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Permalink

<https://escholarship.org/uc/item/0t86r0wr>

ISBN

978-1-60761-601-6

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Publication Date

2010

DOI

10.1007/978-1-60761-602-3_17

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Melatonin, Oxidative Stress, and the Aging Brain

Stephen Bondy and Edward H. Sharman

Abstract The changes associated with brain aging are discussed with emphasis on altered oxidative and inflammatory events and on mitochondrial dysfunction. Many of these changes are exacerbated in a variety of age-related neurologic diseases. This commonality has led to the idea that similar therapeutic approaches may be used in the treatment of several apparently unrelated neurodegenerative disorders. When aspects of these diseases are modeled in experimental animals and cell lines, the application of melatonin has been reported to be advantageous. The means by which melatonin can be protective probably is mediated by way of activation of melatonin receptors, of which several subtypes can be identified. This can initiate a sequence of intracellular signaling events and by activation of transcription factors lead to altered gene expression. The culmination of this cascade can lead to increased levels of antioxidant enzymes and depressed levels of inflammation. Melatonin may be useful both in the retardation of nonpathologic brain aging and in the amelioration of chronic brain disease associated with aging. The inexpensive nature and ready availability of melatonin together with its very low toxicity reinforce the need to place the beneficial properties of this agent on a firmer basis.

Keywords Melatonin · Aging · Neurologic disease · Neurodegeneration · Oxidative stress · Inflammation

1 Introduction

Brain senescence involves excess free radical generation, elevated levels of basal immune and inflammatory activity, together with impaired mitochondrial function.

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A large number of genetic phenotypic changes occur with senescence. Some of the general changes taking place include deletions of specific portions of mitochondrial DNA [1, 2], altered immune function, and an increasingly pro-oxidant milieu concomitant with reduced antioxidant activity. Such changes have often been described as associated with brain aging [3–6]. Common neuropathologic changes include the deposition of lipofuscin and other insoluble materials such as amyloid plaques and neurofibrillary tangles. These inclusions are resistant to normal intracellular proteolytic processes and thus accumulate within and around the cell. Though such changes may characterize specific neurodegenerative disorders, they are also found with normal aging. For example, as well as being characteristic of Alzheimer's disease, amyloid plaques are present in half of the brains from an apparently normal elderly population [7]. Such indigestible inclusions consist of protein and carbohydrate components. Their accumulation is likely to disrupt cell function, in a parallel manner to the more spectacular accretion and consequent distortion of neuronal geometry seen in genetic gangliosidoses. Peptides within these complexes are cross-linked in a β -configuration, and the formation of β -sheets forms the basis for their resistance to normal ubiquitylation and cleavage by proteases.

1.1 Oxidative Stress and Brain Aging

There are several reports suggesting that some age-related damage to the brain may be caused by excessive activity of reactive oxygen species [3, 6]. Many key intracellular constituents are vulnerable to oxidative or nitrosylative damage, and this may increase with age (reviewed in [8]). Macromolecules are especially liable to injurious oxidative modification. These include proteins [8–11], nucleic acids [12], and lipids [13]. Although an increased level of pro-oxidant activity with age has frequently been reported, the establishment of a causal relation whereby oxidant events result in impaired neurologic or behavioral status is more difficult to unequivocally demonstrate. Evidence of this nature includes the finding that treatment of aged gerbils with a free radical spin trapping agent, α -phenyl-*N*-*tert*-butyl nitron (PBN), can reverse some age-associated loss of recall ability as tested by the use of a radial arm maze [14]. In a mouse line developed for an unusually rapid onset of senescence, PBN can also diminish the degree of free radical-induced protein oxidation, and this is concomitant with improved behavioral performance [15]. Together with PBN-induced improvement of ischemic damage in stroke models using rats and marmosets, this has led to a phase 3 clinical trial for treatment of acute ischemic stroke with a derivative of PBN, disodium 4-[(*tert*-butylimino) methyl] benzene-1, 3-disulfonate *N*-oxide (NXY-059) [16].

