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The role of photoperiod and melatonin in the control of seasonal reproduction in mammals

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ABSTRACT

Melatonin secreted by pineal cells is a hormone whose biosynthesis is coordinated by neurons of the master clock located in the hypothalamic suprachiasmatic nuclei (SCN), characterized by the generation of a 24-hour rhythm. In many species of mammals, fluctuations in melatonin secretion affect reproductive functions, e.g. by regulating the frequency and amount of pulsatile secretion of hypothalamic and gonadotropic hormones. Seasonal breeding is a common adaptive strategy among mammals, allowing them to reproduce during the periods of the year that are most favourable for the later survival and growth of the offspring. This type of reproduction is characteristic of sheep, with winter reproductive activity, and hamsters, with summer reproductive activity. In these animals, melatonin synthesis is largely regulated by the photoperiod, which indirectly influences the period of reproductive activity or passivity. The aim of this study was to gather available knowledge on melatonin as a key element controlling seasonal reproduction. The paper presents the general shape of the circadian rhythm and the neuroendocrine mechanism regulating animal reproduction depending on the variable photoperiod. The collected results suggest that melatonin, kisspeptins, gonadotropin-releasing hormone (GnRH), sex hormones and thyroid hormones participate in the regulation of seasonal reproduction in mammals.

KEY WORDS: melatonin, photoperiod, seasonal reproduction, sheep, hamster

INTRODUCTION

The pineal gland has always attracted the attention of those seeking a better understanding of the nature of the human body. This interest has been aroused in part by the fact that it is the only unpaired organ present in the brain, as all other areas of the brain have right and left counterparts. Due to its

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unique location deep in the central part of the brain, it remained something of an anatomical curiosity for almost two millennia (Klein 2006; Santoro et al., 2009; Lopez-Munoz et al., 2011; Lopez-Munoz et al., 2012: Berhouma 2013). It was only in the second half of the 20th century that progress was made in understanding the physiological role of the pineal gland. Before that time, many scientists did not attach much importance to it, claiming that it did not play an important functional role in the body. It was treated as a relic of the evolution process – the brain's equivalent of the appendix (Lopez-Munoz et al., 2011; Halberg et al., 2001; Lopez-Munoz et al., 2012; Berhouma 2013).

A breakthrough in explaining the importance of the pineal gland came in 1958, when Lerner and his colleagues isolated melatonin, the hormone secreted by this gland (Lerner et al., 1958). This discovery led to the conclusion that the pineal gland is an endocrine organ (Lerner et al., 1958; Santoro et al., 2009; Patel et al., 2020). Melatonin, secreted by pineal gland cells – pinealocytes, is a small and highly lipophilic molecule that quickly diffuses through membranes and into the bloodstream (Amaral and Cipolla-Neto 2018; Cipolla-Neto and Amaral 2018; Patel et al., 2020). It is synthesized from tryptophan in a multi-step process in which one of the intermediates is serotonin. The stages of melatonin biosynthesis are now well known, and the enzymes catalysing them are known as well. One of the best described enzymes is aralkylamine-N-acetyltransferase (AANAT) (Sapède and Cau 2013; Falcon et al., 2014; Patel et al., 2020). The most important element coordinating melatonin biosynthesis is the neurons of the master clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, which generate a 24-hour rhythm. This is the basis for the nocturnal pattern of melatonin production and secretion (Sapède and Cau 2013; Falcon et al., 2014; Vasantha 2016), which is high at night and low during the day. The pineal gland, through its ability to synthesize melatonin, plays the role of a functional neuroendocrine messenger. It takes part in the conversion of the visual (light) signal into a hormonal signal, which is received by tissues containing specific melatonin receptors, e.g. in the pituitary gland. In many mammalian species, fluctuations in melatonin secretion affect reproductive function. Melatonin regulates the frequency and amount of pulsatile secretion of hypothalamic hormones and pituitary gonadotropic hormones regulating reproduction (Ebling 2010; Dardente 2012; Klein 2015; Dardente et al., 2016; Helfer et al., 2019).

