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Static and Extremely Low Frequency Electromagnetic Field Exposure: Reported Effects on the Circadian Production of Melatonin

Russel J. Reiter

Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284-7762

Abstract The circadian rhythm of melatonin production (high melatonin levels at night and low during the day) in the mammalian pineal gland is modified by visible portions of the electromagnetic spectrum, i.e., light, and reportedly by extremely low frequency (ELF) electromagnetic fields as well as by static magnetic field exposure. Both light and non-visible electromagnetic field exposure at night depress the conversion of serotonin (5HT) to melatonin within the pineal gland. Several reports over the last decade showed that the chronic exposure of rats to a 60 Hz electric field, over a range of field strengths, severely attenuated the nighttime rise in pineal melatonin production; however, more recent studies have not confirmed this initial observation. Sinusoidal magnetic field exposure also has been shown to interfere with the nocturnal melatonin forming ability of the pineal gland although the number of studies using these field exposures is small. On the other hand, static magnetic fields have been repeatedly shown to perturb the circadian melatonin rhythm. The field strengths in these studies were almost always in the geomagnetic range (0.2 to 0.7 Gauss or 20 to 70 μtesla) and most often the experimental animals were subjected either to a partial rotation or to a total inversion of the horizontal component of the geomagnetic field. These experiments showed that several parameters in the indole cascade in the pineal gland are modified by these field exposures; thus, pineal cyclic AMP levels, *N*-acetyltransferase (NAT) activity (the rate limiting enzyme in pineal melatonin production), hydroxyindole-O-methyltransferase (HIOMT) activity (the melatonin forming enzyme), and pineal and blood melatonin concentrations were depressed in various studies. Likewise, increases in pineal levels of 5HT and 5-hydroxyindole acetic acid (5HIAA) were also seen in these glands; these increases are consistent with a depressed melatonin synthesis. The mechanisms whereby non-visible electromagnetic fields influence the melatonin forming ability of the pineal gland remain unknown; however, the retinas in particular have been theorized to serve as magnetoreceptors with the altered melatonin cycle being a consequence of a disturbance in the neural biological clock, i.e., the suprachiasmatic nuclei (SCN) of the hypothalamus, which generates the circadian melatonin rhythm. The disturbances in pineal melatonin production induced by either light exposure or non-visible electromagnetic field exposure at night appear to be the same but whether the underlying mechanisms are similar remains unknown.

Key words: mammalian pineal gland, nocturnal suppression of melatonin, serotonin metabolism, light and pineal function, static magnetic field exposure, sinusoidal electric and magnetic field exposure

Melatonin, a ubiquitously acting hormone derived from the pineal gland, exhibits a marked circadian rhythm in the blood of mammals with high levels always being associated with the dark phase of the light:dark cycle [Reiter, 1991a]. Because of its almost exclusive production and secretion at night, melatonin has been designated the "chemical expression of darkness" [Reiter, 1991b]. The circadian production of melatonin is strictly synchronized by the prevailing light:dark environment and its presence in the blood provides an important time-of-day message to those organs that are incapable of responding directly to light. Likewise, since the duration of elevated melatonin is roughly proportional to the duration of the daily dark period and inasmuch as day length (and consequently night length) varies on a seasonal basis, the melatonin signal also provides important time-of-year information to many organs [Reiter, 1987].

The light:dark environment regulates pineal melatonin synthesis via the eyes in mammals. Visible electromagnetic radiation, i.e., light, striking the retinas activates a series of neurons that project from the eyes to the suprachias-

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matic nuclei (SCN) of the hypothalamus; the neural pathway connecting the retinas to the SCN is referred to as the retinohypothalamic tract. Light detection by the retinas results in the inhibition of neurons in the SCN which ultimately project, via a multisynaptic pathway, to the pineal gland. During darkness the inhibitory influence on the SCN is lifted, at which time the nuclei signal the pineal gland to produce and secrete melatonin. The neural pathway from the SCN to the pineal gland includes descending SCN axons which synapse on intermediate neurons in the paraventricular nuclei and eventually on parikarya in the intermediolateral cell column of the upper thoracic cord; this column of neurons gives rise to preganglionic sympathetic fibers, some of which make synaptic contact with postganglionic sympathetic neurons in the superior cervical ganglia. The postganglionic sympathetic fibers eventually end in the pineal gland, among the pinealocytes, the hormone-producing cells of the gland. The neural connections between the eyes and the pineal gland are summarized in Figure 1.

