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Development and use of recombinant gonadotropin-releasing hormone vaccines to sterilize cattle: a review

Abstract
A possible alternative to conventional castration methods is the use of vaccines that can be injected in order to sterilize animals. One promising approach involves the use of a vaccine that causes cattle to produce an immune response against one of their own reproductive hormones, gonadotropin releasing hormone (GnRH). Immunization against GnRH results in a decrease in the amount of GnRH circulating within the animal's blood. Therefore, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are not stimulated to be released, and, subsequently their levels required for reproductive function. Experimentation has shown that immunization against GnRH can effectively block reproductive function in an age-independent manner but has little effect on carcass and growth parameters. However, about 10% of cattle tested do not respond when immunized against GnRH, regardless of dosing regimen. Further research is needed to improve the efficiency of potential GnRH immunocastration vaccines.; Dairy Day, 1997, Kansas State University, Manhattan, KS, 1997;

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DEVELOPMENT AND USE OF RECOMBINANT GONADOTROPIN-RELEASING HORMONE VACCINES TO STERILIZE CATTLE: A REVIEW

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Summary

A possible alternative to conventional castration methods is the use of vaccines that can be injected in order to sterilize animals. One promising approach involves the use of a vaccine that causes cattle to produce an immune response against one of their own reproductive hormones, gonadotropin releasing hormone (GnRH). Immunization against GnRH results in a decrease in the amount of GnRH circulating within the animal's blood. Therefore, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are not stimulated to be released, and, subsequently, their levels within the body fall below the levels required for reproductive function. Experimentation has shown that immunization against GnRH can effectively block reproductive function in an age-independent manner but has little effect on carcass and growth parameters. However, about 10% of cattle tested do not respond when immunized against GnRH, regardless of dosing regimen. Further research is needed to improve the efficiency of potential GnRH immunocastration vaccines.

(Key Words: Gonadotropin Releasing Hormone, Follicle Stimulating Hormone, Luteinizing Hormone, Antibody, Immunization.)

Introduction

Gonadotropin releasing hormone (GnRH) is a neuropeptide synthesized by neurons in the hypothalamus of the brain. GnRH travels to the anterior pituitary via the hypothalamic-hypophyseal portal system, where it triggers subsequent releases of FSH and LH. Released into general circulation, FSH and LH travel to the gonads, where they regulate steroid production, folliculogenesis in the ovary, and spermatogenesis in the testis.

The amino acid sequence of GnRH is common to all mammalian species; pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2. In theory, immunizing an animal against GnRH would elicit endogenous production of anti-GnRH antibodies within the animal's body. These antibodies then would recognize and neutralize endogenously produced GnRH. Immunization of cattle against GnRH would result in decreased releases of LH and FSH, which, in turn, would inhibit both testicular and ovarian development and function.

Immunization Effects in Heifers

Active immunization of postpubertal beef heifers, using a vaccine in which GnRH was conjugated to ovalbumin in complete Freund's adjuvant (CFA), was found to induce antibodies against GnRH at a level that could be detected in the serum. These same heifers also were found to have retarded follicular growth, with most ovaries showing no developing follicles. Pregnancy tests were negative for all immunized heifers (n=7) at the time of slaughter following an 8-week breeding period. In contrast, control animals had a pregnancy rate of 71%. Further studies found that active immunization of heifers against similar GnRH constructs resulted in decreases in: the number of receptors for GnRH within the pituitary, concentrations of LH within the pituitary, serum progesterone levels, ovarian weight, uterine weight, follicular development, and cyclic activity. Multiple immunization of cyclic beef heifers with GnRH conjugated to human serum albumin (HSA) and injected in diethylaminoethyl (DEAE)-dextran adjuvant not only invoked and maintained anti-GnRH titers, but also induced a state of anestrus in 29 of 34 heifers for 82.8 ± 6.9 days. This effect was not dependent on the dose of vaccine.

