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Review

VARIOUS APPROACHES TO INFLUENCE MELATONIN LEVEL IN SHEEP REPRODUCTION

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Abstract

A new field of research in reproductive biology was heralded by the discovery of melatonin in 1958. The concentration of melatonin follows light-dark cycles with significantly higher concentrations during darkness. The authors present the importance of the melatonin protein hormone by focusing on the reproductive processes in domestic sheep. In their literature review, they report that sheep melatonin levels show daily and seasonal rhythms. In sheep as a seasonal breeder and short-day animal species, seasonal increases in melatonin production stimulate sexual activity. The authors describe innovative possibilities for regulating melatonin levels in sheep production. The use of exogenous melatonin brings forward the expression of the sexual cycle. It increases the fertility rate, the number of lambs born, and the chances of survival of twin lambs. Melatonin is a neuroprotection compound against cerebral hypoxia and the development of inflammatory processes in the growing foetus and the newborn lamb.

Key Words: antioxidant, assisted reproductive technology, melatonin (endogenous, exogenous), photoperiod

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INTRODUCTION

The authors' aim is to discuss the importance of the pineal gland hormone, melatonin and how it affects the reproductive biology of the sheep as a short-day breeder. The study of both endogenous and exogenous melatonin has been the subject of human and animal research in recent years. The results of ongoing research have implications for the processes of profitable animal production.

The hormone of darkness

Melatonin is a protein hormone, synthesised in the pineal gland (epiphysis cerebri) located near the hypothalamus (Bartha et al., 2021). Histologically, the pineal gland is composed of two units: pinealocytes and glial cells (Kárpáti et al., 2021a). The organ can be influenced by peptides entering from the blood, due to the fact that the organ is not under the tight control of the blood-brain barrier. The pineal gland is not in direct contact with the central nervous system either, but is innervated by postganglionic sympathetic nerve fibres. Pinealocytes contain numerous biogenic amines (dopamine, serotonin, histamine) and are also rich in hypothalamic peptides (GnRH, TRH, somatostatin, neurophysin). The endocrine activity of the pineal gland is greatly influenced by light intensity, so the organ can be considered an "endocrine transducer": it "translates light effects into the language of endocrinology" (*Rudas and Frenyó*, 1995).

Light mainly induces the production of serotonin in the pineal gland. However, in the absence of light at night, an indoleamine-like substance, melatonin (*N-acetyl-5-methoxytryptamine*), isolated first by Lerner et al. in 1958, is produced through the methylation of serotonin (Liebich, 2010). The neuronal pathway of hormone action is as follows: melanopsin in retina - optic nerve - retinohypothalamic tracts - cervical cranial ganglion. In certain mammals (long-day animals e.g. horses and hamsters) melatonin production in response to light deprivation leads to a lack of hypothalamic GnRH and pituitary FSH and LH production, whereas in short daylight animals (e.g. sheep and goats) the reverse is true. It has also been described that in the sheep, intracerebral administration of melatonin precedes the expression of the sexual cycle, whereas in the horse, the manifestation of the sexual cycle is inhibited by melatonin (Kárpáti et al., 2021b). With this knowledge, it can be concluded that melatonin is a fundamental determinant of the gonadal activity of seasonal breeding animals. Melatonin acts directly on the reproductive organs, which contributes to the maintenance of a healthy reproductive biology (Vriend and Reiter, 2015). Pars tuberalis of the pituitary gland did not appear to be targeted by melatonin to modulate the secretion of gonadotropin productions in ewes (Malpaux et al., 1999). However, they found melatonin binding sites in the corpus mamillare section of hypothalamus, which stimulated the secretion of gonadotropins in pituitary glands. These authors concluded that the effect of melatonin is transmitted on the neuroendocrine axis by the hypothalamus (Malpaux et al., 1999). Melatonin protects spermatozoa from oxidative stress and studies of spermatogenesis have shown that it promotes their motility and increases their fertility (Cruz et al., 2014).

Differences in the location and number of receptors are thought to be responsible for the differential effect between species. These differences between species serve an important purpose, namely to ensure that the offspring are naturally born at the most suitable time of the year (Ortavant et al., 1985; von Engelhardt, 2009). In his literature review, Hardeland (2017) describes melatonin as having innumerable sites of formation outside the pineal gland, and a significantly higher level of melatonin is formed outside the pineal gland, particularly in the weed-gut system. This so-called extrapineal melatonin is also synthesised in various regions of the central nervous system, in particular in the cerebellum, retina, lens of the eye, cholangiocytes of the liver, bone marrow, various white blood cells, thymus, spleen, kidney, heart, ovary, placenta, skin and respiratory epithelial cells; the list is lengthy.

Melatonin also has strong antioxidant properties (Bonnefont-Rousselot and Collin, 2010). The extent of antioxidant activity is directly related to free radical scavenging capacity (Galano et al., 2013), expression of antioxidant enzymes (Rodriguez et al., 2004) and mitochondrial protection (López et al., 2009; Zhang and Zhang, 2014). It is also an important immunomodulatory substance, and in addition, there is evidence that melatonin stabilises cell membranes, thereby helping to ward off oxidative damage (Kurutas, 2016). Another important function of melatonin is to regulate the complex developmental processes of the embryo and foetus, including the protection of foetal organs from oxidative damage, as well as to induce circadian rhythm and stimulate the neuroendocrine system (Voiculescu et al., 2014).

Animals with seasonal polyoestrus

In sheep, in temperate climates, the anoestrous lasts from spring to late summer, and then, as the days shorten, the mating cycle begins (Kárpáti et al., 2022). By using subcutaneous melatonin implants, the breeding season of the sheep can be brought forward (Haresign et al., 1990; Wheaton et al., 1990; Forcada et al., 1995). In sheep the sexual cycle lasts between 16 and 18 days. Seasonality also affects the economy of rearing short-day species, since the laws of supply and demand mean that seasonality can also be observed in meat and milk prices. There are many ways to interfere with the natural reproductive cycle of small ruminants, most commonly by light programmes or exogenous melatonin administration, which increases productivity and allows lambs to be born out of season and mothers to be milked during the main milking season (Abecia et al., 2011). However, research of this kind has also shown that melatonin can increase fertility rates and the number of lambs born (Abecia et al., 2011; Palacín et al., 2011). The implants induce high plasma concentrations of melatonin for a day, but do not suppress endogenous nocturnal pineal secretion. This results in a response similar to the short daytime (Malpaux et al., 1997). When anoestrous ewes are treated with melatonin, there is a significant increase in LH-releasing hormone (LHRH) secretion

40 days after treatment, but a significant fluctuation in LHRH and LH levels 74 days later according to Viguié et al. (1995). Further studies have confirmed that during anoestrus, melatonin stimulates the secretion of GnRH (gonadotropin-releasing hormone) and LH (luteinising hormone) by reducing the activity of the enzyme tyrosine hydroxylase in eminentia mediana (Viguié et al., 1997).

The length of the day also regulates the production of oestradiol. Oestradiol suppresses LH secretion, thus regulating the seasonal rhythm of ewe reproduction (Bittman and Karsch, 1984). Under certain conditions, some ewes lose their reproductive response to photoperiod, a state of insensitivity to light known as photoreactivity. This condition is likely to be crucial in the development of the annual reproductive cycle of ewes; photoreactivity leads to natural transitions at the beginning and end of the joining season (Worthy and Haresign, 1983; Robinson et al., 1985; Worthy et al., 1985).

