# Edition Wissenschaft

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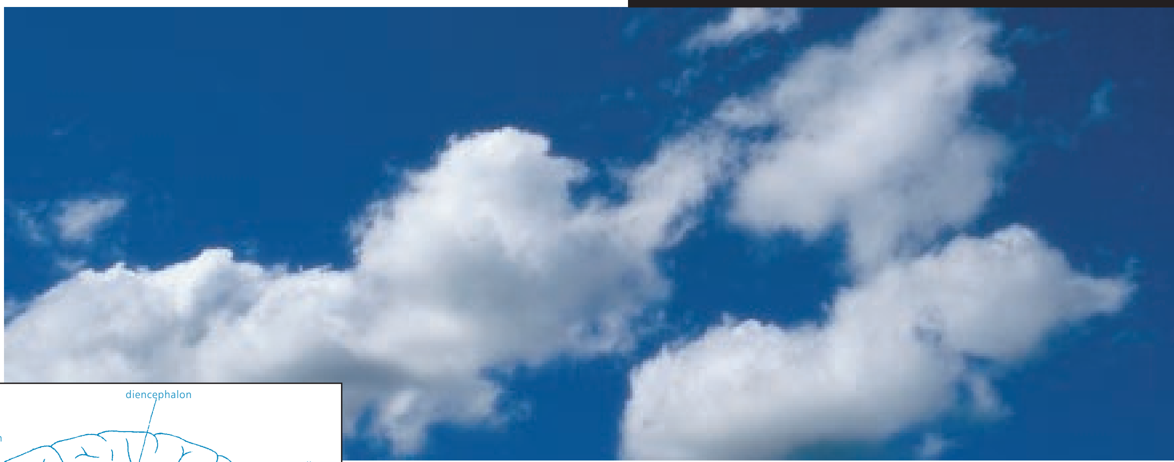

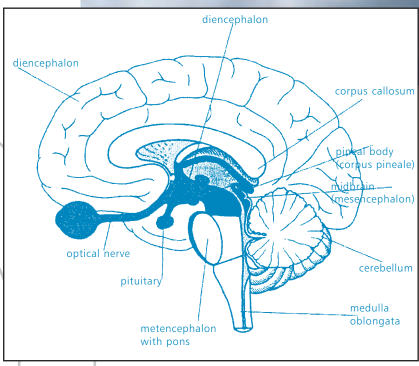


Prof. Dr. rer. nat. Alexander Lerchl

## The Melatonin Hypothesis – an Introduction

Forschungsgemeinschaft Funk

## Dear readers:

After a four-year break, in the second issue – running number 16 – of its publication series 'EDITION WISSENSCHAFT', the Forschungsgemeinschaft Funk e.V. addresses the melatonin hypothesis.

A short version of the following exposé has already been published in the NEWSLETTER #1, 2002.

In his introduction to the topic, the author, Prof. Dr. Alexander Lerchl, deals with the significance of melatonin at the endocrine and at the physiological level, under special consideration of effects caused by magnetic, electric, and electromagnetic fields. A comprehensive reference appendix is added to this article. Through this issue of EDITION WISSENSCHAFT, the FGF is convinced to provide a good overview of the current state of the scientific debate on the topic 'melatonin'.

Best regards,
**Gerd Friedrich**

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Prof. Dr.rer.nat. Alexander Lerchl

# The Melatonin Hypothesis: An Introduction.

## 1. Introduction

### 1.1. Preface

The pineal gland (*epiphysis cerebri*)[1] produces the hormone melatonin, generally dependent on the light-dark cycle of the environment (photoperiod). The main task of the pineal gland is to transform the physical parameters of daytime and season into an endocrine signal which can be interpreted as a 'time cue' by the organism. Thus a sensible coordination of daytime (diurnal) as well as seasonal physiological processes with the external world is ensured. As melatonin nearly exclusively is produced during the night it is often called 'hormone of darkness' [1].

The ecological background of seasonal adjustment, for example, is that the survival of offspring often would only be ensured, if they were born during a certain season (seasonal reproduction). In contrast, diurnal synchronisation is important for a whole range of physiological adjustment mechanisms (circulation, digestion, sleep, etc).

There are other processes potentially affected to a certain extent by the pineal gland and melatonin, respectively. It is speculated that the hormone slows down or even inhibits aging processes and cancer development. In the following paper a survey is presented on melatonin synthesis, the hormone's effects, and non-photoperiodic influence factors which may affect melatonin production. In particular, the potential effects of weak electric, magnetic, and electromagnetic fields will be addressed. Due to the ever-increasing single data available on the topic this overview does not claim to be exhaustive or complete. For example, the database MedLine® alone contains more than 16,000 original studies. On the other side, it is necessary to know about most aspects outlined in the following to better understand the current debate on the 'melatonin hypothesis' as a possible explanation of epidemiological data.

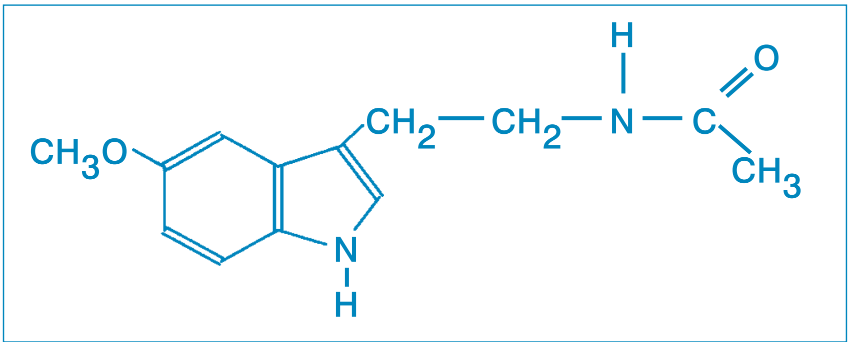



**Figure 1: Structural formula of melatonin (N-acetyl-5-methoxytryptamine)**

[1] The pineal gland of vertebrates (epiphysis cerebri) ontogenetically originates from a part of the brain (cerebrum; therefore cerebri) and is anatomically located above it (therefore epiphysis). Its shape - reminiscent of a pine cone – explains the term pinealis.

## 1.2. Historical overview

The special anatomy of the pineal gland has been subject of observations and speculation long before modern age. The Greek philosopher Herophilos of Alexandria is claimed to have done the first reliable anatomical map of the different brain regions as early as around 330 BC. For religious reasons, for a long time brain sectioning was banned. So Galen (131-205) was the first to provide an exact description of the pineal gland. For René Descartes the pineal gland was the 'seat of the rational soul' where soul and body are interlinked (fig. 2). We will not delve into the philosophical debate of that time ultimately being responsible for this view. However, it must have been important that the pineal gland is one of the few unpaired (and thus quite conspicuous) brain compartments.

