Review

Melatonin and brown adipose tissue: novel insights to a complex interplay

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ABSTRACT

As a chronobiotic molecule, melatonin finely tunes a variety of physiological processes including energy metabolism, reproduction and sleep-wake cycle, collaborating for the survival of the organisms. Since its pineal production occurs exclusively during the night, melatonin is responsible for signaling the circadian and circannual cycles to the organisms. This involves different ways of action that need to be considered when analyzing its effects in a given tissue/organism. Non-shivering thermogenesis (NST) is a crucial process for homeothermic animals and increasing pieces of evidence show its importance for the energy metabolic balance due to its influence in body weight control. The highly seasonal brown adipose tissue (BAT) is the site for NST and its metabolism is importantly influenced by melatonin. This review focuses on melatonin actions over BAT and the attention should be given to the relation between this signaling molecule and such a seasonally expressed tissue.

Key Words: melatonin, brown adipose tissue, rhythm, energy metabolism, non-shivering thermogenesis, UCP-1, seasonality.

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1. INTRODUCTION

Melatonin's importance and actions in the organisms have been extensively studied and reviewed over the past 60 years. Its chronobiological function, however, is not always seen with the importance it deserves. Melatonin interaction with brown adipose tissue (BAT) has also been described and the studies relating BAT metabolism to the photoperiod showed a clear seasonal influence over this tissue (1, 18, 28). The uses of photoperiod manipulation and melatonin administration are currently adopted in many studies involving BAT activation and recruitment. In spite of this, the rhythmicity involving BAT physiology is usually set aside. The purpose of this review is to shed light on melatonin actions in BAT, considering the chronobiotic actions that this hormone may exert in this tissue. Thus, a view that also considers rhythmicity is necessary for the complete comprehension of BAT functioning throughout the day and over the seasons, bringing a new understanding of the actual picture.

2. MELATONIN: THE TIME KEEPER

Characterized as an indolamine, melatonin has been the focus of several studies since it was identified in 1958 (2). It is a hormone produced by the pineal gland exclusively during the night and in the absence of light (3). The internal clock, located in the suprachiasmatic nuclei (SCN), is responsible for the temporization of pineal melatonin production (4). This unique synthesis guarantees melatonin's action as a chronobiotic molecule, signaling the circadian and circannual cycles to the organism (5).

The importance of this hormone is more complex than it seems. A recent review introduced new concepts on how melatonin interacts with the metabolism, pointing out its immediate and prospective effects (6). Basically, the immediate effects can be noticed at the time melatonin is present in the bloodstream and cerebrospinal fluid. In other words, they can be seen during melatonin release at night, such as its role as a potent antioxidant (7, 8), its hypotensive effects (9) and the central temperature nocturnal decrease (10). The prospective effects, in turn, are triggered during the night but are only perceived in the next day, when low level of melatonin is present in the biological fluids. This means they occur due to a previous melatonin preparation of the cells. In summary, these effects are mediated by melatonin interference in the cGMP signaling and clock genes expression. Therefore, both immediate and prospective effects are important for the daily and seasonal regulation of the organisms (6).

The daily rhythm refers to the circadian cycle, which means that the organisms present different behaviors and physiological processes over the 24 hours (h). Good examples involving 24 h cycles that are directly or indirectly influenced by melatonin are the sleep/wake cycle (11, 12), the nocturnal decrease of central temperature (10), the cortisol rhythm (13), and the insulin secretion and glucose metabolism (14).

The circannual cycle refers to the seasonal changing over the year, when melatonin signals the passage of the seasons according to the duration of the night. As the winter approaches the nights become longer, with prolonged melatonin production until the winter solstice. In contrast, as the summer approaches and the nights become shorter, melatonin production is shortened until the summer solstice (5). This is an important signal to the organisms to prepare their metabolism to the extreme conditions during the winter, since it is necessary to conserve energy during the food shortage. On the other hand, food availability is more abundant over the summer, which facilitates other functionalities of the organism. The regression of the gonads is a good example of melatonin seasonal effect, which happens when winter comes (15) in long photoperiod reproductive species. Melatonin administration can also promote gonadal regression even in 12:12 h light/dark exposed animals (16), as it can mimic the effects of short photoperiod exposure (5). Besides, melatonin absence prevents this seasonal change (17).

