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Dissertation title

Effects of osteopontin therapy at the first insemination after calving to improve fertility in dairy cows and the underlying changes in epidermal growth factor and leptin receptors in the endometrium

(分娩後初回授精時の乳牛に対するオステオポンチン投与による受胎性改善効果とその背景となる子宮内膜での上皮成長因子およびレプチン受容体の変化)

In cattle, endometrial epidermal growth factor (EGF) concentrations exhibit two distinct peaks on days 2–4 and 13–14 of the estrous cycle. The normal range of endometrial EGF concentrations on day 3 of the estrous cycle has been reported to be 4.70–13.50 ng/g tissue weight, whereas concentrations below 4.70 ng/g tissue weight indicate an altered EGF profile. In repeat breeder (RB) and high-yielding cows, a decrease or disappearance of these EGF peaks is associated with reduced fertility.

In RB cows, treatments with hormones (high-dose estradiol benzoate and an intravaginal progesterone device), partially purified milk-derived osteopontin (OPN), recombinant OPN (rOPN) expressed in *Escherichia coli*, and a partial peptide of OPN containing two integrin-binding motifs has been shown to normalize the EGF profile and improve fertility. However, the economic impact of OPN therapy would be further enhanced, if it could promote postpartum recovery of the endometrial EGF profile and improve fertility at the first artificial insemination (AI) after the voluntary waiting period (VWP). Therefore, Chapter 1 of this thesis examined the effects of OPN alone and in combination with hormonal therapy on EGF profile normalization and fertility at the first AI after the VWP.

In postpartum high-yielding cows with abnormal EGF profiles, treatment with rOPN (n = 23) and OPN peptide (n = 49) increased the normalization rates of the EGF profile (78.3% and 53.1%, respectively) and improved conception rates (47.8% and 61.2%, respectively), with both outcomes being higher than those observed in the control group (n = 40) (25.0% and 20.0%, respectively). Then the effect of combined treatment with hormone and OPN therapies

was examined since the two treatments are thought to improve fertility through different mechanisms. The combined treatment with OPN peptide (320 nmol) and hormonal therapy (n = 131) significantly increased both EGF normalization (40.5%) and conception rates (35.1%) compared with OPN peptide (320 nmol) treatment alone (n = 105) (21.9% and 19.0%, respectively). Treatment with the two doses of OPN peptide (320 and 1,600 nmol) showed no difference in EGF normalization and conception rates. The combined treatment of both doses of OPN peptide with hormone therapy (n = 226) increased EGF normalization (40.3%) and conception rate (39.1%) compared with both doses of OPN peptide treatments alone (n = 216) (26.4% and 30.1%, respectively).

Chapter 2 of this thesis investigated the relationship between endometrial EGF concentrations and Ob-R expression at the first AI after calving, as well as the effects of heat stress on these parameters in postpartum cows. Heat stress is one of the factors that may reduce EGF concentration and cause resistance to OPN treatment. Previous studies have reported that RB cows resistant to OPN therapy for normalization of endometrial EGF concentrations exhibit increased expression of the leptin receptor (Ob-R). Based on these findings, I hypothesized that a similar mechanism may underlie the reduced therapeutic effect of OPN during the hot season in postpartum high-yielding cows at the first AI after calving. Accordingly,

There was a positive correlation ($y = 46,604x + 4.3275$) between EGF concentration and Ob-R expression (6.16 ± 1.28 ng/g tissue weight and $3.39 \pm 2.02 \times 10^{-5}$, respectively) during the non-heat stress period; both EGF and Ob-R values (2.46 ± 1.54 ng/g tissue weight and $1.69 \pm 1.19 \times 10^{-5}$, respectively) decreased, and as a result, the correlation was lost during the summer heat stress period. The correlation observed during the non-heat-stress period suggests that leptin signaling may contribute to the regulation of endometrial EGF production under thermoneutral conditions. Conversely, the negligible correlation during the heat stress period indicates a functional uncoupling of leptin signaling from EGF production under heat stress conditions.

In conclusion, this thesis demonstrates that OPN treatment at the first AI after the VWP increases the proportion of cows with normal endometrial EGF profiles and improves conception rates. The findings further indicate that combining hormonal therapy with OPN treatment yields greater therapeutic efficacy than either treatment alone. Moreover, leptin signaling appears to support endometrial EGF production under thermoneutral conditions, whereas this relationship is disrupted under heat-stress conditions. Future studies are required to elucidate the molecular mechanisms by which OPN exerts its effects and to validate the observed association between EGF and Ob-R using larger sample sizes.