The light-insensitive state can also be induced artificially by keeping sheep in long or short daylight exposure for extended periods (Thwaites, 1965; Wodzicka-Tomaszewska et al., 1967). Two hypotheses have also been accepted that shed light on the importance of melatonin in photoreactivity. One hypothesis is that the explanation lies in the alteration of the response to melatonin signalling (Bittman, 1978). In the example of Karsch et al. (1986), despite prolonged melatonin infusion, reproductive function comes to an end in pinealectomised ewes.

Melatonin receptors

The importance of the field is demonstrated by the intensive research being conducted not only on melatonin but also on the function of its receptors (Talpur et al., 2018). The melatonin receptor family belongs to the G-protein coupled receptor (GPCR) superfamily. Three subtypes are distinguished that bind melatonin and a melatonin-related receptor (MRR). The latter receptor has significant sequence identity (> 40%) with the three subtypes but does not bind melatonin (Barrett et al., 2003).

In many physiological processes involving melatonin, at least two high affinity G-protein coupled receptors, namely melatonin MT1 and MT2 receptors, must be activated. Melatonin MT1 receptors modulate the neuronal response (when a neuron releases an action potential or nerve impulse), arterial vasoconstriction, cancer cell proliferation, and reproductive and metabolic functions, while MT2 receptors affect the circadian rhythm of the neuronal response in the suprachiasmatic nucleus, inhibit dopamine release in the retina, induce vasodilatation, promote leukocyte adhesion to the vascular endothelium in inflammatory processes by enhancing the immune response. Melatonin plays an important role in many physiological processes. For this to happen, both the MT1 and MT2 receptors need to be activated. In general, MT1 receptors are involved in neuronal activities, triggering arterial contraction and influencing cancer cell proliferation. They also play important roles in reproductive biology and metabolic regulation. MT2 receptors in the suprachiasmatic nucleus affect circadian rhythms, inhibit dopamine release in the retina, induce vasodilation and promote leukocyte adhesion to the vascular endothelium by enhancing the immune response in inflammatory processes (Dubocovich and Markowska, 2005). The activation of MT2 receptors depends on the multicellular signalling pathway and inhibition of adenylyl cyclase activity, which is usually coupled to the MT1 signalling pathway. Several previous studies have recognised the essential contribution of melatonin receptors to the function of the reproductive organs of sheep (Cogé et al., 2009).

In mammals, the highest density of melatonin receptor expression is detected in the pars tuberalis. In sheep, this value is around 100 fmol/mg protein density (Morgan et al. 1989). Polymorphisms of melatonin receptors have also been demonstrated in different species (Brydon et al., 1999; Barrett, 1997), which may be associated, for example, with sleep disorders in humans and reproductive seasonality in sheep (Ebisawa et al., 1999; Pelletier et al., 2000).

In sheep, the expression or non-expression of the MT1 receptor gene polymorphism is closely related to the out-of-season breeding and fertility of different breeds. This has been demonstrated in Mediterranean sheep breeds, for example by Carcangiu et al. (2009) and Martínez-Royo et al. (2012), while research on Dorset sheep was carried out by Mateescu et al. (2009). In addition, the presence of MT1 and MT2 receptors has been detected in ram spermatozoa (Casao et al., 2012).

In the female, both receptors (MT1 and MT2) are expressed in oocytes, cumulus cells and granulosa cells (Tian et al., 2017). Casao et al. (2018) have succeeded in detecting gene expression of both receptors in sheep blastocytes using quantitative polymerase chain reaction (PCR).

Effect of melatonin treatment in assisted reproductive procedures

Uterus and fallopian tubes

Several studies have addressed the effects of melatonin on the uterus, in particular on uterine receptors, prostaglandin (PGF2α) secretion or uteroplacental haemodynamics. Uteroplacental blood flow and foetal growth during supplementation with dietary melatonin (5 mg/day) were investigated using a mid- and late-gestation sheep model (Lemley and Vonnahme, 2017). Melatonin supplementation increased umbilical arterial blood flow compared to the control group without melatonin treatment.

Ovarian transplantation

When melatonin is added to the collection medium, it reduces the level of reactive oxygen species (ROS) and there is also an increase in the proportion of blastocytes. *Goodarzi et al.* (2018) added melatonin at different concentrations (levels 0, 500, 600, 700 or 800 mM) to the preservation medium of sheep oocytes kept at 4°C or 20°C for 24 h and determined the effect of the hormone on in vitro embryo production parameters. Melatonin reduced the deterioration of fertilisation rates, increasing the total cell number of blastocysts (as an indicator of embryo quality).

Follicles

Granulosa cells are the only somatic cells that interact closely with the ovum from the initial moment of follicular formation until ovulation. Therefore, the presence of melatonin receptors in granulosa cells may suggest that melatonin is involved in the maturation of oocytes in vivo (Tamura et al., 2009).

Tsiligianni et al. (2009) evaluated follicle development and oocyte quality in anoestrous ewes. The oocytes collected via laparoscopic ovum pick up (OPU) procedures underwent IVM (in vitro maturation), IVF (in vitro fertilisation) and IVC (in vitro cultivation) treatments. Compared with the untreated group, the melatonin-treated group had a more pronounced proportion of large follicles, a better fertility rate and a more successful subsequent development of oocytes collected from the treated group in in vitro processes. It can be concluded that melatonin is beneficial in regulating follicle development and oocyte fertilisation success during anoestrus.

Oocytes

There have been many publications on the measurement of the effects of melatonin on the maturation, growth and development of sheep oocytes. In the study of Casao et al. (2009), oocytes from sheep ovaries (collected at slaughterhouses) were treated with different concentrations of melatonin (10^{-6}, 10^{-8} or 10^{-10} M melatonin) and then fertilised, and the embryos were matured in the medium for 8 days while maintaining the concentration of melatonin. Melatonin did not have a significant effect on maturation or division in all cases; however, 10^{-8} M melatonin significantly increased the proportion of blastocysts in the embryo culture after 8 days.

The cumulus cells are responsible for some oxidative damage, but this is reduced by the melatonin that is synthesised here and then accumulates in the preovulatory follicles (Tamura et al., 2012).

The addition of melatonin increased the cGMP levels but decreased the cAMP levels in oocytes and cumulus cells (Tian et al., 2017).

Effect of exogenous melatonin and nutritional level of diet was investigated by Vázquez et al. (2010a) in synchronised ewes after early weaning of lambs and fertilisation. They observed that neither diet nor melatonin significantly affected oocyte quality parameters in the reproductive season of the year, while melatonin implants significantly reduced the number of abnormal oocytes in the malnourished group. In the out of season period of the year, exogenous melatonin appeared to elevate the number of healthy and cleaved oocytes, as well as the blastocyst rate in undernourished ewes ($p < 0.05$).

Melatonin secretion decreases with age in animals and humans alike (Reiter, 1992). In older ewes, exogenous melatonin increases LH levels following GnRH injection, suggesting that melatonin is able to restore the reduced neuroendocrine function associated with ageing (Forcada et al., 2007).

