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MELATONIN: IT'S ROLE IN SEASONALITY AND BREEDING IN FARM ANIMALS- A REVIEW

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INTRODUCTION

The seasonality of reproduction is an adaptive physiological process utilized by wild animals to deal with seasonal changes in temperature and food availability. Domestication has led to an almost complete loss of this adaptation in cattle and pigs but it is retained in most breeds of sheep, goats, horses and yaks originating from temperate latitudes (Wuliji et al., 2003). At these latitudes, photoperiod is the main environmental factor that determines the onset and duration of breeding seasons. The timing of the breeding season depends on the length of the gestation period so that parturition occurs in the spring. Thus, sheep and goats (5 month gestation period) are short-day breeders with conception occurring in autumn and winter, whereas horses (11 months gestation period) breed during the long days of spring (Ortavant et al., 1985). Photoperiodic information is integrated through a complex pathway involving both neural and humoral steps. Photoperiod is first perceived by the retina and transmitted via a multistep neural pathway, which involves the suprachiasmatic nuclei (SCN) and superior cervical ganglia, to the pineal gland where the message modulates the rhythm of melatonin secretion (Karsch et al., 1984). Melatonin is released only at night and, therefore, the duration of secretion differs between long and short days. This duration of melatonin secretion is then processed to regulate the activity of the hypothalamo-hypophysial and gonadal axis (Karsch et al., 1988).

PHOTOPERIODIC PERCEPTION AND SIGNAL TRANSDUCTION

Photoperception (retina), discriminate light at intensities even as low as 5 lx. Light impinging on the eye stimulates retinal photoreceptors that transmit an inhibitory signal to the pineal gland through a series of interneurons via the retino-hypothalamic tract (Fig. 1). The pineal secretes a no. of hormones, but the indoleamine melatonin is the active mediator of photoperiodic responses. Light inhibits activity of the rate-limiting enzyme in melatonin synthesis, N-acetyl-transferase. Secretion of melatonin is low during light exposure. When lights are off, the inhibition is removed, and melatonin secretion rapidly increases, such that elevated concentrations of melatonin are present in the scotophase or dark period. Requirement of a dark phase for the responsiveness to persist (Misztal et al., 2002).

Seasonal breeders such as sheep, horses and yaks, entry and egress from the breeding season can be timed through appropriate manipulation of photoperiod (Sarkar and Prakash, 2005). Cattle are not seasonal breeders, but return to estrous cyclicity is longer in cows that calve in winter relative to those calving in the summer. Timing of puberty is also influenced by season of birth. Long days

increase growth rates in cattle, as well as hastening onset of puberty.

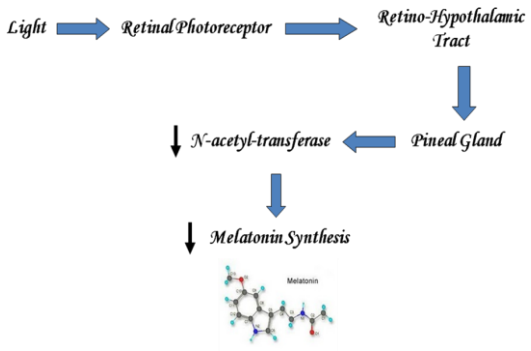

Fig. 1. Photoperiodic perception and signal transduction (Adopted from: Goldman, 2001)

SITES OF ACTION OF MELATONIN

Although melatonin may act at different levels of the reproductive axis, the main action involves events within the central nervous system. Indeed, melatonin treatment induces significant changes in the release of luteinising hormone-releasing hormone (LHRH). In ovariectomised and oestradiol treated ewes exposed to inhibitory long days, the frequency of LHRH and LH release is low (one pulse every 6 h) and subcutaneous insertion of a melatonin implant causes a dramatic increase in LHRH and LH pulse frequency (10 pulses every 6 h), which occurs after a delay of 40-50 days. These variations in LHRH and LH pulse frequencies are responsible for the change in activity of the gonads between long and short day photoperiods (Karsch et al., 1984).

