Review

Melatonin and chromatin

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ABSTRACT

Melatonin affects chromatin remodeling, thereby activating or silencing specific genes and, presumably, also by modulating circadian-mediated changes in chromatin structure. Melatonin has been shown to exert effects on chromatin under conditions of toxin exposure, treatment with other hormones such as glucocorticoids or leptin, in cancer, and during developmental processes. Most of the documented actions concern histone modifications or their reversal that facilitate or prevent nucleosome eviction. Less information is available on DNA methylation or demethylation at regulatory CpG islands. To date, this has been mainly studied under conditions of early development, occasionally concerning seasonality or shiftwork with light at night. Another emerging field, which is still insufficiently studied, concerns regulation via DNA-interacting noncoding RNAs, in particular, super-enhancer lncRNAs. Although the direct information on actions by melatonin is widely missing, this field promises to become important, as numerous RNAs of this type have been shown to be rhythmically expressed. The circadian aspect of melatonin's role in chromatin remodeling and control of gene expression deserves future attention. This includes the role of sirtuin 1, which participates in the circadian machinery and apparently mediates several effects of melatonin that are suppressed by sirtuin inhibitors or sirtuin 1 knockdown.

Keywords: Circadian, DNA methylation, Histone modification, Noncoding RNAs, Super-enhancer RNAs

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1. INTRODUCTION

Melatonin has been shown to modulate the expression of numerous genes, under various conditions and in the context of highly divergent biological and pathophysiological functions or alterations. With regard to the remarkable pleiotropy of melatonin, this broad spectrum of gene-regulating actions is not surprising [1-3]. Of course, many effects of this type can be explained by the branches of signaling pathways of the G protein-coupled melatonin receptors, MT_1 and MT_2 [4]. However, many other actions are not easily compatible with the primary signaling routes and may, thus, be attributed to secondary signaling by downstream factors that are under melatonergic control [5]. The control of ERK1/2 may serve as an example for opposing findings. While ERK1/2

activation is part of a canonical signaling pathway of both MT_1 and MT_2 receptors [4,6], suppression of ERK1/2 activation by melatonin has also been repeatedly reported [7-10].

The insight that various effects of melatonin cannot be explained by the canonical pathways of cAMP reduction and MAP kinase activation, but rather have to involve secondary signaling by other factors regulated by melatonin should be a good reason to re-think the mechanisms of its gene expression control. The manifold epigenetic processes that modulate gene transcription as well as posttranslational steps have to be in-depth considered in melatonin research, too [11-14]. This is primarily an encouraging demand to the researchers working in this field, since the mechanistic relationships between melatonin and the described effects will require a lot of future work to identify the details of signaling step by step. As far as chromatin alterations are involved, in particular, via DNA methylation/demethylation and histone modification, two important connections of melatonin deserve particular attention, (1) the relationship to the circadian system and (2) the modulation of sirtuins [12,14-17]. The circadian system controls gene expression by various mechanisms, (1) by oscillator proteins such as BMAL1, CLOCK and NPAS2 via E-boxes, (2) by other oscillator proteins such as RORα and REV-ERBα (= NR1D1) via ROREs, which are present in the respective promoters of circadian-controlled genes (CCGs), and (3) by daily chromatin remodeling as a basis of global gene regulation. Periodic chromatin decondensation provides a basis for allowing gene expression via more specific regulation mechanisms by transcription factors. Interestingly, sirtuins are involved in all these three processes, in particular, SIRT1 and the constitutively chromatin-associated SIRT6 [12,14,15,18-22]. SIRT1 has a specific role in both central and peripheral oscillators, whereas the histone acetylation status is influenced, among others, by both SIRT1 and SIRT6. In addition to these processes, various RNA-based regulation mechanisms have to be taken into account, which often may require further elucidation. In the circadian system, over 600 clusters of lncRNAs (long noncoding RNAs) were shown to be rhythmically expressed, among which more than 280 were associated with enhancer regions, and 50 were identified as super-enhancer lncRNAs (super-lncRNAs, super-eRNAs), which pleiotropically target several genes [16,23]. Therefore, as much as melatonin has an influence on circadian oscillators, either directly or by upregulating SIRT1, as recently summarized [24], it can be expected to also modulate super-enhancer lncRNAs with their multiple transcriptional effects. Moreover, various epigenetic cross-connections exist. For instance, the lncRNA *116HG*, which derives from a precursor that is spliced to also generate several snoRNAs (small nucleolar RNAs), forms cycling clouds that are associated with large-scale chromatin decondensation [25]. Deletion of that locus leads, in turn, to dysregulation of the oscillator components PER2, CRY1 and CLOCK [25]. Another nexus concerns variants of histone modification and expression of different categories of noncoding RNAs. For example, histone H3 acetylation (H3K56ac) is required for the expression of asRNAs (antisense RNAs) and upstream-directed transcription of 2D eRNAs (enhancer RNAs that are two-directionally transcribed), whereas H3 trimethylation of lysine 4 (H3K4me3) is necessary at the transcription start of coding genes and several lncRNA genes, while monomethylated lysine 4 (H3K4me) is typically found at transcription starts of 2D eRNAs [26]. These findings also underline the importance of the position of modified lysines within the histone molecule, since H3K64me3 is usually regarded as a repressive modification, whereas H3K64ac is enriched at the transcription starts of actively transcribed genes. The roles of SIRT1 and SIRT6 as histone deacetylases indicate that these two sirtuins should participate in the histone modification balance and, thus, control of gene expression. However, it is of utmost importance to distinguish between the various actions of especially SIRT1 as (1) a histone deacetylase, (2) a deacetylase of regulatory proteins, and (3) as a rhythm-promoting agent in circadian oscillators. The effects on a specific gene may entirely differ between these three routes. The case of histone methyltransferase

MLL1 may serve as an example for these differences. MLL1, which is involved in a rhythm of H3K4me3 formation, is deacetylated by SIRT1 [27].

Finally, it should be noted that an interplay exists between histone modification and DNA methylation patterns [28-31], also in a circadian context [12]. This includes actions of SIRT1 [28,29]. Although these alterations have been partially observed as being related to gene silencing, the reversibility of histone modification processes also indicates the existence of opposite effects that lead to transcription induction. Erasure of methyl groups in CpG islands by TET enzymes (ten-eleven-translocation enzymes), followed by base excision repair via thymine DNA glycosylase (TDG), is meanwhile an established mechanism [32,33]. The coordination of histone modification and the DNA methylation/demethylation balance appears to be a necessity, because activating processes at the histone level can only be effective if the promoter is open for binding proteins and not silenced by DNA methylation. Correspondingly, modified histones of the deactivating type have to conform to DNA silencing by CpG methylation.

