Hormonal Regulation of the Estrous Cycle

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All reproductive events are regulated by hormones. In simple terms, if the organs of reproduction correspond to the "plumbing," the endocrine system can be called the "wiring". A delicate balance exists between the nervous system and the endocrine system. We are entering an era in which artificial control of the estrous cycle with hormones promises to become more commonplace. Thus, hormones can be considered valuable management tools. If producers are to use the tools effectively, we must develop a better understanding of the complex hormonal interrelationships between the hypothalamus, pituitary and ovary.

Hormones Defined

A classical definition for a hormone is that it is a substance produced in one tissue that is transported to another tissue to exert a specific effect. (Some of the confusion about hormone actions should be clarified in the next section.) Hormones have many chemical classifications; some of the most common reproductive hormones are briefly described here. Gonadotropin-releasing hormone (GnRH) is composed of amino acids and is thus a polypeptide in nature. The follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are glycoproteins. This means they are composed mostly of protein, with some carbohydrate attached to the protein. Estrogen and progesterone are steroids that are synthesized from cholesterol. Prostaglandins are produced from a fatty acid—arachidonic acid. The diversity of the composition of hormones leads to the variation in their biological functions. Most hormone concentrations are in billionths or trillionths of a gram per milliliter of blood.

How Do Hormones Work?

The fact that a hormone is produced by a tissue does not necessarily imply that it will exert a physiological effect somewhere else. The ability of one tissue to respond to a particular hormone rests in whether that tissue possesses a **receptor** to the particular hormone. A receptor functions as the lock, and the hormone functions as the key that fits the lock. Therefore, as an example, if a tissue is going to respond to estrogen, its cells must possess estrogen receptors. After a hormone is bound to its receptor, a cellular response is initiated in the target tissue. A target tissue may possess receptors for several different hormones, and exposure to the various hormones can modulate the final response.

The Hypothalamus

The hypothalamus is located at the base of the brain. It contains nerve endings to integrate sensory information and sorts out hormonal signals as well. The major reproductive hormone of the hypothalamus is gonadotropin-releasing hormone (GnRH) that is sometimes called luteinizing-hormone-releasing hormone (LHRH). For purposes of this discussion we will use GnRH nomenclature. GnRH is transported in blood vessels to the pituitary gland to regulate secretion of FSH and LH from the pituitary.

The Pituitary

The pituitary is positioned underneath the hypothalamus directly above the roof of the mouth. The major reproductive hormones produced in the anterior lobe of the pituitary are called gonadotropins, which means to stimulate the gonads. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the two gonadotropins that regulate the ovary. They are secreted by the pituitary and transported in the circulation to the ovary where they interact with their respective receptors to affect ovarian functions. The main action of FSH is to initiate growth of follicles on the ovary. Continued follicle growth depends on the presence of both FSH and LH. The major effect of LH is to promote ovulation, but there is increasing evidence that FSH can exert a major influence to facilitate ovulation.

The Ovary

The ovary has two biological functions: (1) to provide the eggs (ova) for the female genetic contribution to the next generation, and (2) to produce hormones to coordinate behavioral changes with ovulation and prepare the reproductive tract for pregnancy.

Estrogen is the hormone produced by follicles as they develop on the ovary. As the predominant follicle or follicles approach ovulatory size, the increased amounts of estrogen are transported to the hypothalamus to cause behavioral heat. The pituitary also responds to the elevated estrogen by releasing a surge of LH which leads to ovulation. Thus, estrogen coordinates behavioral acceptance of a male when the egg will be released into the female tract. This is Mother Nature's attempt to ensure that the probability of fertilization occurring is maximized.

After ovulation has occurred, the tissue that a moment ago was a follicle starts a dramatic change into becoming a corpus luteum (yellow body). The corpus luteum produces progesterone to prepare the female tract for a possible ensuing pregnancy. The corpus luteum forms, regardless of whether or not mating occurs in farm animals. If the corpus luteum remains functional due to pregnancy occurring, the sustained production of progesterone prevents cyclicity. Until the corpus luteum regresses, the typical pattern of cyclic hormonal changes is absent.

The Follicle

In a simple sense, the follicle is the dwelling of the ovum. Ovulation of a follicle is the exception rather than the rule because over 99 percent of all potential oocytes are never shed from the ovary. This loss is called atresia. Atresia can occur at any time during follicle growth. When animals are injected with gonadotropins to induce superovulation, some follicles that would have undergone atresia are rescued. This supports the hypothesis that continued follicle growth is dependent upon continued exposure to gonadotropins and the presence of gonadotropin receptors in the follicle.

Ovulation

Once the LH surge has been elicited from the pituitary, the follicle starts to undergo a series of changes to prepare for impending ovulation. The cells lining the inside of the follicle begin to luteinize and secrete progesterone as the major steroid rather than estrogen. The oocyte commences its maturational steps to get it in the proper meiotic configuration for chromosome pairing with the meiotic contribution from a sperm.

Enzymes are activated to degrade the follicle wall and permit the egg to pass into the oviduct. Biochemical studies have pointed to FSH being responsible for stimulating production of those enzymes. FSH also promotes the spreading apart of cells that are tightly surrounding the egg, which then leads to some of the subsequent maturational changes in the egg. Prostaglandins are required for normal ovulation. Substances known to inhibit prostaglandin formation prevent ovulation. Due to the enzyme, steroid, and prostaglandin effects, a hypothesis was formulated comparing the ovulatory process to an inflammatory reaction.

The Corpus Luteum

The scar tissue remaining after ovulation becomes the corpus luteum; this endocrine tissue has been studied extensively. Low amounts of LH from the pituitary are essential for establishment and continued function of the corpus luteum. In all livestock species, the corpus luteum functions to maintain early pregnancy by secreting progesterone. Progesterone prevents cyclicity. The placenta of the developing fetus eventually sustains the pregnancy by producing progesterone in the bovine, equine and ovine. In the porcine, the corpus luteum is required to support the entire gestational period.

