

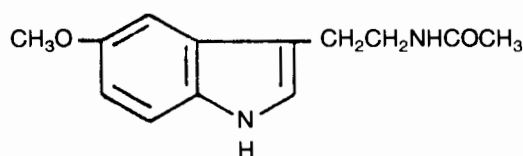
BIOLOGICAL RHYTHMS AND MEDICINE.

II. MELATONIN

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The Hormone Melatonin (M), which is synthesized in the pineal gland, receives now increasing attention because of its value for restoring disturbed circadian rhythms (e.g. jet lag), for its influence on the immune system and the growth of malignant tumors, for its ability to scavenge radicals and protect DNA, and for its importance for longevity and health in old age.



MELATONIN
(5-Methoxy-N-acetyltryptamine)

Synthesis of M starts with tryptophan, which is taken up by cells in the pineal body (pinealocytes) and converted to M via 5-hydroxytryptophan (enzyme: tryptophan hydroxylase), serotonin (aromatic amino acid decarboxylase), and n-acetylserotonin (n-acetyltransferase). The final step from n-acetylserotonin to M is mediated by the well-known enzyme hydroxyindole-O-methyltransferase (8). After synthesis, M is released into the blood. Due to its hydrophobicity, M can permeate biological membranes, and appears

in all tissues and bodily fluids at a similar concentration as found in the blood. Synthesis of M is dependent on the activity of sympathetic nerve fibers that come from the superior sympathetic ganglion and enter the pineal gland to innervate pinealocytes. Release of the transmitter noradrenaline (= norepinephrine) activates the second messenger system by producing cyclic AMP, which activates the enzymes involved in M synthesis (see above). Thus, it follows that application of beta-1 blockers interrupts M synthesis.

When the concentration of M in the blood is measured continuously over the 24 h period, it can be seen that M is mainly produced during night (2), with a peak (= acrophase) around 2 o'clock in the morning. This circadian rhythm of M production is controlled via a neuronal pathway that starts in the retina from where optic nerve fibers project to the suprachiasmatic nucleus (SCN) in the hypothalamus (see 4). From the SCN, the chain of neurons projects to the habenula in the diencephalon, and via further unknown stations in the brainstem (reticular formation) to the superior cervical ganglion, which sends fibers to the pineal body (10). Thus, the rhythmic activity/inactivity of SCN neurons (pacemaker) during day and night, respectively, controls the synthetic activity

in pinealocytes. Again, it follows that any lesion in this long pathway by tumors, strokes etc. disturbs M production. M synthesis during the night can be already partly suppressed by light influence from about 300 lux onwards (room light!), and is completely suppressed at 2500 lux and more. Even greater sensitivity to light has been reported in some individuals, especially those suffering from manic-depressive disease. It follows that nightly walks to the toilet should be undertaken with the help of very dim light, only. The findings also favour the idea of a very regular, rhythmic (and boring!) life-style for optimal health (see below).

M is produced in great amounts during childhood and might therefore have an antigonadotrophic effect. At puberty and during adulthood, levels are much lower and decrease even further in old age (9). These age-dependant changes affect only night levels of M; day levels are consistently low at all ages. M has also been shown to influence the rhythmic release of the hormones LH, cortisol, prolactin and thyroxin. Levels of all these hormones show circadian rhythmicity, and if these rhythms are disturbed, M administration can re-synchronize their rhythms (2,3). Moreover, M has been shown to be mildly hypnotic and to reduce body temperature directly or via its metabolites (see 3,5).

