The Role of Melatonin in Ewes Reproduction: A Review

Laith Sofian Younis1*, Saad Akram Hatif2 and Qusay Mohammed Aboud2

1 Department of Theriogenology, College of Veterinary Medicine, University of Fallujah, Iraq.
2 Department of Theriogenology, College of Veterinary Medicine, University of Baghdad, Iraq.
*Corresponding Author: E-mail: laythsufyan@uofallujah.edu.iq. Phone: 07718070154

DOI: https://doi.org/10.37940/AJVS.2019.12.2.15
This article is licensed under a CC BY (Creative Commons Attribution 4.0)
http://creativecommons.org/licenses/by/4.0/.

Abstract

This review was assigned to illustrate the melatonin (MLT) effect on reproduction in sheep (ewes). However, the pathway by which MLT charge the seasonal reproduction are imperfectly understood in sheep, the researchers consents that MLT regulates reproduction under influence of day length (photoperiod) to guarantee that birth happen in appropriate date of the year, it’s called neuro-endocrine process. This mechanism mediates by the pineal hormone (MLT). The major role of MLT in ewes is to translate the photo signals into endocrine pulses (gonadotropin-releasing hormone (GnRH) secretion) at the end of the retino-pineal pathway. In sheep, the MLT receptors distributed in premammillary hypothalamus (PMH), pituitary gland and Suprachiasmatic nucleus (SCN), therefore, many brain loci are participating for MLT pathways to modify the seasonal reproduction. Melatonin stimulates GnRH secretion through effect in different regions and neurons in hypothalamus such as a pre-mammillary nucleus, Arcuate and several factors like kisspeptin, RF-amide related peptide-3 (RFRP-3) and Tyrosine Hydroxylase (TH). In addition, its indirectly control prolactin (PRL) output via an effect on Tuberalin release, which is mediate the mechanism of MLT activity on pituitary PRL secretion and regulate his seasonal cyclicity. The alter in day length is the principle ecological factor that control the breeding in seasonal domestic animals. Several reproductive activities are related to short days and begin during autumn when the day becomes short and a decline in temperature (short-day breeder). While expanding in the duration of light lead to a cessation in reproduction activities during late winter and early spring. In conclusion, according to the major physiological role of MLT, it can be used in different aspects in ewes reproduction industry such as induce oestrus, increment the ovulation rate and In vitro embryo production.

Keywords: Melatonin, Reproduction, Ewe.
Introduction

The MLT of cattle Pineal gland (PG) is discovered in 1958, the and distinguished as (N-acetyl-5-methoxy-tryptamine) by dermatologist Aaron Lerner and his colleagues, the MLT is came from lightening skin of Lerners coworkers during the work on amphibians, certain fishes and reptiles (1). Melatonin is a small indole molecule that has the following chemical names: ‘5-Methoxy-N-acetyltryptamine’ and ‘N-Acetyl-5-methoxytryptamine’ with atomic formula: C13H16N2O2 (Hattori et al., 1995), MLT half-life in sheep is (16-18) min. (2). Melatonin has a major factor that coordinate the reproduction in seasonal estrous animal model, in ewes, the MLT can prompt estrous and enhance litter size (3), increment the ovulation rate (4), improve luteal activity by a reduction in the antiluteolytic mechanisms, it also increases embryo viability and improve lamb production (5). Furthermore, the MLT treatment have an effect on ovine fecundity, fertility and sex ratio (6). In ram, MLT could improve the spermatozoal progressive motility and the fertile spermatozoa quantity (7).

Melatonin was considered as direct potent and indirect antioxidants (free radical scavengers) that maximized many antioxidant enzymes expression like superoxide dismutase and glutathione peroxidase (8). This review was designed to describe the MLT effect on reproduction in ewe.

1. Biosynthesis of Melatonin

Biosynthesis of MLT occured through the precursor tryptophan in four enzymatic steps hydroxylation, decarboxylation, acetylation and methylation (9). Firstly, ‘L-tryptophan’ is hydroxylated at indole ring through ‘tryptophan hydroxylase’ (10). Then, the intermediate ‘5-hydroxyl-L-tryptophan’ is decarboxylated via ‘5-hydroxy-L-tryptophan decarboxylase’ to produce serotonin called ‘5-hydroxytryptamine’ (11). After that, ‘serotonin’ is transformed into ‘N-acetyl-serotonin’ via ‘serotonin arylalkylamine N-acetyl transferase’ (AA-NAT) and by ‘acetyl-CoA’ (12). At the end, ‘N-acetyl-serotonin’ changed over into MLT by ‘Hydroxyindole O-methyl transferase (HIOMT)’ through methylation of the hydroxyl group (13). Whereas levels of HIOMT action stay decently consistent, the diurnally MLT production is controlled by a concurrent rhythm of AA-NAT enzyme action (14). The Pineal is a unique endocrine gland that is affected strictly by outer/external conditions by means of retina and changes over natural environmental signals into neuroendocrine messages (15). The neural information that is produced in the retina passed to hypothalamic SCN via retino-hypothalamic tract (16). The SCN is connected to the PG by many synaptic ways include hypothalamus (paraventricular nucleus) that connects and sends neural signals into ‘spinal cord’, the spinal neurons (sympathetic spinal neurons) send the neural signals to ‘superior cervical ganglion (SCG)’ neurons (17). Finally, the noradrenergic sympathetic neurons of the SCG are synapses to the PG via noradrenergic fibers (18).

