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Melatonin reduces neuronal loss and cytoskeletal deterioration: implications for psychiatry*

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SUMMARY

This review article summarizes the potential role of circadian rhythmicity and melatonin in psychiatric disorders. The melatonin rhythm, with high blood levels at night and low values during the day, is a reflection of the biological clock, i.e., the suprachiasmatic nucleus (SCN). The SCN receive information about the prevailing light: dark conditions from specialized ganglion cells (only 1-2% of the total ganglion cells) in the retina. These unique cells contain a newly-discovered photopigment, melanopsin, which responds to a rather narrow band width of light that peaks at roughly 480 nm. The axons of these ganglion cells project via the retinohypothalamic tract through the optic nerve to the SCN, located just above the optic chiasm in the anterior hypothalamus. Via this pathway, light detected by the retina synchronizes the circadian clock to precisely 24 hours. In the absence of light, i.e., darkness, the SCN signals the pineal gland to produce melatonin via a complex neural pathway that involves fibers that project from the hypothalamus to the preganglionic sympathetic neurons in the intermediolateral cell column of the upper thoracic cord. Axons of these neurons exit the spinal cord to eventually synapse on neurons in the superior cervical ganglia. Then, postganglionic fibers convey the information to the pineal gland mediating the nighttime rise in melatonin synthesis. Because melatonin is only elevated at night, it is referred to as the «chemical expression of darkness». Disturbances in the rhythmicity of the biological clock and/or the melatonin rhythm likely contribute to psychophysiological disturbances and mood disorders.

Major disturbances occur in circadian rhythmicity when light, which activates the SCN and inhibits melatonin production, is imposed during the normal dark period. Thus, even brief periods of light at night are readily detected by the specialized ganglion cells mentioned above; this sets off a chain of events that alter biological clock physiology and depresses nighttime melatonin levels when they should be elevated. Depressed circulating melatonin levels at night provide misinformation to all cells that can «read» the message. This misinformation contributes to alterations in mood and negative psychological feelings of well-being.

Melatonin has several major functions which probably assist in protecting humans from psychiatric illnesses. This indoleamine is widely known as a sleep-promoting factor. As such, it reduces the latency to sleep onset and improves sleep hygiene. Melatonin has been tested for its beneficial effects on sleep in children with neurodevelopmental disabilities, in individuals with delayed sleep phase syndrome and in elderly patients with insomnia. In each of these situations, melatonin has proven to be beneficial. Sleep disturbances are often associated with and probably contribute to psychiatric illness.

Melatonin is also a potent free radical scavenger and antioxidant. It, as well as several of its metabolites, are powerful protectors against oxidative stress and free radical-mediated, mitochondrial-dependent cellular apoptosis. Melatonin seems to be particularly effective in protecting the brain from oxidative mutilation and loss of cells resulting from apoptosis. Given that a variety of neurodegenerative diseases, e.g., Alzheimer disease, parkinsonism, amyotrophic lateral sclerosis, have a free radical component, it is assumed that melatonin may be useful in forestalling the consequences of these debilitating conditions and improving the psychological makeup of these patients. Preliminary clinical trials suggest melatonin will be useful in this regard.

A major action of melatonin in the Central Nervous System is protection of the neuronal cytoskeleton from oxidative damage. Structural damage to the cytoskeleton is consequential in the function of neurons and is not uncommonly associated with psychological illness and with neurodegenerative diseases. For example, tauopathies (tau is an important cytoskeletal protein) contribute to neuropsychiatric disorders. Damage to the tau protein, resulting from the hyperphosphorylation of this important molecule, disrupts intraneuronal microtubules and alters synaptic physiology.

The destruction of normal cytoskeletal function is often a result of excessive free radial generation. The free radical-mediated changes result in loss of neuronal polarization and cells die of apoptosis leading to neurobehavioral disorders and dementia. Given that melatonin is an antioxidant, it has been tested for its efficacy in reducing damage to the cytoskeleton as well as limiting the behavioral effects. In this capacity melatonin has been found highly effective in reducing damage to essential cytoskeletal elements and improving neurobehavioral outcomes.