Another important seasonal signal triggered by melatonin production over the year is BAT activation, which promotes the animal preparation for surviving the winter cold exposure (18).

3. BROWN ADIPOSE TISSUE OVERVIEW

Brown adipose tissue was first described in some mammals near 1551 by K. Gessner and located in many anatomical and strategic regions of the organism (Reviewed by 19). This tissue presents a considerable number of vessels and its innervation is due to a complex network of sympathetic nerves (20). The brown adipocytes are well identified by the presence of multilocular lipid droplets and a great amount of mitochondria, which gives its characteristic brown color (Reviewed by 21). Additionally, brown adipocytes present high expression of uncoupling protein-1 (UCP-1), a transport channel located in the inner membrane of the mitochondria. The oxidative reactions of the Krebs cycle and β oxidation promote mitochondrial proton accumulation that is usually exclusively used by ATP synthase complex

for energy generation. However, in BAT, part of this energy is redirected to the UCP-1 channels, dissipating this energy as heat, decoupling the oxidative phosphorylation from ATP synthesis, and promoting non-shivering thermogenesis (NST) (19, 20, 22).

This kind of heat production is important to animal survival since it promotes animal adaptation to environmental changes, such as cold exposure and winter season (23, 24). However, animal cold adaptation and survival are not the only reasons for heat production by BAT. This tissue is also important for the maintenance of energy metabolism, guaranteeing a good balance between energy intake and expenditure. This means that extra energy accumulated, during high-fat diet exposure or overfeeding, can be dissipated as heat by BAT (25). The activation of the NST occurs by the sympathetic nerves, which release norepinephrine that activates adrenergic receptors (α_1 and β_3). These receptors promote adenylate cyclase activation and increase the second messenger cyclic adenosine monophosphate (cAMP) intracellular levels. The presence of intracellular cAMP causes activation of cAMP-protein kinase A (PKA), which is responsible for activating transcription factors and increasing UCP-1 expression. Also, PKA activates hormone-sensitive lipase (HSL), stimulating intracellular lipolysis and releasing fatty acids. The presence of fatty acids is an important signal for the respiratory chain activation in the mitochondria, causing an extensive proton production. The protons in the intermembrane space return to the mitochondrial matrix via activated UCP-1, triggering NST (Reviewed by 19, 20, 22). The thyroid hormone, T3, which is converted from its inactive form, T4, by deiodinase 2 (Dio2), is also known as an important activator of this tissue, increasing its thermogenic capacity (26, 27).

Since NST is importantly activated during cold exposure, BAT is highly recruited during winter and less activated during summer. Then, it is of extreme importance that BAT responds to the passage of the seasons. Some reports already correlated BAT activation with seasonal influence (28), which introduces our discussion about melatonin and the photoperiod involvement in the activation and recruitment of this tissue.

4. BROWN ADIPOSE TISSUE AND PHOTOPERIOD

As a seasonal tissue, it is to expect that BAT is influenced by changes in the photoperiod over the year. Reports show that winter is related to BAT mass increase in different non-hibernating species, while summer is correlated to its mass decrease (1,29–31). It is important to notice that, in nature, BAT needs to be recruited for the winter coming in order to allow the organism survival. However, it needs to be less activated during summer, since extra heating production could be harmful for the energy metabolism and for the organism survival. Another study not only confirmed these changes in BAT throughout the year, but also noticed changes in NST, food intake, and body weight (32).

Since the winter approaching is marked by decreased daylight duration and increased dark period length, it is natural to think that short photoperiods may influence BAT recruitment and activation. Studies have shown that short day exposure (8 h light and 16 h dark, between 3 weeks and 11 months) are responsible for enhanced thermogenic capacity, increasing animals resistance to cold and proving that changes in photoperiod are very important to the seasonal acclimation in different species of small mammals (33–35). This augmented NST may be due to an increase in total mitochondria number (36) and in UCP-1 expression (37, 38). Short photoperiod was also proven to raise energy intake of different animal species, like gerbils (39), different species of voles (40, 41) and tree shrews (42). This increase in food consumption during short photoperiod shows a relevant adaptation to cold exposure and BAT activation, as this tissue is also activated by diet and free fatty acids availability (25, 43).

