REPRODUCTIVE PHYSIOLOGY-ENDOCRINOLOGY

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Contents

Summary

This chapter describes the main physiological mechanisms involved in the control of reproductive function in seasonal and non-seasonal breeder farm animals. Emphasis has been placed on the interrelationships between internal and external factors that are

integrated at the central level for the development of puberty, maintenance of adequate reproductive function in the adult, and the regulation of seasonal reproductive activity. An important part of this chapter has been devoted to the description of reproductive physiology in sheep, goats, cattle, pigs and horses, intending to highlight the most important reproductive features of each species.

1. Introduction

Reproduction in farm animals is highly affected by environmental factors and when environmental conditions are favorable, reproductive activity expresses its full potential. Favorable conditions must include adequate photoperiod, thermoneutral conditions, food availability in quantity and quality, and a low stress environment. Inadequate conditions may lead to a decrease in reproductive capacity, varying from sub-fertility to infertility. Therefore, the expression of the reproductive potential is only possible when animals develop and establish a homeostatic equilibrium with their external environment.
External and internal conditions are perceived by way of specialized neural functions which influence reproduction through the hypothalamic-pituitary-gonadal (HPG) axis. In mammals, the reproductive function is finely tuned by the HPG axis through several feedback loops using different chemical messengers such as neurotransmitters, hormones and growth factors. In this chapter we will discuss the relationship between the neuroendocrine system and reproductive function in farm animals.

2. Central control of Reproductive physiology: The Hypothalamus-Pituitary–Gonadal axis

The reproductive function in these animals is governed by the HPG axis, a complex neuroendocrine system. This axis is composed of three anatomically and functionally distinct structures that, in proper coordination, regulate animal reproduction.

2.1. The Hypothalamic Level

The hypothalamic area that controls reproduction is represented by scattered neurons producing gonadotropin releasing hormone (GnRH) located in the forebrain, mainly in the preoptic, anterior hypothalamic and ventromedial hypothalamic areas as well as in the supraoptic nucleus, arcuate nucleus, medial basal hypothalamus and medial eminence. The dispersed GnRH neurons, collectively called “GnRH pulse generator”, receive and integrate endogenous cues, neurotransmitters, hormones, growth factors, which originate in different types of cells sensitive to internal (e.g. growth, nutritional status) or external stimuli (e.g. photoperiod, temperature, social, stress). The action of these stimuli translates into changes in the synthesis and secretion patterns of GnRH, a decapeptide hormone considered as the master molecule for the reproductive control in mammals. GnRH controls gonadal activity by regulating the production and release of pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It is well known that pulsatile GnRH secretion induces an identical pattern of LH secretion and increases the FSH synthesis at the pituitary level. Thus, the pattern of pulsatile GnRH secretion present in the pituitary portal blood can be studied through the characterization of pulsatile LH concentrations found in peripheral blood. These

gonadotropins then stimulate gametogenesis, steroidogenesis and secondary sexual characteristics. In turn, gonadal steroid or peptide hormones regulate the hypothalamic/pituitary function by feedback mechanisms, completing the loop of endogenous control of reproductive activity.

2.1.1. Hypothalamic Control of Puberty and Seasonal Reproduction

Hypothalamic GnRH production begins during fetal life and its regulation depends on the physiological status of the individual animal. Although, GnRH secretion is already present during early postnatal development, it seems that GnRH is inhibited until the beginning of the pubertal process. Maturation of GnRH neurons and resumption of GnRH release and production are key factors related to puberty in domestic animals. Reproductive cyclicity in females depends on the release of GnRH into the hypothalamic–pituitary portal vessels to induce production and release of FSH and LH from the gonadotropes cells in the pituitary gland. In mammals, the pattern of GnRH secretion includes both pulse and surge phases which are regulated independently. Pulsatile GnRH secretion controls gonadal development and function, including steroidogenesis in both females and males, while surge GnRH secretion drives ovulation in the females. The surge center in the male is eliminated during the fetal stage. The GnRH pulse generator drives endocrine signals that allow the onset of reproductive activity, either by the transition from a pre-pubertal state to puberty, or the transition from seasonal anestrous to a full reproductive activity, as well as the maintenance of proper reproductive activity during adulthood.