Overall, melatonin may well find utility in reducing neural deterioration with age as well as improving the psychological well-being of individuals. Melatonin is an inexpensive non-toxic molecule which should be considered for use in a number of psychiatric diseases and circadian rhythm disorders.

Key words: Melatonin, mood disorders, neuronal apoptosis, cytoskeleton, cognitive impairment, psychopathology.

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RESUMEN

La melatonina (N-acetil-5-metoxitriptamina) es una indolamina que produce la glándula pineal durante la noche. Se libera directamente en la circulación general con un ritmo circadiano. En las enfermedades psiquiátricas se presentan alteraciones en los ritmos biológicos. La melatonina es un cronobiótico ya que sincroniza los ritmos biológicos como el ciclo sueño-vigilia, el de la temperatura corporal y el ciclo de liberación de cortisol, con el fotoperiodo. Esta indolamina no actúa como un hipnótico clásico. Los efectos que ejerce sobre el sueño son acortar su latencia, prolongar el periodo de sueño natural y reducir los despertares nocturnos. Por lo anterior, se ha descrito como un compuesto que «abre la puerta del sueño». En humanos se ha demostrado que produce una mejoría en la calidad de sueño en niños con patología neurológica, así como en pacientes con enfermedad de Alzheimer, en personas de edad avanzada con insomnio, en pacientes con esquizofrenia de larga evolución, depresión mayor y trastornos de ansiedad, etc.

Otras características de la melatonina, importantes para la psiquiatría, es que esta molécula cruza la barrera hematoencefálica y actúa como un antioxidante. En 1993 se descubrió que la melatonina es un potente captador de radicales libres, que son moléculas que producen daño y muerte celular. La melatonina y los metabolitos que se generan cuando esta indolamina interacciona con las especies libres de oxígeno y de nitrógeno son eficaces en la eliminación de estas moléculas dañinas. Además, la melatonina activa las enzimas antioxidantes, incluidas la superóxido dismutasa, la glutatión peroxidasa, la glutatión reductasa y la catalasa, y facilita el transporte de electrones a través de la cadena respiratoria mitocondrial, con lo que reduce la pérdida neuronal por apoptosis.

Las acciones antioxidantes de la melatonina han sido bien documentadas en modelos experimentales de las enfermedades de Alzheimer, Parkinson y Huntington. En el caso de la toxicidad que produce el péptido beta amiloide, por la generación de una gran cantidad de radicales libres, la melatonina previene la apoptosis, la lipoperoxidación, la formación de carbonilos y el daño al ADN. La melatonina mejora también algunos de los síntomas de la enfermedad de Alzheimer —como la agitación y la falta de sueño que se presentan al atardecer—, mejora el ciclo sueño-vigilia y disminuye el deterioro cognoscitivo y la atrofia bilateral grave de los lóbulos temporales.

La pérdida de memoria que se produce en la enfermedad de Alzheimer también se presenta después del daño producido por el procedimiento de isquemia-reperfusión y, en la enfermedad de Parkinson, debido a una excesiva liberación de glutamato, que a su vez causa daño en las células piramidales por los radicales libres que se generan. La melatonina abate la pérdida de neuronas piramidales producida por el ácido kaínico, un agonista glutamatérgico, y preserva la memoria de los animales expuestos a daño por el procedimiento de isquemia-reperfusión.

A la fecha no se conoce con exactitud con qué porcentaje colabora cada uno de los mecanismos de acción de la melatonina para proteger a las células del deterioro morfo-funcional. Sin embargo, es el antioxidante más potente descrito a la fecha e incrementa los niveles de enzimas antioxidantes a través de la estimulación de los receptores membranales.

Las enfermedades neuropsiquiátricas se han considerado como enfermedades del citoesqueleto. Esto se sustenta en el hecho de que existe una pérdida de las conexiones sinápticas, que son estructuradas por el citoesqueleto, entre el hipocampo y la corteza prefrontal en el caso de la esquizofrenia, la depresión y el trastorno bipolar. En el caso de las demencias existe una organización aberrante del citoesqueleto en filamentos helicoidales apareados. En modelos experimentales de células en cultivo se han logrado reproducir condiciones moleculares semejantes a las que se presentan en las demencias y en la esquizofrenia. La melatonina previene el daño producido por los radicales libres sobre neurocitoesqueleto e inhibe la hiperfosforilación de la proteína tau, que cumple un papel crucial en la estabilización de los axones, en la formación de nuevas neuritas y, por lo tanto, en el establecimiento de las conexiones sinápticas. Además, los daños que producen los antipsicóticos sobre el citoesqueleto, con concentraciones semejantes a las que se alcanzan durante tratamientos prolongados, son revertidos y bloqueados por la melatonina.

