ENDOCRINOLOGICAL APPROACHES FOR COMMERCIAL RABBIT PRODUCTION

J.I. McNitt

Center for Small Farm Research/Department of Animal Science
P.O. Box 11170
Southern University and A&M College
Baton Rouge, LA, USA 70813

TABLE OF CONTENTS

INTRODUCTION

For rabbit production to be profitable, it is necessary that the does produce as many live kits as possible per unit time, that these kits survive to market age, and that they grow as efficiently as possible to the desired stage of maturity. All three of these aspects can, to some extent, be manipulated by proper reproductive management of the rabbits.

The reproductive physiology of the rabbit was reviewed in detail by Nordio-Baldissera (1980) for the Second World Rabbit Congress. That review summarized the work to that time with primary emphasis on the rabbit as a laboratory animal. There have been many advances since then relating to our understanding of the reproductive functioning of the rabbit and to the potential for manipulation to increase production. Much of this work has been presented in reviews covering specific topics including functioning of the corpus luteum (Keyes, et al,. 1983; Keyes and Wiltbank, 1988), regulation of the corpus luteum (Rothchild, 1981), regulation of progesterone secretion by the rabbit corpus luteum (Holt, 1989), neuroendocrine control of the ovarian cycle (Ramirez and Beyer, 1988), prostaglandins in relation to follicular function, (Armstrong, 1981), hormonal control of prostaglandin synthesis (McCracken, et al., 1981), relaxin (Sherwood, 1988), prolactin (McNeilly, 1987), and the role of the prostaglandins in control of gonadotrophin secretion (Behrman, 1979).

This review has been undertaken with the objective of reviewing the work since 1980 to pull together ideas and information from several areas and specialties to provide an overall picture that might suggest areas where further research is warranted. An additional benefit might be identification of applications of research techniques and findings that can be used to increase the efficiency of commercial rabbit production. The intent has been to include salient works rather than to provide an exhaustive review.

Because of the broad nature of reproductive physiology and the endocrine control of the various phenomena, this review has been organized at the first level by sex with primary emphasis on the female. Within the female section, the hormones are grouped according to chemical nature as prostaglandins, steroids, protein hormones and pheromones. A section is included at the end that discusses the rather sparse literature relating to the male.

FEMALE

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PROSTAGLANDINS

Prostaglandins are 20-carbon, unsaturated fatty acids attached to a cyclopentane ring. The primary precursor for the prostaglandins is arachidonic acid. In terms of reproduction, the two most important types are prostaglandin $F_{2\alpha}$ and prostaglandin E_2. Both can be synthesized and metabolized in the corpus luteum (Schlegel et al., 1988), and blastocyst (Dey et al., 1980; Harper et al., 1983, 1989; Jones and Harper, 1988, 1984; Pakrasi and Dey, 1982; Racowsky and Biggers, 1983). Conversion between prostaglandin $F_{2\alpha}$ and prostaglandin E_2 is mediated by the enzyme prostaglandin E-2-9 ketoreductase (Schlegal and Daniels, 1989). Most prostaglandins act at or near the site of production and can affect a variety of reproductive functions including ovulation, fertilization, embryonic development and implantation, luteolysis and parturition, and lactogenesis.

Ovulation

Ramirez and Beyer (1988) described three distinct neural subsystems associated with sexual cycles in animals. These include an ultradian pulse generator that controls basal pituitary function, a cyclic LH surge generating subsystem triggered by sex steroids that is related to ovulation in spontaneous ovulators, and a reflex LH surge subsystem related to ovulation in induced ovulators such as the rabbit. The last is affected by the prostaglandins that have a direct role in ovulation both in terms of LH release (Carlson et al., 1977) and the connective tissue breakdown and thinning ultimately leading to ovulation (Espey et al., 1981).

The process of ovulation and remodeling of a mature follicle into a corpus luteum has been likened to an inflammatory process that may be mediated by prostaglandins and/or histamine - both products of inflammation (Espey, 1980). Kitai et al., (1985) demonstrated that both could induce ovulation, but there was no interdependency in formation or action of prostaglandins and histamines in the ovulation process. Kobayashi et al., (1983) showed that histamine was involved in follicle rupture, but that it did not support ovum maturation. Bradykinin, another inflammatory agent, also may be involved in ovulation but it may be through mechanisms other than prostaglandin stimulation (Yoshimura et al., 1988).

When indomethacin is used to inhibit prostaglandin synthesis, ovum maturation continues. This indicates that the two processes are independent (Kobayashi et al., 1981; Schlaff et al., 1983.) Espey et al. (1986) found two periods of elevated prostaglandin production during the ovulation process. The first stage started approximately two hours after ovulation was induced by hCG. The second, sharper, increase began roughly three hours before follicle rupture, i.e. seven to eight hours after the hCG treatment. The authors suggested that the first rise might be associated with an increase in ovarian steroidogenic activity whereas the latter might be related to an increase in follicular proteolytic activity near the time of ovulation. Indomethacin treatments applied within the last hour before ovulation had no effect on ovulation although there was a sharp drop in the prostaglandin level. Thus, at that late stage, the processes leading to ovulation are no longer under prostaglandin control.

Fertilization

The effects of prostaglandins on fertilization rates are not well documented. Prostaglandin $F_{2\alpha}$ applied systemically will increase the fertilization rate in rabbits (Spilman et al., 1973.) This response might, however, be a result of local effects on the female genital tract causing an increase in sperm transport efficiency (Alvarino and Rebollar, 1991; El-Menoufy et al., 1985; Hawk and Cooper, 1979; Schlegel et al., 1983). Prostaglandin $F_{2\alpha}$ added to semen has been shown to have detrimental effects on sperm integrity (El-Gaafry, et al. 1991.)

