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Drug of Darkness

Can a pineal hormone head off everything from breast cancer to aging?

By JANET RALOFF

The camera closes in on a young-looking 40-year-old woman examining her troubled face in the mirror. The voice-over asks: "Do you have trouble falling asleep? Are you concerned about unplanned pregnancies? Does jet lag keep you from getting the most out of your vacation or business travel? Want to postpone aging and the chronic diseases that can accompany it?

"If any of this describes you, ask your doctor about MelaTonics. There's a good chance one of our growing family of products can help you. And remember, each is safe, nontoxic, and based on Mother Nature's own recipe."

Sound far-fetched? Today, perhaps. But a host of medical laboratories around the world are addressing these health problems and more with a new class of drugs they hope to introduce within the next decade — some in as little as 3 years.

Each would rely on a synthetic form of melatonin.

Discovered in 1959, melatonin occurs naturally throughout the living world, from algae to primates. Secreted in larger animals by the pineal gland, located in the center of the brain, it is the chemical embodiment of night. In fact, dusk or darkness triggers melatonin production and sunlight inhibits it.

A decade ago, many of melatonin's functions in humans — let alone its mechanisms of action — remained shrouded in mystery. Today, scientists variously describe its primary role as the regulator of the body's internal clock, a defense against biologically damaging free radicals, an age-retarding chemical, the trigger for sleep, and a coordinator of the hormones involved in fertility.

So it's not surprising that most researchers express skepticism about one another's findings.

Endocrinologist Michael M. Cohen of Applied Medical Research (AMR) in Fairfax, Va., sums up the situation: "There are differences of opinion between scientific groups on the function of this hormone. And as time progresses, all of us will probably learn we had some things right and some things wrong."

Some pharmacies and health food stores already stock melatonin as a sleep aid. However, the chemical's true soporific value is only just emerging, says Richard J. Wurtman, director of the Massachusetts Institute of Technology's Clinical Research Center.

Wurtman began studying what eventually became recognized as melatonin while in medical school, "about 8 million years ago." By 1963, he and his colleagues had written the first paper designating melatonin a hormone. It took another 19 years before they would offer evidence that melatonin can facilitate sleep.

"The trouble was, we had no idea what dose to use," Wurtman recalls. "So we gave people 240 milligrams [mg]" — which seemed reasonable, based on animal studies. While the hormone indeed made people "verrrrry sleeeeepy," he notes, it also saddled them with a miserable hangover the next day. The MIT scientists concluded that melatonin offered little promise as a sleeping pill.

Now, however, Wurtman and his coworkers report in May CLINICAL PHARMACOLOGY AND THERAPEUTICS that an eight-hundredth of that earlier dose induces sleep without side effects. And unlike hypnotic sedatives, they find, melatonin does not alter the normal architecture of sleep, including the timing and duration of dream phases characterized by rapid eye movements.

"This compound produces natural sleep," Wurtman concludes.

The data suggest that "very tiny doses" of melatonin can combat insomnia, particularly in the elderly. Over time, the pineal gland accumulates deposits of calcium that diminish its melatonin production. That may be one reason many older people have trouble getting a good night's sleep, he says. The low-dose supplement the MIT team now administers appears to foster sleep by raising concentrations of melatonin in the blood from the 10 picograms per milliliter (pg/ml) typical of daytime to the 100 pg/ml that normally circulates at bedtime.

In work published last year, the group found that melatonin can even induce sleep at midday. This suggests, Wurtman says, that the hormone exerts its soporific effect independent of any effects on circadian rhythms, the daily cycles of varying body chemistry, temperature, and wakefulness.

Alfred J. Lewy, a psychiatrist at the Oregon Health Sciences University in Portland, disagrees. He suggests that any sleepiness probably constitutes a "side effect" of melatonin's effects on circadian rhythms. "The most noncontroversial claim that's generally accepted by everyone in the field is the ability of melatonin to phase shift — or reset — the body clock," he contends.

In 1980, Lewy and his coworkers showed that bright light, such as sunlight, affects human melatonin production. This finding led them to use light to treat seasonal affective disorder, or winter depression (SN: 12/20/86, p.390). Since then, the team has experimented with melatonin to reset the biological clock of travelers, shift workers, and blind people.

"It's when the [body's internal] clock doesn't expect [this hormone] that it's most effective," Lewy says. That's typically the first thing in the morning, to trick the body into thinking dawn has not yet arrived, or during the afternoon, to advance the internal clock to nightfall. "This effect is quite remarkable," he adds, because the 0.5 milligram doses result in concentrations "no greater than those normally [occurring in] the person at night."

Cohen, in fact, has observed no sleepiness among 1,600 Dutch women taking 75 mg of melatonin daily as part of a trial, begun in 1988, examining its prospects for birth control.

Wurtman, who's familiar with the study, concedes the finding is puzzling. However, he says, the doses are so high that they may overwhelm melatonin receptors, which ordinarily undergo stimulation only a few hours a day.

Why add melatonin to the Pill?

Breast cancer risk has been linked to a woman's cumulative exposure to estrogen, which stimulates breast tissue during each reproductive cycle. Exposure really adds up if a woman doesn't become pregnant periodically, shutting down ovulation for a year or so at a time.

Cohen designed an oral contraceptive that suppresses ovulation and reduces the breasts' exposure to estrogen. Together with coworkers in Amsterdam and Jerusalem, he outlines the reasoning behind these pills in the March Breast Cancer Research and Treatment. Unlike conventional birth control pills, his contain no estrogen. They do contain the usual progesterone, coupled in this case with melatonin, which can shut down ovulation in seasonally breeding animals.

