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Review

Do Magnetic Fields Cause Increased Risk of Childhood Leukemia via Melatonin Disruption?

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Epidemiological studies have reported associations between exposure to power frequency magnetic fields and increased risk of certain cancer and noncancer illnesses. For childhood leukemia, a doubling of risk has been associated with exposures above 0.3/0.4 μT. Here, we propose that the melatonin hypothesis, in which power frequency magnetic fields suppress the nocturnal production of melatonin in the pineal gland, accounts for the observed increased risk of childhood leukemia. Such melatonin disruption has been shown in animals, especially with exposure to electric and/or rapid on/off magnetic fields. Equivocal evidence has been obtained from controlled laboratory magnetic field exposures of volunteers, although the exposure conditions are generally atypical of neighborhood exposures. In contrast, support for the hypothesis is found in the body of studies showing magnetic field disruption of melatonin in human populations chronically exposed to both electric and magnetic fields associated with electricity distribution. Further support comes from the observation that melatonin is highly protective of oxidative damage to the human haemopoietic system. Aspects of the hypothesis are amenable to further investigation. Bioelectromagnetics Supplement 7:S86–S97, 2005

Key words: ELF; power frequency; pineal; oxidative damage

INTRODUCTION

Various reports [NIEHS, 1999; NRPB, 2001a; CHD, ch. 8, 2002] have discussed the pooled analyses of epidemiological studies by Ahlbom et al. [2000] and Greenland et al. [2000], indicating an approximate doubling of risk associated with magnetic field exposures above 0.3/0.4 μT and such fields have been classed as a possible carcinogen [IARC, 2002]. In addition, there is a body of epidemiological evidence suggesting increased risk of certain other cancer and noncancer illnesses associated with magnetic field exposures. Currently, the strongest evidence appears to relate to increased risk of amyotrophic lateral sclerosis, ALS [NRPB, 2001b; CHD, ch. 15, 2002], brain cancer, and leukemia in adults with recent evidence suggesting a link with miscarriage [CHD, chs. 8, 10, and 13, 2002].

The melatonin hypothesis has been widely discussed in terms of exposure to light-at-night, magnetic fields, and breast cancer [Cohen et al., 1978; Stevens, 1987]. However, melatonin disruption by magnetic fields might also account for increased risk of the otherwise disparate range of reported adverse health outcomes. Here we apply the hypothesis specifically to childhood leukemia, namely that exposure to magnetic fields associated with the electricity supply causes increased risk via the disruption of the nocturnal production of melatonin in the pineal gland.

Melatonin (*N*-acetyl-5-methoxytryptamine) has been identified in a wide range of organisms from bacteria to human beings. Its principal source in man is as the chief secretory product of the pineal gland. This follows a marked circadian rhythm, the majority of production occurring at night regulated by nonrod, noncone receptors in the eye sensing the absence of light.

Melatonin is remarkably nontoxic and has been found to be a radical scavenger and antioxidant, more

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effective than either vitamins C or E in vivo [Tan et al., 2003]. The indoleamine has been found to protect cells, tissues, and organs against oxidative damage induced by a variety of free radical generating agents and processes, for example, the carcinogen safrole, lipopolysaccharide, kainic acid, Fenton reagents, potassium cyanide, ischemia-reperfusion, and ionizing radiation [Reiter et al., 1997]. Melatonin is an antioxidant, effective in protecting nuclear DNA, membrane lipids, and cytosolic proteins from oxidative damage [Allegra et al., 2003]. It has been reported to alter the activities of enzymes which improve the total antioxidative defence capacity of the organism [Rodriguez et al., 2004].

Obviously, melatonin's ability to protect DNA from oxidative damage has implications for many types of cancer, including leukemia, considering that DNA damage due to free radicals is believed to be the initial oncostatic event in a majority of human cancers [Cerutti et al., 1994]. In addition to cancer, free radical damage in the central nervous system is a significant component of a variety of neurodegenerative diseases of the aged including Alzheimer's disease and Parkinsonism. In experimental animal models of both of these conditions, melatonin has proven highly effective in forestalling their onset and reducing their severity [Reiter et al., 2001]. Thus, a reduction in melatonin due to any means may be consequential in a number of diseases.