Implantation

Prostaglandins play a role in the implantation of blastocysts. The effects include changes in vascular permeability in the stroma near the site of implantation (e.g. Hoos and Hoffman, 1980; Jones et al., 1986). Prostaglandins are produced by the blastocysts and by the uterine endometrium (Dey et al., 1982; Harper et al., 1983, 1989; Jones and Harper, 1984, 1988; Kasomo et al., 1986; Pakrasi and Dey, 1982;

366

Racowsky and Biggers, 1983). Furthermore, the blastocysts are able to accumulate prostaglandins from the uterine milieu and to store them in vivo in a non-metabolized form for up to 21 hours (Jones et al., 1990.) Snabes and Harper (1984) suggested that the uterine endometrium was responsible for production of the prostaglandins involved in implantation although Kasomo et al., (1986) indicated that the prostaglandins produced by the blastocyst might be the trigger for implantation. Prostacyclin, a prostaglandin with important effects in several species, is of less importance in the implantation reaction of rabbits than prostaglandin $F_{2\alpha}$ or prostaglandin E_2 (Jones and Harper, 1988).

Luteolysis and Parturition

Prostaglandin $F_{2\alpha}$ produced by the uterus has been shown to be an important luteolytic agent in a number of species (McCracken et al., 1981). In the rabbit, however, the uterus need not be present for luteal regression to occur (Kehl and Carlson, 1981; Keyes, et al. 1983; Keyes and Wiltbank, 1988). Increasing systemic levels of arachidonic acid or prostaglandin E_2 did not result im declines in circulating progesterone levels in pseudopregnant rabbits. Prostaglandin $F_{2\alpha}$ and its metabolite 13,14-dihydro-PGF-2α applied systemically did, however, result in declines in progesterone indicating luteolysis (Kehl and Carlson, 1981). Fischer et al. (1980) found that application of prostaglandin $F_{2\alpha}$ during the pre- and peri-implantation periods caused corpus luteum degeneration in pseudopregnant animals within 48 hours.

The corpus luteum can synthesize prostaglandin $F_{2\alpha}$ (Rothchild, 1981) so luteal regression may be stimulated by increased intraluteal prostaglandin synthesis. Miller et al., (1983) found that luteal regression was associated with increased production of prostaglandins $F_{2\alpha}$ and E_2 in the uterus but they were unable to detect any increases in the luteal levels of these hormones on days 8, 12 or 15 of pseudopregnancy. They suggested, however, that the prostaglandins produced by the ovary were very rapidly removed from the tissue pools and thus might not have been detected by their tests. That this might be the case was borne out by Schlegel et al., (1988) who found that the corpus luteum contains enzymes to convert prostaglandin E_2 to prostaglandin $F_{2\alpha}$ and to metabolize both. Those authors found a significant difference in prostaglandin levels between pregnant and pseudopregnant animals only on day 15. Moy and Marcinkiewicz (1988) reported differences over time and in luteal sensitivity to prostaglandins when they compared pregnant and pseudopregnant animals. Lammers and Petersen (1987) used the prostaglandin analog Tiaprost to induce luteolysis and subsequent ovulation on day 12 in pseudopregnant rabbits.

Prostaglandin $F_{2\alpha}$ has been postulated to be the primary luteolytic agent, but other prostaglandins such as

prostaglandin E_2 and 6-keto-prostaglandin F_{1a} may be of equal or greater importance (Dharmarajan et al., 1989).

Prostaglandin $F_{2\alpha}$ has been implicated in collagenolytic activity of the cervix similar to that seen with relaxin (MacLennan et al., 1985). These authors used a porcine preparation that was applied vaginally to evaluate the histological changes caused by these compounds.

Regardless of the mode of action, prostaglandins and their synthetic analogs will induce parturition in rabbits (e.g. Partridge et al., 1986; Ubilla et al., 1989). The implications of this in terms of production efficiency will be discussed below.

Lactogenesis

Prostaglandin $F_{2\alpha}$ is capable of inducing lactogenesis in pregnant rabbits. This may be an indirect result because of luteolysis removing the inhibitory effect of progesterone, or a direct result of triggering prolactin release (Deis et al., 1980).

Commercial Applications of Prostaglandins

Several studies using prostaglandin $F_{2\alpha}$ to induce parturition in rabbits were reported by Ruffini-Castrovilli and Nordio-Baldissera (1980) at the Second World Rabbit Congress. Work involving larger numbers of animals and the synthetic prostaglandin analog Cloprostenol injected on day 28 of pregnancy was reported by Partridge et al. (1986). More recently, Ubilla et al. (1988), Rebollar et al. (1989), Ubilla et al. (1989), and Ubilla and Rodriguez (1989a, b) used the analog Etiproston on day 29 of pregnancy to induce parturition. The results reported were similar for all authors. Prostaglandin treatment significantly decreased the length of gestation with a significantly greater proportion of the does kindling between 24 and 60 hours after treatment. Because of the shortened gestation, the kits were lighter at birth but there was a significant reduction in the proportion of kits born dead. Except for very small kits at birth, there was no effect on mortality during the suckling period (Partridge et al., 1986.)

Perhaps the most exciting and potentially useful benefit of induction of parturition with prostaglandin analogs is the reduction in the proportion of kits born dead. Substantial losses are sustained by the rabbit industry as a result of perinatal kit deaths. Perinatal and neonatal deaths play a major part in determining the overall profitability of a rabbit enterprise (Hugh-Jones, 1975). Partridge et al., (1981) reported 25% mortality of kits before weaning. In a later study (Partridge et al., 1984) 26% of the kits died at birth.

