

Neuroinflammation and Aging: Significance of Declining Circadian Functions and Melatonin

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Abstract

With regard to the complexity of aging, orchestrating mechanisms that decline by age and influence numerous physiological and cell biological processes are of particular interest. The circadian multioscillator system, actions by melatonin and Sirtuin 1 (SIRT1) exhibit such properties. Moreover, they are in multiple ways intimately coupled: Melatonin formation by the pineal gland depends in mammals on the input by the circadian master clock, the Suprachiasmatic Nucleus (SCN). In turn, melatonin feeds back to the SCN, and it also influences cellular oscillators outside the SCN. Increasing evidence shows that melatonin induces SIRT1 expression, in the context of aging and of inflammation. Both melatonin and SIRT1 are capable of increasing circadian rhythm amplitudes and some melatonergic actions seem to be mediated by SIRT1. The circadian system, melatonin and SIRT1 jointly act in a beneficial way in the fields of low-grade neuroinflammation, antioxidative protection and support of mitochondrial functions.

Keywords: Aging; Circadian; Inflammaging; Melatonin; Neuroinflammation; Sirtuin 1

Introduction

Aging is a highly complex and multifaceted process with considerable inter-individual differences concerning the decay velocities of the various physiological functions. Importantly, aging is much more than just natural wear and tear, although such alterations may contribute to the age-related decline and accelerate functional deterioration. Numerous detrimental and often interrelated cell biological, biochemical and physiological changes are known that impair the health state and can limit lifespan, such as DNA damage, mitochondrial dysfunction, high rates of apoptosis and other forms of cell death, telomere attrition, decreased hormone secretion and immuno-senescence. This complexity indicates a necessity for identifying connections between these processes and, especially, to seek for orchestrating mechanisms and regulators that decline by age. The circadian multioscillator system and melatonin, which is part of the former, display such properties. In the youthful organism, they control countless cellular and physiological functions, which gradually lose rhythmicity and efficacy by age [1-3].

Inflammatory responses play a substantial part in aging processes and strongly contribute to the deteriorations resulting thereof. This connection has been given rise to coining the term of inflammaging [4,5]. Inflammaging has not only to be seen as an aspect of immuno-senescence, but its relevance also concerns the inflammation-related oxidative and nitrosative/nitrative stress with its numerous effects of damage to DNA and mitochondria [3-6]. Moreover, the enhanced formation and release of reactive oxygen species and nitric oxide initiate vicious cycles based on the mutual communication between neurons, astrocytes and microglia [3,6,7]. Another specific aspect of inflammaging concerns the Senescence-Associated Secretory Phenotype (SASP), which is apparent in mitotically arrested DNA-damaged cells that release proinflammatory cytokines and chemokines [6,8-10]. Notably, the affected cells are not immune cells in the strict sense, but turn into immunologically relevant players, which attract leukocytes, especially macrophages, and cause persistent local inflammation. In the brain, SASP was observed as a property of DNA-damaged astrocytes, which develop neurotoxic properties and stimulate microglia [11,12]. An additional, recently discovered aspect of inflammaging concerns its relation to the so-called garb-aging, which consists in the contribution of inflammatory responses to altered molecules produced by damaged

or dying cells that have become unable to efficiently eliminate them by proteasomal and autophagic processes [13].

Relevance of Low-Grade Neuroinflammation and Neuroinflammaging

The processes of inflammaging, which seem to be involved in the majority of age-related diseases [14] are of particular significance to the brain, because low-grade neuroinflammation strongly contributes to aging and is additionally involved in various neurodegenerative pathologies [2,6,15]. Moreover, detrimental alterations in the central nervous system have countless consequences for peripheral organs, too. Neurodegenerative changes also affect the circadian system, thereby cause sleep disturbances, which, in turn, promote proinflammatory responses [7,16,17]. This role of neuro-inflammation is not only relevant to disease progression, but, importantly, also to disease onset. In Alzheimer's Disease (AD), inflammaging has been shown to be prodromal to later, more severe manifestations of this pathology [18]. This conclusion conforms with other findings that have identified brain insulin resistance as an early pro-inflammatory change of AD [6,19-23]. Amyloid- β peptides and oligomers further contribute to the inflammatory processes by activating microglia [24,25] and causing neurons to release pro-inflammatory cytokines and chemokines [26].

