Open Access

Mini-review: CNS Melatonin Receptors and Signaling: Focus on Aging-Related Diseases and Future Perspectives

Jane E. Cavanaugh and Paula A. Witt-Enderby*

Duquesne University School of Pharmacy, Division of Pharmaceutical Sciences, Pittsburgh, PA 15282, USA

Abstract: Melatonin plays important roles in modulating brain function especially in the entrainment of the sleep/wake cycle. This occurs in the suprachiasmatic nucleus of the hypothalamus (master biological clock) through melatonin receptors, MT_1(MT_1R) and MT_2(MT_2R) and the coordinated release of melatonin from the pineal gland that result in peak nocturnal levels of circulating melatonin followed by daytime troughs [1]. Besides sleep, melatonin, acting through melatonin receptors, affects the release of hypothalamic/pituitary hormones involved in reproduction and stress [2-4] and modulates other brain centers involved in pain and blood pressure [5-8]. Though these areas of study are important and affected by age, the focus of this review will be on the role of melatonin and melatonin receptors in brain function greatly impacted by age, with an emphasis on those affecting memory, mood, and movement.The cellular mechanisms underlying melatonin and melatonin receptor action will be discussed in the context of the literature but also will highlight other potential targets to guide future studies in this area.

Keywords: Melatonin receptors, CNS, melatonin, mitogen activated protein kinases, ERK1/2, ERK5.

MELATONIN AND AGING

According to the US Census Bureau, the fastest growing segment of the U.S. population is individuals over the age of 65. The number of people 65 or older is expected to increase to 53.2% by 2050. Similarly, the number of people aged 85 and older is expected to increase from 4.3 million in 2000 to 8.5 million in 2030 and 18.2 million in 2050. One of the most widely accepted hypotheses of aging is the free radical or oxidative stress theory of aging [9]. This hypothesis states that aging occurs due to an accumulation of oxidative insults throughout the lifespan. Adding to this, decreases in defense mechanisms against free radical damage have been reported with age. Therefore, therapies to boost antioxidant mechanisms and scavenge free radicals would, in turn, decrease age-related illnesses and increase the quality of life in the elderly, are needed. One such potential therapy is the natural hormone melatonin, which is reported to be a potent anti-aging compound by many research groups [10-12]. Although somewhat controversial, the increasing evidence for a role of melatonin in neuroprotection during non-diseased and diseased brain aging cannot be ignored.

As mentioned, melatonin levels fluctuate throughout the 24h cycle. With age, circulating melatonin levels (particularly the nocturnal peaks) have been shown to decrease in rodents and humans [13-15], which may further exacerbate free radical damage in the aging brain. In aged female rats, nocturnal melatonin levels are decreased in comparison to young animals [16]. Similarly in humans, the amplitude of the nocturnal peak of melatonin secretion decreases with age until between ages 60 and 70 there is no longer a difference in melatonin levels during the night as compared to the daytime [17]. This decreased peak of melatonin secretion may lead to sleep disturbances, alterations in circadian rhythms, and immune suppression which may, in turn, lead to significant health problems in the elderly [18,19].

Oxidative Stress

Several studies suggest that there is an increase in oxidative damage with aging [20,21] and that oxidative stress plays a role in neurodegeneration [22]. Melatonin has been shown to be a potent antioxidant in many cell types, animal models and humans [23-28]. These antioxidant effects of melatonin are most likely due melatonin's receptor-independent mechanisms of action. Melatonin alone or its brain kynuramine derivatives [29], N^1-acetyl-N^2-formyl-5-methoxykynurenamine (AFMK) and N^1-acetyl-5-methoxykynuramine (AMK), may modulate distinct signaling pathways that could be important in brain function [30,31]. Melatonin has been reported to directly scavenge reactive oxygen species (ROS) [32]. Following an interaction with ROS, melatonin is metabolized to its brain kynuramine derivatives, AFMK and AMK, which also act to decrease free radical damage, protect neurons from damage and promote their survival [30,31]. Additionally, melatonin can enhance the expression of antioxidant enzymes to protect the brain from oxidative insults. Using a rat model of aging, Akbulut and colleagues [33] reported that melatonin treatment caused a significant increase in the endogenous antioxidant glutathione (GSH) in the cortex and cerebellum of aged animals as compared to aged animals that were not treated with melatonin. In a mouse model of accelerated aging (senescence accelerated mice; SAMP8) melatonin reduced the levels of oxidative damage and neurodegeneration

*Address correspondence to this author at the 421 Mellon Hall, Division of Pharmaceutical Sciences, School of Pharmacy, Pittsburgh, PA 15282, USA; Tel: 1-412-396-4346; Fax: 1-412-396-5599; Email: wittp@duq.edu

1876-5289/10 2010 Bentham Open

via an increase in retinoic acid receptor (ROR-alpha1) shown to be important for the control of the neuronal response to oxidative stress [34,35]. In this same model, melatonin treatment leads to a reduction in DNA damage and oxidative damage and cerebral cortical cell loss [36-38]. Moreover, melatonin has been shown to stimulate several antioxidant enzymes including superoxide dismutase, glutathione peroxidase and glutathione reductase [32]. Finally, iron-induced oxidative damage of the locus coeruleus, a brain region rich in norepinephrine neurons that is damaged in several neurodegenerative diseases, was decreased by melatonin administration [39].

Mitochondrial Function

A significant source of ROS is complex I of the respiratory chain in mitochondria. Impairments in mitochondrial function have been noted with age [40] that may contribute to the age-related increase in oxidative stress. Mitochondria isolated from young and old animals treated with melatonin were healthier compared to mitochondria from untreated young and old animals [41]. Melatonin prevented the elevated production of hydrogen peroxide and complex I activity noted with age. Similarly, melatonin treatment completely inhibited mitochondrial dysfunction in the SAMP8 mouse model [42]. In fact, melatonin not only prevented a decrease in ATP production, which is indicative of mitochondrial respiratory chain function, but it increased ATP production in these mice.

Immune System and Inflammation

As one ages, increases in inflammation and decreases in immune defenses occurs. Melatonin has been reported to stimulate the production of granulocyte and macrophage progenitors, natural killer cells and cytokine release as reviewed in [19]. The modulation of melatonin on the gene expression of immune system proteins and inflammatory mediators with age has also been observed using mouse CNS microarray analysis [43]. Overall, melatonin shifted the gene expression pattern in the old mice to that of the young mice and many of the genes altered by melatonin were for proteins that are involved in inflammation and the immune system. Similar results were obtained in mice injected with lipopolysaccharide (LPS) to induce an inflammatory response [44]. Gene expression in old LPS injected mice treated with melatonin was similar to that in young melatonin treated mice exposed to the same LPS challenge. Together these data suggest melatonin may decrease age-related CNS inflammation and boost the immune system with age thereby promoting healthy aging.