Ubilla and Rodriguez (1989b) used Etiproston routinely on 25 does from the first to the eighth litters. There was no effect on prolificacy or litter size at weaning, but the neonatal mortality was reduced by almost 50% and there seemed to be a tendency for more litters to have no dead kits. Lack of a difference in litter size at weaning might have been a result of the lighter birth weights that may have reduced survival rates during the nursing period.

Ubilla et al. (1989) routinely injected 50 μg Etiproston at 10:00 a.m. on day 29 of gestation between June and December, 1988. There was no effect on fertility, numbers of kits born alive, number of kits per litter, mortality during nursing, or mortality of does. There was, however, a significant reduction in the litter interval from 49.06$\pm$1.68 days to 40.04$\pm$.62 days. This, in the course of a year, would be equivalent to 1.34 more litters or, based on the results in that herd, 73.7 vs. 62.2 kits born. The authors attributed the difference to an increase in sexual receptivity and post-partum fertility in the does that had been treated. In a later study it was shown that this was, in fact, the case with increases of receptivity on days 6 to 9 post partum from 43.0% to 70.4% and conception rate from 66.6% to 82.2% for non-treated and treated does, respectively (Ubilla and Rodriguez, 1989a.) This increase in conception rate and litter size could represent a significant financial benefit for the commercial rabbit raiser.

Rebollar et al., (1989) found that induction of the previous parturition increased the fertility of the does in the next litter. They attributed this to a more rapid fall in the level of plasma progesterone leading to an increased secretion of GnRH, thus FSH and LH, which resulted in a larger crop of follicles that could develop for the next cycle.

Despite the great potential for the use of prostaglandin analogs to increase reproductive efficiency in commercial rabbit production, these are not widely used. In Spain, where much of the research has been carried out, Etiprostin has only recently become commercially available and, for various reasons, the technology has not been widely presented to farmers (E. Ubilla, personal communication.) No work with prostaglandins in rabbit production has been carried out in the United States.

Other uses of prostaglandins in rabbit reproduction have been reported. Lammers and Petersen (1987) reported using a prostaglandin analog (Tiaprost) to induce luteolysis and subsequent ovulation at day 12 in pseudopregnant does. Rodriguez et al., (1989b) worked with does that were palpated negative 11 days after induction of ovulation with GnRH at the time of artificial insemination. After the negative palpation, luteolysis and ovulation were induced by injection of Etiproston. A dose of 100 μg on day 11 or 50 μg on day 14

after induction resulted in a significant increase in fertility when the does were inseminated three days after treatment.

Injection of does with prostaglandin $F_{2\alpha}$ at the time of insemination increased the proportion of the spermatozoa that reach the oviduct (El-Menoufy et al., 1985; Hawk and Cooper, 1979). Addition of prostaglandin E_2 to the semen resulted in a significant increase in fertility but there was no effect on the total number of embryos or the number of dead embryos (Alvarino and Rebollar, 1991). The authors suggested that the effect might be a result of increased motility of the female tract which increased the numbers of sperm reaching the oviduct. Abo Elezz et al. (1988) injected does with prostaglandin $F_{2\alpha}$ at the time of mating and found an increase in conception rate, litter size and meat production. Injection of the prostaglandin $F_{2\alpha}$ analog Enzaprost intramuscularly in Angora rabbits shifted the sex ratio of the offspring in favor of the males whereas injection of GnRH at the time of insemination increased the number of females (Gabor and Zoldag, 1989).

STEROIDS

Estrogen Control of Luteal Steroid Production

Estradiol has been identified as the "ultimate luteotropin" for maintaining the corpus luteum and stimulating progesterone production in the rabbit (Hilliard, 1973). Holt (1989) provided an historical review of the work leading to this conclusion, outlined the mechanisms by which this control might be exerted, and briefly discussed some aspects of steroidogenesis within the luteal cell. The pituitary gonadotrophins also may be involved in control of progesterone production (Damle et al., 1984), but the effects are probably overshadowed by the effects of estradiol (Holt, 1989.) Orstead et al., (1988) reported pulsatile release patterns for LH, FSH, estradiol, and progestins during estrus and pseudopregnancy. The patterns of release of LH and the progestins differed markedly between estrus and pseudopregnancy whereas those of FSH and estradiol did not. This suggests a relationship, possibly causal, between LH and progestin secretion.

After formation, the corpus luteum has the ability to secrete progesterone for several days without a requirement for pituitary hormones or estradiol. If estradiol is not available by about day 5, the development of the corpus luteum is arrested and progesterone synthesis begins to decrease in situ (Miller and Keyes, 1975, 1978) and in culture (Yuh et al., 1986). When estradiol is applied to the corpus luteum there is a response time of 5 to 6 hours before the progesterone production reaches a stable level (Holt et al., 1981; McLean and Miller, 1985). After ovulation, there is a temporary depletion of large follicles but the population of these large, active, secretory follicles increases after about 6 days. This

370

may be the source of the luteotrophic estradiol (Osteen and Mills, 1980).

Gadsby (1989) summarized work that showed a physiological role for estradiol in maintenance of the secretory activity of the corpus luteum. In addition, a putative "placental luteotrophin" secreted by the trophoblast cells of the fetal placenta was shown to have a role in control of luteal secretory activity. The precise mechanism of action of these two luteotrophins remains to be elucidated. A possible mechanism of action of estradiol is that it regulates, at a cellular level, the uptake and storage of cholesterol used for steroid synthesis, and controls the rate of conversion of cholesterol into progesterone (McLean and Miller, 1987; Miller and McLean, 1987.)