Melatonin and the central nervous system

Premammillary hypothalamus (PMH) is an important target for melatonin in regulating reproductive activity. Melatonin stimulates LH secretion if delivered into this site. Changes in the duration of melatonin secretion constitute a signal to the neural structures controlling the secretion of gonadotropins from the pituitary gland that a long duration is stimulatory and a short duration is inhibitory (Malpaux et al., 1993). A sustained high melatonin level led to the activation of the hypothalamo-pituitary GnRH/LH axis. Activation of the gonadotropic system in anestrous animals leading to the onset of estrus requires several weeks of exposure to melatonin, during which a change in the feedback action of estradiol on GnRH/LH plays a pivotal role (Lincoln, 1994).

Adeno-hypophysial region has the greatest density of melatonin receptors (Fig. 2), but does not seem to be a crucial target for the reproductive action of melatonin. Pars tuberalis (PT) mediates the effect of melatonin due to the lack of melatonin receptors on lactotrophs. PT secretes a prolactin-releasing factor under long day conditions, which is inhibited by melatonin under short day conditions (Morgan, 2000).

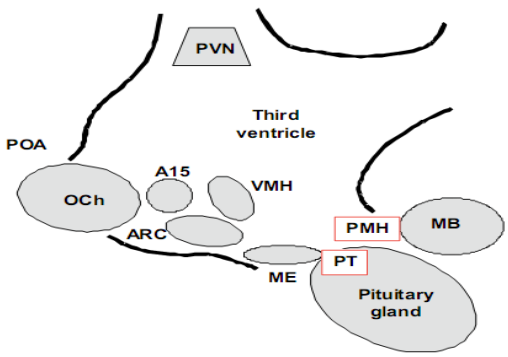

Fig. 2. Schematic drawing of the ovine hypothalamus showing the distribution of melatonin binding areas. PMH, premammillary hypothalamus and PT, pars tuberalis. Other visible brain structures: POA, preoptic area; OCh, optic chiasma; PVN, paraventricular nucleus; A15, dopaminergic A15 nucleus; VMH, ventromedial nucleus; ARC, arcuate nucleus; ME, median eminence; MB, mammilary bodies (Misztal et al., 2002) .

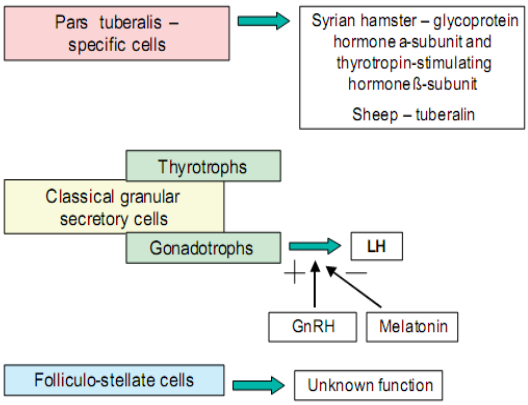

Fig. 3. The identified structures and products of the pars tuberalis cells. Gonadotrophs of the ovine pars tuberalis secretes LH in re sponse to GnRH (*in vitro*). Melatonin attenuates the GnRH-induced increase in LH (Adopted from: Skinner and Robinson, 1997).

Tuberalin, secreted by PT, affects pars distalis (PD) lactotrophs to increase *c-fos* gene expression and to stimulate prolactin release. The secretion of tuberalin is enhanced by forskolin (adenylate cyclase activator) and the forskolin stimulated tuberalin secretion is inhibited by melatonin (Morgan et al., 1996). The endocrine effect of tuberalin is of importance in the pituitary mechanism of melatonin action, especially in regards to the control of the seasonal cycle of prolactin. Melatonin attenuates the GnRH-induced increase in LH secretion from the PT, but not from the PD (Skinner and Robinson, 1997) (Fig. 3). "Melatonin-sensitive" LH, secreted by the PT, may act on the brain to influence the reproductive neuroendocrine axis via a short loop feedback system.

