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Report

Melatonin: The Brain Hormone

By Stephen Fredericks

Melatonin was introduced to the United States in **1992** as a “*sleep hormone*.”

While some find melatonin helps restore restful sleep, scientists are finding far more consistent applications for melatonin in the area of **brain protection**.

New discoveries are validating melatonin’s ability to guard the brain from oxidative stress and the neurodegeneration that occurs as a result of aging and environmental factors.¹ With this research, melatonin deserves the title of “brain hormone.”

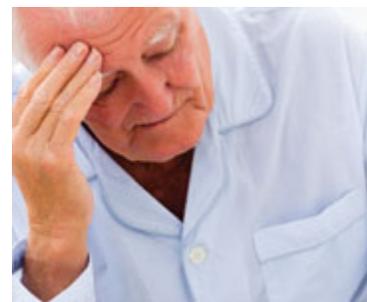


Scientists are increasingly finding that the age-related decline in melatonin levels may be one factor for the age-related increase in neurodegenerative diseases.²⁻⁴ In fact, some symptoms of melatonin deficiency are seen in patients with Alzheimer’s, such as disruption of day/night patterns, mood changes, and delirium.⁵

Fortunately, supplementing with melatonin in middle age and beyond has been shown to protect against Alzheimer’s as well as reduce the risk of Parkinson’s disease, shrink the size of the infarct area involved in a stroke, and minimize the brain swelling and dysfunction following a head injury.^{2,6-13}

As if this were not enough, research is also finding that in lab studies melatonin can play a role in longevity by increasing the “longevity protein” SIRT1.^{14,15} Clearly, melatonin’s beneficial properties extend far beyond sleep.

Melatonin’s Role in Neurodegenerative Diseases



Some scientists think the increase in neurodegenerative diseases as we age may be directly related to the age-related decline in melatonin levels.²⁻⁴ Fortunately, oral melatonin supplements are available, which may combat this decline by increasing blood and brain levels of melatonin.^{6,7}

Supplementation with low-cost melatonin thus offers an opportunity to restore the brain’s natural antioxidant protection and potentially prevent age-related changes to the brain.^{2,4,6,16,17} In fact, melatonin’s effects are so powerful that it’s been designated a drug by

the European Medicines Agency (EMA).¹⁷

With the onset of menopause, animals (like humans) experience a marked increase in oxidative damage, leading to brain cell dysfunction.¹⁸ Studies show that in such animals, melatonin supplementation reverses those harmful effects in a similar manner to hormone replacement—but without the associated risks.¹⁸

Melatonin Deficiency Linked to Alzheimer’s Disease

Melatonin deficiency and Alzheimer's disease are closely linked; profound reductions in melatonin levels have been found in Alzheimer's disease patients. Melatonin, which is maintained at high levels in the brain and spinal fluid throughout youth and middle age, begins to decline sharply with advancing age—in a fashion that closely parallels the rise of Alzheimer's incidence.^{2,19,20}

One impressive study found that melatonin levels in the spinal fluid of adults older than 80 were just half those of younger, healthy individuals.²¹ But older adults who had Alzheimer's had dramatically lower levels yet—roughly one-fifth of those in healthy young people.

This connection is often overlooked, but vitally important—especially because some of the symptoms that arise as a result of melatonin deficiency are detected long before other more obvious cognitive Alzheimer's symptoms present themselves.²² This makes melatonin deficiency one of the earliest indicators of Alzheimer's disease.

Most notably, these include symptoms such as insomnia and *sundowning*. Sundowning is a “circadian” (daily rhythm) disturbance in which agitation and activity increase, rather than slow down, as the day wanes.^{23,24} Sleep disorders (such as insomnia, restlessness, and poor sleep quality) generally increase with age and are a sign of declining melatonin production. Such disorders occur in about **45%** of those with Alzheimer's.

Fortunately, clinical research has demonstrated the value of melatonin supplementation in reversing these and other changes associated with Alzheimer's, particularly when implemented early in the course of the disease.^{24,25}

Melatonin Fights Brain Changes in Alzheimer's Disease

In animals given the drug haloperidol (Haldol[®]), which impairs melatonin synthesis, memory deficits and brain protein changes resembling Alzheimer's disease arise.^{26,27} However, when the animals are then supplemented with melatonin, the changes disappear, indicating a critical role for melatonin in protecting neurons.