Embryo production

Melatonin has a beneficial effect on the quality of gametes and the developing embryo. It provides protection against oxidative and nitrosative stress and inhibits apoptosis at the mitochondrial level, as well as stimulating the activity of antioxidant enzymes (Loren et al., 2017).

McEvoy et al. (1998) were the first to experiment with superovulated ewes during the anoestrous period to increase their embryo production but found no difference in the number and quality of embryos between melatonin-treated and untreated ewes. Similar results were reported by other researchers (Buffoni et al., 2014; Abecia et al., 2019), who used external melatonin to improve embryo production in multiple ovulation and embryo transfer (MOET) programmes, outside the breeding season as well. In contrast, Mitchell et al. (2002) found no effect of melatonin supplementation on ovulation, fertilisation or viability rates, nor on the number of viable embryos per ewe; however, the number of degenerate embryos in the anoestrous period was highest in the melatonin-treated group, probably due to seasonal shifts in LH secretion and/or its effect on follicular function.

Succu et al. (2014) evaluated the effect of different melatonin concentrations on embryo viability after deep-freezing. The beneficial effect of melatonin on embryonic function was observed only at the lowest concentration (10^{-9} M). They concluded that higher concentrations of melatonin may be to some extent toxic to prenatal embryos, as evidenced by an increase in the apoptotic index of the blastocyst.

Corpora lutea and progesterone

Vázquez et al. (2010b) looked at the effect of melatonin treatment (at parturition) in undernourished ewes in the seasonal anoestrus. It was found that melatonin administration significantly improved the number of fertilised embryos/corpus luteum (CL) and that neither feedstuff rations nor melatonin administration had a significant effect on ovulation rate and oocytes per ewe.

Melatonin acts directly on the CL by enhancing its progesterone (P4) production. Both the use of the in vivo melatonin perfusion cannula system and in vitro culture of luteinised granulosa cells with melatonin supplementation significantly stimulated P4 secretion for 30-60 min after melatonin administration (in vivo) and by granulosa cells (in vitro) after two days of culture (Durotoye et al., 1997).

In another experiment (Abecia et al., 2002), ewes were treated with melatonin intravenously (3 mg/(kg body weight)$^{0.75}$) after withdrawal of progestagen pessaries. Ewes, on day 10 showed an improving luteal function in form of defined increase in the plasma progesterone concentration as a response to melatonin challenge.

Another report (*Manca et al.,* 2014) studied the impact of melatonin deprival on ovarian status. It showed that the mean area of CL and plasma P4 concentration was significantly lower in pinealectomised ewes than sham-operated ewes. They concluded that melatonin influences follicle growth and the steroidogenic capacity of CL.

Vázquez et al. (2013) first reported the sensitisation of the endometrium to steroids in melatonin-treated underfed ewes. Exogenous melatonin increased progesterone receptor expression in the deep myometrium and decreased oestrogen receptor alpha (ERα) expression in the deep stroma. However, neither melatonin nor the effect of feeding affected ERα and progesterone receptor expression in the endometrium during anoestrous. Furthermore, in anoestrous malnourished ewes, melatonin implantation had a positive effect on embryo viability. Overall, the intrauterine expression of PGR (progesterone receptor) mRNA was decreased by melatonin treatment ($P < 0.01$), which was not dependent on breeding season.

Gestation period and foetal development

During gestation, maternal blood plasma melatonin levels increase, eventually reaching a peak and returning to a baseline level soon after parturition (Kivela, 1991).

It is thought that for mammalian foetuses, melatonin is involved in the developmental circadian rhythm (Davis, 1997). A different and perhaps more diverse role of melatonin in embryonic and foetal development compared to adults is suggested by the higher density and affinity of melatonin binding sites (Morgan et al., 1994).

In mammals, the effects of melatonin during in utero development are primarily due to maternal melatonin; during gestation, melatonin production shows a strong rhythmicity (Kivela, 1991). Although the foetus may produce melatonin, its level is low and without rhythmicity. In the ewe, melatonin diffuses the placenta and melatonin measured in foetal plasma is derived from the dam. This is confirmed by the absence of foetal plasma melatonin when the pineal gland is ectomysed in the mother (Yellon and Longo, 1988). Pinealectomy in ewes affects the phase of the foetal respiratory rhythm, and there is evidence that melatonin treatment can restore the normal rhythm (Houghton et al., 1993). In addition, keeping the ewe in constant light, which suppresses the melatonin rhythm of the ewe’s pineal gland, disrupts the expression of antidiuretic hormone, vasopressin (ADH) rhythm in foetal cerebrospinal fluid (Stark and Daniel, 1989).

Prolactin is higher in foetal plasma when ewes are kept on a long photoperiod (compared with a short photoperiod) or are pinealectomised; melatonin implants reduce prolactin levels (Houghton et al., 1995).

Oxidative stress during pregnancy is common and can have serious cardiovascular and neurological consequences. Melatonin is readily transmissible across the human and ovine placenta, offering an opportunity for prophylactic treatment of foetuses at high risk of perinatal hypoxia (Robertson et al., 2012).

Drury et al. (2014) found that melatonin given at low doses to mothers provides partial neural protection to foetal lambs in asphyxia. Foetuses were clamped for 25 min, but 15 min before the procedure the ewes were given melatonin. Maternal infusion of melatonin induced faster recovery of foetal electroencephalography (EEG) and prolonged reduction in carotid blood flow. Maternal prophylactic melatonin supplementation has a foetal protective effect, which, however, may be partially hampered by the ethanol used to dissolve melatonin.

When progeny are born under extreme conditions (like in habitats with altitudes above 2500 m) or preterm, they can suffer from neonatal pulmonary hypertension. As an antioxidant, melatonin can improve pulmonary vascular function when lambs are given per os melatonin supplementation at 4-11 days of age with 1 mg/kg in 1.4% ethanol at 0.5 ml/kg of dosing for 8 days (Torres et al., 2015).

Melatonin is associated with effective foetal brain responses to acute foetal hypoxia during parturition. Results from Thakor et al. (2015) show that melatonin treatment reduces foetal arterial blood pressure, forearm vascular resistance (FVR), blood glucose, blood lactate and attenuates circulating plasma catecholamines (epinephrine and norepinephrine) during acute stress of hypoxia. Furthermore, results support the hypothesis that melatonin provides a significant effect in the protective response by increasing nitric oxide (NO) bioavailability.

In 2015, Seron-Ferre et al. investigated the role of maternal melatonin levels during gestation on the development of lambs' brown adipose tissue and, thus, their thermoregulation and adaptation to extrauterine life. The results supported a role for prenatal maternal melatonin in the development of postnatal perirenal adipose tissue function in lambs.

The effect of supplementing pregnant ewes with melatonin was investigated by Flinn et al. (2020) on lamb survival, birth weight and behaviour under intensive conditions. Single and twin pregnant ewes were treated with melatonin (2 mg capsule daily; 18 mg subcutaneous implant daily) twice in the second half of gestation. The treatment increased the survival rate of twin lambs, especially those born from pluriparous dams.