Among the first experimental applications of M was to test, whether it could relieve the symptoms of jet lag. The latter annoys tourists and scientists going to overseas conferences, as the rapid change of time-zones confuses the body-clock, where the continuing pacemaker function of the SCN makes most travellers feel tired and miserable during the new day time (low body temperature and blood pressure!) and alert during night time. The worst symptoms disappear after several days, but hormone levels, digestive functions etc. can be disrupted for much longer, until the rhythmic influence of retinal fibers ("Zeitgeber") adjusts neuronal activity in the SCN to the local day/night rhythm. Roger V. Short (in Armstrong et al. 1986) was the first to apply M on himself and on interested human "guinea pigs" (including myself) during transmeridian travel with excellent results. Each volunteer took one capsule containing 5 mg M at the new local bedtime for altogether 3 nights, which usually caused good sleep and full alertness during the following day. I had to travel from Australia to Europe, and from there to the east coast of the USA, then to the west coast, Hawaii and back to Australia, changing time zones 5 times

within 21 days. I took M every night and felt good during the whole trip, sleeping well at night and feeling well awake during the day while listening to many talks at several conferences. The same has been reported by many other volunteers in the meantime. Unfortunately, it does not look like M being marketed as a jet lag drug, as natural substances can apparently not be patented in the USA, and the pharmaceutical firms shy away from the enormous costs to satisfy the Food and Drug Administration (FDA). Ironically, M has no known toxicity, although as a substance influencing circadian rhythms of at least a number of bodily functions, its intake needs to be well timed. Although short-term application of M seems to be completely harmless, the question is, whether there are undesirable effects after long-term intake. This is important, as M could be of great therapeutical value for shift workers (doctors, nurses etc) and professional transmeridian travellers (pilots, flight attendants). One concern is the potential anti-gonadal effect of M, which however appears to come about only after prolonged release. This can happen naturally, e.g. during the long northern nights in winter (Kauppila, in 2). Also, an increased amplitude of M release may depress gonadal activity (Berga et al. in 2). However, it stands to reason that long-term application of M at physiological levels and with normal duration has no significant effect on reproductive functions at all. Nevertheless, further studies are needed with the help of courageous shift workers to fine-tune the appropriate dose. It should also be clear that constantly monitored volunteers would not experience an irreversible gonadal depression, as it is e.g. well known that people living in northern latitudes emerge from their long winter nights in an excellent reproductive mood in springtime.

Recent reports show that M has an extraordinarily high capacity as a scavenger of free radicals (e.g. superoxide anions and hydroxyl radicals). Antioxidative protection of organisms may even have been the primary function of M in phylogeny (for lit. see 5). It is now hypothesized that the circadian rhythmicity of M, which is destroyed during the day time due to exposure to radicals, but is preserved during the night, could have made this substance suitable as a Zeitgeber for bodily functions. M has been shown to protect DNA from damage by hydroxyl radical generating carcinogens. This protection is direct, as M binds to chromatin in all tissues (see 5).

There is also increasing evidence of M influencing the immune system (immunomodulation), with e.g.

specific binding of M on lymphocytes potentiating cyclic AMP production (see 5).

This fits with observations that the incidence of certain malignant tumors is increased after pinealectomy, whereas M administration decisively decreases the incidence of such tumors. It has also been shown that estrogen-receptor positive breast cancers are associated with low M levels. Also, the growth of cancer cells in vitro can be suppressed by M (see 2).

There is now an urgent need for clinical trials, as the importance of M for the therapy of malignant tumors has become more evident.

An interesting hypothesis has been put forward that light "pollution" of modern societies could be an important factor for the high incidence of malignancies (6). As we often use electric light until late at night, M production is reduced and shortened, which increases the risk of DNA damage and weakens the immune system.

The production of M in the pineal gland is further reduced in old age compared with adulthood. This goes in parallel with an increased incidence of malignancies (lack of DNA protection and lack of immunomodulation), as well as disturbances of circadian rhythms with sleep problems being the most prominent complaint. Recent research has shown that animals fed with M live longer than normal. Thus, restoring the M concentration in the blood back to adulthood levels is likely to improve the quality of life and longevity of older people.

Much further research is clearly needed on all the above mentioned aspects of M function. M concentrations can be easily assayed in the blood, and - even more conveniently - in the saliva (1,7). However, M concentrations often need to be monitored over the whole 24 h period, which requires a dedicated team

of scientists, who alternate "night duties" during the time of the experiment. The natural desire of researchers to sleep at night is therefore delaying progress in this important field.

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