THE MELATONIN HYPOTHESIS

The chief source of melatonin in man arises from its synthesis in the pineal gland, the majority production occurring at night triggered by a signal from the eye indicating light falling below a threshold $\sim$10 lux. Recent experiments indicate the presence of nonrod, noncone receptor cells in the eye which are uniquely responsible for communicating light information to the pineal gland, thereby synchronizing regulation of the pineal with the day–night cycle [Freedman et al., 1999; Lucas et al., 1999, 2001, 2003; Foster and Hankins, 2002; Hattar et al., 2003; Sekaran et al., 2003; Foster and Kreitzman, 2004].

Cohen et al. [1978] suggested that reduced pineal melatonin production, brought about by environmental lighting, might increase human breast cancer risk. This suggestion was followed by Stevens [1987] who noted that breast cancer was a disease of modern life associated with industrialization. He proposed that the use of electric power might increase the risk of breast cancer. The risk theoretically arose from reduced production of nocturnal melatonin brought about by exposure to two principal agents, namely light-at-night (LAN) from domestic as well as street lighting and magnetic fields associated with the electricity supply. Strong support for LAN affecting breast cancer risk has come from experiments in animals exposed to constant light [Stevens and Davis, 1996]. Additionally, support in humans comes from the observation of reduced hormone related cancer rates in the blind and partially sighted and increased breast cancer rates in nightshift workers [Hahn, 1991; Feychting et al., 1998; Verkasalo et al., 1999; Hansen, 2001a,b; Swerdlow, 2003].

MAGNETIC FIELD SUPPRESSION OF MELATONIN

Suppression in Animals

Effects on melatonin by magnetic fields have been studied in a number of animal species. Kato and Shigemitsu [1997] found 6 weeks of exposure to a circularly polarized but not to horizontal or vertically plane-polarized fields, at intensities above 1.4 μT, suppresses plasma and pineal melatonin concentration in Wistar–King rats. The authors also found that the ability to suppress melatonin depended on the degree of ellipticity and field intensity. Polarized fields induce higher currents in the body compared with their plane-polarized counterparts. This may be of importance, given that human populations are commonly exposed to polarized fields [Ainsbury, 2004]. Wilson et al. [1981] also showed that 65 kV/m electric fields were effective in suppressing melatonin in rats exposed for 30 days. Reiter et al. [1998] found inconsistent suppression of nocturnal pineal melatonin synthesis and serum melatonin in rats exposed to pulsed DC magnetic fields. The authors suggested that an observed drop on serum melatonin could theoretically be explained by an increased uptake of melatonin by tissues that were experiencing augmented levels of free radicals as a consequence of MF exposure [Reiter, 1998].

In hamsters, Wilson et al. [1999] found reduced pineal melatonin from a combination of exposure to steady state and on/off magnetic fields for 16 days. Yellon [1994] found melatonin suppression by magnetic fields in adult Djungarian hamsters but not in adult Siberian hamsters [Yellon and Truong, 1998]. Brendel et al. [2000] found both 50 and 16 2/3 Hz magnetic fields effective in suppressing melatonin production in isolated pineal gland from Djungarian hamsters in vitro.

In baboons, Rogers et al. [1995a] found that a combination of exposure to slow onset electric and magnetic fields were ineffective at suppressing melatonin, but when these fields were applied in a rapid on/off mode, after 9 days exposure melatonin levels were reduced to between 4% and 15% of those pre-exposure [Rogers et al., 1995b]. The authors suggested that

TABLE 1. Human Population Studies on Effects of Magnetic Fields (EMFs) on Pineal Melatonin Production