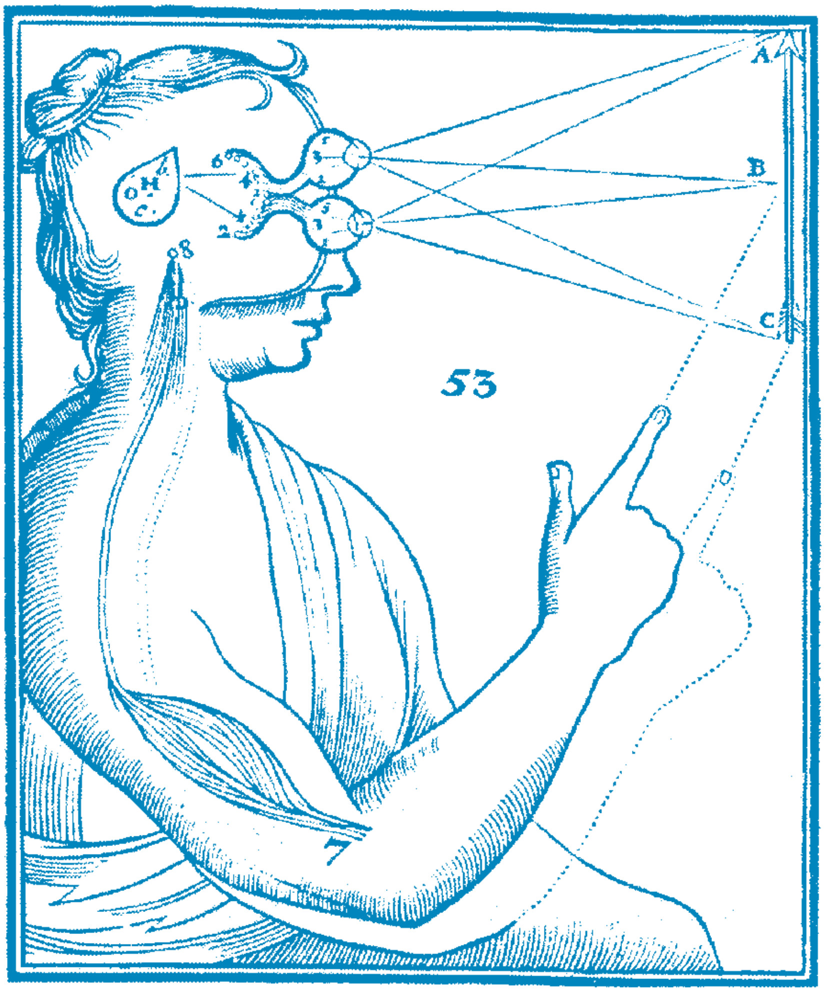



Figure 2: The pineal gland – as seen and depicted by René Descartes (1596-1650) – is the 'seat of the rational soul' thus connecting soul and body. This schematic shows the pine cone shape of the pineal gland as well as a link between the chiasma opticum (crossing of optical nerves) and the hormonal gland – an amazing anticipation of to-date knowledge.

A first big step towards elucidation of the pineal gland's functions was made in 1917 when McCord and Allen fed cattle pineal glands to tadpoles. Thereafter they observed a dramatic blanching of the animals due to a contraction of melanophores within the skin [2][2]. Althoug this study is also standing out because of its carefully made schematics and its brilliant writing, it did not receive due attention.
In 1954 modern pineal gland physiology only really began when Kitay and Altschule published a book called 'The Pineal Gland' presenting and discussing most studies (about 1,800) having dealt with the pineal gland since 1880. The pineal organ gradually was shown to possibly be involved in

- gonadal functions
- pigmentation and
- brain functions (behavior).

All three hypotheses are known to be more or less true for many animal species. But initially, clinical findings in children with pineal gland tumors led to the assumption that the disease could result either in delayed or precocious puberty (pubertas tarda / pubertas praecox). Though our perspective on this findings has changed, at that time plausible conclusions were drawn. Subsequent experimental findings in rats confirmed these theoretical findings (survey in [3]). Then, in the early fifties of the last century, Aaron B. Lerner became interested in the substance behind the effects of cattle pineal glands on tadpoles observed by McCord and Allen in 1917. From 1955, Lerner and

[2]It is pure coincidence that the adjacent article in the same magazine reports effects of rapidly changing magnetic fields on visual perception (magnetophosphenes).

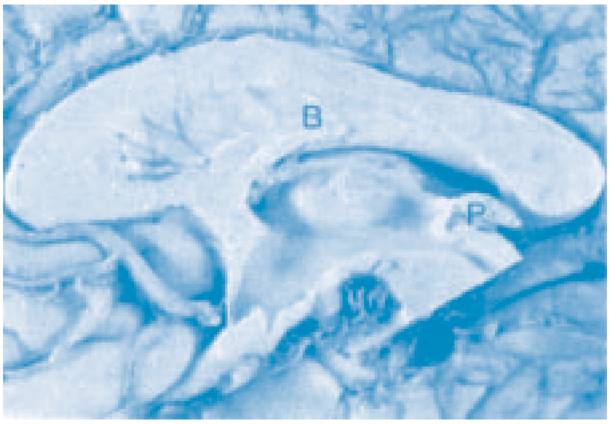



Figure 3: The human pineal gland (P) inside an anatomical preparation (see also the schematic on the title page).

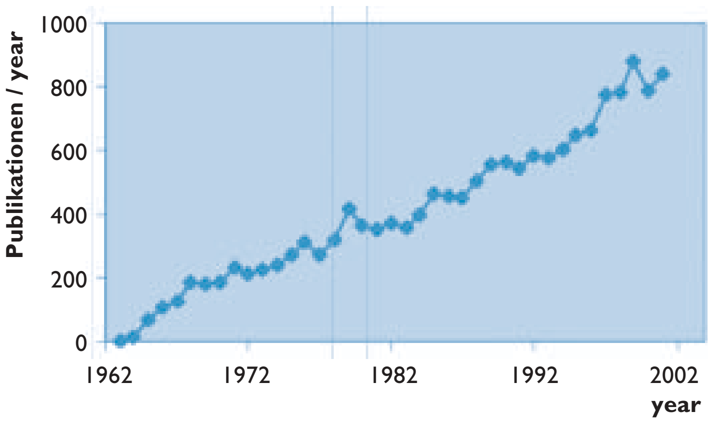



Figure 4: Increase in the number of publications on the terms 'melatonin' and/or 'pineal' from 1963 to 2001. Data taken from the database MedLine®.

Y. Takahashi first developed a so-called bioassay for melatonin determination based on a quantification of frog skin blanching. In 1956, J.D. Case joined the group.

In a huge effort, until 1957 about 250,000 cattle pineal organs were processed, however, without reaching breakthrough results though they pointed to an uncharged indol derivate. One week before the final deadline, Lerner suddenly had the idea that the searched-for substance would be a methoxyderivate of serotonin (the term 'melatonin' derives from its effects on melanophores and refers to the fact that it is a serotonin derivate). Within a very short time, melation was synthesised and its chemical structure was confirmed. Melatonin was shown to be up to 100,000-fold stronger in its impact on melanophores as adrenaline and acetylcholine (survey in [3]).

After elucidation of the enzymatic cascade leading to melatonin synthesis, in 1965 Hoffman and Reiter proved that the decrease of gonad weights in hamsters induced by short photoperiods (daily light duration) is blocked by the removal of the pineal organ [4]. However, prior to that Czyba et al. already demonstrated that there is an antagonism between seasonality and pineal function [5]. For unknown reasons – but probably related to the fact that Czyba's article was written in French – this paper is rarely referred to.

Finally, Wurtman and Axelrod presented two concepts which were an important impulse for pineal research. On the one side, the pineal organ would be a 'neuroendocrine transducer', that is an organ with neuronal input and an endocrine (hormonal) output. Secondly, melatonin should be seen as a hormone mediating photoperiod effects via the blood.

Since these pioneering papers, very much knowledge has been gained about the effects of melatonin as a hormone which will be dealt with in this survey. An unexpected development began in the eighties and in the early nineties of the last century when it was shown that

- melatonin is an 'old invention' of evolution
- melation not only occurs in animals, but also in plants and single-cell organisms
- melatonin is a potential scavenger of highly reactive and destructive oxygen radicals.

The increasing knowledge of this substance also is reflected by the growing number of publications on the topic (fig. 4).

## 1.3. Biochemistry of melatonin synthesis

The synthesis of melatonin takes place in the pinealocytes, the cellular units of the pineal gland. Generally, the synthesis of the hormone is controlled by external light inhibiting its formation. However, two basic differences within vertebrates are relevant: whereas the pineal organ itself is not light sensitive in mammals, in birds and especially in reptiles as well as amphibians there is a direct effect on melatonin synthesis caused by external light. In these animals we also can find photoreceptors similar to those of the retina [6]. As the unpaired pineal organ in reptiles sometimes is very well visible and only covered by a transparent skin layer, it is also called the 'third eye' [7].

Connected to this, there is another relevant difference: Whereas isolated pineal organs of mammals are not capable to produce melatonin by themselves, melatonin synthesis in isolated pineal organs of birds occurs without the help of external stimuli if the synthesis is not suppressed by light. Therefore, bird pineal organs can be held in culture over several days where they rhythmically produce melatonin under conditions of permanent darkness (free-running rhythms of about 24 hrs period length). In contrast, isolated pineal organs of mammals always need a pharmaceutical stimulus for melatonin production. For practical reasons, in the following we will concentrate on mammalian pineal organs.