These sympathetic fibers spur both MLT receptors (α- and β-adrenergic receptors) in the pinealocyte to made intracellular increment of ‘cyclic Guanosine Monophosphate (cGMP)’ and ‘cyclic Adenosine Monophosphate (cAMP)’; these increase in intracellular cAMP improved Nacetyltransferase (NAT) activity (19). The AA-NAT function is controlled by ‘retino-pineal path’, and that represent crucial component of MLT synthesis (20). (Figure 1).
2. Secretion and excretion of Melatonin

The MLT which is synthesized by pinealocyte and diffuses directly into cerebrospinal Fluid (CSF) and capillary blood without store inside the PG (22). The MLT could reach the CSF via two ways, the first deliver during daytime via the little number of distended pinealocytes of the PG which is located at the basal part of pineal recess, so the interstitial fluid discharged into ventricular lumen or through the connection with CSF (23). The rest pinealocyte of PG that secreted the MLT straight forward to blood flow and are taken up from the blood to CSF by the choroid plexus (24). The brain conveyed MLT through the blood capable to elicit the effectiveness of light (photoperiod) on reproduction (23).

The metabolism of MLT occurs via cytochromes P450 (P450s) in liver through changing over it to 6-Hydroxy-MLT as a final product and is cleared through the liver after a single passage, a little amount is discharged into urine and a small amount is found in saliva (25).

3. Melatonin receptors and signaling pathway

Melatonin receptor 1 (MTNR1) is referred to the first type of MLT receptors which is cloned and has characterized (26). It is mediate inhibition of the cAMP through a G protein-coupled receptor (27). According to the same researchers, the the pituitary gland specially pars tuberalis (PT) contains a vast number of MTNR1. It also presents in PMH, that considered as a target structure of MLT for it is reproductive effects (28).

Melatonin receptor 2 (MTNR2) refers to the ovine MLT2 receptor, it is a ‘pertussis toxin (PTX)-sensitive (Gi) protein-linked receptor’, which is able of inhibit cGMP and cAMP production, it also spurs ‘Protein Kinase C (PKC)’ action in SCN, additionally, the receptor was expressed in PT, choroid plexus and retina (29). Both MLT receptors have a general motif and which have 7 trans-membrane á-helical sections containing a (20-25) hydrophobic residues, these á-helical segments span the cell membrane, and it associated with extra and intracellular loops, the structure also bind with the amino acids at the end of the external membrane side and on the ‘carboxyl term group’ at the internal side (30). About 350 amino acids which encoded by MLT1 receptor gene and 362 amino acid by MLT2 receptor gene, additionally, two consensus locales for ‘N-terminal asparagine connected glycosylation’ demonstrated by MLT1 receptor and single site in MLT2 receptor (31). The inner receptors (2 n) have consensus sites for regulatory signal enzymes like PKC, casein kinase I and casein kinase II at carboxyl end (32).

The signaling pathway of both MLT receptors are firmly associate to the Gi/cAMP path that inhibits cAMP production via Gi proteins, so the activation of both MLT receptors diminishes cAMP formation by forskolin stimulation (33). The signaling of MTNR1 can couple to both Gi and ‘PTX-insensitive (Gq) proteins’ (34). The activation of MTNR1 diminishes forskolin-stimulated cAMP formation via Gi protein, therefore, the inhibition includes ‘Protein kinase A(PKA)’ and ‘cAMP responsive
element-binding protein (CREB)’ (35). Godson and Reppert (1997) (36) mentioned that the βγ subunit of Gi protein of MTNR1 mediate the phospholipase via prostaglandin F2α (PGF2α) stimulation that prompts to increment in phosphoinositide (PI3) turnover. The intracellular calcium is rised by activation of the endogenous MLT1 receptors in PT cells of sheep, this mechanism happened through Gi proteins/ PI3 of MTNR1 likewise control ion fluxes pathway (37) (Figure 2).

The MTNR2 signaling inhibits both of cGMP and cAMP forming (38). In SCN, MLT activate the MTNR2 signaling throughout PKC, this pathway mediates the MLT at both night and dawn (phase-shifting effects of MLT) (39). The MTNR2 signaling by Gi proteins pathway can shut down the ‘PKC-mediated c-fos induction’ in the PT cells (40). Additionally, MTNR2 inhibit neurotransmitter liberation in the retina by through intracellular calcium regulation (41) (Figure 2).

Figure 2: A- Signaling pathways of MLT1A through activation of the MTNR1, B- Signaling pathways of MTNR2 activation (42). PLC: phospholipase C, PKA: protein kinase A, PGF2α: prostaglandin F2α, GTP: guanosine triphosphate, DAG: diacylglycerol, PIP2: phosphatidylinositol bisphosphate, GMP: guanosine monophosphate.

4. Mechanism of action of melatonin

4.1. Effect on GnRH

In ewes, the large environmental factor that controls the breeding is the day length (photoperiod) (43). The day light exposure variance modify the production and releasing of MLT from PG, and in turns that binds to the nuclei of hypothalamus and regulate the pulses releasing of GnRH (44).