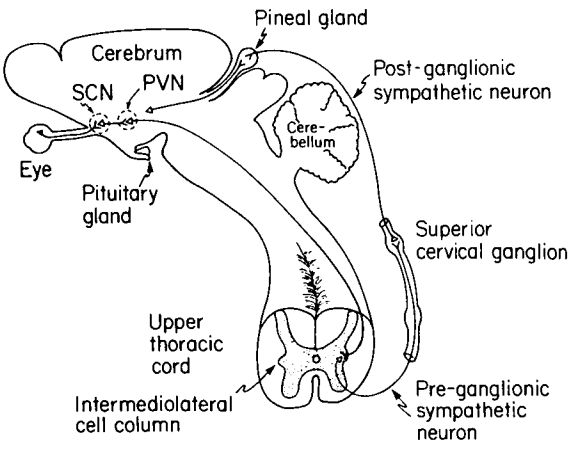

Fig. 1. Neural connections between the eyes and the pineal gland of mammals. An intermediate synapse in the pathway occurs in the body's biological clock, the suprachiasmatic nuclei (SCN). PVN = paraventricular nuclei. (Reproduced from Reiter, 1992; with permission of the publisher, Academic Press, Inc., San Diego, CA.)

THE CIRCADIAN MELATONIN RHYTHM AND ITS REGULATION

The nighttime production of melatonin is a neurally regulated event. During darkness the postganglionic sympathetic neurons that end in the gland release the catecholaminergic neurotransmitter norepinephrine (NE), which then interacts with β- (βAR) and α-adrenergic receptors on the pinealocyte membrane [Reiter, 1991c]. The βARs in particular are important in mediating the rise in melatonin production; these receptors are linked via a G stimulatory (Gs) protein to adenylate cyclase and their stimulation by NE leads to large intracellular increases in the second messenger cAMP. This eventually leads to the expression of the enzyme *N*-acetyltransferase (NAT), the rate limiting enzyme in melatonin production. NAT, in the presence of the co-factor acetyl CoA, *N*-acetylates serotonin (5HT) to *N*-acetylserotonin which is quickly *O*-methylated to *N*-acetyl-5-methoxy-tryptamine (melatonin) by the enzyme hydroxyindole-*O*-methyltransferase (HIOMT) in the presence of the co-factor S-adenosyl methionine. Whereas the magnitude of the nighttime rise in pineal NAT activity varies widely (depending on species, from 2- to 100-fold) [Rudeen et al., 1975], the increase in pineal and blood melatonin levels are rather similar among species, i.e., 5–20-fold higher values at night compared to those measured in the day in most cases. Once melatonin is produced in the pinealocyte it is rapidly released by mechanisms that remain undefined.

Whereas all mammals exhibit a nighttime rise in melatonin production and release, the pattern of the nighttime rise varies among species [Reiter, 1987]. Thus, in some mammals the nocturnal melatonin rise in represented by a short-term peak in the latter half of the night; in others, melatonin rises quickly after darkness onset to reach a plateau which is maintained essentially to the end of the dark period. Finally, in a third group of mammals, including the human, melatonin levels rise gradually during the first half of the night to reach a peak at mid darkness; during the latter half of the night the melatonin levels drop gradually and reach daytime levels at about the time of light onset [Reiter, 1987]. The physiological significance of these variations in the nocturnal pattern of melatonin production remains unknown. However, regardless of the melatonin pattern a specific species manifests, extension of the dark phase likewise prolongs the duration of elevated melatonin. The duration of elevated melatonin, which is dependent on night length, provides an annual signal which can be used by all species to adjust their physiology on a seasonal basis.

Once produced in the pinealocyte, melatonin seems to be quickly released into the rich capillary bed in the gland. Like the release of many other hormones, melatonin is generally considered to be discharged in pulses; this episodic

release results in short-term melatonin spikes, both during the day and at night, which are detectable when blood is collected from veins near their exit from the gland [Reiter and Vaughan, 1991]. This ultradian release of melatonin is superimposed on the circadian variation of melatonin synthesis and secretion.

The 24 h blood levels of melatonin follow a pattern similar to the production of the hormone in the pineal gland. Melatonin in the peripheral circulation readily escapes into other bodily fluids with a resultant day:night variation in the concentration of melatonin in these fluids as well. In these fluids the melatonin rhythm is of lower amplitude than that in the blood. Circadian melatonin rhythms have been reported in the cerebrospinal fluid, saliva, fluid of the anterior chamber of the eye, male seminal fluid, ovarian follicular fluid, and amniotic fluid. Besides passing readily into fluid compartments, because of its high lipophilicity, melatonin also presumably enters all cells with equal facility. Whereas membrane-bound melatonin receptors have been identified [Dubocovich, 1992], it is possible that melatonin which diffuses into cells may have direct intracellular actions [Benitz-King et al., 1991]. It is well established that melatonin's actions are widespread [Reiter, 1991a].