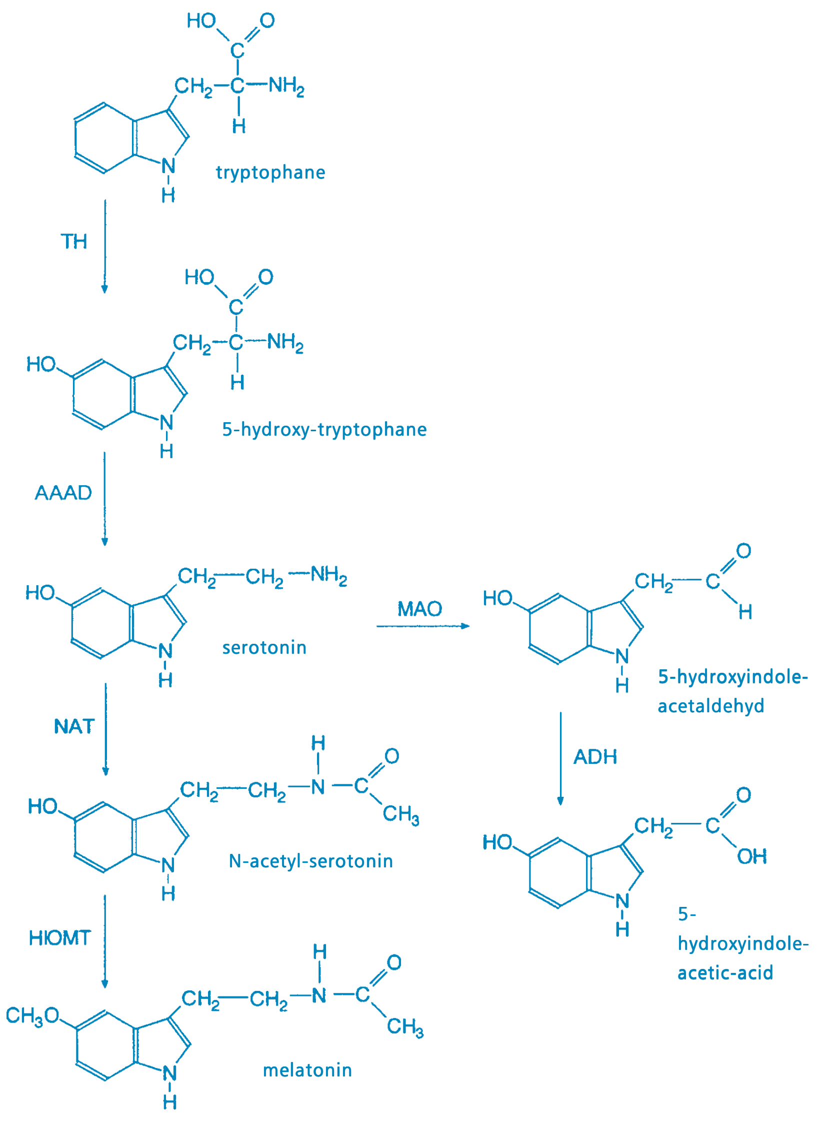



Figure 5: Biosynthesis of melatonin. Based on the active absorption of the amino-acid-tryptophane from the blood at first 5-hydroxy-tryptophane is formed through tryptophane-hydroxylase (TH). Subsequently, the transformation into 5-hydroxy-tryptamine (serotonin) takes place by the enzyme aromatic-amino-acid-decarboxylase (AAMD). The next step is the transformation of serotonin into N-acetylserotonin through N-acetyl-transferase (NAT) as the limitating step for melatonin synthesis. Finally, the synthesis of melatonin (N-acetyl-5-methoxy-tryiptamine) through the enzmye hydroxyindole-O-methyltransferase (HIOMT) takes place. Apart from this pathway, serotonin can be transformed by monoaminoxidase (MAO) into 5-hydroxyindole-acetaldehyd and further into 5-hydroxyindole-acedic-acid (5HIAA) by aldehyd-dehydrogenase.

## 1.4. Rhythms of the melatonin synthesis

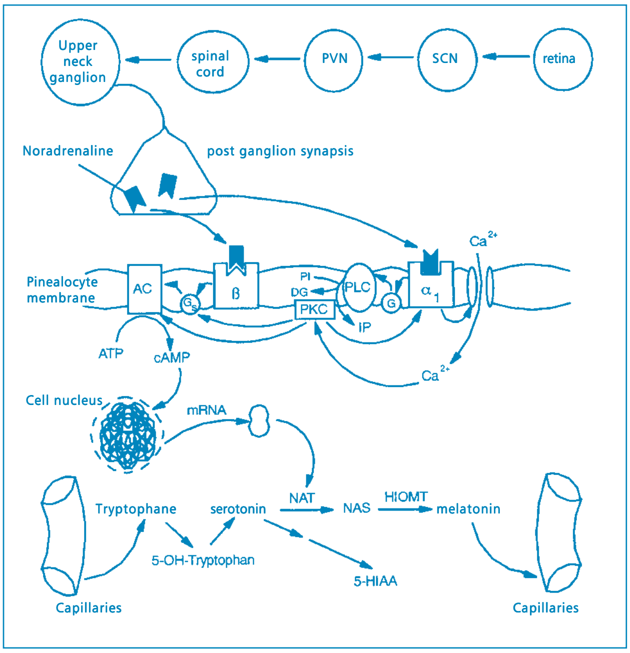
As already mentioned, melatonin synthesis is suppressed by light. Thus, there is a high level of melatonin synthesis during the night in contrast to scarcely measurable daytime values. These differences are responsible for the diurnal physiological parameters being controlled by melatonin.

However, as daily light duration is dependent on the season (except in equatorial regions), melatonin synthesis duration alters correspondingly (fig. 8). This general principle is crucial for the seasonally different physiological processes [9-15]. A dependency of melatonin synthesis on the season was also observed in humans [16].

On the other side, one must not assume that melatonin synthesis in the absence of light over longer time periods always occurs at peak values. Instead, there is a pronounced endogenous rhythm of melatonin development ('biological clock'). In fig. 9, this process is depicted.

## 1.5. Light during darkness

Under natural conditions, there scarcely will be a considerable light exposure during normal night (the only exception may be lightning). The reactions to artificial light pulses during the night result in a suppression of melatonin synthesis. However, light intensities required for this differ widely for the different animal species. So the mostly night-active rodents are most sensitive (about 1 lux [17; 18]), but sensitivity of day-active goats with about 3 lux



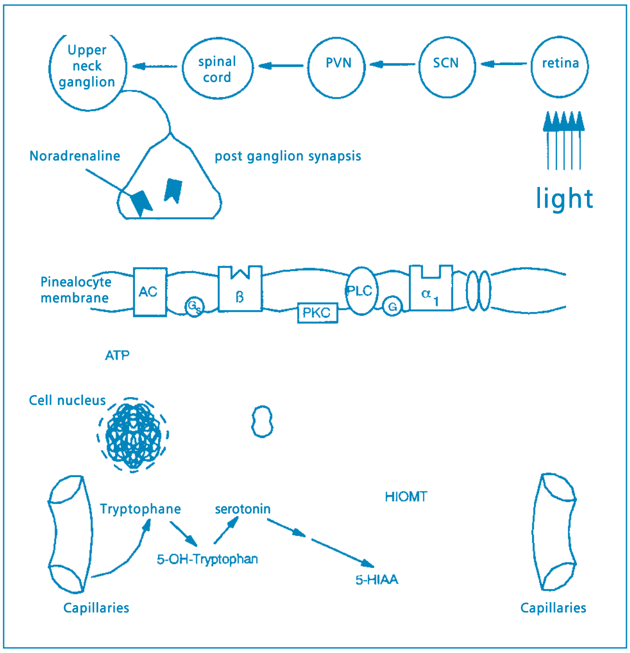




Figure 6 (left): Regulation of melatonin synthesis (schematic) in the pineal organ of mammals. Without irradiation of the retina by surrounding light (that is, under natural conditions during the night) there is a secretion of noradrenaline from the synapses of post ganglion nerves. Hereby, two types of adrenal receptors are activated. Activation of a-adrenergic receptors leads to an activation of stimulating G-proteins (Gs) which in turn activate adenylate cyclase (AC). Under the influence of this membrane-bound enzyme cyclic adenosine-monophosphate (cAMP) is formed – the classical 'second messenger' of cellular signal cascades. Hereby, the de-novo RNA synthesis for N-acetyltransferase is initiated; this enzyme is the limitating factor for melatonin synthesis. Another process mediated by noradrenaline is the stimulation of a-adrenal receptors. These receptors in turn, on the one side, open membrane-bound $Ca^{2+-}$ channels, while, on the other side, protein lipase C (PLC) is activated. This enzyme leads to the development of inositoltriphosphate in turn leading to a release of $Ca^{2+}$ from intracellular $Ca^{2+-}$ reservoirs. Further, activation of the a-adrenal receptors results in a synergistic effect on the ß-adrenal receptors via protein kinase C. For other abbreviations see fig. 5. Taken from [8].

