaned for 8 h. Before infusion, 200 mg naloxone were administered to elevate quickly concentrations of naloxone. Blood samples were collected from sows at 15 min intervals for 24 h, beginning 8 h before and continuing until 8 h after imposition of treatments during the middle 8-h segment. Frequency of episodic release of LH and concentrations of prolactin were similar before, during and after infusion of saline. Average concentration of LH was greater during the last than during the middle 8-h segment when sows were given saline. Frequency of episodic release of LH increased and concentrations of prolactin decreased during infusion of naloxone or transient weaning; however, average concentration of LH increased during transient weaning, but not during infusion of naloxone. After transient weaning or infusion of naloxone, frequency of release of LH decreased, returning to pretreatment values in sows infused with naloxone but remaining above pretreatment values in sows subjected to transient weaning. At the resumption of suckling by litters in sows subjected to transient weaning, prolactin increased to levels not different from those observed during the 8-h pretreatment segment. Prolactin did not increase until 4–5 h after cessation of naloxone infusion. We conclude that continuous infusion of naloxone altered secretory patterns of LH and prolactin. Collectively these results provide evidence that the immediate effects of weaning on LH and prolactin in sows are mediated in part through a mechanism involving endogenous opioid peptides.

Introduction

Lactation in the sow is normally characterized by an absence of preovulatory-sized follicles, low blood concentrations of gonadotrophins and hyperprolactinaemia (reviewed by Britt *et al.*, 1985). Hourly administration of gonadotrophin-releasing hormone (GnRH) stimulates follicular growth, oestrus and ovulation in lactating sows (Cox & Britt, 1982a). Weaning results in increased GnRH in the hypothalamus, increased LH in the anterior pituitary (Cox & Britt, 1982b), an increase in frequency of episodic release of LH and a decrease in prolactin (Shaw & Foxcroft, 1985; Cox & Britt, 1986). Suckling therefore limits follicular growth by reducing secretion of GnRH by the hypothalamus.

Studies utilizing opiate agonists and antagonists have demonstrated that endogenous opioid peptides inhibit LH and stimulate prolactin (Meites *et al.*, 1979; Grossman & Rees, 1983; Bicknell,

1985; Malven, 1986). Administration of naloxone, an opioid antagonist, during lactation resulted in increased LH in rats (Sirinathsinghji & Martini, 1984), ewes (Gregg *et al.*, 1986), cows (Whisnant *et al.*, 1986), women (Ishizuka *et al.*, 1984) and sows (Barb *et al.*, 1986; Mattioli *et al.*, 1986) and suppressed serum prolactin in rats (Ferland *et al.*, 1978; Miki *et al.*, 1981; Sirinathsinghji & Martini, 1984), ewes (Gregg *et al.*, 1986) and sows (Mattioli *et al.*, 1986).

The objective of the present study was to test the hypothesis that endogenous opioid peptides mediate the effects of suckling on LH and prolactin in the sow. In preliminary studies, Armstrong *et al.* (1986b) were unable to establish that a single injection of naloxone (0.5–2 mg/kg) would consistently stimulate secretion of LH in lactating sows, even though each dose caused a significant suppression of serum prolactin concentration. In this study, therefore, we compared the effects of continuous antagonism of opioid receptors by infusion of naloxone for 8 h with those of physical removal of the suckling stimulus (transient weaning of litter) for 8 h on secretion of LH and prolactin.

Materials and Methods

Animals and treatments. Multiparous crossbred sows ($N = 16$, 187 ± 7 kg, mean \pm s.e.m.) that farrowed during April or July 1985 were used. Litter sizes were standardized within 48 h after parturition and sows and piglets were penned in individual farrowing crates throughout lactation. Sows were fed to appetite twice daily (07:00 and 16:00 h) a corn-soybean meal diet supplemented with vitamins and minerals according to NRC (1979) guidelines.

Lactating sows were used in two replicates to evaluate whether continuous blockade of opioid receptors by infusion of naloxone would cause changes in secretion of LH and prolactin similar to those which occur during physical removal of the suckling stimulus (transient weaning). In Replicate 1 (April 1985), sows were randomly assigned to one of the following treatments: (1) infusion of saline ($N = 4$), (2) infusion of naloxone (200 mg/h, $N = 4$), or (3) transient weaning of litters ($N = 4$). In Replicate 2 (July 1985), transient weaning alone was re-evaluated to corroborate its effect on frequency of release of LH. In both replicates, the designated treatment was imposed during the middle 8-h segment of a 24-h sampling interval.