ELECTROMAGNETIC FIELD EXPOSURE AND PINEAL MELATONIN PRODUCTION

That light suppresses the melatonin forming ability of the pineal gland is well documented [Reiter, 1985]. Indeed, light detected by the eyes in mammals both inhibits the nocturnal rise in melatonin production and release and acutely suppresses its synthesis and discharge at night when animals or humans are exposed to visible wavelengths. In humans, once the threshold of light intensity required for inhibition is reached, melatonin can be suppressed in a fluence-dependent manner. Also, very brief periods (< 1 sec) of light exposure at night lead to significant inhibition of the 5HT-to-melatonin cascade in the pineal gland in animals.

Besides visible electromagnetic radiation, extremely low frequency (ELF) electric and magnetic fields as well as perturbed static magnetic fields, e.g., geomagnetic fields, also impair the melatonin forming ability of the pineal gland [Olcese, 1990; Reiter, 1991d]. Depending on the latitude at which the geomagnetic field strength is measured, it ranges from approximately 0.2–0.7 G (20–70 μtesla). The geoelectric field strength varies widely, from about 100 V/m at the Earth's surface on a clear day to several kV/m during an intense thunderstorm. These geomagnetic and geoelectric fields are defined as static or dc fields although they may vary rapidly according to the weather conditions.

ELF electric and magnetic fields have been introduced by humans and are especially prominent in highly industrialized countries. In North America these are primarily 60 Hz while in Europe and Japan they are 50 Hz. The field strengths of these human-made fields often exceed those of the natural static fields by several orders of magnitude. The major sources of ELF field exposure are electrical appliances and high power transmission and distribution lines.

The first report implicating 60 Hz electric fields in the regulation of pineal melatonin synthesis came from the work of Wilson and colleagues [1981; 1983]. According to these reports, the exposure of young adult male rats to ELF electric fields ranging from 1.2–1.9 kV/m for 20 h daily for 4 weeks dramatically attenuated the nighttime rise in both melatonin and its rate limiting enzyme NAT. In these studies, NAT activity and melatonin levels were measured at a single time point near the mid-dark period so it cannot be definitively stated that the melatonin rhythm, rather that being suppressed, was not simply either phase advanced or phase delayed; however, this is unlikely and the clear implication of these findings is that during 60 Hz electric field exposure the amount of melatonin produced in the pineal gland at night was severely reduced.

This finding was confirmed by the same group several years later [Wilson et al., 1986], in a paper in which they also showed that within 3 days after the ELF electric field exposure was discontinued, the normal circadian melatonin rhythm, with elevated levels at night, was reestablished. Thus, the electric fields clearly had not permanently compromised the melatonin forming ability of the gland.

The above summarized studies using adult rats were replicated using sexually immature rats, but the degree of nocturnal melatonin suppression in the young animals was not as great as that seen in the older rats [Reiter et al., 1988]. In the study using young animals three different field strengths were utilized, i.e., 10, 65, and 130 kV/m; within this range no fluence-response curve was observed.

In recent years, replication of the studies using sine wave electric fields have not confirmed their ability to inhibit nocturnal melatonin formation in adult rats [Sasser et al., 1991; Grota et al., 1991]. To date, no adequate explanation for the apparent disappearance of the response has been provided. Certainly, the magnitude of the response reported in the early studies of Wilson and colleagues [1981, 1983, 1986] was dramatic, so the recent failures to document the change are perplexing. Presently, some investigators question whether the observations of Wilson et al. [1981, 1986] were real or an artifact of either the method of melatonin measurement used, i.e., gas chromatography-mass spectrometry, or difficulties with some other methodological procedure.

Perturbed static magnetic fields have been widely tested in terms of their ability to alter the circadian rhythm of melatonin production [Olcese et al., 1988; Reiter, 1991d; 1992; Reiter and Richardson, 1992]. These studies were prompted by the observation that cells in the pineal gland of the guinea pig and pigeon change their firing rate when an artificial magnetic field is applied [Semm, 1988]. In pigeons, the ability of the pinealocytes to alter their firing pattern when the direction of the static magnetic field is altered does not require the eyes, suggesting that the pineal gland itself contains magnetoreceptors.