Figure 7 (right): Under the influence of light no melatonin is synthesized in the pineal socytes since the development of the key enzyme N-acetyltransferase (NAT) is completely suppressed. Abbreviations like in fig. 5 and 6.

also is rather high. In humans, considerably higher light strenghts are necessary (depending on the individual study 200 to about 2000 lux; survey in [19]). Interestingly, in to-date examined animals moonlight was not sufficient to significantly affect melatonin synthesis [20; 21].

As an example of effects of nocturnal light exposure a study in humans is shown (fig. 10). Different light intensities lead to different degrees of melatonin synthesis suppression.

A peculiarity of nocturnal light exposure has been observed in Djungarian hamsters: when exposed to a 1-min light pulse during the night, the animals respond by a collapse of melatonin synthesis as already known from other studies. However, when they were exposed to the same light pulse and sacrificed in the following night (with no light), there was an almost identical curve: melatonin synthesis collapsed at the same time (fig. 11; [23]).

This result leads to the important insight that the melatonin-generating system obviously has a 'memory', a fact that is of relevance for further discussion since also magnetic fields can possibly have long-time effects.

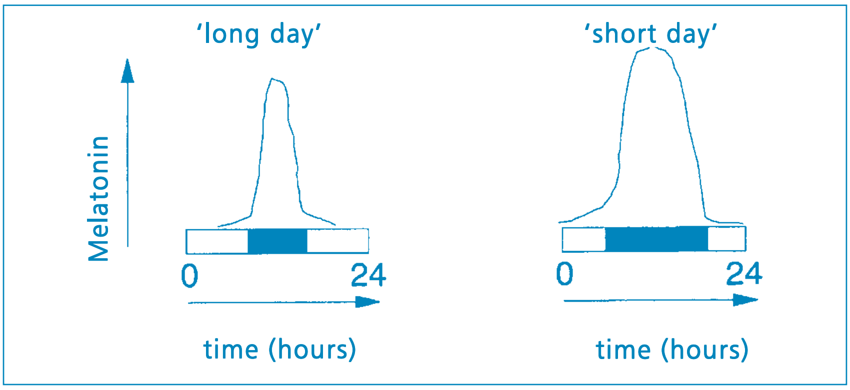



Figure 8: Dependency of melatonin synthesis duration on the daily light cycle (photoperiod). During long photoperiods (summer) there is a short nocturnal synthesis of the hormone, whereas melatonin synthesis during short photoperiods is clearly prolonged. Further, there is evidence that also melatonin synthesis amplitude is increased during short photoperiods. The black bars symbolise dark periods.

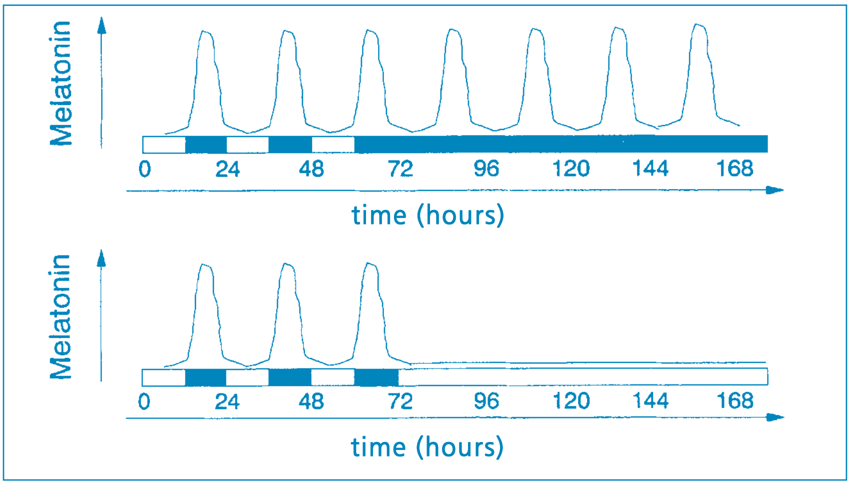



Figure 9: Under normal conditions melatonin synthesis is coupled with the 24-hs rhythm of environmental light (in the shown example for the first 72 hours). Whereas the melatonin synthesis pattern during the subsequent 'permanent dark' (upper part of image) continues to be observed – with a period length of about 24 hrs –, permanent light (bottom part of image) strongly suppresses its synthesis.

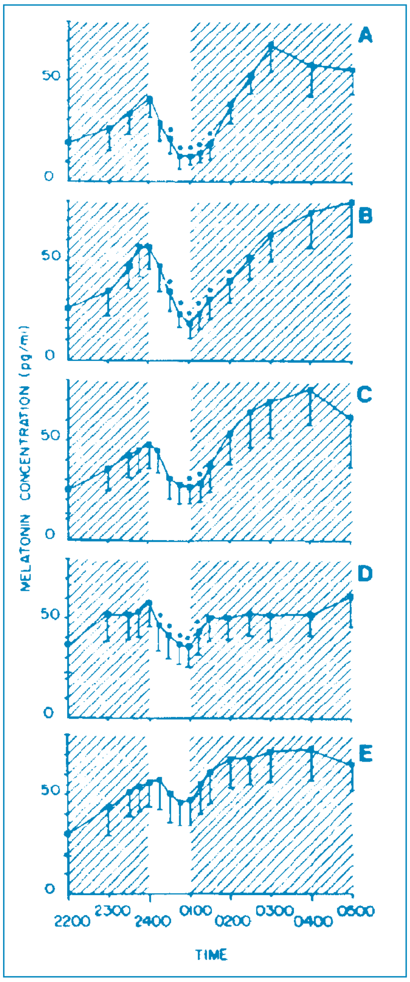



Figure 10: Suppression of melatonin synthesis in humans caused by different light intensities during the night. The clear areas show the time when light sources were switched on. Individual tests were separated by 2 weeks each. A: 3000 lux; B: 1000 lux; C: 500 lux; D: 350 lux; E: 200 lux. Already at 350 lux there is a significant decrease of melatonin development. According to [22].

## 2. Endocrine significance of melatonin

As already depicted above, melatonin as the 'hormone of darkness' is the endocrine correlate of photoperiod. This signal is used by many animals to adjust physiological and other endocrine systems to daytime and/or season. The necessity for seasonal synchronization particularly makes sense with respect to the survival of young animals in temperate and extreme climatic regions. Here, it is indispensable that the offspring are born during a season offering optimal survival chances. Mostly, this is about the availability of food. Consequently, the most favorable seasons for birth and upbringing are spring or early summer.

A consequence of the fact that different animal species have different gestation lengths (a few weeks to about a year) is the crucial importance of the time of mating. Interpretation of the photoperiod and/or the melatonin signal leads to a synchronisation of reproduction and the 'right' season.

It is easily explained why photoperiod often is preferred over other 'time cues' (for example temperature variations, light strength or precipitation). Compared to all other climatic variations photoperiod variations are highly precise (and thus reliable) and, apart from that, have remained unchanged over millions of years.

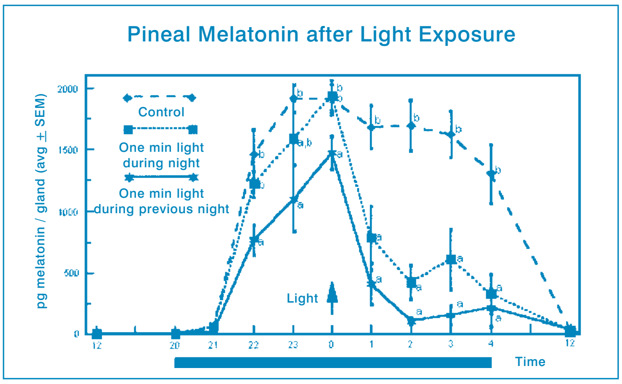



Figure 11: Effects of 1-min light exposure on melatonin synthesis in Djungarian hamsters. Whereas the control group shows the normal course of nocturnal increase, hamsters having been exposed to the light pulse respond by a collapse of the synthesis of the hormone. The third group, having been exposed to the same light pulse the night before, showed an even stronger reaction than acutely exposed animals. This result allows us to conclude that the melatonin-generating system has a certain memory function. Taken from [23].