MELATONIN RECEPTORS, AGEING AND DISEASE

Receptor Density

Age-related changes in melatonin receptor density have been reported especially in diseases associated with aging like Alzheimers Disease (AD) [45-48]. Some of these disease states result in differential expression of each of the melatonin receptor subtypes perhaps as a means to compensate for the loss of the other. For example, in the hippocampus of AD patients, MT_1R expression increases while MT_2R levels decrease [45,46]. Age-dependent decreases in the number of MT_1R- expressing neurons are seen without a concomitant decrease in vasopressin or vasoactive intestinal peptide neurons [48]. As the SCN is the central biological clock, a decrease in SCN MT_1R expression may lead to and/or exacerbate clinical circadian disorders and sleep disturbances in the elderly. In fact, a loss of SCN sensitivity to melatonin in the aged mice has been reported [49]. However, it should be noted that an earlier study in aged mice, melatonin-induced phase shifts of circadian rhythm were unaltered although an age-related loss of daytime SCN MT_1R mRNA expression was reported [50]. In a rodent model, SCN MT_2R has been shown to play a role in the phase shift effects of melatonin [51,52]. Perhaps, an imbalance between MT_1R and MT_2R expression and/or function in the SCN is leading to the modulation of signaling pathways regulating circadian rhythms. Melatonin receptors are expressed in the SCN and circadian rhythm disturbances occur in those afflicted with neurodegenerative disorders [18,53,54].

Depression

The incidence of depression has been shown to increase with age and depression is a co-morbidity with many age-related diseases [55]. Interestingly, serum melatonin levels are decreased in patients with major depressive disorders and an increase in melatonin release has been noted following antidepressant treatment that coincides with the clinical effectiveness of these medications [56-58]. Moreover, chronic antidepressant treatment has been shown to modulate melatonin receptor sensitivity and alter the ratio of MT_1R to MT_2R such that the therapeutic effectiveness of antidepressants is increased with nocturnal release of melatonin [59]. Therefore, with aging and age-related diseases in which melatonin secretion is decreased at night, nocturnal supplementation with melatonin may be a useful therapy and, as such, anti-depressant drugs like agomelatine may be more effective than the ones currently on the market.

Memory

Similar to depression, a decrease in memory and processes which support memory, such as long term potentiation (LTP) in the hippocampus, have been noted with aging [60,61]. Several studies have supported a role for melatonin in the reduction of age-related increases in memory deficits [62,63] and these may, in part, occur through melatonin receptors as 2-[^{125}I]-iodomelatonin binding sites and both receptor subtypes have been detected in the hippocampus [45,46,64,65]. Prieto-Gomez and colleagues [66] report that melatonin increases the expression of MAP-2, a dendritic marker, in the hippocampus with age. In the SAMP8 model, Cheng and colleagues [67] noted that melatonin treatment increased hippocampal pyramidal cell number and improved performance on the Y-maze and eight-arm radial maze tests for memory. Similarly, it has been shown that melatonin reverses age-induced memory deficits in normal age mice in the elevated plus-maze and passive avoidance behavioral paradigms [68]. Even though the effects of melatonin on LTP are mixed with many studies showing inhibitory actions on LTP [64,69-73] and many showing stimulatory actions on LTP [63,74-76], among the studies that suggest melatonin increases LTP, the consensus is that this effect of melatonin occurs *via* activation of the MT_2R. In MT_2R knockout mice,

burst stimulation-induced LTP was decreased as compared to wild-type mice [63]. Furthermore, in the elevated plus maze behavioral test for memory, the MT_2R knockout animals did not improve with training as compared to their wild-type counterparts. Together these studies suggest that melatonin *via* its actions at the MT_2R plays a role in hippocampal memory processes and synaptic plasticity. It is important to note that in a zebrafish model, melatonin has been shown to suppress learning and memory in an operant conditioning paradigm [77]. The zebrafish did not perform as well on this behavioral test when they were tested in the nighttime as opposed to the daytime. Furthermore, daytime melatonin supplementation caused a decrease in learning and memory similar to the zebrafish tested at night while pinealectomy or treatment with a melatonin antagonist improved memory formation during the night. These data underscore the importance of paying mind to the temporal pattern of melatonin secretion in order to determine the best time of day or night for melatonin therapy so as to maximize the beneficial effects and minimize the detrimental effects of this hormone.

Alzheimer's Disease

In addition to the effects on the brain with normal aging, an increase in oxidative stress has also been shown to play a role in neurodegenerative diseases such as Alzheimer's and Parkinson's disease [78,79]. Therefore, melatonin has received much interest as a possible therapeutic treatment for these neurodegenerative diseases [80,81]. Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that alters mood, mental and motor function, leads to cognitive impairments and ultimately results in death. It has been suggested that the incidence of AD will increase approximately 3-fold from 4.5 million persons with AD in the year 2000 to 13.2 million persons with AD by 2050 [82]. Therefore, it is imperative that new discoveries are pursued that may provide treatments for AD patients or even prevent AD.Characteristics of AD include neurofibrillary tangles composed of hyperphosphorylated Tau protein, plaque formation and cell death in the cortex and hippocampus. Accumulation of βamyloid (Ab) peptides produced from cleavage of the amyloid precursor protein (APP) is also a common feature of sporadic and familial AD. Fibrillar Ab induces apoptosis in neurons and that this cell death is partially responsible for the cognitive decline experienced by AD patients.

Interestingly, melatonin levels are dramatically decreased in AD patients and may contribute to or further exacerbate the neuronal cell death observed in AD and melatonin administration may serve to alleviate the Ab burden of these patients and, in turn, decrease cell death and cognitive decline [56,83-87]. Administration of melatonin protected glial cell cultures from Ab-induced cell death [88]. In animal studies, both long and short forms of Aþ that are involved in Ab deposition and plaque formation were found to be reduced in aging mice following dietary melatonin supplementation [89]. Moreover, melatonin treatment inhibited the elevation of Ab, increased neuronal survival, and reversed cognitive impairment of working and spatial memory in a transgenic mouse model (Tg2576) of AD [90,91]. In addition to a reduction in Ab pathology, melatonin has been shown to decrease tau hyperphosphorylation that contributes to the formation of fibrillary tangles [83,92]. However, in one study that utilized the same amyloid plaque-bearing transgenic model as mentioned above, chronic melatonin did not reduce Ab levels [93]. One explanation for this offered by the authors is that melatonin treatment was not given until after plaque formation. Therefore, the results of this study suggest that melatonin may be more useful in early stages or as prophylactic treatment of AD.

Alterations in melatonin receptor expression in the SCN, as seen with non-diseased aging, have been reported to be even more pronounced in AD [18,45-48]. For example, MT_1R expressing neurons have been shown to decline in the late, but not early, stage of AD [48]. Therefore, sleep disorders resulting from disturbances in circadian rhythm are even more noticeable in AD patients. In addition to increasing age, family history is a risk factor for AD. Specifically, alterations in the apolipoprotein E4 gene has been shown to increase the deposition of toxic Ab fragments. Melatonin addition to Ab decreased apoE4-induced Ab plaque formation. Furthermore, melatonin treatment blocked Ab and ApoE4 neurotoxicity *in vitro* [94]. Taken together, the data that support a role for melatonin in neuroprotection in AD, has lead some investigators to propose that the FDA approved drugs for AD, such as memantine and acetylcholinesterase inhibitors may be more effective when given with melatonin supplementation [95].