Besides all the data relating photoperiod and BAT activation and recruitment, some reports found different results for this interaction. For Collared lemmings short day exposure (8 h light

and 16 h dark for up to 11 days) caused a decrease in energy expenditure and UCP-1 levels with reduced BAT activity (44). This result may be due to a short experiment period (11 days) that may not be able to stimulate BAT recruitment when compared to other studies mentioned earlier (between 3 weeks and 11 months). Also, Mongolian gerbils exposed to short days (8 h light and 16 h dark for 4 weeks) did not present an increase in the thermogenic capacity (45). Even if the survival of these mammals to cold exposure may require a prolonged adaptation (a couple of weeks), it is necessary to understand that each species may present distinct thermoregulatory mechanisms, generating different results (46, 47).

5. MELATONIN ACTIONS OVER BROWN ADIPOSE TISSUE

As previously stated, melatonin is responsible for signaling the environmental information, like seasonal or circadian changes, to the internal organs. Its pineal synthesis occurs during the night and nocturnal light exposure interrupts this production (48). Light captured by specific receptors in the retina is transduced to the SCN through the retinohypothalamic tract and signals, by a complex neuronal circuitry, the inhibition of melatonin production (5, 48–50). Since the presence of light (every day for 15 min) during the dark phase of a short day exposed animal (8 h light and 16 h dark, for 10 weeks) decreases NST (51), it is possible to infer that photoperiod modulation over BAT is due to nocturnal melatonin production. Also, melatonin actions mediate the animals seasonal acclimatization (52, 53). Therefore, the different photoperiods along the year modulate BAT through the alterations caused in pineal melatonin synthesis (Figure 1).

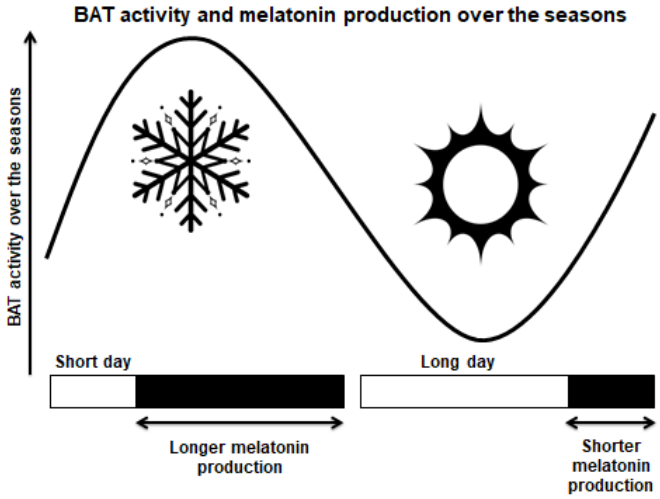

Fig. 1. Brown adipose tissue and melatonin production over the seasons.

Longer melatonin production takes place during longer winter nights, which is correlated to the higher BAT activity during the season. In contrast, shorter melatonin production is related to short summer nights and, consequently, to lower BAT activity.

This information is reinforced by other researchers that studied animals housed at a long photoperiod (16 h light and 8 h dark for 4 weeks) that received melatonin supplementation. In the first experiment, melatonin (3.1 mg) was administered by subcutaneous pellets implanted in the animals intrascapular BAT (54). In another experiment, daily melatonin injections (25 µg or 75 µg) were administered along the day (55). Even with the animals being exposed to a long photoperiod, both experiments showed an increase in BAT mass and in NST, confirming melatonin stimulation of this tissue. Also, some reports indicate that melatonin may improve the animals cold resistance and mitochondrial activity (18, 56, 57). In addition, pinealectomy

(melatonin absence) prevents BAT mass increase (17) and melatonin replacement normalizes these parameters (57, 58).

Analysis of the available data shows the absence of a pattern for melatonin administration have been used over time, such as: subcutaneously implanted pellets, which release melatonin (3.1 mg to 5 mg) directly into the tissue during the whole day (52, 54, 59, 60); daily injections (5 µg to 100 µg) (55, 58, 61–63); and oral administration (10 mg/kg/day) (64). All these experiments found similar results, which confirm that melatonin stimulates BAT growth and NST, increasing cold resistance and supporting animal survival.