In addition, melatonin has been found to help combat Alzheimer's disease by reducing the damage caused by two harmful proteins: *amyloid beta proteins* and *tau proteins*.^{6,20,26,28,29} High levels of these two proteins contribute to the death of brain cells and have been linked to Alzheimer's disease.

Melatonin also helps fight Alzheimer's disease by guarding against the harmful effects of aluminum, which is known to produce Alzheimer's-like oxidative changes in brain cells.²⁸

Together, these biochemical effects help to explain why melatonin supplementation has been found to reduce learning and memory deficits in animal models of Alzheimer's disease.^{7,30}

Why It's Important to Start Melatonin Early

Researchers agree that it's best to start taking melatonin before symptoms arise and before physical changes in brain cells have occurred.

One particular animal study demonstrated just how dramatic melatonin's preventive properties really are. For the study, scientists used mice that had human genes predisposed to Alzheimer's disease (these are called transgenic mice).⁷

By late-middle age, the unsupplemented mice proceeded to develop the behavioral and cognitive deficits typical of the disease. In fact, *even before signs of disease were visible*, the animals' brains already manifested the typical increased oxidation and decreased intracellular antioxidant defenses seen in Alzheimer's.⁷ Soon their brain cells began to die off.

However, mice that were supplemented with melatonin before any disease was evident showed none of those pathological changes—and they performed normally on cognitive and behavioral tests.

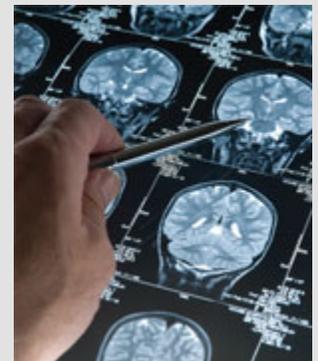
This shows just how powerfully melatonin works as a preventive agent. Unfortunately, it's been difficult to prove these preventive benefits in people because human trials of interventions for Alzheimer's tend to start only after the disease has become apparent—and well after the window of opportunity for intervention has closed. Nonetheless, very encouraging findings come from studies showing that Alzheimer's patients taking melatonin experience improved sleep patterns, less sundowning, and slower progression of cognitive impairment.^{23,24}

Still more evidence that it's best to start melatonin supplements as early as possible comes from several recent studies of *mild cognitive impairment*, a condition defined as impairment that precedes actual dementia.³¹ About **12%** of people with mild cognitive impairment proceed to develop dementia each year. In a series of studies, researchers have now shown that people taking between **3 and 24 mg** of a fast-acting formulation of melatonin daily for 15 to 60 months performed significantly better on a host of cognitive assessment scales and tests of memory.^{23,31,32}

WHAT YOU NEED TO KNOW

Melatonin: The Brain Hormone

- Melatonin, a hormone produced in the pineal gland of the brain, is well known as a sleep aid; it is registered as a drug for that purpose in Europe.
- Melatonin also has incredible neuroprotective effects.
- Studies now reveal that melatonin levels begin to decline at just the time when neurodegenerative diseases begin to rise, and there's good scientific evidence for a strong connection between these phenomena.
- Supplemental melatonin restores normal, youthful levels of the hormone, and provides powerful antioxidant protection for the brain.
- Laboratory and early clinical studies show that melatonin supplementation can protect against the age-induced brain changes leading to Alzheimer's and Parkinson's diseases, to increased stroke risk, and to susceptibility to brain trauma.
- To achieve the most benefit from melatonin, begin supplementation as early as possible.