En conclusión, la información descrita en esta revisión indica que la melatonina puede ser útil en el tratamiento de las enfermedades neuropsiquiátricas ya que es un potente antioxidante, que protege a las neuronas y a las células de la glía de la muerte neuronal y protege al neurocitoesqueleto que determina la polaridad morfofuncional y el establecimiento de las conexiones sinápticas. Estas propiedades y la capacidad de la melatonina de cruzar la barrera hematoencefálica hacen que esta molécula sea un agente neuroprotector relevante en la psiquiatría. Sin embargo, es necesario realizar estudios clínicos controlados para determinar los efectos benéficos de la melatonina en las enfermedades neuropsiquiátricas.

Palabras clave: Melatonina, trastornos del éstado de ánimo, apoptosis neuronal, citoesqueleto, desacoplamiento cognoscitivo, psicopatología.

INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously generated molecule whose level in the blood normally exhibits a circadian rhythm due to its exclusive nighttime production in and release from the pineal gland.[1] Normally, plasma melatonin levels are 10-15 times higher during the night than in the daytime. Because of this obvious rhythm, which uniformly occurs in all vertebrates, melatonin is referred to as the «chemical expression of darkness».[2] The circadian production of melatonin is cued by sympathetic neural impulses that arrive in the pineal gland from the suprachiasmatic nucleus (SCN: master biological clock). Moreover, after its release into the blood and perhaps into the cerebrospinal fluid (CSF), melatonin feeds back onto neurons of the SCN where it functions to adjust and/or strengthen circadian rhythmicity.[3] Thus, melatonin is an important chronobiotic and it has been used for this purpose to manipulate the circadian rhythm of humans.

Given that some psychiatric disorders have a rhythmic pattern of manifestation, e.g., some mood disorders, seasonal affective disorder, premenstrual dysphoric disorder, etc., it is expected that melatonin would find interest among psychiatrists and psychologists. As a consequence of the association between biological rhythmicity and mood disorders, a recent issue of *Dialogues in Clinical Neuroscience*[5] was devoted to reviewing the

evidence that supports the role of biological clocks and melatonin in psychiatry.

In addition to its function as a chronobiotic, melatonin has other features that make it useful as a potential treatment of psychiatric mood disorders. Hence, melatonin is also a powerful free radical scavenger and antioxidant that readily crosses the blood-brain barrier where it protects both neurons and glia from oxidative injury and death.[6] The action of melatonin as an antioxidant is particularly important in preserving the integrity of the intracellular cytoskeleton of neurons.[7] The function of melatonin in safeguarding the cytoskeleton, which in neurons includes microtubules, microfilaments and intermediate filaments, is essential in maintaining several critical functions of these cells.[8]

Within all cells, including neurons and glia, melatonin also aids in the transport of electrons through the mitochondrial electron transport chain thereby reducing free radical generation and the loss of brain cells via apoptosis.[9,10] These combined protective actions of melatonin in the Central Nervous System (CNS) are likely to have a major importance in influencing psychopathology, as will be discussed herein. Finally, melatonin is a sleep promoting agent which makes its potential utility as a treatment for sleep disorders which frequently accompany neurodegenerative diseases and psychiatric illnesses and neurodevelopmental disabilities obvious.[11,12]

MELATONIN: A SLEEP-PROMOTING AGENT

Sleep quality and quantity are major determinants of physical and psychological well-being and poor sleep hygiene is often characteristic of individuals with neurodevelopmental disabilities, neurodegenerative diseases, or with psychopathological disorders.[12-14] Melatonin, as shown in many clinical trials, is a sleep promoting agent when it is administered 30-90 minutes in advance of normal nighttime sleep onset.[15] Melatonin, however, is not a classic hypnotic but rather it permits the earlier onset of sleep and prolongs the natural sleep period; melatonin is usually described as an agent that «opens the sleep gate».[16]