As shown by this outline, the understanding of gene expression control by melatonin requires consideration of various details of chromatin structure and cannot be exclusively based on the – necessary - identification of transcription factors and their activation. The details presented in the subsequent sections have to be understood as a summary of the actual knowledge, but not as a consolidated scheme of universally valid actions. Especially the comparability of systems studied is often limited. Therefore, caution is due before translating findings to other experimental systems. System-related discrepancies, gaps and inconsistent findings will be repeatedly addressed in the following sections. Nevertheless, results obtained to date may serve as a stimulus for further research at a broader range.

2. MELATONIN AND HISTONE MODIFICATION

The expression and modification of histones has been investigated in numerous studies. However, relatively little is known on the effects of melatonin under basal conditions (Table 1A). Moreover, the cell types or tissues used are mostly poorly comparable. Therefore, a decrease of histone H4 expression in the thymus of young rats [34], which would indicate a reduction in nucleosome formation and, thus, lower DNA replication and cell division rates, may not reflect the situation in other cells and tissues. The question of generalization should be judged by comparing rhythms of S-phase and cell division relative to the melatonin profile.

Available data on histone modification in the absence of pharmacological or toxicological challenges only concern histone acetylation [9,35-40] (Table 1A), although corresponding data on histone mono-, di- and trimethylation would be highly desirable. In all studies in neural tissues and cells, including neural stem cells, melatonin caused increases in histone acetylation [9,35,37,38], as shown by measurements of acetylated histones H3 and H4 as well as histone acetyltransferase (HAT), either specifically identified as p300 or without discrimination between CBP (CREB-binding protein) and p300. The increased acetylation can be taken as indicating enhanced gene expression, because of the nucleosome-relaxing effect of acetylated nucleosomal histones. In one study [37], contrasting findings were obtained, as increases in both H3 acetylation and histone deacetylases (HDACs) were observed. The upregulation of HDACs was discussed in terms of a compensatory response to the increase in H3ac. To date, most of the results concerning neural cells have not yet considered the specific lysine residues that are modified, in earlier publications because of the lack of tools that were not yet available.

Table 1: Effects of melatonin on histone expression and modification, under basal conditions and pharmacological or other challenges.

Organism/system	Main findings	Comments	Refs.
A. Findings under widely basal conditions or in developmental processes			
Thymus of young rats	H4 mRNA ↓	Circadian rhythm of H4 inverse to melatonin	34
Rat hippocampus	H3ac ↑ H4ac ↑		35
Rat striatum	H4ac ↑		35
Human SH-SY5Y neuroblastoma cells	p300 ↑; H3ac ↑ H4ac ↑		9
Murine neural stem cells	H3ac ↑, but HDAC3 ↑ HDAC5 ↑ HDAC7 ↑	HDACs ↑ compensatory response to H3ac↑ ?	36
Murine neural stem cells	CBP/p300 HAT activity ↑ H3K14ac ↑	Expression of neurogenin and neuroD1 ↑	37
Pig oocytes	H3K27ac ↓ H4K16ac ↓	Maturation genes ↑ *	38
Mouse oocytes	H4K12ac ↓	Correlated with ROS ↓	39
B. Compensation of pharmacological and other challenges			
Murine macrophage RAW 264.7 cell line	p300 ↓		40
Mouse fetuses from LPS-treated mothers	HAT activity ↑ H3ac ↑		41
High glucose/ human diabetic dental pulp	p300 ↓		42
High glucose or proinflammatory cytokines/ murine β-cells	Prevention of decrease of p300	Normalization by melatonin	43
Dexamethasone/kidney of rat pups	HDAC1 ↓ HDAC2 ↓ HDAC3 ↓	Counteraction of dexamethasone on HDACs	44
Dexamethasone/kidney of rat pups	HDAC1 ↑ HDAC2 ↑ HDAC8 ↑	Maternal mel treatment (prenatal)	45
Dexamethasone/liver of rat pups	HDAC activity ↓	Counteraction of dexamethasone on HDAC	46
Leptin/rat sperm	HAT ↓ HDAC1 ↓ HDAC2 ↓	HAT vs. HDACs !	47,48
Induced SASP[3]/human fetal lung fibroblasts	Prevention of CBP-mediated H2BK120 acetylation	Antagonism to SASP gene expression	49
Spinal nerve ligation/rat	HDAC4 dephosphorylation	Nuclear localization	50
Deoxynivalenol (mycotoxin)/mouse oocytes	Prevention of decrease of H3K9me2	Normalization by melatonin	52
BPA[1] or DEHP[2]/mouse testis	Prevention of decrease of H3K9me2	Suppression of action of endocrine disruptor	53
Bovine oocytes exposed to paraquat	H3K4me3 ↓ H3K9me3 ↑	Reversal of paraquat effects	54
Cr(VI)/murine spermatogonial stem cells	Prevention of increases in H3K9me3 and H3K27me3	Counteraction of oxidative stress	55

*[1]BPA, bisphenol A; [2]DEHP, diethylhexylphthalate; [3]SASP, senescence-associated secretory phenotype; *contrast of histone deacetylation and maturation gene expression; arrows indicate up- or downregulation.*

Moreover, most of these studies did not follow the genes that were presumably upregulated in response to nucleosome eviction. As an exception, a more recent study identified K14 of H3 as the modification target and correlated these changes with upregulation of the transcription factors neurogenin and neuroD [38], indicating promotion of neuronal differentiation. Moreover, the rises in HAT activity were interpreted by ERK signaling, i.e., by one of melatonin's canonical pathways.

By contrast with these results obtained in neuronal cells, downregulation of histone acetylation was observed in pig and mouse oocytes [38,39]. This difference has to be seen in the context of oocyte maturation, which follows another genetic program. However, the observed decrease in acetylated histones H3 and H4 is not easily compatible with the also described upregulation of maturation genes [38]. Therefore, the links between presumably reduced expression of some genes to the transcription of maturation genes remains to be clarified.