Study no.	No. of cases/controls	Type of EMF exposure	Location and time of year	Key observations
1. Wilson et al. [1990]	42 volunteers: 32 women; 10 men, volunteers acted as own controls	Volunteers used electric blankets for approximately 8 weeks (AC compared with DC)	Washington State, USA around winter solstice	No overall effect, but statistically significant 6-OHMS decrease (~25%) in seven individuals using blankets with 50% higher MFs (mean 0.42 μT) and which switched on and off at twice the rate of conventional blankets
2. Pfluger and Minder [1996]	108 men: 66 engineers and 42 controls (train attendants & station managers with average exposure over 1 μT) both groups work shifts	Electric railway lines, average exposure: 20 μT in most exposed 1 μT in least exposed (E)[a]	Switzerland, early autumn, 1993	Lowered 6-OHMS daytime levels (factor of 0.81) in engineers compared to controls but no difference in nocturnal levels, evidence of a rebound of levels during leisure days
3. Burch et al. [1998]	142 men 20–60 years, mean age 41 years; 29 generation workers; 56 distribution workers and 57 controls (utility maintenance & administration staff)	Electric utility workers highest exposure occurred in generation workers: geometric mean 0.22 μT (E)	Colorado, USA Morning 6-OHMS daily for 4 days	Association between residential MF exposure and lower nocturnal 6-OHMS levels, modest reductions in levels after work MF exposure, greatest reductions (35%) when work and home exposures combined
4. Wood et al. [1998]	30 adult males 18–49 years, subjects acted as their own controls	Laboratory generated, circularly polarized, 20 μT, 50 Hz magnetic fields, for three successive Friday night/Saturday mornings	February–September over a 2 year period 1994–1996	Exposure during a certain time window caused a mean 1 h delay in nightly melatonin onset in a subset of subjects, square wave fields produced more marked reduction in maximum melatonin levels compared with sinusoidal fields
5. Burch et al. [1999a]	142 men as in Study 3	Electric utility workers highest exposure bin >0.135 μT (E)	Colorado, USA 1 year period	Reduction in 6-OHMS on the second and third days of occupational exposure to MF, bigger effects (up to 35% reduction) with low RCMS[b] values, negligible MF effects in subjects with high visible light exposure
6. Burch et al. [2000]	149 men mean age 44 years: 50 generation workers, 60 distribution workers, 39 controls (utility maintenance & administration staff)	Substations (3 phase–circularly polarized) Study compared ≥2 h with >2 h to geometric mean fields in the range 0.04–0.27 μT (E)	Colorado, USA January–September 1997	No effect due to 1 phase exposure, 6-OHMS reduction found due to exposure >2 h to 3 phase, low RCMS fields had greatest effect, up to 44% reduction in mean 6-OHMS between upper and lower exposure tertiles
7. Juutilainen et al. [2000]	60 women, mean age 44 years (workers) & 43 years (controls); 39 garment workers (8 of whom did not operate machines but were 'possibly exposed'), 21 controls	Sewing machine workers, eye level exposures >1 μT compared with 0.3–1 μT, likelihood of exposure to switched fields	Kuopio, Finland 3-week period around spring equinox	No week/weekend variations, but between 25% and 40% lower 6-OHMS levels in workers compared to controls, authors suggest effects on melatonin may require chronic exposures
8. Graham et al. [2000]	30 men 18–35 years, mean age 22 years (volunteers acted as their own controls)	Laboratory generated, circularly polarized, 28.3 μT, 60 Hz magnetic fields for 4 consecutive nights	Missouri, USA spring and summer	Compared with controls, repeated nightly exposure was associated with reduced consistency of 6-OHMS levels, results suggestive of cumulative effect

9. Davis et al. [2001]	203 women, 20–70 years	Night time residential 60 Hz magnetic fields, mean night time exposures were <0.2 μT	Washington State, USA two 72 hperiods at different seasons over 14 months	Higher bedroom MF associated with lower 6-OHMS levels during the same night, maximum 14% reduction in summer solstice for fourfold increase in mean MF above 0.04 μT
10. Levallois et al. [2001]	221 women subjects and 195 women controls, mean age 45.5 years (subjects) & 45.8 years (controls)	Subjects <150 m from 735 kV Power Lines, controls >400 m away, exposure quartiles 1st versus 4th: <0.13 μT & ≥0.37 μT; <4.7 V/m & ≥ 12.2 V/m. (E)	Quebec City, Canada, 6-OHMS sampled over 2 consecutive days February–December 1998	Decrease in 6-OHMS levels in relation to age and body mass index, more pronounced in women living near the powerlines, Maximum 30% reduction between highest and lowest quartiles
11. Burch et al. [2002]	Study 1: 149 as in Study 6; study 2: 77: 22 generation workers; 29 distribution workers; 23 controls	Cell telephone use in electric utility workers, arithmetic mean exposure to tertiles: 1st 0.05 μT; 3rd 0.5 μT (E)	Colorado, USA total overnight and post-work 6-OHMS on 3 consecutive workdays: Study 1, January–September '97; Study 2, April–June '98	Study 1—no effect, study 2—exposure-related 6-OHMS reductions in cell phone use >25 min per day, reduction (40%) between highest and lowest exposure tertiles, a combined effect of telephone use and occupational exposure to 60 Hz magnetic fields was observed
12. Touitou et al. [2003]	15 men 31.5–46 years with exposures 0.1–2.6 μT compared with 15 men 34.5–47 years with exposures 0.004–0.092 μT	Chronic exposure in those who worked and lived near extra high voltage substations (E)	Paris, France autumn	No statistically significant differences in nocturnal plasma melatonin or the melatonin metabolite between the workers and controls
13. **Geomagnetic** Burch et al. [1999b]	132 male electric utility workers	Geomagnetic (GM) disturbances in conjunction with 60 Hz MF exposure, changes in GM fields >30 nT compared with ≤ 30 nT	Colorado, USA March '95–March '96	Lower 6-OHMS levels on days with high geomagnetic activity, effect enhanced when activity combined with high MF or low light levels, statistically significant 20% reduction between <and >30 nT disturbance
14. **Geomagnetic** Weydahl et al. [2001]	25 volunteers: 9 men, 16 women	Geomagnetic disturbances at latitude 70° N	Tromsø, Norway November–December '92–September '96	Statistically significant trend in reduced melatonin with indices of geomagnetic disturbance over 3 h above 80 nT, approximately, reduction (50%) in plasma melatonin for a 330 nT change in disturbance