Parkinson's Disease

Parkinson's disease (PD) is the most common age-related neurological disease of motor function, affecting 1% of all individuals above the age of 60 that results largely from the loss of dopamine-containing neurons projecting from the substantia nigra to the striatum. Since the late 1960s the primary treatment for PD has been levodopa (L-dopa). Although L-dopa therapy has been improved since that time, dyskinesias and motor fluctuations, the major side effects of L-dopa, still occur and, in many cases, can be more debilitating than PD itself. Therefore, there is a great need for complementary or alternative therapies for PD patients.

Although the data from few studies suggest a limited benefit of melatonin supplementation in PD [84,96], most studies report a beneficial effect of melatonin in diverse animal models and human and animal cell culture models of PD [97]. For example, melatonin treatment has been shown to protect against rotenone-induced dopamine neuronal loss and dopamine transporter downregulation *in vivo* [98]. Similarly, melatonin inhibited striatal dopaminergic cell death produced by the dopamine neurotoxin 6-hydroxydopamine [99]. Finally, *in vivo* and *in vitro* dopamine neuronal degeneration induced by treatment with the dopamine specific neurotoxin, 1-methyl-4-phenylpyridinium (MPP+), is alleviated by melatonin treatment [100-102].

MELATONIN RECEPTORS AND BRAIN ASSOCIATED SIGNALING MECHANISMS

The role of melatonin on influencing brain processes is complicated by the fact that melatonin may be working through its receptors [64,69] or independent of its receptors to impact on the brain in different ways, for example, by modulating LTP, neuronal excitability, neuronal differentia-

tion and neuronal survival. Melatonin can act through MT_1Rs and MT_2Rs that are coupled to G-proteins [103-106] that can link to diverse signaling pathways [107]. More recently, melatonin receptor subtypes, MT_1 or MT_2 can homodimerize, or heterodimerize with each other or with GPR50 [108-110] to influence receptor function and possibly downstream cellular processes. Most important to brain function would be those pathways involved in neuronal excitability, long-term potentiation, survival and differentiation. These, in turn, would impact greatly on diseases like AD and PD that result in cognitive deficits, motor impairment and depression.

Regarding memory, melatonin can impact on memory processes through its actions on LTP and neuronal differentiation and these occur through different signaling pathways. For example, in one study, melatonin is shown to inhibit LTP in the hippocampus through MT_2R coupled to an inhibition of cAMP and PKA [71]. How PKA modulates LTP in the hippocampus is still not clear. PKA may increase LTP by enhancing NMDA receptor ($NMDA_R$) activity through phosphorylation processes or, perhaps, through its actions on CREB and CRE-containing genes as shown in Fig. (**1**). Therefore, melatonin-mediated inhibition of PKA and their effects on $NMDA_R$ activation in the hippocampus should be explored. Also, seeing that kynuramine derivatives could influence $NMDA_R$s on their own [31], the effect of the melatonin brain derivatives, AFMK or AMK, on hippocampal $NMDA_R$s and LTP should also be assessed.

Complicating things further are the recent findings that melatonin receptor subtypes and their expression levels can influence melatonin-mediated effects on LTP and downstream signaling processes. For example, mice lacking MT_2Rs show attenuation in LTP induced by melatonin in hippocampal slices when compared to their wild-type counterparts, which also is paralleled by memory deficits [63]. These data suggest that melatonin receptor subtypes play critical roles in modulating brain function and their expression in tissues and cells influence downstream signaling mechanisms. For example, co-expression of both MT_1Rs and MT_2Rs in cerebellar granule cells (CGCs) produces melatonin-mediated decreases in cAMP that are dependent upon Gi proteins. However, removal of one of the receptor subtypes from the cells prevents melatonin-mediated decreases in cAMP. The same holds true for ERK1/2 and Akt activation in CGCs. In MT1/MT2R-expressing CGCs, melatonin (1nM) attenuates ERK1/2 and Akt activity. However, removal of either receptor from the cells such that only one of the receptor subtypes is being expressed causes these cells to become non-responsive to this same concentration of melatonin [111]. Because recent evidence using recombinant models shows that melatonin receptors, MT_1, MT_2, can heterodimerize [108,109], then, perhaps, heterodimerization between the melatonin receptor subtypes (i.e, MT_1R/MT_2R) or between receptor tyrosine kinases (RTKs) [112] (i.e., MT_1R/RTK or MT_2R/RTK) is occurring in CGCs and impacting on signaling cascades involved in memory. In keeping, it is possible that conditions like disease or drug treatments that result in differential modulation of the melatonin receptor subtypes could influence melatonin heterodimerization processes. This could impact on the brain in a positive or negative manner depending on the role of the melatonin receptor subtype being influenced by the condition. For example, in hippocampal regions of those afflicted with AD, differential expression of hippocampal melatonin receptors occurs where levels of MT_1Rs are high and levels of MT_2Rs are low [45,46]. This reduction in MT_2R expression may be contributing to the memory loss associated with AD perhaps due to alterations in MT_1R/MT_2R heterodimerization states in the hippocampus. Attenuation in melatonin-induced LTP and memory occurs in MT_2R knockout mice [63] and changes in MT_1R and MT_2R expression patterns in CGCs influence downstream mechanisms thought to participate in memory processes [111].

By contrast, chronic drug therapy could be used to influence melatonin receptor expression that produces positive effects in the brain, for example, chronic anti-depressant actions on melatonin receptor expression in the hippocampus. It is hypothesized that chronic anti-depressant action may alter the brain ratios of MT_1R and MT_2Rs (i.e., increase MT_1R and decrease MT_2Rs) to enable endogenous melatonin released during the night to further improve the anti-depressant actions in the brain [59]. This is a plausible hypothesis because of the findings that chronic anti-depressant treatment increases MT_1R mRNA levels while decreasing MT_2R mRNA levels in mouse hippocampus [113] and that MT_1R-deficient mice display depressive actions greater than wild-type mice [114]. More studies should be conducted to determine if these changes in melatonin receptor mRNA levels translate to changes in melatonin receptor protein function thus modulating signaling pathways involved in brain function. Studies in the CGCs are a good start and suggest that melatonin acting through melatonin receptors modulates the mitogen activated protein kinases (MAPKs). MAPKs play an important role in neuronal proliferation, differentiation and survival and melatonin's influence on MAPK activity may underlie melatonin's effects on memory and plasticity.