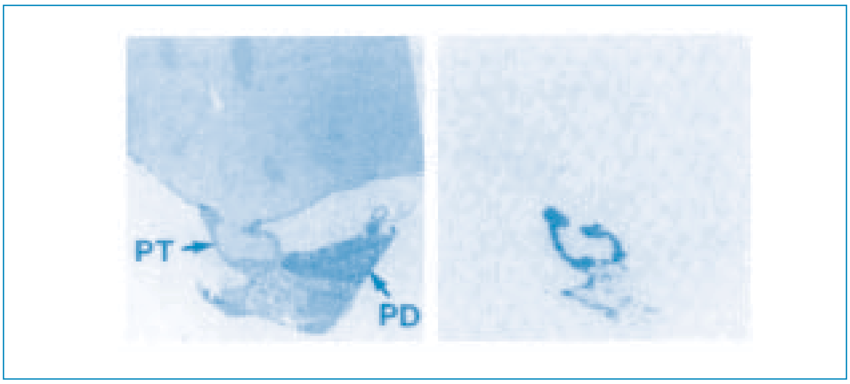



Figure 12: Specific and highly concentrated binding sites for melatonin in the pars tuberalis (PT) of the pituitary (sheep). The left panel of the schematic shows a histological staining, whereas the right panel shows the autoradiography of the same region (to this end two adjacent section preparations were used; for the autoradiography, the section was incubated with radioactively marked melatonin resulting in an accumulation at existing binding sites). It is easy to see that the pars tuberalis is clearly marked, while the rest of the regions show only weak binding. PD = pars distalis. Taken from [23].

## 2.1. Pro- and antigonadotrophic effects

When looking at photoperiodic effects we must distinguish two types of seasonal reproduction: in one case, animals react to a shortening of the photoperiod by increased readiness for mating (so-called 'short-day breeder'), whereas in the other case a lengthening leads to the same effect ('long-day breeder'). Nonetheless, these diametral effects both are caused by melatonin synthesis alterations.

Known examples of 'long-day breeders' are different hamster species, hares, hedgehogs, as well as some mice species. Typical 'short-day breeders' are: sheep, foxes, some primates and deer species. For many other species however, either none or only weak seasonal fluctuations of reproduction are known, f.e. for cats, pigs, guinea pigs, and some laboratory rodents. A survey is found in [24].

It is proven that humans have seasonal reproduction cycles, too, even though these are relatively indistinct (about 10-20% around annual average) compared to the often drastic differences in animals. In a large-scale global study, Roenneberg and Aschoff could show that such trends exist, depending on the latitude, and that often a secular phase shift of these rhythms is observed [25]. Some papers describe a corresponding phase shift for Germany [26].

But what is behind these seasonal variations and whether they can be explained by different melatonin profiles, remains unclear. However, it has been suggested that phase shifts are evidence for formerly biological rhythms which have been superseded by a social component. We must bear in mind that different melatonin profiles also in humans are a function of season [16].

## 2.2. Melatonin and human puberty

The precise mechanisms controlling the onset of puberty are not fully known yet. The maturing of ovaries and/or testes is triggered by the secretion of the hormones FSH (follicle stimulating hormone) and/or LH (luteinising hormone) from the pituitary. In turn, this pituitary function is dependent on GnRH (gonadotropin releasing hormone secretion from the hypothalamus, a central control unit of the brain. But, ultimately, we do not know what triggers the function of the hypothalamus with regard to puberty. A possible candidate is melatonin, since there is a strong decline of nocturnal concentrations of the hormone particularly before and during puberty. Thus it is hypothesized that high-level melatonin inhibits hypothalamus function in humans.

Evidence for this assumption is that very low melatonin values are found in children with precocious puberty (pubertas praecox), very high values, however, in children with delayed puberty (pubertas tarda). But there is controversial discussion about its general significance for puberty onset in normal children [27-35].

## 2.3. Melatonin and hormone levels in adults

There is some evidence for melatonin affecting synthesis or functions of other hormones in humans. To these belong

- steroids (e.g., estrogens, testosterone, progesterone)
- prolactin
- gonadotropines (LH and FSH)
- growth hormone (GH)

(according to different authors [36-54]). In particular, there seems to exist a phase relation between melatonin and the synthesis of prolactin and growth hormone. For the time being, we still cannot say to what extent this relation is endocrinologically relevant.

It has been repeatedly discussed to use melatonin as an oral contraceptive in combination with gestagenes ('pill') [55-58]. But due to melatonin's side effects (especially sleep induction, etc) this possibility now is seen rather skeptically.

[3] Normally, for low-frequency experiments so-called Helmholtz coils are used producing sufficiently homogenous magnetic fields.

# 3. Physiological significance of melatonin

## 3.1. Temperature regulation

The role melatonin plays in thermoregulation is known for quite some time [59-62]. Seasonal physiological adjustment to the food supply is mostly assumed to be mediated via seasonal variations of melatonin synthesis. Part of this process is the descrease of the own energy turnover to anticipate shortage of nutritional energy.

Here, a special role is played by the brown adipose tissue which in some rodent species appears to have one task only: to support heat production. Normally, fat serves as an energy depot which, if necessary, is supplied to digestion like regular nutrition. Brown adipose tissue, however, directly produces heat through certain biochemical peculiarities; the blood flowing through is heated like in a continuous-flow water-heater. Melatonin has a stimulating effect on this brown adipose tissue [63-66; 59; 60; 67-69]. The main advantage of this type of heat generation is the direct transformation of stored metabolism energy into heat ('non-shivering thermogenesis'). In contrast, heat gain through shivering ('shivering thermogenesis') is an indirect and thus energy-wasting type of heat production.

With the exception of infants, brown adipose tissue in humans plays a subordinate role. In spite of that, melatonin has a distinct effect on body temperature. This is true for both the natural conditions under which melatonin is inversely correlated with the temperature course, as well as for exogenously administered melatonin: here, a significant and reproducible decrease of body temperature is achieved [70-74].

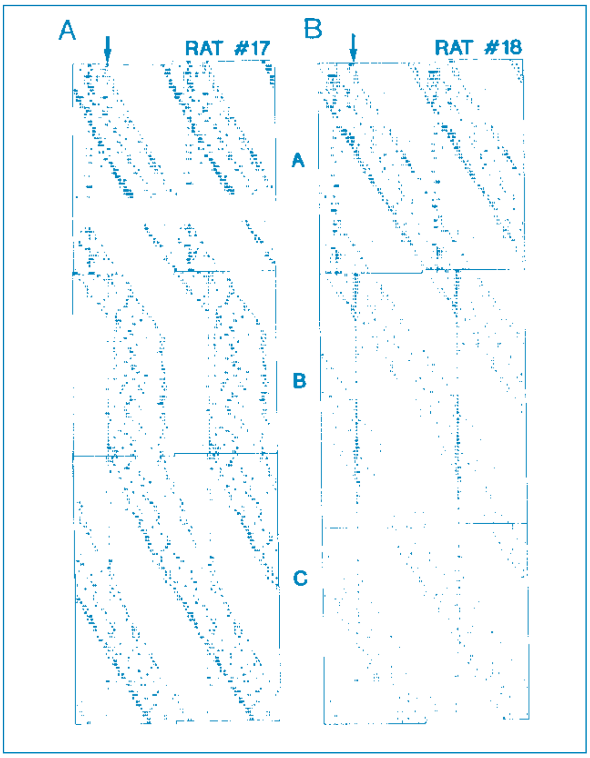



Figure 13: Synchronisation of free-running activity of rats by melatonin. Over the time period A (60 days) there was no treatment, whereas the animal #17 in section B8 over several weeks received daily melatonin injections at the same time; the animal #18 served as a placebo-treated control. Section C shows again free-running rhythms after finishing injections. Taken from [81].

## 3.2. Diurnal and circadian rhythms

'Diurnal' rhythms are cyclic alterations showing 24-hr period length at a stable periodicity of the "zeitgeber" (time cue), that is, for example, the sleep-wake rhythm during the normal 24-hr day. We speak of 'circadian' rhythms if there is no detectable zeitgeber, that is, for example, under constant conditions. Then 'free-running' rhythms develop showing approximate (therefore circa) 24-hr period length. Very famous are the experiments of Aschoff and Wever where volunteers spent longer time periods in bunkers shielded from all external time cues (for reviews see [75; 76]. Under such test conditions, most people develop circadian rhythms of about 25 hours; here, not only activity rhythms but also those of body temperature and of melatonin secretion show a circadian rhythm [77]. These experiments have considerably extended our understanding of the structure of endogenous rhythms in humans showing that they have to be synchronised with external conditions.