Given that sleep inefficiency is commonplace in children with neurodevelopmental problems as well as in healthy elderly and in individuals with a neurodegenerative condition or psychiatric illness, melatonin would be expected to improve sleep quality in people in each of these categories. Clinical trials with melatonin as a sleep-promoting agent have, in fact, found indoleamine to be beneficial in this regard. Thus, sleep inefficiency in children with neurological pathology,[17] insomnia in the elderly,[18] and restless sleep in individuals with Alzheimer's disease[13] have been shown to diminish when these individuals are treated with melatonin prior to nighttime sleep. While melatonin is not universally effective in correcting sleep problems in elderly individuals or in patients with sleep deficiencies, it generally reduces sleep latency, limits nighttime awakenings and prolongs sleep duration in a high percentage of subjects.

In patients suffering from psychiatric disorders, melatonin has also been shown to be efficacious in treating sleep problems. Thus, melatonin reportedly improved sleep quality in patients with chronic schizophrenia,[14] especially in those who were the poorest of sleepers. These observations were made in a randomized, double-blind cross-over, clinically-based trial in which the nightly melatonin dose was 2 mg (controlled-release). Rest activity was measured by actigraphy. Also consistent with previous studies, Shamir and colleagues[14] found that schizophrenic patients have unusually low endogenous melatonin levels (estimated by measuring urinary 6-hydroxymelatonin sulfate, a major melatonin metabolite). Given the known association between the circadian melatonin rhythm and optimal sleep, the attenuated melatonin levels, and in particular, the low nighttime values, may be consequential in the sleep problems that schizophrenic patients experience. In other psychiatric disorders where insomnia is a major symptom, e.g., major depressive disorder, anxiety disorders, etc., melatonin has yet to be tested for its ability to rectify their sleep inefficiencies.[19,20]

MELATONIN AS AN ANTIOXIDANT

In 1993, melatonin was discovered to be a potent scavenger of the highly destructive hydroxyl radical ($^{\cdot}OH$) which is a normal consequence of oxygen utilization by aerobic organisms.[21] The importance of this observation relates to the fact that the $^{\cdot}OH$ is estimated to be responsible for >50% of the total free radical mutilation that cells and subcellular organelles, including those in neurons and glia, sustain. Subsequent studies documented that not only melatonin, but several metabolites that are generated when melatonin interacts with free radicals are also highly effective scavengers of both toxic reactive oxygen (ROS) and reactive nitrogen species (RNS).[22,23]

In addition to its ability to directly detoxify ROS/RNS, melatonin has other means of quelling the oxidation of essential molecules. Thus, melatonin reduces electron leakage from the mitochondrial respiratory chain complexes thereby limiting free radical generation.[9,24] This beneficial process is referred to as melatonin's radical avoidance function.[25]

Additionally, melatonin is known to promote the activities of a variety of antioxidative enzymes including the superoxide dismutases (SODs), glutathione peroxidase (GPx), glutathione reductase (GRd) and catalase (CAT).[26,27] While the direct free radical scavenging activity of melatonin is receptor independent, its action on the

activities of the antioxidative enzymes likely involves an action on both membrane and nuclear receptors for the indoleamine.[28]

The percentage contributions of each of the described actions of melatonin in protecting cellular organelles from morphological deterioration and physiological dysfunction remain unknown. However, the combined actions of melatonin in protecting neurons and glial from destruction are unequaled by any other antioxidant. These actions, combined with their ability to rapidly cross the blood-brain barrier and enter cells, make melatonin highly relevant as a neuroprotective agent. These multiple actions of melatonin may be of particular importance in psychiatric illnesses, where free radical generation may be elevated[29,30] and in elderly and demented individuals where endogenously produced oxidizing agents are also increased.[31]