Many studies support a role for MAPKs in modulating cellular differentiation induced by melatonin *via* melatonin receptors [112,115-117]. However, it should be mentioned that melatonin, acting independent of receptors and through PKC and Rho/ROCK signaling cascades increases cellular differentiation [118]. Besides regulating cellular differentiation, the MAPKs extracellular signal-regulated kinases 1 and 2 (ERK1/2), play a role in inhibiting antioxidant-induced cell death and providing neuroprotection in general [119]. Specifically, melatonin has been shown to attenuate cortical cell death induced by ischemic injury *via* activation of the ERK1/2 cascade and its downstream targets [120]. Therefore, melatonin modulation of MAPK pathways may improve memory by enhancing neuronal differentiation while protecting existing neurons from age-related damage. In a similar model of cell death, Kilic and colleagues [121], noted that ERK1/2 may be more important for the long-term neuroprotective effects of melatonin while other signaling pathways, such as the phosphatidyl-inositol-3 kinase/Akt cascades, may play a greater role in neuroprotection induced by acute melatonin treatment. These findings underscore the importance of paying close attention to the type of melatonin exposure (i.e., low dose, high dose; acute vs. chronic) and type of melatonin receptor being activated especially when elucidating cellular mechanisms downstream from melatonin receptor activation.For example, in primary cultures of

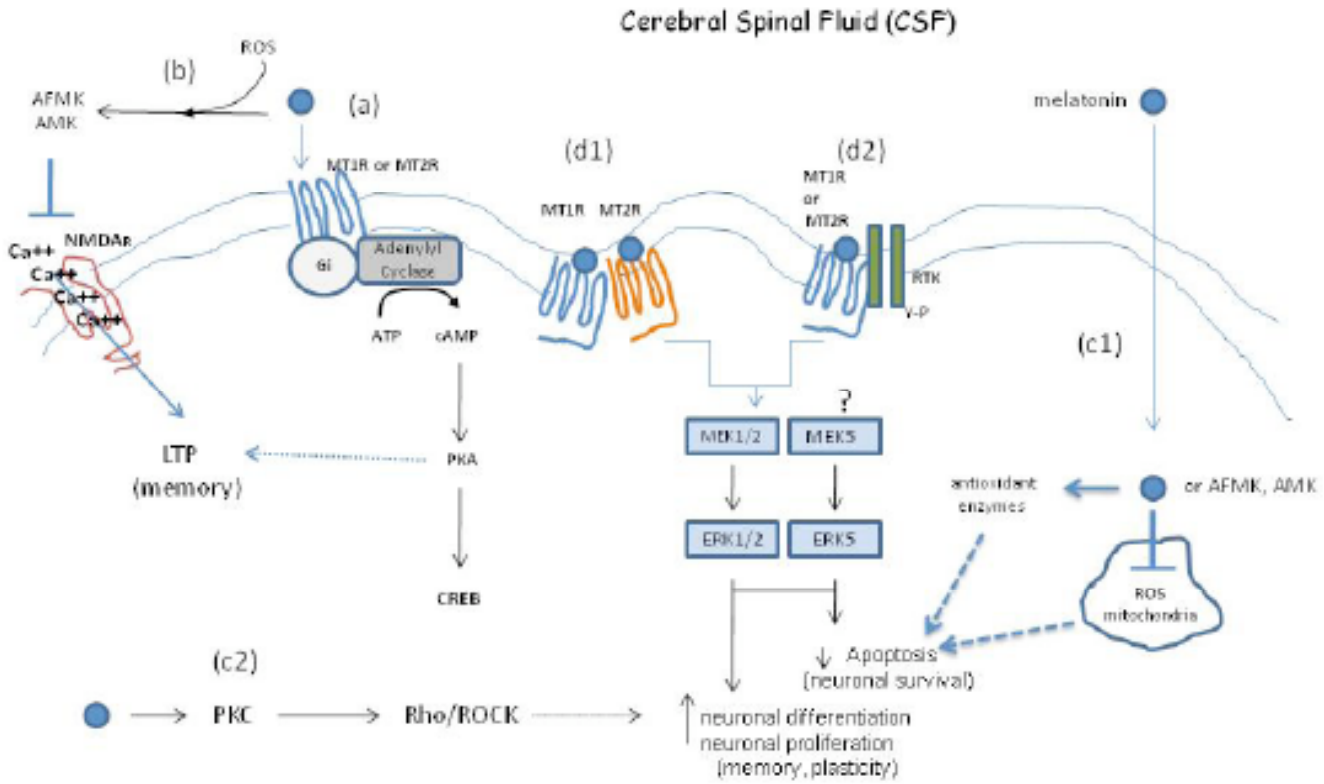

Fig. (1). Schematic of potential signaling pathways underlying melatonin's effects in neurons. As shown, melatonin is proposed to act through multiple signaling pathways. In (a) melatonin, acting through melatonin receptors, MT_1R, MT_2R, may inhibit long-term potentiation (LTP) *via* an inhibition of cAMP and PKA as mediated through Gi proteins. In (b), melatonin, acting as a free-radical scavenger in the CSF to produce AFMK and AMK may inhibit NMDR receptor ($NMDA_R$) activation preventing calcium influx into the neuron to inhibit LTP. In (c1), melatonin may act to scavenge free radicals within the neuron to protect it from oxidative damage and promote survival or in (c2) may act on PKC to promote neuronal differentiation *via* activation of Rho and ROCK to modulate neuronal plasticity. In (d), melatonin, acting through melatonin receptors and heterodimerization processes between MT_1Rs and MT_2Rs (d1) or between melatonin receptors and receptor tyrosine kinases (d2) may modulate mitogen activation protein kinase (MAPK) pathways known to be involved in neuronal differentiation and proliferation (MEK1/2/5) or survival *via* apoptotic mechanisms (MEK5).

CGCs expressing both MT_1Rs and MT_2Rs, an acute (10 min) melatonin exposure decreases ERK1/2 activity in a concentration-dependent manner [111] whereas a longer exposure to melatonin (30 min) attenuates these inhibitory actions on ERK1/2 activity. Perhaps, this is due to melatonin receptor desensitization and internalization processes, mechanisms proposed to underlie cellular differentiation induced by melatonin through scaffolding with β-arrestins [116]. Densensitization and internalization processes are involved in melatonin receptor signaling and these processes, indeed, have been shown to be dependent upon the duration of agonist exposure, the concentration of agonist being used and the melatonin receptor subtype being expressed in the particular model [115,116,122-124].

Besides ERK 1/2, a new MAPK family member, ERK5, may be playing a role in melatonin-induced responses in cells. ERK5 is a particularly interesting protein because like ERK1/2 it is widely expressed in neurons. However, unlike ERK1/2, the role of ERK5 in neuroprotection is just beginning to be elucidated [125,126]. Moreover, many studies have relied on the use of the inhibitors PD98059 and U0126 to implicate ERK1/2 in neuroprotection. Interestingly, PD98059 and U0126 also block the activation of ERK5 [127]. This suggests the interesting possibility that some of the functions attributed to ERK1/2, including melatonin-induced neuroprotection *via* ERK1/2 activation, may be mediated by ERK5. However, ERK5 activation by melatonin has not yet been explored. Interestingly, however, both melatonin treatment [117] and ERK5 activity [128] been shown to increase neurite outgrowth in separate studies by different research groups. This is an area of great interest to our laboratories and we hypothesize that ERK5 pathway will be activated by melatonin to increase neurite outgrowth and neuronal survival. Furthermore, as a decrease in ERK5 signaling has been observed in the developing brain [125], we hypothesize the ERK5 activity decreases with age and melatonin therapy may be useful in counteracting this age-related decline in ERK5 signaling.