If cyclicity is to resume, the corpus luteum must regress and cease progesterone production. In pregnant animals, an embryonic signal leads to maintenance of the corpus luteum, (discussed in the next section). In nonpregnant animals, the uterus recognizes the absence of an embryo and secretes prostaglandins. Those prostaglandins are transported to the corpus luteum and cause it to regress. Thus, the inhibitory effects of progesterone are removed, new follicles start to develop, and heat occurs in a few days.

Pregnancy Recognition

The corpus luteum continues to function to provide a signal from the embryo to the dam. These signals are hormones identified in the human as chorionic gonadotropin (HCG) and in the mare as pregnant mare serum gonadotropin (PMSG). These two gonadotropins can be used to regulate the estrous cycle of animals. PMSG is biologically similar to FSH, and HCG exerts an action similar to LH. Thus, PMSG can be used to induce follicle growth and HCG will promote ovulation of these follicles. However, both PMSG and HCG are recognized as foreign proteins by livestock, and the animals build up antibody resistance to them, if they are used too frequently.

An ideal pregnancy test would be the identification of the embryonic signal in the bovine, ovine and porcine. Experiments have shown that embryonic extracts will maintain a corpus luteum in an animal that has not been bred. However, even with sophisticated biochemical tests, specific signals from embryos in the dam's circulation have not been detected. The livestock industry could benefit significantly from pregnancy tests of these types if they are ever developed successfully. Since an embryonic signal would have to be apparent to prevent a subsequent heat in the dam, a pregnancy test would also pinpoint which animals would be returning to heat within a few days.

Hormonal Regulation of the Cycle

The preceding sections indicate that follicle growth, ovulation, and corpus luteum formation are a dynamic process of sequential steps in an intricate balance. Administration of a hormone to mimic the effect of that hormone in the animal can be used to regulate the cycle. If hormone administration is to produce the desired result, it must be given at a time that is physiologically compatible with the cycle. The common hormones that have been used experimentally or commercially are progesterone-like drugs (progestins), GnRH and prostaglandins.

Progestins. These compounds were the first to be experimentally employed to regulate the cycle. Progestins have been injected, fed, implanted, or administered via vaginal sponges. Regardless of what stage of the cycle an animal is in when the progestin commences, cyclic fluctuations in other hormones are arrested. As long as progestin is administered, cyclicity ceases. Removal of the source of the progestin results in renewed follicle growth, and estrus, within a few days. Field trial data suggest that fertility at the first estrus after progestin withdrawal is lowered. Thus, it is usually recommended that breeding be done at the second estrus, since the cycles of the animals will still be in close synchrony.

Prostaglandins. These compounds have largely replaced the use of progestins because (1) only one or two injections are required, and (2) fertility is not affected by use of prostaglandins. Prostaglandins are only effective if the animal possesses a functional corpus luteum. Contrary to some opinions, prostaglandins are not a heat-inducing drug. Rather, they cause a corpus luteum to regress, and the animal secretes her own gonadotropins to regulate the ovary and cause a physiological heat. Success has occurred regularly by breeding animals at a predetermined time after prostaglandin injection. Greater success in conception rates can occur if animals are watched for estrual behavior after receiving prostaglandins and are bred in relation to standing heat. Care must be exercised with prostaglandins, because injections into an animal with a functional corpus luteum sustaining a pregnancy could induce an abortion.

GnRH. GnRH is composed of 10 amino acids. It can now be chemically synthesized in a laboratory, and this has permitted chemists to develop some powerful analogs. There are no noticeable ill effects from administering GnRH; its action is to promote a release of gonadotropins from the pituitary. Maximum gonadotropin output occurs approximately 2 to 4 hours after GnRH injection.

A common use for GnRH is to initiate cyclicity in animals with anestrous. GnRH is the most widely used therapy for treating cystic ovarian degeneration. Cystic ovaries usually result from inadequate gonadotropin production. Thus, GnRH triggers release of gonadotropins to restore ovarian function.

A new use for GnRH is for injection after prostaglandin administration; the interval to the gonadotropin surge, and hence, ovulation, can be coordinated more closely. This reduces the variation in time between prostaglandin injection and standing heat that is ordinarily seen among animals.

We have an ongoing study at the University of Wisconsin to evaluate the efficacy of GnRH injections at the time of insemination in dairy cattle. The heifers receiving GnRH have shown no advantages over heifers receiving the saline control. In lactating cows, administration of GnRH 14 days postpartum or at the first artificial insemination has improved first-service conception rates by 15 percent to 19 percent. In cows presented for third service (and thus classified as "repeat" breeders in commercial herds) conception rates were about 30 percent higher for cows that received the GnRH. The physiological effect elicited by GnRH has yet to be experimentally established. We have postulated that gonadotropins produced in response to GnRH cause a corpus luteum to form that may have otherwise been deficient and led to early embryonic death. GnRH could also promote what would have been a delayed ovulation to occur sooner or have a direct effect on the ovary. The lactational stress imposed on a dairy cow may make her unique to respond to GnRH in this manner. Experiments with other farm animals are needed to determine if similar effects result.

Summary

The reproductive cycle is regulated by fluctuations in different hormones. The cycle can be regulated by administering hormones to mimic the effect that would occur in the animal. Therefore, producers have endocrine tools to assist them in managing their animals. For maximum success the producers must understand how the hormones work biologically and realize that they are powerful drugs. We will see an increasing frequency of producers regulating the reproductive cycle to maximize reproductive efficiency. AJ

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