MELATONIN IN NEUROPROTECTION: IMPLICATIONS FOR PSYCHIATRY

Melatonin's antioxidative actions have been well documented in experimental models of Alzheimer's disease (AD),[32] Parkinsonism (PD),[33] and Huntington's disease (HD).[34] In the case of AD, senile plaques, which are composed of extracellular accumulations of toxic amyloid β (Aβ) peptide in the brain, are a major feature. The Aβ deposits generate excessive numbers of ROS which destroy neighboring neurons which in turn contribute to the tissue loss and dementia of AD. In experimental models where neurons are incubated with Aβ,[42] alone or in combination with melatonin, the protective actions of the indoleamine against Aβ toxicity are readily apparent.[35] Thus, melatonin prevents lipid peroxidation, protein carbonyl formation, DNA damage and apoptosis of neurons and glia exposed to Aβ. This protection is widely accepted as being a consequence of melatonin's ability to scavenge ROS/RNS that are are a consequence of senile plaques which are rich in Aβ. The most compelling animal study which illustrated the potential of melatonin as a treatment for deferring AD progression is that of Matsubara and co-workers.[36] In mice transfected with the human gene for amyloid precursor protein (APP), which gives rise to Aβ deposits once it enters the Central Nervous System, melatonin not only prevented many of the damaging neurobiological consequences of Aβ deposition in the brain, but highly reduced the number of senile plaques and greatly slowed the death rate of mice with AD-like neurodegeneration.

In humans as well, melatonin treatment has been shown to ameliorate some of the signs of AD. The dementia which accompanies AD is often associated with psychological disturbances that tend to worsen as the disease progresses.[37] Additionally, disturbances of sleep and the rest-activity cycle are common, including a feature referred to as sundowning.[38] Sundowning is a disruptive feature characterized by increased wandering, aggression, vocalization and agitation and including alterations in polysomnographic sleep measures. When melatonin is given to AD patients nightly, these features are usually attenuated and sleep efficiency increases so the quality of life of the subjects is improved.[39,40] To date, however, the number of AD patients in which melatonin has been tested is small and the measures have all been subjective.

There is one particularly interesting report of a set of monozygotic twins who were both diagnosed with AD within a one-month period when they were 73 years old. One of them was given 600 IU of vitamin E following the diagnosis, while his twin was given the same dose of vitamin E but, supplemented with 6 mg melatonin daily.[41] When the twins were neurologically evaluated as to the severity of their AD 36 months after onset, the twin who had received vitamin E only was at stage 7a. The tests used to evaluate the two partners were the Functional Assessment Tool (FAST) for AD and Mini-Mental Test. The twin at stage 7a understood only simple words and had severe memory deficits and markedly impaired walking. The twin who had received vitamin E plus melatonin for the same 36-month period was at stage 5. Unlike his twin, he had not shown the same deterioration of clinical and behavioral signs. He was still capable of performing simple word tasks, had a preserved memory and only minor difficulty was experienced while walking. The twin who had been given both vitamin E and melatonin was clearly at a less severe behavioral stage of AD. Moreover, when MRIs of their brains were compared, severe bitemporal lobe atrophy was only obvious in the twin given vitamin E only.[41]

The result of this case report suggests that melatonin may have significant benefits in deferring the progression of AD when treatment is begun early after the disease is diagnosed. The report obviously has several limitations since only two patients were studied. The strength of the observations relates to the fact that the subjects were genetically identical and had similar living environments. The findings revealed by the monozygotic twin study have been confirmed by Asayama and co-workers,[42] who showed that treating AD patients with melatonin improved not only their sleep-wake rhythm, but their cognitive and non-cognitive functions as well.

A major feature of dementia, including that accompanying AD, is anterograde memory loss. This memory deficit is not only common in AD but can also occur after ischemia/reperfusion injury of the brain and as a result of PD. This memory deficit is often associated with damage to and/or loss of pyramidal neurons in the hippocampus. Axons of granule cells that terminate on pyramidal neurons release the excitatory neurotransmitter, glutamate. Glutamate, which can be toxic via free radical mechanisms, is released in excess in the aforementioned conditions, causing damage to and

eventually killing the pyramidal cells; this results in an inability to consolidate memories.