1.2 Inflammation and the Aged Brain

The dysregulation of immune response mechanisms within the aging brain has been widely reported in recent years. Several indices of immune activity in the nervous system are persistently elevated with age despite the absence of provocative stimuli [17–20]. The microglia of the brain can act as the brain's macrophages, and

their level of activation is markedly increased in the white matter of the brains of aged rats [21] and primates [22]. The significant role of microglia in promoting adverse inflammatory processes is exemplified by the report that inhibition of microglial activation reduces the degree of damage to dopaminergic neurons caused by the selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [23]. However, elevated basal inflammatory activity in aged animals is not accompanied by keener immune surveillance and an improved ability to respond to an inflammatory stimulus of exogenous origin. On the contrary, the ability of the intrinsic immune system within the CNS to react to a material such as lipopolysaccharide is considerably diminished in the elderly mouse [19]. Such a dampening of the ability of immune defenses to detect relevant extraneous stimuli implies an impaired ability to mount an effective response to pathogens. Persistent levels of basal low-level inflammatory activity in the absence of exogenous stimuli is likely to be undesirable and to have deleterious consequences. The lung illustrates the injurious nature of a prolonged and futile immune response where the chronic presence of mineral particles leads to an ineffectual phagocytic attack by alveolar macrophages. This ultimately leads to severe pathologic changes involving inflammatory cytokines [24]. Analogous futile inflammatory responses in the brain may be toward aggregated amyloid peptide and other insoluble proteinaceous inclusions [25]. Thus, the elevated levels of microglial activity found in aged animals [22] may reflect a nonproductive aberrant response to endogenous factors, which cannot be resolved by raising an immune response.

1.3 Mitochondrial Dysfunction and Brain Aging

The mitochondrion is the site of the respiratory chain, and a side effect of this activity is the generation and diffusion into the cytoplasm of reactive oxidizing species; hence it also constitutes a major target of cumulative oxidative events. In fact, most of the reactive oxygen species produced within the cell have their origins from such leakage out of the respiratory chain. The electron transport is a very efficient process, but it has been estimated that around 2% of oxygen utilized escapes complete reduction to water and can form transient reactive intermediates [26]. Moreover, the efficiency of mitochondrial respiration may be further reduced with aging leading to a greater production of superoxide and other oxidant species [27–29]. After a chemical challenge, mitochondria from aged mice produce more reactive oxygen species than do mitochondria from the corresponding young mice [30]. The reduced efficiency of aged mitochondria can thus elevate levels of oxidative damage. The closest targets are most likely to be at risk, and these are structural elements of the mitochondria themselves.

It has been proposed that the increased levels of free radical generation within the aged brain are attributable to reduced efficiency of mitochondrial energy production [31, 32]. Impaired respiratory function may lead to oxidative stress and also to impairment of antioxidant enzyme systems [33]. Decline of mitochondrial functioning has also been associated with various age-related neurodegenerative

diseases including Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis [34]. Potential targets of oxidative damage to mitochondria include both their inner and outer membranes, and mitochondrial DNA (mtDNA). mtDNA is relatively exposed in comparison with nuclear DNA as it is located near the mitochondrial inner membrane and not enclosed within basic histones as is nuclear DNA. Furthermore, the mitochondrial DNA repair mechanism lacks the effectiveness and sophistication of its nuclear counterpart. Consequently, the degree of DNA damage in aging humans is 10 times greater in the mitochondria than in the nucleus [35]. In addition, the extent of mitochondrial damage is 15-fold greater in people over 70 years of age than in the younger population. This is evidenced by greater levels of gene deletions and by a much higher level of 8-hydroxy-2-deoxyguanosine in mtDNA [36]. As judged by deletion frequencies, the mutation rate of mtDNA is many fold greater in old mice relative to their young counterparts [37]. A high level of mtDNA deletions has been found to lead to reduced efficacy of mitochondrial respiration [38]. The substantia nigra is especially vulnerable to oxidative damage due to the potential of dopamine for catalytic oxidation. This may account for the selective vulnerability of dopaminergic midbrain neurons to DNA deletions in both Alzheimer's disease and Parkinson's disease [39]. Mitochondrial deletions are a driving force behind premature aging and may also have a causal role in many age-related pathologies [40]. It may be that mitochondria containing characteristic deletions, although less efficient in performing oxidative phosphorylation than normal mitochondria, are able to divide faster [41]. This raises the issue of whether such "malignant mitochondria" can gradually supplant healthy mitochondria during aging [42].