Neonates and colostrum

While the melatonin produced by the mother before birth is significant in the foetal bloodstream, the production of melatonin by the lambs increases shortly after birth. As early as week 1, nocturnal melatonin levels begin to increase. Over the next five weeks, a normal rhythm of melatonin secretion is established, which follows the changes in the length of the night and is involved in the photoperiodic response. The establishment of the lamb melatonin rhythm does not appear to depend on maternal melatonin production (Foster et al., 1989; Nowak et al., 1990).

Colostrum is of paramount importance for development of immunity. Melatonin has an immunomodulatory effect, affecting immunoglobulin production directly. Immediately after lambing, colostrum samples were collected and analysed for immunoglobulin G (IgG) by Abecia et al. (2020). The mean IgG concentration in the colostrum of melatonin-treated ewes (55.54 ± 3.09 mg/ml) was higher ($p < 0.05$) than that of control ewes (49.50 ± 4.36 mg/ml). They concluded that melatonin implants applied in the fourth month of gestation resulted in higher colostrum quality based on a higher IgG concentration.

Exogenous melatonin in ewes affects the composition of the milk and the developmental vigour of the lambs. Abecia et al. (2021) conducted experiments where both mothers and their lambs either did or did not receive a subcutaneous melatonin implant immediate after parturition (within 24 hours after lambing). At day 45, fat and total solid content in the milk were higher ($P < 0.05$) in implanted ewes than in control ewes. Lambs reared by implanted ewes exceeded the control lambs for average daily gain and weaning weight.

Reproductive biology in male sheep

Melatonin in vivo is able to cross the blood-testis barrier and enter the testicular cells. Melatonin may play an important role in the regulation of spermatogenesis and cell differentiation (Smirnov, 2001) and act directly on accessory glands, probably through binding of melatonin receptors.

Gonzalez et al. (2016) demonstrated in the testes of rams the presence of melatonin-producing enzymes, which are mainly detected in Leydig cells, spermatocytes and spermatids.

In rams treated with melatonin, FSH, LH and testosterone levels show increases (Rekik et al., 2015). After long-term melatonin treatment of rams, more testosterone is secreted in the somatic cells of the testis (Deng et al., 2016). Melatonin is also likely to have an effect on spermatogenesis, which is manifested in cell growth, proliferation, metabolism and oxidative status. It also plays a key role in testicular physiological functions (sexual steroid synthesis, spermatogenesis), especially in seasonally reproducing animals (Frungieri et al., 2017).

Deng et al. (2018) investigated whether melatonin promotes testosterone secretion by culturing sheep Leydig cells in co-culture with Sertoli cells. The results of that study showed that androgen synthesis by Leydig cells can be significantly enhanced by Sertoli cells when melatonin is present. Melatonin increased the expression of stem cell factor and insulin-like growth factor-1 (IGF-1), but decreased oestrogen production in Sertoli cells. Melatonin promoted IGF-1 via the MT1 receptor and inhibited oestrogen synthesis.

Seasonal variations in the seminal plasma of rams have been observed (Perez-Pe et al., 2001; Casao et al., 2010) and treatment with melatonin alters the animals' biological structure (Casao et al., 2013). Melatonin treatment outside the reproductive period has a positive effect on seminal vesicles (Mokhtar et al., 2016; Santiago-Moreno et al., 2013), increasing their size.

Human studies have shown that melatonin, detectable in the testis, is able to protect spermatozoa from oxidative damage (Bejarano et al., 2014).

CONCLUSION

This review provides a comprehensive overview of melatonin's physiological roles and its use in efficient sheep production and reproduction. Melatonin has a myriad of effects in the body that can be exploited in the fields of animal sciences and veterinary medicine. Melatonin may not only be important as a regulator of circadian rhythms, but its role in developing breeding work and its antioxidant function may become even more of a focus of scientific interest. Melatonin receptor polymorphisms influence off-season breeding performance, and the use of exogenous melatonin contributes significantly to the efficacy of sheep production. As an antioxidant, melatonin may be of great importance in IVF work and in neonatology. In conclusion, based on all the references and results discussed in this review, melatonin could open a new perspective in the field of animal production.

Authors' contributions

AG conceived and supervised the compilation and had substantial inputs into the completion of manuscript with co-supervision of ZsB and LG. EK, DF and AMP participated in the collection and processing of literature and had role in creation a first draft of the paper.

Competing interests

The authors declare that they have no competing interests.

REFERENCES

Abecia J.A., Forcada F., Zuniga O. 2002. The effect of melatonin on the secretion of progesterone in sheep and on the development of ovine embryos in vitro. Veterinary Research Communications, 26: 151–158. https://doi.org/10.1023/A:1014099719034.

Abecia J.A., Forcada F., González-Bulnes A. 2011. Pharmaceutical control of reproduction in sheep and goats. Veterinary Clinics of North America: Food Animal Practice, 27:67–79. https://doi.org/10.1016/j.cvfa.2010.10.001.

Abecia J.A., Forcada F., Vázquez M.I., Blanco T.M., Cebrián-Pérez J.A., Pérez-Pe R., Adriana Casao A. 2019. Role of melatonin on embryo viability in sheep. Reproduction, Fertility and Development, 31:82–92. https://doi.org/10.1071/RD18308.

Abecia J.A., Garrido C., Gave M., García A.I., López D., Luis S., Valares J.A., Mata L. 2020. Exogenous melatonin and male foetuses improve the quality of sheep colostrum. Journal of Animal Physiology and Animal Nutrition, 104:1305– 1309. https://doi.org/10.1111/jpn.13362.

Abecia J.A., Luis S., Canto F. 2021. Implanting melatonin at lambing enhances lamb growth and maintains high fat content in milk. Veterinary Research Communications, 45:181–18. https://doi.org/10.1007/s11259-021-09799-y.

Barrett P., Conway S., Jockers R., Strosberg A.D., Guardiola-Lemaitre B., Delagrange P., Morgan P.J. 1997. Cloning and functional analysis of a polymorphic variant of the ovine Mel 1a melatonin receptor. Biochimica et Biophysica Acta, 1356:299–307. https://doi.org/10.1016/S0167-4889(96)00179-6.

Barrett P., Conway S., Morgan P.J. 2003. Digging deep – structure–function relationships in the melatonin receptor family. Journal of Pineal Research, 35:221–230. https://doi.org/10.1034/j.1600-079X.2003.00090.x.

Bartha B., Harmat L., Somoskői B., Cseh S., Fekete S.Gy., Gáspárdy A. 2021. The role of melatonin in horse and donkey reproduction. Literature review. (In Hungarian). Magyar Állatorvosok Lapja, 143(10): 599–608.

Bejarano I., Monllor F., Marchena A.M., Ortiz A., Lozano G., Jiménez M.I., Gaspar P., García J.F., Pariente J.A., Rodríguez A.B., Espino J. 2014. Exogenous melatonin supplementation prevents oxidative stress-evoked DNA damage in human spermatozoa. Journal of Pineal Research, 57(3):333–339. https://doi.org/10.1111/jpi.12172.

Bittman E.L. 1978. Hamster refractoriness: the role of insensitivity of pineal target tissue. Science 202:648-650. https://doi/10.1126/science.568311

Bittman E.L., Karsch F.J. 1984. Nightly duration of pineal melatonin secretion determines the reproductive response to inhibitory daylength in the ewe. Biology of Reproduction, 30:585–593. https://doi.org/10.1095/biolreprod30.3.585.