About 10 years ago, two reports appeared in close succession claiming that the synthesis of melatonin in the rat pineal gland was suppressed when the animals were exposed to an altered geomagnetic field [Semm, 1983; Welker et al., 1983]. According to Welker and coworkers [1983], a single inversion of the horizontal component of the natural magnetic field using Helmholtz coils at night rapidly depressed high nighttime levels of pineal NAT activity and melatonin and caused a similar drop in the concentration of melatonin in the blood. Likewise, the exposure of rats to the inverted field for 24 h with the pineal glands being collected 2 h after the horizontal component of the geomagnetic field reverted to normal also showed that the melatonin forming ability of the gland was compromised. Finally, these workers reported that changing the inclination of the local magnetic field at night decreased the ability of the pineal to produce melatonin.

Semm's [1983] findings were essentially identical. Thus, when freely moving rats were subjected to an inversion of the horizontal component of the geomagnetic field, nighttime pineal melatonin levels were depressed for at least 2 h. Neither Welker et al. [1983] nor Semm [1983] offer much incite on how the magnetic stimuli are coupled to the observed changes in pineal function, although Semm considered both the visual system and the pineal itself as potential sites of magnetoreception.

The initial studies related to the ability of changes in the direction of the geomagnetic field to interact with the pineal and reduce the synthesis rate of its chief hormone have been both confirmed and extended. Olcese et al. [1985] reported that a 50° rotation of the Earth's ambient magnetic field caused, within 30 min, a reduction in the melatonin forming ability of the rat pineal gland; they furthermore noted that the response of the pineal gland to the altered fields was abolished in rats that had been surgically blinded. The clear implication is that the eyes contain the receptors that detect changes in the ambient magnetic field. The levels of melatonin in the retina, however, were not influenced in the intact rats that were exposed to the altered magnetic field [Olcese et al., 1987].

On the basis of an experiment conducted about the same time, Reuss and Olcese [1986] claimed that, in addition to the eyes being required for a pineal response to magnetic fields, the retinas had to be stimulated with a weak red light. Thus, when rats were exposed to a 0.5 $\mu W/cm^2$ intensity red light at night, a 50° inversion of the magnetic field depressed pineal melatonin production, but not when the animals were maintained in darkness without retinal stimulation by red light. It is their opinion that the combination of stimulation of the retinal photoreceptors by red light and weak magnetic fields generates sufficient activation of these cells so that electrical messages are sent to the SCN; since these messages inhibit SCN activity, pineal melatonin production drops accordingly. This speculation remains, however, unproven.

Claims have been made that there may be some systemic factors which modify the ability of magnetic stimuli to alter melatonin production. According to Olcese and Reuss [1986], the pineal gland of both albino and pigmented rats exhibits an equal sensitivity to combined magnetic field inversion and weak red light exposure. In both rat strains, 50% reductions in nighttime NAT activity and melatonin levels were apparent 30 min after application of an

artificial magnetic field. In contrast, the nocturnal melatonin synthetic pattern of the Syrian hamster pineal gland was allegedly not changed by the exposure. Reuss and Olcese [1986] assume the inability of the hamster pineal gland to respond to the treatment may be a species specific trait.

Another mitigating factor, at least in Mongolian gerbils, may be cutaneous pigmentation. Thus, when both albino and pigmented gerbils were exposed during the night to a 60° rotation of the horizontal component of the Earth's magnetic field, only the albino animals responded with reduced pineal NAT activity and melatonin [Stehle et al., 1988]. Furthermore, this report indicates that male gerbils are slightly more sensitive to magnetic stimuli than are females. Neither of these conclusions, however, would seem to be definitive.

To this point, NAT activity and melatonin levels were the usual endpoints measured in the studies which examined the pineal consequences of magnetic stimuli. Rudolph et al. [1988] considered the signal transduction mechanisms related to catecholamine induced melatonin production via the βAR on the pinealocyte membrane. They found that in exposed rats pineal cAMP levels were depressed by geomagnetic field perturbations, compared to levels in unexposed animals. Thus, magnetic fields may alter the interactions of NE with the βAR, change the interactions of the βAR with the Gs protein, or alter the interrelationship of the Gs protein with adenylate cyclase. In any event, the drop in cAMP would explain the reduction in NAT activity and melatonin production [Reiter, 1991c].

