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## Neuro-endocrine mechanisms controlling reproductive seasonality in sheep: A review

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### Abstract

The two-third of the Indian rural community is directly or indirectly dependent on sheep and goat farming systems for their sustenance. The contribution of sheep in terms of meat and wool production as well as ability of this animal to survive under harsh climatic conditions points towards a promising source of income for small and marginal farmers but due to seasonal breeding behaviour the full reproductive efficiency of this species is underutilized. Sheep is a small day breeder limiting its reproductive potential and only one lambing can be achieved annually. Sheep is a seasonally polyestrous animal with average estrous cycle length of 16 to 17 days and estrus period lasting for approximately 24 to 36 hours. Seasonality is one of the most special characteristics of ovine reproduction described as “nature’s contraceptive”, a naturally occurring phenomenon to induce a reversible pattern of fertility and infertility in adult mammals but it seem to be undesirable from animal production point of view. This review deals with interplay of various neuro-endocrine mechanisms controlling the seasonal breeding in sheep.

**Keywords:** Neuro-endocrine, mechanisms, controlling, reproductive, sheep

### Introduction

The rearing of small ruminants by the small and marginal farmers is a promising source of livelihood in India. The two-third of the Indian rural community is directly or indirectly dependent on sheep and goat farming systems for their sustenance. The total world sheep population in 2016 was 1173.35 million (FAO statistical book, 2018) out of which India comprises about 5.6% (65.1 million; 19<sup>th</sup> Indian livestock census, 2012). Sheep is mostly reared for wool and meat purposes with an important contribution in the economy. The total meat production in the country was pegged at 7.4 million tons in 2016-17 out of which sheep contributed about 7% whereas the total wool production of India was 43.5 million kg (DAHDF, MoAFW, GOI Annual Report 2017-18). The contribution of sheep in terms of meat and wool production as well as ability of this animal to survive under harsh climatic conditions points towards a promising source of income for small and marginal farmers but due to seasonal breeding behaviour the full reproductive efficiency of this species is underutilized. Sheep is a small day breeder limiting its reproductive potential and only one lambing can be achieved annually. The present review highlights the reproductive cycle and various neuro-endocrine mechanisms controlling the seasonal breeding in sheep.

### Reproductive cycle of sheep

Sheep is a seasonally polyestrous animal with average estrous cycle length of 16 to 17 days and estrus period lasting for approximately 24 to 36 hours (Hafez, 1966; Patterson, 1986); however, in the transition period between anestrus and breeding season as well as after lambing, short cycles of less than 12 days, are particularly common (Hunter, 1991). The pool of primordial follicles during the pre-natal life in ewe lambs ranges from 40000-300000 which further decreases by 20-35 fold during the late pre-natal and post-natal life due to cellular death via apoptosis (Driancourt *et al.*, 1993) [18]. With the attainment of puberty the primordial follicles develop into the pre-antral follicles under the effect of ovarian steroids and gonadotropin hormones. The ovarian follicles of size 1-2 mm can be visualized through ultrasonography at this stage (Bartlewski *et al.*, 2011) [4] which later attains the preovulatory size of about 4 mm (Turnbull *et al.*, 1977) [68]. The estrous cycles length during the breeding season in sheep are usually consistent with differences between the breeds not exceeding one day without any significant effect of age of animal (Goodman, 1994) [22].

On the basis of the ovarian structures the estrous cycle has been divided into a follicular phase of duration 3-4 days and the luteal phase of average 14-15 days, luteal phase is characterized by the maturation of the corpus luteum and high levels of progesterone that reach a maximum peak about 6 days after ovulation (Jordan, 2005) [39].