Bonnefont-Rousselot D., Collin F. 2010. Melatonin: action as antioxidant and potential applications in human disease and aging. Toxicology, 278:55–67. https://doi.org/10.1016/j.tox.2010.04.008.

Brydon L., Petit L., de Coppet P., Barrett P., Morgan P.J., Strosberg A.D., Jockers R. 1999. Polymorphism and signalling of melatonin receptors. Reproduction Nutrition Development, 39:315–324.https://doi.org/10.1051/rnd:19990304.

Buffoni A., Vozzi P.A., Gonzalez D.M., Rios G., Viegas-Bordeira H., Abecia J.A. 2014. The effect of melatonin and season on in vivo embryo production of Dohne merino ewes. Small Ruminant Research, 120:121–124. https://doi.org/10.1016/j.smallrumres.2014.05.003.

Carcangiu V., Mura M.C., Vacca G.M., Pazzola M., Dettori M.L., Luridiana S., Bini P.P. 2009. Polymorphism of the melatonin receptor MT1 gene and its relationship with seasonal reproductive activity in the Sarda sheep breed. Animal Reproduction Science, 116:65–72. https://doi.org/10.1016/j.anireprosci.2009.01.005.

Casao A., Ait A., Meziane M., Cebrián-Pérez J.A., Muiño-Blanco T., Abecia J.A., Forcada F. 2009. The effects of low concentrations of melatonin on in vitro maturation and fertilization of oocytes and on early embryo development in sheep. Conference AIDA, 2009. Jornadas SobreProducción Animal, 13., Zaragoza (España), 12-13 May 2009, AGRIS Spanish Journal of Agricultural Research 2010 8(1), 35-41. 696–698.

Casao A., Cebrián I., Asumpção M.E., Pérez-Pé R., Abecia J.A., Forcada F., Cerbián-Pérez J.A., Muiño-Blanco T. 2010. Seasonal variations of melatonin in ram seminal plasma are correlated to those of testosterone and antioxidant enzymes. Reproductive Biology and Endocrinology, 8(1):59.https://doi.org/10.1186/1477-7827-8-59.

Casao A., Gallego M., Abecia J.A., Forcada F., Pérez-Pé R., Muiño-Blanco T., Cebrián-Pérez J.A. 2012. Identification and immunolocalisation of melatonin MT1 and MT2 receptors in

Rasa Aragonesa ram spermatozoa. Reproduction, Fertility and Development, 24(7):953–961. https://doi.org/10.1071/RD11242.

Casao A., Pérez-Pé R., Abecia J.A., Forcada F., Muiño-Blanco T., Cebrián-Pérez J.Á. 2013. The effect of exogenous melatonin during the non-reproductive season on the seminal plasma hormonal profile and the antioxidant defence system of Rasa Aragonesa rams. Animal Reproduction Science, 138(3):168– 174. https://doi.org/10.1016/j.anireprosci.2013.02.002.

Casao A., Perez-Pe R., Cebrian-Perez J.A., Muino-Blanco T., Forcada F., Abecia J.A. 2018. 125 Presence of melatonin receptors in ovine blastocysts. Reproduction Fertility and Development, 31(1):188. https://doi.org/10.1071/RDv31n1Ab125.

Cogé F., Guenin S.P., Fery I., Migaud M., Devavry S., Slugocki C., Legros C., Ouvry C., Cohen W., Renault N., Nosjean O., Malpaux B., Delagrange P., Boutin J.A. 2009. The end of a myth: cloning and characterization of the ovine melatonin MT2 receptor. British Journal of Pharmacology, 158(5):1248–1262. https://doi.org/10.1111/j.1476-5381.2009.00453.x.

Cruz M.H., Leal C.L., Da Cruz J.F., Tan D.X., Reiter R.J. 2014. Role of melatonin on production and preservation of gametes and embryos: A brief review. Animal Reproduction Science, 145:150– 160.https://doi.org/10.1016/j.anireprosci.2014.01.011.

Davis F.C. 1997. Melatonin: Role in Development. Journal of Biological Rhythms, 12(6):498-508. https://doi.org/10.1177/074873049701200603.

Deng S.L., Chen S.R., Wang Z.P., Zhang Y., Tang J.X., Li J., Wang X.X., Cheng J.M., Jin C., Li X.Y., Zhang B.L., Yu K., Lian Z..X, Liu G.S., Liu Y.X. 2016. Melatonin promotes development of haploid germ cells from early developing spermatogenic cells of Suffolk sheep under in vitro condition. Journal of Pineal Research, 60:435-47. https://doi.org/10.1111/jpi.12327.

Deng S.L., Wang Z.P., Jin C., Kang X.L., Batool A., Zhang Y., Li X.Y., Wang X.X., Chen S.R., Chang C.S., Cheng C.Y., Lian Z.X., Liu Y.X. 2018. Melatonin promotes sheep Leydig cell testosterone secretion in a co-culture with Sertoli cells. Theriogenology, 106:170-177. https://doi.org/10.1016/j.theriogenology.2017.10.025.

Drury P.P., Davidson J.O., Bennet L., Booth L.C., Tan S., Fraser M., van den Heuij L.G., Gunn A.J. 2014. Partial neural protection with prophylactic low-dose melatonin after asphyxia in preterm fetal sheep. Journal of Cerebral Blood Flow & Metabolism, 34:126–135. https://doi.org/10.1038/jcbfm.2013.174.

Dubocovich M.L., Markowska M. 2005. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine, 27:101–110. https://doi.org/10.1385/ENDO:27:2:101.

Durotoye L.A., Webley G.E., Rodway R.G. 1997. Stimulation of the production of progesterone by the corpus luteum of the ewe by the perfusion of melatonin in vivo and by treatment of granulosa cells with melatonin in vitro. Research in Veterinary Science, 62:87–91. https://doi.org/10.1016/S0034-5288(97)90126-0.

Ebisawa T., Kajimura N., Uchiyama M., Katoh M., Sekimoto M., Watanabe T., Ozeki Y., Ikeda M., Jodoi T., Sugishita M., Iwase T., Kamei Y., Kim K., Shibui K., Kudo Y., Yamada N., Toyoshima R., Okawa M., Takahashi K., Yamauchi T. 1999. Alleic variants of human melatonin 1a receptor: function and prevalence in subjects with circadian rhythm sleep disorders. Biochemical and Biophysical Research Communications, 262(3):832–837. https://doi.org/10.1006/bbrc.1999.1308.

Flinn T., McCarthy N.L., Swinbourne A.M., Gatford K.L., Weaver A.C., McGrice H.A., Kelly J.M., Walker S.K., Kind K.L., Kleemann D.O., van Wettere W. H.E.J. 2020. Supplementing Merino ewes with melatonin during the last half of pregnancy improves tolerance of prolonged parturition and survival of second-born twin lambs. Journal of Animal Science, 98(12). https://doi.org/10.1093/jas/skaa372.

Forcada F., Zarazaga L., Abecia J.A. 1995. Effect of exogenous melatonin and plane of nutrition after weaning on estrous activin, endocrine status and ovulation rate in Salz ewes lambing in the seasonal anestrus. Theriogenology, 43(7):1179–1193. https://doi.org/10.1016/0093-691X(95)00090-U.