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Melatonin Fights Parkinson's at the Earliest Stages

Animal studies demonstrate that melatonin supplementation can prevent—and to some extent, even *reverse*—the changes in behavior and motor function induced by Parkinson's disease.³³⁻³⁵ Parkinson's disease robs its victims of normal movement, slowing them down, making their walk erratic, and blocking normal facial expressions.³⁵ All of this occurs through the loss of neurons that produce the neurotransmitter *dopamine*.³³

Parkinson's has a number of similarities to Alzheimer's. Both can lead to dementia. Both are the result of out-of-control oxidation (in the case of Parkinson's focused on brain regions that control movement and balance).^{20,35} And in both diseases, brain cell death and dysfunction is brought on by an abnormal, oxidizing, and inflammatory protein accumulation. In Parkinson's, that protein is called *alpha-synuclein*.^{36,37}

Working with various laboratory models of Parkinson's disease, scientists have demonstrated that melatonin can attack Parkinson's disease at each of its critical junctures:

- It prevents the production of *alpha-synuclein* in brain cells, at the same time attacking existing molecules of the toxic protein and making them available for cellular cleanup.^{36,37}
- It reverses the inflammatory changes seen in the brains of people with Parkinson's disease.³⁸
- It restores normal activity of a key enzyme involved in dopamine production.^{8,24}

Melatonin's ability to prevent—and reverse—the changes in behavior and motor function induced by the disease is the result of enhanced survival of the dopamine-producing cells that become damaged or destroyed in Parkinson's disease.⁸⁻¹⁰

THE HIDDEN DANGERS OF SLEEP DRUGS

Because of the high prevalence of sleep disorders in older adults—even those without dementia—use of benzodiazepine drugs is widespread.⁶⁴ But these drugs, which include alprazolam (Xanax[®]), diazepam (Valium[®]), and Lorazepam (Ativan[®]), and others, have a nasty but little-known side effect—they suppress melatonin levels.



In studies going back 25 years, benzodiazepines have been proven to suppress melatonin levels.⁶⁵ In fact, a single dose (**2 mg**) of alprazolam at 9:00 p.m. was shown to significantly suppress blood melatonin levels at 11:00 p.m., midnight, 1:00 a.m., 6:00 a.m., and 7:00 a.m.⁶⁶

That's troubling because this drug, so often taken for sleep, is in fact depleting the body of its own most potent sleep-inducing hormone. It's even more troubling because regular benzodiazepine use is now recognized as a risk factor for dementia.⁶⁴

Research showed that people who used benzodiazepines at any time in their life were at approximately a **50%** greater risk for developing dementia than non-users.⁶⁷ And for those with benzodiazepine dependence, the risk of probable cognitive impairment *more than quintupled!*⁶⁸

Given what we know about melatonin's powerful neuroprotective properties, the conclusion is inescapable that these melatonin-depleting drugs are triggering dementia in people who use them regularly.

If you are using one of these drugs, it would be wise to begin regular melatonin supplementation to restore your levels to the safe range. And if you are using the drugs purely for sleep, consider replacing them (gradually) with melatonin at bedtime.

Melatonin Cuts Stroke Risk

As you age, waning melatonin levels place your brain at risk for both immediate and long-term neurological damage. In particular, decreased melatonin levels have been associated with a greater presence of stroke, with the odds appearing to rise more than **2%** for each **1 pg/mL** decline in melatonin.³⁹ In people whose pineal gland (the source of melatonin) has become

calcified and non-functional, the risk of stroke is increased by **35%**.⁴⁰

Plenty of biochemical evidence is available to explain this increased risk. Much of the damage done in either type of stroke —ischemic (insufficient blood flow) or hemorrhagic (bleeding into the brain)—is the result of free radical production. In an animal model of ischemic stroke, melatonin improved cognition by scavenging and neutralizing free radicals.⁴¹

It also reduces *indirect* risk factors for stroke, such as elevated cholesterol and blood pressure. It has been shown to suppress cholesterol formation by **38%**, reduce LDL-cholesterol accumulation by **42%**, and reduce blood pressure into the normal range.⁴²

Melatonin Limits Stroke Damage

Once a stroke has begun to develop, melatonin can prevent the death of neurons in the stroke area—limiting the damage done by the stroke.¹¹ Researchers conducted an experiment in which they removed the pineal glands of rats to make them deficient in melatonin. They found that these rats experienced significantly greater brain damage after a stroke or seizure than the rats that still had sufficient melatonin levels.⁴³