With regard to the detrimental and aging-promoting actions of low-grade brain inflammation, counteracting mechanisms and factors are of particular interest. Without wanting to oversimplify the mechanistic networks and options of interventions, this short article shall only focus on two ubiquitously acting regulators, melatonin and Sirtuin 1 (SIRT1). Moreover, these two factors cannot be discussed in a meaningful way

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without appropriately considering their relationships to the circadian oscillator system [27].

Melatonin in the Brain

Melatonin is usually known as the hormone of the pineal gland, which is, however, only the main source of circulating melatonin, but not the main site of overall synthesis, since quantities in extrapineal sources exceed by orders of magnitude those in the pineal gland [1,17]. From the pineal gland, melatonin is released both into the circulation and, *via* the pineal recess, into the third ventricle of the brain [28-30]. As melatonin is synthesized and released by the pineal gland preferentially at night, the chronobiological information of high melatonin is delivered *via* the circulation primarily to the peripheral tissues. Although melatonin can also cross the blood-brain barrier and is taken up *via* the choroid plexus, the direct release into the third ventricle has been recently judged to be more important with regard to the influence on the hypothalamic circadian master clock, the Suprachiasmatic Nucleus (SCN) [29,30]. Additional routes of melatonin delivery to the brain are possible *via* the aqueduct of the midbrain into the fourth ventricle, from there *via* the medial foramen of Magendie and the two lateral foramina of Luschka to the subarachnoid space [29]. However, in quantitative terms, highest concentrations are found in the third ventricle, from where the adjacent SCN pair is easily reached [29,30]. Moreover, melatonin is formed in some parts of the central nervous system [1,31]. A recent study demonstrated enhanced melatonin synthesis in response to inflammation in the cerebellum, however, without substantial release to other parts of the brain [32].

In mammals, melatonin is mutually interconnected to the SCN, in terms of being both an output and an input factor of the master clock [33]. The light/dark information that the SCN receives from melanopsin-containing retinal ganglion cells is transmitted *via* a neuronal pathway to the pineal gland, where melatonin synthesis is mainly stimulated by norepinephrine from postganglionic sympathetic fibers, with some modulation by other neuronal connections [34]. On the other hand, the SCN receives information from melatonin by virtue of a high density of melatonin receptors present in this place [1]. Melatonin can phase shift circadian rhythms generated in the SCN [1,35], but there is additional evidence that it also influences semi-autonomous and almost autonomous peripheral and other central oscillators [27,36]. Although the mammalian pineal gland also harbors an endogenous clock [37], this is sensitive to the input by norepinephrine, and melatonin synthesis strongly declines when this input is reduced. Therefore, a functional weakening of the SCN, e.g., by reduced light transmission or by neurodegeneration, and likewise by degenerative impairments of the neural transduction pathway to the pineal gland, also lead to a flattening of the melatonin rhythm in the pineal gland, in the circulation and, expectably, in the third ventricle [2,27]. In fact, aging is typically associated with functional losses of the circadian system. This concerns the rhythm amplitudes in both the SCN [38] and numerous peripheral clocks [39]. In some oscillators, amplitudes are reduced, in others shifted and, thus, more poorly coupled, whereas some are only moderately affected. In other peripheral clocks, overt rhythmicity appears to be completely lost, but can be reactivated by appropriate stimuli [39]. Reductions of nocturnal melatonin levels are typically observed during aging, but also occur in numerous diseases and disorders of different etiologies [2,40]. The decrease in pineal and circulating melatonin levels is particularly obvious in neurodegenerative diseases and, in these cases, clearly associated with SCN dysfunction. In AD, melatonin levels are not only reduced, but the remaining small maxima also dysphased and temporally strongly scattered [41]. In

post-mortem pineals of AD patients, the melatonin rhythm seemed to be completely lost, whereas this rhythmicity was clearly preserved in age-matched controls [42]. As a consequence, age- or disease-related reductions of melatonin signify the loss of an important orchestrating regulator molecule that displays numerous beneficial actions. These concern antioxidant, antiexcitatory, anti-inflammatory, and antifibrillogenic effects [1-3,6,27,43-46], in addition to the losses in coordinative functions within the circadian system [1]. With regard to neuroinflammation, the antiexcitatory, mitochondria-protective and activation of microglia suppressing effects are of particular importance. Moreover, recent findings concerning an increase of α -secretase activity in cells overexpressing human β -Amyloid Precursor Protein (β APP) to generate the non-amyloidogenic and neuroprotective fragment sAPP α [47] and the inhibition of the amyloidogenic β - and γ -secretases [48] indicate additional neuroprotective properties. Generally, neuroprotection belongs to the most amply documented actions of melatonin, which have been studied under various conditions and multiply reviewed, e.g., in refs. [1,6,31,43,44,49-53].