Farm animals are mostly seasonal breeders, their breeding period is influenced by either long or short days. This strategy is associated with length of gestation and allows deliveries to occur when environmental conditions are optimal, in order that enough food is available for the mother to achieve an adequate lactation. Thus, animals with long gestations (e.g. mare, 11 months) display reproductive activity during long days, and short gestation animals (e.g. sheep, 5 months) during short days. Some species that have been subjected to intensive selection and management (e.g. cows, pigs) have lost their reproductive seasonality, and their endocrine system responds minimally to photoperiod. Reproductive activity in non-seasonal species begins when, under a proper nutritional regimen, they achieve a body development of approximately 60% of adult weight. In addition, the change of the GnRH secretion pattern, from low to high frequency pulses, is regulated by metabolic cues indicating physical maturation and nutritional status.

It is well accepted that changes in GnRH pulse frequency, which occur from pre-pubertal period to puberty or during the transition from non breeding to breeding season, depend ultimately on gonadal steroid feedback on GnRH secretion. In the pre-pubertal state or during non-breeding season in adults, low frequency GnRH pulses are observed, resulting from enhanced sensitivity to the negative feedback effect of estrogens on the pulse generator centre. At the onset of puberty or breeding season, the negative feed-back to the estrogens disappears, resulting in an increase of GnRH concentration and pulse frequency that induces reproductive activity. However, this phenomenon is not mediated by a direct response of GnRH neurons, because these cells do not express the estrogen receptor Erα, the subtype receptor that mediates the

feedback effect of estradiol. GnRH secretion must therefore respond to sex steroid by means of interneuron and its neurotransmitters. Several neurotransmitter systems are involved in the modulation of amplitude and frequency of GnRH pattern. In this regard, it has been described excitatory and inhibitory neurotransmitters on the synthesis and secretion of GnRH. For instance, the amino acids glutamate and aspartate increase GnRH/LH secretion pulsatility while GnRH/LH pulsatility can be decreased by gamma aminobutyric acid (GABA) and neuropeptide "Y" (NPY). It has been reported that endogenous opioid peptides also have an inhibitory effect on the secretion of GnRH during sexual development until the time of puberty. In addition, catecholamines (dopamine and noradrenalin) and serotonin may modulate GnRH response to ovarian steroids through mechanisms where opioids and GABA play important regulatory roles.

During the last 10 years, there have been significant advances in the understanding of the mechanisms responsible for the neurohormonal regulation of GnRH secretion related to puberty or seasonal reproduction. One important milestone in this respect was the discovery of kisspeptin, a family of neuropeptides encoded by the *Kiss1* gene. It is expressed in discrete areas of the hypothalamus, along with its G protein-coupled receptor GPR54, also called *Kiss1R*. Hypothalamic expression of kisspeptin has been described in ruminant and monogastric farm animals, and it has been related to the regulation of GnRH secretion. Kisspeptin is mainly expressed in the arcuate (ARC) and periventricular nuclei (PVN), and in the preoptic area (POA) of the hypothalamus, but the population of kisspeptin cells in the ARC nucleus appears to be responsible for the translation of both internal and external stimuli, leading to puberty or seasonal reproduction. However, kisspeptin cells localized in the ARC do not project directly to GnRH cells, therefore the PVN kisspeptin cells may act as an interface between the ARC and GnRH pulse generator. Evidence found in several different animal species support the role of kisspeptin/*Kiss1R* during course of puberty or seasonal reproduction. In general, an increase in the amount of cells expressing *Kiss1*, as well as, in the number of their close appositions with GnRH neurons, has been observed. Therefore, the pubertal development is associated with increased tone of kisspeptin and enhanced kisspeptin signaling efficiency on GnRH cells.