The strong involvement of melatonin in the development of diurnal rhythms is made particularly clear by the example of blind people. If blindness is complete, that is, if even the light-dark rhythm cannot be detected, these people develop a free-running rhythm seriously interfering with their well-being, since their own rhythm in regular intervals is phase shifted to external conditions. In practice, this means that these people often suffer from sleep disorders and/or often are extremely overtired when they should be fully awake. Long-term examinations have proven that also melatonin rhythms of such persons are free-running thus potentially being the cause of the disorders.

Background of this assumption are tests having demonstrated that melatonin is capable to resynchronise free-running rhythms of rats (fig. 13; [78-80]). This finding is explained by the theory that melatonin may affect the rhythm of its own synthesis: as shown in fig. 6, the synthesis of the hormone normally is controlled by external light. Without such a time cue, circadian rhythms evolve (fig. 9). The spontaneous rhythms are caused by the activity of the nucleus suprachiasmaticus (SCN), an accumulation of certain nerve cells and the seat of the biological clock (fig. 6). These nerve cells have specific binding sites for melatonin (fig. 14) and thus can be affected by melatonin in their rhythm.

## 3.3. Jet lag

Travellers who have flown across several time zones know the difficulties of adjusting to the new local time. Frequent symptoms summed up by the term ‘jet lag’ are sleep disorders, digestive troubles, headaches, lack of appetite and fatigue. After several days in the new time zone as a rule these symptoms disappear. Another thing is the situation of people who fly regularly, often staying on another continent only for a few days followed by a new change of time zones. Here, jet lag is much more serious, since also the capacity for work is impaired.

In the meantime, carefully controlled studies have shown that exogenous melatonin is capable to significantly reduce the effects of jet lag (fig. 15) [83; 84; 73; 85-90]. The hypothesis

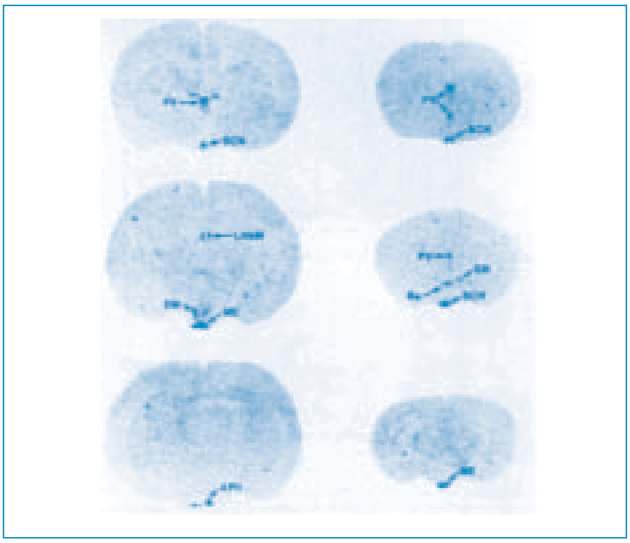


Figure 14: Binding sites (black areas) for melatonin in the Syrian (Golden) Hamster (left) and in the Djungarian hamster (right). Crucial for synchronisation of diurnal rhythms with the photoperiodi is the nucleus suprachiasmaticus (SCN). Taken from [82].

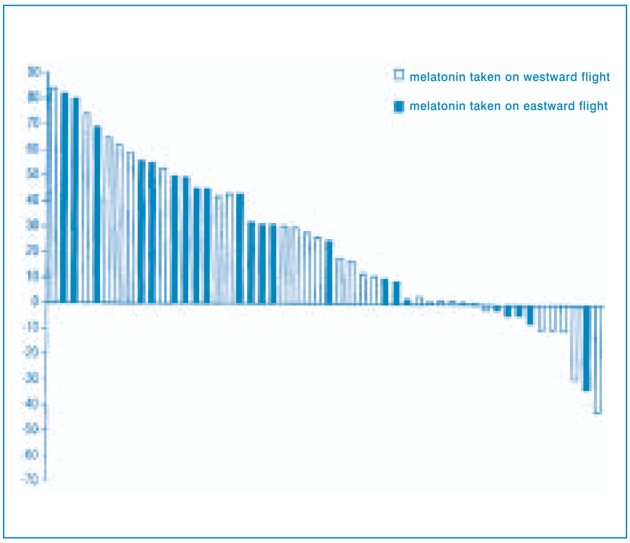



Figure 15: Subjectively perceived improvements (positive values) and/ or worsening (negative values) of jet lag by taking melatonin during a double-blind experiment. Passengers either flew from the USA to Australia (eastwards) or the reverse route westwards. In both cases, the improvements caused by melatonin are highly significant. Taken from [81].

is that by taking melatonin the biological clock in the nucleus suprachiasmaticus is 'reset' and thus more quickly adjusted to the new 'right' time [91].

## 3.4. Melatonin as an oncostatic agent

It is well known that the pineal organ in vivo may have an inhibitory effect on the growth of malignant tumors, that is, an oncostatic effect (surveys in [92; 939]). Apart from the often examined breast cancer and the melanoma, this concerns a number of other cancer types, among others colon cancer [94], lung cancer [93], and leukemia [95]. For a long time, the cause behind these findings has been unknown. However, now it is assumed that melatonin characteristics as a potential scavenger of free radicals are of crucial significance (see below). But also peptides from the pineal organ are discussed as a cause [95].

These effects not only occur *in vivo* but also when cancer cells are treated with melatonin *in vitro* (fig. 16; [97]). Effects on tumor growth with up to 80% growth inhibition are very pronounced.

Interestingly, melatonin here is often found to have effects only within a concentration window of about the same order of magnitude as the concentration of the hormone in the blood during the night (about 5 x $10^{-10}$ M). Further, there is evidence for a continuous presence of melatonin being less effective than one imitating physiological variations [98].

The field of oncostatic effects of the pineal hormone is one of the currently most interesting areas of melatonin research and is promoted correspondingly. In this context, we should mention that already quite a number of melatonin analogues have been developed to intensify melatonin effects [99]. However, for the time being we do not know to which extent the hormone can be of help in the struggle against malignant diseases.

## 3.5. Melatonin as a scavenger of radicals

The insight that melatonin is a natural and potent scavenger of oxygen-derived radicals came as a surprise [100; 101]. Radicals are highly reactive molecules due to unpaired electrons, and they easily bind to other molecules. This may result in genetic alterations in turn leading to malignant tissue growth. Fig. 17 shows the formation of the particularly damaging hydroxyl-radical (HO·).

Melatonin is capable to neutralize these radicals. The concentrations of the hormone required for this are substantially smaller than those of known antioxidants like f.e. glutathione. Apart from artificial administration of relatively high doses of melatonin, it could be

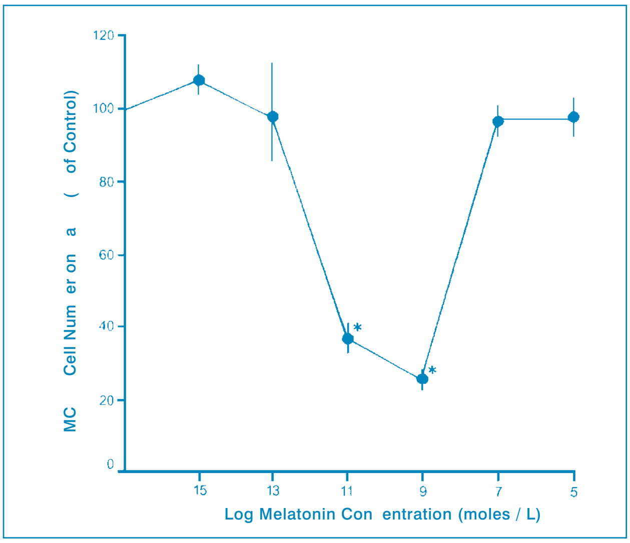



Figure 16: Growth inhibition of MCF7 cells affected by melatonin. This cell type is a model often used for lung cancer research. Taken from [97].