Vena cava catheters were inserted (Armstrong *et al.*, 1986a) at least 24 h before the start of blood sampling. Sows were fitted with single (transient weaning) or dual (control and naloxone) catheters, and blood samples were collected at 15-min intervals for 24 h (06:00 to 06:00 h) encompassing the three 8-h segments before, during and after infusion or transient weaning. Samples were stored at 4°C for 18 h, centrifuged at 3000 g for 30 min and serum was decanted and stored at -20°C until assayed.

Transient weaning was accomplished by removing litters from farrowing crates and isolating them from sows for 8 h. Saline or naloxone (200 mg/h or 1.1 mg/kg/h) was infused (i.v.) at the rate of 24 ml/h through two identically calibrated Harvard (South Natick, MA) infusion pumps. Naloxone (E. I. DuPont de Nemours & Co., Wilmington, DE) was administered in solution with 0.87% (w/v) sodium chloride. Before infusion, 200 mg naloxone were administered (i.v.) to elevate concentrations of the opioid antagonist quickly. Control sows were treated with 10 ml saline before continuous infusion of saline.

Hormone assays. Luteinizing hormone was measured by validated radioimmunoassay procedures (Stevenson *et al.*, 1981) except that the antiserum (GDN No. 566) was used at an initial dilution of 1:90 000 and the period of incubation with antiserum was increased from 24 to 48 h. These changes reduced the mean assay sensitivity from 0.4 to 0.2 ng/ml. All samples collected were analysed for LH and intra- and inter-assay coefficients of variation (CVs) for 4 assays were 9.0 and 10.6%, respectively. Prolactin concentrations were determined as previously described (Kraeling *et al.*, 1982). Every fourth sample collected was analysed for prolactin and the intra-assay CV was 9.0%.

Statistical analyses. Data for serum concentrations of LH and prolactin were analysed by split-plot analyses of variance (Gill & Hafs, 1971) using general linear models procedures (SAS, 1982). The 24-h sampling interval was divided into three 8-h segments representing the sampling times before, during and after treatment. Data were analysed first using a model with treatment, sow, segment and sample as discrete (class) variables. Treatment and segment and the segment \times treatment interaction were tested with sow within treatment and segment \times sow within treatment as the error terms, respectively. A split-plot analysis was then performed within treatment or within segment to define more clearly the effects of segment or treatment on prolactin or LH secretion. Error terms used to test treatment and segment in these two analyses were sow within treatment and the sow \times segment interaction, respectively. In all analyses, comparisons among means were made by Duncan's multiple range test (Steele & Torrie 1980) using the appropriate error mean square.

An episodic release of LH (LH peak) was defined by the method of Goodman & Karsch (1980). Basal LH was the mean of all samples during an 8-h segment excluding those associated with peaks. Amplitude of an LH peak was the difference between the maximal concentration during a peak and basal LH for that specific 8-h segment. Frequency and amplitude of LH peaks were analysed using a model with treatment, sow and segment as the independent variables as described for prolactin and LH concentrations.