Despite the fact that MLT work at several aspects of the reproductive system in ewes, the MLT principle activity in the premammillary region of the caudal hypothalamus within the central nervous system (45).

In the ewes, Malpaux et al (2001) (46) listed various evidences about the target site of MLT is pre-mammillary nucleus of premammillary hypothalamus (PMH) to which acts to modulate GnRH/gonadotropin releasing and regulate reproductive actions. While, the short time MLT administration into central nervous system of ewes does not spur GnRH and LH secretion during seasonal anestrus (47).

The ovine PMH region of the cerebrum engages the caudal district of Arcuate region (ARC) and the ARC containing an intensive population of kisspeptin cells (45). These cells are responsible for Kisspeptin output by the expression of the Kiss1 gene, its a peptide hormone that empower GnRH production (48) (49).

The MLT treatment control the expression of Kiss1 in cell lines (50). The expression of Kiss1 was higher three time in the ARC region in Soay ovary-intact ewes that placed in a photoperiod of 16 dark hrs. and eight hrs. light (16D:8L) than other ewes on longer photoperiods (51). In ewes, a minimize kisspeptin function is related with loss of cyclicity at non-breeding period or season, and the kisspeptin injection in
such animals can prompt ovulation (52). Additionally, Kisspeptin treatment stimulate the hypothalamic–pituitary–gonadal axis during non-breeding season in goat, the removal of inactivity is associated with rising of plasma testosterone concentration (53). Otherwise, Median Eminence (ME) is also the target of MLT in ewes, the MLT caused block the TH activity (is a crucial enzyme in dopamine synthesis), so the MLT induce alteration (decline) in TH function on the dopamine secretory ME neurons can regulate GnRH pulsatile secretion because an rise in dopamine inhibits of GnRH and therefore LH secretion is diminish, these opinion was confirmed by the experiment of Viguie et al (1998) (54), they find that LH secretion was stimulated by suppress of TH in the ME long day inhibited ewes. In addition, Goodman et al (2012) (55) support the speculation that dopamine prevents synthesis and release of GnRH and LH at anestrus phase in sheep by exert a repressing role on the ‘ARC kisspeptin neurons’ because these neurons are critical for reproductive function and seasonal changes.

A new observation is suggested that MLT control of season through its effect on Gonadotropin-inhibitory hormone termed RFRP-3 that influence the GnRH neurons (negative correlation) (56). In sheep, RFRP3 expressing cells are found transcentdently in the specific part of hypothalamus (dorso-medial nuclei) and these cells project to the ME, that region of GnRH cells (57). In ewes model, the increases in RFRP-3 gene expression happen at long daylight hrs. (20L: 4D) (58). In addition, the impacts of season on RFRP-3 hormone seemed to be based on on seasonal MLT fluctuations and the response to photoperiod is anticipated by pinealectomy and neutralized by MLT treatment (59). Moreover, the melatonin implantation give a good results for improving seminal quality in Holstein bulls, conception rate and reproductive performance in cows (60)(61).

4.2. Effect on Prolactin

In seasonal mammals, PT plays a direct role in regulating the annual PRL cycle (62). The researchers reported a PRL releasing factor called Tuberalin, which is released by the ovine PT specific thyrotrophs that impacts on increment of c-fos gene expression and to stimulate PRL promoter activity in a subpopulation of lactotrophs to prompt Messenger Ribonucleic acid (mRNA) expression and PRL secretion (63) (Figure 3). Over 90% of ovine PT cells are chromophobe cells that produce Tuberalin (64).

In ewes, the PT has a high concentration of MLT receptors (65). The hypothalmo-pituitary-disconnected rams showed well-defined seasonal cycles in PRL release with low PRL blood concentration under short day conditions (66). On the other hand, the MLT implants in post-partum ewes caused a decline in PRL secretion under long photoperiod occurred in spite of the high stimulation of suckling (67).

The release of Tuberalin is enhanced by forskolin and the cAMP that activated Tuberalin secretion is inhibited by MLT that lead to decrease in PRL production (63). Because of the absence of MLT receptors on lactotrophs, it is reasonable to propose that PT may mediate the monitored effect of MLT by secretes Tuberalin and proposed that endocrine effect of Tuberalin which is necessary in the pituitary mechanism of MLT activity specially in regards to the regulation of the seasonal cycle of PRL (68).
Figure 3: Regulation of PG the secretion of MLT by photoperiod and Model of intra-pituitary mechanisms driving photoperiodic PRL secretion (69)(70).

5. Factors effecting melatonin biosynthesis and secretion

The biosynthesis and secretion of MLT follow a circadian rhythm with high level at night and low levels during the day in both blood and CSF (71). The exposure to light quickly inhibits MLT synthesis and its secretion into the blood (72). Hence, because of changes in the time of night and day, the rhythm of MLT secretion is effected by the cycle of the seasons (73).

The concentration of MLT secretion varies highly between species, the sheep and Siberian hamsters considered type C animals; that mean the MLT levels reach a peak slightly after the onset of the dark night (10-30 min.) and stay elevated along the entire night and decline at the time of the light onset (74). In sheep which kept in the same conditions, the night-time concentration in circulating blood varies between individuals of similar age, which is originated from the variances in MLT production but not from catabolism (2). This changeability is under hereditary control because of the heritability coefficient which was observed to be 0.53 in humans and 0.45 in sheep (75).

