Melatonin and its metabolites are potent antioxidants by virtue of their ability to scavenge both oxygen-based and nitrogen-based radicals and intermediates but also as a consequence of their ability to stimulate the activity of antioxidative enzymes. Melatonin also prevents electron leakage from the mitochondrial electron transport chain thereby diminishing free radical generation; this process is referred to as radical avoidance. The fact that melatonin and its metabolites are all efficient radical scavengers indicates that melatonin is a precursor molecule for a variety of intracellular reducing agents. In specific reference to the brain, melatonin also has an advantage over some other antioxidants given that it readily passes through the blood-brain-barrier. This, coupled with the fact that it and its by-products are particularly efficient detoxifiers of reactive species, make these molecules of major importance in protecting the brain from oxidative/nitrosative abuse. This review summarizes the literature on two brain-related situations, i.e., traumatic brain and spinal cord injury and ischemia/reperfusion, and the neurodegenerative disease, amyotrophic lateral sclerosis, where melatonin has been shown to have efficacy in abating neural damage. These, however, are not the only age-associated neurodegenerative states where melatonin has been found to be protective.

**Key words:** melatonin, antioxidant, free radical scavenger, central nervous system, traumatic brain injury, ischemia-reperfusion, amyotrophic lateral sclerosis

**INTRODUCTION**

Melatonin’s function in relation to the central nervous system is of special interest for several reasons. The brain, even under resting conditions, uses a disproportionately large amount (20%) of the total oxygen (O₂) inhaled even
though the organ accounts for only 2% of the body weight. At work, the brain even uses more O$_2$. O$_2$, due to its ability to be chemically reduced to reactive oxygen (ROS) and reactive nitrogen species (RNS), is highly toxic to all organs including the central nervous system. The resulting molecular debris is referred to as oxidative or nitrosative stress.

Despite its importance, the brain is not equipped with a particularly efficient antioxidative defense system. For example, the level of antioxidative enzymes in the central nervous system are relatively deficient. Additionally, some of the better-known dietary free radical scavengers, e.g., vitamins C and E, are rather inept in their ability to enter the brain, i.e., they do not easily cross the blood-brain-barrier.

Melatonin readily enters the brain given that the blood-brain-barrier poses no impediment to the passage of this highly lipid soluble molecule. Within minutes after its administration, melatonin is already in high concentrations within neural tissue. Moreover, melatonin concentrations in the cerebrospinal fluid (CSF) of the third ventricle are reportedly much higher than in other fluids or tissues. From this strategic location, melatonin can readily diffuse into the surrounding neural tissue.

Melatonin and its metabolic derivatives are uncommonly effective direct free radical scavengers while also stimulating the activities of several antioxidative enzymes. Simultaneously, melatonin or its by-products restrain the activities of pro-oxidative enzymes. Finally, the indoleamine reduces free radical generation within the mitochondria.

Considering this combination of processes, melatonin may be in a highly advantageous position to protect the brain from oxidative/nitrosative stress while the other neural defenses may not have the ability to do so. This brief review summarizes the data, which is now voluminous, that documents the high efficacy of melatonin in preserving the morphological and functional integrity of the central nervous system. There are other reviews on this subject that could be consulted for additional information that is not covered in this summary (1-8).

MELATONIN AND THE BRAIN

While there are some unique or special characteristics that would seemingly make melatonin a more efficient antioxidant in neural tissue, additionally, there are features of melatonin in terms of its ability to enter the brain that may afford it some particular advantages. As an example, the classic antioxidative vitamins, C and E, are not readily accessible to the central nervous system because of their inability to efficiently pass through the blood-brain-barrier (9, 10). Nevertheless, both vitamins eventually enter the brain after their pharmacological administration over long periods. Because of their rather retarded uptake,
however, they have limited ability to protect against acute oxidative/nitrosative stress in the brain.