Since this indolamine is a seasonal marker responsible for promoting the organism seasonal adaptation (52), it is necessary to take into account that melatonin administration should occur only in the dark period and not during the light period. Melatonin being present during the light phase could cause chronodisruption (65) and its immediate and prospective effects may not be as effective in the activation of BAT as they could be if the hormone was solely present during the dark phase, when it is naturally expected. The presence of melatonin throughout the 24 h could also impair its prospective effects, as they just occur when the hormone is no longer present in the body fluids (6). Then, this melatonin "excess" during the day could harm properly BAT activation and recruitment, worsening the animal adaptation to the winter coming.

A good example is a case where melatonin capsules implants could not activate BAT and NST in *Rattus norvegicus* (66), which may be explained by the fact that melatonin was present throughout the 24 h, being unable to signal the artificial seasonal change, as its presence represents the length of the dark period and a 24 h night is not expected in nature. Also, it is necessary to observe that different species may show different results, since melatonin was able to improve cold resistance in Siberian hamsters even in the absence of a correspondent NST increase (67). Moreover, even in the absence of circulating melatonin, BAT is still activated or recruited by chronic cold or high-fat diet exposure (68–70). However, these animals probably present impaired thermogenic capacity and/or resistance to cold when compared to their matching controls that produce melatonin, as the tissue lacks the preparing signal to the seasonal challenges (57, 71).

6. MELATONIN AND ITS POSSIBLE WAYS OF ACTION IN BROWN ADIPOSE TISSUE

Due to its amphiphilic characteristic (72), melatonin can exert its influence over the tissues using different ways of action, being able to act through the presence of membrane receptors, nuclear receptors or by the direct interaction with intracellular molecules (6). The same may be seen when melatonin interacts with BAT as it may act in different sites that control this tissue, such as the central nervous system (CNS) and the peripheral nervous system. It has been shown that melatonin membrane receptors (MT1 and/or MT2) are present in a wide variety of locations in the CNS, mainly in the SCN and in other hypothalamic nuclei (73, 74). Exogenous melatonin added to the SCN and the anterior hypothalamus caused changes in the reproductive tract and BAT hypertrophy (75), which are characteristic body changes that take place during the adaptation for the upcoming winter. Also, MT1 and/or MT2 receptors were found in different CNS regions responsible for BAT activation and modulation, such as the preoptic area (median preoptic subnucleus and medial preoptic area), the parabrachial nucleus, the dorsomedial nucleus of the hypothalamus and the raphe nucleus (76, 77). In contrast, other studies mention that an intact dorsomedial posterior arcuate nucleus is not necessary for promoting UCP-1 expression increase in BAT during short day exposure (78). In addition, it has also been reported that melatonin administration (16 µg for 10 weeks) and/or short day exposure (8 h light and 16 h dark, for 10 weeks) are responsible for increasing sympathetic nervous system activity, causing increased UCP-1 expression and general lipid mobilization in

BAT (79). Thus, these evidences point to the possible influence of melatonin over BAT activation through the central and peripheral nervous systems.

However, as mentioned earlier, melatonin can also directly interact with peripheral tissues, such as BAT. Melatonin binding sites have already been described in this tissue. In humans, MT1 and MT2 receptors are present in BAT and in a brown adipose cell line, with a possible important participation of MT2 receptor in BAT homeostasis (80). The receptor-mediated interaction of melatonin in rodents BAT is still poorly understood and MT1 and MT2 presence in Siberian hamsters BAT was not confirmed. Nonetheless, there is a report of a binding site that does not match to the melatonin receptors described so far (81). Also, Siberian hamsters have been considered a natural knock-out for MT2 receptor (82). These results may suggest that melatonin receptors (or binding sites) in humans may be different from those encountered in Siberian hamsters. Another receptor, GPR50, is also related to melatonin signaling and was described to modulate NST (83).

In addition, this hormone may exert its actions not only through its interaction with membrane receptors, but also through nuclear receptors. It has been thought that melatonin may be a natural ligand for retinoid orphan receptors, such as RORα (84, 85). Knock-out mice for RORα nuclear receptors demonstrate elevated BAT mass and activity (86,87), increased energy expenditure (88) and higher cold resistance when compared to controls (89). Moreover, these nuclear receptors are involved in the control of energy metabolism, regulating several lipid and glucose metabolic genes. These modulations are important factors that contribute to maintaining energy homeostasis and insulin sensitivity (87). However, it has recently been said that RORα is not exactly a receptor for melatonin, but melatonin and its metabolites would be able to indirectly modulate RORα and its activity (91).