There are several factors that effect on MLT like location of sampling, pregnancy status, flock, ewe age interaction (76). The MLT concentration in old age ewes lower than ewes in 12-18 months old and in three years old ewes (77). Furthermore, Redondo et al (2003) (78) point out that the plasma MLT levels are higher in pubertal sheep than in infants or matured sheep. On the other hand, a decline in reproductive activity is observed correlated in the aging sheep with decease in MLT concentration that is restored by administration of MLT (79). The daily MLT concentration is different between in Seasonal and Aseasonal ewes. Hatif and Laith (2018a) (80) clarified that the relative MLT level was significant higher in non-seasonal as a compare with seasonal Awassi ewes under same circumference.

The MLT secretion may be affected by extra factors, since the precursor tryptophan is provided to the PG by the circulating blood, dietary intake of tryptophan may impact MLT fluctuation (81). In spite of the fact that the AA-NAT is a rate limiting enzyme, serotonin availability is one of the major factor that play an important regulatory role in MLT synthesis (82) and some evidences supposed that MLT synthesis is a part under serotonergic control (83). In addition, MLT is inhibited by benzodiazepines via benzodiazepine receptors in the PG (84). Moreover, many reports pointed out that the polymorphism (genetic effect) in AA-NAT and MLTR genes influenced the sheep seasonal reproduction via effect on MLT output and affinity of its own receptor (85) (86) (87).

6. The use of MLT in Reproductive Techniques

The earlier induce reproductive activity in ewes showed by persistent MLT implant treatment (88), therefore, it been used in vivo to induce oestrus.
Melatonin was utilized to enhance embryo production in Ovine multiple ovulation and embryo transfer (MOET) technique (89). The MLT implant was used for 3 months to promote the collected embryos viability and the ratio of oocyte reaching blastocysts for Rasa Aragonesa breed (90). In another way, the MLT has been demonstrated to keep most favorable conditions for homeostasis and mitochondrial function (91). This happen by reducing mitochondrial oxidative stress and consequently restrict subsequent apoptotic events and cell death (92), therefore, the MLT uses to improving oocyte quality in sheep superovulation (93). Both ovulation rate and the retrieve embryos number from ewes were significantly improved after MLT used (93).

Melatonin implicated in in vivo oocyte maturation, this suggestion came because existence of MLTR in granulosa cells (94). Its stimulate ovarian steroidogenic gene expression (95) and luteinisation of graffian follicle (96). During the anoestrous period, MLT regulate a follicular growth (have a strong role in regulation and development) and oocyte efficiency (97). Exogenous MLT conserve cumulus cells from DNA damage during In vitro maturation (IVM) (98) (99), and the MLT supplementation to the IVM and culture medium can reduced Reactive oxygen species (ROS) (antioxidant effect) and get better competence of oocytes, which led to rise the quality and quantity blastocyst proportions and improve the embryos quality.

Conclusions

Based on this review, there were a vast benefit for MLT uses. The induce estrus during breeding season by effect on GnRH is the major role for MLT. Its a part of IVM medium, because its preserve the oocyte competence and improve the embryo quality. The litter size is important in sheep industry, so the using of MLT showed a partial advantage.

References

1. Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W. Isolation of melatonin, the pineal gland factor that lightens melanocyteS1. J. Am. Chem. Society. 1958;80(10):2587-2587.

2. Zarazaga LA, Malpaux B, Guillaume D, Bodin L, Chemineau P. Genetic variability in melatonin concentrations in ewes originates in its synthesis, not in its catabolism. Am. J. Physiol. Meta. 1998b;274(6):1086-1090.

3. Scott PR, Sargison ND, Macrae AI, Gough MR. Melatonin treatment prior to the normal breeding season increases fetal number in United Kingdom sheep flocks. Vet. J. 2009;182(2):198-202.

4. Zuniga O, Forcada F, Abecia JA. The effect of melatonin implants on the response to the male effect and on the subsequent cyclicity of Rasa Aragonesa ewes implanted in April. Anim. Reprod. Sci. 2002;15:72(3-4):165-174.

5. Abecia JA, Forcada F, Casao A, Palacín I. Effect of exogenous melatonin on the ovary, the embryo and the establishment of pregnancy in sheep. Reprod. Dom. Anim. 2008;2(3):399-404.

6. Bonev G. Effect of melatonin treatment on fertility, fecundity, litter size and sex ratio in ewes. Agri. Sci. Techno. 2012;4(2):113-116.

7. Casao A, Vega S, Palacín I, Pérez-Pe R, Lavina A, Quintin FJ, Sevilla E, Abecia JA, Cebrian-Perez, JA, Forcada F, Muino-Blanco T. Effects of Melatonin Implants During Non-Breeding Season on Sperm Motility and Reproductive Parameters in Rasa Aragonesa Rams. Reprod. Dom. Anim. 2010;45(3):425-432.

8. Galano A, Tan DX, Reiter RJ. Melatonin as a natural ally against oxidative stress: a physicochemical examination. J. pineal Res. 2011;51(1):1-16.

9. Ganguly S, Coon SL, Klein DC. Control of melatonin synthesis in the mammalian pineal gland: the critical role of serotonin acetylation. Cell Tissue Res. 2002;309(1):127-137.