Different compounds that may provide feedback information of metabolic status have been studied and identified as potential endogenous mediators between body growth and/or nutritional status and the GnRH cell activity that triggers puberty or resumption of seasonal reproductive activity. These include glucose, insulin, leptin, ghrelin and some fatty acids, all of which have been shown to be involved in this process.

Since the discovery of leptin in the mid 1990's, this peptide hormone synthesized by adipose tissue has contributed greatly in deciphering the mechanisms and signals responsible for the endocrine control of energy balance and reproduction. Despite the different behavior of leptin in response to acute or chronic changes in nutritional status between ruminant and monogastric species, it has been shown to serve as primary metabolic signal to regulate the secretory activity of GnRH pulse generator. Moreover, leptin supports the hypothesis that animal reproduction is possible when energy demands for body growth and maintenance are met, and should have an energy surplus able to be stored as body fat. Consistent with this, there is a positive correlation between energy balance and plasma leptin concentrations. There is also a positive correlation

between leptin levels and concentrations and pulsatility of GnRH/LH in blood plasma. In addition, it is well established that in pre-pubertal malnourished animals or fasted adult animals, administration of exogenous leptin restores a pattern of GnRH/LH compatible with puberty or reproductive activity, respectively. The action of leptin on GnRH secretion must therefore be regulated through interneuronal signaling mechanisms, since no leptin receptors on GnRH cells have been described. In farm animals, leptin signal could act on GnRH cells by means kisspeptin cells. Due to the presence of functional receptors for leptin on kisspeptin cells found in the mouse, in addition to the fact that low concentrations of leptin in sheep is associated with low expression of kisspeptin, it may be suspected that, in farm species, leptin could act through kisspeptin cells to modulate GnRH secretion. However, information coming from experiments in lean animals shows that leptin treatment restores only partially the expression of *Kiss1* and gonadotropin secretion, suggesting additional interneuronal pathways in GnRH regulation. Consistent with the aforementioned, it is known that the effects of leptin, as a hormone regulating energy balance, are mediated by at least one orexigenic (appetite-increaser) peptide (neuropeptide Y, NPY) and another anorectic (appetite-reducer; proopiomelanocortin, POMC), which also can modulate the secretion of GnRH. In turn, kisspeptin can stimulate the expression of NPY and inhibit those of the POMC *in vitro* hypothalamic cells, indicating complex hypothalamic connections for the simultaneous control of leptin-mediated metabolism and reproduction.

Ghrelin, another peptide involved in the physiologic coupling of energetic metabolism and reproduction, has emerged as important endocrine signal acting on the hypothalamus for regulation of reproduction and puberty. Ghrelin, as well as leptin, is highly conserved across several species and, although it is mainly secreted by gastric/abomasum mucosa cells, it is widely expressed in different tissues. From the functional point of view, ghrelin antagonizes the effects of leptin on energetic metabolism. In rats, ghrelin and its receptors GSHR-1a are expressed in the ARC, particularly in cells expressing orexigenic peptides like NPY, which favor feed intake and weight gain. Recent experiments in sheep show that high levels of amino acids in plasma can stimulate ghrelin secretion, but no effects of plasma glucose or insulin on ghrelin were observed. Regarding the effects of ghrelin on reproduction, it has been demonstrated that intracerebroventricular administration of ghrelin inhibits LH secretion in cyclic and ovariectomized rats. It has also been demonstrated that ghrelin decreases GnRH release by hypothalamic explants (technique used for the isolation of cells from a tissue in order to harvest these cells in culture dishes), favoring conceptually the proposition that the primary site of action for the inhibitory effect on HPG axis is the hypothalamus. Although ghrelin's effects on hypothalamus have not been clarified in farm animals, previous observations suggest that ghrelin might mediate at least, in part, the well-known suppressive effect of energy deficit at the onset of puberty and the conservation of normal gonadal function and fertility.