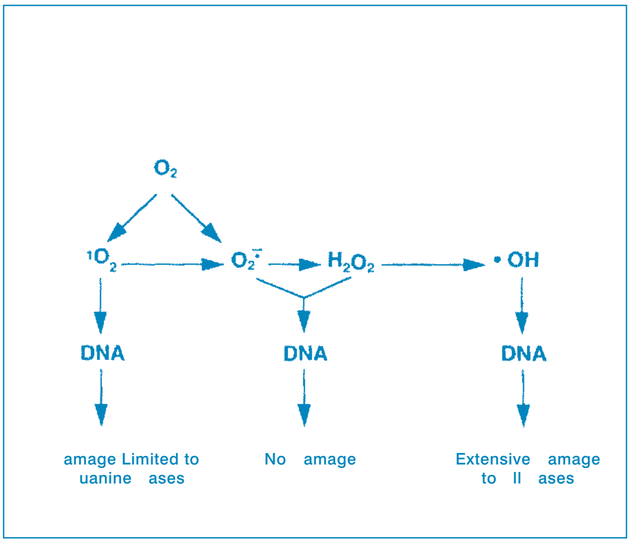



Figure 17: Formation of the especially aggressive hydroxyl-radical (HO·) from oxygen. These molecules are extremely reactive thus possibly causing particular damages to the DNA. Taken from [102].

shown that also physiological concentrations of melatonin are capable to considerably diminish the harmful effects of certain HO·-forming substances [103-106; 101]. It is of substantial relevance for the antioxidative effects of melatonin that the hormone as an extremely lipophile substance easily passes the blood brain barrier and accumulates in nerve cells. All this considered, melatonin is assumed to be of relevance for protecting the nervous system [102].

Surprising at first, too, was the finding that melatonin not only is produced in the pineal organ of vertebrates, but obviously is an 'old invention' of evolution. Melatonin and connected enzymes were found among others in the retina [107], in the intestines [108], in insect heads and hemolymphs [109], in insect eyes [110], and even in plants [111; 112].

Of particular interest is that melatonin also is produced in single-cell organisms as first has been reported in 1991 [113]. However, in the examined dinoflagellates *gonyaulax polyedra* not only melatonin was found, but also a distinct day course with high values during the night was identified. From these findings it has been concluded that melatonin possibly was 'invented' at a very early stage of evolution. Here, possibly the antioxidative characteristics of the molecule were a crucial selective advantage.

[3] Generally so-called Helmholtz coils are used in low-frequency experiments to produce satisfactorily homogenous magnetic fields.

# 4. Effects of fields on the pineal gland

## 4.1. Magnetic fields

The first report on effects of weak magnetic fields was presented by Semm and colleagues [114]. Neurophysiological tests in pineal glands of guinea pigs had shown that activity (fire rate) decreased when an artificial static magnetic field was switched on. The applied flux density had the size of the geomagnetic field (about 35 $\mu$T). It was hypothesised that this impact could be part of the biological compass whose existence is well-confirmed. However, evidence for the biophysical explanation is lacking. As the pineal organ is important for the temporal organization of an organism – so the hypothesis went on –, effects of magnetic fields could point to a spatial/temporal orientation.

Unfortunately, exposure conditions of this test, like those of many others, were badly characterized and/or insufficiently described. In particular, none of the studies mentioned to which extent induction effects were prevented. In this context, one must bear in mind that air-coils[3] in part show high induction values and that these inductions can lead to unwarranted effects. So, an uncontrolled switching-off of a coil as a rule leads to rapid alterations of the magnetic field only being prevented by a diode free-wheeling. Insofar, we cannot exclude that not the magnetic field as such but induction currents caused by fast magnetic field alterations were responsible for the observed effects.

But let us return to the follow-up tests:

Stimulated by the study of Semm, many experiments were performed dealing with the effects of weak magnetic fields on the function of the pineal organ, particularly in view of melatonin synthesis [115-129]. To the main part, decreases of melatonin synthesis and diminished activity of N-acetyltransferase were found. Noticeable single results are that field effects obviously take place at the level of the cell membrane (suppression of cAMP values; [126]), and that melatonin suppression caused by magnetic fields seemingly is coupled to the existence [121] and/or a certain illumination of the retina [123].

A study of Khoory [130] showed that local compensation of the geomagnetic fields has no effect on melatonin synthesis at all. This finding is of crucial importance since an existing biological 'pineal compass system' should also register such an alteration and should react correspondingly meaning that not the magnetic field as such but its temporal variations are responsible for the published findings.

This suspicion was confirmed by own studies during which mice and rats were exposed to rapidly changing magnetic fields [131; 132]. Only rapid changes led to a decrease of melatonin synthesis, whereas slow alterations showed no effect at all. Surveys on this topic are found in [133-136].

More recent own studies have dealt with the possibility that magnetic fields have a direct effect on melatonin synthesis in isolated pineal organs. To this end, pineal organs of Djungarian hamsters were brought into special chambers perfused with buffer solution (fig. 18).

To-date results give evidence for weak magnetic fields ($16^{2/3}$ and/or 50 Hz, 86 $\mu$T) having an inhibitory effect on melatonin synthesis [137]. However, it became clear that significant results were obtained only when single results were combined (4 experiments each per frequency). This result is relevant for the still discussed general significance of variances between experiments.

Another test series dealt with the question to which extent a longer-duration exposure to magnetic fields (50 Hz) leads to an alteration of the development of Djungarian hamsters not being fully grown at the time of test start. As a control parameter body weight was used, whereas at the end of exposure cell composition in the testes was analysed by flow cytometric methods and melatonin values were detected. It was shown that despite a relatively high flux density (450 $\mu$T) exposure to a *sinusoidal* magnetic field practically had no effect at all. Quite a different situation evolved at exposure to *rectangular fields* of the same frequency and comparable flux density: Here, a significant slowing of body weight gain as well as distinct stimulation effects on testis cells were observed. In both experiments, melatonin values in the pineal organs remained unaltered, whereas melatonin concentrations in the serum at rectangular exposure significantly increased [138]. This surprising finding might be seen as evidence for the hamsters responding to a longer-duration exposure by an increase of melatonin synthesis (in the sense of a compensatory reaction).

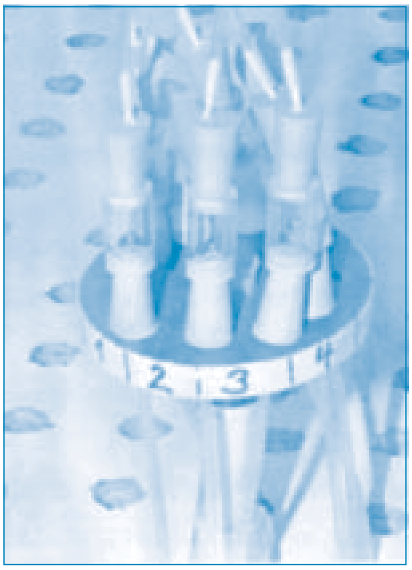



**Figure 18: Test chambers designed for direct exposure of pineal organs to weak magnetic fields. In each chamber pineal organs of adult Djungarian hamsters were perifused with buffer solution. Subsequently, in the eluate melatonin was determined. For melatonin production it is necessary to pharmaceutically stimulate the organs. Taken from [137].**

Results concerning the effects of low-frequency magnetic fields are very heterogeneous: the studies on magnetic fields (mostly 60 Hz) at the working place ('occupational exposure') showed both decreased melatonin values [139-142] as well as no effects at all [143]. Tests of Pflüger [144] demonstrated that the release of 6-hydroxy-melatonin-sulfate in drivers of electric locomotives were significantly reduced. Of great interest for the American scientific community were studies on possible effects on melatonin of electric blankets. The main part of the studies performed on this issue showed negative effects [145; 146]. Neither a recently published study in many participants on possible effects of residential exposure presented evidence for a decrease of melatonin synthesis [147].

Likewise, tests under defined laboratory conditions in the low-frequency range did not result in painting a clear picture, as both decreased as well as unaltered melatonin values were found [148-158].

## 4.2. Electric fields

For some time now, possible effects on pineal organs caused by electric fields are the subject of scientific studies, too [159-162; 135; 163-171]. Like as for possible effects of magnetic field exposure, there is a lack of plausible explanations of observed effects for electric fields, too. But at least we know that many organisms have a quite high sensititivity towards electric fields in the magnitude of about $10^{-7}$ V/m, above all serving as a means of localisation of other living organisms (search for mates or prey). Insofar, biological effects of far bigger fields strengths principally do not surprise, though this, of course, is not sufficient as a basis for risk assessment.

## 4.3. Electromagnetic fields

To date, relatively few published studies on effects of electromagnetic fields[4] on melatonin synthesis are available. This is mainly due to technical reasons, since defined and controlled exposure to high-frequency fields requires considerable effort both in view of the equipment used and, above all, theoretical electrical engineering. Field distributions and absorbed energy values only can be determined by sophisticated calculations almost excluding autonomous work on the topic done by an individual laboratory. Here, interdisciplinary cooperation is indispensable. In any case, to-date pulished studies have not given evidence for melatonin synthesis suppression [172-175].