[a](E) Indicates associated exposure to powerline electric fields, although field values generally not given.
[b]RCMS = Standardized rate of change metric: low values correspond to temporarily stable fields.

while organisms may adapt to constant conditions, they may be less able to adapt to conditions that are rapidly or randomly changing.

Löscher et al. [1993, 1994] and Löscher and Mevissen [1997] carried out a series of experiments which reported direct experimental evidence of the hypothesis of Stevens [1987], showing that chronic exposure to 60 Hz magnetic fields resulted in increased incidence of mammary gland tumors in female Sprague–Dawley rats. The authors pointed out that since melatonin physiologically suppresses oestrogen production by ovary and prolactin production by the pituitary [Reiter, 1991], a melatonin reduction would in turn result in increased oestrogen and prolactin production and thereby induce increased turnover of the breast epithelial stem cells at risk of malignant transformation. In addition, in view of the oncostatic effect of melatonin on breast cancer growth [Blask, 1993], the development and growth of breast cancer, once initiated, would be facilitated by reduced melatonin levels. Löscher and Mevissen showed increased incidence of mammary tumors with magnetic field exposure in rats treated with the chemical carcinogen 7,12-dimethylbenz[a] anthracene (DMBA). The data were consistent with a monotonic increase in risk from 1 to 100 μT where a 50% increase in tumor risk was observed. Later evidence suggests that this result is species dependent, owing to varying sensitivities to DMBA [Anderson et al., 2000; Fedrowitz et al., 2004].

In relation to human breast cancer, Ishido et al. [2001] amongst others have shown that in vitro 1.2 μT magnetic fields suppress the antiproliferative action of physiologically relevant concentrations of melatonin in inhibiting the growth of MCF-7 breast cancer cells. Epidemiological studies have generally suggested a small increased risk of breast cancer with magnetic field exposures [Erren, 2001], although higher risks have been reported when both residential and occupational exposures are taken into account [Kliukiene et al., 2004].

Suppression in Humans

The central question is whether exposure to typical neighborhood power frequency magnetic fields to which human populations are exposed either reduces or otherwise disrupts the nocturnal production of melatonin in the pineal gland. This has been addressed in both laboratory and observational (population) studies.

Laboratory controlled acute exposures. Considerable effort has been exerted on studies in which volunteers were exposed to laboratory generated magnetic fields well above those usually encountered by the general population and melatonin assayed either by levels in blood (plasma melatonin) or by measurement of the melatonin metabolite 6-hydroxymelatonin sulphate (6-OHMS) in urine [Graham et al., 1996a,b; Selmaoui et al., 1996, 1997; Wood et al., 1998; Crasson et al., 2001; Griefahn et al., 2001; Hong et al., 2001; Kurokawa et al., 2003; Selmaoui and Touitou, 2003; Warman et al., 2003a,b]. The rationale for volunteer studies is that exposures can be well characterized and control for factors such as light exposure is better achieved in laboratory conditions. Some studies also attempted to mimic neighborhood fields by artificially imposing on/off and transient features [Crasson et al., 2001; Kurokawa et al., 2003].

Graham et al. [1996a,b] reported that men with pre-existing low levels of melatonin showed significantly greater suppression of melatonin when they were exposed to light and also when exposed to 20 μT magnetic fields for 8 h on 1 night. However, this finding was not confirmed in their later study. With the exception of Wood et al. [1998] discussed below, the other short term exposure volunteer studies have failed to provide statistically significant evidence of melatonin suppression, although some show effects short of statistical significance [Selmaoui et al., 1996; Crasson et al., 2001; Hong et al., 2001].