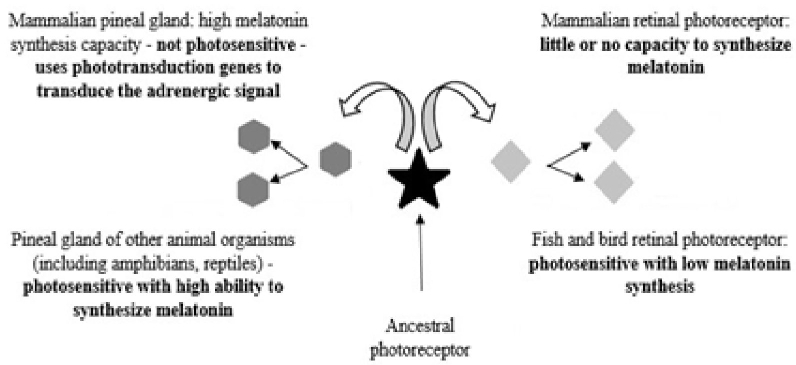

Fig. 1. The evolution of photoreceptor cells and pinealocytes in animals. Adapted from Klein 2015.

Evolutionary aspects

The prevailing view on the evolution of the pineal gland is that it evolved from a primitive photodetector that was also the ancestor of retinal photoreceptors, about 500 million years ago in the Cambrian period (Klein 2006; Halberg et al., 2001; Falcon et al., 2014). This theory is based on the anatomical, biochemical and functional similarity of the two types of cells (Halberg et al., 2001; Falcon et al., 2014). This was followed by independent evolution of photodetector pinealocytes and retinal photodetectors. In mammals, the pineal gland lost its photodetection ability but gained the ability to synthesize melatonin at night (Oksche 1965; Sapède and Cau 2013). Melatonin has thus become the ‘hormone of darkness’, whose increase is synonymous with the onset of night. The outline of the evolutionary process is presented in fig. 1 (Klein 2015).

Neuroendocrine regulation of seasonal reproduction

Melatonin, whose secretion is regulated by a photoperiod in animals with seasonal breeding, coordinates production of thyroid-stimulating hormone (TSH) in the pars tuberalis (PT) of the pituitary (Yoshimura 2010; 2013). Studies on sheep have shown that this process is controlled by the local clock and the following transcription factors: TEF (thyrotroph embryonic factor), SIX1 (SIX homeobox 1), and EYA3 (eyes absent homolog 3) (Dardente et al., 2016). Thyrotropin, produced by the cells of the pars tuberalis, undergoes specific glycosylation, which prevents it from acting on the thyroid. It exerts a paracrine effect by binding to receptors in the lining cells (tanycytes) in the mediobasal hypothalamus (MBH) (Dardente 2012; Helfer et al., 2019). During the long summer days, elevated TSH levels increase the expression of type II iodothyronine deiodinase (DIO2) in the tanycytes via the cAMP (cyclic adenosine monophosphate)/P-CREB (cAMP response element-binding protein) pathway and the mitogen-activated kinase pathway. At the same time, transcription of type III iodothyronine deiodinase (DIO3) is inhibited; however, the mechanisms by which TSH affects the expression of DIO3 remain unclear. DIO2 converts the less active thyroxine (T4) to active triiodothyronine (T3), while DIO3 degrades both T4 and T3 to inactive metabolites. This leads to a transient increase in MBH T3 levels during the lengthening days. Shortening of the length of the day leads to the opposite response, i.e. a decrease in the level of T3 (Sáenz de Miera et al., 2013). The molecular mechanisms of further processes are not fully understood, but the genes encoding the neuropeptides RFRP3 (RF-amide-related peptide-3) and kisspeptin (KISS1) seem to be the key target genes for T3 in the hypothalamus (Dardente 2012; Sáenz de Miera et al., 2013; Weems et al., 2015; Dardente et al., 2016; Vasantha 2016). Kisspeptin is believed to play a central role in the activation and deactivation of the hypothalamic-pituitary-gonadal axis, as a potent stimulant of GnRH secretion (Lehman et al., 2020). In hamsters and sheep, the *KISS1* gene shows higher expression during the breeding period compared to the rest of the year (Moore et al., 2019). RFRP3 is a neuropeptide that exerts a negative or positive effect on GnRH, depending on the species, sex, and experimental conditions. Expression of RFRP3 has been shown to be highest during long photoperiods in both hamsters and sheep. In summary, the seasonal changes in KISS1 and RFRP3 expression are due to melatonin-regulated, seasonal changes in T3 secretion. Thus, the presented mechanism combines the action of melatonin and thyroid hormones in the control of reproductive functions by the photoperiod. Changes in the concentrations of thyroid hormones also have a direct effect on the plasticity of the central nervous system. Other factors, such as social interactions, nutritional parameters, or stress, also influence the hypothalamic-pituitary-gonadal axis, by directly affecting T3 secretion or controlling KISS1 and RFRP3 expression. A diagram illustrating how exogenous signals affect the neuroendocrine mechanisms regulating seasonal reproduction in sheep is presented in fig. 2 (Dardente 2012; Dardente et al., 2016; Vasantha 2016; Moore et al., 2019).