However, in view of widespread fears in general population on the one side, and of available epidemiological data on the other, (f.e. [176]), thorough studies on this topic are urgently required.

[4] Electromagnetic fields are high-frequency fields where the magnetic and the electric component cannot be separated from each other (about > 30 kHz).

## 5. The Melatonin hypothesis

The term ‘melatonin hypothesis’ derives from a study of Stevens [177]. There he assumes that weak magnetic fields at first lead to a decrease of melatonin synthesis which in turn results in an increased production of estrogens in the ovaries and/or of prolactin in the pituitary. This again causes an increased cell division rate of certain cells in breast tissue and to altered responses of these cells to carcinogens. Ultimately, these processes lead to an increased risk of breast cancer (survey in [178]).

In the meantime, this theory has been refined and revised, respectively. It was shown that not only estrogen-dependent tumors are affected by magnetic fields (surveys in [179; 180; 178; 181; 165; 182; 183]). A book on the topic published in 1997 presents an in-depth analysis of this issue [184]. Other surveys are found in [185; 186]).

## 5.1. Epidemiological data

A number of studies dealt with possible health effects of articifial fields (f.e. [187-190; 177; 191; 182; 183; 176; 192; 136]). Mostly, low-frequency fields (50 or 60 Hz) were examined. A good overview of Erren sums up to date available data on breast cancer risk concluding that there is an overall significantly, albeit slightly increased risk both for women and for men [193].

A long-standing difficulty of retrospective epidemiological studies is the fact that determination of field exposure can be done only indirectly, f.e. by means of comparable measurements, examination of cable arrangements in households or in the environment (‘wiring code’), or by affiliation to a certain occupational group. Further, sociologically (f.e. income, housing) and medically relevant factors (f.e. smoking, alcohol consumption) often are coupled to exposure (‘confounding factors’) and are difficult to separate from each other. Therefore, prospective studies could be of use measuring acute exposure values. Appropriate devices, at least allowing to draw conclusions on actual exposure in the low-frequency range, already are on the market. However, for drawing conclusions on potential health dangers case numbers are too small.

## 5.2. Melatonin as an explanation?

The melatonin hypothesis can be tested in experiments. In the past years, the working group around Löscher dealt with the question whether magnetic fields (50 Hz, 1-100 $\mu$T) lead to an increased incidence and/or faster spreading of DMBA (7,12-dimethylbenz(a)-anthracene)-induced breast cancer in rats [194; 180; 195; 178; 196-198]. In this model, female rats were treated with a temporally distributed dose of DMBA inducing tumors in mammary gland tissue in about 50% of the animals. In addition, the animals were exposed or sham-exposed to the field. During exposure, palpation of the animals was done; after 3 months they were sacrificed. An exact pathological examination of the animals followed. As the animals were sacrificed during the night, melatonin could be detected in the pineal organs and in the serum.

To-date results show a flux density dependent suppression of melatonin synthesis as well as a linear relation between flux density and increased tumor incidence [199]. These findings are seen as initial concrete evidence for a possibly increased incidence of induced breast cancer in an adequate animal model caused by weak magnetic fields [195; 178; 200; 201]. These studies were repeated – at high costs – in the United States, however leading to different results [202]. One of the reasons for these discrepancies could be the differences between the examined animals themselves (different breeding lines), between their nutrition and between tumor initiation rates. Moreover, recent studies show that replication experiments on effects on melatonin generally lead to overall highly different results [137; 200; 203].

## 6. Summary and prospects

This short survey was aimed to show that the hormone melatonin is involved in a number of physiological functions and possibly may prevent damages caused by oxygen-derived radicals. On the other side, it was demonstrated that magnetic and/or electric fields can suppress melatonin synthesis. Finally, a whole range of epidemiological data points to the fact that exposure to magnetic, electric and electromagnetic fields may lead to health damages, though absolute effects still are under discussion.

The melatonin hypothesis may present a cause-effect relation between these three aspects. Though this theory to date is not proven, obviously it is sufficiently confirmed to serve as a basis for different research projects.

One of the biggest difficulties in this context is the to-date lacking biological explanation of weak field effects. For thermodynamical reasons, transmitted energy amounts are far too small to cause a significant alteration of the per se existing thermal noise. Therefore, increasingly non-linear systems are used as a basis for possible explanations [204-206].

Energies transmitted by mobile phones in part (up to 50 %, partially above) are absorbed by surrounding biological tissue. In particular, the head and the hand holding the device unintentionally act as absorbers. Transmitted energies can be sufficient to cause a measurable effect (heating) of the exposed tissue. However, this heating is slight and is hugely dependent on antenna type and direction as well as on the construction type of the mobile phone. But nowadays, devices are on the market which cause only slight radiation of the head.

Based upon the here depicted facts it is conceivable that the pineal organ which is located in the center of the brain may be impaired in its functioning by electromagnetic fields from mobile phones. This theoretical possibility could lead to new uncertainties in real and potential users. For this reason, it is necessary to do preventative research in order to discover or to exclude possible effects of high-frequency fields on melatonin synthesis. By doing this research, we could ensure that this relatively new and highly attractive technology may be used unimpaired by unfounded fears, or that the mobile phone industry early on may be warned against real dangers.

## Abstract

This article focuses on the effects of melatonin – a substance secreted by the pineal gland –, its physiological functions, its ability to act as a scavenger of oxygen-derived radicals, and in particular on the role this substance has in possible adverse effects of electric, magnetic and electromagnetic fields. Results of studies using epidemiological methods have shown that these anthropogenic fields do have potential adverse health effects, but effects on the general population still are discussed controversially.

The so-called melatonin hypothesis is meant to determine a cause-effect relation between these different aspects. Though it is not yet proven, it has been used as a rationale by numerous investigations.

One of the major difficulties in this context is the still prevailing lack of commonly accepted mechanisms through which weak fields may interact with biological systems since transmitted energy amounts in comparison with thermal noise obviously are too small for this. Therefore, non-linear mechanisms are discussed as a possible alternative explanation.

The energy released by mobile phones in part (approx. 50%) is absorbed by the surrounding tissue, especially in the head and in the hand of the user. These fields, unlike those emitted by base stations, may cause an increase of tissue temperature. However, increases of absolute temperature values largely depend on tissue type, antenna configuration, and on user habits. Nowadays, there are mobile phones designed to prevent such temperature increases.

In view of the aforementioned facts and results it seems possible that melatonin synthesis is affected by electromagnetic fields emitted by mobile phones. Therefore, further research into this issue is needed which may help to prove or to disprove this hypothesis. The results of such research should be useful both to users as well as to mobile phone manufacturers concerning existing doubts and fears towards electromagnetic field effects as well as safety regulations.

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# The Melatonin Hypothesis – An Introduction

This article focuses on the effects of melatonin, a substance secreted by the pineal gland, on physiological functions, its ability to scavenge oxygen-derived radicals, and especially on the involvement of this substance in possible adverse effects of electric, magnetic, and electromagnetic fields. By using epidemiological methods, it has been frequently reported that those anthropogenic fields may have adverse health effects, whereas the impact of those fields on the general population is still a matter of controversy.

The so-called melatonin hypothesis tries to put these different issues into context. Although this theory is not yet proven, numerous investigations used it as their rationale.

One of the major problems in this context is the still missing, commonly accepted mechanisms by which weak fields are able to interact with biological systems since the energy transmitted seems to be too low in comparison to the thermal noise. Non-linear mechanisms are therefore discussed as possible alternative explanations.

The energy released by mobile phones is partially (up to 50 %) absorbed by surrounding tissues, especially in the head and the hand of the user. These fields, unlike those from base stations, are able to cause increased tissue temperatures, whereas the absolute values of temperature increase depends largely on the type of tissue, the antenna configuration, and the habits of the user. Meanwhile, mobile phones are available which prevent this temperature increase by special designs.

Based on the aforementioned reasons it is possible that the synthesis of melatonin from the pineal gland, which is located in the brain, is affected by electromagnetic fields originating from mobile phones. Thus, research is needed to investigate this possibility to either prove or refute this hypothesis. The results of these experiments may serve as helpful arguments both for the users and for the mobile phone industry with respect to fears from electromagnetic fields, and safety regulations, respectively.

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