However, while these volunteer studies have been carefully designed and well controlled, they nevertheless have a number of drawbacks: (i) the relatively small number of volunteers limits the ability statistically to resolve changes in melatonin secretion against the natural variations between individuals; (ii) exposures have tended to be for short periods compared with chronic exposures in real populations when the evidence in animals suggests that several days or weeks of exposure are required before effects on melatonin secretion become manifest; (iii) laboratory generated exposures may not contain features such as transients or rapid on/off changes in magnetic fields which have been shown effective in demonstrating melatonin suppression in animals; and (iv) volunteer studies have not included exposure to electric fields which may also be a factor in melatonin disruption.

Longer term and chronic exposures. In contrast to the volunteer studies with short term exposure, there is now a body of studies involving either longer term or chronic magnetic field exposures which taken together show evidence of nocturnal melatonin disruption. These are listed in Table 1, numbered 1–14: [Wilson et al., 1990; Pfluger and Minder, 1996; Burch et al., 1998, 1999a,b, 2000, 2002; Wood et al., 1998; Graham et al., 2000; Juutilainen et al., 2000; Davis et al., 2001; Levallois et al., 2001; Weydahl et al., 2001; Touitou

et al., 2003]. The two latter Studies, 13 and 14, looked at the effects of geomagnetic disturbances. Apart from 4 and 14, which measured plasma melatonin only, all other studies assayed 6-OHMS in morning urine samples. Study 12 additionally measured plasma melatonin.

Three volunteer Studies: 1, 4, and 8 are included which involved longer, as apposed to one time acute exposure. In Study 1, while overall melatonin disruption was not seen in electric-blanket users, an approximate 25% reduction in overnight 6-OHMS was seen in seven individuals who slept with CPW electrc blankets that produced 50% higher magnetic fields and that switched on and off at twice the rate of conventional blankets. In Study 4, exposure to 20 μT 50 Hz fields during a certain time window caused a mean 1 h delay in nightly melatonin onset in a subset of subjects, with square wave fields producing a more marked effect compared with sinusoidal fields. In Study 8, repeated nightly exposure to circularly polarized 28.3 μT 60 Hz fields was associated with reduced consistency of 6-OHMS levels and the results were suggestive of a cumulative effect.

Study 12 found no evidence of nocturnal melatonin disruption in men who lived and worked near extra high voltage substations, but the sample size of 15 is small compared with other studies involving chronic exposure. The remaining chronic exposure studies in Table 1 all report evidence of nocturnal melatonin disruption with suppression values ranging up to 50% at low average field exposures. For example, the geometric mean exposure in Study 6 was in the range 0.04–0.27 μT and in Study 9 compared melatonin secretion between average exposures >0.2 and <0.2 μT. The findings in relation to geomagnetic disturbances are particularly noteworthy because of the level and transient nature of the fields. Study 13 reported a statistically significant 20% reduction in 6-OHMS levels for disturbance levels >30 compared with <30 nT and study 14 found an approximate 50% reduction in plasma melatonin for a 330 nT span in disturbances.

It can be inferred that in seven Studies, 2, 3, 5, 6, 10, 11, and 12, there was additional exposure to power-line electric fields, although exposure values are only given in Study 10. Of potential interest is that electric fields induce currents in both the eye humor and the pineal gland well in excess of endogenous currents [Furse and Gandhi, 1998]. Some studies specifically involve exposure to transient or switched fields, 1, 4, 13, and 14, while Study 7 in women sewing mechine operators would have likely involved exposure to on/off fields.

Overall, in Table 1, 11 studies show evidence of melatonin disruption by power frequency magnetic fields and 2 by geomagnetic field disturbances. In some cases there is evidence of a dose response effect and disruption for exposures to fields below 0.3–0.4 μT.

CHILDHOOD LEUKAEMIA AND MELATONIN

Currently there is no appropriate animal model for acute lymphoblastic leukemia (ALL), the predominant leukemia subtype in children. In contrast, acute myeloid leukemia in CBA mice is an established model for adult leukemia. Anisimov et al. [2004] have shown that in addition to other tumors, leukemia can be induced in CBA mice exposed to constant light, a finding interpreted as due to melatonin suppression.