10. Fitzpatrick PF. The aromatic amino acid
hydroxylases. Advances in Enzymol. Related Areas Mol. Biol. 2000;74:235-294.

11. Park M, Kang K, Park S, Back K. Conversion of 5-hydroxytryptophan into serotonin by tryptophan decarboxylase in plants, Escherichia coli, and yeast. Biosciences, Biotechnol. Biochem. 2008;72(9):2456-2458.

12. Klein DC, Roseboom PH, Coon SL. New light is shining on the melatonin rhythm enzyme: the first postcloning view. Trends Endocrinol. Metabol. 1996;7(3):106-112.

13. Tedesco SC, Morton OJ, Reiter RJ. Hydroxyindole-O-methyltransferase activity in the pineal gland of the muskox (Ovibos moschatus). J. Pineal Res. 1994;16(3):121-126.

14. Kraulis PJ. MOLSCRIPT: a program to produce both detailed and schematic plots of protein structures. J. Appl. Crystallography. 1991;24(5):946-950.

15. Skwarlo-Sonta K, Majewski P, Markowska M, Oblap R, Olszanska B. Bidirectional communication between the pineal gland and the immune system. Canadian J. Physiol. Pharmacol., 2003;81(4):342-349.

16. Golombek DA, Rosenstein RE. Physiology of circadian entrainment. Physiol. Rev. 2010;90(3):1063-1102.

17. Moller M, Baeres FM. The anatomy and innervation of the mammalian pineal gland. Cell Tissue Res. 2002;309(1):139-150.

18. Larsen PJ, Enquist LW, Card JP. Characterization of the multisynaptic neuronal control of the rat pineal gland using viral transneuronal tracing. Eur. J. Neurosci. 1998;10:128-145.

19. Ackermann k, stehle, JH. Melatonin synthesis in the human pineal gland: advantage, implications and difficulties. Chronobiol. Int. 2006; 23(1-2):369-379.

20. Zatz M, Gastel JA, Heath JR, Klein DC. Light and Cyclic AMP Control Abundance of Serotonin N-Acetyltransferase Protein. J. Neurochem. 2000;74(6):2315-2321.

21. Hattori A, Migitaka H, Iigo M, Itoh M, Yamamoto K, Ohtani-Kaneko R, Hara M, Suzuki T, Reiter RJ. Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. Biochem. Mol. Biol. Int. 1995;35(3):627-634.

22. Reiter RJ, Tan DX, Kim SJ, Cruz MH. Delivery of pineal melatonin to the brain and SCN: role of canaliculi, cerebrospinal fluid, tanycytes and Virchow–Robin perivascular spaces. Brain Structure and Function. 2014;219(6):1873-1887.

23. Tricoire H, Malpaux B, Møller M. Cellular lining of the sheep pineal recess studied by light transmission and scanning electron microscopy: Morphologic indications for a direct secretion of melatonin from the pineal gland to the cerebrospinal fluid. J. Comp. Neurol. 2003;456(1):39-47.

24. Tricoire H, Moller M, Chemineau P, Malpaux B. Origin of cerebrospinal fluid melatonin and possible function in the integration of photoperiod. Reprod. (Cambridge, England) Suppl. 2002;61:311-321.

25. Ma X, Idle JR, Krausz KW, Gonzalez FJ. Metabolism of melatonin by human cytochromes P450. Drug Metabol. Disposition. 2005;33(4):489-494.

26. Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. Neuron. 1994;13(5):1177-1185.

27. Von Gall C, Garabette ML, Kell CA, Frenzel S, Dehghani F, Schumm-Draeger PM, Weaver DR, Korf HW, Hastings MH, Stehle JH. Rhythmic gene expression in pituitary depends on heterologous sensitization by the neurohormone melatonin. Natr. Neuro. sci. 2002;5(3):234 -238.

28. Migaud M, Daveau A, Malpaux B. MTNR1A melatonin receptors in the ovine pre-mammillary hypothalamus: day-night variation in the expression of the transcripts. Biol. Reprod. 2005;72(2):393-398.

29. Coge F, Guenin SP, Fery I, Migaud M, Devavry S, Slugocki C, Legros C, Ouvry C,
Cohen W, Renault N, Nosjean O. The end of a myth: cloning and characterization of the ovine melatonin MT2 receptor. Br. J. Pharmacol. 2009;158(5):1248-1262.

30. Deupi X, Dolker N, Luz Lopez-Rodriguez M, Campillo M, Ballesteros JA, Pardo L. Structural models of class AG protein-coupled receptors as a tool for drug design: insights on transmembrane bundle plasticity. Curr. Top Med. Chem. 2007;7(10):991-998.

31. Hung AY, Sheng M. PDZ domains: structural modules for protein complex assembly. J. Biol. Chem. 2002;277(8):5699-5702.

32. Ferguson SS. Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. Pharmacol. Rev. 2001;53(1):1-24.

33. Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J. International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol. Rev. 2010;62(3):343-380.

34. Roka F, Brydon L, Waldhoer M, Strosberg AD, Freissmuth M, Jockers R. Association of the human Mel1a-melatonin receptor and Gi: precoupling and constitutive activity. Mol. Pharmacol. 1999;56(5):1014-1024.