More results are available for changes in histone modification upon exposure to hormones, drugs, toxins, irradiation, or surgery (Table 1B). Typically, these changes reflect normalization of intervention-induced changes by melatonin. Although these approaches are of high interest and document the involvement of epigenetic changes in protective actions by melatonin, it is not always easy to distinguish between the reasons for why a correction has taken place. For instance, this might have been caused by a melatonin-mediated reduction of the respective insult. In this case, the observed epigenetic return to normal may not have resulted from a direct melatonin effect on the epigenetic subsystem. This may be assumed in cases in which the insult primarily acts on mitochondria and is known to be reversed by melatonin at the mitochondrial level. Alternately, the normalization may have been caused by a primary effect of melatonin on epigenetic factors. This latter possibility may include epigenetic changes induced by melatonin via the circadian oscillator system, e.g., by upregulation of SIRT1 [14,24]. This may not necessarily be seen in enhanced deacetylation of histones, since the decisive step may consist in the deacetylation of a regulatory protein. Moreover, enhancement of a circadian amplitude by SIRT1 may secondarily lead to increased histone acetylation, as soon as the respective permissive phases of the oscillator are reached. To distinguish between these possibilities would be of importance for future studies, especially with the aim of discriminating between immediate melatonin effects on the epigenetic system and normalization by reduction of damage.

A case in which melatonin seems to act directly on an epigenetic factor seems to exist in LPS-treated macrophages [40]. In addition to effects on NF-κB (p52), melatonin prevented the increase in p300 HAT activity, a coactivator that is involved in the expression of iNOS (inducible NO synthase) and COX-2 (cyclooxygenase 2), effects that explain the reduced transcription of these genes. However, the consequences of LPS treatment and their reversal by melatonin have to be seen in the respective experimental context and that of the system studied. What is observed in a macrophage cell line, may not be relevant to other conditions, even if macrophage and microglia activation occurs. In pregnant mice, LPS treatment of mothers led to preterm birth, pup death and brain damage. However, subcutaneous implantation of melatonin rescued pups and, in the context of histone modification, led to increased HAT activity and histone H3 acetylation [41]. On the other hand, melatonin caused in human diabetic dental pulp tissue exposed to high glucose a decrease in p300 [42]. The situation in insulin target cells and in the insulin-producing β-cells is entirely different. In β-cells, proteasomal degradation of p300 can become critical, as observed under persistent hyperglycemia or exposure to proinflammatory cytokines. The availability of p300 is important for transcription of the proinsulin gene as well as other genes required for cell survival and regulation, including some transcription factors. In β-cells, melatonin preserved the required level of p300 and, therefore, contributed to its functional maintenance [43].

Treatment of rodent mothers with melatonin did not always lead to the same outcome. When melatonin was given to dexamethasone-treated lactating mothers, the steroid-induced increases of renal HDACs were prevented [44], whereas prenatal administration of melatonin was reported to increase renal HDACs, in both dexamethasone-treated and -untreated pups [45]. In experiments on hepatic histone deacetylation in rat pups under the influence of dexamethasone, a reduction of HDAC activity was observed [46], reminiscent of comparable findings in neonatal kidney [44].

Studies on leptin in sperms or spermatogonia led to possibly inconsistent results. Melatonin was found to prevent the leptin-induced upregulation of HAT [47,48], but also that of HDAC1 and HDAC2 [48]. As acetylation and deacetylation are inversely acting processes, the finding on parallel changes into the same direction would only make sense in connection with specific details on affected genes.

Another study on human fetal lung fibroblasts has addressed the highly actual topic of SASP (senescence-associated secretory phenotype). In these nonsenescent cells, SASP was induced by X-ray irradiation or by conditioned media (OIS-CM) from cultures of H-Ras^{V12}-induced senescent cells. These treatments resulted in CBP-mediated acetylation of H2BK120, an effect associated with the expression of SASP-related genes, which was attenuated by melatonin [49]. As poly(ADP-ribose) polymerase-1 (PARP1) was involved in the CBP action, DNA damage may have been a crucial step in the induction of H2BK120ac formation.

A different aspect of the histone acetylation/deacetylation balance has been investigated in experiments on the consequences of spinal nerve ligation, in which the control of HDAC4 was analyzed. This treatment reduced the expression of the catalytic subunit (PP2Ac) of protein phosphatase 2A along with an enhanced phosphorylation of HDAC4 [50]. In the nucleus, pHDAC4 binds, like many other phosphorylated proteins, to a 14-3-3 protein, which escorts the deacetylase from the nucleus to the cytoplasm [51]. Melatonin was shown to upregulate the subunit PP2Ac, thereby reducing HDAC4 phosphorylation, which maintains the deacetylase in the nucleus, the site of its chromatin-modulating action.

While most studies had addressed histone acetylation and, therefore, gene activating processes, a few other investigations have dealt with another modification, histone methylation. Many additional modifications of histones are also known, but have not yet been considered in the context of melatonin research. Several toxicological studies using a mycotoxin, endocrine disruptors, paraquat and chromium(VI) have shown that melatonin prevents changes in H3K4 and H3K27 trimethylation and H3K9 di- or trimethylation [52-55], indicating that melatonin can correct abnormal gene expression induced by toxins or oxidative stress, not only via acetylation-induced histone relaxation, but also at the level of nucleosome rigidization. However, the direction of changes differs between studies, such that generalizations are not yet possible.

Moreover, melatonergic signaling is subject to epigenetic modulation via histone acetylation. The structurally unrelated HDAC inhibitors valproic acid and trichostatin A have been shown to upregulate the melatonin receptors MT_1 and MT_2 [56-59]. Apart from its role in the regulation of classic nucleosomal histones, melatonin has also been studied in the context of H2AX. Its phosphorylated form known as γH2AX is a marker of double strand breaks in the DNA. With regard to its DNA protecting effects [60-63], it is not surprising that melatonin can reduce γH2AX [64,65].

