Chapter 14
Melatonin as a Chronobiotic and Cytoprotector in Healthy Aging

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14.1 Introduction

The impending aging of human population is an undeniably, remarkable event. According to the World Health Organization (WHO), the number of individuals aged 60 and up will double from 1 billion in 2019 to 2 billion in 2050 (WHO, Aging and health), with 80% of all older people living in low- and middle-income countries (WHO, Non-communicable diseases). As individuals live longer, they will encounter a variety of health and quality-of-life concerns, including an increase in the prevalence of non-communicable diseases (NCDs). According to the WHO, NCDs kill 41 million people each year, accounting for 71% of all deaths worldwide (Khan 2019). Over 80% of NCD deaths are caused by cardiovascular illnesses, malignancies, respiratory disorders, diabetes, and neurological diseases. NCDs are highly associated with impairment, dependency, and the need for long-term care.

NCDs are characterized by a chronic low-grade pro-inflammatory condition termed as "inflammaging" (Barbé-Tuana et al. 2020; Franceschi et al. 2018; Fulop et al. 2018). Indeed, as the aging process progresses, the human body's ability to resolve inflammation decreases, resulting in an imbalance of pro- and anti-inflammatory events. Circadian disturbance, as evidenced by interrupted sleep, is

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another critical process in the aging organism. Sleep cycle disruption, as a comorbidity of inflammaging, results in a slew of pathophysiological alterations that hasten the aging process.

Melatonin is a methoxyindole having several features that make it useful for dealing with circadian disturbance and inflammation. It functions as a circadian synchronizer and amplitude enhancer, a direct and indirect antioxidant, an immunological modulator, and a protector and modulator of mitochondrial activity. Melatonin levels tend to drop as people age, and they are even lower in people with NCDs.

This chapter examines melatonin's many functions as a chronobiotic and cytoprotector in relation to age-related NCDs (Cardinali 2019a, b, c). Melatonin attenuates inflammatory responses and progression of inflammation (Cardinali and Hardeland 2017). Furthermore, the late afternoon/night surge in melatonin synchronizes both the central circadian pacemaker found in the hypothalamic suprachiasmatic nuclei (SCN) and a slew of peripheral cellular clocks (melatonin's "chronobiotic action") (Cardinali et al. 2021). The link of melatonin with sirtuins, known by their relevant qualities as aging suppressors and accessory components or downstream elements of circadian oscillators, will be dealt with in depth (Hardeland 2019). SIRT1 and SIRT3 appear to be at the heart of melatonin's chronobiotic and cytoprotective activities in healthy aging.

14.2 Inflammaging

Claudio Franceschi and colleagues coined the word "inflammaging" to describe the imbalance between inflammatory and anti-inflammatory signals that occurs as people age (Fulop et al. 2021). This imbalance contributes to the onset of age-related diseases such as cardiovascular disease, metabolic syndrome, and diabetes, as well as neurodegenerative, renal, lung, and skin diseases. Increased inflammatory indexes such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, IL-6, IL-8, IL-12, IL-17 and IL-22, chemokines, and inflammatory factors like monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein characterize inflammatory aging (Xia et al. 2016).

Macrophages are important players in the delicate balance of pro- and anti-inflammatory reactions. They carry out critical innate immunological tasks, including the clearing of dying cells through phagocytosis (Lu et al. 2021). Macrophages can be divided into two types of polarization states: conventionally activated (M1) and alternatively activated (M2). Genes associated to pro-inflammatory cytokines or oxidative stress, such as TNF-α, IL-6, MCP-1, and inducible nitric oxide synthase (iNOS), are substantially expressed in M1 macrophages, whereas anti-inflammatory cytokine IL-10 is highly expressed in M2 macrophages (Lu et al. 2021).

It is worth noting that, in the absence of acute infection or physiological stress, the levels of inflammatory mediators tend to rise with age. When stress occurs, however, it causes inflammatory damage to cellular components such as proteins, lipids, and DNA, as well as contributing to the age-related decline in physiological functions,

particularly in cells regulating homeostasis, such as neural, immune, and endocrine cells (Bulut et al. 2021). As a result, the functional losses seen with aging include a slow-moving, long-lasting type of oxidative stress caused by increased production of reactive oxygen and nitrogen species (ROS and RNS), which is exacerbated by mitochondrial damage (Bader and Winklhofer 2020; García et al. 2020).

Because of thymic involution and extended germ exposure, which both lead to the depletion of numerous subtypes in developmental stages of leukocytes, an age-related pro-inflammatory propensity is almost unavoidable (Hardeland 2019). However, considerable interindividual differences exist in the velocity of these changes and in the balance between pro-inflammatory and anti-inflammatory cytokines. This could be attributable to a genetic predisposition as well as previous viral load histories, both of which contribute to an immunological risk profile. In centenarians, protective phenotypes include an inverted immunological risk profile (Pawelec 2018; Wikby et al. 2008). A higher proclivity for inflammatory responses could shorten life expectancy. It is likely, then, that a sound immune system is the most reliable predictor of human longevity and healthy aging (Bulut et al. 2021; Fulop et al. 2021; Santoro et al. 2021).

As previously stated, inflammaging is a symptom of oxidative stress, which is defined as an increase in the generation of ROS and RNS compared to the quantity of antioxidants present in the body's natural defensive systems. Melatonin stands out among antioxidants for its anti-inflammatory and antioxidant effects, as well as its role as a metabolic regulator (Cardinali 2019a, b, c; García et al. 2020; Hardeland et al. 2015; Majidinia et al. 2018). Melatonin may have a therapeutic value in promoting healthy aging because it controls several inflammaging-related pathways.

14.3 The Circadian Apparatus

The daily and seasonal changes caused by the planet's rotation and orbit around the sun have a consistent impact on the organisms that live on it. The light–dark cycle is the most visible manifestation of this periodic pattern, which has led to the development of endogenous circadian timing systems that synchronize biological functions with the environment (Foster 2020). This is the basis of predictive homeostasis evolving as an adaptation to anticipate predictable changes in the environment, such as light and darkness, temperature, food availability, or predator activity (Burdakov 2019). Therefore, the circadian clock is one of the most indispensable biological functions for living organisms and acts like a multifunctional timer to adjust the homeostatic system, including sleep and wakefulness, hormonal secretions, immune function, and most other bodily functions, to the 24-h cycle.

The circadian system in mammals is made up of numerous distinct tissue-specific cellular clocks. The phases of this plethora of cellular clocks are controlled by a master circadian pacemaker found in the hypothalamic suprachiasmatic nuclei (SCN) to generate coherent physiological and behavioral responses (Hastings et al. 2018).

Among the environmental photic (natural/artificial light) and non-photic (food, behavioral arousal, etc.) cues, natural light is the pervasive and prominent synchronizer ("zeitgeber"). The retinohypothalamic tract entrains the SCN via neurotransmitters that act as messengers, controlling the differential expression of clock genes and clock-controlled genes inside SCN cells and influencing the observable output in the form of physiology and behavior (Hastings et al. 2020).

Circadian clocks are based on clock genes, some of which encode proteins that can feedback and repress their transcription on a molecular level. These cellular oscillators are made up of interlocked transcriptional and post-translational feedback loops that are controlled by a small number of core clock genes (Welz and Benitah 2020). Transgenic gene deletion technology was used to characterize the negative and positive transcriptional/translational feedback loops that make up the core clockwork in rats. The delay in the feedback loops, which is regulated in part by phosphorylation of the clock proteins that affect their stability, nuclear re-entry, and transcription complex formation, causes clock gene expression to oscillate (Takahashi 2017).