Forcada F., Abecia J.A., Casao A., Cebrián-Pérez J.A., Muiño-Blanco T., Palacín I. 2007. Effects of ageing and exogenous melatonin on pituitary responsiveness to GnRH in ewes during anestrus and the reproductive season. Theriogenology, 67(4):855–862. https://doi.org/10.1016/j.theriogenology.2006.11.002.

Foster D.I., Ebling F.J.P., Claypool L.E., Wood R.I. 1989. Photoperiodic timing of puberty in sheep. In Development of Circadian Rhythmicity and Photoperiodism in Mammals, SM Reppert, ed, 103-153.

Frungieri M.B., Calandra R.S., Rossi. 2017. Local Actions of Melatonin in Somatic Cells of the Testis. International Journal of Molecular Sciences. 18(6):1170. https://doi.org/10.3390/ijms18061170.

Galano A., Tan D.X., Reiter R.J. 2013. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. Journal of Pineal Research, 54(3):245–257. https://doi.org/10.1111/jpi.12010.

Gonzalez M., Hamilton T.D., Gallego M., Gaspar-Torrubia E., Aguilar D., Serrano-Blesa E., Abecia J.A., Pérez-Pé R., Muiño-Blanco T., Cebrián-Pérez J.A., Casao A. 2016. Evidence of melatonin synthesis in the ram reproductive tract. Andrology, 4(1):163–171. https://doi.org/10.1111/andr.12117.

Goodarzi A., Shahneh A.Z., Kohram H., Sadeghi M., Moazenizadeh M.H., Fouladi-Nashta A, Davachi N.D. 2018. Effect of melatonin supplementation in the long-term preservation of the sheep ovaries at different temperatures and subsequent in vitro embryo production. Theriogenology, 106:265–270. https://doi.org/10.1016/j.theriogenology.2017.10.009.

Haresign W., Peters A.R., Staples L.D. 1990. The effect of melatonin implants on breeding activity and litter size in commercial sheep flocks in the UK. Animal Science, 50(1):111–121. https://doi.org/10.1017/S0003356100004517.

Hardeland R. 2017. Melatonin – More than just a pineal hormone. Biomedical Journal of Scientific & Technical Research, 1(4). 10.26717/BJSTR.2017.01.000351.

Houghton D.C., Walker D.W., Young I.R., McMillen I.C. 1993. Melatonin and the light-dark cycle separately influence daily behavioral and hormonal rhythms in the pregnant ewe and sheep fetus. Endocrinology, 133(1):90-98. https://doi.org/10.1210/endo.133.1.8319592.

Houghton D.C., Young I.R., McMillen I.C. 1995. Evidence for hypothalamic control of the diurnal rhythms in prolactin and melatonin in the fetal sheep during late gestation. Endocrinology, 136(1):218-223. https://doi.org/10.1210/en.136.1.218.

Karsch F.J., Bittman E.L., Robinson J.E., Yellon S.M., Wayne N.L., Olster D.H., Kaynard A.H. 1986. Melatonin and photorefractoriness: loss of response to the melatonin signal leads to seasonal reproductive transitions in the ewe. Biology of Reproduction, 34(2):265–274. https://doi.org/10.1095/biolreprod34.2.265.

Kárpáti E., Gulyás L., Gáspárdy A. 2021a. Innovative possibilities for regulating melatonin levels in sheep reproduction. Literature review. (In Hungarian) In Press. Acta Agronomica Óváriensis

Kárpáti E., Gulyás L., Gáspárdy A. 2021b. Innovative possibilities for regulating melatonin levels in sheep reproduction. Poster. XXXVIII. Óvár Scientific Day "Innovation and Digitalisation", Mosonmagyaróvár, November 11, 2021. Posters from the Animal Science and Nutrition Section, Széchenyi István University, Faculty of Agriculture and Food Sciences, Abstract Volume, ISBN: 978-615-5837-94-4.

Kárpáti E., Gulyás L., Gáspárdy A. 2022. Various possibilities for regulating melatonin levels in sheep reproduction. Oral presentation. (In Hungarian). XXX. Hungarian Buiatrics Congress, March 20-23,2022. Eger

Kivela A. 1991. Serum melatonin during human pregnancy. Acta Endocrinologica, 124(3):233–237.

Kurutas E.B. 2016. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutrition Journal, 15(1):71. https://doi.org/10.1186/s12937-016-0186-5.

Liebich H.G. 2010. Funktionelle Histologie der Haussäugtiere und Vögel. 5. Auflage, Stuttgart: Schattauer GmbH. DOI: 10.1055/b-005-148994

Lemley C.O., Vonnahme K.A. 2017. Physiology and endocrinology symposium: alterations in uteroplacental hemodynamics during melatonin supplementation in sheep and cattle. J. Anim. Sci. 95(5):2211–2221. https://doi.org/10.2527/jas.2016.1151.

Lerner A.B., Case J.D., Takahashi Y. 1958. Isolation of melatonin, the pineal gland factor that lightens melanocytes. Journal of the American Chemical Society, 80(10):2587. https://doi.org/10.1021/ja01543a060.

López A., García J.A., Escames G., Venegas C., Ortiz F., López L.C., Acuña-Castroviejo D. 2009. Melatonin protects the mitochondria from oxidative damage reducing oxygen consumption, membrane potential, and superoxide anion production. Journal of Pineal Research, 46(2):188–198. https://doi.org/10.1111/j.1600-079X.2008.00647.x.

Loren P., Sánchez R., Arias M.E., Felmer R., Risopatrón J., Cheuquemán C. 2017. Melatonin scavenger properties against oxidative and nitrosative stress: impact on gamete handling and in vitro embryo production in humans and other mammals. International Journal of Molecular Sciences, 18(6):1119. https://doi.org/10.3390/ijms18061119.

Malpaux B., Viguié C., Skinner D.C. 1997. Control of the circannual rhythm of reproduction by melatonin in the ewe. Brain Research Bulletin, 44(4):431–438. https://doi.org/10.1016/S0361-9230(97)00223-2.

Malpaux B, Thiéry JC, Chemineau P. Melatonin and the seasonal control of reproduction. Reprod Nutr Dev. 1999 May-Jun;39(3):355-66. doi: 10.1051/rnd:19990308. PMID: 10420438.

Manca M.E., Manunta M.L., Spezzigu A., Torres-Rovira L., Gonzalez-Bulnes A., Pasciu V., Piu P., Leoni G.G., Succu S., Chesneau D., Naitana S., Berlinguer F. 2014. Melatonin deprival modifies follicular and corpus luteal growth dynamics in a sheep model. Reproduction, 147(6):885–895. https://doi.org/10.1530/REP-13-0405.

Martínez-Royo A., Lahoz B., Alabart J.L., Folch J., Calvo J.H. 2012. Characterisation of the melatonin receptor 1A (MTNR1A) gene in the Rasa Aragonesa sheep breed: association with reproductive seasonality. Animal Reproduction Science, 133(3-4):169–175. https://doi.org/10.1016/j.anireprosci.2012.06.018.

Mateescu R.G., Lunsford A.K., Thonney M.L. 2009. Association between melatonin receptor 1A gene polymorphism and reproductive performance in Dorset ewes. Journal of Animal Science, 87(8):2485–2488. https://doi.org/10.2527/jas.2008-1688.