In contrast, melatonin may have special access to the central nervous system. It has long been proposed that endogenous melatonin derived from the pineal gland is directly released into the cerebrospinal fluid (CSF) of the third ventricle of the brain (11-13) in addition to being discharged into the perfuse capillary bed that permeates the gland. There are clearly structural modifications of the posterior dorsal aspect of the third ventricle that would allow the pineal gland to secrete melatonin through the ependymal lining directly into the CSF (12, 14). There is new compelling evidence, in fact, that melatonin of pineal gland origin escapes the pinealocytes via the pineal recess directly into the third ventricle (15). This group observed that occlusion of the pineal recess led to a dramatic reduction in the concentrations of melatonin in the CSF of the sheep brain. The study was actually initiated because they had previously shown that the nocturnal rise in third ventricular CSF melatonin concentrations was orders of magnitude greater than the elevation of blood melatonin levels (16). The most likely explanation for the differences in melatonin levels in these two fluids was the release of the indole directly into the CSF thereby avoiding transit via the circulatory system. This was then verified in the follow-up study which confirmed that the obstruction of the posterodorsal aspect of the third ventricle, including the pineal recess, obliterated that massive rise in nighttime melatonin levels without changing the concentrations of the indole in the blood (15). These findings are in direct support of the suppositions of earlier workers who had based their speculation of the anatomical modifications of the ependymal-lined evagination of the third ventricle (11-14).

The observations reported by Skinner and Malpaux (16) and Tricoire et al (15) were made utilizing the sheep which has what is referred to as a subcallosal pineal gland (17), i.e., it is located directly on the posterior dorsal aspect of the third ventricle. In animals where the gland is situated in this location, release of melatonin directly into the ventricle would seem to be an efficient means by which melatonin could gain ready access to the brain. A subcallosally located pineal gland in common in most mammals including the human (17). However, even in species that have a supracallosal pineal gland that is only connected to the diencephalon by a tenuous stalk, there are structural modifications of the third ventricle, e.g., the suprapineal recess or suprahabenular recess (14), which would permit pineal melatonin to easily enter the ventricular system of the brain. Certainly, it seems highly unlikely that the direct discharge of melatonin into the third ventricle is not unique to the sheep (16); more likely, this is a passage that allows endogenous melatonin to rapidly gain access to the brain. Once in the ventricles, melatonin could quickly diffuse into the surrounding neural tissue to influence neural/glial physiology and provide protection against ROS/RNS.

The actions of ventricular melatonin would not be limited to those structures that surround the third ventricle since melatonin may equilibrate in the CSF
including that in the lateral ventricles. Furthermore, as CSF flows through the cerebral aqueduct (iter) into the fourth ventricle it would have a gateway to neurons whose actions subserve the most basic and primitive functions of the brain; for example, via this route melatonin would have access to the area postrema which is involved with the modulation of blood pressure, a function with which melatonin has been linked (18).

When administered peripherally, melatonin also quickly enters the CNS is high concentrations due to its ability to penetrate the blood-brain-barrier. Within minutes after it intraperitoneal or subcutaneous injection, melatonin is already in high concentrations in the brain (19, 20). The rapid uptake of melatonin by various neural structures is also attested to by the fact that when given acutely shortly before or at the time of neural toxin administration or induced oxidative damage, it is quickly taken up in sufficiently high concentrations in the brain to provide significant protection against these processes (1, 2, 5, 8, 21-27).

Another important issue is that melatonin is not in equilibrium in the body. It has already been mentioned that endogenous melatonin levels are much higher in the sheep CSF than in the blood (16). This seems also to be true for the human (28). Likewise, in the ovarian follicular fluid (29) and in the bile (30), melatonin concentrations exceed those in the circulation. Also, the concentrations of melatonin in subcellular organelles (31, 32) may well be higher than those normally measured in the blood. Because of this differential distribution, when physiological concentrations of melatonin are defined, the body fluid, cell or subcellular organelle being considered must be mentioned (33). Certainly physiological melatonin levels in the blood cannot be used as a criterion for judging concentrations of the indoleamine at other sites; unfortunately, this is commonly done but it is erroneous. Finally, organs that produce melatonin, especially those that generate the indoleamine for their own use (34-40), certainly contain concentrations much greater than those that exist in the blood. These widely disparate levels of melatonin in different fluids, organelles, organs and organisms, have clear implications, for any melatonin receptor where the Kd has been defined (41, 42).

MELATONIN: PREVENTING BRAIN ABUSE

There is a very large body of information documenting the ability of melatonin to protect the brain from chemical and excitatory neurotransmitter toxicity (23, 43), in models of Parkinsonism (44, 45), Alzheimer’s (44, 46-48) and Huntington’s disease (49), from amyotrophic lateral sclerosis (ALS) (25, 50), from neural trauma (8, 51) and from ischemia/reperfusion injury (2, 5, 21, 24, 52). The mechanisms by which melatonin and its metabolites limit damage in these widely-varying situations are likely similar and probably involve receptor-mediated and receptor-independent processes. A number of comprehensive
review articles have summarized much of the early data in these areas (1-5, 7, 8, 22). The current survey will primarily consider findings accrued during the last two years which support the use of melatonin in either reducing the severity or delaying the onset of these neurally-debilitating conditions.