The circadian clock's complicated molecular mechanisms are conserved across animals. The transcription factors CLOCK and BMAL1, which form dimers through basic helix-loop-helix domains, are formed when the genes *Clock* and *Bmal1* are transcribed in mammals. The dimer then promotes transcription of two more genes, *Per* and *Cry*, resulting in the creation of the proteins PER and CRY, which dimerize and are then inhibited by CLOCK and BMAL1 expression. As PER and CRY deteriorate with time, the loop must be restarted (Takahashi 2017).

In both nocturnal and diurnal mammals, the levels of *Per* and *Cry* mRNAs in the SCN peak in the middle to late afternoon (Hastings et al. 2020). *Bmal1* mRNA increases around midnight, but *Clock* is expressed in the SCN throughout the whole time (Lee et al. 2001). Through binding to the CLOCK/BMAL1 complex, PER and CRY bind to the E-box element of the promoter regions of *Bmal1*, *Clock*, *Rev-Erb*, and other clock-controlled genes to limit their production (Takahashi 2017). After casein kinase 1 ε/δ phosphorylates PER and CRY, they are translocated to the nucleus (Lee et al. 2001). The master oscillation is modulated further by a secondary regulatory loop comprised of the nuclear receptors REV-ERB and ROR (retinoid-related orphan receptor). REV-ERB inhibits *Bmal1* and ROR promotes it through attaching to the RORE (response element-binding site) sequence in the promoter region of Bmal1 (Fontaine and Staels 2007; Preitner et al. 2003). Phosphorylation and ubiquitylation via the E3 ligase complex govern the stability of PER and CRY, culminating in their proteasomal destruction (Takahashi 2017).

Physiological and behavioral processes are visibly manifested in the complex interaction between the core clock genes and other clock-controlled genes. Interruptions of the circadian rhythm are harmful to one's health (Welz and Benitah 2020). Chronic jet lag and shift work have been linked to heart disease (Crnko et al. 2019), memory loss (Snider and Obrietan 2018), disruptions in hormone timing (Maierova et al. 2016), diabetes (Oosterman et al. 2020; Stenvers et al. 2019; Tsereteli et al. 2021), cancer (Asadi et al. 2021; Stangherlin et al. 2021; Wang et al. 2019), impaired reproductive health (Caba et al. 2018; Pan et al. 2020), and metabolic disorders (Che

et al. 2021; Reinke and Asher 2019; Spiegel et al. 1999). The use of chronotherapies, such as melatonin, to modulate the molecular elements of circadian rhythms to alleviate the ill-effects of circadian rhythm disorders and diseases with a circadian correlate is an area receiving growing attention in the scientific literature (Cardinali et al. 2021).

14.4 Melatonin as a Chronobiotic

Borbély et al. (2016) propose that the physiological regulation of the circadian rhythm of sleep/wakefulness (the body's main circadian rhythm) is divided into two parts: a circadian (24-h) component and a homeostatic component. Melatonin is an important component of the circadian clock, which controls the timing of sleep. In both normal and blind patients, the circadian rhythm in the synthesis and secretion of pineal melatonin is intimately linked to the sleep rhythm (Emens and Eastman 2017). The initiation of nocturnal melatonin secretion occurs roughly 2 h before a person's usual bedtime and has been linked to the onset of evening tiredness. Endogenous melatonin has been implicated in the physiological regulation of the circadian systems that govern sleep propensity in several studies (Auld et al. 2017; Gobbi and Comai 2019).

Aging has been linked to a decrease in sleep efficiency and consistency, as well as a decrease in the amplitude of the melatonin cycle and thus many other circadian rhythms in the body (Duffy et al. 2015; Kim and Duffy 2018). Early morning awakenings and trouble falling asleep have been noted regularly among the elderly. Sleep issues that affect senior insomniacs can be linked to melatonin secretion problems. Indeed, melatonin insufficiency causes a relative circadian desynchrony, which can lead to aging. As a result of its well-known chronobiotic capacity, melatonin supplementation can help to improve the quality of life of the aged.

Melatonin is a key player in circadian rhythmicity's coordination. Melatonin secretion is an "arm" of the biologic clock in the sense that it responds to signals from the SCN and that the timing of the melatonin rhythm reveals the status of the clock in terms of phase (i.e., internal clock time relative to external clock time) and amplitude (Pevet et al. 2021). Melatonin is also a chemical code of night in another sense: the longer the night, the longer the length of its secretion. This pattern of secretion serves as a temporal cue for seasonal rhythms in most mammalian species (Clarke and Caraty 2013; Wahab et al. 2018).

Pineal melatonin production is controlled by a complex neural system originating in the hypothalamic paraventricular nucleus (PVN) and ending in the highest levels of the thoracic spinal cord—the superior cervical ganglion sympathetic system (Pevet et al. 2021). The superior cervical ganglion's postganglionic sympathetic nerve terminals release norepinephrine into the pineal gland, which activates melatonin synthesis by interacting with β- (primarily) and α-adrenoceptors on pineal cell membranes. Melatonin is not kept in the pineal because of its high diffusibility, and it is expelled as soon as it is created (Tan et al. 2018). The SCN-melatonin loop is a group of components that govern circadian rhythms. Melanopsin-containing retinal ganglion cells,

the retinohypothalamic tract, SCN, PVN, intermediolateral cell column, sympathetic cervical ganglia, pineal gland, and the melatonin rhythm, all of which have feedback effects on the SCN, make up this loop (Tan et al. 2018).

In fact, all mammalian species' circadian pineal melatonin production is confined to the dark phase of the light/dark cycle. Melatonin is always synthesized throughout the night, regardless of the species' daily cycle of activity/rest, demonstrating its close link with the external photoperiod. If there is no light in the surroundings, melatonin is created at night (Pevet et al. 2021).

When present at night, blue light activates melanopsin-containing retinal ganglion cells, a specific retinal mechanism that suppresses pineal sympathetic norepinephrine release, reducing or eliminating melatonin generation. Melatonin can synchronize the circadian cycles of various organs and their functions due to the regularity of daily melatonin production, which is associated with high and low blood concentrations during the night and day, respectively. In vitro studies have revealed that a synthetic day and night melatonin profile can act as a pacemaker for most cells' daily rhythmic processes (Hardeland et al. 2011).

The effects of the internal zeitgeber melatonin on the circadian clock are time-dependent, just like the effects of the external zeitgeber light. Melatonin given to rats daily modifies the phase of the circadian clock, which could explain how melatonin affects sleep in humans (Pevet et al. 2021). Clinical trials in blind subjects (who have free running of circadian rhythms) treated with melatonin provide indirect support for such a physiological involvement (Skene and Arendt 2007). The revelation that the phase response curve for melatonin was opposite (i.e., around 180° out of phase) to that of light offered more concrete evidence for this notion (Lewy 2010).

Melatonin receptors have been discovered both in the CNS and in the periphery (Dubocovich et al. 2010). The MT1 and MT2 receptors, which belong to the G-protein coupled receptors (GPCR) families of membrane receptors, have all been cloned. GPR50, a new member of the melatonin receptor subfamily, was recently added (Cecon et al. 2018). GPR50 has a lot of similarities to MT1 and MT2, but it does not bind to melatonin or any other known ligand. The ability of these receptors to form homo- and heteromers with each other and with other GPCRs, such as the serotonin 5-HT2C receptor, is an intriguing property (Cecon et al. 2018).

Although melatonin's major physiological function is to regulate circadian and seasonal rhythmicity, the methoxyindole's activities are not limited to receptor-rich locations. Melatonin influences mitochondrial electron flux, the mitochondrial permeability transition pore, and mitochondrial biogenesis, as well as anti-excitatory activities, immunomodulation, including pro- and anti-inflammatory qualities, antioxidant actions, and energy metabolism (Tan and Reiter 2019). Many of these actions are independent of receptors.