Other compounds, which, for a long time have been considered as mediators between body growth, energy metabolism signals and the onset of reproductive activity are: plasma concentrations of glucose, amino acids, fatty acids, insulin, insulin-like growth factor 1 (IGF-1), growth hormone (GH) and thyroid hormones (T_3/T_4). Thus, while a large amount of experimental evidence has established the effects of these compounds on the secretion and pulsatility of GnRH/LH during pubertal development, the most

recent information has established that these compounds actually play rather a permissive role by acting at the hypothalamic level mainly through leptin and ghrelin.

In seasonal breeders, on the other hand, the pubertal process begins in presence not only of adequate endogenous body growth/nutritional status signals, as described above, but also in presence of endogenous cues that inform the hypothalamus of a permissive environmental photoperiod, all of them leading to the decreased estrogen's negative feedback on GnRH/LH pulse frequency and amplitude. This critical event occurs only when internal and external cues indicate that both size/nutrition and season are favorable for a pregnancy. Thus, both puberty and adult reproductive activity occurs in the same season. It is also considered that in adults the reactivation of the reproductive axis when the breeding season begins after seasonal anoestrus is a physiological phenomenon that essentially responds to the same cues involved in the onset of puberty. Thus, seasonal breeding animals may virtually experience successive puberties throughout their reproductive life.

It is widely accepted that environmental photoperiod cues are translated into endogenous signals, where the hormone melatonin plays a central role. Melatonin is synthesized and secreted mainly by the pineal gland, under a neuronal control system in which the perception of light in the retina blocks the synthesis and secretion of pineal melatonin. Thus, the concentration of melatonin during daylight hours is very low, increasing dramatically during the night-time darkness. Because the almost perfect correlation between the hours of darkness and the presence of high concentrations of melatonin in the blood, the daily pattern of the hormone becomes an annual pattern, in which short photoperiod seasons are consistent with a higher proportion of hours a day with high concentrations of melatonin, in comparison with that observed in long photoperiod seasons. Thus, animals in which puberty onset or reproductive activity occurs under short photoperiod should experience a rise in the number of hours a day with high concentrations of circulating melatonin. The opposite should happen in species with presentation of puberty and reproductive activity under long photoperiod.

At present, the information about the site at which melatonin acts to regulate GnRH secretion is largely incomplete. Experiments in sheep suggest that melatonin may act within the premammillary nucleus of the basal hypothalamus to control seasonal changes in reproduction. However, it is not known how this endocrine signal is translated into a change in GnRH secretion. Some evidence has been documented showing a narrow association between photoperiod, melatonin and *Kiss1* system. For instance, ewes exposed to short photoperiods show higher Kiss1expression in the ARC than those exposed to long photoperiods. In addition, during breeding season the number of *kiss1* neurons contacting GnRH cells is increased. The premammillary area, where melatonin may exert its action, overlaps the caudal region of the ARC, where most *Kiss1* cells are localized suggesting that kisspeptin neurons in the ARC could be candidate targets for melatonin. Nonetheless, whether or not these cells are direct targets for melatonin has not been clearly established. A very recent study in sheep hypothalamus has shown evidence for the expression of prolactin receptors but not for melatonin receptors in *Kiss1* cells, suggesting an indirect effect of melatonin on *kiss1* neurons. Consistent with the above, it has been proposed that melatonin may act by means several neural pathway including catecholaminergic, serotoninergic, opioidergic

and GABA-ergic systems. It is noteworthy, that melatonin is predominantly considered only as an endogenous mediator of photoperiod. However, recent data show that orexigenic peptides like orexin B and ghrelin, as well as anorectic (leptin), have a seasonal influence on the secretion of melatonin in the pineal gland. This evidence may suggest a role of melatonin on both photoperiod and the metabolic status/body growth effects upon the reproductive axis.

