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Popular Article

The Reproductive Role of Melatonin: A Review

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Domestic animals are broadly classified depending upon the number of times they breed during a year as seasonal and non-seasonal breeders. Seasonal breeders are those that have specified period of time in a year during which they actively breed. They use the changes occurring in day length and accordingly regulate many of the physiological and behavioural processes. These are again sub classified into Monoestrus and Polyestrous. Monoestrus animals are those which have only one estrus cycle during the breeding season e.g. horse, donkey, sheep and goat and polyestrous are those which have several cycles during each breeding season e.g. cattle, pigs. These species of animals can also be further categorized as long day and short-day breeders. Non seasonal breeds are those which undergo breeding throughout the year which include polyestrous animals include cattle and pigs. Duration of photo period (day-length) plays a critical role in onset of breeding season for seasonal breeders.

Melatonin, also known as *N*-acetyl-5-methoxy tryptamine, is a hormone that is produced by the pineal gland, a small endocrine gland located in the centre of the brain (Reiter, 1991), also known as "the hormone of darkness", the onset of melatonin at dusk promotes activity in nocturnal (night-active) animals and sleep in diurnal ones including humans. In animals, melatonin is involved in the synchronization of the circadian rhythms including seasonal reproduction, sleep-wake timing, blood pressure regulation and many others (Altun and Ugur-

Altun, 2007). The pineal gland is said to be a neuro-endocrine regulator coverts the visual signal into hormonal signal thereby showing fluctuation in secretion of melatonin. These fluctuations are responsible for altered pulsatile secretion of gonadotropin releasing hormone and so leuteinizing hormone, thereby controlling the reproductive function. In animal including human the picture of melatonin synthesis and secretion is affected by the duration of night hours in summer as compared to winter (Chen, 1981). The change in duration of secretion thus serves as a biological signal for the organization of photoperiodic dependent seasonal functions such as reproduction, behavior, coat growth and camouflage colouring in seasonal animals. In seasonal breeders that do not have long gestation periods and that mate during longer daylight hours, the melatonin signal controls the seasonal variation in their sexual physiology (Chen, 1981). Melatonin can suppress libido by inhibiting secretion of FSH and LH from the anterior pituitary gland, especially in mammals that are long day breeders. That is why the reproduction of long-day breeders is repressed by melatonin, whereas the reproduction of short-day breeders is stimulated by melatonin (Nakao *et al.,* 2008).

Melatonin: Synthesis, Secretion and Receptors:

The precursor to melatonin is serotonin, a neurotransmitter that itself is derived from the amino acid tryptophan. Within the pineal gland, serotonin is acetylated and then methylated to yield melatonin. Synthesis and secretion of melatonin is dramatically affected by light exposure to the eyes. The fundamental pattern observed is that serum concentrations of melatonin are low during the daylight hours, and increase to a peak during the dark.

The mechanism behind this pattern of secretion during the dark cycle is that activity of the rate-limiting enzyme in melatonin synthesis - serotonin N-acetyltransferase (NAT) - is low during daylight and peaks during the dark phase. In some species, circadian changes in NAT activity are tightly correlated with transcription of the NAT messenger RNA, while in other species post-transcriptional regulation of NAT activity is responsible. Activity of the other enzyme involved in synthesis of melatonin from serotonin - the methyltransferase - does not show regulation by pattern of light exposure.

Two melatonin receptors have been identified from mammals: designated Mel1A and Mel1B that are differentially expressed in different tissues and probably participate in implementing differing biologic effects. These are G protein-coupled cell surface receptors. The highest density of receptors has been found in the suprachiasmatic nucleus of the hypothalamus,

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the anterior pituitary (predominantly pars tuberalis) and the retina. Receptors are also found in several other areas of the brain.