Mitochondrial dysfunction can also play an important role in the regulation of processes of cellular self-destruction, apoptosis, autophagy, and necrosis [8, 9, 43]. Control of these processes that relate to cell death is very responsive to imbalances in cellular homeostasis as gauged by such measures as Ca^{2+} levels [44] and cellular redox status [45].

2 The Treatment of Chronic Neurodegenerative Disorders

Therapeutic approaches to the most prevalent disease associated with human brain aging, Alzheimer's disease (AD), have often included anti-inflammatory regimens. These treatments have been validated by epidemiologic studies suggesting that the extended use of anti-inflammatory agents (e.g., the chronic use of aspirin by patients with arthritis) reduces the risk of AD [46]. Other epidemiologic data have suggested that antioxidants may be of value in lowering the incidence of AD [47]. Such reductions in incidence of AD attributed to anti-inflammatory or antioxidant agents could also be the result of deceleration of changes occurring during normal brain aging, rather than from effecting a direct mitigation of AD-specific changes. The search for agents with properties that target the nervous system and restore a biochemical and behavioral profile trending toward that found in younger animals may ultimately be of value in treatment of a range of distinct neurologic diseases.

The selection of appropriate materials whose prolonged usage may lead to beneficial changes within the aging central nervous system poses some distinctive problems. For example, broad, nonspecific reduction of pro-oxidant activity within the brain may disrupt those physiologic signaling events that rely on reactive oxygen species. This includes the involvement of superoxide anion in the inflammatory response. Nitric oxide (NO) is a relatively stable free radical that can combine with superoxide to form a very potent oxidant, peroxynitrite, but NO also plays an important role in the modulation of both intracellular and intercellular signals. NO has a series of key functions relating to blood supply and neurotransmission. Although protein nitrosylation is elevated with aging [22, 48], global inhibition of nitric oxide synthase aimed at protecting against neurotoxic damage [49] could have unanticipated adverse consequences, and thus such a broad-based strategy could be unsuitable. NO may be important in the prevention of cardiovascular aging by modulation of vascular tone [50].

2.1 The Potential Retardation of Brain Aging by Melatonin

The basis for selecting melatonin as an agent having the potential for slowing the onset of age-related oxidant events is based on reports from several laboratories [51–54]. A proportion of ingested melatonin can access the brain in an unmodified form [55]. On the other hand, the ability of several other potentially beneficial compounds to reach the brain is often limited due to their excessively lipophilic or water-soluble characteristics. For example, treatment of humans in one arm of the DATATOP study investigating the potential mitigation of Parkinson's disease (PD) involved α -tocopherol administration. Even after many months of such treatment, levels of this vitamin were not equilibrated within the cerebrospinal fluid, and were still rising [56]. Melatonin may be of *specific* value to the CNS where it is able to induce antioxidant genes [57]. This may account for its ability to attenuate lipopolysaccharide (LPS)-induced inflammatory responses [19, 58, 59] and to ameliorate the indices of anxiety induced by LPS [60]. β -Amyloid-induced interleukin secretion and production of reactive oxygen species are also suppressed by melatonin [61, 62]. Supercoiled mtDNA in a low entropy state in brain can be converted into more random circular and linearized forms by ethanol, and this can be attenuated by concurrent treatment with melatonin [63]. There is a considerable amount of evidence for the utility of melatonin in partially reversing changes in both the biochemical and behavioral profiles of older animals [48, 64]. Pinealectomy, which removes the major source of melatonin synthesis within the brain, may speed up changes characterizing aging [65, 66].

The use of melatonin to slow down the progression of undesirable age-related events is also supported by reports that either melatonin treatment or pineal grafting can retard the thymic involution that characterizes aging [33, 67]. It may be that aging is fundamentally an event programmed by the pineal gland [68].