We have attempted to further define pineal responses that occur following magnetic field exposure, as well as some of the magnetic field parameters which may be consequential in inducing the observed changes. With the aid of a Helmholtz coils system similar to that used in previous studies, rats at night were exposed for 1 h to a repeatedly inverted (pulsed) geomagnetic field; the inversions in this case occurred at 5 min intervals and were accomplished by means of manual relay switch. In male rats and in both male and female mice the pulsed fields caused significant increases in pineal 5HT levels [Lerchl et al., 1990]. A rise in pineal 5HT, the substrate on which NAT acts, would be expected when NAT activity is diminished, a change that was also observed. The large amounts of 5HT were then oxidatively deaminated to 5-hydroxyindole acetic acid (5HIAA) which, like 5HT, increased in the pineal gland. These findings are in keeping with the reduction in melatonin production following magnetic field stimulation.

We then examined a parameter of exposure which we felt may be important in terms of melatonin suppression by magnetic stimuli. In this study 2 groups of rats were exposed to pulsed geomagnetic fields at night (in this experiment, at 1 min intervals) for 1 h. The fields were applied either by means of a relay switch as in the previous report [Lerchl et al., 1991] or the voltage was ramped over a 1 sec interval. With the relay switch, the inversion of the magnetic field required about 7.25 msec. Because of the relatively rapid dB/dt, weak electrical currents (eddy currents) presumably occurred in these rats. When the magnetic fields were inverted slowly by ramping the voltage, the slow dB/dt produced little or no induced eddy currents. These two methods of exposure produced different results in reference to pineal melatonin synthesis. Thus, only the rapid inversion of the field with the consequential induction of eddy currents caused a reduction of NAT and melatonin and the associated increases in 5HT and 5HIAA [Lerchl et al., 1991]; the slow inversions produced none of these effects. The conclusion based on these findings is that the induced electrical transients may be important in causing the pineal changes observed. Whereas these electrical currents may be important, later studies from our laboratory indicate that they may not be solely responsible for the alterations in pineal melatonin synthesis following pulsed magnetic stimuli [Richardson et al., 1992].

Finally, we have examined the differential sensitivity of the 5HT-to-melatonin cascade to magnetic field inversion throughout the dark phase of the light:dark cycle. The findings show that perturbing the geomagnetic field near and after the middle of the night is more detrimental to melatonin synthesis than are magnetic field changes early in the night when maximal stimulation of the pinealocytes by NE is occurring [Yaga et al., 1992].

The collective findings related to the suppression of melatonin synthesis by altered geomagnetic fields are internally consistent. The results are summarized in Figure 2 and indicate that cAMP, NAT activity, HIOMT activity, and pineal and blood melatonin levels may be decreased by magnetic stimuli; on the contrary, and consistent with expectations, pineal 5HT