Steroid Effects on Hypothalamic-Pituitary Relationships

There is a negative feedback action of continuously applied estradiol 17-ß on both the hypothalamus and the anterior pituitary. Both the quantity and rate of discharge of gonadotrophin releasing hormone (GnRH) from the hypothalamus are suppressed by direct application of estradiol 17-ß. The release of LH from the anterior pituitary in response to exogenous GnRH is also suppressed. GnRH release from the hypothalamus is suppressed by 20-α hydroxyprogesterone but there is no inhibitory effect on the pituitary. In fact, in the pituitary, 20-α hydroxyprogesterone may enhance the output of LH by antagonizing the inhibitory effect of estradiol 17-ß (Pau et al., 1986). This effect, however, may be a result of the mode of application. Progesterone is inhibitory when applied in a continuous mode and stimulatory when applied in a pulsatile fashion (Lin and Ramirez, 1988, 1990). Progesterone (Lin and Ramirez, 1988) or pregnanolone, either directly or as a metabolite of progesterone (Lin and Ramirez, 1990) may regulate the activity of the GnRH neural apparatus. This is one of the factors in the control of the surge generator described by Ramirez and Beyer (1988).

Copulation in a pregnant rabbit does not terminate the pregnancy whereas injection with hCG, LH or GnRH will do so. This is a result of dissociation of copulation from gonadotrophin release. The latter is thought to be a result of high levels of plasma progesterone (Mills and Gerardot, 1984.)

Steroidogenesis, Follicle Development and Ovulation

Setty and Mills (1987) found that when progesterone levels were elevated, the final stages of follicular development were inhibited and concluded that the effects of progesterone were directly upon the ovary rather than being indirect by way of inhibition of gonadotrophin secretion. Furthermore, this effect appears to be limited to the individual ovary. When progesterone secretion was manipulated

by removal of corpora lutea, it was found that when one or more CL were present on an ovary, follicle development was inhibited. When these were removed, follicle development occurred even when a CL was present on the contralateral ovary. Ovarian vein progesterone levels were 10-30 times higher when CL were present than when they weren't (Mills and Stopper, 1989).

Yoshimura, et al., (1986) used aminoglutethimide phosphate to inhibit steroid synthesis in an _in vitro_ perfused rabbit ovary preparation. They found that follicular rupture occurred despite inhibition of steroid production and concluded that the ovarian steroids were not essential for ovulation but the steroids might be instrumental in determining the fertilization rate.

Steroidogenesis and the Oviduct

Steroid levels in the oviductal fluid vary during pseudopregnancy. The levels of estradiol tend to parallel the serum concentrations, but the levels of progesterone do not rise as high as the serum levels (Richardson and Oliphant, 1981). Estradiol increases the sensitivity of the progestin receptors of the stroma and muscularis of the entire oviduct. It has little effect on the epithelium of the ampulla, but causes a decrease in the sensitivity of receptors in the epithelium of the isthmus. This may be related to segment specific functions such as secretion and sperm transport (Hyde et al., 1989).

Steroid Involvement in Reproductive Behavior

The reproductive state of the doe affects its response to progestin and estrogens. Stoufflet and Caillol (1988) briefly reviewed the work in this regard that has shown that progesterone inhibits sexual receptivity in non-pregnant rabbits but receptivity can be induced by exogenous estrogens in ovariectomized does. Similarly, when chinning was used as a measure of reproductive activity in ovariectomized does, activity was stimulated by estrogens whereas application of progesterone resulted in almost immediate cessation of chinning activity (Hudson et al. 1990.) Does that failed to mate day 14 post-partum had significantly lower levels of estradiol 17-ß than does that ovulated (Lamb, et al., 1991).

From days 6 to 23 of pregnancy, less than 50% of does were receptive to males. The proportion then increased, reached 100% at the time of parturition and remained high in the early post partum period. Serum progesterone levels rose from day 6 of pregnancy to a maximum at days 12-13 and then declined to a minimum the day after parturition. Estrone and estradiol concentrations were low throughout pregnancy. No relationship was observed between serum levels of progesterone and estrogens and sexual behavior during pregnancy (Stoufflet and Caillol, 1988). Sexual activity does, however, occur during

372

pseudopregnancy and, though serum progesterone levels are high, sexual receptivity tends to be related to the serum estradiol levels (Caillol et al., 1983). There is no clear relationship between receptivity and follicular steroid levels (Caillol et al., 1984). Forcada and Abecia (1990), however, suggested the existence of a negative relationship between plasma progesterone concentrations and sexual receptivity.

Maternal nest building is stimulated by a change from predominantly progesterone control to predominantly estrogen control (Zarrow et al., 1971). This behavior is not seen in hypophysectomized does thus indicating involvement of a pituitary substance that, as will be discussed later, may be prolactin.

Plasma Progesterone and Pregnancy Diagnosis

Plasma progesterone levels rise rapidly during the first third of pregnancy, remain relatively constant during the second trimester and decline throughout the final trimester (Harrington and Rothermel, 1977). These cyclic changes in progesterone levels have allowed the use of enzyme linked immunoassay (ELISA) techniques for pregnancy diagnosis (Hansen, 1990; Morrell, 1990) or to estimate the number of embryos formed after superovulation (Yang et al., 1988). The practical value of an ELISA for pregnancy diagnosis in the commercial context seems uncertain. Morrell (1990) suggested that manual palpation for pregnancy diagnosis may cause damage to the fetuses or that the accuracy may be diminished when there are only one or two fetuses. When an experienced person is carrying out the palpations, the validity of both these assertions is questionable. In the commercial context, the cost of the ELISA kit as well as the necessity for taking blood samples and the accompanying dangers of infection would seem to more than outweigh any gain in accuracy that might be obtained.