Cohen says this "breast-cancer-fighting" birth control pill offers a contraceptive success rate comparable to its estrogen-based competition. U.S. trials of the pill have won Food and Drug Administration approval and will begin after AMR raises the necessary financing.

Meanwhile, Cohen's team is testing a drug that substitutes 75 mg of melatonin for the progesterone normally given daily to postmenopausal women as part of estrogen-replacement therapy (SN: 2/4/95, p.74). In these older women, progesterone can foster breast cancer and risk factors for heart disease.

Earlier this year, Cohen won a patent for a male contraceptive that pairs melatonin and testosterone, the primary male sex hormone. The pill is designed to stop sperm production and to reduce the risk of prostate cancer. Clinical trials could begin within 2 years.

It was melatonin's ability to enhance immunity that initially intrigued immunologist Walter Pierpaoli of the Biancalana-Masera Foundation for the Aged in Ancona, Italy. His early studies showed that when administered to old mice, the hormone reversed some of the age-related shrinkage in the animals' thymus, an organ that produces certain infection-fighting white blood cells. The treatment also revitalized the animals' immune system.

Last year, Pierpaoli and Vladimir A. Lesnikov of the Institute of Experimental Medicine in St. Petersburg, Russia, offered in the ANNALS OF THE NEW YORK ACADEMY OF SCIENCES (vol. 719) experimental evidence that the pineal gland plays some part in regulating the rate at which the body ages.

The pair cross-transplanted pineals between the brains of young and old mice. Transplanting pineals from 18-month-old mice into 4-month-old mice reduced the younger animals' average life span by one-third. But the reverse procedure enabled 18-month-old mice to live to the age of 33 months — one-third longer than untreated mice.

Pierpaoli interprets these and related findings to mean that "we start aging in the pineal gland." Indeed, he says, "we should think of the pineal as the aging clock" and melatonin as a means by which it translates its timekeeping pulses into body changes. Although "we can dramatically interfere with aging by interfering with the [calcifying] of the pineal," that's impractical at present, he concedes. He suspects that medicine will focus instead on melatonin supplements to compensate for aging pineals.

Russel J. Reiter of the University of Texas Health Science Center in San Antonio also suspects melatonin plays a key role in aging. However, his data suggest it does so by quashing many of the free radicals that, in excess, have been linked to the chronic diseases that tend to accompany aging.

Some cells generate free radicals — molecular fragments possessing an unpaired electron — to destroy unwanted material such as bacteria or aging cells. Drugs, radiation, and other toxic environmental agents also produce free radicals.

Two years ago, Reiter and his colleagues suggested that melatonin might be the most effective antioxidant, or scavenger of free radicals (SN: 8/14/93, p.109). Since then, he says, "we've tested it in every conceivable system that we can assemble, and melatonin continues to perform as well as or better than any other antioxidant."

In the January MUTATION RESEARCH, the team showed that lymphocytes (white blood cells important to immunity) incubated with melatonin sustained 70 percent less damage from ionizing radiation than untreated cells did. That same month, the group reported in LIFE SCIENCES that rats injected with melatonin before and after exposure to paraquat, a toxic herbicide, showed none of the devastating lung and liver damage seen in unprotected animals.

The signal to produce melatonin goes from the eyes to the biological clock, or suprachiasmatic nucleus (SCN), at the base of the brain. The messenger for that signal is glutamate, Reiter notes, a free-radical-inducing neurotransmitter. Young animals have ample melatonin to neutralize these free radicals, Reiter believes. But "over a lifetime, the glutamate wins, destroying most of the cells in the SCN that generate the melatonin rhythm."

As a result, he proposes, melatonin production starts to drop, leaving the SCN more vulnerable to glutamate attack, which further blunts the output of melatonin. If this explanation for melatonin's age-related decline is validated, Reiter says, melatonin supplements might allow older people to mimic a 20-year-old's natural rhythm — thereby delaying many of the age-related changes fostered by free radical damage.

In a more immediate application, people about to undergo diagnostic X rays may take a dose of melatonin to protect their healthy tissue.

The one thing on which all melatonin researchers agree is that the hormone is nontoxic, even at fairly high dosages. Toxicology studies by AMR, for instance, indicate that humans could consume 100 times the dosage now used in the Dutch trials without ill effect. Indeed, Cohen argues, on a per weight basis, ordinary table salt is more toxic.

Should consumers hurry to stock up on the supplement? On that, opinions vary widely.

Cohen, whose company expects to become a major melatonin supplier, says go ahead. Pierpaoli agrees. Even Reiter says, "I take a lot of melatonin."

Others argue that consumers should wait until FDA regulates melatonin. To date, FDA lacks the data it needs to evaluate health claims arising from the new animal and clinical trials. Indeed, the agency cautions consumers that if they take melatonin, "they do so without any assurance that it is safe or that it will have any beneficial effect."

At a minimum, Lewy notes, taking melatonin at the wrong time of day might upset an individual's biological clock. That could prove catastrophic for, say, people driving or physicians conducting surgery. Moreover, Wurtman points out, production of the hormone by unregulated companies increases the risk of impurities tainting the product.

Concludes Dan Oren of the National Institute of Mental Health in Rockville, Md., who has studied melatonin, "It's something that I suspect will become available as a commercially regulated drug within a few years. But it is a drug. And its effects have not been adequately studied for people to be responsibly using it on an over-the-counter basis yet." □