In either case, RORα is known to be regulated by another nuclear receptor, REV-ERBα (90). Studies suggest that REV-ERBα is responsible for suppressing UCP-1 expression, being responsible to exert some kind of control in UCP-1 circadian expression and maintain a normal rhythm for BAT activity (92). Also this nuclear receptor promotes BAT development and brown adipogenesis (93). REV-ERBα and RORα are part of a complex clock machinery, regulating the expression of the clock genes, which are all influenced by melatonin immediate and prospective actions, promoting the organism homeostasis (6, 90, 93, 94). Clock genes participation in BAT activation and recruitment was reviewed elsewhere (93, 96).

Melatonin was also shown to be able to activate BAT and NST by other means such as stimulating Dio2 activity in BAT of different species (97–99). However, some authors stated that animals acutely exposed to light at night do not present altered Dio2 activity (100). These results may be explained by the acute light exposure not being sufficient to cause a disruption in Dio2 activity, being necessary a prolonged melatonin absence to provoke it. Moreover, others suggested that Syrian hamsters kept in short days (8 h of light and 16 h of dark for 5 weeks) and exposed to 24 h of acute cold did not present Dio2 activity rhythmicity in BAT (101). In this case, acute cold exposure may be affecting Dio2 activation, which could mask this enzyme activity rhythmicity. Even so, recent research showed a daily rhythm for Dio2 mRNA expression in BAT. It was also demonstrated that pinealectomized animals present altered daily profile expression for this enzyme and that oral melatonin replacement (1 mg/kg for 13 weeks) during the night is capable of partially restoring this rhythmicity (57). Together, these results may indicate an important melatonin role in BAT activation through Dio2 stimulation.

HSL is involved in intracellular lipolysis, a process that induces the respiratory chain activation by the release of fatty acids. Melatonin was shown to directly interfere in the lipolytic activity in white adipose cells (102) and pinealectomized rats (absence of circulating melatonin) presented altered HSL daily profile expression in BAT. Furthermore, exposing

these rats to cold also decreased HSL expression, indicating that melatonin absence impairs lipolysis in BAT (57), which is detrimental to NST.

Another way of influencing BAT activity is directly acting in the mitochondria. Being considered the principal organelle for thermogenesis, since the UCP-1 is expressed in their inner membrane (20), mitochondria are importantly modulated by melatonin. This hormone is able to improve mitochondrial function and integrity through its molecular antioxidant properties that protect the mitochondrial genetic material from free radicals damage and increases the respiratory chain activity (22, 103, 104). It is noteworthy that melatonin can act through MT1 receptor in the mitochondrial external membrane, promoting the autocrine regulation of this organelle (105). Animals exposed to short photoperiod (longer melatonin production) (8 h of light and 16 h of dark) showed an increase in mitochondrial GDP-binding (106, 107), cytochrome c oxidase (complex IV) activity (106), and mitochondrial mass in BAT (108), improving its thermogenic capacity.

Also, melatonin treatment (10 mg/kg of body weight during 6 weeks) increased BAT mitochondrial mass and the activity of citrate synthase and respiratory chain complexes I and IV of obese and control rats (64). Again, it is important to reinforce that melatonin administration during the light period could impair the potential effects that this hormone would cause if it was only administered during the night. In addition, another study revealed that melatonin treatment (10 nM and 0.1 µM for 3 h) was able to decrease mitochondrial transcript contents by around 40% (109), but it was analyzed at only one time point over the 24 h, making it difficult to infer about all possible influences that melatonin could exert over mitochondria during the whole period. Indeed, it has been recently shown that BAT mitochondrial UCP-1, citrate synthase, complexes I, II and IV protein expression and activity present rhythmicity (57). This study has also shown that the lack of melatonin caused by pinealectomy was responsible for altering this daily rhythm profile and that oral melatonin replacement (1 mg/kg for 13 weeks) was able to partially restore it.

It is possible to infer that melatonin can exert its influence over BAT using both central and peripheral ways, acting through membrane and/or nuclear and mitochondrial receptors, or even directly acting in the tissue (Figure 2).