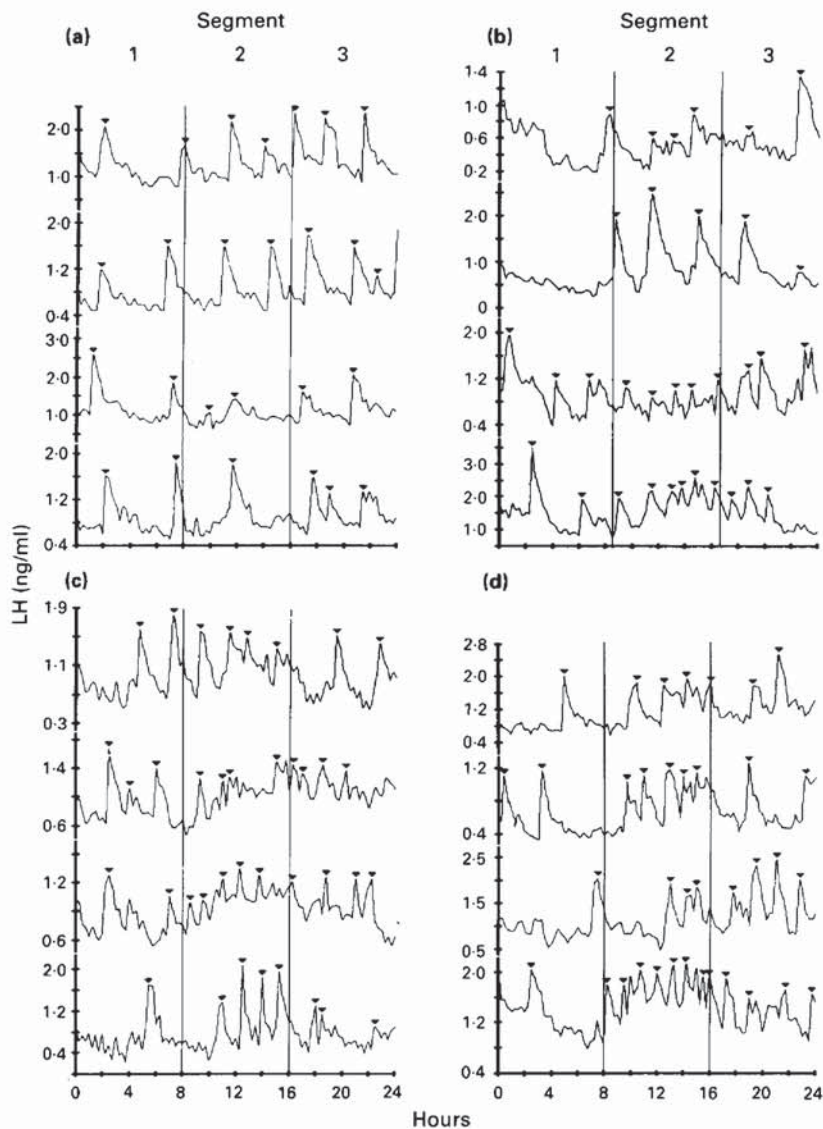


Fig. 1. Profiles of secretion of LH for individual sows before, during and after infusion of saline (a), infusion of naloxone (b), or transient weaning (c, Replicate 1; d, Replicate 2). Samples were obtained at 15-min intervals from 0 through 24 h. Infusion of saline or naloxone, or transient weaning occurred during the second 8-h segment. Note that values of LH on the y axis vary among individual sows. Triangles indicate an episodic release of LH.

Results

Characteristics of secretion of LH and average concentrations of prolactin are given in Table 1. Individual profiles of secretion of LH are in Fig. 1 and average concentrations of prolactin are in Fig. 2.

Neither frequency or amplitude of release of LH (Table 1; Fig. 1a) nor average concentration of prolactin (Fig. 2) was affected by infusion of saline. The average concentration of LH in sows

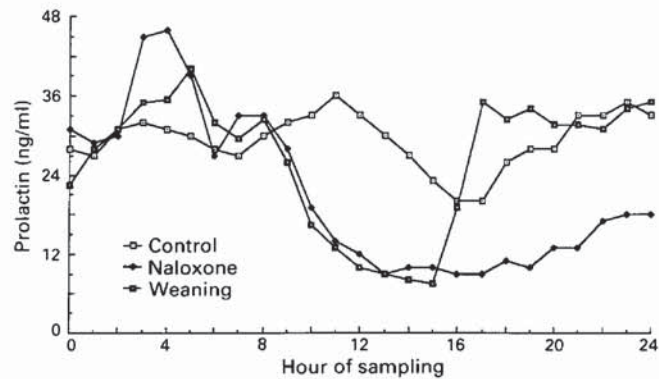


Fig. 2. Concentrations of prolactin before (0–8 h), during (8–16 h) and after (16–24 h) infusion of saline or naloxone or transient weaning (weaning). Standard errors (ng/ml) ranged from 1 to 7, 1 to 18 and 1 to 10 for control, naloxone-treated and transiently weaned sows, respectively.

Table 1. Average concentration of prolactin and characteristics of release of LH in lactating sows for 8-h segments before (Segment 1), during (Segment 2) and after (Segment 3) infusion of saline or naloxone (1.1 mg/kg/h), or transient weaning of the litter

