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TO WHAT EXTENT DOES PHOTOPERIOD AFFECT CATTLE REPRODUCTION? CLINICAL PERSPECTIVES OF MELATONIN ADMINISTRATION – A REVIEW

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Abstract

The seasonality of reproduction in most mammals is dictated by photoperiod, temperature and nutrition. Melatonin, mainly synthesized in the pineal gland, is generally accepted as the active mediator of photoperiod responses including reproduction. While non-pregnant heifers and cows show continuous sexual activity and are therefore not seasonal breeders, it has been suggested that photoperiodicity may influence the appearance of puberty in heifers and the onset of parturition. Further, the light/dark ratio may influence endocrine patterns of gestation and a shorter light period correlates with the incidence of twin pregnancies. This review considers specific aspects of the effects of photoperiod and melatonin on reproduction in dairy cattle and discusses the clinical applications of melatonin.

Key words: dark-light cycles, heat stress, fertility, twin pregnancy, prolactin

The seasonality of reproduction in most animals may be affected by temperature, nutrition and photoperiod (Mohawk et al., 2012; Dardente et al., 2016). Melatonin (N-acetyl-5-methoxytryptamine) is a small lipophilic indoleamine mainly synthesized in the pineal gland from the essential amino acid tryptophan. It is generally accepted that melatonin is the active mediator of photoperiod responses including reproduction in mammals (Reiter, 1980, 1991). Although non-pregnant heifers and cows show continuous sexual activity and are not seasonal breeders, photoperiod responses in their reproduction are also dependent on the pineal gland. It has been suggested that photoperiodicity may influence the appearance of puberty in heifers (Peters et al., 1980; Hansen et al., 1983) and the onset of parturition (Evans and Hacker, 1989). In addition, the light/dark ratio plays a role in endocrine patterns of gestation (Garcia-Ispierto et al., 2009), and a shorter light period correlates negatively with the incidence of twin pregnancies (Andreu-Vázquez et al., 2012 a). With regard to fertility or the possibility of pregnancy, however, in temperate areas, heat stress remains a main factor impairing the reproductive performance of dairy cattle (De Rensis et al., 2015, 2017; Hansen, 2019; Wolfenson and Roth, 2019) and acts as a confounding factor in studies examining the impacts of day length-temperature interactions, making it particularly difficult to determine the specific effects of photoperiod on reproductive behaviour (Mercier and Salisbury, 1947 a, 1947 b). This article reviews the impacts of photoperiod and melatonin on reproduction in dairy cattle and discusses the possible clinical applications of melatonin administration.

The pineal gland

In cows, as in other mammals, light stimulates the retinal photoreceptors to transmit, via the hypothalamic suprachiasmatic nuclei (SCN), an inhibitory signal to the pineal gland (Mohawk et al., 2012). This means that daylight blocks melatonin synthesis while melatonin secretion rapidly increases at night giving rise to a nocturnal pattern of melatonin release by the pineal gland (Hedlund et al., 1977). The effect of this rhythmic daily pattern on reproduction has been well defined in many species (Reiter, 1991) with the exception of cattle.