35. Witt-Enderby PA, Dubocovich ML. Characterization and regulation of the human ML1A melatonin receptor stably expressed in Chinese hamster ovary cells. Mol. Pharmacol. 1996;50(1):166-174.

36. Godson C, Reppert SM. The Mel1a melatonin receptor is coupled to parallel signal transduction pathways. Endocrinol. 1997;138(1):397-404.

37. Brydon L, Petit L, De Coppet P, Barrett P, Morgan PJ, Strosberg AD, Jockers R. Polymorphism and signaling of melatonin receptors. Reprod. Nutr. Dev. 1999;39(3):315-324.

38. Petit L, Lacroix I, De Coppet P, Strosberg AD, Jockers R. Differential signaling of human Mel1a and Mel1b melatonin receptors through the cyclic guanosine 3'5'-monophosphate pathway. Biochem. Pharmacol. 1999;58(4):633-639.

39. Hunt AE, Al-Ghoul WM, Gillette MU, Dubocovich ML. Activation of MT2 melatonin receptors in rat suprachiasmatic nucleus phase advances the circadian clock. Am. J. Physiol. Cell. Physiol. 2001;280(1):110-118.

40. Ross AW, Webster CA, Thompson M, Barrett P, Morgan PJ. A novel interaction between inhibitory melatonin receptors and protein kinase C-dependent signal transduction in ovine pars tuberalis cells. Endocrinol. 1998;139(4):1723-1730.

41. Dubocovich ML. Melatonin receptors: are there multiple subtypes?. Trends Pharmacol. Sci. 1995;16(2):50-56.

42. Masana MI, Dubocovich ML. Melatonin receptor signaling: finding the path through the dark. Sci. STKE. 2001;107(6):39-43.

43. Cameron J, Malpaux B, Castonguay FW. Accelerated lambing achieved by a photoperiod regimen consisting of alternating 4-month sequences of long and short days applied year-round. J. Anim. Sci. 2010;88(10):3280-3290.

44. Hazlerigg DG, Wagner GC. Seasonal photoperiodism in vertebrates: from coincidence to amplitude. Trends Endocrinol. Metab. 2006;17(3):83-91.

45. Sliwowska JH, Billings HJ, Goodman RL, Coolen LM, Lehman MN. The premammillary hypothalamic area of the ewe: anatomical characterization of a melatonin target area mediating seasonal reproduction. Biol. Reprod. 2004;70(6):1768-1775.

46. Malpaux B, Tricoire H, Mailliet F, Daveau A, Migaud M, Skinner DC, Pelletier J, Chemineau P. Melatonin and seasonal reproduction: understanding the neuroendocrine mechanisms using the sheep as a model. Reprod. (Cambridge, England) Supp. 2001;59:167-179.

47. Romanowicz K, Misztal T, Gajewska A, Barcikowski B. Daily GnRH and LH secretion in ewes is not modified by exogenous melatonin
during seasonal anestrus. Acta Neurobiologiae Experimentalis 2001;61(4):289-298.

48. Gottsch ML, Cunningham MJ, Smith JT, Popa SM, Acohido BV, Crowley WF, Seminara S, Clifton DK, Steiner RA. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinol. 2004;145(9):4073-4077.

49. Messager S, Chatzidaki EE, Ma D, Hendrick AG, Zahn D, Dixon J, Thresher RR, Malinge I, Lomet D, Carlton MB, Colledge WH. Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proc. Natl. Acad. Sci. U.S.A., 2005;102(5):1761-1766.

50. Gingerich S, Wang X, Lee PK, Dhillon SS, Chalmers JA, Koletar MM, Belsham DD. The generation of an array of clonal, immortalized cell models from the rat hypothalamus: analysis of melatonin effects on kisspeptin and gonadotropin-inhibitory hormone neurons. Neurosci. 2009;162(4):1134-1140.

51. Wagner GC, Johnston JD, Clarke IJ, Lincoln GA, Hazlerigg, DG. Redefining the limits of day length responsiveness in a seasonal mammal. Endocrinol. 2008;149(1):32-39.

52. Caraty A, Smith JT, Lomet D, Ben Said S, Morrissey A, Cognie J, Doughton B, Baril, G, Briant C, Clarke IJ. Kisspeptin synchronizes preovulatory surges in cyclical ewes and causes ovulation in seasonally acyclic ewes. Endocrinol., 2007;148(11):5258-5267.

53. AL-Ameri, MH, Abdulkareem TA, Taha AA. The effect of hormonal treatment with kisspeptin, GnRH and hCG on semen characteristics in buck Cyprus goats during non-breeding season as compared with breeding season. Al-Anbar Journal of Veterinary Sciences. 2019;12(1), 74-88.

54. Viguie C, Picard S, Thiery JC, Malpaux B. Blockade of tyrosine hydroxylase activity in the median eminence partially reverses the long day-induced inhibition of pulsatile LH secretion in the ewe. J. Neuroendocrinol. 1998;10(7):551-558.

55. Goodman RL, Maltby MJ, Millar RP, Hileman SM, Nestor CC, Whited B, Tseng AS, Coolen LM, Lehman MN. Evidence that dopamine acts via kisspeptin to hold GnRH pulse frequency in check in anestrus ewes. Endocrinol. 2012;153(12):5918-5927.