Since glutamate toxicity involves free radical processes, one would expect that melatonin may reduce the neural damage inflicted by this neurotransmitter. This is the case in experimental animals. When animals are treated with kianic acid, a glutamate receptor agonist, select populations of pyramidal neurons are loss. However, if melatonin is given as a co-treatment with kianic acid, pyramidal neuron destruction is markedly attenuated. This protective action of melatonin against glutamate toxicity has been observed in many studies.[43-45] Moreover, in neural ischemia/reperfusion model (which also leads to pyramidal cell death) in the rat, melatonin protects the cells from death and preserves the memory of the animals as assessed in the Morris water maze.[46] The implication of these studies is that the use of melatonin by patients with AD, PD or with global ischemia/reperfusion of the CNS may help to prevent anterograde memory loss and the associated neurobehavioral deficits.

An additional study in elderly patients with mild cognitive impairment (MCI) supports this argument. MCI has a heterogeneous etiology and an estimated 12% of individuals with this condition progress to AD annually. In a retrospective study,[47] 29 individuals with MCI who had taken 3-9mg fast-release melatonin p.o. at bedtime for 9-18 months were neuropsychologically evaluated and compared to 25 patients with MCI who had not taken the indoleamine. Based on the outcome of each of the following tests, cognitive impairment was lower in the MCI patients who had taken melatonin: Mini-Mental State Examination (MMSE), the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Eog), and a neuropsychological battery of tests that included the Mattis' test, Digital-symbol test, Trail A and B tasks and Rey's verbal test. Also, a 21-item Beck Depression Inventory and global assessment of wakeness and sleep quality were completed. With the exception of the Digital-symbol test, the outcomes of each evaluated parameter indicated that those individuals who had taken melatonin regularly for 9-18 months were neuropsychological significantly better. As with previous studies reviewed above, the benefits of melatonin were presumed to be related to its antioxidative and free radical scavenging properties.[21-23,47-49] The findings are consistent with melatonin having some ability to slow the progression of MCI patients and other forms of dementia.[33,34,41,50]

MELATONIN AND THE CYTOSKELETON: IMPLICATIONS FOR PSYCHIATRY

Another important feature of melatonin for neuroprotection is that it reduces the cytoskeletal deterioration in neuronal cells. Neurons have a highly asymmetrical shape and are structurally polarized to receive and transmit information through specialized cellular processes determined by the cytoskeletal structure.[51,52]

In psychiatric diseases, the polarized morpho-functional structure of neurons is lost in specific brain regions. This structural deterioration found at the cellular and cytoskeletal level is reflected in brain structure, volume changes and in size alterations of the lateral ventricles. At the cellular level, cytoskeletal alterations are reflected in neuronal volume, size as well as by the lack of cytoplasmatic elongations.[53,54]

Neuroimaging and postmortem histopathological studies have demonstrated neuronal abnormalities in prefrontal cortex and in the limbic system in schizophrenia, bipolar disorder, and major depressive disease.[55-58] Axons, dendrites, and dendritic spines are lost in these regions[59-61] and dendritic spines are abnormally distributed and reduced in schizophrenia.[62] In major depressive disorder a decrease in soma size and cellular volume of hippocampal neurons takes place.[68] Together, these findings, and the fact that dendrite and axon formation depends mainly on cytoskeletal organization,[63,64] have suggested that in psychiatric diseases an aberrant cytoskeletal organization occurs in specific brain regions that leads to a loss of synaptic connectivity. A dys-connection of synaptic pathways reduces cognitive abilities and causes affective dysregulations, which are symptoms usually encountered in psychiatric patients.[65-67]

Cytoskeleton alterations also occur in neuro-degenerative diseases.[68] Currently, it is known that in most dementias, tau protein is extensively phosphorylated and assembled in paired helical filaments forming pathologic inclusions.[69] Thus, these neuropsychiatric disorders are referred as tauopathies and include Alzheimer's disease, progressive supranuclear palsy, frontotemporal dementia with parkinsonism linked to chromosome 17, corticobasal degeneration, and Pick's disease.[70] Under normal conditions, tau protein is concentrated and distributed in the axons, binds to microtubules, stimulates microtubule formation, and stabilizes neuronal structure.[71] Hyper-phosphorylated tau loses these abilities and, consequently, microtubules are disrupted, the highly asymmetrical neuronal polarity is lost, and synaptic dis-connectivity results.[72,73]