René Descartes considered the pineal gland received information from the eyes and other sense organs and acted as a tap in the centre of the brain regulating the flow of vital fluids. This seventeenth century philosopher and mathematician was so fascinated with the pineal gland, he described it as the "principal seat of soul and the place in which all our thoughts are formed" (Lincoln, 1982). In mammals, the gland is ascribed a neuroendocrine role in regulating reproduction (Arendt, 1998). Melatonin is the most biologically active indoleamine synthesized in the pineal gland. Although melatonin is also produced in the rat retina (Cardinali and Rosner, 1971), gastrointestinal tract of bovine embryos (Bubenik, 2008), human lymphocytes (Carrillo-Vico et al., 2004) and in the reproductive system, in the human ovary (Itoh et al., 1999), pre-ovulatory follicular fluid (Nakamura et al., 2003) and placenta (Lanoix et al., 2008), in the rat oocyte (Sakaguchi et al., 2013) and in the bovine cumulus oocyte complexes (El-Raey et al., 2011), the pineal gland is the main producer. Once released to the bloodstream, it is rapidly metabolized with a half-life shorter than 10 minutes (Pevet et al., 2017). Early studies revealed that extracts of bovine pineal gland elicited skin lightening in tadpoles (McCord and Allen, 1917). Over the following 40 years, intense efforts were dedicated to identifying the active ingredient. While investigating the pineal gland as a way of lightening skin colour in people, Lerner et al. (1958, 1959) were able to isolate the active compound from the bovine pineal gland. As this molecule was related to serotonin and affected melanin pigmentation in tadpoles, Lerner termed the skin-lightening compound melatonin, which may be translated from the Greek as the "tonic of blackness". Soon it was shown that melatonin had no effect on melanophores, so its name is not particularly appropriate (Lincoln, 1982). Low plasma melatonin contents during the day and high levels during the night, initially linked to the regulation of seasonal reproduction in photoperiodic species (Reiter and Fraschini, 1969), was among the first biological rhythms to be characterized as a true circadian rhythm (Pevet et al., 2017; Korf, 2018). Indeed, it has been even considered one of the first biological signals appearing on Earth (Claustrat et al., 2005).

Physiological responses dictated by melatonin include reproduction, circadian homeostasis, sleep and immune-enhancing actions (Claustrat et al., 2005). Melatonin is also a powerful antioxidant and antiapoptotic agent (Hardeland et al., 2011; Nakamura et al., 2013), improving the viability of mammalian gametes and embryos, especially when used in artificial breeding programmes (Anwar et al., 2015). In seasonal breeders, melatonin regulates reproduction via its inhibitory action at various levels of the hypothalamic-pituitary-gonadal axis (Tamarkin et al., 1985; Malpaux et al., 1996). Particularly, daily changes in the duration of darkness under natural photoperiod conditions determines seasonal variations in reproductive capacity in photosensitive species (Reiter, 1980, 1991). In sheep, implants in the form of slow-release melatonin capsules induce the same effects on seasonal reproduction as photoperiod changes and have been extensively used to control reproduction in small ruminants (Abecia et al., 2008, 2012) and promote pregnancy in buffaloes during summer anoestrus (Kumar et al., 2016; Kavita et al., 2018). In humans, there are data to support the clinical value of exogenous melatonin in sleep disorders, cancer, depression, age-associated dysfunctions, neurodegenerative and cardiovascular diseases, immune function disorders and oxidative damage (Wetterberg, 1999; Pandi-Perumal et al., 2006; Hardeland et al., 2011; Anwar et al., 2015). In cattle, however, the benefits of melatonin treatment have yet to be established.

Day/night cycles and cattle fertility

In the mid-twentieth century, Mercier and Salisbury (1947 a, 1947 b) discovered that there was positive correlation between a long photoperiod, or day length, and cattle fertility in New York and Quebec. Cows of the Ayrshire, Holstein, and beef and dual-purpose Shorthorn breeds were included in these studies. Fertility was defined as the percentage of cows becoming pregnant prior to the fifth service. These authors suggested that the effect of light would be exaggerated because of the extreme length of summer days and shortness of winter days in their geographical area of study (latitudes over 45ºN). These observations were soon confirmed by Sweetman (1950) in Alaska. However, in studies performed at latitudes closer to the equator, the negative effects on fertility of high temperatures could be masking the possible benefits of longer days in hot environments. In temperate areas, highest fertility rates have been linked to a short-day length, or cool period of the year, when cows are not under heat stress conditions (Cavestany et al., 1985; Al-Katanani et al., 1999; López-Gatius, 2003; Garcia-Ispierto et al., 2007; Schuller et al., 2014). Therefore, there is a need for more meticulous studies designed to examine how interrelations between a hot environment and day length influence fertility in dairy cows. In effect, some studies have already allowed for the design of photoperiod management strategies aimed at improving milk production of dairy cows in temperate climates (Dahl et al., 2000, 2012; Dahl and Petitclerc, 2003).

Postpartum anoestrus is a transition period in which the functional hypothalamic-pituitary-ovarian-uterine axis recovers from the previous pregnancy (Crowe, 2008;

Forde et al., 2011). Day length and postpartum anoestrus were negatively correlated in old studies (reviewed by Hansen, 1985). However, irrespective of day length or season, delayed cyclicity postpartum can be prevented by ensuring a healthy peripartum period (Markusfeld et al., 1997; Labèrnia et al., 1998; Peter et al., 2009).

