OPIOID INHIBITION OF LUTEINIZING HORMONE SECRETION DURING THE POSTPARTUM PERIOD IN SUCKLED BEEF COWS

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ABSTRACT

Recent studies have shown that naloxone (N), an opioid antagonist, increases concentrations of luteinizing hormone (LH) in the postpartum anestrous beef cow. However, the LH response to N was influenced by the postpartum interval. For example, a significant LH response to 200 mg of N occurred on d 42 but not on d 14 or 28 postpartum. The present study was conducted to determine the effect of different doses of N on LH secretion during the postpartum period of beef cows. Twelve cows were given 200, 400 or 800 mg of N on d 14, 28 and 42 postpartum in a Latin square design with repeat measures within cells. On d 14, serum concentrations of LH increased (P<0.01) from 0.5 ± 0.1 ng/ml (mean ± SE) before N to a peak of 2.0 ± .5 and 1.4 ± .5 ng/ml for cows given 400 and 800 mg of N, respectively. In contrast, 200 mg of N had no effect on serum concentrations of LH. On d 28 and 42 all three doses of N elevated (P<.01) serum concentrations of LH. Therefore, a larger dose of N was required to increase serum concentrations of LH on d 14 postpartum compared with d 28 and 42. Based on these data we suggest that endogenous opioids participate in the regulation of LH secretion in the early postpartum period. The differential response to naloxone may be due to changes in endogenous opioid inhibition of LH secretion during the postpartum period.

(Key Words: Beef Cows, LH, Opioids, Naloxone.)

Introduction

During the early postpartum period in beef cows, hypothalamic content of gonadotropin releasing hormone (GnRH), pituitary receptors for GnRH and pituitary content of luteinizing hormone (LH) were similar to cycling cows (Moss et al., 1985). In addition, the pituitary of the postpartum cow releases LH in response to GnRH during the early postpartum period (Webb et al., 1977). These findings suggest that the decrease in pulsatile release of LH in postpartum anestrous cows was due to inhibition of GnRH release.

Release of GnRH from rat (Wilkes and Yen, 1980) and human (Rasmussen et al., 1983) hypothalami, in vitro, was stimulated by naloxone (N), suggesting that endogenous opioids inhibit GnRH release. More recently, Chao et al. (1985) found that N directly stimulated LH release from bovine pituitary cells in vitro. Wherever the site of action, N should be capable of releasing LH if endogenous opioids inhibit LH secretion early in the postpartum period. Whisnant et al. (1986b) reported that N increased serum concentrations of LH in postpartum anestrous beef cows. Administration of 200 mg N increased serum concentrations of LH at 42 d postpartum but not at 14 and 28 d postpartum. Lack of LH response to N at d 14 postpartum may indicate that endogenous opioids are not involved in the inhibition of LH secretion or, alternatively, that opioid inhibition is elevated such that 200 mg of N is insufficient to overcome this inhibition. Therefore, the objective of this study was to determine the effects 200-, 400- and 800-mg doses of N on LH secretion on d 14, 28 and 42 postpartum.

Materials and Methods

Twelve multiparous postpartum Angus cows averaging 448 ± 36 kg body weight were used in this study. The cows were given 200 (n = 4),
400 (n = 4) and 800 mg (n = 4) of N\(^8\) iv at 14 ± 1.2 d, 28 ± 1.2 d and 42 ± 1.2 d postpartum in a Latin square design with repeat measures within cells. Blood samples (10 ml) were taken at 15-min intervals for 2 h before and 2 h after the injection of N. On the day prior to blood sampling, a cannula was inserted into a jugular vein and ovarian activity was assessed by rectal palpation.

Blood samples were stored overnight at 4 °C, centrifuged and serum stored at −20 °C until assayed. Serum concentrations of LH were determined in all samples by radioimmunoassay (Whisnant et al., 1986a). The data were subjected to analysis of variance for differences between treatment groups at the sampling times and the interactions between time x day postpartum, time x dose of N and the time x day x dose interaction were determined using the Statistical Analysis System (SAS, 1979).

**Results**

Prior to N treatment on d 14, serum concentrations of LH averaged .5 ± .1 ng/ml (± SE) and were not different among groups. Administration of 400 or 800 mg N increased (P<.01) serum concentrations of LH. Peak serum concentrations of LH averaged 2.0 ± .5 ng/ml for the 400-mg group and 1.4 ± .5 ng/ml for the 800-mg group (figure 1). In contrast, 200 mg of N had no effect at 14 d postpartum. Three of four cows in the 800-mg group had increased serum concentrations of LH after N administration, while all four cows in the 400-mg group had elevated serum concentrations of LH. Cows that did not exhibit increased serum concentrations of LH after N administration were included in statistical analysis.