Oxidative stress is another pathophysiological alteration in neuropsychiatric disorders related to cytoskeletal abnormalities. In animal models, psychological stress causes high levels of free radicals,[74] reduces neuronal volume and produces the loss of synaptic connections between the prefrontal cortex and hippocampus[75] and a defective expression of cytoskeletal associated proteins, GAP 43, MAP1 and synaptophysin.[76] Also, plasma obtained from schizophrenic and major depressive patients contains increased levels of free radicals, decreased levels of

antioxidant enzymes,[77,78] and increased membranal lipid peroxidation in erythrocites and lymphocytes.[79,80]

In cultured cells, oxidative stress causes aberrant organization of cytoskeletal components. High levels of free radicals cause actin despolimerization.[81] Microfilaments and microtubules collapse associated with the loss of neuronal polarization and apoptosis has also been reported in vitro and in neuroblastoma cells, respectively.[82-84] These cytoskeletal changes are followed by neurite damage,[84] microtubule disruption, modifications of beta-tubulin and MAP2 distribution, and neuronal cell death.[84,85] These data strongly suggest that neuropathologic lesions implicating altered cytoskeletal organization related to oxidative stress may play an important role in the loss of synaptic connectivity and the aberrant behavior observed in neuropsychiatric diseases.

The establishment of synaptic contacts requires the concerted reorganization of microtubules, microfilaments, and intermediate filaments to form new neurites that will differentiate into axons or dendrites.[86,87] Development of a neurite involves growth cone formation, a structure constituted by microfilaments organized in lamellipodium.[86] Once the neurite is formed, microtubule dynamics participate in its enlargement and stability. Additionally, axon and dendrite formation require neurite differentiation which involves asymmetric distribution of microtubule-associated proteins, tau and MAPs, into the axonal and somatodendritic domain, respectively.[86,87] In this regard, melatonin can be useful in the treatment of psychiatric and neurodegenerative diseases because, in addition to its antioxidant properties,[88] it is a cytoskeletal modulator and it induces neurite formation.[89]

Melatonin induced a two-fold increase in a number of cells with neurites. Induction of neurite outgrowth is optimal at 1 and 100 nM melatonin, the nocturnal plasma and cerebrospinal fluid concentrations, respectively. Also, microtubule enlargement and intermediate filament reorganization takes place and neurites constitute a fine network that makes contacts with adjacent cells.[90,91] Microfilament phenotypes are formed during neurite formation and melatonin increases their arrangements in stress fibers, growth cones, and microspikes, which drive neurite sprouting, growth and guidance.[92] Thus, melatonin recruits cells for later differentiation by increasing the number of cells with immature neurites.[92] Therefore, melatonin can be useful in the treatment of psychiatric diseases to re-establish the synaptic connectivity loss in damaged brain regions.

Current knowledge indicates that melatonin prevents cytoskeletal damage by reducing oxidative stress and by re-establishing normal organization of disturbed neurocytoskeletons.[53,84] Melatonin attenuates cytoskeletal damage produced by high levels of free radicals generated by hydrogen peroxide, and higher doses of the antypsychotics haloperidol and clozapine.[53,84] N1E-115 cells incubated with either 100 µM hydrogen peroxide, 100 µM haloperidol, or 100 µM clozapine undergo a complete cytoskeletal retraction around the nucleus.[53] In contrast, NIE-115 cells incubated with hydrogen peroxide or either of the antipsychotics, followed by the nocturnal cerebrospinal fluid concentration of melatonin (100 M), showed a well preserved cytoskeleton and neuritogenesis.[53,84] Melatonin restores neurite formation, microtubule enlargement, and microfilament organization in microspikes and growth cones in cells cultured with haloperidol and clozapine with 100 µM.[53] Also, the indole abolished the increased lipid peroxidation and apoptosis caused by these compounds. These results indicate that melatonin is a neuroprotective compound since it protects the neurocytoskeletal organization against damage caused by high concentrations of antipsychotics.

Tardive diskynesia is one of the major side effects of long-term neuroleptic treatment that has been associated with antipsychotic toxicity and neuronal death.[93] Also, toxic effects of clozapine, such as agranulocytosis, have been associated with high levels of free radicals and cytoskeletal alterations.[94] Thus, melatonin may be useful in the treatment of schizophrenia because it reduces the cytoskeletal and neuronal damage caused by prolonged treatment with antipsychotics. Moreover, since cytoskeletal collapse precedes apoptosis,[95] melatonin may improve neuronal survival by cytoskeletal stabilization.