Puberty

Puberty normally commences at around 9–12 months of age in dairy heifers (Le Cozler et al., 2008). Dairy heifers exposed to long days reached puberty earlier than their herd mates experiencing short days (Peters et al., 1980; Hansen et al., 1983). However, the start of puberty is determined by the nutritional status of calves during the prepubertal period and seems more related to body weight than age or photoperiod (Le Cozler et al., 2008). Accordingly, not only photoperiod, but also factors such as nutritional and social status, and environmental temperature may influence the onset of puberty and the subsequent reproductive performance of dairy heifers.

Pregnancy

Pregnancy in mammals is the result of evolutionary changes during millions of years which led to the development of a new organ, the placenta. For a successful pregnancy there has to be coordination among the endocrine system – mainly via the hormones of the pituitary – ovary and placenta. From the start of its formation in ruminants, the placenta adopts the role of an endocrine organ, producing a series of glycoproteins associated with pregnancy (PAGs) that coexist in the cow trophectoderm throughout the gestation period (Garbayo et al., 2008; Wallace et al., 2015). Circulating concentrations of these proteins have been used as a marker of pregnancy status (Zoli et al., 1992; López-Gatius et al., 2007). In studies examining the association between photoperiod and endocrine patterns of gestation, high plasma prolactin concentrations were significantly related to high plasma PAG levels and with a positive photoperiod (increasing day length) throughout gestation (Garcia-Ispierto et al., 2009). In the latter study, a positive photoperiod was found to significantly increase plasma prolactin levels while lactation number, days in milk and milk production had no effect.

Prolactin has been clearly linked to mammary gland growth (Svennersten--Sjaunja and Olsson, 2005) and long days increase circulating levels of prolactin, including the peripartum surge of this hormone (Newbold et al., 1991). However, not less important are the functions of prolactin related to its role in regulating immune system actions (Kooijman et al., 1996; Brand et al., 2004) and thus its role in favouring the gestation period. In fact, photoperiod may influence immunocompetence (Bilbo et al., 2002; Prendergast et al., 2002). The uterine mucosa must tolerate the presence of the semi-allogeneic conceptus in a way that does not compromise the immune uterine response against infectious agents (Raghupathy, 1997; Druckman and Druckman, 2005). A main question that arises is the manner in which pregnancy status, from increasing to decreasing day length, is influenced by a dramatic change in circulating prolactin levels from increasing to declining production. In effect, six types of relationships between photoperiod and plasma prolactin concentrations have been observed throughout gestation: (1 and 2) increasing or decreasing prolactin levels in parallel with increasing or decreasing photoperiod, respectively; (3 and 4) increasing and decreasing prolactin levels in cows in their first half of gestation during the positive photoperiod and second half during the negative photoperiod, respectively; and (5 and 6) decreasing and increasing prolactin levels in cows in their first half of gestation during the negative photoperiod and second half during the positive photoperiod, respectively (Garcia-Ispierto et al., 2009).

From an evolutionary perspective, however, the very high incidence of twin pregnancies during the negative photoperiod (Andreu-Vázquez et al., 2012 a) is probably a remarkable persisting adaptive feature of dairy cattle. Although the birth of twins is welcome for the economy of beef cattle breeding (Echternkamp et al., 2004; Hashiyada, 2017) and was effectively a cultural symbol for early concepts of human fertility (López-Gatius and Hunter, 2018 a), twins are not desirable in dairy cattle. Cows delivering twins have a shorter productive lifespan than cows delivering singletons (Andreu-Vázquez et al., 2012 b). Irrespective of heat stress or season, in a study population of 2015 pregnant cows in which twin pregnancy was recorded in 361 cows, based on the odds ratio, the risk of twin pregnancy was increased by a factor of 1.41 ($P = 0.01$) when artificial insemination was performed during the decreasing photoperiod (Andreu-Vázquez et al., 2012 a). In contrast, the risk of twin pregnancy was reduced by factors of 0.65 or 0.71 when AI was performed during the warm season or an increasing photoperiod. In this study, insemination dates were used to analyse the effect of the photoperiod (increasing day length, December 21: sunrise at 8:20 h and sunset at 17:29 h, to June 20, vs. decreasing day length, June 21: sunrise at 5:23 h and sunset at 20:35 h, to December 20) on the occurrence of twin pregnancies. In commercial dairy herds under our surveillance, results are similar and the twin pregnancy rate greatly increases just as the negative photoperiod starts (unpublished data). This could reflect adaptive features increasing the chances of bearing twins when there is more food available in spring, similarly to seasonal reproduction in photoperiodic species.