**Traumatic brain injury**

Blunt severe trauma to the head (also called closed head injury) causes significant damage to the brain as a consequence of the associated hemorrhage and/or injury of neural tissue due to cranial fracture. This type of injury often occurs in individuals during automobile accidents and involves both the brain (craniocerebral trauma) and spinal cord. The primary neural injury is a consequence of the mechanical force when it is applied while secondary injury occurs after the impact. Secondary injury has been speculated to be a result of any or all of a number of processes including free radical generation, inflammation, production of adhesion molecules, cytokine and chemokine generation, etc (53-56).

That melatonin is protective against molecular and cellular damage resulting from traumatic injury to the central nervous system has been known for almost a decade. The initial report related to this documented that, in the rat, the degree of damage resulting from traumatic injury to the brain was attenuated by melatonin (total of 5 mg/kg) (57). The method used to inflict the damage was a 50g weight falling freely from a height of 22 cm.

Subsequent studies using a much wider variety of endpoints repeatedly confirmed that melatonin is beneficial in reducing the neuropathology and improving neurophysiological outcome when administered near the time of the injury. At a dose of 10 mg/kg ip in advance of the trauma and with three additional injections up to 2 hours after damaging the brain, the contusion volume was substantially reduced (58, 59). The amount of damaged neural tissue, as circumscribed by the contusion volume, is important in estimating the neurophysiological deficits that arise from such injuries. Thus, although corollary functional alterations were not investigated, it can be inferred that the reduced contusion volume resulted in less severe functional pathophysiology. Not unexpectedly, giving melatonin progressively later following the inflicted trauma reduces its efficacy in limiting neural damage (60).

Head injury that damages the hippocampus is not uncommonly associated with spatial memory deficits. Ozdemir et al (61) used such a model to test whether melatonin would improve the morphological integrity of the pyramidal cells of the hippocampus and recover the spatial memory deficits; in this study the animals received 5-20 mg/kg of the indole immediately after induction of head trauma. Indeed, melatonin prevented the loss of both CA1 and CA3 pyramidal neurons and, likewise, reduced the severity of the associated memory deficits.

Beni and colleagues (51) also investigated the efficacy of melatonin in preserving neurophysiology and altering the molecular changes that occur as a
result of closed head injury. This group used a mouse model and doses of melatonin from 1-10 mg/kg ip after trauma induction. The most effective dose of melatonin in reducing damage proved to be 5 mg/kg. Neurobehavioral recovery was evaluated at 1, 4 and 7 days after head injury and was found to be improved in those animals that received melatonin. Additionally, melatonin potentiated the level of neural antioxidants and totally blocked the late-phase marked activation of NF-κB while reducing AP-1 values by half. One implication of these findings is that melatonin preserved the reducing potential of the intracellular milieu by increasing (or preventing their depletion) the levels of intracellular antioxidants. The late-phase reduction in NF-κB and AP-1 would be expected to improve neurological outcome by reducing the inflammatory response to the neural injury.

Information regarding the potential utility of melatonin in reducing or limiting neural damage in humans as a result of blunt trauma is sparse. Markorov and co-workers (62) measured an elevation in CSF melatonin levels in patients with traumatic subarachnoid hemorrhage and surmised that the rise may have been a consequence of the compensatory release of melatonin in an attempt to reduce the neural destruction resulting from the trauma. While it was assumed that the elevated melatonin was derived from the pineal gland (63), now that melatonin synthesis has been tentatively identified in cortical astrocytes (64), it could have originated from a non-pineal site.

Among many consequences resulting from head trauma is the release of free metal ions, e.g., iron. As a transition metal, iron participates in the Fenton reaction which generates the high unstable •OH from H₂O₂. Melatonin as well as its metabolites are potent scavengers of the •OH (48) and, also, melatonin reportedly binds iron and other transition metals thereby reducing their participation in the generation of •OH from H₂O₂ (65). Fig. 1 summarizes some of the multitude of neural pathologies that occur following brain injury; of special interest is that many of these changes have been shown to be prevented by melatonin (66-69) and improve neurological outcome when the brain is damaged due to blunt force.