MECHANISM OF ACTION OF MELATONIN

Melatonin ultimately modifies the pulsatile release of LHRH but a direct action of melatonin on LHRH neurones appears unlikely for three reasons.

a) First, the distribution of most LHRH neurones does not match that of the putative sites of action of melatonin. Most LHRH neuronal perikarya are located in the preoptic area (POA -60%) with a few located in the mammilary bodies hypothalamus (MBH- 15%); some of these project to the median eminence and abut portal vessels (Caldani et al., 1988).

b) Secondly, the long delay between the onset of melatonin treatment and the expression of the response in terms of LHRH or LH secretion suggests a more complex regulation.

c) Thirdly, and most importantly, several neurotransmitters have been implicated in this regulation.

The mechanism by which photoperiod affects growth

a) The secretion of the major reproductive hormones, LH and FSH, together with GH, a component of the somatotropic axis, is regulated by an array of neurotransmitters and neuromodulators.

b) The excitatory amino acids (EAA), glutamate and aspartate, major stimulatory neurotransmitters in the mammalian nervous system, Acting through both N-methyl-D-aspartate (NMDA) and non NMDA receptors, modulate the secretion of LH, GH, and prolactin (Fig. 4).

c) A role for NMDA receptors in the control of seasonal breeding and the stimulatory effect of NMA on LH secretion is amplified in seasonally anestrous rams (Lincoln and Wu, 1991).

d) NMA receptors involved in the regulation of LH, GH, and testosterone secretion in the goat. Furthermore, length of day influences GH secretion in the goat and NMA receptor activation had divergent effects on the secretion of this hormone.

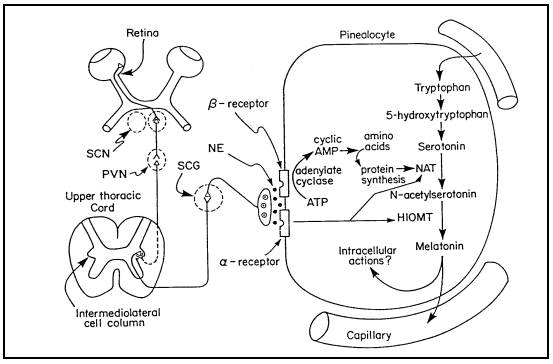

Fig. 4. Pathways of melatonin synthesis

Indirect effect of NMA on testosterone secretion is mediated by the NMA-induced increase LH secretion (greater during seasonal anestrus than during the breeding season). Activation of NMA receptors increased LH and GH secretion in goats exposed to long photoperiod (LP) than short photoperiod (SP). GH secretion is under both stimulatory and inhibitory regulation, as NMA acted by stimulating GHRH secretion (Simonneaux and Ribelayga, 2003) (Fig. 5).

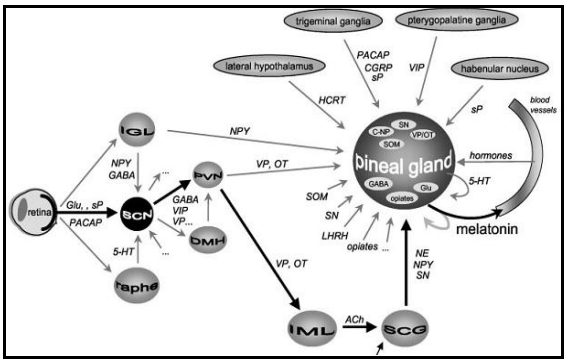

Fig. 5. Schematic representation of the various neural, endocrine, and paracrine inputs of the mammalian pineal gland. The main neural pathway, which transmits light information to the pineal gland, is shown with thick arrows. In addition, numerous other neural or endocrine inputs are known to reach the pineal gland (Adopted from: Simonneaux and Ribelayga, 2003).