PROTEIN HORMONES

Gonadotrophin Releasing Hormone

Ovulation in the rabbit is brought about by physical stimulation of the perineal, pudendal and/or vaginal areas of the doe that result in multiple, broad-based nerve stimuli to the hypothalamus. This results in release of gonadotrophin releasing hormone (GnRH) [also called LHRH by some authors] that causes the LH spike that actually initiates the ovulatory process (Ramirez and Beyer, 1988). As those authors so succinctly stated, GnRH ". . . is the first hormonal efferent limb of the copuloceptive reflex arc." There is a tonic, pulsatile release of GnRH from the hypothalamus that has a period of about one pulse every 45 minutes; the ultradian rhythmic secretion discussed by Ramirez and Beyer (1988). The amplitude of the releases varies with season with the highest

occurring in the spring and early fall and lower levels during early summer (Ramirez et al., 1986). The pattern of output of GnRH from various hypothalamic areas is similar which gives credence to the hypothesis that the surge of GnRH after mating is the result of stimulation of numerous neurons and terminals in the region (Lin and Ramirez, 1991).

In some species, GnRH has direct gonadal inhibitory effects. This, however, may not be the case with the rabbit. Kobayashi et al., (1982) found that continuous infusion of GnRH into the ovarian artery blocked hCG induced ovulation. In the same laboratory however, Eisenberg et al., (1984) found pulsatile, in vitro infusion of GnRH had no effect on ovulatory efficiency, ovum maturity, mean time of ovulation or progesterone production. In an in vitro preparation, GnRH agonist analogs had a direct stimulatory effect on the meiotic activity of follicle-enclosed oocytes. Although the GnRH agonist analogs stimulated prostaglandin production, this was not the mechanism that stimulated the meiotic activity (Yoshimura et al., 1990). Use of GnRH analogs may have application in commercial production. Rodriquez and Ubilla (1988) found that injection of GnRH analogs induced ovulation in does even if they exhibited a low level of sexual receptivity. The response was improved if prostaglandin $F_{2\alpha}$ was also used (Abo Elezz et al., 1988)

Luteinizing Hormone and Follicle Stimulating Hormone

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) reach peak levels about two hours after coitus, and return to pre-estrus levels within 12 hours post-coitum. LH remains at the lower level throughout pregnancy but there is a second surge of FSH at 1-2 days of pregnancy. This surge may be related to the development of the secretory follicles that produce the estrogen which, as previously noted, is required in the doe after five days to maintain the progesterone secretory activity of the corpus luteum. Following this surge, FSH remains low throughout the remainder of the pregnancy (Osteen and Mills, 1979).

When the preovulatory surge of LH and FSH is blocked with pentobarbital so the large ovarian follicles do not rupture, there is no postovulatory surge of FSH (Mills et al. 1981). Control of this surge requires the presence of the ovary (Mills and Copland, 1983) and the control does not seem to be mediated by GnRH (Mills et al., 1983). Based on evidence from other species, Mills et al. (1981, 1983) postulated that this effect is, in fact, related to inhibin. Before ovulation, large follicles secrete inhibin which suppresses FSH release. The LH surge causes rupture of the follicles and a reduction of the inhibin levels. This allows the postovulatory release of FSH that stimulates follicular development. These follicles produce inhibin that again suppresses FSH release. Goodman (1984) showed that rabbit pituitary cells responded to inhibin

374

with a direct, graded and reversible inhibition of FSH. It was also reported that rabbit follicular cells produce an inhibin-like substance.

The amount of LH and FSH secreted in the preovulatory surge does not affect the number of ovulations nor, in most cases, is there any relationship with early embryonic loss (Meunier et al., 1983).

Prolactin

Plasma prolactin levels increase as the animals age and significantly higher concentrations are found in mature females than in mature males. There is a rhythmic, circadian variation with the highest concentrations occurring between 1500 and 1900 hours (Muccioli et al., 1982). At the time of mating, there is a fall in plasma prolactin levels which rises to pre-copulatory levels in about 30 minutes. The plasma half life of prolactin is 8 to 12 minutes (Fuchs et al., 1984) which suggests that mating almost immediately stops prolactin release from the pituitary (Ramirez and Beyer, 1988). Plasma levels are again increased significantly three to four days post-coitus and remain elevated for the first half or two thirds of gestation after which the levels decline (Fuchs et al., 1981; McNeilly and Freisen, 1978; Muccioloi et al., 1982).

Prolactin can inhibit ovulation in the in vitro perfused rabbit ovary (Hamada et al., 1980). This effect has been suggested to be a result of interference with FSH control of estrogen production (Dorrington and Gore-Langton, 1981; Hamada et al., 1980) or it may act directly within the ovary to prevent the mechanical events that are necessary for ovulation to occur (Yoshimura et al., 1990). McNeilly (1988) reviewed evidence in other species that indicates that the inhibition may be a result of opioid inhibition of LH release. Prolactin has been shown to have an important function in maintenance of the steroid producing capacity of the interstitial tissue of the ovary (Hilliard et al., 1968).

The inhibitory effect of prolactin on ovulation may have implications in the application of artificial insemination in rabbits and on rebreeding lactating females. Rodriguez et al., (1983) reported that nulliparous does ovulated well in response to GnRH treatment but lactating does did not respond. The latter would have higher prolactin levels - at least episodically. Rodriguez et al., (1989a) defined three levels of sexual receptivity (high, medium and low) based on vulva color and turgidity. Does with high receptivity generally showed clear responses to the GnRH challenge (40 μg) in terms of increases of LH and FSH and a decline in prolactin. The response was least for the does with low sexual receptivity. Injection of 20μg GnRH into does with low sexual receptivity resulted in increases in plasma prolactin levels. Injection of

40 μg however resulted in significant declines at 45, 75, 105 and 135 minutes after treatment. The authors suggested there might be a dose related prolactin response to this treatment so the lower levels were being over-ridden by higher doses of GnRH. It was further suggested that this might indicate prolactin has a physiological role in regulation of ovarian function. On the other hand, it has been reported by several groups that the number of corpora lutea formed bears no relationship to the color of the vulva at the time of insemination (Forcada and Abecia, 1989; Pla, 1984). Does which failed to ovulate when served 14-d postpartum had reduced plasma concentrations of estradiol 17-ß and prolactin (Lamb et al., 1991).