Repeated animal studies have demonstrated that animals supplemented with melatonin prior to a stroke experienced a decrease in the volume of brain tissue affected by an ischemic stroke (the most common kind).^{11,44-47} This results in improved neurological and behavioral outcomes, and faster recovery from the stroke.^{11,47,48}

One of the most important determinants of a good recovery from a stroke is the degree of “plasticity” in the surviving neurons.⁴⁹ Plasticity involves how well the surviving neurons are able to shift their function and take on some of the activities of damaged or destroyed brain cells.⁴⁹ Melatonin has been found to increase the plasticity of the neurons on both sides of the brain (the affected side and the opposite side)—an effect that hastens recovery.⁵⁰

Another way melatonin helps reduce the damage caused by a stroke is by reducing the activation of destructive “protein-melting” enzymes.^{47,51} An ischemic stroke triggers an increase in “protein-melting” enzymes, which impair the integrity of the normal blood-brain barrier, leading to brain swelling, increased pressure, and occasionally transformation into a hemorrhagic (bleeding) stroke.⁵² However, in experimental models of ischemic stroke, when melatonin is administered during or after ischemia, it reduces the activation of those destructive enzymes, tightens the blood-brain barrier, reduces tissue swelling, and prevents hemorrhagic transformation.^{11,47,51,53}

A SAFER ALTERNATIVE TO PRESCRIPTION SLEEP DRUGS

Supplementing with melatonin may reduce the use of prescription sleep medications in the benzodiazepine family (Xanax[®], Valium[®], and others). In one study, **62.8%** of control subjects received such drugs, while only **9.8%** of melatonin supplemented patients were prescribed them.³¹ As a result, in Europe (where melatonin is a drug), a concerted effort is being made to increase awareness and use of melatonin as a way to get people off of these side effect-laden, abuse-prone medications.⁶⁹



Melatonin Shields Your Brain from Traumatic Injuries

Melatonin has also been found to help protect your brain in the event of a traumatic brain injury (such as head trauma experienced in an automobile accident). Traumatic brain injury is a leading cause of death and disability in younger Americans (but not unheard of in older adults).^{54,55}

Just as in a stroke, oxidative damage to brain cells is the leading culprit in traumatic brain injuries. Also as in a stroke, promoting brain cell plasticity (the ability of surviving neurons to take on some of the activities of damaged brain cells and to promote re-growth of damaged tissue) is a mainstay of treatment.⁵⁶

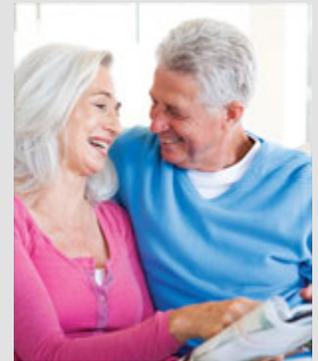
Animal studies show that administration of melatonin after such an injury maintains integrity of the blood-brain barrier, prevents dangerous brain swelling in the hours and days following the injury, and shrinks the size of the bruised and injured tissue.⁵⁵ It has also been found to reduce the mortality rate after a burst aneurysm.^{12,13}

Most of these effects are related to melatonin's direct antioxidant effects, along with its ability to induce otherwise dormant cellular antioxidant systems.¹³

WHAT IS MELATONIN?

Melatonin is a hormone that is primarily secreted in the pineal gland, a minute, pea-sized organ located in the center of the brain between the two hemispheres.^{16,17,22} Shaped like a tiny pine cone (hence the name), the pineal gland is filled with nerve cells that respond to light or darkness (some biologists refer to the pineal as the “third eye” for this reason).^{22,70}

Through its secretion of melatonin, the pineal gland acts as the body's central clock, telling the brain and other organs when it's time to be active and when it's time to rest.^{2,16,17,19,22} That's why melatonin is typically thought of as the “sleep hormone.”¹⁷