Relationship of Melatonin to Sirtuin 1 and Consequences to Circadian Amplitudes

Investigators have mostly regarded the beneficial effects of melatonin from a non-dynamic point of view, which would, however, be important with regard to its role in the circadian system. Circadian rhythmicity itself contributes to protection against damage by free radicals and mitochondrial malfunction [54]. Nevertheless, melatonin can act both directly on cellular processes that are susceptible to melatonergic signaling and indirectly *via* modulation of circadian oscillators [36]. Changes in the expression of circadian core oscillator components by melatonin have been repeatedly observed [36] and melatonin-deficient mice exhibited flattened, almost undetectable variations of such components, contrary to well-pronounced rhythms in melatonin-proficient strains [55,56]. These findings strongly indicate that melatonin represents an amplitude-enhancing regulator in the circadian system [36].

The modes by which melatonin exerts these amplitude-enhancing effects on oscillators has remained for quite some time rather unclear. Although one of the melatonergic signaling pathways, that of PKC-dependent ERK1/2 activation [57], has been shown to be decisive for phase shifting of circadian oscillations [58], this may not yet explain the increases of rhythm amplitudes. Recent data on the relationship between melatonin and SIRT1 may provide a link to this problem. Initially, this connection was largely overlooked, because studies in cancer cells or tissue revealed strong reductions of SIRT1 expression by melatonin. However, melatonin behaves entirely differently in nontumor cells. Especially in the context of aging, melatonin was shown to upregulate SIRT1 expression in various models, as recently summarized [27]. This discrepancy is explained by tumor-cell specific epigenetic silencing of core oscillator components that display tumor suppressor properties, whereas these components undergo normal cycling in non-tumor cells [27].

SIRT1 has been shown to play an important role in circadian oscillators. The profound chronobiological actions of the protein deacetylase SIRT1 were discovered in the group of P. Sassone-Corsi [59-61]. In brief, SIRT1 was identified as an accessory oscillator component. Basis of its cycling activity is the binding of the core oscillator components BMAL1 and CLOCK to an E-box in the promoter of the nicotinamide phosphoribosyltransferase (*Nampt*) gene. The resulting cyclicity in NAMPT protein expression leads to a rhythm in NAD⁺

concentration, which drives the activities of various sirtuins which use NAD⁺ as a substrate and activator. Notably, rhythmic expression of SIRT1 is not required, because the decisive parameter is SIRT1 activity rather than protein concentration.

An important and, in the beginning, surprising property of SIRT1 is its capability of enhancing circadian oscillation amplitudes. This has been explained in two different ways, (1) By physical interaction of SIRT1 with the BMAL1/CLOCK heterodimer; and (2) By SIRT1-dependent deacetylation of PGC-1 α (peroxisome proliferator-activated receptor- γ coactivator-1 α), binding of deacetylated PGC-1 α to ROR α (retinoic acid receptor-related orphan receptor- α), an activator at the ROR response elements in the promoters of the *Bmal1* and *Clock* genes [38]. Regarding these two possibilities, differences may exist between the various cellular oscillators in central and peripheral tissues. An important aspect of aging is the observed senescence-associated decline of SIRT1 expression [17,27,38]. The above-mentioned upregulation of SIRT1 expression by melatonin in the context of aging [27], thus, indicates a mode by which exogenous melatonin might increase circadian amplitudes indirectly by re-initiating enhanced SIRT1 expression. Whether melatonin also upregulates other sirtuin subforms, in particular, the mitochondrially located SIRT3 and the constitutively chromatin-associated SIRT6, would be of great interest, but would still require a broader experimental basis. Both SIRT3 and SIRT6 are driven by the NAD⁺ cycle and transmit circadian information [62,63], but do not seem to feed back to the core oscillator components.

