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Melatonin – a molecule for the modern age

New developments in the continuing saga

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Abstract: *This paper briefly reviews the indoleamine melatonin and its emerging place in nutrition and medicine. Though thousands of studies have now investigated the molecule's proven beneficial effects since its discovery in the 1950s by Aaron Lerner, there is still some reluctance on the part of UK regulatory authorities to allow its supportive place in medicine, despite there being few, if any, contraindications. The advantages of melatonin as a supplementary food are briefly outlined, together with new discoveries such as its synthesis by lymphocytes as part of the cellular immune defence system.*
Keywords: Melatonin, antioxidant, jet lag, oncostatic, anti-aging, Parkinson's, Alzheimer's, sleep, ionizing, non-ionizing radiation.

MELATONIN is an unusually controversial biomolecule. It is not only a powerful hormone, synthesised in the pineal gland and secreted into the cerebrospinal fluid and the circulation - a process dramatically influenced by light and dark, thereby giving melatonin control over the circadian rhythms of most life-forms - but it is also a ubiquitous nutrient food, being found in many common plants from bananas to Morello cherries, and in most cereals. Your average bowl of porridge oats contains a substantial helping of melatonin!

Unsurprisingly, it is one of the safest products around. It has been given at a huge dosage of grams daily for prolonged periods and to 1,500 women at the daily dosage of 300 mg for years, with no observed late side-effects or consequences (Sebra, Bignotto et al., 2000).

Paradoxically, one can only obtain this wonder food in its synthesised version by doctor's prescription in the UK, though it is freely available over the counter in other countries such the USA, Holland and Australia. The world's regulatory authorities are finding it difficult to classify melatonin one way or the other: is it a drug or is it a food? In today's technologically hazardous and fast-moving environment it is now make-your-mind-up time.

Melatonin is the smallest hormone secreted in humans in terms of volume, but it has arguably as powerful effects as any of its more voluminous colleagues. It is a more potent anti-oxidant than any of our familiar vitamins, for example. Though first identified by Aaron Lerner in 1958, and now the object of over 20,000 peer-reviewed scientific studies, scientists are still discovering daily new and vital roles for this small but mighty indoleamine. Scientific, practitioner, and consumer interest in melatonin has never been more intense: a major international conference on childhood leukaemia in London last month, funded by the charity Children with Leukaemia (see: www.leukaemiaconference. org for papers) devoted much time to the way melatonin might benefit cancer sufferers and prevent radiation damage (radiation is the only known cause of childhood leukaemia). A 2002 review of key nutraceuticals also singled out melatonin for special attention (Rapport and Lockwood, 2002; see review this issue).

The reasons for this interest are not difficult to see. Our modern age of jet travel, telecommunications and constant media pressure to look and feel good at any age are all areas where melatonin has a proven contribution to make to modern living.

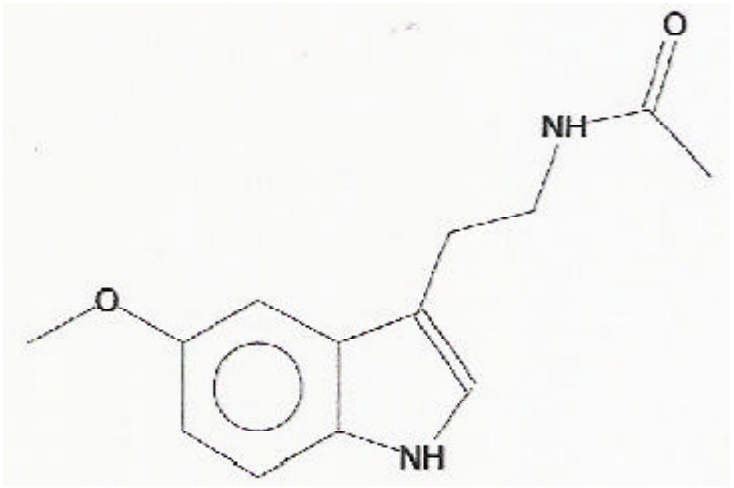

Fig 1. The molecule of melatonin, first identified by Aaron Lerner in 1958.

Moreover, the darker counterpart of our techno-times – high levels of cancer, cardiac diseases, career and family stress, and sleep disturbance – are surprisingly also territories where melatonin is fast securing a noticeable adjuvant position. Yes, melatonin is, by a clear head, a true molecule of our modern age. This article rehearses its main existing applications, reports some important new discoveries and reviews how melatonin is now being applied in areas of health disorder never before considered and in altogether new formats other than the conventional tablets readily bought on the Internet nowadays for minor problems such as jet lag.

Melatonin and Jet Lag

Professor Josephine Arendt, retired recently from Surrey University, has been studying melatonin since 1975 when she developed the first radio immunoassay (RIA) for it, and in the 1980's reported its efficacy in combating jet lag (Arendt, Aldous et al., 1986, 1987).