A distinct wave like pattern of follicular growth has been observed both during the breeding as well as seasonal anestrus period in ewes (reviewed by Bartlewski *et al.*, 2011) [4] where both prolific and non-prolific ewes showed 3-4 wave pattern at follicular emergence during the breeding season. This wave pattern of follicular emergence is initiated prior to onset of puberty and only hindered during the pregnancy and early post-partum period (Bartlewski *et al.*, 2011) [4]. The follicular waves in ewes consist of 1-4 follicles reaching the maturity from the final and penultimate wave of the cycle and can ovulate in prolific breeds (Bartlewski *et al.*, 1999; Gibbons *et al.*, 1999) [5, 23]. The absence of follicular dominance in ewes leads to multiple ovulations either due to ovulation of two follicles simultaneously emerged from two follicular waves or due to maturation of more than one follicle from single follicular wave (Duggavathi *et al.*, 2005) [19] resulting in twinning and triplet births. It has been observed that the follicles attain maturity at a smaller size in prolific breeds of sheep (Driancourt *et al.*, 1986; Souza *et al.*, 1997) [17, 66].

Błaszczuk *et al.* (2004) [11] observed that on the day before estrus 17- $\beta$  estradiol concentration in blood plasma ranges between 10 to 20 pg/ml during spring and autumn season respectively, because one or more than one follicles grow rapidly. The increased estrogen level due to large size follicles leads to behavioural estrus signs like stimulation of cervix to secrete small amount of mucus, increased vascularization in the vulva (edematous vulva) and some changes in the epithelial tissue of the vagina (Hafez, 1980; Anderson, 1991; Theodosiadou *et al.*, 2004) [29, 32, 67]. Estrus in the ewe is less apparent as compared with other ruminant species. During the proreceptivity period, the ewe will be attracted toward the ram, showing mutual sniffing, frequent micturation and licking followed by receptivity when the ewe stands to be mounted. The duration of the estrus behaviour is about 30 to 48 h depending on the breed (Faber-Nys, 1987) [20].

Estrogen acts synergistically with Gonadotropin Releasing Hormone (GnRH) and stimulate release of luteinizing Hormone (LH) from anterior pituitary gland. After beginning of estrus, the concentration of LH in the blood rises to a peak and then both LH and estradiol concentration fall rapidly (Younes, 2008) [76]. LH stimulates ovulation which occurs about 14 hours after the LH peak or 24 hours after the beginning of estrus (Pierson *et al.*, 2001; Alvarez *et al.*, 2001) [58, 1], but throughout the other period of the cycle, the LH concentration remains low (2 to 3 ng/ml). Ewes normally ovulate 24 to 27 hours after the onset of estrus and after ovulation the entire progesterone is secreted from the corpus luteum (Bjersing *et al.*, 1972) [10] formed under the sole effect of LH (Niswender *et al.*, 2000) [54]. The mature size of CL (11-14 mm) is attained around day 6 after the initial luteogenesis and it undergoes atrophy abruptly over 2-3 days about 12-15 days of ovulation under effect of PGF $2\alpha$  (Bartlewski *et al.*, 1999b) [6].

It has been observed that during the transition from breeding period to the seasonal anestrus, the failure of initiation of follicular waves occur due to inability of FSH peaks, low level of luteal progesterone and low estradiol production

(Bartlewski *et al.*, 1999) [5] which may be attributed to decreased sensitivity of ovary to gonadotropins.

### Seasonal breeding in sheep

The periodical fluctuations on daily as well as annual basis in the environment impose great adaptive changes in the physiological functions of the animals including breeding, migration and hibernation (Dardente *et al.*, 2016) [13] which is referred as photoperiodism. Seasonality is one of the most special characteristics of ovine reproduction described as “nature’s contraceptive”, a naturally occurring phenomenon to induce a reversible pattern of fertility and infertility in adult mammals (Lincoln and Short, 1980) [45] but it seem to be undesirable from animal production point of view (Dardente *et al.*, 2016) [13]. Seasonality in reproduction is an adaptation by the animals whereby they give birth to young ones when the period of their survival is at most favorable. The seasonality in breeding is much pronounced in the temperate climates as compared to tropical and sub-tropical. In the tropical zones, sheep tends to breed throughout the year as there is less variation in day length, therefore, when temperate breeds are introduced into the tropics, they gradually lose their seasonality and follow the breeding patterns characteristic of the new environment (Rodrigues *et al.*, 2007) [62].