The potential utility of melatonin in the deceleration of brain aging can be roughly classified into three major areas of study: (1) The application of melatonin as mitigation of overall systemic aging, including beneficial effects not confined

to the CNS such as maintenance of an effective immune function and extension of the life span. (2) The use of melatonin in the mitigation of undesirable changes associated with nonpathologic brain aging not associated with a specific neurologic disease. (3) The potential benefit of melatonin use in treatment of distinct neurologic diseases. This latter benefit has been investigated using genetic mouse lines modeling specific neurodegenerative diseases of humans.

2.1.1 Melatonin and Overall Phenotypic Aging

Extension of life span of both vertebrate and invertebrate species treated with melatonin has been described on several occasions [69–71]. This has been attributed to its ability to induce antioxidant enzymes [72] and to reduce age-related elevation of lipid peroxidation [73]. Such findings imply that melatonin has effects on the general systemic well-being rather than acting on a single organ. Such extension of longevity by melatonin has also been reported for several single-celled organisms [74]. In parallel, pinealectomy can reduce longevity [75]. This apparently beneficial effect of melatonin is further evidenced by the ability of melatonin to restore the reproductive cycle of aged mice [76] and the effective functioning of the systemic immune system of aged animals [77]. The age-related increase in susceptibility to the onset of cancer with age can be partially relieved by melatonin [75]. An inverse relation exists in several tissues, between melatonin levels and age-related oxidative damage to DNA, suggesting that this agent may exert antioxidant effects in a wide range of tissues [78].

2.1.2 Specific Effects of Melatonin on Events Relating to Brain Aging

Some of the biochemical, physiologic, and behavioral changes associated with brain aging in the absence of clinical disease include memory deficits, cerebral arterial thinning, and deposition of lipofuscin and amyloid plaques. All of these may be attenuated by chronic treatment with dietary melatonin [79–83]. Melatonin can restore the ability of the aging brain to respond to an inflammatory stimulus [19], and this is in concordance with reports of favorable effects of melatonin on the circulating immune system (described earlier). However, melatonin can also reduce excess immune responsivity (discussed in a later section). Rather than being simply pro- or anti-inflammatory, melatonin has a subtle immunoregulatory capacity.

2.1.3 The Potential for Melatonin Treatment of Specific Neurologic Disease

There are many descriptions of the potentially beneficial effect of melatonin on various neurologic and psychiatric disorders and their relevant animal models. These disorders typically become increasingly prevalent with age.

A review must judge the preponderance of current evidence and summarize the most established findings to serve as a platform for design of new studies. Considering age-related diseases with a slow rate of progression such as AD and

PD as well as aging itself, an obvious generalization is that any beneficial effects of melatonin are likely to require prolonged administration, most likely preceding the appearance of overt signs of disease. For instance, in the case of AD, a disease characterized by depressed levels of melatonin in the cerebrospinal fluid [84], preventing plaque deposition may require that exposure to exogenous melatonin be initiated in the young animal, preceding the appearance of any amyloid deposits [85].

Several reports suggest the potential effectiveness of melatonin for treating PD. Inhibition of lipid peroxidation, hydroxyl formation, and protection of nigral dopaminergic neurons in MPTP-treated rodents can be protected against by melatonin (reviewed in [86]), and exogenous melatonin has been shown to protect against L-DOPA auto-oxidation in the rat thereby increasing the availability of this drug to the striatum [87]. However, there may be a hazard in using melatonin to treat relatively acute animal models of PD involving MPTP or 6-hydroxydopamine, as the PD-like symptoms in this case may actually be worsened by melatonin application (reviewed in [88]), perhaps by inhibition of dopamine release [89].

Melatonin is also protective in preventing the oxidative damage that follows ischemia/reperfusion brain injury. This effect, which is evidenced by reduced infarct volume, necrotic neuronal death, together with diminished neurologic deficits and increased number of surviving neurons, can shield brain function [90]. The beneficial properties of melatonin in countering stroke injury can be manifested even if administered 24 h after an ischemic lesion [91].