Melatonin in the blood is loosely linked to albumin, and it is hydroxylated in the liver before being conjugated with sulfate or glucuronide (Claustrat and Leston 2015). The primary metabolite in human urine is 6-sulfatoxymelatonin. Melatonin is converted to kynurenine derivatives in the brain. Some of melatonin's metabolites, such as cyclic 3-hydroxymelatonin, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), and, with the highest efficacy, N^1-acetyl-5-methoxykynuramine, share its

well-documented antioxidant effects (AMK). Melatonin administration to experimental animals and people therefore initiates an "antioxidant cascade" (Reiter et al. 2017).

As already stated, circulatory melatonin in mammals is virtually entirely produced from the pineal gland. However, melatonin is also generated locally in most cells, tissues, and organs, including lymphocytes, bone marrow, thymus, gastrointestinal tract, skin, and eyes, where it can have an autocrine or paracrine role (Acuña-Castroviejo et al. 2014). There is now strong evidence that melatonin is synthesized in every animal cell with mitochondria.

Although it is usually assumed that the endogenous melatonin's chronobiotic impact is mediated by MT receptors, a chronobiotic effect can also be detected when pharmaceutical quantities of fast-release melatonin (that saturate receptors) are used. Even at a high dose, melatonin employed as a fast-release preparation administered at a single time point in the day (bedtime) keeps the chronobiotic effects (Fig. 14.1). Hence, the rationale for using melatonin as a preventive medication in NCDs caused by aging is based not only on the amelioration of the immunoinflammatory disorder, but also on the general improvement and prevention of potential complications caused by maintaining optimal circadian rhythmicity.

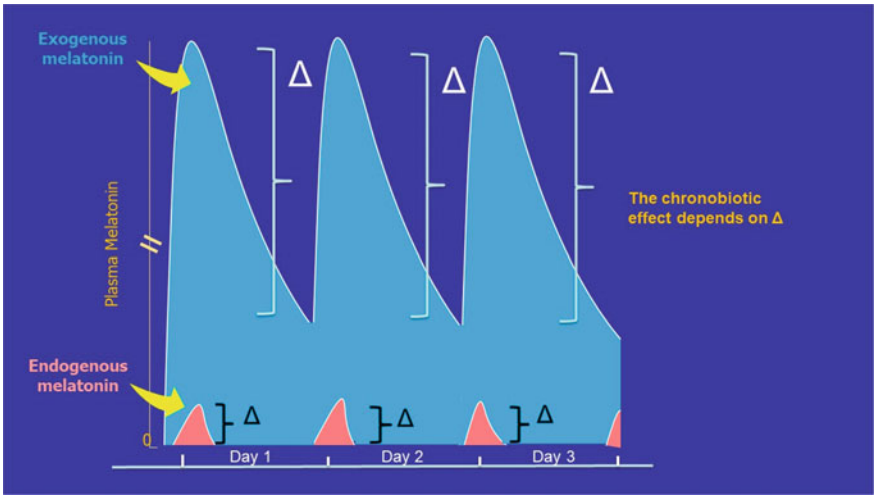

Fig. 14.1 Because of its pharmacokinetic properties, i.e., a very short half-life in the blood, when melatonin is given orally as a fast release preparation at bedtime, melatonin gives rise to a chronobiotic signal regardless of the amounts given (reproduced with permission from Cardinali et al. (2020a, b)

14.5 Use of Melatonin in Aged Sleep

Melatonin is a potent chronobiotic with a mild hypnotic potential. In sighted people who live in environments that are likely to produce a free-running rhythm, daily melatonin doses of 2–10 mg, timed to advance the phase of the internal clock in the SCN, preserve circadian rhythms synchronized to a 24-h cycle (Lewy 2010). After a brief period of free running, melatonin synchronizes the rhythm in people. Giving melatonin to blind subjects with free-running rhythms has been shown to stabilize, or entrain, the sleep/wake cycle to a 24-h period, resulting in improved sleep and mood (Arendt 2019). Melatonin administration helps to minimize the variation in the onset time of sleep in normal aged adults and demented patients with disrupted sleep/wake cycle synchronization. Melatonin's phase-shifting properties also account for its usefulness as a treatment for circadian-related sleep disorders such jet lag and delayed phase sleep syndrome (Burgess and Emens 2018).

The sleep/wake cycle has a bidirectional association with aging. Inadequate sleep, both in terms of duration and quality, can have a negative impact on health and consequently hasten the aging process. Sleep/wake cycle problems, on the other hand, tend to worsen with age due to the flattening and misalignment of circadian rhythms such as melatonin secretion, as well as the sleep-disturbing effects of aging-related ailments and diseases (Hardeland 2015). The most striking examples are immunosenescence, which also affects the brain (Cardinali et al. 2008; Hardeland 2018), and the nearly exponential increase in hydroxyl radical generation reported in the senescent brain (Poeggeler et al. 1993; Reiter 1995).

There is a considerable literature that suggests that the sleep/wake issues become more common as people get older. According to epidemiological studies, more than half of all persons over the age of 65 suffer from a persistent sleep-related ailment (Foley et al. 1995). Several meta-analyses support the view that the chronobiotic/hypnotic properties of melatonin are useful in aged patients with primary sleep disorders to decrease sleep onset latency and to increase total sleep time, with fewer effects on sleep efficiency (Auld et al. 2017; Ferracioli-Oda et al. 2013; Zhang et al. 2019). A role for melatonin in adult insomnia is also supported by several expert consensus reports (Geoffroy et al. 2019; Palagini et al. 2021; Wilson et al. 2019).

Sleep/wake disturbance has been linked to a variety of neuropathologies in numerous studies. In healthy participants, sleep loss or slow wave sleep disruption raised amyloid β (Aβ) levels in the CSF (Olsson et al. 2018; Ooms et al. 2014). A single night of total sleep deprivation was said to prevent the normal decline in CSF Aβ. The brain "glymphatic" hypothesis states that perivascular astrocytes, which are highly enriched in aquaporin-4, and changes in the vascular lumen generate active, lymphatic-like motions in the extracellular space of the brain (Boespflug and Iliff 2018; Braun and Iliff 2020). The exchange of solutes between the CSF and the interstitial fluid takes place mostly during slow wave sleep, when the cortical interstitial space expands by more than 60% and provides a low-resistance conduit for CSF and interstitial fluid movement in the brain parenchyma. The aging human brain has an impact on this. Various neurological disease states, such as stroke, traumatic brain

injury, and AD, have been understood in terms of glymphatic dysfunction's impact (Boespflug and Iliff 2018). It is worth noting that giving melatonin to AD transgenic mice improves their glymphatic clearance of Aβ (Pappolla et al. 2018).

Primary insomnia affects up to ten percent of the general population and up to 25–30% of the elderly, for whom insomnia therapy is an obvious medical necessity. Insomnia's direct and indirect costs add up to a significant socioeconomic burden. The most recommended medicines for the treatment of insomnia in the elderly are benzodiazepines (BZD) and other BZD receptor agonists (Z-drugs such as zolpidem, zaleplon, and zopiclone). Several meta-analyses that investigated the risks and advantages of these therapy choices in older patients found statistically significant improvements in sleep, but also a statistically significant risk of life-threatening side events (Schroeck et al. 2016; Winkler et al. 2014). Due to safety concerns, regulatory agencies have only approved these medications for treatment of older persons for no more than a few weeks. More than 40% of users of both BZD and Z medicines have had negative side effects.

European health authorities are implementing rules and making recommendations to decrease the use of BZD and Z-drug medicines. Despite national guidelines and recommendations, however, the campaigns have been largely unsuccessful, and the usage of these medications has continued to rise (Clay et al. 2013). The more obvious method for reducing chronic BZD use is to discontinue the medicine gradually; abrupt discontinuation can only be justified if a major side effect arises during therapy. There is no clear data about the best way to proceed with BZD withdrawal, and times range from four weeks to several months (Edinoff et al. 2021).