A few investigations on histone modification with relevance to melatonin are related to the circadian system, including the nocturnal upregulation of AANAT in the pineal gland. As the AANAT rhythm of rodents depends, contrary to the situation in primates, on strongly enhanced *Aanat* gene expression [66], mechanisms of gene accessibility involving histone modification have to be inferred. In rat pineals and pinealocytes, a nocturnal, norepinephrine-dependent increase in

the phosphorylation of the Ser 10 histone H3 kinase, aurora C, was described, which paralleled an increase in H3S10p [67,68]. These changes were attributed to the upregulation of the *Aanat* gene [67,68] and also to a corresponding upregulation of the type II deiodinase (*Dio2*) gene [69]. These reports were insofar surprising as aurora C is usually regarded as a component of the chromosomal passenger complex (CPC) with importance in mitosis and, even more, meiosis [70,71], and to additional secondary effects on CpG methylation in cancer [72]. The assumed additional role in the pineal gland may require further clarification. In adipose tissue, the circadian control of the cell cycle had been studied under the influence of melatonin [73]. Melatonin was shown to increase expression and circadian amplitudes of *Bmal1* and *Clock*, whereas *Per1* and *Per2* were slightly reduced. Melatonin also promoted cell proliferation [73], which would be in accordance with the proliferation-associated role of CLOCK [74]. The HAT activity of CLOCK [75] may play a role in this context, but additionally a physical interaction with HDAC3 was observed and binding to the E-box of *c-Myc*. The CLOCK/HDAC3/c-MYC complex was assumed to drive the activation of proliferation-associated genes. Concerning the increase in *Clock* and *Bmal1* rhythm amplitudes, a role of SIRT1 may be considered, which facilitates the binding of RORα to the RORE sequences in their control regions [76]. This would also be of interest with regard to the upregulation of SIRT1 by melatonin [14,24].

Two studies outside the mammals shall be briefly mentioned. In the Indian house crow (*Corvus splendens*), light at night was shown to not only reduce, expectably, the levels of melatonin, but also increased HDAC4 in the hippocampus, with the consequence of reduced H3ac [77]. A study in two plant HDACs (*Oryza* HDAC10 and *Arabidopsis* HDAC14) reported that these enzymes also deacetylate *N*-acetylserotonin to serotonin [78]. These findings are surprising and unusual, as enzymes that deacetylate lysine residues in proteins cannot be expected to also accept a small molecule like *N*-acetylserotonin as a substrate.

Effects of melatonin on histone modification in cancer cells (Table 2) shall be discussed separately, because substantial differences have to be expected, as soon as the circadian oscillator system is involved. This assumption is based on the observation of increased expression of SIRT1 and CLOCK in cancer cell lines, which has to be seen in conjunction with the epigenetic silencing of oscillator genes with tumor suppressor function, such as *Per2*, and the dysregulated state of the oscillator, which seems to be more or less fixed in a proliferation-promoting state [24,74]. The number of studies on histone modulation by melatonin is still limited. Decreases of histone acetylation have been reported in two cases [79,80], whereas the opposite was found in another study [81]. A different situation has been present in a study on a clofarabine-resistant leukemic cell line, in which the resistance to the cytostatic drug was associated with decreases in H3 and H4 acetylation. These changes were reversed by melatonin, an action associated with increased susceptibility to clofarabine [82]. Another study reported that melatonin can enhance the nuclear import of HDAC4 [83]. Concerning the histone methylation status, downregulation of a lysine-specific histone demethylase was described [84]. In total, these findings in cancer cells are of high interest, but do not yet allow generalization.

3. MELATONIN AND DNA METHYLATION

Several studies have addressed this central aspect of epigenetic regulation with regard to the role of melatonin. However, the fields in which effects were described are still rather divergent. In some areas, more data would be highly desired, but these gaps will be certainly closed in the near future.

Relatively many data are available on effects of melatonin during development, from the oocyte and cumulus cells to embryos and later prenatal stages. In ovine cumulus cells, melatonin was shown to upregulate the DNA methyltransferases DNMT1, DNMT3a and DNMT3b [85]. This should result in a reduction of expression of numerous genes in this type of accompanying cells, although the gene-specific methylation state may be considerably different, depending on additional regulation mechanisms. For instance, reduced methylation of 5 CpG islands of the *Dnmt3b* promoter was observed and may explain the upregulation of this enzyme. However, no changes were detected in the *Dnmt1* and *Dnmt3a* promoters, although altered methylation was detected in other CpG islands of these genes [85]. Despite the increase in global DNA methylation, some other genes were upregulated by melatonin, such as *Bcl2*, as known from many other systems, and *MTNR1A*, which encodes the melatonin receptor MT_1. Some genes normally suppressed by melatonin were downregulated, such as *p53*, *Casp3* (encoding caspase-3) and *Bax* [85].

Table 2: Effects of melatonin on histone modification, in the context of cancer.

Organism/system	Main findings	Comments	Refs.
Human breast cancer cells	p300 ↓		79
Human oral squamous cell carcinoma cell line	p300 ↓ CBP ↓ histone acetylation ↓		80
Human lung adenocar-cinoma cells	HDAC1 ↓ H3ac ↑		81
Clofarabine-resistant lymphoblastic leukemia cell lines	H3ac ↑ H4ac ↑	Compensation of decreases in resistant cells	82
Human colorectal cancer cell line	Nuclear import of HDAC4 ↑		83
Patient-derived tumor xenograft (oral cancer)	LSD1 ↓	Expectable increases in histone methylation	84

LSD1, histone lysine-specific demethylase; arrows indicate up- or downregulation.

Concerning oocytes, there has been some interest on changes in DNA methylation in terms of epigenetic inheritance [86]. However, this view emerged at a time when the dynamics of DNA methylation including the erasure of 5mC was not yet a matter of general awareness. Contrary to the data on cumulus cells, some studies reported decreased global methylation levels in oocytes, findings that might not be surprising with regard to the demands of gene activation in the course of development. In goat oocytes, the reduction of global 5mC was in line with downregulation of *Dnmt1*, *Dnmt3a* and *Dnmt3b* genes [87]. However, a complication arose by diverging dose dependencies. Significant reductions of *Dnmt1* were only obtained at 10^{-12} M melatonin, whereas *Dnmt3a* and *Dnmt3b* were downregulated at 10^{-6} and 10^{-9} M, but poorly (statistically not significant) at 10^{-12} M melatonin. Reductions of global 5mC by melatonin were also observed in mouse oocytes, in a study on deoxynivalenol treatment [52]. However, this toxicological study may not be sufficiently comparable with data obtained in the absence of toxins. Anyway, the data on oocytes are not generally fully consistent. Contrary to the findings of ref. [87], upregulation of DNMT1 was reported for porcine oocytes [88]. DNMT1, which had been found to also methylate mitochondrial DNA, was shown to be translocated under the influence of melatonin to

mitochondria. This caused reduced expression of mitochondrial genes, effects that were partially and variably reduced by the DNMT inhibitor, 5-aza-2'-deoxycytidine [88].