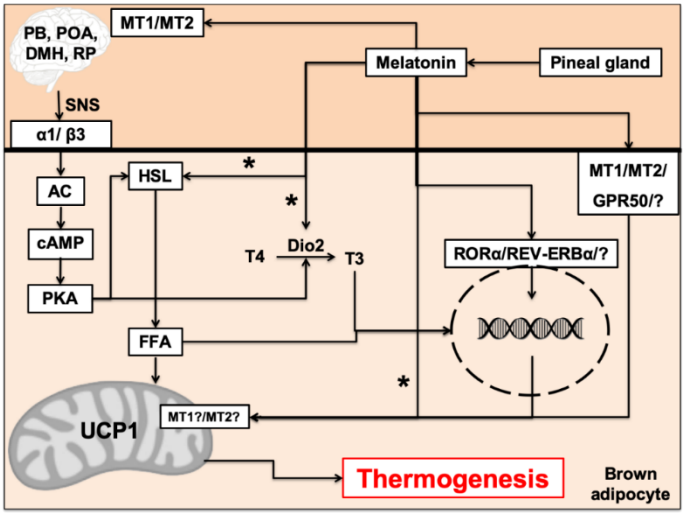

Fig. 2. Melatonin and the possible mechanisms of action in brown adipose tissue.

CNS: central nervous system. PB: parabrachial nucleus. POA: preoptic area. DMH: dorsomedial hypothalamus. RP: raphe nucleus. SNS: sympathetic nervous system. AC: adenylate cyclase. cAMP: second messenger. PKA: cAMP-protein kinase A. HSL: hormone-sensitive lipase. FFA: free fatty acids. Dio2: deiodinase type 2. "?": other melatonin binding sites. "": actions mediated, or not, by receptors.*

Besides promoting activation and recruitment of BAT, melatonin acts upon the differentiation of another adipocyte type: the beige adipocytes. In spite of their different developmental origins, both tissues present similar structural and functional properties, including heat production by UCP-1 (110). Interestingly, the differentiation of those beige cells in the WAT is described in the literature as the browning process (111), which results in beige depots formation. The browning process might be induced by, among other physiological responses, cold exposure and by melatonin itself (56). Melatonin chronic treatment (10 mg/kg for 6 weeks) in Zucker rats increased citrate synthase activity and UCP-1 in the inguinal WAT beige depots, culminating in the thermogenic activity of this tissue, both in sub-thermoneutrality and after cold exposure, as verified by thermographic analyses (56).

7. MELATONIN AND FETAL PROGRAMMING IN BROWN ADIPOSE TISSUE

As a chronobiotic molecule, melatonin is also important during the gestational period. Maternal melatonin freely crosses the placenta (112, 113) and is also transferred to the newborn through breastfeeding (114), being those the only sources of this hormone to the fetus/newborn as it is only going to produce its own melatonin later after birth (115). Thus, maternal melatonin transgenerational actions are responsible for signaling the changes in the environment, such as the light/dark cycle and the seasons of the year, affecting the fetus physiology and promoting its ability to deal with the environmental changes after birth (Reviewed by 6). This molecule allows the offspring to adapt to physiological factors of intra- or extra-uterine life, being primordial for a good development, acting as a neuroprotector, antioxidant and synchronizer (116, 117). As fetal melatonin is synthesized by the mother, any rhythmic disturbance during gestation can result in metabolic alterations in the fetus (117).

BAT is also an important tissue for newborn survival, since it is responsible for heat generation and conservation from the moment of birth until later in life. The transition between intra- and extra-uterine environment is very stressful, since the uterus is much warmer then the outside ambient, being necessary an extra heat production to maintain the newborn central temperature (118). As previously demonstrated, alterations in the mother's health can contribute to metabolic damages in the BAT of the offspring (119,120). Besides being a molecule that modulates brown adipose tissue through the seasons, it has also been demonstrated that melatonin plays an important role in BAT fetal programming metabolism (121, 122).

The presence of melatonin binding sites in sheep's fetal BAT and a stimulatory action of this hormone in brown fat accumulation during fetal life were previously shown (123). Also, newborn lambs gestated in total absence of maternal melatonin (24 h of light exposure for approximately 147 days – last third of gestation) demonstrated an inefficiency to regulate the central temperature and produce heat after 1h of cold exposure. Furthermore, these pups BAT mass decreased when compared to control animals. These changes were reverted by melatonin replacement during gestation (12 mg) (118). The present results show the importance of maternal melatonin production for BAT development during fetal life. Melatonin absence during this period may negatively impact the survival and adaptation of the newborn to the extra-uterine life, provoking impairment in their heat production and energy metabolism homeostasis that could also be prolonged to the adult life, maybe promoting the development of metabolic diseases.