56. Wu M, Dumalska I, Morozova E, Van Den Pol AN, Alreja M. (2009). Gonadotropin inhibitory hormone inhibits basal forebrain vGluT2-gonadotropin-releasing hormone neurons via a direct postsynaptic mechanism. J. Physiol., 587(7):1401-1411.

57. Clarke IJ, Sari IP, Qi Y, Smith JT, Parkington HC, Ubuka T, Iqbal J, Li Q, Tilbrook A, Morgan K, Pawson AJ. Potent action of RFamide-related peptide-3 on pituitary gonadotropes indicative of a hypophysiotropic role in the negative regulation of gonadotropin secretion. Endocrinol. 2008;149(11):5811-5821.

58. Dardente H, Birnie M, Lincoln GA, Hazlerigg DG. RFamide-related peptide and its cognate receptor in the sheep: cDNA cloning, mRNA distribution in the hypothalamus and the effect of photoperiod. J. Neuroendocrinol. 2008;20(11):1252-1259.

59. Revel FG, Saboureau M, Pevet P, Simonneaux V, Mikkelsen JD. RFamide-related peptide gene is a melatonin-driven photoperiodic gene. Endocrinol. 2008;149(3):902-912.

60. Eidan SM, Khalil RI, Ali ZH. Effect of melatonin implantation on Semen quality Holstein bulls: 1-Ejaculate volume and Total normal morphology sperm. Al-Anbar Journal of Veterinary Sciences. 2017a;10(1), 145-153.

61. Eidan SM, Khalil RI, Ali ZH. Effect of melatonin implantation on semen quality Holstein bulls: 2-Total number of motile sperm and integrity plasma membrane. Al-Anbar Journal of Veterinary Sciences. 2017b;10(1), 154-166.

62. Graham ES, Webster CA, Hazlerigg DG, Morgan PJ. Evidence for the Biosynthesis of a Prolactin-Releasing Factor from the Ovine Pars Tuberalis, Which is Distinct from Thyrotropin-Releasing Hormone. J. Neuroendocrinol. 2002;14(12):945-954.

63. Morgan PJ, Webster CA, Mercer JG, Ross AW, Hazlerigg DG, MacLean A, Barrett P. The
ovine pars tuberalis secretes a factor(s) that regulates gene expression in both lactotrophic and non lactotropic pituitary cells. Endocrinol. 1996;37(9):4018-4026.

64. Wood S, Loudon A. Clocks for all seasons: unwinding the roles and mechanisms of circadian and interval timers in the hypothalamus and pituitary. J. Endocrinol. 2014;222(2):39-59.

65. Lincoln GA, Andersson H, Hazlerigg D. Clock genes and the long-term regulation of prolactin secretion: evidence for a photoperiod/circannual timer in the pars tuberalis. J. neuroendocrinol. 2003;15(4):390-397.

66. Lincoln GA, Clarke IJ. Photoperiodically-Induced Cycles in the Secretion of Prolactin in Hypothalamo-Pituitary Disconnected Rams: Evidence for Translation of the Melatonin Signal in the Pituitary Gland. J. Neuroendocrinol. 1994;6(3):251-260.

67. Molik E, Misztal T, Romanowicz K, Zieba DA. The effects of melatonin on prolactin and growth hormone secretion in ewes under different photoperiods, during the early post partum period. Small Rum. Res. 2010;94(1):137-141.

68. Morgan PJ. The pars tuberalis: the missing link in the photoperiodic regulation of prolactin secretion?. J. Neuroendocrinol. 2000;12(4):287-296.

69. Johnston JD. Photoperiodic regulation of prolactin secretion: changes in intra-pituitary signaling and lactotroph heterogeneity. J. Endocrinol. 2004;180(3):351-356.

70. Ungerfeld R, Bielli A. Seasonal and social factors affecting reproduction. Livestock reproduction: bovine, swine and ruminants. Encycl. Life Supp. Sys. 2012;Pp. 1-15.

71. Simonneaux V, Ribelelayga C. Generation of the melatonin endocrine message in mammals:a review of the complex regulation of melatonin synthesis by norepinephrine, peptides and other pineal transmitters. Pharmacol. Rev. 2003;55(2):325-395.

72. Schwartz MD, Wotus C, Liu T, Friesen WO, Borjigin J, Oda GA, Horacio O. Dissociation of circadian and light inhibition of melatonin release through forced desynchronization in the rat. Proc. Natl. Acad. Sci. 2009;106(41):17540-17545.

73. Reiter RJ. Neuroendocrine effects of light. Int. J. Biometereol. 1991;35:169-175.

74. Ravault JP, Chesneau D. The onset of increased melatonin secretion after the onset of darkness in sheep depends on the photoperiod. J. Pineal Res. 1999;27(1):1-8.

75. Zarazaga LA, Malpaux B, Bodin L, Chemineau P. The large variability in melatonin blood levels in ewes is under strong genetic influence. Am. J. Physiol. 1998a;274(4): 607-610.

76. Notter DR, Chemineau P. Nocturnal melatonin and prolactin plasma concentrations in sheep selected for fertility in autumn lambing. J. Anim. Sci. 2001;79(11):2895-2901.

77. Carcangiu V, Mura MC, Parmeggiani A, Piccione G, Bini PP, Cosso G, Luridiana S. Daily rhythm of blood melatonin concentrations in sheep of different ages. Biol. Rhythm Res.2013;44(6):908-915.

