The effect of bromocriptine on luteinizing hormone levels in the lactating sow: evidence for a suppressive action by prolactin and the suckling stimulus

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Abstract. Lactating sows (5 per group) were given no treatment or 10 mg bromocriptine orally twice daily from day 14 to 22 after parturition. Both groups were weaned at day 22. Frequent bleedings at 10 min intervals for 6 h were performed at 12, 16, 20 and 24 days after parturition. Prolactin and LH levels were measured in the collected blood samples by radioimmunoassays. Reduction of Prl by bromocriptine increased mean LH levels significantly and a further significant increase was observed after weaning. From the results it is concluded that in the lactating sow both Prl per se and the suckling stimulus are involved in suppression of LH levels.

That the lactating period is associated with reduced fertility is well established in many species (see for reviews Mc Neilly 1979, 1980). The endocrine mechanism responsible for it is only partly understood. In general, prolactin (Prl) levels are elevated, FSH levels are within the normal range, while LH levels are low. Whether the high levels of Prl or the suckling stimulus, alone or in combination are responsible for the suppression of LH secretion during lactation is not fully clarified. Data for the sheep (Kann et al. 1977) and for the rat (Lu et al. 1976) suggest that Prl alone plays an important role in the suppression of LH secretion. On the other hand data for the cow (Williams & Ray 1980; Carruthers & Hafs 1980) show that the neural suckling stimulus is clearly involved in the maintenance of lation anoestrus.

Under normal circumstances lactation in the domestic sow is characterized by suppressed ovarian follicular development and absence of corpora lutea (Crighton & Lamming 1969). Plasma levels of Prl are increased (van Landeghem & van de Wiel 1978; Bevers et al. 1978; Stevenson et al. 1981), levels of progesterone and oestrogen are low and FSH levels are comparable with non-lactating values (Stevenson et al. 1981; Duggan et al. 1982; Edwards 1982). The levels of LH are reduced with depression of the pulsatile pattern of secretion (Parvizi et al. 1976; Stevenson et al. 1981; Edwards 1982).

The purpose of this study was to investigate if Prl and the suckling stimulus are involved in the suppression of LH release in the lactating sow. Therefore the effect of bromocriptine treatment on LH levels in lactating animals was compared with LH levels in normal lactating and post-weaning sows.

Materials and Methods

Animals and experimental design

Ten lactating White Large sows of the same age and weighing between 110 and 130 kg, individually housed from about 1 week before parturition, were provided with an indwelling catheter in the external jugular vein. After surgery, performed at least 1 week before the start of the experiments, antibiotics (1 g chloramphenicol) were given in the food (a standard pig chow) twice daily. The mean litter size of the sows was 10.7 ± 0.6 (SEM). The piglets were allowed to suckle ad libitum and litter weighing was performed once a week. No additional food was given to the piglets. Before weaning they continuously stayed to the sows. The sows were randomly assigned to one of the two experimental groups (N = 5 for each group). The animals in the first group received
no treatment and served as controls. The second group received 10 mg bromocriptine orally (Parlodel; Sandoz, Basel, Switzerland) twice daily from day 14 to day 22 after parturition. At day 22 the sows in both groups were weaned. At day 12, 16, 20 and 24 after parturition the sows were all bled at 10 min intervals during 6 h (from 09.00–15.00 h), resulting in 37 samples per sow per frequent sampling period. Bloodsamples were collected in heparinized tubes, centrifuged and the plasma stored at −20°C until assayed.

**Hormone determinations**

Plasma hormone concentrations were measured in all bloodsamples by specific, sensitive double antibody radioimmunoassays. Porcine LH was determined according to the method described by Colenbrander et al. (1977). The sensitivity of the assay was 0.2 µg/l. The intra- and inter-assay coefficients of variation were 2.3% (at 44% relative bound) and 16.4%, respectively. Samples with undetectable LH levels, predominantly restricted to a number of samples collected at day 12 after parturition were arbitrarily assigned a value of 0.2 µg/l. Porcine Prl was measured by the method of Bevers et al. (1978). The intra- and inter-assay coefficients of variation were 1.8% (at 46.1% relative bound) and 15.1%, respectively. The sensitivity of the assay was 0.4 µg/l.

**Statistical analysis of the data**

Mean LH values were calculated for each 6 h sampling period (n = 37) to produce a representative hormone concentration for an individual animal. These values were then meaned together within groups for a particular day and designated: overall mean.