The interaction of melatonin with central BZD receptors was initially reported in 1986 (Acuña-Castroviejo et al. 1986) and the first study on the reduction of BZD use in melatonin-treated elderly people was published in 1997 (Fainstein et al. 1997). Melatonin's anxiolytic, antihyperalgesic, and antinociceptive actions are explained by its facilitation of γ-aminobutyric acid neurotransmission (Cardinali et al. 2016). Several clinical investigations have now confirmed melatonin's usefulness in reducing BZD use in chronically treated patients (Morera-Fumero et al. 2020). The results of a pharmaco-epidemiologic study aimed at assessing the impact of anti-BZD/Z-drug campaigns and the availability of alternative pharmacotherapy (melatonin) on BZD and Z-drug consumption in several European countries revealed that campaigns failed unless they were linked to the availability of melatonin on the market (Clay et al. 2013). Melatonin has therefore proven to be an excellent medication for maintaining healthy sleep patterns in the elderly.

14.6 Melatonin and Inflammaging

The significance of melatonin in reducing inflammation and its progression has gotten a lot of attention, especially when it comes to therapy options for people who have low endogenous melatonin levels. Melatonin is one of the hormones that is known to drop with age and, more importantly, in various age-related NCDs (Hardeland 2012; Vasey

et al. 2021). In coronary heart disease, metabolic syndrome, and type 2 diabetes, melatonin levels were found to be lower (Altun et al. 2002; Girotti et al. 2000; Hernández et al. 2007; Nagtegaal et al. 1995; Yaprak et al. 2003). Additional evidence from polymorphisms of human melatonin receptor genes indicates that deviations in melatonergic signaling may favor the development of prediabetic states, diabetes type 2, elevated cholesterol, and coronary heart disease. Furthermore, knocking down the melatonin receptor MT1 in mice resulted in insulin resistance (Contreras-Alcantara et al. 2010).

Melatonin acts as an anti-inflammatory at different levels. One of these is metabolic dysregulation repair, which includes preventing insulin resistance, an inflammation-promoting alteration that is a characteristic of the metabolic syndrome (Cuesta et al. 2013; Lee et al. 2020). Melatonin was found to be efficient in decreasing insulin resistance in a variety of animals, tissues, and induction approaches. Reduced serine phosphorylation of insulin receptor substrate 1 (IRS-1) is the key effect at which the relevant pathways converge in this regard, which is frequently followed by an increase of IRS-1 expression (Du and Wei 2014). Melatonin and the melatonergic agonist piromelatine have been found to reverse insulin signal transduction inhibition (She et al. 2009). Insulin resistance has been found to be an early indicator of low-grade neuroinflammation in neurodegenerative illnesses such as AD and Parkinson's disease (Sun et al. 2020a, b; Verdile et al. 2015).

The avoidance of processes that encourage or lead to inflammation is another level of action. Calcium overload, excessive nitric oxide (NO) release, which leads to the creation of peroxynitrite, peroxynitrite-derived free radicals, and eventually, tyrosine nitration, as well as mitochondrial malfunction because of oxidative stress, are all examples of it (Cardinali and Hardeland 2017; Hardeland et al. 2015). All these alterations are known to generate low-grade inflammation in numerous organs, which is linked to aging. In the central nervous system, this includes microglia activation and vicious cycles caused by overexcitation and oxidant damage, which result in reduced neuronal and astrocytic activities. Melatonin has been proven in animal models to prevent these harmful processes by acting as an anti-excitatory agent, protecting mitochondria, reducing peroxynitrite-related damage, and reducing microglia activation.

Melatonin's immunological effects are a third aspect of inflammaging to consider. Melatonin's many functions as an immunomodulatory drug include both pro-inflammatory and anti-inflammatory effects, resulting in either pro-oxidant or antioxidant equilibrium (Carrillo-Vico et al. 2013; Hardeland 2019; Markus et al. 2021). Melatonin is generally pro-inflammatory in immunosuppressive circumstances. The exact reasons for when melatonin acts pro- or anti-inflammatory are yet unknown, while the severity of inflammation and the chronological sequence of initiation and healing processes are certain to play a part.

Melatonin's anti-inflammatory properties take precedence as people age. Melatonin reduced pro-inflammatory cytokines including TNF-α, IL-1, and IL-6 in the livers of elderly, ovariectomized female rats while increasing the anti-inflammatory cytokine IL-10 (Kireev et al. 2008). Corresponding findings were verified in the

dentate gyrus, along with an increase of sirtuin 1 (SIRT1), a protein with strong anti-inflammatory characteristics. TNF-α and IL-1 levels were reduced, whereas IL-10 levels were elevated, in the liver, pancreas, and heart of the senescence-accelerated mouse strain SAMP8 (Cuesta et al. 2011, 2010; Forman et al. 2011).

Other studies have found that melatonin has anti-inflammatory effects in brain damage, ischemia/reperfusion (I/R) lesions, hemorrhagic shock, and various forms of high-grade inflammation, such as endotoxemia and sepsis. Remarkably, the use of melatonin as a countermeasure to a SARS-CoV-2 infection has been advocated (Reiter et al. 2020a; Zhang et al. 2020). Melatonin has pan-antiviral effects, and it diminishes the severity of viral infections and reduces the death of animals infected with numerous different viruses, including three different coronaviruses. Network analyses, which compared drugs used to treat SARS-CoV-2 in humans, also predicted that melatonin would be a most effective agent for preventing/treating COVID-19 (Cardinali et al. 2020a, b). Finally, when badly infected COVID-19 patients were treated with melatonin alone or in conjunction with other drugs, the severity of infection was reduced, the death rate was lowered, and the length of hospitalization was shortened (Farnoosh et al. 2021; ZT et al. 2021).

From a molecular standpoint, distinguishing between direct and indirect anti-inflammatory effects of melatonin via changes in phase or amplitude of local circadian oscillators is not always attainable (Boivin et al. 2003; Bollinger et al. 2011; Hardeland et al. 2012). Melatonin has been shown to affect metabolic sensing factors such as peroxisome proliferator-activated -activated receptor-γ coactivator-1α (PGC-1α), peroxisome proliferator-activated receptor-γ (PPARγ), phosphoinositide 3-kinase, protein kinase B, including the accessory oscillator components AMP kinase, nicotinamide phosphoribosyl transferase (NAMPT), and SIRT1.

The induction of antioxidant enzymes in the rat liver and pancreas under inflammatory conditions, where melatonin promotes the expression and nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) that mediates the upregulation of the protective enzymes, is an example of a direct melatonin effect not mediated by oscillators (Jung et al. 2010). Melatonin suppresses the expression of nuclear factor-κB (NF-κB) by recruiting a histone deacetylase (HDAC) to its promoter, which decreases pro-inflammatory factors like TNF-α, IL-1, and iNOS.

Various other effects of melatonin on gene expression are mediated by the circadian system. In particular, the role of SIRT1 must be considered, which is not only believed to be an aging suppressor, but acts as a protein deacetylase and, moreover, as a component of circadian oscillators that interacts with the BMAL1/CLOCK dimer and is required for high rhythm amplitudes (Bellet et al. 2011). SIRT1 was activated by melatonin in multiple aging scenarios, including senescence-accelerated animals, and induced increased deacetylation of various of its substrates, including PGC-1α, Forkhead box protein O1 (FOXO1), NF-κB, and p53 (Hardeland et al. 2015). Notably, these effects strongly contrast with the opposite effects in epigenetically dysregulated oscillators of cancer cells (Hardeland 2014). SIRT3 is another sirtuin associated with melatonin effects at the mitochondrial level (Mayo et al. 2017).