Traumatic damage to the spinal cord, although it may lead to fewer mortalities, is no less physiologically debilitating. Many of the changes that occur in the brain after trauma also appear in the spinal cord when it is contused; these alterations include hemorrhage, edema, neuronal apoptosis and/or necrosis, demyelination of axons, infarction and eventually cyst formation (70, 71). It is generally agreed that a major aspect of the overall secondary injurious response is a result of enzymatically-generated toxic reactants or ROS released from infiltrating neutrophils (72). Eventually, the dysfunction of surviving neurons and the death of neurons and glia lead to clinically-relevant neurobehavioral deficits (73).

Several investigations have tested the ability of melatonin to attenuate cord injury following trauma and have shown that the indole has a significant number of protective actions (74-76). Most recently, one studies has examined the ability of melatonin in combination with a steroid in terms of protecting against the
consequences of oxidative/nitrosative stress in the spinal cord (77, 78). Genovese and colleagues (77) injured the spinal cord of mice at the level of T6-T7. After performing a laminectomy, an aneurysm clip with a closing force of 24g was placed on the cord extradurally (duration of application not specified). Dexamethasone (10 mg/kg) plus melatonin (0.025 mg/kg) were administered at 1 and 4 hours after vascular clip application; both drugs were given via the intraperitoneal route. A number of indices of cellular damage were assessed including myeloperoxidase activity (index of neutrophil infiltration), immunocytochemical estimation of inducible nitric oxide synthase (iNOS) activity, TUNEL assay for apoptosis detection, histological evaluation of the damaged tissue, Bax and Bcl-2 by both immunocytochemistry and western blotting, and FAS-1 and TNF- α (estimated from immunocytochemically-stained sections). The motor performance of the functionally impaired mice was also evaluated daily for 10 days after spinal cord injury using methods previously published (79, 80). The combination therapy, i.e., dexamethasone and melatonin, markedly reduced all morphological damage that resulted as a consequence of injury to the cord. Likewise, the neurobehavioral deficits that developed as a result of spinal cord trauma were also significantly attenuated (77). Western blots revealed that the pro-apoptotic protein, Bax, was highly expressed while the anti-

Fig. 1. Multiple changes occur after the central nervous system is damaged due to traumatic brain injury (cerebrocerebral trauma, closed head injury). These changes can result in morbidity and/or mortality. Many of the pathophysiological alterations resulting from such damage have been shown to be ameliorated by melatonin. RNS=reactive nitrogen species; ROS=reactive oxygen species; XO=xanthine oxidase.
apoptotic protein, Bcl-2, was suppressed by the injury with both responses being reversed by the dexamethasone plus melatonin treatment (Fig. 2).

**Fig. 2.** Western blot analyses of Bax and Bcl-2 expression in the spinal cord of control (sham) mice, in animals with spinal cord injury (SCI) and in mice with cord injury but treated with dexamethasone (DEX) and melatonin (MEL). The analyses were performed 24 hours after the cord was injured. The quantified data are represented by means ± SEM of 5 or 6 spinal cords per group. *p<0.01 versus sham; °p<0.01 versus SCI. From Genovese et al (77).
In a second complete series of studies which tested the efficacy of melatonin in reducing experimental spinal cord injury, Samanta and co-workers (78) damaged the spinal cord of rats at T10 using a moderately severe force (40g/cm force). Among several endpoints they measured calpain, a Ca\(^{2+}\)-dependent neutral caspase, which is known to be involved in causing damage as a result of spinal cord injury. Melatonin (45 mg/kg) or vehicle were given ip at 15 minutes post injury and the cords were examined 48 hours later. Treatment with melatonin significantly attenuated calpain expression, inflammation, axonal damage and neuronal death (as estimated with the TUNEL assay) consistent with the neuroprotective actions of melatonin reported elsewhere. The results of this acute study further support clinical trials in which melatonin is tested for its ability to improve the outcome of people whose spinal cord is damaged due to trauma.