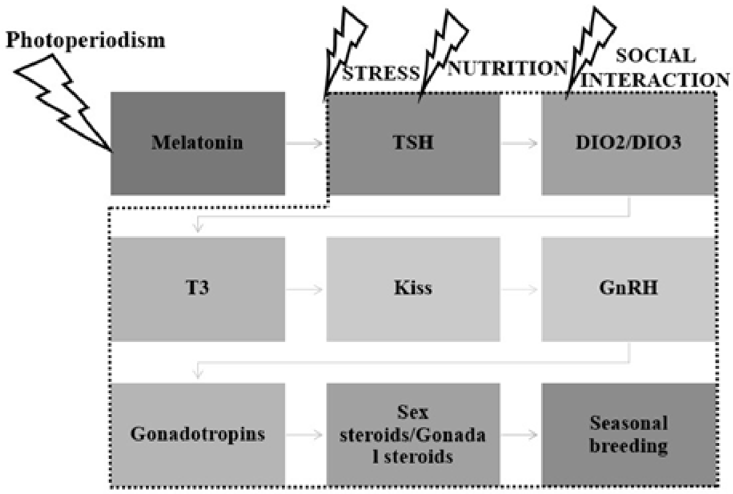

Fig. 2. Factors of the neuroendocrine mechanism of regulation of the seasonality of reproduction in mammals. Adapted from Dardente et al., 2016.

Species with seasonal breeding

Most temperate animal species undergo physiological adaptation to seasonal environmental changes by responding to changes in day length throughout the year. This phenomenon, called photoperiodism, is the basis for the alternation of the reproductive season with periods of inactivity or reduced gonadal function (Yoshimura 2010; 2013; Dardente 2012). In mammals, due to varying lengths of gestation, individual species exhibit reproductive activity at different times of the year. This effect can be simulated in the laboratory by manipulating the length of the photoperiod. Depending on how the photoperiod affects reproductive functions, species of long-day and short-day breeders are distinguished (Reiter 1975; Ebling 2010; Sáenz de Miera et al., 2013; Dardente 2012; Weems et al., 2015; Dardente et al., 2016; Vasantha 2016; Amaral and Cipolla-Neto 2018; Helfer et al., 2019). Sheep and hamsters are two experimental models that have contributed to a better understanding of endogenous rhythms, which are the basic mechanisms governing seasonal reproduction.

Long-day breeders

Long-day breeders reproduce in spring and summer (seasons with a long photoperiod). This type of reproductive activity is characteristic of the majority of wild rodents, including hamsters and bank voles (Reiter 1975; Dardente 2012; Sáenz de Miera et al., 2013; Weems et al., 2015; Vasantha 2016). During the long day, the pineal gland becomes less active, leading to a significant decrease in secretion of melatonin, which has an antigonadotropic effect in these animals (Dardente 2012). Thus, when the prolonged photoperiod eliminates the suppressive effect of melatonin on the hypothalamus, gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and gonadotropins are released from the pituitary gland, activating reproductive processes. Thus long-day animals are fertile in spring and summer and do not exhibit breeding activity in autumn and winter. This pattern of reproductive activity is likely due to an evolutionary adaptation that promotes the reproduction of species with short gestation at a time when environmental conditions are favourable (Dardente 2012; Weems et al., 2015; Dardente et al., 2016; Vasantha 2016).

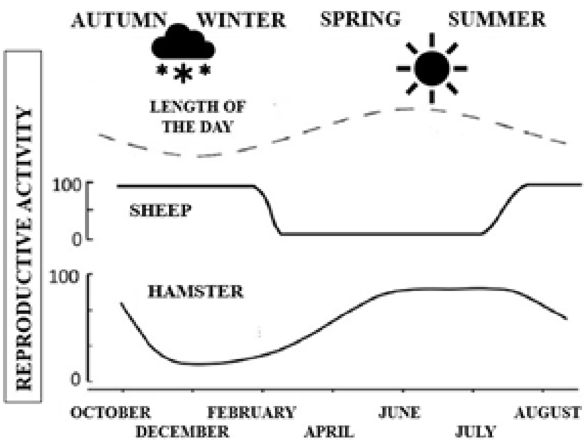

Fig. 3. Comparison of seasonal patterns of reproductive activity in sheep (winter breeding animals) and hamsters (summer breeding animals). Adapted from Weems et al., 2015.