Parametric distribution of the data was confirmed by Davids test. Intra-group differences during lactation were assessed by analysis of variance followed by multiple comparisons according to Scheffé (Sokal & Rohlf 1969). Differences before and after weaning were tested for significance by paired Student’s t-test (one-tailed) and inter-group differences were assessed by non-paired Student’s t-test (two-tailed). Data were judged as being significant at P ≤ 0.05.

**Results**

The overall mean Prl levels in both experimental groups before bromocriptine treatment, confirmed the random assignment of the sows (Table 1). It appeared that oral administration of 10 mg bromocriptine twice daily declined Prl levels in lactating sows to values not significantly different from post weaning levels. In the period from 10 to 22 days after parturition the mean weight gain of the litters in the control group (17.40 ± 1.80 (SEM; n = 5) kg per litter) was not significantly different from the mean weight gain of the litters of the bromocriptine treated group (17.98 ± 4.01 (SEM, n = 5) kg per litter), indicating that total milk yields were not impaired by the treatment. Moreover observations of the sows and their litters revealed no reduced udder size or alterations in suckling behaviour in the bromocriptine group. Often sows continued eating and nursing during the frequent sampling periods, giving no sign of any discomfort.

Overall mean LH levels in the control group were almost equal during lactation but increased significantly after weaning. Addition of bromo-

### Table 1.

Overall mean (± SEM) plasma levels of Prl during lactation and post-weaning in bromocriptine treated and control sows.

<table>
<thead>
<tr>
<th>Days after parturition</th>
<th>Prl µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control sows (N = 5)</td>
</tr>
<tr>
<td>12</td>
<td>11.34 ± 0.85</td>
</tr>
<tr>
<td>16</td>
<td>6.74 ± 0.63</td>
</tr>
<tr>
<td>20</td>
<td>5.66 ± 0.69</td>
</tr>
<tr>
<td>24</td>
<td>0.95 ± 0.14</td>
</tr>
</tbody>
</table>

Bromocriptine treatment from day 14–22 after parturition and weaning at day 22.

### Table 2.

Overall mean (± SEM) plasma levels of LH during lactation and post-weaning in bromocriptine treated and control sows.

<table>
<thead>
<tr>
<th>Days after parturition</th>
<th>LH µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control sows (N = 5)</td>
</tr>
<tr>
<td>12</td>
<td>0.35 ± 0.07</td>
</tr>
<tr>
<td>16</td>
<td>0.35 ± 0.07</td>
</tr>
<tr>
<td>20</td>
<td>0.38 ± 0.04abc</td>
</tr>
<tr>
<td>24</td>
<td>0.56 ± 0.08a</td>
</tr>
</tbody>
</table>

Bromocriptine treatment from day 14–22 after parturition and weaning at day 22. Values with the same superscript (a–d) were significantly different (P ≤ 0.05).
Bromocriptine treatment from day 14–22 after parturition and weaning at day 22.

Table 3.
Mean (± SD) plasma levels of LH in individual sows over a frequent sampling period (6 h) during lactation and post-weaning (n = 37).

<table>
<thead>
<tr>
<th>Sow number</th>
<th>LH µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days after parturition</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>0.21 ± 0.03</td>
</tr>
<tr>
<td>85</td>
<td>0.61 ± 0.35</td>
</tr>
<tr>
<td>87</td>
<td>0.37 ± 0.15</td>
</tr>
<tr>
<td>701</td>
<td>0.33 ± 0.11</td>
</tr>
<tr>
<td>708</td>
<td>0.22 ± 0.05</td>
</tr>
<tr>
<td>Bromocriptine treated</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>0.33 ± 0.11</td>
</tr>
<tr>
<td>82</td>
<td>0.55 ± 0.32</td>
</tr>
<tr>
<td>84</td>
<td>0.29 ± 0.12</td>
</tr>
<tr>
<td>705</td>
<td>0.21 ± 0.05</td>
</tr>
<tr>
<td>704</td>
<td>0.28 ± 0.05</td>
</tr>
</tbody>
</table>

Bromocriptine to lactating sows increased overall mean LH levels significantly during the period of treatment and was followed by a further significant increase after weaning (Table 2).

Mean LH levels of individual animals in both groups during the various periods of frequent bleeding are presented in Table 3. Only sow 85 deviated markedly from the picture of Table 2. The data in Tables 2 and 3 demonstrate that 2 days of bromocriptine feeding already increased LH levels although this was not significant. The standard deviations in Table 3 are an expression of the pulsatile character of LH release, present in almost all the periods of frequent bleeding.

Analysis of the graphic data tended to an increased frequency of LH peaks during bromocriptine treatment and after weaning but this increase did not achieve statistical significance.