There is a steep rise in plasma prolactin concentration 24 hours before parturition and high levels are observed throughout lactation (Fuchs et al., 1981; McNeilly and Friesen, 1978; Muccioli et al., 1982). There is a further increase in the prolactin during and after each daily suckling episode. The release of prolactin is a result of mechanical stimulation of the nipples (McNeilly and Freisen, 1978) and is related to the number of kits suckling (Fuchs et al., 1984). The strength of the response declines over the course of the lactation (Fuchs et al., 1984).

Does treated with ergocornine hydrogen maleate, a prolactin blocking agent, from day 27 of pregnancy did not build nests whereas does treated with ergocornine plus prolactin did so (Zarrow et al., 1971). The authors concluded from this that prolactin plays an important role in certain aspects of maternal behavior. McNeilley and Friesen (1978) reported that prolactin levels of does that killed their young dropped immediately after parturition whereas levels in those does that successfully reared their litters (or at least tried to nurse them) remained high for more than two days after kindling.

Zarrow et al. (1971) demonstrated that prolactin may be required for hair pulling and maternal nest building to occur and McNeilly and Friesen (1978) related prolactin release to suckling success of does. It is tempting to speculate that failure to show an increase in prolactin 24-hours before parturition may be related to the lack of nest building activity and maternal behavior seen in some does. There is a pressing need for further study of the involvement of prolactin in mothering ability because this is a point in the production cycle where large numbers of potentially productive animals are lost. Hudson and Distel (1984) were unable to elicit a chinning response in nonbreeding females by injection of prolactin nor was the response inhibited by injection of the prolactin blocker bromocryptine.

376

Oxytocin

Oxytocin levels increase in response to mating (Fuchs, et al., 1981), parturition (Fuchs and Dawood, 1980), and lactation (Fuchs et al., 1984). The oxytocin release in response to mating is much smaller than seen with parturition and lactation and the physiological significance is questionable. A second release of oxytocin occurs about 5 hours after mating. This may contribute to the uterine and tubal contraction activity seen at about this time when the second wave of spermatozoa enters the oviduct (Fuchs et al., 1981).

During parturition, plasma oxytocin levels increased rapidly to levels of 193 pg/ml 30 - 60 seconds before the expulsive phase began and reached the highest level of 258 pg/ml at the delivery of the first fetus. Levels then returned to baseline values (16.1 pg/ml) within 20 - 60 minutes. These high levels are necessary because of the long birth canal in relation to the length of the umbilicus which necessitates rapid birth to avoid asphyxiation (Fuchs and Dawood, 1980).

Plasma levels of oxytocin are significantly raised within one minute after suckling begins. Peak levels are reached at 3 - 5 minutes after the start of suckling. There was no significant rise in plasma oxytocin when only one kit was suckling and the single kit obtained only a fraction of the milk it obtained at other nursings when it was part of a suckling fraternity of six kits. Differences in oxytocin levels between five, six and seven kits suckling did not appear to be significant (Fuchs et al., 1984).

Once does begin to show nest building and other preparturient behaviors, parturition can be induced by an intravenous injection of oxytocin. After this treatment, labor generally commences within two to three minutes and is usually complete within five minutes (Morgan, 1974.) It is a common practice among many rabbit raisers in the U.S., particularly fanciers, to induce parturition with oxytocin. Oxytocin is often used when a doe appears to be having problems or with breeds with large, square heads such as the Holland Lop (Godfrey, 1990).

Relaxin

The early work with relaxin was related primarily to the changes in the pelvic girdle at the time of parturition. The presence of the hormone in the rabbit was noted and many of the effects elucidated. The early literature has been reviewed by Sherwood (1988).

Relaxin in the rabbit is produced in the secretory granules of the syncytiotrophoblast of the placenta (Eldridge and Fields 1985, 1986) and is found in the endometrium on days 4 to 30 of pregnancy and days 2 to 5 of lactation (Lee and

Fields, 1990). The ovary is not a significant source (Lee and Fields, 1991a). Little is known about the control or synthesis of rabbit relaxin (Sherwood, 1988), but it appears to be affected by progesterone (Lee and Fields, 1991b). Lee and Fields (1990) found relaxin in the endometrium only after the blastocyst migrated to the uterus from the oviduct and, after implantation, found relaxin only in sites adjacent to the embryos. It was hypothesized that the blastocysts initiated, and the placenta maintained, uterine relaxin. The function of relaxin during pregnancy may be related to maintenance of uterine quiescence, preparing the uterus for implantation and, possibly, to enhancement of uterine growth (Lee and Fields, 1990, 1991a). At the time of parturition, relaxin functions in cervical softening (MacLennan et al., 1985; Sherwood, 1988). The presence of relaxin after parturition was hypothesized to be related to regulation of oxytocin secretion, mammary duct development, and uterine involution (Lee and Fields, 1990.)

hCG and PMSG

Artificial insemination has been practiced on a limited scale in rabbits for many years, but an obstacle to widespread use of this technique has been the inadequacy of methods for inducing ovulation. Gonadotrophin preparations such as human chorionic gonadotrophin (hCG) and pregnant mare serum gonadotrophin (PMSG) have been used but suffer the disadvantage of triggering an immune reaction and losing their effectiveness after several treatments (May and Simpson, 1975). The availability of synthetic gonadotrophin releasing hormones that can be repeatedly injected intramuscularly has overcome this problem (Schlolaut, 1989).