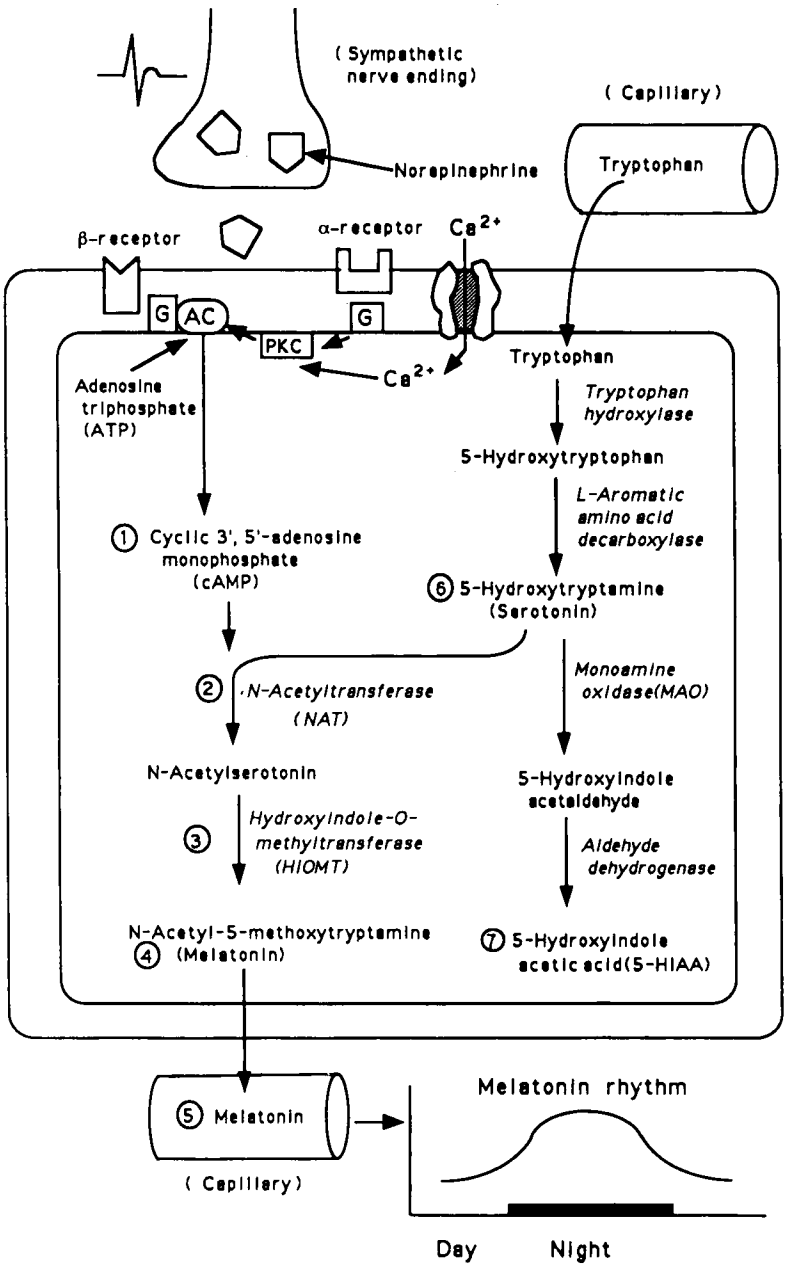

Fig. 2. Diagrammatic interactions of the postganglionic sympathetic neurons with the mammalian pinealocyte and the melatonin synthetic pathway. The items numbered 1–7 are those constituents that have been reported to be altered by electromagnetic field exposure in animals. Numbers 1–5 identify constituents which reportedly decrease, while items 6 and 7 increase.

and 5HIAA levels rise under these circumstances.

Considering the large number of reports dealing with the changes in pineal indoleamine metabolism as a consequence of the exposure of animals to static magnetic fields, surprisingly few studies have examined pineal metabolic activity as a consequence of exposure to sinusoidal magnetic fields. As with the pulsed static fields, however, these exposures reportedly lead to a depression in pineal melatonin production.

Chronic exposure of rats to circularly polarized 50 Hz magnetic fields over a range of field strengths (0.01, 0.05, 0.5, and 2.5 G) led to a drop in nighttime levels of both pineal and serum melatonin in animals that experienced field strengths of 0.05 G and higher [Kato et al., 1992]. Within the range of effective field

strengths, no dose-response relationship was measured. In this study the rats were maintained under a light:dark cycle of 12:12 and the exposure period was 6 weeks. The percentage changes observed in the report of Kato and colleagues [1992] were similar to those reported by Lerchl et al. [1990, 1991], who used pulsed static fields of short duration. Kato et al. [1992] do not offer any novel theories to explain the interactions of electromagnetic fields with tissues and they favor the idea that induced eddy currents are most likely the causative agent of the changes observed.

The only other report that utilized sinusoidal magnetic fields to influence the circadian rhythm of pineal melatonin production is that of Yellon [1991]. In this case, remarkable changes were observed. Adult male and female Djungarian hamsters were exposed to a 1 G 60 Hz horizontal magnetic field for 15 min only, beginning 2 h before darkness onset, and the nocturnal rises in both pineal and serum melatonin were monitored. Pineal melatonin levels increased soon after darkness onset in the sham exposed hamsters; however, in the animals exposed to the sinusoidal magnetic fields the rise was delayed for roughly 4 h (Fig. 3). In the serum the changes were even more dramatic. The usual nocturnal increase in circulating melatonin, which was observed in the sham exposed hamsters, was essentially nonexistent in those hamsters that experienced sinusoidal magnetic field exposure (Fig. 3). The explanation for these results that was advanced by Yellon [1991] is that the short-term daytime exposure to magnetic fields disrupted the timekeeping capabilities of the endogenous biological clock, i.e., the SCN, which normally governs the nocturnal increase in pineal melatonin synthesis. This explanation also implies that the retinas may be involved in magnetic field perception, since the timing mechanisms in the SCN are known to be set by information arriving at the nuclei via the retinohypothalamic tract. If the observation of Yellon [1991] is confirmed in other species, it could have important implications for the human, since many individuals receive the bulk of their exposure to electromagnetic fields during the day in their occupational or domestic setting.