The utility of melatonin to prevent damage in the cytoskeletal structure produced by neurodegenerative processes was demonstrated in N1E-115 neuroblastoma cells cultured with okadaic acid (OA), a specific inhibitor of the serine/threonine protein phosphatases 1 and 2A.[96] This compound induces molecular and structural changes similar to those found in AD.[97] Melatonin prevented microtubule disruption followed by cell-shape changes and increased lipid peroxidation and apoptosis induced by OA.[98] Fifty nM AO induced complete cytoskeletal collapse and increased oxidative stress after two hours incubation.[98] In contrast, an intact microtubule network following a neurite pattern similar to that observed in vehicle-incubated cells was observed when melatonin was added to incubation media two hours before OA.[98] Melatonin effects on altered cytoskeletal organization induced by OA are dose-dependent and were observed at plasma and cerebrospinal fluid concentrations of the indole. Furthermore, increased lipid peroxidation and augmented apoptosis in N1E-115 cells incubated with 50 nM OA are prevented by melatonin.[98] OA causes an extensive tau phosphorylation and paired helical filament formation in animal models and in N1E-115 cells, similar to that found in neurodegeneration.[99] Melatonin prevents these changes because, when the indole is added before, simultaneously or after OA treatment, tau hyperphosphorylation is abolished.[99]

In addition, it has been reported that tau hyperphosphorylation produced by wortmannin, isoproterenol, haloperidol and calyculin A in the rat brain is prevented by the simultaneous administration of micromolar melatonin concentrations.[100-103]

The results strongly suggest that melatonin acts as a neurocytoskeletal protector by decreasing tau hyperphoshorylation and prescerving the microtubular structure. They also suggest that melatonin may improve cognition by impeding neuronal damage caused by tau hyperphosphorylation.

These data support the notion that melatonin may be useful in the treatment of neurodegenerative diseases by both its action as modulator of the phosphorylation/dephosphorylation balance of microtubule associated proteins and its role in re-establishing neuronal pathways.

CONCLUDING REMARKS

Clearly, melatonin's function as a sleep promoting agent may well be relevant to improve the psychological well being of depressed patients. In general, psychiatric illnesses are not uncommonly associated with poor sleep hygiene.

Beyond its ability to improve several aspects of sleep, however, melatonin's role as a ubiquitous free radical scavenger and indirect antioxidant make it potentially highly useful in the treatment of psychiatric and neurodegenerative disorders. The studies performed to date, although limited in number and scope, clearly emphasize its potential importance in the field of psychiatry. In particular, melatonin's ability to attenuate neuronal loss in diseases of the elderly along with its propensity to maintain a more healthy memory conserving network make it of great interest.

Also as noted herein, polarity is intrinsic to neuronal function. In neurons, somatodendritic domains receive and decode incoming information and axonal domains transmit information to target cells. Progressive loss of neuronal polarity is a known histopathologic event in psychiatric and neurodegenerative diseases. Cytoskeletal collapse underlies the loss of structural polarity and it is also known that it precedes neuronal death and the disappearance of synaptic connectivity.

Drugs that prevent the loss of polarity and cytoskeleton retraction intrinsic to these diseases, as well as damage to cytoskeletal structure produced by oxidative stress, can be extremely useful in the treatment of psychiatric diseases. Melatonin is a potent free-radical scavenger that at the same time acts as a cytoskeleton regulator. Thus, it is tempting to speculate that this indoleamine could be useful in the prevention and alleviation of psychiatry diseases that exhibit synaptic connectivity disruption. Clinical trials show that melatonin administration is followed by alleviation of circadian disturbances and cognitive function in various neuropsychiatry diseases. In schizophrenia patients with tardive dyskinesia the indole decreases the abnormal involuntary movements.[104]

As suggestive as this information appears, controlled clinical trials will be necessary to investigate the beneficial effects of melatonin and other drugs in the treatment of neuropsychiatric diseases. Moreover, since melatonin secretion is diminished in neurodegenerative and some psychiatric disorders, diminished endogenous defense against damage caused by oxidative stress present in mental illnesses can be restored by exogenous melatonin administration.

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