**Neural ischemic/reperfusion injury (stroke)**

There are a large number of investigators that have explored the utility of melatonin in ameliorating neural damage following ischemia and reperfusion (I/R) injury. The earlier studies in which melatonin was considered as a protective agent against either neural pathological I/R or so-called physiological I/R have been reviewed on a number of occasions (81-83). Not only in the central nervous system, but in many other organs as well, melatonin protects against the hypoxia of ischemia and the reoxygenation that occurs during reperfusion (84). Models of both focal and global I/R have been employed to determine whether melatonin provides effective protection against neural morphological loss and functional destruction.

Considering that annually thousands of humans die as a consequence of transitory interruption of the blood supply to a portion or all of the brain (such as during cardiac arrest), the fact that melatonin has been found to be protective has important clinical implications. In addition to the large number of fatalities, many survive a stroke but are permanently neurobehaviorally compromised.

Based on the published reports surveyed elsewhere (2, 5, 81, 82, 85) and the data summarized below, melatonin may find utility as a treatment for stroke. Certainly, infarct volume, amount of edema, frequency of apoptosis, degree of glial activation, quantity of oxidized macromolecules, degree of neurological deficits, molecular alterations, etc., have all been shown to be improved if the animals are given melatonin at the time or shortly after induction of transient ischemia and subsequent reperfusion. Also, it should be noted that melatonin proved to be highly protective as an add-on therapy with tissue plasminogen-activator (pTA) which, when used to dissolve blood clots which obstruct blood flow, aggravates neuronal injury due to focal cerebral ischemia (86).

Since the publication of the reviews mentioned above, several reports have appeared that reinforce the evidence that melatonin has substantial benefits as an agent to reduce cellular and molecular damage in neurons and glial during and after hypoxia/anoxia and reoxygenation. To induce global ischemia in adult male
rats, Letechipia-Vallejo *et al* (87) employed the four vessel occlusion method which required interruption of both common carotid and both vertebral arteries; the vertebral vessels were permanently obstructed at the level of the first cervical vertebra while the blood flow in the common carotid arteries were interrupted for a 15 min period. Melatonin (10 mg/kg/h) was continually infused for 6 hours after the ischemic interval. Ninety days later, the rats were evaluated as to place learning (Morris water maze) and working memory (eight-arm Olton radical maze). At 120 days following the transitory global ischemia, brain morphology was assessed. Clearly, as a result of global ischemia alone, an impaired place learning and a delayed working memory acquisition were apparent. These deficits were accompanied by a marked reduction in the number of pyramidal neurons in CA1, CA2 and CA3 regions of the hippocampus. The administration of melatonin to rats that experienced four vessel occlusion of the cerebral blood supply exhibited a significant reduction in pyramidal cell loss and a substantial preservation of the ability to integrate spatial learning memory.

Using a focal I/R model in rats in which the right cerebral artery was occluded by intra-arterial placement of 4.0 nylon suture for 90 min, Lee *et al* (88) found that melatonin (5 mg/kg iv), given at the initiation of reperfusion, limited the neural damage. The cellular inflammatory response was estimated to be reduced by 41% in the damaged cerebral cortex by melatonin. In particular, melatonin treatment resulted in a significantly lowered neutrophil infiltration (Ly6G-positive/CD45-positive cells) and macrophage/activated microglia infiltration (CD11b-positive/CD45-positive cells) into the infarcted brain region. The results of this study (88) along with the findings of Letechipia-Vallejo and co-workers (87) demonstrate the pluripotential nature of melatonin in protecting the brain from a temporarily deficient blood supply. Of additional interest relative to this publication is that melatonin has been reported to enhance neuronal proliferation in the hippocampus of rats (89); thus, the protective actions uncovered 120 days after global ischemia may have been, in part, due to the regeneration of neurons in the hippocampus; this latter response, if validated, would be of major importance and should be investigated further.

Another major aspect that probably contributes to brain damage under a variety of different conditions is opening of the blood-brain-barrier. This commonly occurs during I/R allowing molecules that are toxic/damaging to neurons and/or glia to enter areas from which they are normally excluded. In transient focal cerebral ischemia, Chen and colleagues (90, 91) found that melatonin prevents damage to this important barrier; this would be important in preserving neural morphology and function.

**Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative condition in which motoneurons in the cerebral cortex and the anterior horn of the
spinal cord gradually deteriorate. The disorder causes muscle weakness and eventual muscular atrophy throughout the body as both the upper and lower motoneurons degenerate with mental function generally remaining intact. The disease is invariably fatal due most commonly to respiratory failure; this commonly occurs within 2-5 years after diagnosis of the condition. The average age of onset is 40-60 years and an estimated 5,000 individuals in the United States are diagnosed annually with the disease. Among those individuals with the familial form, roughly 20% have a mutation in the gene for the antioxidative enzyme, superoxide dismutase (SOD). There is no known cure for ALS.