In murine blastocysts, effects of melatonin were demonstrated by *Aanat* knockdown. The suppression of melatonin formation resulted in reduced *Tet2* expression and, consequently, decreased DNA demethylation [89]. Addition of melatonin to blastocysts with *Aanat* knockdown normalized TET2, 5mC and 5hmC levels. In this study on blastocysts, AANAT was also shown to be mainly located in mitochondria. The protection by melatonin was discussed in terms of a requirement of melatonin for optimal embryonic development. In early stages of development, the consequences of in vitro fertilization have been also addressed. Damage to mouse 4-cell embryos by assisted reproductive technologies (ART) was shown to be associated with ART-induced reduction of global DNA methylation, effects that were corrected by melatonin [90]. The beneficial role of melatonin was also demonstrated at considerably later stages of development. In the femoral artery of 12-wk-old mice, ART was shown to have induced increased promoter methylation in the *eNOS* gene, which results in reduced eNOS expression. Again, this dysregulation was reported to be corrected by prenatal melatonin treatment [90]. Effects of melatonin in early developmental stages were also observed in prenatal rat liver, in which glucocorticoid treatment increased DMNT activity and DNA methylation, changes that were corrected by melatonin [46].

Relatively few studies have addressed epigenetic changes of melatonin formation and signaling via DNA methylation. An investigation on blast-related traumatic brain injury reported a moderate reduction (1.2-fold change) in *Aanat* expression, which was explained by increased methylation (1.4-fold) of the *Aanat* gene [91]. The consequences of reduced melatonin were not analyzed, as the study focused on a genome-wide identification of changed DNA methylation patterns in neurons and glia. With regard to melatonergic signaling, a differentially methylated CpG site at the *MTNR1A* gene was related to a paternally transmitted variant associated with comorbidity of asthma and allergic rhinitis [92]. Another case of *MTNR1A* polymorphism was assumed to exist in job-related exhaustion by shift work. Based on an in silico approach, a risk allele was concluded to be particularly sensitive to DNA methylation in the vicinity of the *MTNR1A* gene, with some likelihood in the promoter [93]. In oral squamous cell carcinoma (OSCC) cell lines, the *MTNR1A* gene was shown to be silenced by promoter hypermethylation. The expression of this gene was induced by the DNMT inhibitor, 5-aza-2'-deoxycytidine [94]. Findings were discussed in terms of a role of the melatonin receptor as a tumor suppressing factor.

The aspect of circadian and melatonin formation affecting environmental changes, as occurring, e.g., in shift work, has been addressed without specific reference to melatonin [95]. However, this had prompted other authors to discuss the involvement of melatonin [96], which is suppressed by artificial light at night (LAN). In that review [96], numerous differentially methylated CpG islands have been summarized. The consequences of LAN were also studied in 4T1 breast cancer cells inoculated into Balb/c mice. LAN was shown to enhance tumor growth, an effect reversed by melatonin [97]. LAN was concluded to cause global demethylation and, thereby, to induce aberrant gene activation patterns, whereas melatonin seems to favor methylation in tumors. However, further in-depth analyses will have to discriminate between methylation of tumor suppressor and tumor promoting genes or their promoters, respectively.

This necessary differentiation has been made in a study on melatonin effects in human MCF-7 breast cancer cells [98]. The LAN issue was not experimentally addressed, but one might extrapolate from these data what might be expected under LAN conditions in vivo. Two doses of melatonin were tested, 1 and 100 nM, versus untreated controls. At 1 nM or 100 nM melatonin, 1605 or 3250 promoters, respectively, were found to be hypermethylated, whereas 1925 or 1786 were hypomethylated. These findings reflect, on the one hand, the differential dysregulation of

genes in tumor cells, and, on the other hand, the differential actions of melatonin on genes, presumably due to tumor promoting and tumor suppressive properties. Notably, the gene suppressive actions of melatonin increased by dose. In a limited number of cases, the downregulation of oncogenic genes by hypermethylation was directly shown, and also the upregulation of a tumor suppressor gene, GPC3 (glypican-3) by hypomethylation. Additionally, a few data on miRNA promoters were presented, among which 15 or 20 were hypermethylated and 4 or 9 hypomethylated at 1 or 100 nM, respectively [98]. A study on genes responsible for drug resistance in glioblastomas revealed more specific effects of melatonin on this particular aspect. As known from a stem cell-like sub-population within malignant glioblastomas with multidrug resistance and tumor relapse, overexpression of the ATP-binding cassette (ABC) family of transporters had been reported to be responsible for these highly undesired changes. Melatonin was shown to increase methylation of the *Abcg2/Bcrp* promoter and, thereby, to reduce *Abcg2/Bcrp* mRNA and ABCG2/BCRP protein expression as well as its transporter function according to dye efflux experiments. These effects of melatonin were synergistic to those of the cytostatic drug temozolomide, which is in use as a standard treatment of glioblastomas. No comparable effects on other members of the same transporter family, ABCB1/MDR1 and MRP1, were obtained. The actions of melatonin were blocked by the DNMT1 inhibitor 5-aza-2'-deoxycytidine [99].

Another drug effect of melatonin concerning promoter methylation was recently reported in a study on spinal cord hypersensitivity [100]. In this case, the demethylation process initiated by TET1 at the promoter of the nociceptive metabotropic glutamate receptor mGlu5R was found to be responsible for pain hypersensitivity. Increases in TET1 were induced by different treatments, such as intrathecal *Tet1* gene transfer, spinal nerve ligation or intraplantar Freund's adjuvant injection. Melatonin was shown to reduce TET1-dependent promoter demethylation of the *mGlu5R* gene. The resulting attenuation of mGlu5R expression was shown to cause pain relief.

Finally, changes in DNA methylation have been reported in the context of mammalian photoperiodism, in which short days are associated with a lengthened phase of high melatonin. In the hypothalamus of the Siberian hamster (*Phodopus sungorus*), expression of the type III deiodinase (*Dio3*) gene was shown to be related to photoperiodic time measurement. Both short photoperiods and winter-like melatonin inhibited hypothalamic *Dnmt3b* and *Dnmt1* expression and reduced *Dio3* promoter DNA methylation, with the consequences of *Dio3* upregulation, in conjunction with the induction of gonadal regression [101]. Contrary to the hypothalamus, methylation activities are and have to be different in organs with reduced function under short day conditions. In *Phodopus* testis and uterus, *Dnmt3a* expression and global DNA methylation were shown to be increased, but surprisingly not in the ovary [102]. Melatonin may likely be involved in this response. An effect of melatonin was tested in human embryonic kidney cells (HEK-293). In these experiments, melatonin increased *Dnmt3a* and *Dnmt3b* expression [102]. The interpretation concerning melatonin's role in HEK cells may not be easily generalized or related to photoperiodism, since the respective actions of melatonin are tissue-specific, as shown by the findings obtained in the hypothalamus [101], and are not translatable from a human, embryonic, and transformed cell line to adult *Phodopus*.