ROLE OF MELATONIN

I. Regulation of Seasonal Rhythms

Respond to the annual changes in photoperiod by adaptive alterations of their physiological state. Pineal gland is a neuroendocrine transducer receiving photoperiodic information from the retina and circadian SCN oscillator, and transmitting this to the reproductive system via melatonin (MEL) secretion (Foster et al., 1988) (Fig. 6 and 7).

II. Regulation of Circadian Rhythms

MEL is synthesized during the dark phase of the light/dark cycle and is rapidly delivered to the body via the blood stream. Pinealectomy facilitates the re-synchronization of the animal to a new photoperiod. The daily rhythm of MEL circadian mediator used by the endogenous SCN clock to deliver the circadian message to MEL target structures (containing MEL-R). “chronobiotic” effect by acting directly on the SCN, which contain MEL-R, to affect the circadian clock (Pevet et al., 2002). Exogenous MEL, applied directly into the SCN phase-advances the endogenous MEL peak increases the amplitude of the MEL peak (Bothorel et al., 2002).

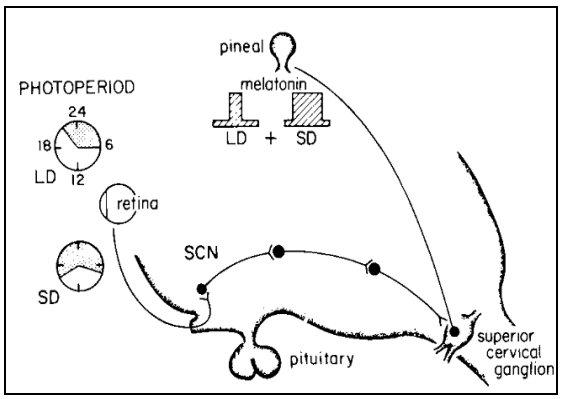

Fig. 6. Pathway for transmission of photoperiod information (Source: Foster et al., 1988)

III. Role in seasonality and breeding

The role of melatonin in the photoperiodism of sheep was clearly established in the early 80s. It is of interest that early breeding is achieved by feeding melatonin only before sunset. The nocturnal secretion of pineal melatonin provides information to vertebrates on changes in day length under the circumstances in which they live. In seasonal breeders, the secretion of

melatonin is also a signal to the neural structures controlling the secretion of gonadotropins from the pituitary gland to drive their activity in accordance with the season of the year (Afify et al., 2004). The photoperiod drives the reproductive cycle, which comprises a season of high sexual activity during short days and an anestrous season that occurs during long days (Dahl and Petitclerc, 2003). Information on changes in the photoperiod is provided to the organism through nightly secretion of melatonin from the pineal gland. Thus, changes in the duration of melatonin secretion constitute a signal to the neural structures controlling the secretion of gonadotropins from the pituitary gland that a long duration is stimulatory and a short duration is inhibitory. Anestrous animals treated with exogenous melatonin, show a sustained high melatonin level in the organism led to the activation of the hypothalamo-pituitary GnRH/LH axis (Arendt et al., 1983; Bittman et al., 1983). Melatonin is able to stimulate LH secretion if it is delivered into this site.