CONCLUSIONS

Overall, melatonin may be a promising therapy for age-related diseases both with non-diseased and diseased aging. Melatonin is a natural hormone that has very limited side effects and can, therefore, be used in an aged population with little worry of toxicity. Importantly, especially in the current economic climate and for the elderly population, melatonin is relatively inexpensive. Melatonin use as an adjuvant therapy to existing therapies targeted at the treatment of

depression or cognitive deficits should be explored. More importantly, melatonin use as a preventative agent against neurodegenerative disorders like AD and PD need to be explored. These types of studies will require assessing the long-term impact of chronic melatonin exposure on the development of AD and PD in rodent models to determine if melatonin can delay or even prevent their development. The hope is to bring melatonin therapies, if shown to be efficacious, to the clinic for use in those at risk for neurodegenerative diseases. Also, since it appears that specific melatonin receptors are involved in specific brain functions, for example hippocampal MT_2Rs in memory, then selective agents need to be developed for further elucidation of these roles. This, in turn, will further the development of drug therapies targeted to the individual melatonin receptors.

ABBREVIATIONS

CRE = Cyclic AMP response element

CREB = Cyclic AMP response element binding protein

LTP = Long-term potentiation

REFERENCES

[1] Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep 2009; 61: 383-410.

[2] Morgan PJ, Barrett P, Howell HE, Helliwell R. Melatonin receptors: localization, molecular pharmacology and physiological significance. Neurochem Int 1994; 24: 101-46.

[3] Hiebert SM, Green SA, Yellon SM. Daily timed melatonin feedings mimic effects of short days on testis regression and cortisol in circulation in Siberian hamsters. Gen Comp Endocrinol 2006; 146: 211-6.

[4] Cagnacci A, Soldani R, Yen SS. Melatonin enhances cortisol levels in aged but not young women. Eur J Endocrinol 1995; 133: 691-5.

[5] Harrod CG, Bendok BR, Hunt Batjer H. Interactions between melatonin and estrogen may regulate cerebrovascular function in women: clinical implications for the effective use of HRT during menopause and aging. Med Hypotheses 2005; 64: 725-35.

[6] Doolen S, Krause DN, Dubocovich ML, Duckles SP. Melatonin mediates two distinct responses in vascular smooth muscle. Eur J Pharmacol 1998; 345: 67-9.

[7] Doolen S, Krause DN, Duckles SP. Estradiol modulates vascular response to melatonin in rat caudal artery. Am J Physiol 1999; 276: H1281-8.

[8] Ekmekcioglu C. Melatonin receptors in humans: biological role and clinical relevance. Biomed Pharmacother 2006; 60: 97-108.

[9] Harman D. Free radical involvement in aging. Pathophysiology and therapeutic implications. Drugs Aging 1993; 3: 60-80.

[10] Anisimov VN, Zavarzina NY, Zabezhinski MA, *et al*. Melatonin increases both life span and tumor incidence in female CBA mice. J Gerontol A Biol Sci Med Sci 2001; 56: B311-23.

[11] Bondy SC, Lahiri DK, Perreau VM, *et al*. Retardation of brain aging by chronic treatment with melatonin. Ann N Y Acad Sci 2004; 1035: 197-215.

[12] Bondy SC, Sharman EH. Melatonin and the aging brain. Neurochem Int 2007; 50: 571-80.

[13] Magri F, Sarra S, Cinchetti W, *et al*. Qualitative and quantitative changes of melatonin levels in physiological and pathological aging and in centenarians. J Pineal Res 2004; 36: 256-61.

[14] Reiter RJ, Tan DX. What constitutes a physiological concentration of melatonin? J Pineal Res 2003; 34: 79-80.

[15] Pandi-Perumal SR, Zisapel N, Srinivasan V, Cardinali DP. Melatonin and sleep in aging population. Exp Gerontol 2005; 40: 911-25.

[16] Reiter RJ, Craft CM, Johnson JE, Jr., *et al*. Age-associated reduction in nocturnal pineal melatonin levels in female rats. Endocrinology 1981; 109: 1295-7.

[17] Karasek M. Does melatonin play a role in aging processes? J Physiol Pharmacol 2007; 58 (Suppl 6): 105-13.

[18] Wu YH, Swaab DF. Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer's disease. Sleep Med 2007; 8: 623-36.

[19] Cardinali DP, Esquifino AI, Srinivasan V, Pandi-Perumal SR. Melatonin and the immune system in aging. Neuroimmunomodulation 2008; 15: 272-8.

[20] Stadtman ER. Protein oxidation and aging. Science 1992; 257: 1220-4.

[21] Sohal RS, Orr WC. Role of oxidative stress in senescence. Aging (Milano) 1998; 10: 149-51.

[22] Reiter RJ. Oxidative processes and antioxidative defense mechanisms in the aging brain. FASEB J 1995; 9: 526-33.

[23] Manda K, Bhatia AL. Melatonin-induced reduction in age-related accumulation of oxidative damage in mice. Biogerontology 2003; 4: 133-9.

[24] Karasek M, Reiter RJ. Melatonin and aging. Neuro Endocrinol Lett 2002; 23 (Suppl 1): 14-6.

[25] Reiter RJ, Tan DX, Qi W, Manchester LC, Karbownik M, Calvo JR. Pharmacology and physiology of melatonin in the reduction of oxidative stress *in vivo*. Biol Signals Recept 2000; 9: 160-71.

[26] Herrera F, Martin V, Garcia-Santos G, Rodriguez-Blanco J, Antolin I, Rodriguez C. Melatonin prevents glutamate-induced oxytosis in the HT22 mouse hippocampal cell line through an antioxidant effect specifically targeting mitochondria. J Neurochem 2007; 100: 736-46.

[27] Reiter RJ, Garcia JJ, Pie J. Oxidative toxicity in models of neurodegeneration: responses to melatonin. Restor Neurol Neurosci 1998; 12: 135-42.

[28] Lezoualc'h F, Skutella T, Widmann M, Behl C. Melatonin prevents oxidative stress-induced cell death in hippocampal cells. Neuroreport 1996; 7: 2071-7.

[29] Acuna CD, Escames G, Carazo A, Leon J, Khaldy H, Reiter RJ. Melatonin, mitochondrial homeostasis and mitochondrial-related diseases. Curr Top Med Chem 2002; 2: 133-51.

[30] Acuna-Castroviejo D, Escames G, Rodriguez MI, Lopez LC. Melatonin role in the mitochondrial function. Front Biosci 2007; 12: 947-63.

[31] Moroni F. Tryptophan metabolism and brain function: focus on kynurenine and other indole metabolites. Eur J Pharmacol 1999; 375: 87-100.

[32] Reiter RJ, Tan DX, Manchester LC, El-Sawi MR. Melatonin reduces oxidant damage and promotes mitochondrial respiration: implications for aging. Ann N Y Acad Sci 2002; 959: 238-50.