In total, the findings on DNA methylation and demethylation under the influence of melatonin cannot be easily placed into a general scheme, not only because of differences between tissues, species and developmental stages, but also with regard to the diversity of topics investigated till date. Nevertheless, findings clearly show that the pleiotropic regulator melatonin also acts at the level of DNA modification, sometimes with profound effects. This insight should strongly encourage investigators to pursue this line of investigation more deeply in the future. In this context, it seems important to differentiate between hypermethylated and hypomethylated

promoters, down- and upregulated genes, on a functional basis. In the case of cancer, this would particularly imply the discrimination between tumor suppressing and tumor promoting genes. Occasionally, this has already been done, but many more studies of this type are required.

4. PARTICIPATION OF THE CIRCADIAN MACHINERY

Epigenetic processes have been studied in the context of circadian rhythms much more frequently than in melatonin research. A complete record would by far exceed the scope of this article. The respective findings have been multiply reviewed under various aspects [16-23,75,76,103-122]. However, a close look reveals countless fields in which effects of melatonin have been also observed, although the circadian literature has considered the roles of melatonin in these cases only exceptionally [112,115].

While most of the publications cited in the previous paragraph have dealt with chromatin structure as changed by histone modification, a substantial number of studies has also addressed the roles of DNA methylation and demethylation in circadian rhythms including consequences of dysregulation that occur especially in cancer. With regard to the oncostatic and cancer-preventing actions of melatonin as well as the influences of this compound on circadian oscillators, these investigations have to be of interest to the research of melatonin, even when its role has not been specifically studied. Circadian rhythms of DNA methylation have been repeatedly described [118,123-126]. These findings covered systems as different as blood cells, liver, and brain regions such as prefrontal cortex and, importantly, the SCN. A rhythm of global DNA methylation in human blood exhibited increased levels at night [123]. This cycle was inverse to plasma homocysteine levels, which showed a peak in the evening, but low nocturnal concentrations. The phase relationship appears plausible, as the metabolite *S*-adenosyl-homocysteine (SAH) acts as a DNMT inhibitor, by interference with *S*-adenosylmethionine (SAM). The SAM/SAH ratio, also known as the methylation potential, exhibited a rhythm in mouse liver, which did not perfectly match that of global hepatic DNA methylation, although the peaks were found in either case at the end of daytime [126]. The ratio was strongly decreased by injection of adenosine-5'-monophosphate, but this did not substantially alter the 5mC content. Instead, a high complexity of differently phased rhythms with additional differences in amplitudes was observed in *Dnmt1*, *Dnmt3a*, *Dnmt3b*, *Tet2*, and *Tet3* mRNAs [126]. The overlap of the methylating and demethylating enzymes may explain the overall 5mC pattern. However, these findings strongly indicate the limits of judging on the basis of enzyme expression or activities, which result in a global pattern, but may not tell much about the changes at individual sites that are under the control of more specific regulation mechanisms. Concerning an eventual role of melatonin in global DNA methylation, to date available data do not support such an idea. The low 5mC levels at night in human blood cells [123] and high levels extending into the night in mouse liver [126] do not speak for a uniform nocturnal action of melatonin in the global range. Instead, actions of melatonin may be sought in (1) specific regulation mechanisms of melatonin-controlled genes and (2) in eventual amplitude-enhancing effects of melatonin on the circadian machinery. The importance of circadian oscillators for generating hepatic rhythms of 5mC, SAM/SAH ratio, expression of *Dnmt*s and *Tet*s was demonstrated by profound changes of their temporal patterns in Per1$^{-/-}$/Per2$^{-/-}$ double knockout mice [126]. Further aspects of changes in oscillator components will be discussed below in the context of aging, cancer and other pathologies, however, mainly with regard to specific changes in the promoters of the oscillator genes. Importantly, it seems necessary to analyze temporal methylation patterns at specific sites, instead of determining global changes. In the mouse cortex, more than 23,000 rhythmically methylated CpGs have been recently identified [127]. Deletion of

the *Snord116* locus, a change that had been previously shown to dysregulate several oscillator components [25], caused losses or phase shifts in the rhythms at most of these CpG sites [127]. The value of the site-specific evaluation of DNA methylation has been impressively shown in a study on the human post-mortem dorsolateral prefrontal cortex, in which 420,132 DNA methylation sites from 738 subjects were included [125]. These data clearly showed that the various sites exhibit considerable differences in terms of amplitude and phasing, or, in a number of cases, arrhythmicity. In rhythmic genes, the nadir of methylation in their control regions was shown to precede peak transcript expression by 1-3 hours [125]. Moreover, the amplitudes of site-specific DNA methylation were shown to be typically decreased by age and, even more, in Alzheimer's disease (AD) [125]. An extensive study on methylatable cytosines in mouse liver and lung not only revealed circadian rhythms in many sites, but also an aging-dependent decrease in the number of cytosines under epigenetic control as well as decreases in circadian amplitudes of DNA methylation [128].

Changes in the methylation of oscillator genes were observed in aging mice, however, tissue-dependently [129]. For instance, in the stomach of older mice, decreased methylation was detected in the *Per1* promoter, whereas increased methylations were described in *Cry1*, *Bmal2*, and *Npas2* promoters of the spleen. The tissue-specific differences may be seen in conjunction with the distinct age-related changes of peripheral oscillators [130]. In a pilot study in patients with dementia, disease-specific alterations in CpG islands of oscillator genes were observed, determined in peripheral blood leukocytes. However, these findings were obtained in a relatively small number of patients, with highest frequency (about 37%) in dementia with Lewy bodies [131]. In early stages of AD, circadian deviations are already detectable. In AD brains and fibroblasts, the rhythms of DNA methylation at the *Bmal1* gene were found to be altered [132]. In early stages of Parkinson's disease (PD), hypomethylation of the *Npas2* promoter was detected [133]. These findings do not yet allow far-going conclusions, especially not in mechanistic terms, but they underline the susceptibility of the circadian system in neurodegenerative processes, with possibly detrimental consequences to the internal time structure of a patient. As melatonin has been shown to possess beneficial actions in models of these neurodegenerative diseases, the changes in oscillators may be of interest to melatonin research.