14.7 Melatonin, Sirtuins, and the Anti-inflammatory Network

Sirtuins, a family of seven proteins encoded by Silent Information Regulator (*Sir*) genes, play a key role in senescence control and survival under adverse conditions (Watroba and Szukiewicz 2021). Sirtuins are nicotinamide adenine dinucleotide (NAD)-dependent HDAC type-III enzymes that control a variety of cellular and molecular processes through deacetylation (Mayo et al. 2017). According to the targeting sequences they include, sirtuins can be cytoplasmic or nuclear (SIRT 1,6,7) and can even be directed to migrate to the mitochondria (SIRT 3,4,5). While nuclear/cytosolic sirtuins regulate cellular processes by deacetylating histone and non-histone targets (Yamamoto et al. 2007), mitochondrial sirtuins regulate energy metabolism by acting as either NAD+ dependent class III histone deacetylase enzymes (e.g., SIRT3), auto-ADP-ribosyltransferases (SIRT6) or as mono-ADP-ribosyltransferases (particularly SIRT4) to control energy metabolism (Watroba and Szukiewicz 2021). They could influence mitochondrial biogenesis, insulin sensitivity, glucose and lipid metabolism (Poulose and Raju 2015), urea cycle, cell cycle, DNA repair, and rDNA transcription due to their deacetylating and ADP-ribosylation properties (Elkhwanky and Hakkola 2018; Singh et al. 2018).

SIRT1 and SIRT3 are two sirtuins that are particularly critical for melatonin's anti-inflammatory properties (Mayo et al. 2017). SIRT1 is a versatile protein that deacetylates both histone and non-histone sites to control gene transcription. P53, FOXO transcription factor, PGC1α and NF-κB are examples of non-histone targets that regulate stress responses, inflammation, cellular senescence, and apoptosis (Watroba and Szukiewicz, 2021) (Fig. 14.2). Because SIRT1's activity is reliant on the co-factor NAD+, it was first thought to be a NAD+-dependent histone deacetylase. Overexpression of *Sirt1* enhances insulin sensitivity by deacetylating PGC-1α, a transcriptional coactivator that regulates glucose homeostasis at the transcriptional level, which influences glucose tolerance (Milne et al. 2007). *Sirt1* overexpression in the progeny of mice fed a high-fat diet decreases insulin resistance, improves glucose tolerance, avoids hepatic steatosis, and lowers ROS generation (Nguyen et al. 2019). SIRT1 also plays several functions in signaling pathways involved in development, cognition impairment, heart disease, aging, cancer, and energy homeostasis, including lipid and glucose homeostasis.

SIRT1 has been linked to a longer lifespan and the prevention of neurodegenerative diseases. The overexpression of SIRT1 in AD reduces the increase in Aβ deposition (Fernando and Wijayasinghe 2021). Overexpression of SIRT1 is also advantageous in Parkinson's disease, as it reduces acetylation of SIRT1 substrate (FOXO3a) and inhibits α-synuclein aggregation by preventing misfolding of α-synuclein protein (Jęśko et al. 2017).

SIRT1 has been shown in numerous studies to have antioxidant and anti-inflammatory properties like melatonin (Mayo et al. 2017). This includes suppressing NF-κB activation, upregulating Nrf2, suppressing NLRP3 inflammasome activation, and inhibiting TLR4 (toll-like receptor 4) signaling. High mobility group

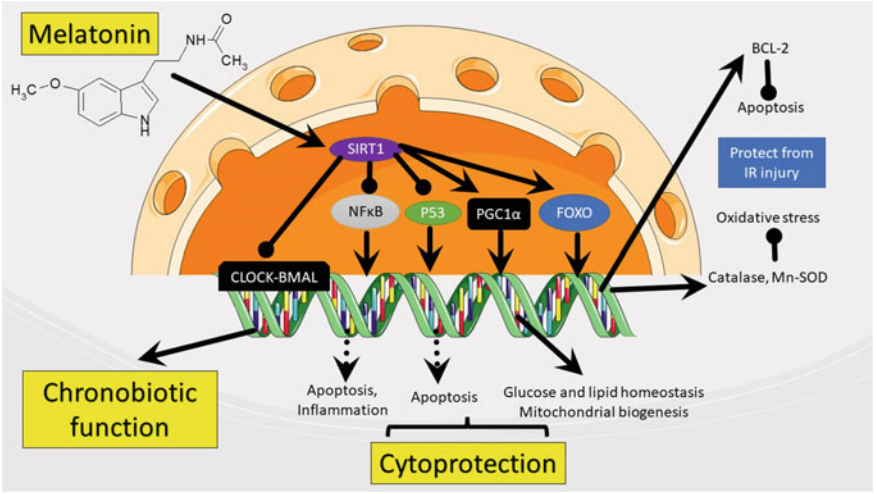

Fig. 14.2 SIRT1 it is a multifunctional protein that controls gene transcription by deacetylating both histone and non-histone targets. Non-histone targets include P53, forkhead homeobox type O (FOXO) transcription factor, peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1α) and nuclear factor (NF)-κB, thus regulating stress responses, inflammation, cellular senescence and apoptosis. In addition, SIRT1 and the circadian clock interact. SIRT1-deficient mice exhibit alterations in the expression patterns of Per1, Per2, Cry1, and Cry2 circadian genes. Melatonin modulates SIRT1 activity, and this modulation may be in the core of the cytoprotective and chronobiotic properties of the methoxyindole

box-1 (HMGB1), an inflammatory signaling protein secreted by monocytes and macrophages, is a key role in TLR4 activation (Hardeland 2019). SIRT1 has been shown to deacetylate HMGB1, preventing its nucleocytoplasmic transfer and release. Importantly, HMGB1 promotes macrophage and microglia polarization toward the pro-inflammatory M1 type (Hardeland 2019). Melatonin has also been shown to have anti-inflammatory properties via inhibition of HMGB1 (Mayo et al. 2017). Under more severe inflammation, several different findings on sirtuin-mediated suppression by melatonin were discovered. This was seen in normal and diabetic rats with cardiac ischemia/reperfusion, in H9C2 cardiomyocytes with endoplasmic reticulum stress, in LPS-treated microglial cell lines, and in mice with brain injury caused by cecal ligation/puncture (Hardeland 2019).

SIRT3 is a key factor in mitochondrial function, as it regulates the pyruvate dehydrogenase complex (PDH) and participates in ATP synthesis. Several investigations have found that melatonin operates at the mitochondrial level via SIRT3 (Mayo et al. 2017) (Fig. 14.3). Higher ATP generation, an elevated ATP production-coupled oxygen consumption rate, and reduced lactic acid secretion resulted from a switch from cytosolic aerobic glycolysis to oxidative phosphorylation (OXPHOS). Melatonin activated SIRT3 and PDH, which increased the mitochondrial membrane potential and the activity of complexes I and IV in the electron transport chain. Melatonin

greatly improved mitochondrial energy metabolism by reversing the Warburg effect via raising PDH activity and stimulating SIRT3.

Melatonin changes pro-inflammatory glycolytic M1 macrophages into anti-inflammatory OXPHOS-using M2 macrophages (Reiter et al. 2020b). Melatonin causes the mitochondrial metabolism of pyruvate, stimulation of the tricarboxylic acid cycle, improved OXPHOS, and reduced ROS by down-regulating hypoxia-inducible factor 1, which leads to PDH disinhibition. Melatonin and its metabolites are particularly effective direct scavengers of partially reduced derivatives of oxygen under these conditions, in addition to lowering mitochondrial ROS production.