Control of melatonin secretion:

In mammals, the daily rhythm of pineal melatonin production is driven by the 'master' circadian clock. This 'clock' is in a region of the brain called the suprachiasmatic nuclei, which expresses a series of genes termed clock genes that continuously oscillate throughout the day. This is synchronised to the solar day via light input from the eyes. The suprachiasmatic nuclei link to the pineal gland through a complex pathway in the nervous system, passing through different brain areas into the spinal cord and then finally reaching the pineal gland. During the day, the suprachiasmatic nuclei stop melatonin production by sending inhibitory messages to the pineal gland. At night however, the suprachiasmatic nuclei are less active, and the inhibition exerted during the day is reduced resulting in melatonin production by the pineal gland. Light is an important regulator of melatonin production from the pineal gland. Firstly, it can reset a specific area of the brain (the suprachiasmatic nuclei clock) and as a result, the timing of the melatonin production. Secondly, exposure to light during the body's biological night reduces melatonin production and release.

Role of melatonin in reproductive function:

Seasonal changes in day length have profound effects on reproduction in many species, and melatonin is a key player in controlling such events**.** In temperate climates, animals like horses and sheep have distinct breeding season. During the non-breeding season, the gonads become inactive (e.g. males fail to produce sperm in any number), but as the breeding season approaches, the gonads must be rejuvenated. Photoperiod - the length of day vs. night - is the most important cue allowing animals to determine which season it is. The pineal gland is able to measure day length and adjust secretion of melatonin accordingly. The effect of melatonin on reproductive systems can be summarized by saying that it is anti-gonadotropic. In other words, melatonin inhibits the secretion of the gonadotropic hormones luteinizing hormone and follicle stimulating hormone from the anterior pituitary. Much of this inhibitory effect seems due to inhibition of gonadotropin-releasing hormone from the hypothalamus, which is necessary for secretion of the anterior pituitary hormones. One practical application of melatonin's role in controlling seasonal reproduction is found in its use to artificially manipulate cycles in seasonal breeders. For example,

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sheep that normally breed only once per year can be induced to have two breeding seasons by treatment with melatonin.

Role of melatonin in regulating reproductive activity:

Seasonal variations in photoperiod are perceived by the photo receptors of the mammalian eye sending signals to the suprachiasmatic nucleus (SCN). The SCN then drives the nocturnal melatonin rhythm (Nakao *et al.,* 2008). Long days have more daylight which in turn has less hours of darkness. There by the secretion of melatonin is reduced in season with less hours of darkness. Melatonin regulates the circannual rhythms in reproductive processes. Melatonin reaching the suprachiasmatic nucleus of the hypothalamus inhibits the frequency and magnitude of the pulsatile secretion of hypothalamic and gonadotrophic hormones thereby inhibiting the release of pituitary hormones essential for initiation of reproductive activity. This pattern of neuro endocrine modulation which is influenced by the external light and via the pineal gland which causes the different effects through the secretion of melatonin is the key behind the initiation of reproductive activities in seasonal breeders (Reiter *et al.,* 2014). Melatonin is also produced from the peripheral reproductive organs including granulose cells, cumulus oophorus and oocyte. It assists in maturation of oocyte, protects from free radical damage and also enhances the development of corpus luteum and progesterone production (Reiter *et al.,* 2014).

Physiological basis of the seasonality of breeding:

Circadian rhythms and the seasonal variations in the length of the day light are the principal components affecting the reproductive activities in both males and females. The orbiting of the tilted earth around the sun causes circadian changes in the length of the daylight or duration of photoperiod at different seasons of the year. There are many other factors that also change length of photoperiod like fluctuations in environmental temperature, climate variation, availability and quality of feed. The changing photoperiod acts as a bioregulator of reproductive activity and fertility through the mediation of central nervous system, hypothalamus, adenohypophysis and the pineal gland. Onset of breeding season in seasonal breeds is much similar to the onset of puberty (Foster, 1988). Transition from non breeding (anestrous) to breeding (estrous) represents sexually quiescent state to active state (Smith, 2010). Non breeding season is characterized by an increase in negative feedback effect of estrogen on GnRH and gonadotrophin secretion as is the case in pre-pubertal period (Smith and Clarke, 2006). This results in reduced frequency of GnRH pulses, suppressing the gonadotrophin drive to the gonads thereby causing the gonadal regression (Barrell