An additional field in which circadian disruption and suppression of melatonin secretion are merging [134] concerns the effects of light at night, which is often associated with shift work. After the original discovery of altered promoter methylations in oscillator genes [95], numerous additional deviations were described. This concerned differential methylation at 50 CpG islands in promoters of 31 microRNAs, among them miR-219 [135], which had been shown to modulate circadian oscillators [136] and to also be of relevance to cancer [135]. Methylation changes in *Per1*, *Per2*, *Cry1*, *Bmal1* and *Clock* were observed in nightshift working nurses, finding that were also discussed in terms of cancer induction [137]. More recently, a comparison of dayshift and nightshift workers revealed methylation differences at 16,135 of 473,800 loci, in 3769 of 20,164 genes, and 7173 of 22,721 CpG islands. Among them, several sites corresponded to the oscillator genes *Per3* and *Csnk1ε* [138]. In other words, unphysiological exposure to light that causes disturbances of the circadian system and suppression of melatonin secretion can have a substantial impact on gene expression. Additionally, disturbances by sleep loss have been shown to affect methylation at oscillator genes, in particular, *Cry1*, *Per1* and *Bmal1* [139].

With regard to the discussed relationship between shiftwork and cancer, it seems important to mention the numerous findings of deviating methylation patterns at core oscillator genes. Depending on type of cancer and study, one or several of the following genes were mainly affected and thereby changed in their expression: *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, and *Bmal1*. These changes

were reported for numerous different types of cancer, such as leukemias/lymphomas [140-143], breast cancer [144-146], cervical cancer [147], endometrial cancer [148], ovarian cancer [149], hepatocellular carcinoma [150], and gliomas [151,152]. Collectively, all these findings demonstrate that circadian oscillators are strongly dysregulated in cancer, because of the necessity to silence the oscillator components with tumor suppressor properties and to favor proliferation-promoting states of the oscillator [24,74].

This dysregulation has also profound consequences for the expression of SIRT1, which interacts with other oscillator components and is also influenced by melatonin. In prostate cancer cells, SIRT1 was found to be strongly upregulated, but substantially suppressed by melatonin [153]. Similar findings in other types of cancer are summarized elsewhere [24]. The fact that melatonin downregulates SIRT1 in tumor cells, although it upregulates the same protein in nontumor cells, indicates that its suppressing action in cancer is mediated via circadian oscillators, which are strongly dysregulated by tumor-specific epigenetic silencing, but become, to some extent, corrected by melatonin [24,74]. In normally operating oscillators, SIRT1 interacts with oscillator components as an amplitude-enhancing regulator [75,76]. The relationship to melatonin gains particular importance as (1) melatonin upregulates SIRT1 in various nontumor cells and as (2) melatonin seems to exert several effects via SIRT1, as far as they were shown to be blocked by sirtuin inhibitors or *Sirt1* siRNA. Therefore, SIRT1 has been concluded to represent a partial mediator of melatonin's actions [5]. Nevertheless, the relationship between these two molecules could well be a mutual one, as amplitude-enhancing actions of SIRT1 in the SCN should have consequences to the steering of the pineal gland. A potentially important aspect of SIRT1-mediated effects of melatonin might be based on the difference in half-life between the two molecules [154]. Melatonin has a very short half-life in the circulation, mostly in the range of 20 - 30 min, but it may induce more persistent effects by upregulating SIRT1, which has a considerably longer half-life, e.g., of about 8 hours in cultured glomerular mesangial cells [155]. Although the lifetime of intracellular melatonin may be higher than that in the circulation and although enhanced proteasomal degradation may shorten that of SIRT1, actions of melatonin via SIRT1 would presumably extend the intracellular effects of the former.

The role of SIRT1 should not only be seen in the context of its histone deacetylase activity. In addition, it displays deacetylating activity towards transcription factors and other regulatory proteins, including oscillator components such as PGC-1α [76], PER2 [156] and BMAL1 [157]. It also deacetylates the histone methyltransferase MLL1 (mixed-lineage leukemia 1), in a cyclic interplay with the protein acetyltransferase CLOCK [27]. Via these interactions, SIRT1 should be able to influence numerous processes at the chromatin, on a circadian basis. Moreover, SIRT1 seems to modulate DNA methylation by deacetylating DNMT1 [158]. Additionally, physical associations of SIRT1 with DNMT3b were reported to occur in condensed chromatin [159] and under conditions of cell stress [160]. Effects of SIRT1 on DNA methylation were observed at specific genes [28,29]. Concerning the control of DNA demethylation, SIRT1 was also shown to deacetylate TET2 [161]. However, it is still unclear whether these findings made in stem cells are relevant to circadian and melatonin-related functions. Other data obtained in stem cells concerning effects of SIRT1 on indirect inhibition of TET3 expression [162] would require confirmation in other systems to allow generalizations.

5. MELATONIN AND NONCODING RNAS

Both melatonin and the circadian system modulate various noncoding RNAs (ncRNAs) and are also subject to regulation by such RNAs. Several aspects of these mutual relationships have been

addressed elsewhere [12-14,16,17,74,163]. Within the frame of this article, many of these actions will not be considered if they are related to posttranscriptional regulation. For instance, most of the known effects of microRNAs are exerted by targeting other RNAs, in particular mRNAs or lncRNAs, but have no direct impact on transcription. Therefore, the focus will be on actions that concern the modulation of local chromatin structure or activity.