Treatment	Measure	Segment 1	Segment 2	Segment 3
Saline	LH ng/ml	1.02 ± 0.3 ^{a,b}	0.99 ± 0.03 ^a	1.17 ± 0.04 ^b
	Peaks/8 h	2.00 ± 0.00	1.8 ± 0.3	2.5 ± 0.3
	Amplitude	0.98 ± 0.10	0.85 ± 0.14	0.82 ± 0.14
	Prolactin ng/ml	29 ± 1	29 ± 2	29 ± 11
Naloxone	LH ng/ml	0.88 ± 0.04	1.03 ± 0.03	0.92 ± 0.02
	Peaks/8 h	1.5 ± 0.6 ^a	4.3 ± 0.8 ^b	2.5 ± 0.3
	Amplitude	0.65 ± 0.31	0.66 ± 0.25	0.82 ± 0.05
	Prolactin ng/ml	35 ± 4 ^a	14 ± 2 ^b	13 ± 2 ^b
Transient weaning	LH ng/ml	0.93 ± 0.04 ^a	1.12 ± 0.03 ^b	1.06 ± 0.03 ^{a,b}
	Peaks/8 h	1.8 ± 0.3 ^a	4.5 ± 0.4 ^b	3.1 ± 0.4 ^c
	Amplitude	0.95 ± 0.14	0.65 ± 0.20	0.76 ± 0.11
	Prolactin ng/ml	32 ± 3 ^a	14 ± 2 ^b	33 ± 2 ^a

Values are mean ± s.e.m.

Means in same row with different superscripts are different ($P < 0.05$).

infused with saline was greater ($P < 0.05$) during the third than during the second 8-h segment (Table 1).

Infusion of naloxone resulted in an increase in frequency of release of LH ($P < 0.05$; Table 1; Fig. 1b) and a decline in prolactin ($P < 0.05$; Fig. 2). There was variation ($P < 0.05$) among

naloxone-infused sows in absolute frequency of LH release (Fig. 1b). Average concentration of LH and amplitude of LH release were not affected by naloxone ($P > 0.10$; Table 1).

Frequency of LH release during the 8-h segment after the end of the naloxone infusion was similar ($P > 0.10$) to the frequency during the 8-h pre-infusion segment (Table 1; Fig. 1b). Concentration of prolactin remained suppressed for 4–5 h after cessation of naloxone infusion (Fig. 2). Concentration of prolactin during the last 8-h segment in naloxone-infused sows was lower ($P < 0.05$) than concentrations during the pre-infusion segment and lower than concentrations observed during the last 8-h sampling segment in sows of the two other treatment groups (Table 1).

Changes in patterns of secretion of LH in individual sows in response to transient weaning are depicted in Fig. 1(c) (Replicate 1) and Fig. 1(d) (Replicate 2). Concentrations of prolactin and characteristics of LH release in sows subjected to transient weaning were similar between Replicates 1 and 2; therefore, values were averaged and are depicted in Table 1 and Fig. 2. Average concentration and frequency of episodic release of LH increased ($P < 0.05$) during transient weaning, but amplitude of release of LH was similar before, during and after transient weaning (Table 1; Figs 1c & d). Frequency of episodic release of LH declined ($P < 0.05$) after replacement of litters; however, it was still greater during the last 8-h segment than during the initial 8-h segment (Table 1). Average prolactin concentration decreased during transient weaning ($P < 0.01$, Table 1) and increased after replacement of litters (Fig. 2). Concentrations of prolactin during the last 8-h segment were similar between saline-treated sows and those subjected to transient weaning (Table 1; Fig. 2).

Discussion

In this experiment, transient weaning or chemical antagonism of opioid receptors with naloxone caused similar increases in frequency of episodic release of LH. The effects of naloxone reported herein are in agreement with results from other studies in which naloxone stimulated release of LH in lactating rats (Sirinathsingji & Martini, 1984), cows (Whisnant *et al.*, 1986), ewes (Gregg *et al.*, 1986) and sows (Barb *et al.*, 1986; Mattioli *et al.*, 1986).

Transient weaning for 8 h resulted in increased serum LH values (Fig. 1; Table 1), which is consistent with results from other experiments (Shaw & Foxcroft, 1985; Cox & Britt, 1986) in which samples were collected frequently for several hours. For example, Shaw & Foxcroft (1985) obtained samples at 15-min intervals from 12 h before until 48 h after weaning and demonstrated that frequency of release and concentration of LH increased after weaning.