Because macrophages and associated cells are key participants in inflammation, their differentiation into pro-inflammatory M1 or anti-inflammatory M2 phenotypes is critical for maintaining the pro-/anti-inflammatory balance (Fujisaka 2021). By promoting M2 polarization and disfavoring M1 polarization, melatonin can move this balance toward the anti-inflammatory side (Reiter et al. 2020b). One of the major anti-inflammatory effects in the inhibition of M1 function consists in the MT1 receptor-mediated activation of NF-κB degradation. Additionally, suppression of NF-κB actions has been reported for RORα. Because ROR is unable to bind melatonin,

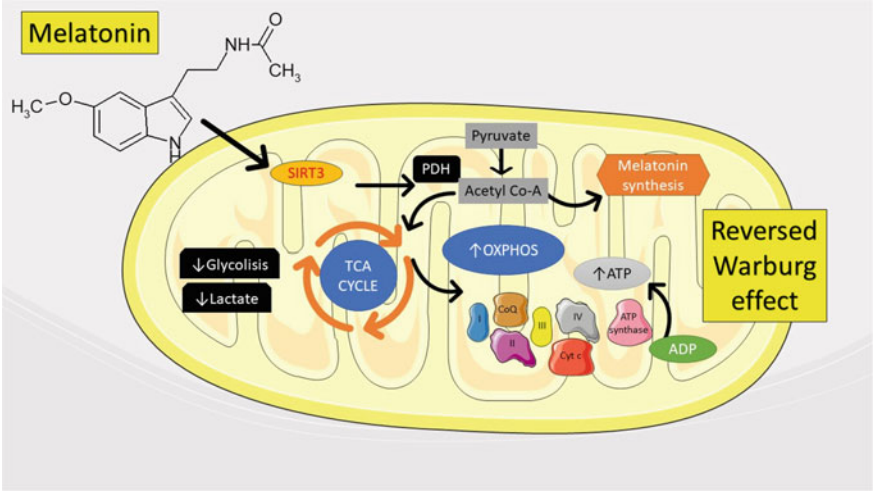

Fig. 14.3 In resting macrophages (M2), the glucose metabolite pyruvate enters the mitochondria where it is enzymatically converted to acetyl-coenzyme A by the enzyme pyruvate dehydrogenase complex (PDH). Acetyl-CoA feeds the tricarboxylic acid cycle (TCA) and supports oxidative phosphorylation (OXPHOS). Additionally, acetyl-CoA is an essential co-factor/substrate for the rate-limiting enzyme in melatonin synthesis, arylalkylamine *N*-acetyltransferase. Mitochondrial melatonin functions intracellularly and is released into the cellular microenvironment, but not into the blood. Melatonin scavenges ROS generated during OXPHOS and improves mitochondrial membrane potential and the activities of complexes I and IV in the electron transport chain. Additionally, melatonin stimulates SIRT3 allowing PDH stimulation and the activation of superoxide dismutase 2. As a result of these changes, melatonin significantly enhanced mitochondrial energy metabolism to reverse the Warburg effect

the methoxyindole's effect on the transcription factor must be indirect (Hardeland 2019). A possibility of particular interest concerns the effect of SIRT1 on RORα, in its function as a partial mediator of melatonin effects. Upregulation of SIRT1 deacetylates PGC-1α and facilitates the binding of RORα to its response elements.

SIRT1 and the circadian clock interact (Fig. 14.2). SIRT1 influences the circadian clock in both the brain and in peripheral tissues (Masri, 2015; Soni et al. 2021). The expression patterns of *Per1*, *Per2*, *Cry1*, and *Cry2* circadian genes are altered in Sirt1-deficient mice. *Sirt1* and *Per2* work together to suppress each other (Wang et al. 2016). SIRT1 deacetylates and degrades PER2 in the liver. SIRT1 also regulates circadian rhythms by binding to the CLOCK-BMAL1 complex in a rhythmic way. As a result, the acetylation and deacetylation of its components affect the molecular circadian clock.

Sirtuins and circadian clock proteins work cooperatively to regulate oxidative metabolism via NAD+ and NADH responses (Anderson et al. 2017; Griffiths et al. 2020). Apart from activating the clock genes *Per* and *Cry* and other clock-controlled genes, the heterodimer CLOCK-BMAL1 also regulates the activity of the gene *Nampt*, which encodes the rate-limiting enzyme nicotinamide phosphoribosyltransferase, whose metabolite is NAD+ . Because of oscillations in NAMPT levels, NAD + synthesis has a specific circadian cycle. The cellular redox status is maintained by the distribution of NAD+ in the cytosol, nucleus, and mitochondria, which is necessary for the normal functioning of the bioenergetic enzymatic machinery (Anderson et al. 2017; Griffiths et al. 2020). These findings suggest that a complex system of regulators, of which SIRT1 is a key component, controls the molecular circadian clock's stability via various pathways (Griffiths et al. 2020; Xu et al. 2021).

Melatonin regulates SIRT1 activity, which may be at the heart of the methoxyindole's cytoprotective and chronobiotic effects (Bonomini et al. 2018; Emamgholipour et al. 2016; Favero et al. 2020; Stacchiotti et al. 2019) (Fig. 14.2). Melatonin's cardioprotective action during I/R is mediated by SIRT1 signaling in antioxidative response pathways. SIRT1 deacetylation activates FOXO1, which in turn produces the antioxidant enzymes manganese superoxide dismutase (MnSOD) and catalase. Apoptosis is aided by the presence of acetylated FOXO1 (Ac-FOXO1). SIRT1 and Ac-FOXO1 expression were dramatically increased and lowered in melatonin-treated myocardial I/R rats, respectively. In I/R plus vehicle group, SIRT1 expression was reduced and Ac-FOXO1 expression was significantly boosted (Yu et al. 2014). Melatonin therapy boosted the expression of the antiapoptotic gene *Bcl-2* via upregulating SIRT1 and thereby lowering Ac-FOXO1. Hence, melatonin works with SIRT1 to alleviate oxidative stress and to prevent apoptosis (Fig. 14.2).

SIRT1 is also the effector responsible for melatonin's protective role in kidney function in badly burned rats, since it reduces oxidative stress, regulates inflammatory responses, and inhibits apoptotic pathways (Bai et al. 2016; Owczarek et al. 2020). In a C57BL/6 J mouse model of sepsis, SIRT1 contributes to the protective role of melatonin following cecal ligation and puncture (Zhao et al. 2015). Melatonin reduces the load of neuroinflammatory and oxidative stress caused by septic encephalopathy (Hu et al. 2017). This benefit was reduced by a SIRT1 inhibitor,

implying that melatonin's beneficial effect was mediated through SIRT1 (Zhao et al. 2015).

Activation of the NLRP3 inflammasome in various systems, under different conditions and counteractions by melatonin, has been recently reviewed (Sayed et al. 2021; Volt et al. 2016; Zheng et al. 2021). Melatonin's regulation of NF-κB signaling, which is also critical in the prevention of oxidative damage, was linked to these findings. In addition, NF-κB has been shown to cause pyroptosis in adipose tissue, which is suppressed by melatonin.

TLR4 activation, for example, via the IFN-γ-adaptor protein, a toll-receptor-associated activator of interferon (TRIF), is another pro-inflammatory mechanism (Feng et al. 2022; Lwin et al. 2021). By inhibiting TRIF and TLR4, melatonin has been found to reduce the release of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8. Because TLR4 also causes pro-oxidant actions via NF-κB, melatonin's impacts on this pathway are likely to be more widespread.

14.8 Therapeutic Value of Melatonin in Animal and Clinical Models of Age-Related NCDs

As already mentioned, circulating melatonin levels in humans are consistently reduced in age-related NCDs. In a limited number of clinical trials employing melatonin in the 2–5 mg/day range, partial beneficial effects were obtained. However, in animal model studies of NCDs, melatonin was highly effective in curtailing symptomatology. Allometric calculations derived from animal studies indicate projected cytoprotective melatonin doses for humans in the 40–100 mg/day range, doses that are rarely employed clinically.