McEvoy T.G., Robinson J.J., Aitken R.P., Robertson I.S. 1998. Melatonin treatment of embryo donor and recipient ewes during anestrus affects their endocrine status, but not ovulation rate, embryo survival or pregnancy. Theriogenology, 49(5):943–955. https://doi.org/10.1016/S0093-691X(98)00043-0.

Mitchell L.M., Dingwall W.S., Mylne M.J.A., Hunton J., Matthews K., Gebbie F.E., McCallum G.J., McEvoy T.G. 2002. Season affects characteristics of the pre-ovulatory LH surge and embryo viability in superovulated ewes. Animal Reproduction Science, 74(3-4):163–174. https://doi.org/10.1016/S0378-4320(02)00190-2.

Morgan P.J., Lawson W., Davidson G., Howell H.E. 1989. Guanine nucleotides regulate the affinity of melatonin receptors on the ovine pars tuberalis. Neuroendocrinology, 50:359–362. https://doi.org/10.1159/000125245.

Morgan P.J., Barrett P., Howell H.E., Helliwell R. 1994. Melatonin receptors: Localization, molecular pharmacology and physiological significance. Neurochemistry International, 24(2):101-146. https://doi.org/10.1016/0197-0186(94)90100-7.

Mokhtar D.M., Abd-Elhafeez H.H., Abou-Elmagd A., Hassan A.H. 2016. Melatonin administration induced reactivation in the seminal gland of the soay rams during non-breeding season: An ultrastructural and morphometrical study. Journal of Morphology, 277(2):231– 243. https://doi.org/10.1002/jmor.20491.

Nowak R., Young I.R., McMillen I.C. 1990. Emergence of the diurnal rhythm in plasma melatonin concentrations in newborn lambs delivered to intact or pinealectomized ewes. Journal of Endocrinology, 125(1):97-102. https://doi.org/10.1677/joe.0.1250097.

Palacín I., Forcada F., Abecia J.A. 2011. Meta-analysis of the efficacy of melatonin implants for improving reproductive performance in sheep. Spanish Journal of Agricultural Research 9(3):730–743. https://doi.org/10.5424/sjar/20110903-348-10.

Pelletier J., Bodin L., Hanocq E., Malpaux B., Teyssier J., Thimonier J., Chemineau P. 2000. Association between expression of reproductive seasonality and alleles of the gene for Mel(1a) receptor in the ewe. Biology of Reproduction, 62(4):1096–1101. https://doi.org/10.1095/biolreprod62.4.1096.

Perez-Pe R., Barrios B., Muino-Blanco T. 2001. Seasonal differences in ram seminal plasma revealed by partition in an aqueous two-phase system. Journal of Chromatography B: Biomedical Sciences and Applications, 760(1):113– 121. https://doi.org/10.1016/S0378-4347(01)00259-6.

Reiter R.J. 1992. The ageing pineal gland and its physiological consequences. BioEssays, 14(3):169–175. https://doi.org/10.1002/bies.950140307.

Rekik M., Taboubi R., Ben Salem I., Fehri Y., Sakly C., Lassoued N., Hilali M.E. 2015. Melatonin administration enhances the reproductive capacity of young rams under a southern Mediterranean environment. Animal Science Journal, 86(7):666-672. https://doi.org/10.1111/asj.12350.

Robinson J.E., Wayne N.L., Karsch F.J. 1985. Refractoriness to inhibitory daylength initiates the breeding season of the Suffolk ewe. Biology of Reproduction, 32(5):1024-1030. https://doi.org/10.1095/biolreprod32.5.1024.

Robertson N.J., Tan S., Groenendaal F., van Bel F., Juul S.E., Bennet L., Derrick M., Back S.A., Valdez R.C., Northington F., Gunn A.J., Mallard C. 2012. Which neuroprotective agents are ready for bench to bedside translation in the newborn infant? The Journal of Pediatrics, 160(4):e544-552. https://doi.org/10.1016/j.jpeds.2011.12.052.

Rodriguez C., Mayo J.C., Sainz R.M., Antolín I., Herrera F., Martín V., Reiter R.J. 2004. Regulation of antioxidant enzymes: a significant role for melatonin. Journal of Pineal Research, 36(1):1–9. https://doi.org/10.1046/j.1600-079X.2003.00092.x.

Rudas P., Frenyó V.L. 1995. Az állatorvosiélettanalapjai. Budapest: Springer HungaricaKiadóKft, Ortavant R., Pelletier J., Ravault J.P., Thimonier J., Volland-Nail P. 1985. Photoperiod: main proximal and distal factor of the circannual cycle of reproduction in farm mammals. Oxford Reviews of Reproductive Biology, 7:306–345.

Santiago-Moreno J., Toledano-Díaz A., Castaño C., Coloma M.A., Esteso M.C., Prieto M.T., Delgadillo J.A., López-Sebastián A. 2013. Photoperiod and melatonin treatments for controlling sperm parameters, testicular and accessory sex glands size in male Iberian ibex: A model for captive mountain ruminants. Animal Reproduction Science, 139(1-4):45– 52. https://doi.org/10.1016/j.anireprosci.2013.04.006.

Seron-Ferre M., Reynolds H., Mendez N.A., Mondaca M., Valenzuela F., Ebensperger R., Valenzuela G.J., Herrera E.A., Llanos A.J., Torres-Farfan C. 2015. Impact of maternal melatonin suppression on amount and functionality of brown adipose tissue (BAT) in the newborn sheep. Frontiers in Endocrinology, 6(5):232. https://doi.org/10.3389/fendo.2014.00232.

Smirnov A.N. 2001. Nuclear melatonin receptors. Biochemistry (Moscow), 66:19-26. https://doi.org/10.1023/A:1002821427018.

Stark R.I., Daniel S.S. 1989. Circadian rhythm of vasopressin levels in cerebrospinal fluid of the fetus: Effect of continuous light. Endocrinology, 124(6):3095-3101. https://doi.org/10.1210/endo-124-6-3095.

Succu S., Pasciu V., Manca M.E., Chelucci S., Torres-Rovira L., Leoni G.G., Zinellu A., Carru C., Naitana S., Berlinguer F. 2014. Dose-dependent effect of melatonin on postwarming development of vitrified ovine embryos. Theriogenology, 81(8):1058–1066. https://doi.org/10.1016/j.theriogenology.2014.01.032.

Talpur H.S., Chandio I.B., Brohi R.D., Worku T., Rehman Z., Bhattarai D., Ullah F., Jiajia L., Yang L. 2018. Research progress on the role of melatonin and its receptors in animal reproduction: A comprehensive review. Reproduction in Domestic Animals, 53(4):831-849. https://doi.org/10.1111/rda.13188.

Tamura H., Nakamura Y., Korkmaz A., Manchester L.C., Tan D.X., Sugino N., Reiter R.J. 2009. Melatonin and the ovary: physiological and pathophysiological implications. Fertility and Sterility, 92(1): 328–343. https://doi.org/10.1016/j.fertnstert.2008.05.016.

Tamura H., Takasaki A., Taketani T., Tanabe M., Kizuka F., Lee L., Tamura I., Maekawa R., Aasada H., Yamagata Y., Sugino N. 2012. The role of melatonin as an antioxidant in the follicle. Journal of Ovarian Research, 5:5–14. https://doi.org/10.1186/1757-2215-5-5.