Other components involved in the seasonal control of GnRH have emerged. One of them corresponds to the hypothalamic dopaminergic system, which is considered as mediator of the seasonal estrogen negative feedback. Dopaminergic cells are activated by estradiol during seasonal anestrous, an effect presumably mediated by glutaminergic cells of the POA, because no ERα in dopaminergic cells has been described. Even though dopaminergic cells do not appear to project directly to GnRH cells, they are projected predominantly to the caudal region of ARC and median eminence, where they probably connect with kisspeptin cells. Furthermore, an important proportion of kisspeptin cells co-express dynorphin or neurokinin B neuropeptides, thought to be involved in seasonal regulation of reproduction. There is also a small population of *Kiss1* neurons which co-express both peptides. Dynorphin have an inhibitory effect on the reproductive axis, while neurokinin B has shown dual stimulatory and inhibitory effects. It is now apparent that both dynorphin and neurokinin B cells can express Erα and progesterone receptors, suggesting that these cells are involved in the seasonal sex steroid control of GnRH secretion. It may also be supported because their density may vary according to reproductive seasonality and they receive inputs from a variety of neural systems involved in controlling puberty and seasonal reproduction.

A gonadotropin-inhibitory hormone (GnIH), described about ten years ago in birds, whose presence has been demonstrated in mammals, has emerged as a new regulatory element of reproductive seasonality in farm animals. Neurons expressing GnIH have been located in hypothalamic regions, surrounding the PVN and dorsomedial hypothalamus (DMH), and project to GnRH cells. GnIH receptors have been found distributed in different regions of the hypothalamus (suprachiasmatic, PVN and supraoptic) and in the pituitary *pars tuberalis*. In ruminants, GnIH expression is decreased during short days breeding season. Also, GnIH administration diminishes LH pulse amplitude *in vivo* and LH secretion from cultured pituitary cells. However, considering mammals in general, GnIH appears to be increased under long days regardless whether the species is a long or short breeder. Information on how GnIH can act in the regulation of reproductive seasonality is still scarce, but available data suggest that it should be considered as an important factor in controlling reproduction in farm animals.

As noted above, both the pubertal process and the resumption of seasonal reproductive activity in adult animals requires the decrease of estradiol negative feedback on GnRH secretion and pulsatility. Accordingly, in pigs, it has been reported that estrogen induces a decreased expression of *Kiss1* in a small group of cells in the most caudal ARC. This fact may lend support to diminished secretory GnRH activity observed in pre-pubertal animals. The decline in estradiol negative feedback on the secretory activity of GnRH at the time of puberty, may depend on the increase in the population of cells expressing *Kiss1* having a positive feedback to estradiol. Studies in rodents show the presence of

PVN cell groups up-regulating expression of *Kiss1* by estradiol effect. Despite the above, the mechanisms that explain this change in sensitivity to estradiol are still largely unknown. One possibility that emerges from the current information is that both metabolic/body growth and photoperiod signals may act through the maturation and plasticity of neuron populations modulating GnRH cells. The most suitable candidates for this, in sheep at least, are dopaminergic neurons from the A 15 region of the hypothalamus. During non-breeding season these cells, activated by estrogens, decrease GnRH secretion. Interestingly, these cells do not respond to estrogen in the breeding seasons.

Most of the information about neuroendocrine mechanisms controlling puberty or seasonal reproduction has been obtained from females. However, collected evidences from studies in male animals indicate that, in general, the model described for females could be satisfactorily applied to males. The internal and external cues modulating the male reproductive activity are qualitatively the same as in the female, but each sex may have different quantitative requirements to start the physiological changes leading to puberty or seasonal reproduction. There are, however, remarkable differences between males and females. The onset of puberty in males is an earlier phenomenon, and the reproductive seasonality is noticeably less marked than in females. These differences may be explained by a reduced hypothalamic sensitivity to estradiol negative feedback in males, which is present earlier during postnatal development. Experiments in sheep demonstrate that this partial hypothalamic desensitization to estrogens is a part of the testosterone-dependant fetal programming. In fact, when female fetuses are exposed to testosterone between 30 and 90 days of intrauterine life, postnatal sensitivity to estrogen negative feedback is reduced, while there is an advance in the pubertal rise of GnRH. Although no information is available on farm animals, data from experiments in rats indicate that *in utero* androgenization is associated with plastic changes in the *Kiss1* system during the transition to puberty. These differences would explain why male reproductive activity is a more stable phenomenon, less cyclical and less sensitive to environmental variations.

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