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UPDATE

New Findings On Melatonin

The number of published studies on melatonin are increasing rapidly. There are now more than 5,400 melatonin studies in the scientific literature. The reason for the explosion of studies on this pineal gland hormone is the evidence that melatonin has a multitude of benefits. Here are short reviews of some of the latest of these studies.

NEUROPROTECTIVE EFFECTS OF MELATONIN

Two recent studies showed that melatonin protected brain cells (neurons) against two different mechanisms of action that can induce cell death-excitotoxicity and apoptosis.

At the University of Padova in Italy, melatonin protected cerebellar neurons (which control movement and coordination) in rats from a process called excitotoxicity, which is induced by exposure to glutamate and glutamate receptor agonists. There have been many studies showing that excitotoxicity causes a cascade of intracellular damage that can lead to the death of brain neurons.

Scientists have described a precise mechanism of cell death involving such a cascade called apoptosis, which is mediated by a "chain reaction" of increasingly toxic free radicals. Scientists at the Alleghany-Singer Research Center in Pittsburgh recently showed that melatonin protected rat cerebellar neurons against singlet oxygen-induced mitochondrial impairment leading to neuronal death by apoptosis. Some scientists believe this process plays a key role in a variety of neurodegenerative diseases.

MELATONIN AS AN ANTIOXIDANT

It was only a few years ago that Russel J. Reiter of the University of Texas Health Science Center in San Antonio produced convincing evidence that melatonin is a very potent antioxidant that fights excessive free radical activity throughout the body. Today, the evidence that melatonin is an antioxidant is increasing by leaps and bounds.

COUNTERACTING LIPID PEROXIDATION

One of the primary free radical intermediates is hydrogen peroxide (H202), which commonly promotes lipid peroxidation-induced damage in cell membranes. In a recent study by Reiter's group at the Texas Health Sciences Center in San Antonio, melatonin added to brain homogenates from five different regions of the brains of two different strains of rat reduced lipid peroxidation damage caused by H2O2 significantly, as measured by concentrations of brain malonaldehyde (MDA) and 4-hydroxyalkenals (4-HDA).

The effectiveness of melatonin in this study was dose dependent in all areas of the brain studied, including the cerebral cortex, the cerebellum, the hippocampus, the hypothalamus and the corpus striatum in both Sprague-Dawley and Wistar rats. The degree of protection by melatonin against lipid peroxidation was similar in all five brain regions.

In another study at the Texas Health Sciences Center, melatonin prevented lipid peroxidation induced by carbon tetrachloride (CC14) in the kidney, but not the liver, of rats. Melatonin failed to restore normal enzyme activity, which had been induced by CC14, suggesting that it only provides partial protection against this toxin.

MELATONIN PREVENTS GLUTATHIONE LOSS

In a third study by the San Antonio scientists, interperitoneal (IP) injections of melatonin prevented reductions in levels of free-radical fighting *glutathione* and *glutathione peroxidase* caused by exposure to lipopolysaccharide (LPS) and the drug phenobarbital in the liver of rats.

In another study at the San Antonio Center, injections of melatonin completely abolished the toxic effects of paraquat in the lung and liver of rats. Among the effects of paraquat that melatonin protected against were lipid peroxidation, and reductions in

glutathione and *glutathione peroxidase*.

ANTICANCER EFFECTS OF MELATONIN

We've reported on many studies showing that melatonin helps to fight various types of malignancy, such as breast cancer, in conjunction with immunotherapies such as interleukin-2 (IL-2). The evidence of the anti-cancer effects of melatonin continues to be published at a rapid rate. Here are a few recent examples.

TAMOXIFEN AND MELATONIN FOR BREAST CANCER

In the last few years, there has been considerable interest in the use of tamoxifen to help prevent and treat breast cancer. One problem with tamoxifen is its potential toxicity which, while not as great as that of traditional chemotherapy, is still a concern.