Short-day breeders

Another type is the short-day breeders, which reproduce in autumn and winter (when the day is short). Examples include sheep and goats (Dardente 2012; Sáenz de Miera et al., 2013; Weems et al., 2015; Vasantha 2016). A longer period of darkness increases melatonin secretion, which in turn stimulates pulsatile GnRH secretion in these animals. This results in secretion of the gonadotropic hormones of the pituitary gland, which initiate the reproductive process. In short day breeders, melatonin therefore has a progonadotropic effect (Dardente 2012). Sheep have relatively long gestation periods; they have ovulatory cycles in the autumn and winter, and the young are born in spring, when environmental conditions are favourable for survival (Walton et al., 2011; Abecia et a., 2007) As in other mammals, sheep GnRH neurons do not express oestrogen receptor alpha (ERα), while expression of oestrogen receptor beta (ERβ) is observed in nearly 50% of sheep. In Suffolk sheep, seasonal reproductive changes have been observed to be associated with changes in GnRH secretion and negative oestradiol feedback (Xiong et al., 1997; Skinner and Dufourny 2005; Walton et al., 2011). More precisely, they are a direct result of changes in the ability of oestradiol, most likely acting through ERβ receptors, to suppress GnRH and LH secretion during anoestrus (Goodman et al., 2000; Weems et al., 2015).

It has also been demonstrated that during the breeding season, GnRH neurons in sheep are stimulated more than twice as much as in sheep that are not breeding (Xiong et al., 1997; Walton et al., 2011). This means that as the mating season progresses, sheep become photo-resistant, so that the short days lose their stimulating effect and mating behaviour ceases. Exposure to long days in summer is not necessary to restore sensitivity to short days, suggesting a cyclic photosensitivity underlying the reproductive cycle of seasonal breeders. Changes in reproductive activity controlled by changes in day length during the year are shown in fig. 3 (Weems et al., 2015; Dardente et al., 2016; Vasantha 2016). The evidence supporting the hypothesis regarding reproductive control by variable photoperiod in humans is inconsistent, in contrast with factors such as food availability, cultural differences or climate change, where a correlation with these factors has been shown in human reproduction (Wehr 2001; Bronson 2004; Bronson 2009).

CONCLUSION

The reproduction of animals sensitive to photoperiod changes is controlled by the integrated effects of the circadian rhythm and the neuroendocrine mechanism involving melatonin. A deeper understanding of the molecular and neuroendocrine mechanisms underlying the seasonality of breeding has led to the successful use of melatonin as a pharmacological agent to advance the sheep breeding season and regulate oestrus cycles, resulting in an increase in the total number of lambs obtained during the year. In a broader context, the ability to control breeding, especially of livestock, may find practical application in developing new strategies in animal husbandry.

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Rola fotoperiodu i melatoniny w kontroli rozrodu sezonowego ssaków

Streszczenie

Melatonina wydzielana przez komórki szyszynki jest hormonem, którego biosynteza jest koordynowana przez neurony nadrzędnego zegara biologicznego zlokalizowane w jądrach nadskrzyżowaniowych podwzgórza (SCN), których cechą charakterystyczną jest generowanie 24-godzinnego rytmu. U wielu gatunków ssaków fluktuacje wydzielania melatoniny wpływają na funkcje rozrodcze m.in. poprzez regulacje częstotliwości i wielkości pulsacyjnego wydzielania hormonów podwzgórzowych i gonadotropowych. Rozmnażanie sezonowe jest powszechną strategią adaptacyjną wśród ssaków, która pozwala na rozmnażanie w okresach roku, w których jest to najbardziej korzystne dla późniejszego przeżycia i wzrostu potomstwa. Tego typu rozród charakterystyczny jest u owiec, zwierzą o zimowej aktywności rozrodczej i chomików o letniej aktywności rozrodczej. U tych zwierząt synteza melatoniny regulowana jest w duże mierze przez fotoperiod, który pośrednio wpływa na okres aktywności lub bierności rozrodczej. Celem niniejszej pracy było zebranie dostępnej wiedzy dotyczącej melatoniny jako kluczowego elementu kontrolującego rozród o charakterze sezonowym. W pracy przedstawiono ogólny kształt rytmu okołodobowego oraz neuroendokrynnego mechanizmu regulujące rozrodczość zwierząt w zależności od zmiennego fotoperiodu. Zebrane wyniki sugerują udział melatoniny, Kisspeptyn, gonadoliberyny (GnRH), hormonów płciowych a także hormonów tarczycy w regulowaniu sezonowego rozmnażania u ssaków.

SŁOWA KLUCZOWE: melatonina, fotoperiod, rozród sezonowy, owce, chomiki