Parturition

During pregnancy, there is interplay between the foetal and maternal endocrine systems for both the maintenance of gestation and the process of parturition. The foetal genotype and maturation of the foetal pituitary-adrenal-placental axis determine the day of parturition, but the precise hour of birth may be dictated by the mother (Liggins, 1982). This maternal ability is likely the result of selective survival advantages during evolution for both the mother and newborn to initiate the time of parturition at night, when predation pressures are greatly reduced. However, circadian rhythms of the mother in programming when parturition begins are very different among species. For example, most foals are born at night (Rossdale and Short, 1967) whilst rats prefer daylight hours (Lincoln and Porter, 1976) even when the photoperiod is shifted artificially in both species (Mitchell and Yochim, 1970; Bosc et al., 1988). A much less pronounced circadian timing of parturition has been observed in women, pigs, sheep, mice and Chinese hamsters (Liggins, 1982). In cattle, parturition times seem uniformly spread over the 24-hour period (Bazer and First, 1983; Makarechian, 1984). However, several experiments have led to the grouping of parturitions over the hours of day light. Accordingly, Evans and Hacker (1989) reported a photosensitive stage of dairy cows between 13 and 15 hours after subjective dawn. All cows kept under conditions of artificial lighting during the photosensitive period showed an additional eating peak during this extra lighted period and calved the next day during normal working hours (13:15 ± 1.5 hours). Similarly, dairy cattle fed during the late afternoon calved in a non-random pattern and 56% parturitions occurred from 06:01 to 18:00 hours (Stevenson, 1989). In contrast, in beef cows a late evening feed delayed the start of parturition until the following day (Lowman et al., 1981; Yarney et al., 1982; Aoki et al., 2006). Thus, it seems that cows prioritize eating over calving and that photoperiod does not affect circadian timing of parturition in cattle.

Clinical applications of melatonin in cattle

The effects of melatonin treatment on day 220 of gestation on subsequent reproductive performance and milk production were explored in dairy heifers (n = 25) and cows (n = 114) kept under heat stress conditions during the longest days (long photoperiod) of the year (May-August) (García-Ispierto et al., 2013). Melatonin treatment given as subcutaneous slow release implants (9 to heifers or 12 to cows) containing 18 mg melatonin each (Melovine®, CEVA Salud Animal, Barcelona) reduced the postpartum-pregnancy interval by 20 days, the number of artificial inseminations per pregnancy and there was a 5.2 times lower risk of pregnancy loss (first trimester) than in control animals. In this experiment, plasma melatonin levels were significantly increased for at least 49 days and with an estimated half-life of 116 days. Probably the long half-life of this dose could explain the positive and long-term effects of melatonin treatment, even reducing the risk of pregnancy loss in the subsequent pregnancy. Prolonged light conditions at treatment should favour effects of exogenous melatonin in already deficient melatonin animals. The antioxidant and antiapoptotic actions of exogenous melatonin could favour placental function during the end of gestation (Milczarek et al., 2010; Lanoix et al., 2013) along with subsequent ovarian function and oocyte viability (Woo et al., 2001). In essence, exogenous melatonin may improve bovine oocyte maturation and embryo development (El-Raey et al., 2011; Tamura et al., 2013; Marques et al., 2018; Cavallari de Castro et al., 2019) and is highly effective in reducing oxidative stress throughout the body (Maldonado et al., 2007; Tamura et al., 2013).