With regard to direct melatonin effects via ncRNAs at the chromatin, evidence is still restricted to a very few aspects, although future studies will likely expand the basis of evidence considerably and soon. Despite the existence of numerous results concerning melatonin effects on miRNAs and a few on lncRNAs [12-14,16,17,163], data on their physical interaction with chromatin are practically missing. Even indirect effects on chromatin are mostly restricted to DNA damage and to telomeres. For instance, poly(ADP-ribose) polymerase-1 (PARP-1) was shown to be a regulator of the senescence-associated secretory phenotype (SASP), which is downregulated by melatonin [49]. Connections to chromatin exist in two ways. First, PARP-1 is a sensor of DNA damage and, therefore, relevant to the DNA damage response (DDR) and stimulated by SASP. Second, PARP-1 interacts with the ncRNA *TERRA* (telomeric repeat-containing RNA), an effect believed to further stimulate SASP [49]. In the context of cancer, melatonin was shown to sensitize hepatocellular carcinoma cells to DNA damage by chemotherapy and radiotherapy. In this case, melatonin was reported to induce the lncRNA *RAD51-AS1*, which inhibits the translation of *RAD51* mRNA required for effective DNA repair [164]. Although no direct evidence for an involvement of melatonin is available for further epigenetic aspects of DNA damage, SASP and DNA repair, it is worth to be noted that these processes are also co-regulated by microRNAs [165,166]. It is also important to not generally reduce miRNA effects to posttranscriptional actions. Mutual interactions exist between miRNAs and DNA methylation and, therefore, gene transcription [167,168]. Important proteins involved in DNA methylation and reading, such as DNMTs, MeCP2 (methyl CpG binding protein), MBD2 and 4 (methyl-CpG binding domain proteins 2, 4) are known to be controlled by miRNAs [168]. The role of intranuclear miRNAs is increasingly perceived and mechanisms of both transcriptional gene silencing and transcriptional activation have become known [169]. Apart from actions via DNA methylation and also histone methylation, several miRNAs can directly interact with DNA. For instance, miR-552-3p was shown to bind to a hairpin loop in the cruciform structure of CYP2E1 promoter, thereby preventing the association with the transcriptional activator SMARCE1 [170]. Gene transcription can be stimulated by miRNAs that associate with enhancers [169], an effect demonstrated, e.g., for miR-24-1 [171].

In addition to these possibilities, which are awaiting further research in the melatonin field, several indirect effects of melatonin can be expected to exist by modulating circadian oscillators and by upregulating sirtuins. Several microRNAs are known to influence the oscillator machinery, such as miR-96, miR-132, miR-182, miR-183 and miR-219-1 [172]. By affecting circadian clocks, the miRNAs should be able to influence gene expression via chromatin remodeling, and melatonin might modulate these actions due to its own chronobiotic properties. However, the relationship between melatonin and these miRNAs would require further clarification. While miR-96, miR-182, and miR-183 have been related to the control in the pineal gland itself [173], other effects have been observed in brown adipocytes [174], sensory organs and in cancer [175], but have not been related to melatonin. The MeCP2-targeting miR-132 was found to be a regulator of seasonal changes in the murine SCN, but these were explicitly concluded to be independent of melatonin [176]. However, another study had recently shown that melatonin protects primary neurons against Aβ toxicity via a miR-132-mediated pathway [177].

Potentially, lncRNAs can have the potential of directly interacting with chromatin. However, this is not generally the case, because they may also act by binding to other RNAs, either directly

or indirectly by generating miRNAs. To date, some effects of melatonin on the expression of nontelomeric lncRNAs have been described [163,164,178-181]. However, in all these cases, it seems that the respective lncRNAs have not directly targeted sites at or close to transcription, but rather acted indirectly via RNA interactions and subsequent changes of transcription factors such as NF-κB or HIF-1α. In the future, it would be of particular interest to study effects of melatonin on chromatin-interacting RNAs, such as 1D and 2D eRNAs and, even more, super-enhancer lncRNAs. To find this kind of effects is highly likely, since many of these RNAs have been found to be rhythmically expressed. If they are not influenced by melatonin directly, they may be modulated by melatonin's actions on SIRT1. However, information of SIRT effects on enhancer or super-enhancer RNAs is still missing. As mentioned in the Introduction, several hundred rhythmic lncRNAs were found to be associated with enhancer regions, only in mouse liver [23]. Many more will be found on an organ-wide scale. In the murine liver, already 50 of them were classified as super-enhancer lncRNAs [23]. These super-lncRNAs multiply interact with the chromatin including the DNA. They, or at least, one category of them, are known to bind to anchoring regions at the DNA that are distant to the binding sites of master transcription factors [16,182]. This is explained by the formation of local lncRNA:DNA:DNA triplex structures based on specific triplex-forming repeat domains that interact with DNA anchor sites [182]. This also indicates an independence of classic transcription factors, because these cannot be expected to interact with triplexes.

CONCLUSION

In the literature summarized in this article, various effects of melatonin related to chromatin have been described. To date, most of the evidence is restricted to the regulation of expression of specific genes, as controlled by histone modification. Additionally, some effects on the DNA methylation/demethylation balance have been reported. Much more research of this type would be desired. The modulation of DNA-interacting ncRNAs represents another field that merits future attention in studies on melatonin. To date, the evidence for chromatin-affecting actions of melatonin is still fragmentary and, sometimes, not fully consistent to a degree that allows generalization. This will foreseeably change in the course of more expanding research on this topic.

A particularly promising route of investigation appears to be the systematic cell biological analysis of melatonin effects on circadian oscillators, not only concerning the SCN, but importantly also the numerous peripheral oscillators that deviate from each other in details of tissue- and cell-specific control of gene expression. Although there is certainly an overlap of CCGs among different cell types, many others of them are cell specifically expressed. The future importance of considering oscillator-directed actions of melatonin may be also seen in the possibility of the global, but partially cell-specific chromatin remodeling within the circadian cycle.

The signaling routes by which melatonin influences chromatin structure, both gene-specifically and globally, require further investigation. Notably, some findings that that have been reported on downregulation of ERK1/2 signaling may be seen as conflicting with the known canonical actions via ERK1/2 activation, as mentioned in the Introduction. Therefore, it may be necessary to more generally include secondary signaling [5,14] into the experimental approaches and interpretations. One of the promising routes concerns the role of SIRT1 and, presumably, other sirtuin subforms, too. The repeatedly demonstrated upregulation of SIRT1 by melatonin in nontumor cells and the suppression of related melatonin effects by sirtuin inhibitors or *Sirt1* knockdown strongly indicate that SIRT1 mediates several actions of melatonin. The additional role of SIRT1 in oscillators is another good reason for assuming a more extended spectrum of melatonin effects via this sirtuin.

With regard to the thoughts outlined in this review, it will be of utmost importance to consider contextual differences between, in particular, (1) conditions of aging, in which melatonin, sirtuins and the circadian system are declining, (2) cancer, in which melatonin frequently does the opposite of that what is known from nontumor cells, (3) other pathologies, especially those with an inflammatory component, and (4) development, in which regulation processes exist or are prevailing that differ from those in the adult organism. To distinguish between these fields will avoid unnecessary controversies caused by inappropriate disregard of the contextual differences.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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