In an attempt to improve the safety and efficacy of tamoxifen, scientists at San Gerardo Hospital in Milan, Italy gave 14 women with metastatic breast cancer who had not responded to tamoxifen therapy, 20 mg of melatonin (in addition to tamoxifen) every evening. They found fewer side effects in these patients than those receiving tamoxifen alone, as well as significant tumor regression in 4 of the 14 patients receiving melatonin.

IL-2 AND MELATONIN FOR ENDOCRINE CANCERS

In another study, the Italian scientists studied the combination of low-dose IL-2 and melatonin in 12 patients with previously untreatable metastatic endocrine tumors including thyroid and pancreatic cancers. The patients were given 3 million lU/day of IL-2 every morning at 8 am and 40 mg/day of melatonin at 8 pm. There was a marked reduction in the toxicity of IL-2 therapy in patients receiving melatonin.

The major finding of the study was a partial regression of tumors in 3 of the 12 (25%) patients receiving IL-2 and melatonin. These included a reduction in the size of a carcinoid tumor, a lung tumor and a pancreas tumor. Another patient with a gastric tumor showed more than a 50% reduction in tumor markers.

MELATONIN SUPPRESSES EFFECTS OF CARCINOGEN

Dr. Reiter's group in San Antonio recently reported evidence that melatonin had suppressed liver DNA adduct formation induced by the chemical carcinogen safrole. DNA adducts are molecular crosslinks that can cause mutations leading to transformed and proliferating cancer cells throughout the body. The Texas scientists believe that melatonin's ability to suppress DNA adduct formation may be related to its ability to potentiate mixed function (P-450) oxidase activity, which counteracts various toxins, and its ability to scavenge hydroxyl radicals, the most damaging type of free radical.

NEW MELATONIN SLEEP STUDIES

The most common use of melatonin by far is as a natural, physiologic sleep agent that works primarily in people over 40 by replacing melatonin lost as a result of aging. In the early 1990s, we were the only ones offering melatonin in the United States because of the widespread fear of FDA intervention. Today, with the FDA permitting the sale of melatonin, millions of Americans are enjoying its benefits as a natural sleeping pill. Here are some recent studies that support its use for this purpose.

MELATONIN FOR ELDERLY INSOMNIACS

Changes in sleep patterns are one of the hallmarks of biological aging. Recently, scientists at the Technion-Israel Institute of Technology reported that impaired melatonin secretion is associated with sleep disorders in old age. They then investigated the effects of melatonin replacement therapy in melatonin-deficient elderly insomniacs who were given 2 mg of fast-release melatonin or 2 mg of sustained-release (or placebo) two hours before bedtime for 7 days followed by two months of 1 mg of sustained-release melatonin per night or placebo.

They found that treatment with 2-mg of fast-release or sustained-release melatonin improved the quality of sleep of the elderly insomniacs. Analysis showed that sleep initiation was improved by fast-release melatonin, while sleep maintenance was improved by sustained-release melatonin, and that this improvement continued when the regimen shifted to 1-mg of sustained-release melatonin, but deteriorated after cessation of treatment.

In another study at the E. Wolfson Medical Center in Holon, Israel, the quality of sleep was improved significantly in 12 elderly people who had been receiving various medications for chronic illnesses and who complained of insomnia. The subjects received 2 mg per night of controlled release melatonin for 3 weeks followed by 3 weeks on placebo, with a week's washout period.

The Israeli scientists found that sleep efficiency was significantly greater, and wake time after the onset of sleep was significantly shorter with melatonin than with placebo. Their conclusion was:
"Melatonin deficiency may have an important role in the high frequency of insomnia among elderly people. Controlled release melatonin replacement therapy effectively improves sleep quality in this population."

ESSENTIAL ROLE OF MELATONIN FOR SLEEP

Further evidence for the essential role of melatonin for sleep comes from a case report in a young child with a pineal gland tumor, who was treated at the Rambam Medical Center in Haifa, Israel. The child's tumor markedly suppressed melatonin secretion, which produced *severe* insomnia. However, when the child was given 3 mg of melatonin every evening for two weeks, normal sleep quality was restored, as assessed by objective monitoring of sleep-wake cycles.

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