But in addition to its hormonal actions, melatonin is one of the body's most powerful intrinsic **antioxidants**.^{2,18,28} Melatonin has several antioxidant mechanisms: it directly scavenges free radicals of both oxygen and nitrogen, neutralizes a host of other radicals, and stimulates gene expression of powerful intracellular antioxidant systems.^{2,3,28} But melatonin has an additional action that sets it apart from other antioxidants: It readily crosses the blood-brain barrier and enters brain cells and their organelles.³

Unfortunately, the pineal gland's production of melatonin declines rapidly after middle age.^{2,6,16} Since the brain lacks other oxidative defense mechanisms, the decline in melatonin production leaves brain cells increasingly vulnerable to oxidative damage, resulting in dysfunction at the level of molecules and cells.³

We see the effects of that dysfunction in the various diseases of the aging brain, such as Alzheimer's, Parkinson's, Huntington's, and others.^{2,3} Oxidative damage also produces the disastrous effects of a stroke or a traumatic brain injury, effects which may be attenuated by melatonin.^{2,3,42}

Can Melatonin Extend Your Life?

There's no question that melatonin exerts powerful protective effects on brain tissue. We've seen how it can mitigate oxidative damage that contributes to neurodegenerative diseases, stroke, and head trauma.

But melatonin is a potent antioxidant that's also found in the blood, making it accessible to other tissues throughout the

body.⁵⁷ Could melatonin, then, offer true life extension by preventing damage not just to the brain, but to the entire body?

It's too early to say definitively, of course. Humans live so long that it's challenging to conduct an ethical, randomized, placebo-controlled study of most interventions. But studies in other animals yield considerable reason for hope.

In the single-celled organism *Paramecium tetraurelia*, melatonin treatment increased both the mean and the maximal life span by up to **24%** over control animals.⁵⁸ In fruit flies (*Drosophila melanogaster*), melatonin-fed flies had a **33%** increase in maximum life span and a nearly **14%** increase in median life span.⁵⁹

In higher organisms such as mice and rats, data are promising but incomplete. Melatonin increases expression of the “longevity protein” SIRT1, which triggers the expression of a host of self-healing genes (SIRT1 is activated by calorie restriction).¹⁴ One study in mice found no increase in mean life span, but an increase in the life span of the last surviving **10%** of the population.⁶⁰ Another study did show increases in longevity in mice engineered to age rapidly.⁶¹

Research also shows that animals undergoing calorie restriction—a documented means of extending life span—substantially increase their production of melatonin.¹⁹ And melatonin activates (and synergizes with) some of the same brain-protective mechanisms activated by resveratrol, another life-extending supplement.^{15,62,63}

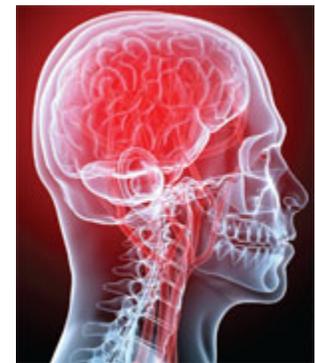
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Summary



Melatonin has been ignored or trivialized as simply a “sleep aid” ever since *Life Extension* introduced it to the world in **1992**. But a burst of new studies now reveals that melatonin can protect your brain from many of the ravages of aging.

When we're young, melatonin protects our brains from free radical attack. But after middle age, melatonin levels drop precipitously, leaving our brains increasingly susceptible to the growing impact of oxidative damage. Such damage leads to increased risk of neurodegenerative diseases and stroke, and increased vulnerability to the effects of head trauma.

Studies now show that melatonin supplementation can normalize oxidative damage in brain tissue. It can protect against the pathological changes seen in Alzheimer's and Parkinson's diseases, can shrink the size of the brain area involved in a stroke and can minimize brain swelling and dysfunction following a head injury.

But, like all preventive measures, brain protection with melatonin requires early action. You likely won't get much benefit from melatonin if you wait until after onset of symptoms of neurodegeneration or until after a stroke or head injury claims some of your brain cells.

In order to keep your brain functioning in top condition, you need to support your dwindling supplies of brain-protective melatonin now.

If you have any questions on the scientific content of this article, please call a Life Extension[®] Health Advisor at 1-866-864-3027.

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