As noted above, the photoperiod and circulating prolactin show a consistent relationship in the cow (Garcia-Ispierto et al., 2009). Accordingly, when the animals were treated with melatonin during the longer days, plasma prolactin levels were expectedly high and decreased significantly after melatonin treatment and recovered during the postpartum compared to control cows. No significant effects on milk production were observed in the subsequent lactation (García-Ispierto et al., 2013). Melatonin treatment at the same early dry-off time during summer or winter did not modify milk production during the subsequent lactation (Morini et al., 2018). Since melatonin treatment reduces circulating prolactin concentrations (Auldist et al., 2007; García-Ispierto et al., 2013; Lacasse et al., 2014), it is likely that the optimal time to treat dairy cows is when this treatment does not affect their milk production, that is, the dry-off period (García-Ispierto et al., 2013; Morini et al., 2018).

Evidence exists that melatonin enhances *in vitro* oocyte maturation (El-Raey et al., 2011; Cavallari de Castro et al., 2019) and embryo survival (Papis et al., 2007; Takada et al., 2012; Wang et al., 2014; Marques et al., 2018). The fertility of *in vitro* produced (IVP) embryos used in embryo transfer programmes is lower than for *in vivo* derived (IVD) embryos (Sartori et al., 2016). A pregnancy rate equal to or greater than that obtained by natural mating or the best AI programme may be achieved with IVD embryos (Ott, 2019). However, the worldwide use of bovine IVP embryos has increased during the past two decades, surpassing in 2016, for the first time, the number of transferrable IVD embryos (December IETS Newsletter, 2018). The main reason could be the increasing benefits and lower costs of generating IVP embryos. The use of IVP embryos could be an alternative to insemination, especially in older cows (López-Gatius and Hunter, 2019). Cows in their third or more lactation are less fertile and carry a greater risk of twin pregnancy (López-Gatius et al., 2017). The transfer of a single developing blastocyst may eliminate the risk of a twin pregnancy. Further, this procedure should improve fertility under heat stress conditions. Oocytes are highly sensitive to hyperthermia and heat-induced alterations at early stages of follicular development can be expressed later, such that fertility is low in autumn, when cows are not under heat stress (reviewed by Roth, 2017; Hansen, 2019). This scenario should promote the use of melatonin to improve the quality of IVP embryos.

Concluding remarks

In temperate areas, there is marked seasonal variation in feed availability, temperature, humidity and photoperiod. However, while some species of the family Bovidae have adapted to seasonal changes, reproductive patterns in *Bos taurus* species probably do not respond to seasonal components of the environment. Heat stress remains a major factor impairing fertility and possibly masks photoperiod-associated effects on reproduction. It is clear that photoperiod management may increase milk production and improve dairy cattle health in temperate regions (Dahl et al., 2000, 2012; Dahl and Petitclerc, 2003). This success is due, at least in part, to the possibility of isolating the effects of temperature and photoperiod on milk production and composition (Aharoni et al., 2000; Barash et al., 2001). Hence, future studies will help producers maximize the beneficial effects of photoperiod management on reproduction.

The increased twin pregnancy rate produced when day length shortens (Andreu--Vázquez et al., 2012 a) probably remains as the only remarkable adaptive feature of dairy cattle. More extensive studies targeted at separating temperature and day length effects should confirm this finding. Efforts should focus on reducing, or better still preventing, twin pregnancies, especially during the negative photoperiod. For example, one such measure involves ultrasound-guided puncture and drainage (with no suction) of the smaller pre-ovulatory follicle at timed AI in cows with a pre-ovulatory follicle in each ovary, and seems to prevent twin pregnancy without reducing fertility (López-Gatius and Hunter, 2018 b; López-Gatius et al., 2019).

The benefits of treatment with slow melatonin-releasing capsules at early dry-off need to be assessed in more extensive studies and throughout the year. Treatment under heat stress conditions approximately 60 days before parturition improved reproductive performance and had no effects on subsequent milk production. In contrast, melatonin treatment at early lactation may prolong postpartum anoestrus (Sharpe et al., 1986). The use of melatonin in *in vitro* procedures could improve the quality of embryos. In addition, melatonin used to improve oocyte quality has been related to an increased pregnancy rate in women undergoing IVF cycles (Batıoglu et al., 2012).

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