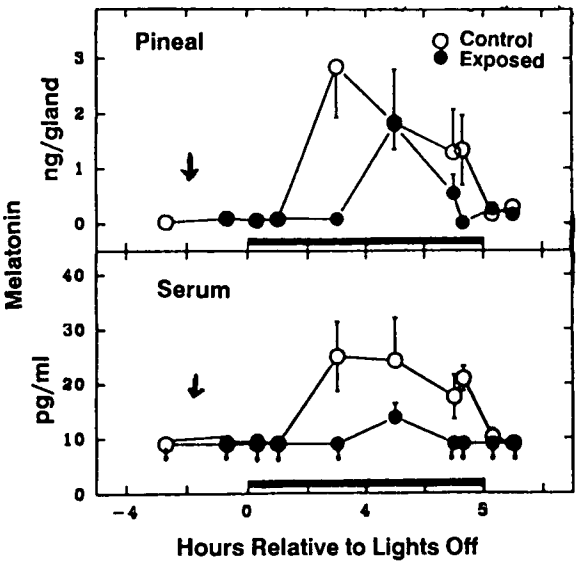

Fig. 3. Pineal and serum melatonin levels in control Djungarian hamsters and in hamsters exposed to a 60 Hz 1 G magnetic field for 15 min beginning at 1800 h (arrow), 2 h before lights off. Lights were turned off at 2000 h. Magnetic field exposure delayed the nighttime rise in pineal melatonin and severely blunted the nocturnal increase in serum melatonin levels. From Yellon [1991].

POTENTIAL MECHANISMS AND CONCLUDING REMARKS

This brief review surveys the reported changes in pineal melatonin synthesis and secretion in animals exposed to either ELF sinusoidal electric and magnetic fields or to perturbed geomagnetic fields. When changes were observed, a reduction in the activity of the synthetic machinery governing the conversion of 5HT to melatonin was typical. Whereas the effects of sinusoidal electric field exposure on melatonin synthesis were initially reported to be dramatic [Wilson et al., 1981, 1986, 1989], recent studies have had difficulty in confirming these findings [Sasser et al., 1991; Grota et al., 1991]. Thus, interest in the alleged consequences of ELF electric field exposure in reference to the pineal gland has waned in recent years.

On the contrary, reports related to magnetic stimuli and the melatonin synthetic pathway seem to be on the increase. During the last decade, beginning with the reports of Welker et al. [1983] and Semm [1983], numerous publications have demonstrated that perturbed static geomagnetic fields significantly change the ability of the pineal gland to produce melatonin [Olcese et al., 1988; Reiter, 1992; Reiter and Richardson, 1992]. Each of these reports noted a reduction in melatonin synthesis as a consequence of the specific magnetic field exposures used; furthermore, when associated parameters or constituents in the pineal gland or blood were

measured, they changed in a predictable manner consistent with the reduced melatonin formation (Fig. 2). The magnitude of the changes varied among reports, possibly related to slightly different field parameters used. As the papers are perused, the authors not uncommonly mention that some attempts to modify melatonin synthesis with magnetic fields yielded negative results; yet, collectively, the findings require that these interactions be further investigated since there could be physiological consequences of alterations in the melatonin rhythm [Reiter, 1992].

Like static magnetic field perturbations, sinusoidal magnetic field exposure also reportedly changes melatonin production by diminishing the synthesis of this key hormone [Yellon, 1991; Kato et al., 1992]. Whereas these papers present rather convincing data, there are only two reports and, of these, one set of findings has yet to be peer-reviewed [Yellon, 1991].

Also unresolved is whether it is, in fact, the presence of the magnetic fields or the induction of eddy currents in the animals after rapid changes in the fields that account for the pineal alterations observed. Semm [1988] feels that the mere presence of a rotated geomagnetic field is sufficient for detection by the organism, leading to the observed pineal changes. On the other hand, the work of Lerchl et al. [1991] suggests electrical transients following rapid magnetic field inversion may account for the observed physiological perturbations that have been measured. The critical aspects of these exposures will be identified only by workers who carefully monitor the exposure parameters. It is likely that the best chance for success in these studies will require the cooperation of biological and physical scientists in both the planning and execution of the experiments.

If we accept that electric and/or magnetic fields can influence a biological event such as melatonin synthesis, it is necessary to explain how the fields are coupled to the organism and/or tissue. The energy transferred as a consequence of the field exposures used is very low and seemingly below the thermal noise of the organism; thus, some physical scientists argue against there being any effects of such exposures [Adair, 1991]. Just as adamantly, however, others offer explanations which, at least theoretically, justify the cellular changes observed [Adey, 1991; Kirschvink, 1992].