Discussion
Low basal Prl levels as a consequence of twice daily orally administration of 10 mg bromocriptine to lactating sows have already been described (Benjamnsen 1981; Bevers et al. 1981). These low Prl levels did not result in an inhibition of lactation as can be concluded from the weight gain data of the litters in both experimental groups. Benjamnsen (1981) also reported that a similar treatment of lactating sows with the same dose of bromocriptine had no effect on growth and suckling behaviour of the piglets. A dose-dependent lactation suppression with bromocriptine in minipigs and pigs has been described by Flückiger (1972). Orally treatment of pregnant sows with 10 mg bromocriptine twice daily from about 1 week before parturition causes a complete inhibition of udder development and impedes the onset of lactation (Taverne et al. 1982). Bromocriptine treatment of sows shortly after parturition also suppresses lactation (Smith & Wagner 1980). Similar data have been published for the cow (Schams 1974) and the goat (Hart 1973) in which animals bromocriptine is also a potent inhibitor of Prl secretion but inhibition of lactation is only achieved when the drug is given shortly before or after parturition. Obviously in these species Prl is essential for lactogenesis, but less important for galactopoiesis (Schams 1975).

It is accepted that a major factor controlling the
lack of sustained follicular development during lactation is the inadequate secretion of LH. Previous studies (Parvizi et al. 1976; Edwards & Foxcroft 1983) reporting suppressed LH levels during lactation followed by an increase after weaning are in agreement with the presented results concerning the control sows. The close coupling of hyperprolactinaemia to the suckling stimulus (van Landeghem & van de Wiel 1978; Bevers et al. 1978; Mulloy & Malven 1979) makes it difficult to find out which of both factors is responsible for the inhibition of LH secretion. The data presented in this paper indicate that both PRL per se and the suckling stimulus per se are involved. Depression of the elevated PRL levels, with maintenance of the suckling stimulus, resulting in a significant LH increase strongly indicates an inhibitory action by PRL itself. As the growth of the piglets in the litters of the bromocriptine treated sows is not retarded we assume that the suckling stimulus is not different from that of the control sows. When milk production is not inhibited there is no reason to suspect a change in suckling behaviour the more so as bromocriptine does not depress the milk ejection by suppression of oxytocin release as has been shown for several other ergot compounds (Thorner et al. 1981). A reduced availability of milk would have resulted in a higher suckling frequency and therefore even in more depressed LH levels instead of the observed increase during bromocriptine treatment.

Weaning again significantly increases LH levels, indicating a depression of LH by the suckling stimulus, possible by a direct neural suppression of LH releasing hormone secretion. The mechanism suggested for the rat by Minaguchi & Meites (1967), although later changed (Meites et al. 1978), that suckling acts on the hypothalamus to suppress release of LRH and of PIF, subsequently leading to decreased LH and increased PRL secretion seems not to be true for the sow. The delayed significant effect of bromocriptine treatment on the LH levels in contrast to the faster clear LH response after weaning could be another indication that two different blockades are involved. Meites et al. (1978) also reported a delayed increase of LH in the rat after PRL inhibition with ergocornine methan sulphonate.

In this discussion it is assumed that the increase in LH levels, observed after bromocriptine treatment is primarily a consequence of the reduction of circulating PRL levels, although the dopaminergic system is involved in the regulation of gonadotrophin secretion (McNeilly 1980). However, infusions of dopamine into rats (Vijayan & McCann 1978) and men (Leblanc et al. 1976) suppress serum levels of LH. Bromocriptine inhibits the pre-ovulatory LH surge in adult rats at doses many times higher than those necessary to inhibit PRL secretion (Markó & Flückiger 1974). Subcutaneous injection of 120 mg bromocriptine into lactating sows, resulted in a decreased LH level for the 24 h period after the treatment (Kraeling et al. 1982).

In conclusion, the results of this study showed that PRL per se is involved in the suppression of LH release during lactation. From the data of previous studies (Elsaesser & Parvizi 1980; Stevenson et al. 1981; Bevers et al. 1981) it is supposed that the blockade of PRL is primarily at the hypothalamic level. However, the mechanism behind such a blockade requires more research. The absence of an effect of castration during lactation on LH levels (Stevenson et al. 1981) makes it unlikely that PRL acts in the sow by increasing the sensitivity of the hypothalamus to the negative feedback of gonadal steroids (McNeilly 1980) unless this effect is masked by the neural suckling stimulus, the other suppressor of LH levels during lactation in the sow.

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