There is evidence that large, pre-ovulatory follicles are always present in the ovary (Kranzfelder et al., 1984) although Diaz et al., (1987) found definite cycles in the numbers of antral follicles. Not all the follicles ovulate; especially in the non-estrus rabbit. This is caused by a lack of LH discharge and can be overcome by injection of hCG (Hulot et al., 1988). Over 90% of non-ovulatory does can be induced to ovulate with hCG injection (Amero et al., 1991).

PMSG has been used to overcome reproductive problems in does. Khalifa et al. (1989) injected 12.5, 25 or 50 IU PMSG into does that had refused mating. There was a significant increase in the number of does accepting service (95.4% vs 31.6%) and conception rate (74.2% vs 50.0%) for treated and controls, respectively. There was no effect of the treatment on gestation length or litter size nor was there a carry over-effect to breeding behavior or conception rates on the next breeding. The best response was seen with the 25 IU dosage. Lee et al. (1991) used PMSG to superovulate does for embryo transfer studies. There were marked seasonal differences in response in terms of the number of does that would accept service with the best response in the spring and the poorest in

378

the summer. Treatment of non-responding does with 0.5 mg prostaglandin $F_{2\alpha}$ seven or eight days after PMSG treatment resulted in all does accepting service within 48 hours.

To increase ovulation rates, some commercial growers in Europe inject does with PMSG about 48-hours before natural or artificial insemination (Bonanno, et al., 1990; Canali, et al. 1990; Castellini, et al. 1991). Although there is a doe-dependent increase in the numbers of follicles which rupture (Bonnano, et al. 1990), there is evidence of loss of efficiency as a result of antibody formation after repeated dosages of PMSG. A significant reduction, however, was found in only about 50% of the cases. The intensity of the response was related to the total number of treatments and their frequency (Canali et al. 1989, 1991).

Inhibin

Goodman (1984) showed that rabbit pituitary cells in vitro responded to inhibin with a direct, graded and reversible inhibition of FSH activity. Goodman (1984) also reported that granulosa cells from antral follicles appeared to secrete an inhibin like substance. No further work on inhibin in rabbits has been found. A later review article dealing with inhibin (Steinberger and Ward, 1988) contained no references at all to inhibin in rabbits.

Endogenous Opioid Peptides

The role of opioid peptides and their relationship to the control of gonadotrophin secretion in various species has been reviewed by Yen et al., (1985) and Behrens and Parvizi (1988). In most species, the opioids inhibit secretion of GnRH, thus LH, and stimulate the release of prolactin. Only one report of work related to endogenous opioids in rabbits was found in the literature. Orstead and Spies (1987) demonstrated that in the rabbit, as in other species, endogenous opioids had a role, possibly secondary to the ovarian steroids, in the control of secretion of GnRH by the hypothalamus.

As previously mentioned, McNeilly (1988) suggested that the inhibition of LH during lactation might be a result of the endogenous opioids. This was based on evidence that suckling resulted in an increased secretion of ß-endorphin, one of the opioids, in the ewe. This may be an explanation of the reduced breeding efficiency of lactating does reported by Rodriguez et al., (1983).

Practical Implications and Applications of the Protein Hormones

It is apparent that the information regarding the actions and interactions of the protein hormones in rabbits is fragmentary, often from the biomedical literature, and leaves some very large gaps in our knowledge. There are some

important questions regarding the application of these hormones in the commercial context that remain unanswered.

A fascinating, yet poorly explained area is the relationship of prolactin to maternal behavior. Many producers suffer high losses of kits as a result of poor mothering behavior of the does. The control of this behavior and, thus, the potential for intervention or modification, is inadequately defined. The perinatal relationship between oxytocin and prolactin is not well explained either, yet is of vital importance in terms of those does that exhibit abnormal behaviors in terms of nest building or suckling behavior. Some does also exhibit a seeming chronological disassociation of kindling, milk production and milk let-down. Oxytocin is commercially available and regularly used to induce parturition. Would similar application of prolactin to induce the behavioral concomitants of parturition be useful or advisable? Since prolactin may mediate reproductive behavior (McNeilly and Freisen, 1978; Zarrow, et al. 1971), a combination of the two hormones might provide better results than either alone.

The effects of prostaglandin $F_{2\alpha}$ in relation to oxytocin and prolactin also must be considered. As noted, prostaglandin $F_{2\alpha}$ injected at day 29 of pregnancy effectively shortens the gestation with a larger proportion of the kits being born alive. This result is intriguing in relation to the suggestion of Fuchs and Dawood (1980) that high levels of oxytocin are required at the time of parturition because of the need for rapid passage through the long birth canal of the rabbit. Does prostaglandin $F_{2\alpha}$ also cause such rapid passage? The effect of the prostaglandins might be enhanced by addition of oxytocin, prolactin, or both.

Further work is needed to determine methods to augment the effect of GnRH in inducing ovulation. Although the gonadotrophins are effective in this respect, the development of immunity is a serious barrier to regular use. There may be benefit to the use of endogenous opioid antagonists to overcome the depressing effects of the opioids on GnRH and LH. Before such usage, much more needs to be learned about the functions and actions of opioids in rabbits.

PHEROMONES

Chinning

Female rabbits mark items in their surroundings with secretions from their submandibular skin glands. This behavior is related to the estrous state of the doe and is thought to be a signal used to attract mates. The intensity of this behavior diminishes during pregnancy but reappears at about the time of parturition (Soares and Diamond, 1982). Chinning occurs in

380

waves with peaks of activity at intervals of four to five days. Within an hour after mating, there is marked decrease in the incidence of chinning (Gonzalez-Marsical et al., 1990). The intensity of chin marking activity is greatest with long day light cycles and least with short day cycles (Vodermeyer, 1989; Hudson and Vodermeyer, 1991). This activity is correlated with other measures of sexual behavior such as vulva color and lordosis responses and can be modified by application of estrogens (Hudson et al., 1990; Hudson and Vodermeyer, 1991; Vodermeyer, 1989) and melatonin (Hudson, 1991).