In reference to the coupling of a perturbed static magnetic field with tissues and the consequential altered melatonin production, several requirements apparently must be met. Thus, according to Olcese and colleagues [1985, 1987, 1988], either removal of the eyes or loss of the retinal photoreceptors eliminates the ability of magnetic fields to cause pineal changes. The clearly stated implication of these findings is that the eyes, and specifically the photoreceptors, are the site of magnetoreception in mammals. This idea arguably receives further support from the claim that minimal red light stimulation of the mammalian retinas is a prerequisite for magnetic field exposure to be effective as a melatonin suppressing treatment [Olcese et al., 1988; Olcese, 1990]. Thus, supposedly only when the photoreceptor cells are activated by a combination of red light and magnetic field stimuli is the stimulus sufficiently intense to alter the firing pattern of the neurons in the retina-SCN-pineal pathway. To date, this theory is unproven and, indeed, whether combined red light and magnetic stimulation of the retinas is required for pineal melatonin suppression is still open to debate.

In fact, there are some data which hint that the eyes may not be involved in the magnetoreception required to inhibit pineal melatonin secretion. For example, inverted geomagnetic field exposure has been shown to inhibit βAR-stimulated melatonin production in in vitro cultured rat pineal glands [Richardson et al., 1992]. Thus, at least under the conditions of these studies, the pineal tissue itself proved to be directly responsive to magnetic stimuli. This does not, however, mean that under in vivo conditions the eyes are not involved in coupling magnetic stimuli with melatonin suppression.

When the retinas are considered as the site of magnetoreception, the photoreceptor cells are also usually implicated. It has even been suggested that within the rod photoreceptor, it may be the isomerization of the chromophore substituent of rhodopsin which leads to activation of the retinohypothalamic tract and the eventual inhibition of nocturnal melatonin synthesis. If so, both light and magnetic field exposure at night would cause the isomerization of 11-*cis*-retinal to all-*trans*-retinal [Hargrave and McDowell, 1992]. In an attempt to prove whether this phototransductive process is involved, we compared the ratio of 11-*cis* to all-*trans*-retinal in the retinas of rats exposed to either light or

magnetic stimuli at night. Whereas light exposure caused the expected conversion of 11-*cis* to all-*trans*-retinal, we could not statistically document this change after magnetic field exposure. This preliminarily implies that rhodopsin per se is not involved in magnetoreception, although to prove this point additional studies must be performed. Additionally, there could be non-photoreceptor cells in the retina that are able to detect changes in the geomagnetic field environment. For example, retinal amacrine cells respond to electromagnetic radiation in the visible range even when very few rods and cones are present [Morgan and Kamp, 1980].

There is general agreement that reduced pineal melatonin synthesis is a consequence of electromagnetic field exposure under certain conditions. The primary event responsible for this change probably involves an alteration in the retina-SCN complex, with the altered melatonin rhythm being merely an epiphenomenon of the underlying neural disturbance. However, an evaluation of the cyclic production of melatonin remains the most convenient and reliable endpoint to measure in such studies.

A confounding problem with the data is that the pineal gland of pigmented and albino gerbils responds differently to static magnetic field exposures [Olcese and Reuss, 1986], while the melatonin synthetic pathway in the pineal gland of the Syrian hamster reportedly is totally unresponsive to these fields [Stehle et al., 1988]. Whether these differences are valid or due merely to some experimental quirk should be resolved. If real, they would detract considerably from the generalized claim that the retina-SCN-pineal system can react to static magnetic stimuli with a suppressed conversion of 5HT to melatonin. A robust pineal response within and across species would be a strong argument for the physiological relevance of the observations reported to date.

The data of Yellon [1991], albeit published only in abstract form, is compelling because of the magnitude of changes observed (Fig. 3). They are also of special interest because in this study daytime exposure to 1 G 60 Hz magnetic fields severely altered the pineal and blood melatonin rhythms the subsequent night. The 1 G field strength is within the range of that to which individuals could be exposed in the domestic and work place environment. However, to put significant emphasis on these findings before they are confirmed in other laboratories and in other species is not justified and could be misleading in terms of directing subsequent research. The original reports of Wilson and coworkers [1981, 1986] were also convincing, but they seem not to have withstood the "test of time."

Clearly, there are some discrepancies and apparent inconsistencies in the data which link electromagnetic stimuli to a modification of pineal metabolism. Nevertheless, there are a sufficient number of positive reports to justify additional investigation of these potential interactions. Thus, whereas the findings to date are not incontrovertible, they should not be categorically dismissed. After all, magnetoreception in the animal kingdom is not an unusual phenomenon [Gould, 1984; Frankel, 1986; Lohmann and Willows, 1987; Burda et al., 1990; Kirschvink et al., 1992]. Since this is the case, it does not seem unreasonable to assume that magnetoreception, and the consequential physiological changes, is a generalized phenomenon in vertebrates.

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