[33] Akbulut KG, Gonul B, Akbulut H. Exogenous melatonin decreases age-induced lipid peroxidation in the brain. Brain Res 2008; 1238: 31-5.

[34] Caballero B, Vega-Naredo I, Sierra V, *et al*. Favorable effects of a prolonged treatment with melatonin on the level of oxidative damage and neurodegeneration in senescence-accelerated mice. J Pineal Res 2008; 45: 302-11.

[35] Caballero B, Vega-Naredo I, Sierra V, *et al*. Melatonin alters cell death processes in response to age-related oxidative stress in the brain of senescence-accelerated mice. J Pineal Res 2009; 46: 106-14.

[36] Gutierrez-Cuesta J, Tajes M, Jimenez A, Coto-Montes A, Camins A, Pallas M. Evaluation of potential pro-survival pathways regulated by melatonin in a murine senescence model. J Pineal Res 2008; 45: 497-505.

[37] Morioka N, Okatani Y, Wakatsuki A. Melatonin protects against age-related DNA damage in the brains of female senescence-accelerated mice. J Pineal Res 1999; 27: 202-9.

[38] Gutierrez-Cuesta J, Sureda FX, Romeu M, *et al*. Chronic administration of melatonin reduces cerebral injury biomarkers in SAMP8. J Pineal Res 2007; 42: 394-402.

[39] Chen KB, Lin AM, Chiu TH. Oxidative injury to the locus coeruleus of rat brain: neuroprotection by melatonin. J Pineal Res 2003; 35: 109-17.

[40] Ames BN, Shigenaga MK, Hagen TM. Mitochondrial decay in aging. Biochim Biophys Acta 1995; 1271: 165-70.

[41] Petrosillo G, Fattoretti P, Matera M, Ruggiero FM, Bertoni-Freddari C, Paradies G. Melatonin prevents age-related

mitochondrial dysfunction in rat brain *via* cardiolipin protection. Rejuvenation Res 2008; 11: 935-43.

[42] Carretero M, Escames G, Lopez LC, *et al*. Long-term melatonin administration protects brain mitochondria from aging. J Pineal Res 2009; 47: 192-200.

[43] Sharman EH, Bondy SC, Sharman KG, Lahiri D, Cotman CW, Perreau VM. Effects of melatonin and age on gene expression in mouse CNS using microarray analysis. Neurochem Int 2007; 50: 336-44.

[44] Perreau VM, Bondy SC, Cotman CW, Sharman KG, Sharman EH. Melatonin treatment in old mice enables a more youthful response to LPS in the brain. J Neuroimmunol 2007; 182: 22-31.

[45] Savaskan E, Olivieri G, Meier F, *et al*. Increased melatonin 1a-receptor immunoreactivity in the hippocampus of Alzheimer's disease patients. J Pineal Res 2002; 32: 59-62.

[46] Savaskan E, Ayoub MA, Ravid R, *et al*. Reduced hippocampal MT2 melatonin receptor expression in Alzheimer's disease. J Pineal Res 2005; 38: 10-6.

[47] Savaskan E, Olivieri G, Brydon L, *et al*. Cerebrovascular melatonin MT1-receptor alterations in patients with Alzheimer's disease. Neurosci Lett 2001; 308: 9-12.

[48] Wu YH, Zhou JN, Van Heerikhuize J, Jockers R, Swaab DF. Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. Neurobiol Aging 2007; 28: 1239-47.

[49] von Gall C, Weaver DR. Loss of responsiveness to melatonin in the aging mouse suprachiasmatic nucleus. Neurobiol Aging 2008; 29: 464-70.

[50] Benloucif S, Masana MI, Dubocovich ML. Responsiveness to melatonin and its receptor expression in the aging circadian clock of mice. Am J Physiol 1997; 273: R1855-60.

[51] Dubocovich ML, Yun K, Al-Ghoul WM, Benloucif S, Masana MI. Selective MT2 melatonin receptor antagonists block melatonin-mediated phase advances of circadian rhythms. FASEB J 1998; 12: 1211-20.

[52] Hunt AE, Al-Ghoul WM, Gillette MU, Dubocovich ML. Activation of MT(2) melatonin receptors in rat suprachiasmatic nucleus phase advances the circadian clock. Am J Physiol Cell Physiol 2001; 280: C110-8.

[53] Wu YH, Fischer DF, Kalsbeek A, *et al*. Pineal clock gene oscillation is disturbed in Alzheimer's disease, due to functional disconnection from the "master clock". FASEB J 2006; 20: 1874-6.

[54] Weaver DR, Reppert SM. The Mel1a melatonin receptor gene is expressed in human suprachiasmatic nuclei. Neuroreport 1996; 8: 109-12.

[55] Gareri P, De Fazio P, De Sarro G. Neuropharmacology of depression in aging and age-related diseases. Ageing Res Rev 2002; 1: 113-34.

[56] Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B, Hardeland R. Melatonin in Alzheimer's disease and other neurodegenerative disorders. Behav Brain Funct 2006; 2: 15.

[57] Crasson M, Kjiri S, Colin A, *et al*. Serum melatonin and urinary 6-sulfa-toxymelatonin in major depression. Psychoneuroendocrinology 2004; 29: 1-12.

[58] Beck-Friis J, Ljunggren JG, Thoren M, von Rosen D, Kjellman BF, Wetterberg L. Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. Psychoneuroendocrinology 1985; 10: 173-86.

[59] Hirsch-Rodriguez E, Imbesi M, Manev R, Uz T, Manev H. The pattern of melatonin receptor expression in the brain may influence antidepressant treatment. Med Hypotheses 2007; 69: 120-4.

[60] Lynch G, Rex CS, Gall CM. Synaptic plasticity in early aging. Ageing Res Rev 2006; 5: 255-80.

[61] Barnes CA. Long-term potentiation and the ageing brain. Philos Trans R Soc Lond B Biol Sci 2003; 358: 765-72.

[62] Feng Z, Cheng Y, Zhang JT. Long-term effects of melatonin or 17 beta-estradiol on improving spatial memory performance in cognitively impaired, ovariectomized adult rats. J Pineal Res 2004; 37: 198-206.

[63] Larson J, Jessen RE, Uz T, *et al*. Impaired hippocampal long-term potentiation in melatonin MT2 receptor-deficient mice. Neurosci Lett 2006; 393: 23-6.

[64] El-Sherif Y, Witt-Enderby P, Li PK, Tesoriero J, Hogan MV, Wieraszko A. The actions of a charged melatonin receptor ligand, TMEPI, and an irreversible MT2 receptor agonist, BMNEP, on mouse hippocampal evoked potentials *in vitro*. Life Sci 2004; 75: 3147-56.

[65] Nonno R, Lucini V, Stankov B, Fraschini F. 2-[125I]iodomelatonin binding sites in the bovine hippocampus are not sensitive to guanine nucleotides. Neurosci Lett 1995; 194: 113-6.

[66] Prieto-Gomez B, Velazquez-Paniagua M, Cisneros LO, *et al*. Melatonin attenuates the decrement of dendritic protein MAP-2 immuno-staining in the hippocampal CA1 and CA3 fields of the aging male rat. Neurosci Lett 2008; 448: 56-61.