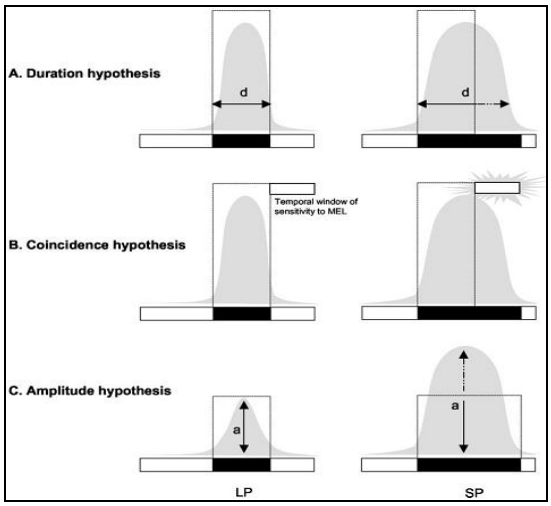

Fig. 7. Schematic representation of the different theoretical models explaining how the photoperiodic MEL endocrine message is decoded. In response to a change in the photoperiod, the daily MEL profile displays substantial changes, primarily affecting the duration and/or the amplitude of the nocturnal peak. Distortion of the MEL message, in turn, has an impact on many physiological functions. How the organism "reads" the modifications of the MEL profile is still largely hypothetical and appears species-dependent. The duration of the nocturnal peak seems to be an important parameter in many photoperiodic species. Photoperiodic dependent changes may rely on the absolute duration of the nocturnal MEL peak (A) or on the presence of a time-window of sensitivity to MEL (B). In addition, in some species, the amplitude of the nocturnal MEL peak may be an important parameter (C). a, amplitude of the nocturnal MEL peak; d, duration of the nocturnal peak of MEL; LP, long photoperiod; SP, short photoperiod (Adopted from: Simonneaux and Ribelayga, 2003).

An increase in LH release is observed in luteal-phase ewes during the first hours of darkness. However, it appears that a central interaction between melatonin and estradiol is needed to sustain a high level of LH secretion during the reproductive period. Importantly, LH secretion is stimulated in all animals with micro-implants placed correctly with respect to the higher binding area, suggesting that the PMH is an important target for melatonin in regulating reproductive activity in ewes. The easiness of diffusion of melatonin from the pineal recess of the third ventricle to its ventral part (Tricoire et al., 2002) indicates, in turn, that the pineal hormone may be caught by the PMH cells directly from the cerebrospinal fluid.

Photoperiodic control of gonadal function is probably a result of changes in gonadotropin secretion. In both long-day and short-day breeding species, exposure to inhibitory photoperiods caused a decline in pituitary and blood levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), while exposure to stimulatory day lengths caused opposite effects. Light exposure can regulate gonadotropin secretion by altering responsiveness of the hypothalamic – pituitary axis to the negative feedback actions of gonadal steroids. There is a negative relationship between

gonadotropins and melatonin. This means that the increase of MLT concentration during winter months lead to poor reproductive in livestocks (Kassim et al., 2008). It indicates a high concentration of P4 and E2 at estrous stimulated by decline of MLT. Treatment of ruminants by extending light during autumn and winter (dark season) decrease serum concentration of MLT, particularly after puberty and increase the serum concentrations levels of P4, E2 and PGF2 (Sarkar and Prakash, 2005). Treatment of adult ewes with melatonin implants results in decreased prolactin secretion, apparently mimicking the prolactin changes observed when the daily photoperiod is shortened (Kennaway et al, 1982). In cattle, as in other species, there is dependence on the pineal for photoperiodic responses. Indeed, blinding and pinealectomy eliminate rhythmic patterns of melatonin release and, thus, photoperiodic responses (D'Occhio and Suttie, 1992). If light is perceived (i.e., low melatonin) approximately 15 h after dawn, a time termed the photosensitive phase, that is the cue for a long day. In contrast, the presence of darkness (i.e., high melatonin) during the photosensitive phase will be perceived as a short day (Daramola et al., 2006).

Timed exogenous melatonin administration to anoestrous ruminants would promote an early onset of breeding activity (Afify et al., 2004). Exogenously administered melatonin could mimic the physiological effects of short daylength. When anoestrus ewes are treated with silastic envelopes containing melatonin the breeding season is advanced by five to 10 weeks (Dahl and Petitclerc, 2003).

IV. Other Roles of Melatonin

Autocrine/Paracrine Effects:

In addition to the pineal gland, MEL is synthesized in several other structures (retina, Harderian gland, gut) where the genetic expression and biochemical activity of the MEL-synthesizing enzymes have been detected (Djeridane et al., 2000). In the retina, MEL is rhythmically synthesized in the photoreceptors in a circadian manner. MEL alters various aspects of retinal metabolism. Most of the retinal effects of MEL are indirect, and probably consist primarily in the inhibition of dopamine (DA) release from amacrine cells (Jaliffa et al., 2000; Tosini and Dirden, 2000).

