



Melatonin

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It's the hot sleeping pill, natural and cheap. Now scientists say this hormone could reset the body's aging clock, turning back the ravages of time.

By: Geoffrey Cowley

Turning back the clock has long been the domain of crackpots and charlatans. Take one look at the claims that enthusiasts are making for melatonin, a hormone sold as a supplement in health-food stores, and you'll quickly sense that nothing much has changed. "Senescence, the downward spiral that we have come to associate with aging, does not have to occur," Drs. Walter Pierpaoli and William Regelson declare in their forthcoming book, "The Melatonin Miracle." "Melatonin can stop the spiral". Strip away the bombast, and it turns out these guys are on to something interesting. Like most animals, we produce melatonin abundantly throughout early life. But the levels in our blood drop slightly before puberty and decline steadily into old age. When Pierpaoli, an Italian immunologist, restores youthful levels of the hormone in mice, they outlive their life expectancies by nearly third. And his findings are consistent with a burgeoning scientific literature. Recent studies suggest that supplementing the hormone may bolster our immune systems, keep our cells from disintegrating, slow the growth of tumors and cataracts, and ward off heart disease. All that while helping us sleep better.

Proven or not, melatonin is poised to become one of the hottest pills of the decade. It's cheap and readily available a month's supply costs less than \$10 in health-food stores and it's gaining popularity among people who have heard nothing about its anti-aging properties. Travelers and office workers are using it as an antidote to jet lag, stress and insomnia. And sales are soaring. One manufacturer, Source Naturals of Scotts Valley Calif., expects to move a million jars of lozenges this year—three times the number it sold in 1990. Skeptics cringe at the thought of people gulping down a supplement whose long-term effects are largely unknown. But since studies have yet to document any hazards, even scientists are taking the plunge.



"I take a milligram or less every night," says Russel Reiter a University of Texas cellular biologist who has studied

melatonin for 30 years. "I want to die young as late in life as possible and I think this hormone could help."

First identified just four decades ago, melatonin is now recognized as one of life's most ubiquitous molecules. It turns up in such diverse organisms as people and protozoa suggesting it dates back a billion years or so. Humans secrete it cyclically from the pineal gland, a pea-size structure nestled at the center of the brain, in response to the amount of light hitting our eyes (chart). Physiologists know melatonin as the hormone that keeps us in sync with the rhythms of the day and the season. Through its actions on other hormones, it helps determine when people sleep and horses breed, when birds migrate, dogs shed their coats and certain frogs change color. But cellular biologists have recently discovered that melatonin has an even more basic function, which is to protect oxygen-based life from the toxic effects of oxygen.

Yes, oxygen. As we metabolize this life sustaining gas, we generate highly reactive molecules called free radicals, which can corrode our cellular membranes and damage our DNA. The process, known as oxidation, weakens our minds and muscles as we age, and contributes to at least 60 degenerative diseases, including cancer, heart disease, and Alzheimer's. The body produces several enzymes to inhibit oxidation, and nutrients such as vitamin C, vitamin E and beta carotene can provide extra protection. But most of these so-called antioxidants work only in certain parts of certain cells. Melatonin readily permeates any cell in any part of the body—including the brain. And as Reiter's research team has recently shown in animal experiments, the hormone



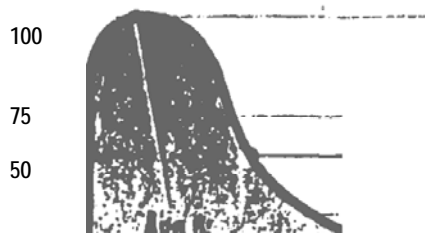
can protect tissues from an amazing array of assaults.

The evidence started stacking up just two years ago, when Reiter and his colleagues showed that a small dose of melatonin could shield rats from a cancer-causing chemical called safrole. Given alone, safrole quickly oxidizes liver cells, causing extensive DNA damage. But when rats got tiny doses of melatonin before their safrole shots they exhibited 41 percent less damage than their untreated counterparts, and those receiving a slightly larger dose of melatonin suffered just 1 percent as much liver damage as the controls. In more recent studies, Reiter's team has shown that melatonin's antioxidant action can protect rats from ionizing radiation (halving the death rate from a normally lethal dose), and can shield the animals' lungs from common afflictions of old age. Where cancer is concerned, the evidence isn't limited to mouse studies. Autopsy studies suggest that pineal calcification (a condition that hardens the gland and reduces melatonin output) is most common in countries with high rates of breast cancer and least common in countries where breast cancer is rare. By the same token, women taking chlorpromazine, an antipsychotic medication that raises melatonin levels, enjoy unusually low rates of the disease.