Melatonin treatment reduces obesity, type 2 diabetes, and hepatic steatosis in rats (Martínez Soriano et al. 2020; Pan et al. 2006) Melatonin injections normalized most of the identified changes and corrected the altered biochemical pro-inflammatory profile in many animal models of hyperadiposity (Cardinali 2019a, b, c). Melatonin treatment of streptozotocin-induced type 1 diabetic mice results in the regeneration and proliferation of β-cells in the pancreas, lowering blood glucose levels (Hajam et al. 2021; Kanter et al. 2006). The loss of melatonin in the circulation following pinealectomy causes hyperinsulinemia and lipid buildup in the rat liver (Nishida et al. 2003). Melatonin improves lipid metabolism in type 2 diabetic mice by improving insulin sensitivity after long-term treatment (Nishida et al. 2003). Melatonin administration increased glycogen content in the liver of rats, while intraperitoneal injection of 10 mg/kg melatonin improved glucose consumption, insulin sensitivity, and alleviated hepatic steatosis in high-fat diet-induced diabetic mice (Shieh et al. 2009).

The causes for the drop in body weight after taking melatonin in the absence of major changes in food intake should be investigated further. The fact that melatonin plays a role in seasonal changes in adiposity by increasing the activity of the sympathetic nervous system, which innervates white and brown fat, is an important piece of

evidence in this respect (Bartness et al. 2002; Ryu et al. 2018). Melatonin influences not only white adipose tissue, but also brown adipocyte recruitment and metabolic activity in mammals (de Souza et al. 2019; Fernández Vázquez et al. 2018; Halpern et al. 2019, 2020; Tan et al. 2011). Melatonin's hypertrophic impact and functional activation of brown adipose tissue have been suggested as potential treatments for obesity in humans.

The human equivalent dose (HED) of melatonin for a 75 kg adult was estimated by normalizing body surface area from the doses of melatonin used in animals (Blanchard and Smoliga 2015; Nair et al. 2018; Reagan-Shaw et al. 2008). Body surface area has been advocated as a factor to use when converting a dose for translation from animals to humans because it correlates well with several biological parameters such as oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function across several mammalian species. It is worth noting that theoretical HED of melatonin derived from various research studies are 2–3 orders of magnitude higher than those used in people.

For a summary of the effect of melatonin in animal models of age-related NCDs, see Cardinali (2019a, b, c). Melatonin reduced 87% of the area of injury and 80% of the number of injured myocardium regions in a rat model of myocardial infarction (caused by closure of the left anterior descending coronary artery 3 h earlier) (Castagnino et al. 2002). Several investigations in rats and mice have shown that melatonin can lower heart damage signs, boost cardiac antioxidant defenses, and normalize lipid profiles (see for ref. Cardinali 2019a, b, c). The same was observed in cardiomyopathy induced by streptozotocin (Kandemir et al. 2019) or doxorubicin (Kandemir et al. 2019). Melatonin boosts the therapeutic efficacy of cardiac progenitor cells for myocardial infarction in a mouse model of myocardial infarction treated with cardiac progenitor cells (Ma et al. 2018). A study of the subcellular distribution of melatonin in the heart of rats found that at a dose of 40 mg/kg b.w., the nucleus and mitochondrion attained their maximum concentration of melatonin. The authors calculated a HED of melatonin $\geq$ 112 mg/day for therapeutic purposes in a 70 kg human adult (Acuña-Castroviejo et al. 2018).

Cell line studies regarding AD and melatonin have delineated important melatonin mediated mechanisms in AD prevention. For comprehensive reviews on melatonin activity to reverse disrupted signaling mechanisms in neurodegeneration, including proteostasis dysfunction, disruption of autophagic integrity, and anomalies in the insulin, Notch, and Wnt/β-catenin signaling pathways, see (Melhuish Beaupre et al. 2021; Shukla et al. 2019).

The results obtained in transgenic models of AD are consistent with the hypothesis that melatonin affects Aß metabolism mostly during the early stages of the pathogenic process (Corpas et al. 2018; Jürgenson et al. 2019; Sun et al. 2020a, b). From the doses of melatonin used in the different transgenic models employed, the HED of melatonin for a 75 kg adult ranged from 2- to 3-orders of magnitude greater than those employed in humans.

The mechanism through which melatonin inhibits the production of Aβ is unknown. Melatonin inhibits progressive-sheet and/or amyloid fibrils via interacting with Aß40 and Aß42 (Pappolla et al. 1998), an interaction which appears to depend

on structural melatonin characteristics rather than on its antioxidant properties. Melatonin may help peptide clearance by enhancing proteolytic breakdown by blocking the production of secondary sheets. Oxidative stress is involved in Aß-induced neurotoxicity and cell death, and melatonin efficiently protects cells in vitro and in vivo. Melatonin was found to protect against Aβ toxicity, particularly at the mitochondrial level (Cardinali 2019a, b, c).

Melatonin effectively reduces tau hyperphosphorylation in neuroblastoma cells by influencing protein kinases and phosphatases (Solís-Chagoyán et al. 2020). Melatonin increases the clearance of Aß in the glymphatic system in AD transgenic mice (Pappolla et al. 2018). As a result, sleep disturbance as a comorbidity in AD may contribute to the disease's development and progression through a failure of Aß clearance (Bitar et al. 2021).

The activation of microglia, which results in increased expression of pro-inflammatory cytokines, is another element in the pathophysiology of AD. Melatonin reduced pro-inflammatory cytokine production in microglia triggered by Aß, NF-kB, and NO (Baeeri et al. 2021; Rosales-Corral et al. 2003; Zhang et al. 2021a, b). In addition, the DNA binding activity of NF-kB was inhibited by melatonin (Hardeland 2019).

As far as clinical studies on melatonin therapeutic value in age-related NCDs, type 2 diabetic patients have low circulating levels of melatonin with a simultaneous and expected regulation of mRNA expression of the melatonin membrane receptors (el Aghoury et al. 2020; Otamas et al. 2020; Tanaka et al. 2021; Tütüncü et al. 2005). In addition, allelic variants for melatonin receptors were associated with an increase in fasting blood glucose levels and/or an increased risk of type 2 diabetes (Bai et al. 2020; Bonnefond and Froguel 2017; Bouatia-Naji et al. 2009; Prokopenko et al. 2009; Tam et al. 2010) and with the polycystic ovarian syndrome (PCOS) (Song et al. 2015; Yi et al. 2020).

Melatonin secretion is reduced in patients with coronary artery disease (Brugger et al. 1995; Domínguez-Rodríguez et al. 2002; Girotti et al. 2003, 2000; Misaka et al. 2019; Sakotnik et al. 1999; Yaprak et al. 2003), and among the elderly hypertensive patients, nocturnal urinary melatonin excretion was inversely associated with the non-dipper pattern of hypertensive disease (Jonas et al. 2003; Obayashi et al. 2013). Melatonin therapy ($\leq$ 5 mg/day) reduced nocturnal blood pressure in hypertensives and mitigated age-related cardiovascular rhythm abnormalities (Cagnacci et al. 2005; Campos et al. 2020; Gubin et al. 2016; Grossman et al. 2006; Imenshahidi et al. 2020; Scheer 2005).

Melatonin (5 mg/day) treatment improves metabolic syndrome in obese and PCOS patients (Alizadeh et al. 2021; Koziróg et al. 2011; Mohammadi et al. 2021; Tagliaferri et al. 2018), and in bipolar and schizophrenic patients receiving second generation antipsychotics (Agahi et al. 2018; Duan et al. 2021; Modabbernia et al. 2014; Romo-Nava et al. 2014). Melatonin treatment improves the enzyme profile in alcoholic hepatic steatosis patients (Abdi et al. 2021; Gonciarz et al. 2010). In several studies melatonin therapy improves glycemic control in type 2 diabetes patients (Anton et al. 2021; Bazyar et al. 2021; Kadhim et al. 2006; Ostadmohammadi et al. 2020; Pourhanifeh et al. 2020; Raygan et al. 2019; Satari et al. 2021).