78. Redondo E, Regodon S, Masot J, Gázquez A, Franco A. Postnatal development of female sheep pineal gland under natural inhibitory photoperiods: an immunocytochemical and physiological (melatonin concentration) study. Histol Histopathol. 2003;18(1):7-17.

79. Forcada F, Abecia JA, Casao A, Cebrian-Perez JA, Muino-Blanco T, Palacin I. Effects of ageing and exogenous melatonin on pituitary responsiveness to GnRH in ewes during anestrus and the reproductive season. Theriogenol. 2007;67(4):855-862.

80. Hatif SA, Younis LS. Nocturnal and diurnal plasma melatonin in season and non-seasonal sheep during spring. Onl J Vet Res. 2018a;22(6), 513-517.

81. Kennedy SH. Melatonin disturbances in anorexia nervosa and bulimia nervosa. Int. J. Eating Disorder. 1994;16(3):257-265.

82. Klein DC. Evolution of the vertebrate pineal
gland: the AANAT hypothesis. Chronobiol. Int. 2006;23(1-2):5-20.

83. Den Boer JA, Westenberg HG. Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. Psychopharmacol. Berl. 1990;102(1):85-94.

84. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Alterations to plasma melatonin and cortisol after evening alprazolam administration in humans. Chronobiol. Int. 1993;10(3):205-213.

85. Giantsis IA, Laliotis GP, Stoupa O, Avdi M. Polymorphism of the melatonin receptor 1A (MNTR1A) gene and association with seasonality of reproductive activity in a local Greek sheep breed. Journal of Biological Research-Thessaloniki. 2016;23(1), 9.

86. Younis LS, Hatif SA. AA-NAT melatonin gene polymorphism in ewes lambing out of season. Onl J Vet Res. 2017;21(3):118-125.

87. Hatif SA, Younis LS. Effect of aryl alkyl amine-N-acetyl-transferase gene polymorphism on melatonin in non-seasonal ewes, Onl J Vet Res. 2018b;22 (5):356-361.

88. Nowak R, Rodway RG. Effect of intravaginal implants of melatonin on the onset of ovarian activity in adult and prepubertal ewes. Reproduction, 1985;74.1: 287-293.

89. Buffoni A, Vozzi PA, Gonzalez DM, Rios G, Viegas-Bordeira H, Abecia JA. The effect of melatonin and season on in vivo embryo production of Dohne merino ewes. Small Rumin. Res. 2014;120, 121–124.

90. Forcada F, and Abecia JA. The effect of nutrition on the seasonality of reproduction in ewes. Reprod. Nutr. Dev. 2006;46, 355–365.

91. Leon J, Acuna-Castroviejo D, Sainz RM, Mayo JC, Tan DX, Reiter RJ. Melatonin and mitochondrial function. Life Sci. 2004;75(7):765-790.

92. Rodríguez MI, Carretero M, Escames G, López LC, Maldonado MD, Tan DX, Reiter RJ, Acuña-Castroviejo D. Chronic melatonin treatment prevents age-dependent cardiac mitochondrial dysfunction in senescence-accelerated mice. Free Radical Res. 2007;41(1):15-24.

93. Zhang L, Chai M, Tian X, Wang F, Fu Y, He C, Deng S, Lian Z, Feng J, Tan DX, Liu, G. Effects of melatonin on superovulation and transgenic embryo transplantation in small-tailed han sheep (Ovis aries). Neuroendocrinol. Lett., 2013;34(4):294-301.

94. Tamura H, Nakamura Y, Korkmaz A, Manchester LC, Tan DX, Sugino N, Reiter R J. Melatonin and the ovary: physiological and pathophysiological implications. Fertil. Steril. 2009;92, 328–343.

95. Maganin CC, Simoes RS, Fuchs LF, Sasso GR, Simoes MJ, Baracat EC, Soares JM. Melatonin influences on steroidogenic gene expression in the ovary of pinealectomized rats. Fertil. Steril. 2014;102, 291–298.

96. He C, Ma T, Shi JM, Zhang ZZ, Wang J, Zhu KF, Li Y, Yang MH, Song YK, Liu GS. Melatonin and its receptor MT1 are involved in the downstream reaction to luteinizing hormone and participate in the regulation of luteinization in different species. J. Pineal Res. 2016;61, 279–290.

97. Tsiligiani T, Valasi I, Cseh S, Vainas E, Faigl V, Samartzi F, Papanikolaou T, Dovolou E, Amiridis GS. Effects of melatonin treatment on follicular development and oocyte quality in Chios ewes – short communication. Acta Vet. Hung. 2009;57, 331–335.

98. Takada L, Martins A, Junior Mingoti GZ, Balieiro JC, Cipolla Neto J, Coelho LA. Effect of melatonin on DNA damage of bovine cumulus cells during in vitro maturation (IVM) and on in vitro embryo development. Res. Vet. Sci. 2012;92, 124–127.

99. Loren P, Sa´nchez R, Arias ME, Felmer R, Risopatron J, Cheuqueman C. Melatonin scavenger properties against oxidative and nitrosative stress: impact on gamete handling and in vitro embryo production in humans and other mammals. Int. J. Mol. Sci. 2017;18, 1119.