Cure -All?

Melatonin's benefits are still debatable, but studies point to many possible uses. The drug tray help:

- Ease Insomnia
- Combat jet lag
- Prevent pregnancy (in large doses)
- protect cells from free radical damage
- Boost the immune system



Average nighttime melatonin peaks in micrograms per milliliter of blood

Age 8: Melatonin levels peak during childhood

Age 18: The first sharp decline triggers puberty

Age 45: Middle-Aged adult secrete only half as much as children
 Age 88: Production slows to a trickle in old age

Age 10 20 30 40 50 60 70 80 90
 Diagram: Christopher Blumrich



Regulating the Body's Rhythms

Secreted cyclically from the pineal gland, a pea-size structure nestled at the center of the brain, melatonin keeps us in sync with the rhythms of the day and the season. By orchestrating the action of other hormones, it determines when people sleep and horses breed when birds migrate, dogs shed their coats and certain frogs change color.

The explanation, says Dr. Michael Cohen of Fairfax Va., involves estrogen. Prolonged exposure to that hormone (due to early puberty, infrequent childbearing or late menopause) increases a woman's risk of breast cancer. But melatonin dampens the release of estrogen. In fact, high melatonin levels can temporarily shut down the reproductive system. That's why females in most species are fertile only at certain times of year. Exploiting this principle, Cohen has combined a stiff (75 mg) dose of melatonin with progestin to create a new oral contraceptive. The drug, called B-Oval, has performed as well as conventional birth-control pills in European studies involving the deadly herbicide parquat. Melatonin may also help prevent cataracts, the cloudy lesions that appear on our eyes as oxidation damages cells in the lenses. When the Texas researchers gave 18 newborn rats a toxic compound called BSO, all 18 developed cataracts within two weeks. But when 15 animals got the same treatment plus melatonin, 14 maintained perfectly clear eyes.

Oxidation isn't the only reason we fall apart as we age. We also lose our immune function. The thymus gland shrinks over time, sapping our ability to generate infection-fighting T cells, and we produce fewer of the antibody molecules that bind with and neutralize foreign invaders, such as viruses and bacteria. Could all of this follow from a loss of melatonin? Test-tube studies have identified receptors, or specialized portals, for melatonin on the cells and glands of the immune system. And animal experiments are showing that the hormone can preserve, or even restore, a creature's defenses.

One of the best examples comes from Pierpaoli's mouse lab. A few years ago he paired 10 young mice with 10 old ones and

had a microsurgeon switch their pineal glands (old to young and vice versa). Before long, the youngsters were hobbling around with cataracts in their eyes and bald patches on their backs. The old ones gained muscle and energy, and their coats grew thick and shiny. Autopsies revealed what was probably part of the reason. The young mice had all but lost their thymus glands after the pineal transplant. The oldsters had had theirs restored.

In other animal studies, Italian researchers have shown that a nightly melatonin supplement can boost the performance of immune systems compromised by age, drugs or stress. And scientists in Israel and Switzerland have found that when mice receive melatonin, their odds of surviving infection with an encephalitis virus more than double.

No one knows just how neatly any of these findings will apply to people. But together they suggest that melatonin could help us prevent, and even treat, the most common afflictions of old age. Where cancer is concerned, the evidence isn't limited to mouse studies. Autopsy studies suggest that pineal calcification (a condition that hardens the gland and reduces melatonin output) is most common in countries with high rates of breast cancer and least common in countries where breast cancer is rare. By the same token, women taking chlorpromazine, an antipsychotic medication that raises melatonin levels, enjoy unusually low rates of the disease.

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1,000 women, and has shown no toxicity. Cohen plans to launch U.S. trials within two years, but his goal is not simply to market another contraceptive. If his hypothesis about melatonin, estrogen and breast tumors bears out, the new pill would help women prevent cancer as well as unwanted pregnancies.

Melatonin may also prove useful for fighting existing malignancies. Several studies have shown that it can slow the growth of human tumor cells in a test tube and some cancer specialists are now testing its effects on patients. In a 1992 study, Dr. Paoli Lissoni and his colleagues at San Gerardo Hospital in Monza, Italy, found that a nightly melatonin supplement (10 mg) significantly improved one-year survival rates among patients with metastatic lung cancer. The same lab has since reported that melatonin can enhance the effect of interleukin-2 shots (IL-2 is a hormone that helps T cells proliferate) on cancers of the lung, kidney, liver, colon and pancreas. IL-2 causes horrific fevers and nausea at the doses normally required to tame tumors.