Melatonin's use to counter the effects of jet lag is probably one of the safest and best-tested uses of the hormone to date, according to one practitioner. When travelling to points east, on the day of your flight, take one dose of melatonin, as directed on the bottle, between 6 and 7 pm your time; you may have to take the melatonin on the plane. On the day you arrive and for the next four days, take one dose of melatonin at bedtime (between 9 and 10 pm) local time of where you now are. If you will not be staying in this time zone for four days and will instead be travelling further east, take one dose of melatonin on the day before flying onward, again between 6 and 7 pm local time (but not at bedtime). On the day of arrival at your second destination, take one dose of melatonin at bedtime (local time) and for the next four days.

One of Arendt's students, Jennifer Luke, produced evidence in her PhD thesis that fluoride lodges in the pineal and thereby inhibits melatonin synthesis. Given that some 65-75 percent of the USA has fluoridated drinking water, this could partly explain why some 560,000 American citizens die of cancer each year (Luke, 2001).

Anti-Aging

The media, from *OK* and *Hello* to the *Financial Times*, all demand that everyone looks and performs 'young and beautiful'. With over half of Britons likely to be fifty-something in the next decade, the pressure is on for anything that keeps us glamorous and libidinous. Working out on the rowing machine or using creams and lotions for reducing wrinkles is one thing (and who has not been encouraged by unsolicited email to extend one part of their anatomy if not two, lose volume in others, or to increase the size of their libido?). But beauty is only skin deep. Melatonin has a real and enviable record in its ability to keep animals alive and well, probably due to its anti-oxidative capability. Among many others, one study on rats found that when melatonin was added to their drinking water they lived 12 percent longer, with commensurate sexual prowess (Pierpaoli, Regelson et al., 1994).

Other clues that melatonin has an anti-aging effect is that women, who have more melatonin than men, also live longer than men. Moreover, as we age the level of melatonin in our bodies declines, suggesting that additional melatonin supplementation may offset aging (Sack, Lewy et al., 1986). Studies with human beings are confirming the hypothesis.

Alleviation of sleep disturbance

If the anti-aging effect and combating jet lag were its only features melatonin would merit a place in medicine or nutrition, but it also has an important beneficial effect on sleep. In one four-week trial of 14 patients with sleep disorders (average age 50) taking 3gm of melatonin each evening induced significantly more REM sleep (Kunz et al., 2004). This is important since most sleeping tablets do not help maintain the level of REM sleep, which is indispensable for good health, and worse, unlike melatonin, they are often addictive. This ability would guarantee melatonin a large market in a world where sleep disturbances occur in about 12% to 25% of the general population (Walsleben, 1982) and are often associated with situational stress, illness, aging, and drug treatment (Kaempfer, 1985; Savard and Morin, 2001). The Savard and Morin study showed that in cancer cases sleeplessness affects 45 per cent of sufferers.

One political problem facing melatonin as an inexpensive and more effective aid to sounder sleep is that it will inevitably tread on the toes of the existing sleeping pill manufacturers. The sleeping pill market is estimated to be huge and sleeping pills are becoming an increasingly appealing market for drug firms. More than 40 million Americans have chronic sleep disorders and 20 million more experience occasional sleep problems.

Melatonin, Parkinsonism, and Alzheimer's

One curious thing about the pineal gland is that, unlike the rest of the brain, it is not protected by the blood brain barrier, but its secretions of melatonin (being of lower molecular mass than most hormones) can nevertheless pass through. This may help explain how melatonin also appears to be adjuvant for repairing disordered neurotransmitters, as seen in such illnesses as Parkinsons and Alzheimer's. It had already been noted that Alzheimer's patients have lower than normal melatonin levels.

Melatonin may therefore have the potential to treat Alzheimer's, perhaps because of its capacity to reduce the development of a protein complex that is a hallmark of the disease. In a 2001 *in vitro* study from the University of South Alabama the researchers added melatonin to animal and human cell cultures containing the building blocks of abnormal brain amyloid fibrils as well as human apoE4 - a protein associated with strong risk for developing Alzheimer's - with encouraging results. A combined Japanese group has been since then reporting further success (Poegeler, Miravalle et al., 2001: Matsubara, Bryant-Thomas et al., 2003). This effect was structure-dependent and unrelated to the antioxidant properties of melatonin, since it could be reproduced neither with the structurally related indole, N-acetyl-5-hydroxytryptamine, nor with the antioxidants, ascorbate, alpha-tocophenol, and PBN.

The grand-daddy of melatonin research, however, is undoubtedly Professor Russel J Reiter of Texas University, who has studied the molecule for over a quarter century and has written several books about its powers. He also edits the *Journal of Pineal Research* where much of the published work on melatonin can be found. In June, 2004, at a conference in Dallas on Man and His Environment, this world authority on melatonin once again stole the show. His data convincingly demonstrated that melatonin can reduce injury to the brain in such neurodegenerative diseases of the aged as Alzheimer's Disease and Parkinsonism as well as neural ischemia/reperfusion injury in strokes.