Thakor A.S., Allison B.J., Niu Y., Botting K.J., Serón-Ferré M., Herrera E.A., Giussani D.A. 2015. Melatonin modulates the fetal cardiovascular defense response to acute hypoxia. Journal of Pineal Research, 59(1):80–90. https://doi.org/10.1111/jpi.12242.

Thwaites C.J. 1965. Photoperiodic control of breeding activity in the Southdown ewe with particular reference to the effects of an equatorial light regime. The Journal of Agricultural Science, 65(1):57-64. https://doi.org/10.1017/S0021859600085361.

Tian X., Wang F., Zhang L., He C., Ji P., Wang J., Zhang Z., Lv D., Abulizi W., Wang X., Lian Z., Liu G. 2017. Beneficial effects of melatonin on the in vitro maturation of sheep oocytes and its relation to melatonin receptors. International Journal of Molecular Sciences, 18(4):834–849. https://doi.org/10.3390/ijms18040834.

Torres F., González-Candia A., Montt C., Ebensperger G., Chubretovic M., Serón-Ferré M.V., Reyes R.J., Llanos A., Herrera E.A. 2015. Melatonin reduces oxidative stress and improves vascular function in pulmonary hypertensive newborn sheep. Journal of Pineal Research, 58(3):362–373. https://doi.org/10.1111/jpi.12222.

Tsiligianni T., Valasi I., Cseh S., Vainas E., Faigl V., Samartzi F., Papanikolaou T., Dovolou E., Amiridis G.S. 2009. Effects of melatonin treatment on follicular development and oocyte quality in Chios ewes – short communication. Acta Veterinaria Hungarica, 57(2):331–335. https://doi.org/10.1556/avet.57.2009.2.13.

Vázquez M.I., Forcada F., Casao A., Abecia J.A., Sosa C., Palacín I. 2010a. Undernutrition and exogenous melatonin can affect the in vitro developmental competence of ovine oocytes on a seasonal basis. Reproduction in Domestic Animals, 45(4):677–684. https://doi.org/10.1111/j.1439-0531.2008.01329.x.

Vázquez M.I., Abecia J.A., Forcada F., Casao A. 2010b. Effects of exogenous melatonin on in vivo embryo viability and oocyte competence of undernourished ewes after weaning during the seasonal anestrus. Theriogenology, 74(4):618–626. https://doi.org/10.1016/j.theriogenology.2010.03.007.

Vázquez M.I., Forcada F., Sosa C., Casao A., Sartore I., Fernández-Foren A., Meikle A., Abecia J.A. 2013. Effect of exogenous melatonin on embryo viability and uterine environment in undernourished ewes. Animal Reproduction Science, 141(1-2):52–61. https://doi.org/10.1016/j.anireprosci.2013.07.007.

Viguié C., Caraty A., Locatelli A., Malpaux B. 1995. Regulation of luteinizing hormone-releasing hormone (LHRH) secretion by melatoninin the ewe. I. Simultaneous delayed increase in LHRH and luteinizing hormone pulsatile secretion. Biology of Reproduction, 52(5):1114–1120. https://doi.org/10.1095/biolreprod52.5.1114.

Viguié C., Thibault J., Thiéry J.C., Tillet Y., Malpaux B. 1997. Characterization of the short day-induced decrease in median eminence tyrosine hydroxylase activity in the ewe: temporal relationship with the changes in LH and prolactin secretion and short day-like effect of melatonin. Endocrinology, 138(1):499–506. https://doi.org/10.1210/endo.138.1.4865.

Voiculescu S.E., Zygouropoulos N., Zahiu C.D., Zagrean A.M. 2014. Role of melatonin in embryo fetal development. Journal of Medicine and Life., 7(4): 488–492.

Vriend J., Reiter R.J. 2015. Melatonin feedback on clock genes: a theory involving the proteasome. Journal of Pineal Research, 58(1):1–11. https://doi.org/10.1111/jpi.12189.

Von Engelhardt W. 2009. Physiologie der Haustiere. 3., Vollständigüberarbeitete Auflage, Stuttgart: Enke Verlag. pp 736.

Wheaton J.E., Pohl H.A., Windels H.F. 1990. Effects of melatonin and progesterone administered to ewes in spring and summer. Journal of Animal Science, 68(4):923–930. https://doi.org/10.2527/1990.684923x.

Wodzicka-Tomaszewska M., Hutchinson J.D., Bennett J.W. 1967. Control of the annual rhythm of breeding in ewes: effect of an equatorial daylength with reversed thermal seasons. The Journal of Agricultural Science, 68(1):61-67. https://doi.org/10.1017/S002185960001786X.

Worthy K., Haresign W. 1983. Evidence that the onset of seasonal anoestrus in the ewe may be independent of increasing prolactin concentrations and daylength. Journal of Reproduction and Fertility, 69(1):41-48. https://doi.org/10.1530/jrf.0.0690041.

Worthy K., Haresign W., Dodson S., McLeod B.J., Foxcroft G.R., Haynes N.B. 1985. Evidence that the onset of the breeding season in the ewe may be independent of decreasing plasma prolactin concentrations. Journal of Reproduction and Fertility, 75(1):237-46. https://doi.org/10.1530/jrf.0.0750237.

Yellon S.M., Longo L.D. 1988. Effect of maternal pinealectomy and reverse photoperiod on the circadian melatonin rhythm in the sheep and fetus during the last trimester of pregnancy. Biology of Reproduction, 39(5):1093-1099. https://doi.org/10.1095/biolreprod39.5.1093.

Zhang H.M., Zhang Y. 2014. Melatonin: a well-documented antioxidant with conditional pro-oxidant actions. Journal of Pineal Research, 57(2):131–146. https://doi.org/10.1111/jpi.12162.

INOVATIVNE MOGUĆNOSTI U REGULACIJI NIVOA MELATOTINA KOD OVACA

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Kratak sadržaj

Pronalaskom melatonina 1958. godine, nove mogućnosti su se otvorile na polju reproduktivne biologije ovaca. Koncentracija melatonina prati dnevno-noćnu cikličnost, pri čemu su nivoi ovog hormona značajno veći tokom mraka. U ovom revijalnom preglednom radu autori ističu značaj melatonina, proteinskog hormona, sa posebnim osvrtom na njegovu ulogu u reproduktivnim procesima kod ovaca. Autori ukazuju na činjenicu da kod ovaca nivo melatonina pokazuje ritmičnu promenu, ne samo tokom dana, već i tokom cele sezone. Kod ovaca, kao životinja sa sezonalnom polnom aktivnošću i kao kod "kratkodnevnih životinja", sezonalni porast nivoa melatonina podstiče polnu aktivnost. Primena veštačkog melatonina stimuliše ekspresiju seksualne aktivnosti, povećava plodnost, broj novorođenih jagnjadi, mogućnost preživljavanja jagnjadi blizanaca. Nadalje, melatonin ima ulogu u zaštiti protiv cerebralne hipoksije, kao i tokom razvoja zapaljenjskih procesa kod fetusa i novorođenih jagnjadi.

Ključne reči: antioksidans, potpomognuta reproduktivna tehnologija, melatonin (endogeni, egzogeni), fotoperiod