[67] Cheng S, Ma C, Qu H, Fan W, Pang J, He H. Differential effects of melatonin on hippocampal neurodegeneration in different aged accelerated senescence prone mouse-8. Neuro Endocrinol Lett 2008; 29: 91-9.

[68] Raghavendra V, Kulkarni SK. Possible antioxidant mechanism in melatonin reversal of aging and chronic ethanol-induced amnesia in plus-maze and passive avoidance memory tasks. Free Radic Biol Med 2001; 30: 595-602.

[69] Musshoff U, Riewenherm D, Berger E, Fauteck JD, Speckmann EJ. Melatonin receptors in rat hippocampus: molecular and functional investigations. Hippocampus 2002; 12: 165-73.

[70] Ozcan M, Yilmaz B, Carpenter DO. Effects of melatonin on synaptic transmission and long-term potentiation in two areas of mouse hippocampus. Brain Res 2006; 1111: 90-4.

[71] Wang LM, Suthana NA, Chaudhury D, Weaver DR, Colwell CS. Melatonin inhibits hippocampal long-term potentiation. Eur J Neurosci 2005; 22: 2231-7.

[72] Hogan MV, El-Sherif Y, Wieraszko A. The modulation of neuronal activity by melatonin: *in vitro* studies on mouse hippocampal slices. J Pineal Res 2001; 30: 87-96.

[73] Zeise ML, Semm P. Melatonin lowers excitability of guinea pig hippocampal neurons *in vitro*. J Comp Physiol A 1985; 157: 23-9.

[74] Leon J, Vives F, Gomez I, *et al*. Modulation of rat striatal glutamatergic response in search for new neuroprotective agents: evaluation of melatonin and some kynurenine derivatives. Brain Res Bull 1998; 45: 525-30.

[75] Nonno R, Pannacci M, Lucini V, Angeloni D, Fraschini F, Stankov BM. Ligand efficacy and potency at recombinant human MT2 melatonin receptors: evidence for agonist activity of some mt1-antagonists. Br J Pharmacol 1999; 127: 1288-94.

[76] Wan Q, Man HY, Liu F, *et al*. Differential modulation of GABAA receptor function by Mel1a and Mel1b receptors. Nat Neurosci 1999; 2: 401-3.

[77] Rawashdeh O, de Borsetti NH, Roman G, Cahill GM. Melatonin suppresses nighttime memory formation in zebrafish. Science 2007; 318: 1144-6.

[78] Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov 2004; 3: 205-14.

[79] Butterfield DA, Kanski J. Brain protein oxidation in age-related neurodegenerative disorders that are associated with aggregated proteins. Mech Ageing Dev 2001; 122: 945-62.

[80] Reiter RJ, Guerrero JM, Garcia JJ, Acuna-Castroviejo D. Reactive oxygen intermediates, molecular damage, and aging. Relation to melatonin. Ann N Y Acad Sci 1998; 854: 410-24.

[81] Cardinali DP, Brusco LI, Liberczuk C, Furio AM. The use of melatonin in Alzheimer's disease. Neuro Endocrinol Lett 2002; 23 (Suppl 1): 20-3.

[82] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003; 60: 1119-22.

[83] Wang JZ, Wang ZF. Role of melatonin in Alzheimer-like neurodegeneration. Acta Pharmacol Sin 2006; 27: 41-9.

[84] Srinivasan V, Pandi-Perumal SR, Maestroni GJ, Esquifino AI, Hardeland R, Cardinali DP. Role of melatonin in neurodegenerative diseases. Neurotox Res 2005; 7: 293-318.

[85] Lahiri DK, Chen D, Ge YW, Bondy SC, Sharman EH. Dietary supplementation with melatonin reduces levels of amyloid beta-peptides in the murine cerebral cortex. J Pineal Res 2004; 36: 224-31.

[86] Liu RY, Zhou JN, van Heerikhuize J, Hofman MA, Swaab DF. Decreased melatonin levels in postmortem cerebrospinal fluid in

relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype. J Clin Endocrinol Metab 1999; 84: 323-7.

[87] Frank B, Gupta S. A review of antioxidants and Alzheimer's disease. Ann Clin Psychiatry 2005; 17: 269-86.

[88] Feng Z, Zhang JT. Protective effect of melatonin on beta-amyloid-induced apoptosis in rat astroglioma C6 cells and its mechanism. Free Radic Biol Med 2004; 37: 1790-801.

[89] Lahiri DK, Chen D, Lahiri P, Rogers JT, Greig NH, Bondy S. Melatonin, metals, and gene expression: implications in aging and neurodegenerative disorders. Ann N Y Acad Sci 2004; 1035: 216-30.

[90] Matsubara E, Bryant-Thomas T, Pacheco Quinto J, *et al*. Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer's disease. J Neurochem 2003; 85: 1101-8.

[91] Olcese JM, Cao C, Mori T, *et al*. Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease. J Pineal Res 2009; 47: 82-96.

[92] Yin J, Liu YH, Xu YF, *et al*. Melatonin arrests peroxynitrite-induced tau hyperphosphorylation and the overactivation of protein kinases in rat brain. J Pineal Res 2006; 41: 124-9.

[93] Quinn J, Kulhanek D, Nowlin J, *et al*. Chronic melatonin therapy fails to alter amyloid burden or oxidative damage in old Tg2576 mice: implications for clinical trials. Brain Res 2005; 1037: 209-13.

[94] Poeggeler B, Miravalle L, Zagorski MG, *et al*. Melatonin reverses the profibrillogenic activity of apolipoprotein E4 on the Alzheimer amyloid Abeta peptide. Biochemistry 2001; 40: 14995-5001.

[95] Lahiri DK, Chen DM, Lahiri P, Bondy S, Greig NH. Amyloid, cholinesterase, melatonin, and metals and their roles in aging and neurodegenerative diseases. Ann N Y Acad Sci 2005; 1056: 430-49.

[96] Tapias V, Cannon JR, Greenamyre JT. Melatonin treatment potentiates neurodegeneration in a rat rotenone Parkinson's disease model. J Neurosci Res 2010; 88(2): 420-7.

[97] Chiueh CC, Andoh T, Lai AR, Lai E, Krishna G. Neuroprotective strategies in Parkinson's disease: protection against progressive nigral damage induced by free radicals. Neurotox Res 2000; 2: 293-310.

[98] Lin CH, Huang JY, Ching CH, Chuang JI. Melatonin reduces the neuronal loss, downregulation of dopamine transporter, and upregulation of D2 receptor in rotenone-induced parkinsonian rats. J Pineal Res 2008; 44: 205-13.

[99] Sharma R, McMillan CR, Tenn CC, Niles LP. Physiological neuroprotection by melatonin in a 6-hydroxydopamine model of Parkinson's disease. Brain Res 2006; 1068: 230-6.