At 28 d postpartum, serum concentrations of LH prior to N administration on d 42 averaged .7 ± .1 ng/ml (figure 2) and were not different among groups. All three doses of N increased (P<.01) serum concentrations of LH. Serum concentrations of LH averaged 2.2 ± .5 ng/ml, 1.3 ± .5 ng/ml and 2.5 ± .5 ng/ml at 30 min after N treatment for the 200-, 400- and 800-mg groups, respectively. There were no differences among groups in the mean peak concentrations of LH after N administration. Three of four cows had increased serum concentrations of LH in the 200- and 400-mg groups while all four cows had increased serum concentrations of LH in the 800-mg group.

Serum concentrations of LH prior to N administration on d 42 averaged .7 ± .1 ng/ml and were not different among groups (figure 3). All three doses of N increased (P<.01) serum concentrations of LH in cows at 42 d postpartum.

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\(^8\) Sigma Chemical Corp., St. Louis, MO. Mention of a trade name, proprietary product or specific equipment does not constitute a guarantee or warranty by the USDA or the Univ. of Georgia and does not imply its approval to the exclusion of other products.
NALOXONE ON POSTPARTUM LH RESPONSE

2.2 2.1 Day 42
1.9 ~ 1.8
1.7 ~ 1.6
1.4 ~ 1.3
1.2 IT A
1.1 ~ 1.0
0.9 ~ 0.8
-120 -60
60 120
MINUTES BEFORE AND AFTER NALOXONE

Figure 3. Mean serum luteinizing hormone concentrations before and after naloxone treatment on d 42 postpartum (n=4/group; pooled SE = .4983). Naloxone was given at time 0.

Discussion

The results of this study add evidence that opioid inhibition of LH secretion decreases during the postpartum interval. This observation was supported by the fact that larger doses of N were required to increase serum concentrations of LH on d 14 than d 28 and 42 postpartum. In agreement with our previous research, (Whisnant et al., 1986b), 200 mg of N failed to increase serum LH concentrations of d 14 postpartum. In contrast to the previous research, 200 mg of N increased serum concentrations of LH on d 28. The reasons for these differences are not readily apparent. Perhaps nutritional status or other environmental factors were responsible for these differences. Recently, Gregg et al. (1985) reported that N administration increased concentrations of LH in beef cows between 24 and 35 d postpartum.

Naloxone administration stimulated LH release in postpartum women on d 14, 18 and 25, but not on d 10 (Yen, 1984). These results are similar to the present study in that the effect of a single dose of N on serum concentrations of LH changed during the postpartum period. Schulz et al. (1982) found that the ability of N to increase serum concentrations of LH increased from d 10 to 16 of life in prepuberal female rats. Both studies demonstrate an interaction between N response and changing physiological states.

The differential effect of N on LH secretion could be due to changing endogenous opioid concentrations in the hypothalamus. Wardlaw et al. (1982) reported that brain β-endorphin levels were highest in rats in late pregnancy and at parturition and then decreased postpartum. After weaning of calves from their dams, Malven et al. (1986) reported increases in Met-Enk and DYN-17 concentrations in the preoptic area and hypothalamus which were concurrent with similar increases in LHRH concentrations. In the same tissue areas, β-endorphin concentrations were negatively associated with luteinizing hormone–releasing hormone (LHRH) in stalk-median eminence tissue.

The type of opioid receptor involved in modulation of LH secretion may change during the postpartum period. Naloxone binds with different classes of opioid receptors with different affinities (Snyder, 1984). Therefore, larger doses of N may be required to antagonize opioid affects mediated through kappa receptors compared with effects mediated through Mu receptors (Snyder, 1984).

There are other possible explanations for the results of the present study which do not directly involve endogenous opioids. For example, releasable pools of GnRH may increase with time postpartum, although Moss et al. (1985) found no difference in hypothalamic content of GnRH during the postpartum period. Furthermore, the ability of pituitary cells from postpartum cows to release LH was similar to luteal phase cows after 10 d postpartum. Webb et al. (1977) and Williams et al. (1982) reported that the LH response to GnRH increased until d 20 postpartum in beef cows. It is possible that differences observed in the present experiment could be attributed to a differential response to the pituitary during the postpartum period. However, it should be
noted that the response after N closely resembled a pulsatile release of LH, both in magnitude and duration (Whisnant et al., 1986b). On the other hand, the response after GnRH (Webb et al., 1977; Williams et al., 1982) represents an exaggerated response. It is unlikely that single pulsatile release of LH after N would deplete releasable pools of LH from the pituitary.

Finally, the opioid-adrenergic model proposed by Kalra and Kalra (1983) postulates an axo-axonic link between the endogenous opioid neurons and catecholamine neurons that control LHRH secretion. It is reasonable to suggest that the responsiveness of the adrenergic system changes during the postpartum period and that the limiting factor may reside in this neuronal circuitry.

In summary, the involvement of the endogenous opioid peptides in regulation of LH secretion during the postpartum period of the beef cow is suggested. While the present study neither defines the specific area(s) of inhibition nor mechanisms of action, the data add evidence that opioid inhibition of LH secretion may decrease during the postpartum period of the beef cow.

Literature Cited