There are a limited number of studies related to melatonin’s utility as a potential treatment for ALS. The most complete study is that performed by Weishaupt et al (25); this comprehensive report had been preceded by a pilot investigation by the same research team (50). In addition to these, other investigations claim to have carried out studies in relation to the ALS/melatonin issue, but the disease models used were highly indirect (92, 93).

Given that oxidative stress has been associated with ALS, Weishaupt and colleagues (25) examined the ability of melatonin to attenuate neural damage in a genetic mouse model of ALS (SOD1^{G93A}-transgenic mouse) and in 31 patients with sporadic ALS. In the mouse model, orally administered melatonin (in the drinking water) delayed disease progression and extended survival. In this report, disease progression was defined as the time span between the onset of hind limb tremor and premature death; this was delayed by 25% in the melatonin-treated mice.

![Fig. 3. Oxidized protein (protein carbonyls) levels in the serum of patients with amyotrophic lateral sclerosis (ALS); some of the patients were given melatonin as a potential treatment to abate the disease. The melatonin-treated ALS patients had serum protein carbonyl levels similar to those in healthy age-match control subjects. From Weishaupt et al (25).](image-url)
In the ALS patients, melatonin (5 mg/kg) was applied nightly as a suppository; duration of treatment varied among the patients and ranged from 2-24 months. Melatonin was well tolerated with some patients, as anticipated, reporting improved sleep quality. As evidence that free radical damage was attenuated in the ALS patients given melatonin, circulating protein carboxyls were reduced in the blood after more than 4 months of treatment compared to levels before treatment onset; these values were lowered to protein carboxyl levels in healthy age-matched control subjects (Fig. 3).

The authors of this report noted that melatonin may not be a cure for ALS but it may delay progression and increase life expectancy (25). Oxidative stress is believed to be responsible for cell death in sporadic ALS; thus, the beneficial actions of melatonin were presumably related to the efficacy of melatonin (48, 82, 94-96) as well as its metabolites (96-100) in scavenging not only the •OH but other ROS as well (101, 102). Combining melatonin with the conventional drugs used for treatment, due to their presumed synergistic actions, may improve the outcome of ALS patients. Additional trials with melatonin, alone and in combination with other drugs, are needed to clarify the potential benefit of melatonin in subjects with ALS.

CONCLUDING REMARKS

The data summarized in this report document that melatonin is a decisive weapon against oxidative/nitrosative abuse in the central nervous system. One important function of both melatonin and its metabolites is to troll for free radicals and when they locate them, to quickly detoxify these damaging agents (81, 94, 95). Moreover, melatonin commandeers antioxidative enzymes and makes them more effective in converting ROS to innocuous molecules (103, 104). Finally, melatonin insinuates itself into mitochondria where it mutes electron leakage, thereby limiting the reduction of oxygen to free radicals by stimulating the efficient flow (44, 106, 107) of electrons through the ETC (67, 96, 105). In all species including the human (44, 106, 107), melatonin levels diminish with age thereby presumably increasing the likelihood of oxidative/nitrosative to the brain and other organs (2, 4, 21, 47).

These functions of melatonin in neural tissue translate into highly protective actions against brain abuse by ROS/RNS. This neural damage is known to contribute to a variety of neurological deficits associated with the conditions described in this brief review. Beyond melatonin’s ability to protect against brain destruction and neural/glial loss in models of traumatic brain injury, ischemia/reperfusion damage and degenerative amyotrophic lateral sclerosis, the indoleamine and its metabolic metabolites are equally effective in reducing the morphophysiological and neurobehavioral changes found in models of Alzheimer’s disease, Parkinsonism and Huntington’s disease. The details related
to melatonin’s actions in benefiting these age-related neurodegenerative diseases can be found in other review articles (1, 6, 46, 108).

The implications of all the reports published to date strongly indicate that preserving endogenous melatonin levels, or the use of melatonin supplements, may be beneficial in forestalling the decline in neural physiology that is a normal consequence of neurological damage associated with aging. Melatonin is available in pharmacologically pure form, it is relatively inexpensive, it is absorbed when administered via any route, and its toxicity is remarkably low.

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