Distinguishing core symptoms (glucose homeostasis) from diabetes-associated pathologies, such as those resulting from increased oxidative stress, such as liver steatosis, cardiovascular disease, retinopathy, nephropathy, or osteoporosis, is crucial in human investigations (Banerjee et al. 2021). Melatonin has been shown to have therapeutic efficacy in the majority of these related diseases.

CSF melatonin levels fall even in the preclinical phases of AD, when patients do not show any cognitive impairment, suggesting that CSF melatonin reduction could be an early trigger and marker for the disease (Colwell 2021; Liu et al. 1999). Although it is unclear if relative melatonin shortage is a result or cause of neurodegeneration, it is apparent that melatonin deficiency exacerbates AD and that early circadian disturbance can be a significant deficit to consider. Melatonin levels were found to differ significantly between mild cognitive impairment and AD patients, with a negative relationship between neuropsychological examination and melatonin levels (Şirin et al. 2015; Zhang et al. 2021a, b). Melatonin therapy is beneficial in improving sleep in dementia patients, according to meta-analyses and consensus reports (Xu et al. 2015; Trotti and Karroum 2016; Zhang et al. 2016; Fatemeh et al. 2021).

It is unclear whether melatonin can help people with fully developed AD. It should be highlighted that heterogeneity of the sample studied is one of the issues with AD patients with fully developed illness. Review of published evidence on the use of melatonin in the early stages of cognitive decline, on the other hand, consistently revealed that taking melatonin every night before retiring improves sleep quality and cognitive performance in this stage of the disease (see for ref. Cardinali 2019a, b, c; Liu et al. 2021; Sumsuzzman et al. 2021; Wade et al. 2014; Wang et al. 2017).

14.9 Concluding Remarks

NCDs linked to aging provide a significant public health challenge. Over 80% of NCD deaths are caused by cardiovascular illnesses, malignancies, respiratory diseases, diabetes, and neurological diseases, and NCDs are closely associated with disability, reliance, and long-term care demands. In this Chapter, we have covered two key etiopathogenic processes that contribute to NCDs: inflammaging and circadian disturbance, the latter of which is a result of living in a 24/7 society that affects sleep. As a result, dysregulation of the sleep/wake cycle causes a slew of pathophysiological alterations that hasten the aging process.

Melatonin emerges as a viable non-toxic chronobiotic/cytoprotective approach in this context. It is worth noting that melatonin has a very high level of safety. The lethal dose 50 for the intraperitoneal injection of melatonin was determined for rats (1168 mg/kg) and mice (1131 mg/kg), but the lethal dose for oral administration of melatonin (assessed up to 3200 mg/kg in rats) could not be determined and for melatonin subcutaneous injection (tested up to 1600 mg/kg in rats and mice) (Sugden 1983). Melatonin has an excellent safety profile in humans and is generally well tolerated (Schrire et al. 2021).

Melatonin, as discussed herein, combines two properties that are extremely important for the prevention and treatment of age-related NCDs: it is an effective chronobiotic that aids in the correction of circadian disruption, and it is a phylogenetically well preserved cytoprotective agent that addresses the treatment of inflammaging. Beyond melatonin's well-known antioxidant and anti-inflammatory properties, which have demonstrated its efficacy in the treatment of diseases/conditions in which excessive free radical-mediated oxidative damage and hyperinflammation are causative factors, the studies summarized herein support its use as a viable preventive agent in the low-degree inflammation found in age-related NCDs.

Numerous interrelated factors found in inflammaging, including the development of pro-inflammatory M1 macrophages, conversion to Warburg-type metabolism of immune cells, damage to mitochondria, release of cytokines, oxidative stress, etc. are counteracted by melatonin. A center piece of this series of cytoprotective processes may be the alterations in mitochondrial physiology and the shift of glucose oxidation to cytosol mediated via the melatonin effect on sirtuins, particularly SIRT3. This change in glucose handling markedly alters the metabolism of the mitochondria, which is critical to limiting cellular dysfunction, resisting disease and preventing organismal death. Indeed, there are numerous maladies that are specifically classified as mitochondria-related diseases (Chaiyarit and Thongboonkerd 2020; Cloonan et al. 2020; Kłos and Dabravolski 2021; Medala et al. 2021; Vaamonde-García and López-Armada 2019; Xin et al. 2021) with this category including viral infections such as SARS-CoV-2 (Swain et al. 2021).

When intracellular glucose metabolism is reprogrammed from the mitochondria into the cytosol, the mitochondria can no longer synthesize acetyl-coenzyme A (acetyl-CoA). This has high importance, since acetyl-CoA is a required co-substrate for intramitochondrial melatonin production, which normally occurs in these organelles of healthy cells but likely not in the mitochondria of inflamed cells (Reiter et al. 2021a, b, 2020c). Thus, in the absence of local melatonin synthesis, the loss of this locally produced potent anti-inflammatory and antioxidant agent, the mitochondria lose a major portion of their protection against ROS, inflammatory cytokines, etc., leading to their dysfunction. The ability of melatonin to reverse the Warburg effect in pathological cells in humans was recently documented, presumably allowing the mitochondria also to synthesize melatonin (Reiter et al. 2021a, b).

Melatonin is commonly used as a dietary supplement or dietary product to treat sleep disturbances in many countries. Melatonin reduces sleep onset delay, according to the European Food Safety Authority (EFSA). This allows for the introduction of melatonin as a meal to promote "sleep–wake cycle regulation," "relaxation," and "sleep patterns" (Agostoni et al. 2011). Melatonin, melatonin-rich foods, and bio-extracts of melatonin can now be developed as nutritional supplements, dietary products, and pharmaceuticals for the general population, as specified by the EFSA.

Melatonin is very effective to alleviate oxidative stress in plants (Anderson and Kim 2021; Tiwari et al. 2021), as it does in animal tissues. Since its discovery in plants two decades ago, researchers have made significant progress in understanding the effects of melatonin that contribute to the plant's ecological success (Back et al. 2021). Melatonin overexpression in plants promotes seed germination and increases

root development and maturation, protecting plants from biotic and abiotic stress (Anderson and Kim 2021; Tiwari et al. 2021). Melatonin's presence in plants has ramifications not only for plant development and crop productivity, but also for human and animal nutrition. Melatonin is easily absorbed and exerts its actions at the cellular level when plant products containing it are ingested. Melatonin is a beneficial chemical that neutralizes the physiopathological processes that undermine a healthy lifestyle in both animals and plants. Melatonin enrichment in foods is required to attain the levels that give efficient cytoprotection. As a result, the creation of functional meals containing high quantities of melatonin is a hot topic. The modest doses of melatonin usually utilized are not very advantageous if melatonin is supposed to be effective in enhancing health, especially in the elderly.

The question of whether melatonin has a therapeutic value in the prevention or treatment of NCDs deserves further analysis. Multicenter double-blind studies are needed to explore and further investigate the potential and utility of melatonin. The doses of melatonin used should be re-evaluated in view of the HED of melatonin derived from preclinical data. However, the failure of melatonin to attract attention as a potential treatment for healthy aging is somewhat disappointing considering the number of scientific/medical papers that have recommended its use. This may relate to several factors including the lack of promotion of its therapeutic use for this disease by any influential group. Since melatonin is non-patentable and is inexpensive, the incentive of the pharmaceutical industry to support its use is lost. Melatonin would be particularly helpful because it may be self-administered orally, is inexpensive, and has low toxicity. This is especially true in disadvantaged areas of the world, where people have fewer financial resources to spend on age-related NCD treatment.

Compliance with Ethical Standards: Writing—original draft preparation, D.P.C.; writing—review and editing, G.M.B. and S.R.P.-P. All authors have read and agreed to the published version of the manuscript.

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