Melatonin and cancer

The anti-oxidant capability of melatonin is shown at its best in cancer prevention and treatment. The myth that melatonin is secreted mainly in the pineal gland has recently been hit on the head by the discovery that human lymphocytes release melatonin in large quantities when challenged by a mitogen such as phytohaemagglutinin (PHA). Since lymphocytes patrol our bodies to seek and destroy cancer cells, this is an important part of their armoury when faced with potentially DNA-damaging free radicals, which melatonin scavenges proficiently. Such radicals can originate from radiation but also from the process of ATP formation and, more importantly, mitosis. Not surprisingly then melatonin seems to concentrate in the nucleus and in the mitochondria where ATP is synthesised. When melatonin was offered as a supplement to chemotherapy the survival rate for many cancers improved compared with unsupplemented controls (for full review, see Vijayalaxmi et al, 2002).

Melatonin as radio-protective agent

Melatonin's anti-oxidant properties really come to the fore in cases of ionising radiation, affording protection against free radical action from external and internal emitters. Many studies have confirmed that not only if applied immediately before exposure, but even afterwards, there is a significant increase in survival and a lowering of tumour formation and haemopoietic insult (for review, see Vijayalaxmi et al, 2004). If those entering the Chernobyl region immediately after the 1986 nuclear accident had been given high doses of melatonin, their fate might have been improved, as would those exposed in the vicinity. In these days when terrorist activists may at any time detonate 'dirty' bombs containing radioactive waste on civilian populations, to have on hand radio-protective supplies of melatonin would seem a prudent precaution.

Melatonin may also be a useful protection for chronic non-ionising electromagnetic fields (EMF) and radiation exposure. Telecommunications, TV, desktop PCs, mobile telephony, and a myriad electric and electronic appliances in the home, office, and factory have created a veritable ocean of weak but persistent electromagnetic energy fields around us. A growing number of scientists are concerned that we are not prepared by evolution for these new, man-made insults and that even at much below thermal guidance levels they may be doing actual harm to health. Sixteen out of 18 epidemiological studies have shown that people living near power lines or exposed routinely to electric and magnetic fields from appliances have a higher risk of childhood cancer, depressive illness, immune incompetence, and other serious disorders.

Studies of long duration cellphone users reveal that they have higher incidence of brain tumours and these more frequently occur on the same side as the handset is applied to the head. A new review of this epidemiology particularly refers to uveal melanomas where melatonin deficiency is also implicated (Kundi, Mild et al., 2004).

Finally, studies of young people living near radiofrequency and microwave sources have found a lowered phagocytosis index (ie. their immune systems have been compromised) (Chiang, Yao et al., 1989). Taken together, it is clear that chronic, low-level EMF exposure is an insult for which melatonin's radio-protective powers may be a solution, taken as a regular supplement.

Time for regulatory reaction?

That EMFs emanating from every electric and electronic gadget in

domestic and industrial use today inhibit the synthesis of melatonin in the pineal gland, thereby exposing the body to free radical risk, has now been demonstrated in no less than five independent laboratories (see Liburdy, 2003, for a detailed review). Sadly, with so many vested and commercial interests at stake, this scientific issue is still hotly debated and denied by the world's power utilities, by the military and by the telecommunications industries, into whose selectively biased hands the burden of research has largely fallen. For this reason, perhaps, the regulatory advice about exposure to EMF is much more lax in the West than in China and the Eastern bloc (Zhao Z, Yang G et al, 1994).

There is also some evidence that our own Medicines and Healthcare products Regulatory Agency (MHRA) needs to buck up and get its science right. A recent *Panorama* programme castigated the agency for its poor scientific expertise and delayed actions in exercising its regulatory duties in respect of the potentially dangerous antidepressant drug Seroxat, licensed 13 years ago, but since allegedly causing addiction among an alarming number of users. The head of a leading mental health charity also told *Panorama* that the UK's medicines watchdog was not doing its job properly on drug regulation.

One hopeful discovery of late is that the melatonin made by plants can be transferred and used by animals and man as if it had been made in the brain, and that even very small quantities of the organic version at picogram levels are efficacious. This opens the door for organic versions at physiological rather than pharmacological levels which, suitably presented, may escape the rigours of restrictive MHRA regulation and make this wonder molecule more available to the public for its remarkable benefits to organic life in general and man in particular.

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Some basic definitions

1 Hertz (Hz) = one cycle per second. 1 kiloHertz (kHz) = 1000 Hz;
1 MegaHertz (MHz) = 1,000,000 Hz;
1 GigaHertz (GHz) = 1,000,000,000 Hz.
ELF (Extremely Low Frequency) refers to the region 1-300 Hz, in which falls the power frequency of 50/60 Hz (UK/USA).
Radiofrequency (RF) spans approximately 100 KHz to 300 MHz; microwave (MW) 300 MHz to about 30 GHz (radar usually 3-20 GHz).
Below 30 MHz electric and magnetic fields are measured in volts and amps per metre (V/m; A/m).
Magnetic flux density, to assess biological exposure, is measured in milli-, micro- or nanotesla (mT; µT; nT = 1,000th, millionth, one thousand millionth of a Tesla, respectively.)
1uT = 10 milligauss (mG), an older unit.
Above 30 MHz electric/magnetic fields can be measured but the more usual unit is power density, expressed in watts per square metre (W/m^2), milli- or micro-watts/square centimetre (mW; $\mu W/cm^2$).