Considering all that, the exposure to light at night, inhibiting maternal melatonin synthesis, has been described as a cause for several damages to the pups during the gestational phase, affecting their metabolic fetal programming (124,125). However, little is known about the absence of maternal melatonin consequences in the offspring BAT metabolism, which might also affect their adult life. Nevertheless, it is known that the uterine and postnatal environment

play important roles in the life of the offspring, both preventing possible metabolic disorders and adapting the fetal predictive and adaptive responses.

8. CONCLUDING REMARKS

As a chronobiotic molecule, melatonin has the important task of signaling environmental changes to the organisms. This important hormone not only signals the circadian cycles, but also the passage of the seasons over the year. It acts through immediate, prospective and transgenerational effects, synchronizing the central and peripheral organs with the light/dark cycle and promoting metabolism homeostasis (6). Being importantly affected by seasonality, BAT is a tissue where melatonin influence can be easily perceived. Some of these actions were discussed in this review. Since pineal melatonin is only produced during the night, care is needed when studying the relation between melatonin and such a seasonal tissue, as the results could not represent what may be observed in nature. Also, the immediate, prospective and even transgenerational effects of this hormone need to be considered, since they may show different results that together may help to better interpret BAT physiology (Figure 3). Then, the day/night fluctuations over 24 h, the passage of the seasons and the way this tissue is programmed during pregnancy stages need to be considered when studying BAT metabolism. In addition, differences between species also need to be taken into account, since different organisms respond differently to seasonal challenges (46,47). In summary, knowing and studying BAT rhythmicity is indispensable for the proper understanding of its physiology.

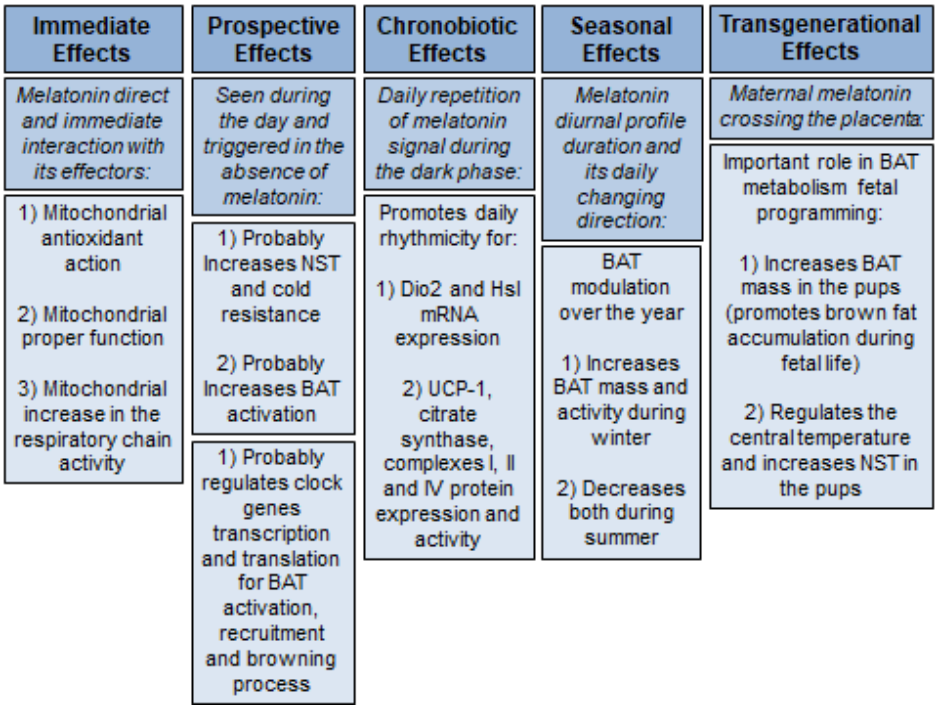

Fig. 3. Melatonin and the possible ways of action in brown adipose tissue [figure adapted from (126)].

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AUTHORSHIP

PVVC, CAPS, CCG contributed to the concept/design of the manuscript. IFO, LSC and FGA contributed to the concept/design, drafting and critical revision of the manuscript. All authors approved the final text.

CONFLICT INTEREST

The authors declare no conflict of interest.

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