### Role of photoperiod in seasonal breeding

Day length or photoperiod is a key regulator of reproduction in seasonal breeder mammals (Lincoln and short, 1980) [45]. Photoperiod along with different factors seem to be responsible for seasonal behaviour in animal reproduction. Day length has a dominant controlling influence on initiation and termination of breeding season in temperate regions. As the ratio of daylight to darkness decreases the breeding season of sheep is initiated and increasing day length i.e. equal daylight and darkness leads to ending of breeding season. The short day length during winter season is having stimulatory effect on the reproductive neuroendocrine axis in sheep which leads to ovulatory cycles and fertility resumption while the long day length has an inhibitory effect on hypothalamo pituitary gonadal axis leading to anestrus (Hazlerigg and Simonneaux, 2015) [34]. So, ewes are classified as short day breeders in contrast to long day breeder such as the mare (Yeates, 1949; Legan and Karsch, 1980, Robinson and Karsch, 1987) [74, 40, 61]. Sheep usually breed during the short day with a gestation period of about 5 months. The offspring are born in spring and summer with chances of their survival at that time are at most. Sheep are intermittently polyestrous or seasonally polyestrous animals because during the period of sexual activity they exhibit multiple estrous cycles until the end of season or to become pregnant (Bearden and Fuquay, 1984) [7].

It has been evidenced that eye of the mammals is the only photoreceptor organ responsible for the photoperiodism (Yoshimura, 2013) [75] and the retina of mammals transmits the photoperiodic information to suprachiasmatic nuclei (SCN) of the hypothalamus which exerts its control over pineal gland for nocturnal production of melatonin (Pevet *et al.*, 2011). [57] SCN seem to be the master circadian pacemaker located in the hypothalamic region of the brain in mammals (Yoshimura, 2013) [75], while photoperiod is the main determinant of the seasonality. Besides other factors like genetical, management practices (male effect) and social causes (Wingfield *et al.*, 1983; Deviche *et al.*, 2001) [72, 16] etc.

can influence reproductive pattern.

### Melatonin a regulator of seasonal breeding

Melatonin is a hormone synthesized and secreted by the pineal gland in diurnal fashion where the level is highest during night while undetectable in the morning (Karsch *et al.*, 1984). The nocturnal secretion of melatonin guards the length of night. Malpaux *et al.* (1997)<sup>[47]</sup> demonstrated that the night time elevation of melatonin serve as code of the external photoperiod indicating short day length with stimulatory effect on reproduction in sheep. Melatonin does not seem to be directly involved in the seasonal reproductive behaviour in sheep (Malpaux *et al.*, 1998)<sup>[46]</sup> but it has been seen that enucleation, pinealectomy as well as SCN lesions in hypothalamus disrupts the photoperiodic responses (Reiter, 1980)<sup>[60]</sup>. Synchronization of the circadian rhythms by melatonin seemed to be analogous to the ability of light to entrain circadian rhythms in SCN and other brain tissues (Van Esseveldt *et al.*, 2000)<sup>[69]</sup>. Melatonin receptors subtypes MT1 and MT2 are expressed by different body tissues but pars tuberalis (PT) region of the anterior pituitary express the maximum MT1 subtype with its pivotal role in seasonality via control over production of gonadotropins (LH and FSH) and prolactin (Barett *et al.*, 2012; Wood *et al.*, 2014)<sup>[73]</sup>. It is known that this effect of melatonin involves modulation of the secretion of Gonadotropin-releasing hormone which leads to induction of estrus cycle in the sheep (Viguie *et al.*, 1995)<sup>[70]</sup>. Melatonin also governs the control over production of thyrotropin hormone (TSH) from the pituitary which is secreted in high quantity during long summer days (Yoshimura, 2013; Dardente *et al.*, 2014)<sup>[75, 37]</sup>.