Conclusion

A concept of jointly increasing melatonin and SIRT1 levels is highly attractive in gerontological terms, especially with regard to neuroinflammation. Melatonin, which is very short-lived in the circulation because of a half-life mostly in the range of 20-30 min, may induce more persistent effects by upregulating SIRT1, which, as a protein, should have a considerably longer half-life. In cultured glomerular mesangial cells, the half-life of SIRT1 was about 8 h [64]. Under certain conditions and in certain cells, this may be shortened by stimuli that enhance SIRT1 ubiquitinylation, followed by proteasomal degradation [64]. Corresponding data in brain tissue would be required for a definite judgment, but the half-life of SIRT1 in neurons will be, with some likelihood, in the range of several hours and, therefore, much longer than that of melatonin. Independently of the rather moderate effects of melatonin on sleep maintenance [2], daily repeated and appropriately timed application of this hormone may improve, *via* SIRT1, circadian rhythms in elderly patients, as far as the decline in the circadian system has not been caused by irreversible neurodegeneration. Moreover, the antioxidant, mitochondria-protective and anti-inflammatory actions of melatonin might be complemented and enhanced by corresponding actions of SIRT1, which displays beneficial effects in the same fields and may, according to recent data, partially mediate actions by melatonin [65-74] (Figure 1). Anti-inflammatory effects of SIRT1 deserve further attention and extension towards studies on levels of proinflammatory cytokines in the brain would be required, especially concerning TNF- α , IL-2 and IL-6. To date, most pertinent information has been based on the application of powerful proinflammatory agents such as LPS (bacterial lipopolysaccharide) in combination with sirtuin activators and inhibitors, whereas investigations on upregulation of SIRT1 in the otherwise non-compromised aging brain, along with measurements of cytokine levels, are urgently desired. Nevertheless, the already available data on neuroprotection and anti-inflammatory properties of SIRT1 are encouraging [75]. The enhancement of melatonin, SIRT1 activity and, thereby, circadian amplitudes seems to be a worth-while aim for