Evidence from several studies indicates that the effect of suckling in the pig is mediated through the hypothalamus. Weaning results in an increase in GnRH in the hypothalamus and LH in the anterior pituitary (Cox & Britt, 1982a). Suckling does not block the anterior pituitary's ability to release LH in response to GnRH (Bevers *et al.*, 1981) and hourly pulses of GnRH in lactating sows results in follicular growth and ovulation (Cox & Britt, 1982a). Most evidence also indicates that the effects of opioids on LH are mediated through the hypothalamus and GnRH secretion (Drouva *et al.*, 1981; Ferin *et al.*, 1982; Rasmussen *et al.*, 1983; Wiesner *et al.*, 1984) rather than through effects exerted at the pituitary gonadotrope. For example, suckling suppressed GnRH levels in the medial basal hypothalamus and stalk median eminence (Cox & Britt, 1982a) in pigs and stimulated release of β -endorphin into hypophysial portal blood in ewes (Gordon *et al.*, 1987). However, two reports demonstrated that antagonists or agonists of opioid peptides could alter LH release from pituitary cells *in vitro* (Chao *et al.*, 1986; Blank *et al.*, 1986). While it is possible that opioids might have exerted direct effects on pituitary secretion of LH in the current study, this seems unlikely since Armstrong *et al.* (1986b) previously found that exogenous GnRH alone or GnRH plus naloxone caused the release of similar amounts of LH in lactating sows. Suckling and opioids therefore apparently modify LH in the pig through the hypothalamus. Although we did not measure changes in brain opioids in response to transient weaning, results reported herein are consistent with the concept that transient weaning alters opioid activity in the hypothalamus. In support of this

concept, we observed that administration of the opioid agonist, morphine, blocked the stimulatory effects of transient weaning on LH (Armstrong *et al.*, 1986c).

Results from these experiments also provide indirect evidence that suckling affects prolactin secretion in sows through a mechanism that involves opioids. Both transient weaning and infusion of naloxone resulted in similar declines in serum prolactin values. Others reported that weaning of the litter (Stevenson *et al.*, 1981; Shaw & Foxcroft, 1985) or administration of naloxone (Mattioli *et al.*, 1986) resulted in a decline in prolactin in the sow. Agonists of opioids typically elevate prolactin values (Bruni *et al.*, 1977; Meites *et al.*, 1979; Shaar & Clemens, 1980; Selmanoff & Gregerson, 1986) and suckling caused an increase in serum prolactin and β -endorphin concentrations in rats (Riskind *et al.*, 1984) and sheep (Gordon *et al.*, 1987).

The observation that prolactin increased slowly (Fig. 2) after cessation of naloxone infusion may be partly explained by the half-life of naloxone (30–40 min; Ngai *et al.*, 1976). Concentrations of prolactin began increasing in all naloxone-infused sows about 4–5 h after infusions were stopped. A single, small dose of naloxone (0.5 mg/kg) is sufficient to suppress serum prolactin values for about 60 min in lactating sows (Armstrong *et al.*, 1986b); therefore, the 4–5 h delay before prolactin began to increase in naloxone-infused sows in the present study may be related to the higher dose and to the difference in pharmacokinetics associated with constant infusion rather than a single intravenous injection. Alternative explanations for the slow increase in prolactin after cessation of naloxone infusion could be the development of acute tolerance or differences in sucking patterns by the litter. Owens & Cicero (1981) demonstrated that pretreatment with naloxone reduced naloxone-induced increases in serum LH in male rats. Naloxone administered to male sheep at 4-h intervals was associated with an incremental decline in the increase in LH after each injection of naloxone (Ebling & Lincoln, 1985). Differences in prolactin observed during the 8-h segment following cessation of naloxone or transient weaning may have been related to differences in the suckling activity of the litter. Although occurrence of suckling bouts was not recorded, litters in the transient weaning group initiated immediate vigorous sucking when returned to their dam, in contrast to the regular periods of sucking by litters in sows infused with naloxone.

Our results indicate that other factors may also contribute to the effects of suckling on LH and prolactin. Although both transient weaning and naloxone caused a significant increase in frequency of episodic release of LH, only transient weaning caused an increase in average concentration of LH (Table 1). Differences in LH and prolactin values between naloxone-infused and transiently-weaned sows were also observed during the 8-h segment after treatment. Frequency of episodic release of LH returned to pre-treatment levels after cessation of naloxone; however, frequency remained greater than pre-treatment values following cessation of transient weaning. Prolactin remained suppressed following cessation of naloxone, but returned to pre-treatment levels after cessation of transient weaning (Table 1). As discussed previously, the difference in response of prolactin to treatments may have been in part due to the half-life of naloxone or occurrence of suckling bouts; however, the same explanations cannot be true for the disparity in LH secretion observed after cessation of treatments. For example, if the effects of suckling were mediated exclusively by opioids, one would expect the stimulatory effects of naloxone on LH to persist after cessation of infusion (as was observed for the inhibitory effects toward prolactin). The opposite was observed; frequency of LH release was greater after cessation of transient weaning than after cessation of naloxone. This response would be consistent with the development of acute tolerance (Owens & Cicero, 1981; Ebling & Lincoln, 1985) or factors in addition to opioids may mediate some of the effects of suckling on LH.

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