Research has shown that immunization of prepubertal heifers against GnRH can delay the onset of puberty. In 12-month-old heifers receiving two injections of GnRH-HSA in CFA 6 weeks apart, puberty was delayed by an average of 175 days. A single immunization delayed the onset of puberty by an average of 112 days. Presumably, these delays were due to decreases in the secretion of LH and FSH, which ordinarily stimulate development of the ovaries at the time of puberty.

A potential concern about the use of sterilization vaccines is that the immunization ultimately may cause a decline in the release of certain growth-promoting (anabolic) steroids. Multiple studies have demonstrated that GnRH-immunization treatments reduced average daily gain (ADG) in feedlot heifers but did not affect overall carcass quality. This decreased growth performance likely was due to reduced estradiol secretions from acyclic ovaries in GnRH-immunized individuals. This theory is supported by early research showing ovariectomized heifers as generally having reduced ADG rates. We should note, however, that reductions in ADG in both pre- and postpubertal heifers immunized against GnRH can be overcome by the use of estradiol implants. Additionally, these losses in ADG are less than those seen when heifers become pregnant in the feedlot.

A commercial anti-GnRH vaccine, Vaxtrate®, is currently in use in Australia. Vaxtrate is a GnRH-ovalbumin conjugate administered in a DEAE-dextran and mineral oil adjuvant. This vaccine is used primarily to prevent pregnancy in feedlot cows and heifers at times when pregnancy is of biological and economical disadvantage (pregnant animals generally gaining less and bringing a lower price per pound at slaughter). Cattle usually are dosed twice at an interval of 4 or 16 weeks. Currently, producers using Vaxtrate® are seeing an 80% decline in the incidence of pregnancy among vaccinated animals. Unfortunately, Vaxtrate® is not available in the United States because of restrictions placed on vaccine production by the Food and Drug Administration (FDA).

Immunization of Steers and Bulls

Both single- and double-dose administration of a vaccine consisting of GnRH conjugated to keyhole limpet hemocyanin (KLH) induced long-lasting, high levels of anti-GnRH antibodies. In these animals, LH concentrations in the serum were decreased, and immunized bulls also had retarded testicular growth and decreased epididymal weight. Immunization also elicited atrophy of secondary sex organs, including the prostate and seminal vesicles.

Immunization against GnRH did not affect the average daily gain in bulls and steers to the extent seen in heifers, and carcass characteristics of the immunized animals were comparable to those of control individuals. Immunization effects also were not dependent on age.

Considerations for Vaccine Production

In both bulls and heifers, one problematic aspect of vaccination against GnRH is the failure of some treated animals to respond to treatment—overall about 10% of all injected animals failed to respond to GnRH immunization whether given one or two injections. Additionally, research has shown that, in order to maintain castration status, repeated dosage is necessary in at least part of the cattle population. Success rate is dependent on several factors, including vaccine construct and adjuvant. Current research at Kansas State University is examining the efficiency of various construct/adjuvant combinations as well as investigating the potential use of an "immunological cocktail", which would elicit an immunological response against GnRH, LH, and FSH. The aim of these studies is to create an efficient, permanent vaccine for use in both male and female cattle, as well as satisfying the previously mentioned FDA requirements for vaccines used in food animals. One of these requirements is that the vaccine must have an easily identifiable structure that is perfectly consistent from batch to batch. Current conjugation techniques (such as those used to

produce Vaxtrate®) do not meet these criteria. Therefore, we are utilizing recombinant DNA techniques to produce vaccines against GnRH that will evoke an immune response, as well as have an identifiable structure (by reading the DNA sequence of the construct) that is consistent from batch to batch.

Conclusions

Development of a reliable, permanent, immunological, castration vaccine has obvious economical and ethical advantages. Castration via injection would reduce veterinary costs and man-hours spent castrating and treating domestic livestock species--this is particularly true for the females who are not so easily or economically sterilized. It also provides obvious reduced risks of infection and complications, not to mention less stress on the animal. Although immunological castration agents are not yet ready for commercial use, such vaccines likely will be viable future alternatives to conventional castration methods.