Studies using animal models have often focused on the effect of melatonin on three major processes associated with many neurologic diseases as well as non-pathologic brain aging. This classical triad consists of (i) oxidative damage to macromolecules, (ii) persistent inflammation, and (iii) low level but prolonged hyperexcitation (excitotoxicity). All of these have been described as being mitigated by melatonin. These three classes of event, though differing, are closely interrelated and can often occur together. In consequence, it can be difficult to pinpoint the primary event that leads to a cascade of secondary changes. However, the antiexcitatory properties of melatonin are likely to be indirect changes derived from the initial antioxidant properties of melatonin [92, 93].

The problem of determining the primary initial locus of melatonin's actions and elucidating the likely chain of events that ensues is discussed next.

3 Processes That May Underlie the Ability of Melatonin to Modulate the Aging Process

3.1 Melatonin as an Antioxidant

Melatonin is present in bacteria, plants, eukaryotes, and fungi as well as all phyla of multicellular animals, and it has been suggested that its initial evolutionary role was as an antioxidant [74]. Melatonin has been reported to possess antioxidant properties

in both tissue culture and in intact animals. An unresolved issue is whether melatonin acts as an antioxidant *directly* or acts by promotion of key pathways involved in the disposition of free radicals [94]. The evidence for a direct effect rests on the fact that melatonin can act as a powerful free radical scavenger in isolated cell-free systems [95, 96]. However, it has also been reported that melatonin can act as a pro-oxidant in such systems [52, 97]. A key factor in determining this issue may be consideration of levels of free melatonin within the brain. Melatonin is present there at a concentration (around 4 pM) that is only 5% of that found in serum [55]. Therefore – unless it were to be highly concentrated in a localized area – melatonin can make little direct free-radical scavenging contribution in comparison with predominant antioxidant species such as glutathione (present in millimolar amounts) and α -tocopherol (in cells at ca. 1 μ M [98]).

Melatonin is present in cerebrospinal fluid (CSF) at concentrations actually higher than serum, suggesting that the pineal may be a source of blood-borne melatonin [99]. This could account for the diurnal flux of melatonin content in both blood and cerebrospinal fluid [100]. The evidence for the involvement of activation of melatonin receptors in accounting for melatonin's antioxidant potential is described in Section 3.3.

3.2 The Role of Melatonin in the Regulation of Immune Function

Basal levels of inflammatory cytokines, their transcription factors, and glial fibrillary acidic protein (GFAP), a marker of astroglial and intrinsic immune activation, are elevated within the aging brain [46, 101, 102]. These evidences of immune activation are even more pronounced in AD [102]. Melatonin treatment reduces these age-related increases in proinflammatory activity [48, 103, 104]. The causal relation between inflammatory and oxidative events is unclear as inflammation involves oxidative activity, and free radicals can reciprocally recruit an immune response.

3.3 Melatonin Receptors and Enzyme Induction

Within the brain, there are three major plasma membrane receptors for melatonin (Table 1). Two of these, MT1 and MT2, are coupled to G-proteins whose activation leads to depression of levels of cyclic AMP. The third, MT3 or NQO2, is a quinone reductase with poorly understood *in vivo* function. However, the existence of additional melatonin binding sites in the nucleus of many cell types suggests mechanisms of action other than through plasma membrane receptors [105]. The specificity of melatonin may reside in its properties as a neurohormone, which affects transcriptional events in the CNS [57], rather than as a nonspecific antioxidant.

Table 1 Melatonin receptor subtypes and characteristics

Name	GenBank designation	UniProt designation	Other designations	Properties
Melatonin receptor type 1a	Mtnr1a	MTR1A (Q61184)	Mel1a, ML1a, ML1, MT1	353aa plasma membrane GPCR
Melatonin receptor type 1b	Mtnr1b	MTR1B (Q8CIQ6)	Mel1b, ML1b, MT2	364aa plasma membrane GPCR
NAD(P)H dehydrogenase, quinone 2; NRH:quinone oxidoreductase 2	NQO2	NQO2 (Q9JI75)	ML2, MT3	230aa zinc-binding cytoplasmic enzyme

Note: aa = amino acid

A wide range of antioxidant enzymes is induced by melatonin including glutathione peroxidase, catalase, and superoxide dismutases [106]. These protein changes are paralleled by altered levels of gene expression of oxidative enzymes [107]. In addition, levels of some pro-oxidant enzymes such as lipooxygenase and nitric oxide synthetase are depressed after melatonin treatment [48, 108]. Several kinds of cytoplasmic melatonin receptor involve G-protein transduction and modulate transcription. MT1 activation depresses cAMP responsive-element binding protein (CREB) and stimulates extracellular-signal-regulated kinase (ERK) [109]. MT2 levels are depressed in AD [110]. Changes in these signaling pathways may form the basis of the alteration in gene expression effected by melatonin.