### Role of thyroid hormones in seasonal breeding

It is known from the decades that thyroid hormones also have key role in seasonality (Nicholls *et al.*, 1988; Dawson *et al.*, 2001)<sup>[53, 14]</sup> and thyroidectomy leads to suppression of change in reproductive state from breeding to non-breeding (Moenter *et al.*, 1991; Dawson, 1993; Parkinson and Follett, 1995)<sup>[51, 15, 55]</sup>. Thyroid hormones are required for transition from breeding to anestrus state but not for the reverse transition from anestrus to breeding season (Dahl *et al.*, 1995)<sup>[12]</sup>. In short day breeders, the longer photoperiod induces the expression of DIO2 (Deiodinase 2) which converts T<sub>4</sub> into T<sub>3</sub> leading to termination of breeding season (Hanon *et al.*, 2008)<sup>[31]</sup> and also T<sub>4</sub> administration terminates breeding season via decreasing serum LH (Billings *et al.*, 2002; Anderson *et al.*, 2003)<sup>[9, 32]</sup>.

Sheep usually breed during the autumn/winter season of the year when day length is short (Hut *et al.*, 2014)<sup>[37]</sup> and displays TSH-DIO2 response whereby leading to increased production of tri-iodothyronin (T<sub>3</sub>) during the long summer days with impaired breeding activity (Hazlerig *et al.*, 2014)<sup>[34]</sup>. It has been proposed that T<sub>3</sub> acts via the nuclear receptors in the medio-basal hypothalamus (MBH) and other areas of brain (Mullur *et al.*, 2014)<sup>[52]</sup> and *Kiss1* and *Rfrp* genes which encode the neuropeptides KISS1 and RFRP3 (RF-amide-related peptide-3) seem to be major targets of thyroid hormones in MBH with context to seasonal breeding (Dardente *et al.*, 2016)<sup>[13]</sup>. It has been evidenced that local activation of metabolism of thyroid hormone in MBH has key role in photoperiodic responses in sheep (Hanon *et al.*, 2008)<sup>[31]</sup>.

KISS1 is a potent stimulator of GnRH and expressed at its peak during breeding season (Beltramo *et al.*, 2014)<sup>[8]</sup> and

RFRP3 can have negative as well as positive control over GnRH production depending upon species, sex and experimental conditions and is expressed at peak during the non-breeding season in sheep (Dardente *et al.*, 2008)<sup>[31]</sup>. It has also been demonstrated that expression of *Kiss1* and *Rfrp* genes during different seasons is under the control of melatonin dependent parathyroid (PT) derived TSH (Klosen *et al.*, 2013)<sup>[41]</sup> which ultimately provides the clue about the role of T<sub>3</sub> in seasonal breeding (Henson *et al.*, 2013)<sup>[35]</sup>.

### Neural mechanisms as regulator of seasonal breeding

Seasonal breeding in animals is under control of hypothalamus-pituitary-gonadal (HPG) axis where secretion of gonadotropins (LH and FSH) is activated during the breeding season (Ikegami and Yoshimura, 2013)<sup>[75]</sup>. The pronounced seasonal changes in the hypothalamus response to estradiol also has a well-known effect on seasonality where the negative feedback effect during the anestrus period and positive feedback effect during the breeding season are shown by estradiol on GnRH secretion (Legan *et al.*, 1977; Goodman *et al.*, 1982; Platt *et al.*, 1983)<sup>[42, 24, 59]</sup>. During the seasonal anestrus under long days light exposure, the intensity of the estradiol negative feedback on LH secretion increases, which leads to a decrease in the pulsatile release of GnRH (Legan *et al.*, 1977; Goodman *et al.*, 1982; Martin *et al.*, 1983; Viguie *et al.*, 1995; Goodman *et al.*, 2000)<sup>[42, 24, 48, 70, 27]</sup>. The impaired GnRH activity prevents the rise in LH which is necessary for the late follicular phase peak in estradiol which induces GnRH/LH pulses for ovulation (Goodman *et al.*, 2010)<sup>[25]</sup>. This striking increase in the responsiveness of GnRH neurons to the negative feedback of estradiol is the major mechanism involved in interruption of ovarian activity leading to seasonal anestrus in the sheep (Weems *et al.*, 2015)<sup>[71]</sup>.