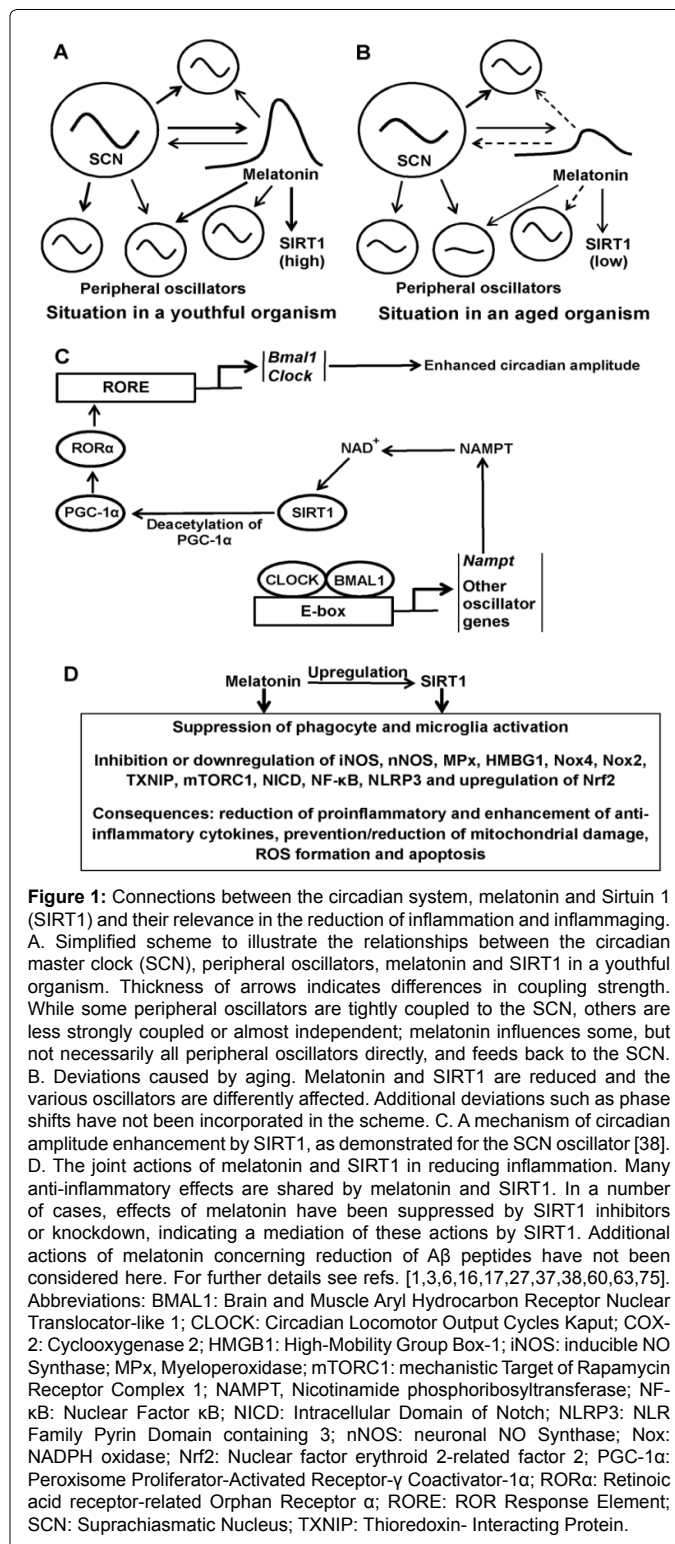


Figure 1: Connections between the circadian system, melatonin and Sirtuin 1 (SIRT1) and their relevance in the reduction of inflammation and inflammaging. A. Simplified scheme to illustrate the relationships between the circadian master clock (SCN), peripheral oscillators, melatonin and SIRT1 in a youthful organism. Thickness of arrows indicates differences in coupling strength. While some peripheral oscillators are tightly coupled to the SCN, others are less strongly coupled or almost independent; melatonin influences some, but not necessarily all peripheral oscillators directly, and feeds back to the SCN. B. Deviations caused by aging. Melatonin and SIRT1 are reduced and the various oscillators are differently affected. Additional deviations such as phase shifts have not been incorporated in the scheme. C. A mechanism of circadian amplitude enhancement by SIRT1, as demonstrated for the SCN oscillator [38]. D. The joint actions of melatonin and SIRT1 in reducing inflammation. Many anti-inflammatory effects are shared by melatonin and SIRT1. In a number of cases, effects of melatonin have been suppressed by SIRT1 inhibitors or knockdown, indicating a mediation of these actions by SIRT1. Additional actions of melatonin concerning reduction of A β peptides have not been considered here. For further details see refs. [1,3,6,16,17,27,37,38,60,63,75]. Abbreviations: BMAL1: Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocator-like 1; CLOCK: Circadian Locomotor Output Cycles Kaput; COX-2: Cyclooxygenase 2; HMGB1: High-Mobility Group Box-1; iNOS: inducible NO Synthase; MPx, Myeloperoxidase; mTORC1: mechanistic Target of Rapamycin Receptor Complex 1; NAMPT, Nicotinamide phosphoribosyltransferase; NF- κ B: Nuclear Factor κ B; NICD: Intracellular Domain of Notch; NLRP3: NLR Family Pyrin Domain containing 3; nNOS: neuronal NO Synthase; Nox: NADPH oxidase; Nrf2: Nuclear factor erythroid 2-related factor 2; PGC-1 α : Peroxisome Proliferator-Activated Receptor- γ Coactivator-1 α ; ROR α : Retinoic acid receptor-related Orphan Receptor α ; RORE: ROR Response Element; SCN: Suprachiasmatic Nucleus; TXNIP: Thioredoxin- Interacting Protein.

reducing low-grade neuro-inflammation and for improving health and life quality in elderly subjects. As a consequence, the hypothesis should be experimentally examined that, in aging mammals, exogenous melatonin not only elevates the levels of SIRT1, but that this upregulation also increases circadian amplitudes, which may also influence the rhythmicity of endogenous melatonin. With regard to

the anti-inflammatory actions of both melatonin and SIRT1 and to the circadian control of several immunological functions, concomitant improvements of the three orchestrating regulators, melatonin, SIRT1 and the circadian system, may reduce aging-related inflammation and enhance physiological functioning.

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