The interaction of melatonin with its MT3 receptor may contribute to understanding melatonin's action at pharmacological concentrations, for, despite tight binding to MT3 ($K_i = 280$ nM), melatonin inhibits MT3 only modestly ($IC_{50} = 43$ μ M). MT3 has been characterized as a "toxicity enzyme" [111], based on the reduced sensitivity of MT3-knockout mice to the toxic effects of the MT3 substrate menadione [112]. Thus, melatonin inhibits the (possibly toxic) activity of MT3 activity at just the concentrations where it is found to be protective pharmacologically [111].

Knockout strains of mouse lacking either MT1 or MT2 have been developed [113]. These mutants indicate that there is a limited functional redundancy between the receptor subtypes in the suprachiasmatic nucleus.

3.4 The Link Between Aging and Circadian Events

While the endogenous circadian clock seems to decline more slowly with age, the body's ability to synchronize properly with external light cycles is diminished more rapidly [114]. There is a connection between the length of the photoperiod and aging. The mean life span of the prosimian primate *Microcebus murinus* is

decreased 28% by an accelerated photoperiodic regimen [115]. Moreover, a shortened diurnal cycle is associated with diminished nocturnal melatonin secretion [116] and can hasten the appearance of several behavioral deficits associated with aging [117]. It is interesting that the extreme longevity of healthy centenarians is associated with a pronounced diurnal flux of melatonin [118]. Light suppresses melatonin production in humans. In consideration of other evidence presented, this linkage between reduced melatonin levels and accelerated aging may be more than merely correlative. Levels of both MT1 and MT2 receptors are very high within the suprachiasmatic nucleus (SCN), the site of circadian rhythm regulation. However, levels of expression of both MT1 and MT2 mRNAs in the SCN are identical in senescence-accelerated and senescence-resistant mouse strains [119].

3.5 Melatonin and Mitochondria

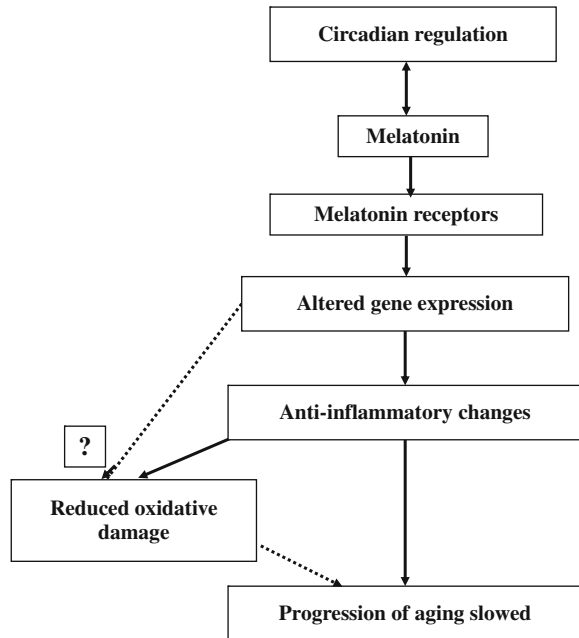
There are many references documenting the ability of melatonin to maintain indices of mitochondrial health. These include downregulation of Bax, caspases, and inhibition of mitochondrial DNA fragmentation, apoptosis, cytochrome c release, and closure of the permeability transition pore. Depression of these adverse events is accompanied by induction of Bcl-2 and improved function of the respiratory chain and ATP synthesis [120–122]. Maintenance of mitochondrial glutathione levels has been also attributed to melatonin [94, 123].