Nipple Search Pheromones

Rabbit kits nurse only once daily. The patterns of behavior of the kits and of the does at the time of nursing are highly stereotyped and well described (e.g. Hudson and Distel, 1983, 1984, 1989; McNitt and Moody, 1987). Location of nipples by the kits is based on pheromonal cues on the doe's ventrum (Hudson and Distel, 1983) and in fresh rabbit milk (Keil et al., 1990). These pheromones may be produced by all females under appropriate stimulation (Hudson and Distel, 1984; Hudson et al., 1990). The responses of the kits to these pheromones are highly stereotyped and can be elicited at any time of day. As a result, the kits provide an excellent behavioral bioassay for the pheromone (Keil et al., 1990; Hudson and Distel, 1990).

Secretion of the suckling pheromone is related to the daily light cycle with non-breeding does stimulated to secrete under long-day conditions and suppressed by short-day conditions. Under constant long-day conditions, pheromone emission, readiness to mate, conception rate and litter size all remain high. An hour change in either direction is, however, sufficient to result in a change in these parameters. These changes occur within two to three weeks of the light change (Hudson and Distel, 1990). This high degree of sensitivity could have important implications for the commercial rabbit breeder and may be one of the factors involved in seasonal variations in productivity (McNitt and Moody, 1990).

MALE

Recent information on the reproductive endocrinology of the male rabbit is limited. The material found relates to seasonality of breeding, the effects of androgens and estrogens on protein synthesis in the epididymis and the effects of adding prostaglandin $F_{2\alpha}$ to semen.

Seasonality of Breeding in the Male Rabbit

In the wild, bucks show a seasonal breeding pattern with the peak activity occurring in the spring. Boyd and Myhill (1987), in England, found males with testes exhibiting active

spermatogenesis during every month of the year, but peak fecundity occurred during April, May and June. Changes in the scrotal testis length provide a good indicator of the reproductive status of the male (Boyd, 1985). This measure can be influenced by changes in photoperiod (Boyd, 1985, 1986) or by implantation of melatonin (Boyd, 1985).

Response to photoperiod change is at the hypothalamic level and is a result of changes in GnRH release (Boyd, 1987). Lin and Ramirez (1988) reported pulsatile releases of GnRH with a pulse frequency of about one hour. There was a significantly higher level of GnRH release in the evening than in the afternoon hours. There are also seasonal variations in GnRH that occur even in bucks maintained in fixed 12L:12D photoperiod (Lin and Ramirez, 1991). There were strong seasonal changes in the output of GnRH with the lowest values occurring just before the winter solstice. There was then a marked increase in the frequency of GnRH pulses after the winter solstice and a marked increase in GnRH release during and within one month after the summer solstice. Testis weight was highest in August and lowest during the winter.

Hsu, et al. (1987) reported improvement after GnRH treatment of a small number of Angora bucks with low libido and(or) poor sperm production. This relationship between GnRH and sexual activity may provide a method for treatment of poor reproductive performance of bucks.

Steroid Control of Epididymal Protein Synthesis

Toney and Danzo (1989a,b) studied the uptake of $[^{35}S]$methionine by immature and mature rabbit epididymides in vitro. Both testosterone and estradiol influenced protein synthesis in the immature rabbit. In the mature rabbit estrogenic effects were reduced or eliminated entirely. The authors postulated that estradiol receptor sites in the adult are downregulated by synthesis of an androgen dependent protease. This downregulation maybe necessary to prevent deleterious effects of the estradiol.

Prostaglandins and Semen

Prostaglandins added to the semen can affect fertility. Schlegel et al. (1983) inactivated the prostaglandins in semen with prostaglandin-15-hydroxydehydrogenase or antisera before insemination and found a dose dependent reduction in fertilization rate. Addition of prostaglandin $F_{2\alpha}$ depressed sperm motility and kindling rates (El-Gaafry, 1989; Alvarino and Rebollar, 1991). The authors suggested that the negative effect might be a result of changes in the acrosome affecting the release of the enzymes. This was borne out by later work (El-Gaafry et al., 1991) that showed that addition of more than 300 $\mu g/ml$ prostaglandin $F_{2\alpha}$ to the semen resulted in an increase in the number of sperm with damaged acrosomes and an

increased release of the acrosomal enzymes glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase and lactate dehydrogenase.

Addition of prostaglandin E_2 caused an increase in fertility that was suggested to be a result of increased uterine motility that moved the sperm more rapidly to the ampulla (Alvarino and Rebollar, 1991).

SUMMARY

It is apparent that there are exciting opportunities to improve the efficiency and profitability of commercial rabbit production through application of new knowledge in endocrinology. There are also several areas where further knowledge is needed to develop potentially useful techniques.

Among the applications and areas needing further study, we can list the following:

- The use of prostaglandins to induce kindling with a resultant increase in the proportion of live born kits;

- "Recycling" of pseudopregnant does;

- The use of GnRH to improve reproductive performance of bucks;

- The relationship of prolactin to maternal behavior;

- The perinatal relationship of oxytocin, prolactin and prostaglandin $F_{2\alpha}$;

- Methods to enhance the effect of GnRH for induction of ovulation;

- The relationship of the endogenous opioids to reproductive phenomena, especially as they relate to the release of GnRH;

- The effects of day length changes on reproductive phenomena including behavioral and endocrinological parameters;

All of these have great potential value for the commercial rabbit producer. None has easy answers, but knowledge is building and, with a focused approach, production can be improved.

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387

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