[100] Huang JY, Hong YT, Chuang JI. Fibroblast growth factor 9 prevents MPP+-induced death of dopaminergic neurons and is involved in melatonin neuroprotection *in vivo* and *in vitro*. J Neurochem 2009; 109: 1400-12.

[101] Chuang JI, Chen TH. Effect of melatonin on temporal changes of reactive oxygen species and glutathione after MPP(+) treatment in human astrocytoma U373MG cells. J Pineal Res 2004; 36: 117-25.

[102] Chen ST, Chuang JI, Hong MH, Li EI. Melatonin attenuates MPP+-induced neurodegeneration and glutathione impairment in the nigrostriatal dopaminergic pathway. J Pineal Res 2002; 32: 262-9.

[103] Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. Neuron 1994; 13: 1177-85.

[104] Reppert SM, Godson C, Mahle CD, Weaver DR, Slaugenhaupt SA, Gusella JF. Molecular characterization of a second melatonin receptor expressed in human retina and brain: the Mel1b melatonin receptor. Proc Natl Acad Sci USA 1995; 92: 8734-8.

[105] Witt-Enderby PA, Dubocovich ML. Characterization and regulation of the human ML1A melatonin receptor stably expressed in Chinese hamster ovary cells. Mol Pharmacol 1996; 50: 166-74.

[106] Brydon L, Roka F, Petit L, *et al*. Dual signaling of human Mel1a melatonin receptors *via* G(i2), G(i3), and G(q/11) proteins. Mol Endocrinol 1999; 13: 2025-38.

[107] Witt-Enderby PA, Radio NM, Doctor JS, Davis VL. Therapeutic treatments potentially mediated by melatonin receptors: potential clinical uses in the prevention of osteoporosis, cancer and as an adjuvant therapy. J Pineal Res 2006; 41: 297-305.

[108] Ayoub MA, Couturier C, Lucas-Meunier E, *et al*. Monitoring of ligand-independent dimerization and ligand-induced conformational changes of melatonin receptors in living cells by bioluminescence resonance energy transfer. J Biol Chem 2002; 8: 8.

[109] Daulat AM, Maurice P, Froment C, *et al*. Purification and identification of G protein-coupled receptor protein complexes under native conditions. Mol Cell Proteomics 2007; 6: 835-44.

[110] Levoye A, Dam J, Ayoub MA, *et al*. The orphan GPR50 receptor specifically inhibits MT1 melatonin receptor function through heterodimerization. EMBO J 2006; 25: 3012-23.

[111] Imbesi M, Uz T, Dzitoyeva S, Giusti P, Manev H. Melatonin signaling in mouse cerebellar granule cells with variable native MT1 and MT2 melatonin receptors. Brain Res 2008; 1227: 19-25.

[112] Imbesi M, Uz T, Manev H. Melatonin receptor agonist ramelteon activates the extracellular signal-regulated kinase 1/2 in mouse cerebellar granule cells. Neuroscience 2008; 155: 1160-4.

[113] Imbesi M, Uz T, Yildiz S, Arslan AD, Manev H. Drug- and region-specific effects of protracted antidepressant and cocaine treatment on the content of melatonin MT(1) and MT(2) receptor mRNA in the mouse brain. Int J Neuroprot Neuroregener 2006; 2: 185-9.

[114] Weil ZM, Hotchkiss AK, Gatien ML, Pieke-Dahl S, Nelson RJ. Melatonin receptor (MT1) knockout mice display depression-like behaviors and deficits in sensorimotor gating. Brain Res Bull 2006; 68: 425-9.

[115] Radio NM, Doctor JS, Witt-Enderby PA. Melatonin enhances alkaline phosphatase activity in differentiating human adult mesenchymal stem cells grown in osteogenic medium *via* MT2 melatonin receptors and the MEK/ERK (1/2) signaling cascade. J Pineal Res 2006; 40: 332-42.

[116] Bondi CD, McKeon RM, Bennett JM, *et al*. MT1 melatonin receptor internalization underlies melatonin-induced morphologic changes in Chinese hamster ovary cells and these processes are dependent on Gi proteins, MEK 1/2 and microtubule modulation. J Pineal Res 2008; 44: 288-98.

[117] Bordt SL, McKeon RM, Li PK, Witt-Enderby PA, Melan MA. N1E-115 mouse neuroblastoma cells express MT1 melatonin receptors and produce neurites in response to melatonin. Biochim Biophys Acta 2001; 1499: 257-64.

[118] Benitez-King G. Melatonin as a cytoskeletal modulator: implications for cell physiology and disease. J Pineal Res 2006; 40: 1-9.

[119] Hetman M, Xia Z. Signaling pathways mediating anti-apoptotic action of neurotrophins. Acta Neurobiol Exp (Wars) 2000; 60: 531-45.

[120] Koh PO. Melatonin attenuates the focal cerebral ischemic injury by inhibiting the dissociation of pBad from 14-3-3. J Pineal Res 2008; 44: 101-6.

[121] Kilic U, Kilic E, Reiter RJ, Bassetti CL, Hermann DM. Signal transduction pathways involved in melatonin-induced neuroprotection after focal cerebral ischemia in mice. J Pineal Res 2005; 38: 67-71.

[122] Gerdin MJ, Masana MI, Rivera-Bermudez MA, *et al*. Melatonin desensitizes endogenous MT2 melatonin receptors in the rat suprachiasmatic nucleus: relevance for defining the periods of sensitivity of the mammalian circadian clock to melatonin. FASEB J 2004; 18: 1646-56.

[123] Gerdin MJ, Masana MI, Dubocovich ML. Melatonin-mediated regulation of human MT(1) melatonin receptors expressed in mammalian cells. Biochem Pharmacol 2004; 67: 2023-30.

[124] Gerdin MJ, Masana MI, Ren D, Miller RJ, Dubocovich ML. Short-term exposure to melatonin differentially affects the functional sensitivity and trafficking of the hMT1 and hMT2 melatonin receptors. J Pharmacol Exp Ther 2003; 304: 931-9.

[125] Liu L, Cavanaugh JE, Wang Y, Sakagami H, Mao Z, Xia Z. ERK5 activation of MEF2-mediated gene expression plays a critical role in BDNF-promoted survival of developing but not mature cortical neurons. Proc Natl Acad Sci USA 2003; 100: 8532-7.

[126] Shalizi A, Lehtinen M, Gaudilliere B, *et al*. Characterization of a neurotrophin signaling mechanism that mediates neuron survival in a temporally specific pattern. J Neurosci 2003; 23: 7326-36.

[127] Mody N, Leitch J, Armstrong C, Dixon J, Cohen P. Effects of MAP kinase cascade inhibitors on the MKK5/ERK5 pathway. FEBS Lett 2001; 502: 21-4.

[128] Obara Y, Yamauchi A, Takehara S, *et al*. ERK5 activity is required for nerve growth factor-induced neurite outgrowth and stabilization of tyrosine hydroxylase in PC12 cells. J Biol Chem 2009; 284: 23564-73.

Received: September 29, 2009 Revised: October 20, 2009 Accepted: October 24, 2009

© Cavanaugh and Witt-Enderby; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/-licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.