Modulation of Neurotransmission:

MEL can alter the release of several neurotransmitters, especially DA, 5-HT, norepinephrine (NE), acetylcholine (ACh) and can modulate the postsynaptic response. MEL, through activation of its different receptor subtypes, can differentially modulate the function of type A gama amino butyric acid ($GABA^A$) receptors (Wan et al., 1999).

Effects on the Immune System:

In vivo, high exogenous doses of MEL show a general stimulation of the immune system (Reiter et al., 2000a). It increases T cell activity, lymphocyte growth, humoral responses, and may inhibit thymus involution with age (Maestroni, 2001). In vitro MEL also increases T helper and NK cell activities, the production of interleukin 2 and interferon gamma, and the expression of interleukin 1 mRNA in monocytes. In summary, there is an immuno-stimulating effect of MEL. These effects may occur via a direct action of MEL on its receptor since MEL-R have been identified in various tissues of the immune system, namely thymus, spleen, lymphocytes, and T helper cells. In addition, MEL acting as a chronobiotic may be involved in the circadian organization of the immune system (the number and activity of lymphocytes T, B, and NK displaying a daily rhythmicity). It has also been proposed that MEL may mediate seasonal changes in immune function, which is enhanced in short days with longer MEL peak duration (Nelson and Drazen, 2000).

Antioxidant/ Antiaging Property of Melatonin:

The lipophilic MEL diffuses into the cell cytosol and nucleus to protect cytosolic

and nuclear macromolecules from free radical cytotoxicity (Reiter et al., 2000b). The use of oxygen in cell metabolism leads to the production of cytotoxic by-products that are reactive free radical species (superoxide anion radical, peroxynitrite anion, hydrogen peroxide, nitric oxide, and the highly toxic hydroxyl radical), which destroy macromolecules like DNA, lipids, and proteins leading to cell death via apoptosis. High doses of MEL (in the micromolar range) are reported to neutralize most of these cytotoxic molecules, but especially the hydroxyl radical, which is scavenged in vivo by MEL, producing cyclic 3-hydroxyMEL excreted in the urine. In addition, MEL is reported to stimulate the activity of various antioxidant enzymes, like superoxide dismutase or glutathione peroxidase, but inhibits the pro-oxidant enzyme nitric oxide synthetase. MEL could be a very powerful antioxidant molecule, that the production of MEL decreases with age, and that the free radical effects are involved in the processes of aging and cancer, maintaining MEL at a high level could slow age- and cancer-related alterations. MEL also affects estrogen receptor transcriptional activity by regulating signal transduction pathways. In addition, MEL has been described as a potent supplement in the treatment or cotreatment of cancer: as an antioxidant, it may protect cell damage caused by carcinogens; as a chronobiotic, it may help determine optimum timing for carcinogen best efficiency; and it may act in synergy with the carcinogen retinoic acid to markedly reduce mammary tumor genesis in vivo (Kiefer et al., 2002).

CONCLUSION

In conclusion, long day light length during autumn and winter seasons decrease melatonin concentration in blood flow during optical gland which modifies that to inhibit MLT secretion. Decreased MLT secretion is related to increased sexual hormones during estrous hours. Long photoperiod during estrous period especially during autumn and winter is considered more beneficial in ruminant. It can be recommended to supplement and increase of artificial light during autumn and winter seasons after sun set to 4 hours to induce strong and clear estrous in livestock. A reappraisal of photostimulation as a treatment for out-of-season breeding is now possible to consider melatonin treatment, due to its availability, as an alternative to the costly long night phase. However the widespread commercial appeal of this new approach to out-of-season breeding will greatly depend on the development of alternative methods of melatonin administration.

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