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et al., 1992). Until puberty the hypothalamo-gonadal axis is under the negative feedback effect of the estrogen**.** The pulse frequency of GnRH/LH is insufficient to stimulate the development of follicles thus sustained increase in estrogen activates the surge centre of the hypothalamus thereby creating a positive feedback effect on the hypopthalamus causing surge release of GnRH/LH. Pre puberty, the small content of estrogen from the developing follicle exerts a negative feedback effect on the hypothamaus**,** while at puberty the consistently high estrogen exerts a positive feedback effect there by activating the surge center of the hypothalamus and causing for the surge release of LH which causes for the maturtation of the follicle (Foster and Ryan, 1979). Pre pubertal period is comparable to non-breeding or anestrous period while the puberty is comparable to the onset of breeding season. Similar kind of transition occurs in both the cases (Karsch *et al.,* 1993). Therefore, the primary mechanism in seasonal breeding is the neural control of pattern of GnRH from hypothalamus. Pulsatile secretion of GnRH in turn increases the LH and FSH from the pituitary thereby activating the gonads (Wood and Loudon, 2014). The seasonal change in sensitivity to oestrogen is the major mechanism for shift from breeding to non-breeding season (Smith, 2010).

Role of melatonin in seasonal and non-seasonal breeders:

Seasonal short-day breeders: As the name indicates these animals specifically breed during short periods of day light or short photo periods. Changing photoperiod from longer day light to shorter days with more periods of darkness initiates the reproductive activity in sheep and goat due to increase in melatonin secretion. The increased melatonin secretion reaching the hypothalamus, then stimulates the pulsatile secretion of GnRH. Subsequently, FSH and LH secretion from the pituitary gland increases, which in turn results in the onset of ovarian activity and the commencement of the breeding season.

Seasonal long day breeders: As the name indicates these animals specifically breed during long periods of day light or long photo periods. Changing in photoperiod from the short periods of day light to long periods of day light, the photo receptors sensitize the same and the same information is passed to the pineal gland which then removes its inhibitory action on the hypothalamus. In these long day breeders, the inhibitory effect of the pineal gland occurs during the short days of late fall and winter. This is the reason for which mares, stallions and other equids remain in anestrous during the short days. Once the season changes with increasing photoperiod into long days, the pineal gland becomes less active and thereby the secretion of melatonin is also reduced

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considerably. The inhibitory influence on the hypothalamus is removed. As a result of which the hypothalamic releasing factors and pituitary hormones are also secreted to initiate the reproductive process for the onset of breeding and the young ones are produced during spring and summer.

Non seasonal breeders (Polyestrous): In domestic pig and in other seasonal breeders, melatonin relays photoperiodic information about season to the pituitary-gonadal axis. Although photoperiod is considered the primary environmental cue to seasonal infertility, other environmental factors also seem to interact with season to affect the infertility. These include housing (group vs. individual), feeding level, light conditions, boar exposure, group size, ambient temperature and interactions between females. The significance of seasonal infertility has increased in recent years as group housing of dry sows has become more common (Nakao, 2008).

Opportunistic breeders: They are typically capable of breeding at any time or becoming fertile within a short period of time. They are distinct from seasonal breeders that rely on changes in day length to induce estrus and to cue mating and continuous breeders like humans that can mate throughout the year. An example is the golden spiny mouse where changes in dietary salt in its desert habitat due to rainfall appear to cue reproductive function (Shanas and Haim, 2004).

Conclusion

Pineal Gland, a small endocrine gland secretes a hormone, melatonin, also known as *N*-acetyl-5-methoxy tryptamine plays an important role in the synchronization of the circadian rhythms including seasonal reproduction, sleep-wake timing, blood pressure regulation and many others. Seasonal changes in day length have profound effects on reproduction in many species, and melatonin is a key player in controlling such events. The secretion of melatonin is reduced in season with less hours of darkness. The changing photoperiod acts as a bioregulator of reproductive activity and fertility through the mediation of central nervous system, hypothalamus, adenohypophysis and the pineal gland.

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