It has been seen that the ovulation is inhibited during anestrus period due to increased estradiol negative feedback but the exogenous estradiol can induce a positive feedback effect and trigger the GnRH/LH surge (Karsch *et al.*, 1980)<sup>[40]</sup> which suggest that the positive feedback control is not under the seasonal control (Weems *et al.*, 2015)<sup>[71]</sup>. Alpha isoform of the estrogen receptors, which is responsible for the negative feedback of estradiol on GnRH (Hardy *et al.*, 2003)<sup>[32]</sup> is absent on GnRH neurons in the sheep brain (Lehman *et al.*, 1993)<sup>[44]</sup>.

Dopaminergic neurons in the retrochiasmatic area (RCh), known as A15 group of neurons also had been displayed to have role in seasonal breeding in sheep (Smith *et al.*, 2008; Singh *et al.*, 2009)<sup>[65, 64]</sup>. The lesions in the A15 neurons block the estrogen negative block in the anestrus ewes (Havern *et al.*, 1994)<sup>[33]</sup> while direct stimulation of the A15 neurons inhibits GnRH/LH pulses frequency irrespective of the season (Martin and Thiery, 1987)<sup>[87]</sup>. Estradiol also increases the neural activity of tyrosine hydroxylase (TH) which is rate limiting enzyme in the synthesis of dopamine (Gayrard *et al.*, 1994)<sup>[22]</sup>. D2 dopamine receptors are present in the GnRH neurons of sheep where dopamine directly inhibits the GnRH pulses by acting at the GnRH axons (Goodman *et al.*, 2012)<sup>[26]</sup>.

### Kisspeptin: A gatekeeper of hypothalamus

Kisspeptin protein is a key regulator of the GnRH secretion and has important regulatory role in seasonal breeding in sheep (Smith *et al.*, 2008)<sup>[65]</sup>. KNDy (Kisspeptin/neurokinin-B/dynorphin) cells present in arcuate nucleus (AN) have become a center of focus in the neuroendocrine regulation of

seasonal breeding (Lehman *et al.*, 2010) [25]. The strong inhibition by estradiol decreases the number of kisspeptin peptide as well its m-RNA expressing cells during anestrus in sheep decreasing the positive input by kisspeptin to GnRH neurons within MBH (Smith *et al.*, 2008) [65]. KNDy cells also express the D2 dopaminergic receptors which also have inhibitory effect on seasonal GnRH pulses with 80% expression during anestrus as compared to 40% in breeding season (Meyer and Goodman, 1986; Goodman *et al.*, 2012) [50, 26].

Weems *et al.* (2015) [71] proposed that during anestrus estradiol acts on the cells having alpha isoform of estrogen receptors in the ventro-medial pre-optic area and RCh area of brain, where these neurons stimulates A15 dopaminergic neurons using glutamate as a neurotransmitter and dopamine is released by the A15 group cells in MBH where dopamine acts on GnRH neurons either directly in medial eminence or indirectly via Kisspeptin cells in ARC (Arcuate nucleus) to inhibit the GnRH frequency in sheep. Neurokinin B (Sakamoto *et al.*, 2012) [63] and dynorphin (Goodman *et al.*, 2012) [26] has also been reported to have their role in seasonal reproduction in ovaries.

### Conclusion

Reproductive seasonality is a characteristic of breeding pattern in sheep regulated by various hormones like Kisspeptin, GnRH, Melatonin with their neuro-endocrine mechanisms. This breeding pattern is prominent mainly in temperate countries while, in tropics there is less distinction between day and night lengths causing breeding of sheep throughout the year. Various strategies like male effect, photoperiodic management and estrus synchronization protocols could be used to combat reproductive seasonality. However, there are scopes for further molecular innervations for exact knowledge of this neuro-endocrine display and to combat the breeding for improving reproductive efficiency in sheep.

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