Concepts concerning the possible mechanisms of melatonin's protection of mitochondrial function fall broadly into two classes; namely, direct effects of melatonin upon mitochondria and indirect effects after induction of repression of key proteins. There is little evidence of a direct effect of melatonin upon mitochondrial constituents. Direct inhibition of the mitochondrial permeability transition pore has been shown in isolated systems, but this requires micromolar concentrations of melatonin [124]. The weight of evidence suggests that mitochondrial protection is largely consequent to the induction of antioxidant enzymes and repression of apoptotic pathways. The low levels of melatonin present in tissues cannot afford much direct antioxidant power, but much amplification is provided by any action by way of gene regulation.

3.6 Summary of Mechanisms of Melatonin Action and Suggestions for Future Work

The simplest way to account for the multiplicity of effects of melatonin is to posit an early alteration of gene expression consisting of depression of mRNAs for immune-related cytokines and elevation of those for antioxidant proteins. This would lead to many of the reported enzymic changes resulting from melatonin treatment. Upstream of this may be activation of transcription factors after binding to cytoplasmic melatonin receptors or changes due to melatonin acting directly on

Fig. 1 Potential relationships between regulated melatonin levels and their consequent effect on brain aging



nuclear receptors. Melatonin receptors are not well characterized, and no specific antagonists are available. Thus, circulating melatonin levels, which fluctuate under circadian influence but which are depressed with age, could dynamically influence levels of oxidative and inflammatory activity (Fig. 1). Further research in characterizing melatonin receptors could lead to better delineation of the sequence of events by which melatonin exerts its effects.

4 Conclusions

The median age of the U.S. population is rapidly increasing, and this will lead to a corresponding increase in the incidence of many age-related syndromes. Aging is often associated with both memory and motor deficits including impaired locomotor, postural, and balancing skills. The potential for major increases in incidence of neurodegenerative disorders will be especially pronounced in view of the declining cardiovascular death rate. Retardation of the appearance of changes found with non-pathologic aging could postpone the clinical onset of diseases such as Parkinsonism and Alzheimer’s disease. It may be that one of the most rewarding approaches to mitigation of the societal effects of these diseases lies in the deceleration of changes associated with normal cerebral senescence that are not specifically associated with any neurologic disease. Although the onset of neurologic disease generally does not represent merely an acceleration of normal aging, it is obviously based on a platform

of aging. Both normal aging and pathologic processes in part involve changes in the same loci. The identification and protection of such common targets can be valuable in the development of strategies designed to delay the manifestation of common neurodegenerative disorders. The slow progression over a substantial portion of an individual's adult life span with these conditions suggests that, to be effective, treatments such as dietary supplementation need to be followed over many years. This lengthy treatment of essentially "well" patients requires that both the effectiveness and safety of such regimens be rigorously investigated – initially in animal models – before their widespread use can be confidently advocated.

As only 9% of Americans eat the recommended five servings of fruits and vegetables daily [4], the opportunity for retarding neural aging by modifying the intake of exogenous nutrients is high. Dietary supplementation as a means of delaying age-related neural disorders is more likely to be adhered to than any regimen based on caloric restriction, which is known to retard aging processes. However, no dietary supplement has yet been found as effective as caloric restriction in extending life span [125]. The consumption of melatonin on a regular basis may help to mitigate some aspects of brain aging and appears to pose very little downside risk. Any potential benefits will occur over a long time and will thus be hard to definitively document in humans. Data derived from animal studies suggest the value of melatonin. Aging is a multifactorial process, and the advocacy of a single remedial agent is clearly incomplete. Unlike the focused pharmacological remediation for a specific disorder, amelioration of the wider range of changes associated with normal aging is obviously best addressed with a multiplicity of nutritional and physiologic modifications. However, melatonin has utility as a means of retarding some aspects of brain aging. In addition to the experimental evidence described above, melatonin has several positive features that enhance its candidacy as a therapeutic agent. Melatonin is an evolutionarily ancient neurohormone that has very low toxicity and no carcinogenic properties, and this makes it a very safe compound. It is also readily available and has a low cost. Melatonin is likely to constitute an inexpensive and nonhazardous means of maintaining the functionality of the aging brain.

Acknowledgments This work was supported in part by a grant from the National Institutes of Health (AG 16794) and by a UC Davis Center for Human and Nutrition Pilot Award (CHNR08-318).

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