Melatonin Protects Against Oxidative Damage to the Human Hemopoietic System

The potential importance of melatonin suppression to leukemia risk arises from the observation that the indoleamine is highly protective of oxidative damage to the human haemopoietic system. Vijayalaxmi et al. [1996] administered 300 mg of melatonin to four healthy volunteers. Immediately and 1 and 2 h later, blood samples were taken and irradiated with 1.5 Gy ^{137}Cs gamma radiation. Compared with blood samples taken immediately, those taken at 2 h had significantly decreased (50%–70%) chromosome aberrations and micronuclei. The authors concluded that the observations might have important implications for the protection of human lymphocytes from genetic damage induced by free radical producing mutagens and carcinogens. The authors investigated the mechanism of melatonin protection in terms of both direct scavenging in the cell nucleus of radiation-induced free radicals, including the hydroxyl radical, and action at the cell membrane and in the cytosol to trigger activation of existing DNA repair enzymes and/or activation of a set of genes that lead to de novo protein synthesis associated with DNA repair [Vijayalaxmi et al., 1998]. In a further experiment, Vijayalaxmi et al. [1999] irradiated mice with 8.15 Gy gamma radiation; mice were either untreated or pretreated with 125 and 250 mg melatonin. In the untreated mice, 45% were alive after 30 days, but 85% were still alive among those pretreated with 250 mg melatonin.

There is another issue, which relates more directly to leukemia and melatonin suppression. A variety of bone marrow cells have been shown to produce melatonin [Tan et al., 1999; Conti et al., 2000; Carrillo-Vico et al., 2004]. While its specific function in these cells remain unknown, if their melatonin levels are depressed by magnetic field exposure, as has been shown to be the case for pineal melatonin in a variety of studies, it could have clear implications for leukemia. A reduction in

melatonin in the leucocytic precursor cells would be expected to enhance free radical-mediated DNA damage, thereby increasing the likelihood of these cells developing tumors.

Melatonin Protects Against Oxidative Damage to the Fetus in Animals

There is compelling evidence that the initiating event(s) in childhood (ALL) appear to take place in utero [Greaves, 2002]. It is therefore of interest to note that in animals melatonin has been shown to be highly protective of oxidative damage to the fetus [Wakatsuki et al., 1999a,b, 2001; Okatani et al., 2000]. Nakamura et al. [2001] showed that in pregnant women, serum melatonin shows a diurnal rhythm which increases after 24 weeks gestation until term, and levels are related to the feto-placental unit. Okatani et al. [1998] showed that there is efficient maternal-fetal transfer of melatonin near term. These observations may reflect a role for melatonin in protecting the human fetus against oxidative damage.

DISCUSSION

Melatonin Suppression by Magnetic Fields

A feature of experiments in animals is that prolonged expose, from days to weeks was required to suppress melatonin and in rats effects were induced at relatively low fields [Kato and Shigemitsu, 1997]. There was also a suggestion that the effects of electric fields and/or rapid onset/offset magnetic fields may be particularly effective in suppressing melatonin. Such features characterize many of the exposures in Table 1 and transients magnetic fields are characteristic of neighborhood exposures generally [Kaune et al., 2000].

The findings from acute laboratory exposure contrast sharply with those in animals and in long term or chronically exposed populations, but as already discussed laboratory exposures have a number of drawbacks. Another issue is the control fields to which volunteers were exposed. For example, Warman et al. [2003b] employed acute exposes up to 300 μT and found no real evidence of melatonin disruption. However, their control level is given as <0.2 μT, which could be seen as the region where chronic exposure still results in nocturnal melatonin suppression. The situation might parallel that for visible light where linearity of pineal response extends from $\sim$10 to 200 lux but higher exposures up to 50 000 lux have little influence on melatonin levels [Zeitzer et al., 2000].

The longer term and chronic exposure studies in Table 1 lend support for melatonin disruption as assayed from the melatonin metabolite 6-OHMS in urine. However, the exposure conditions differ between studies, which were carried out at different times of the year and at widely different locations. As such it is difficult to compare studies with respect to factors such as latitude, season, and light-at-night, all of which may affect melatonin secretion. This suggests that a program of further human population studies could usefully be carried out, but with better defined and agreed protocols [see also recommendations in Warman et al., 2003a]. This should include better characterization of EMF exposures including electric fields, polarization, and transients.

Central to future work is the specific effect of EMF exposure on melatonin in children. In the unborn human fetus melatonin synthesis does not occur. Instead, melatonin may be supplied by transplacental transfer from the mother [Okatani et al., 1998]. Interestingly, maternal melatonin production increases throughout pregnancy [Nakamura et al., 2001]. Newborns do not produce significant amounts of melatonin until 6 months after birth [Tauman et al., 2002]. Thus, during fetal development and in early life there is a relative deficiency of melatonin. In a longitudinal study of 46 boys and 38 girls, Griefahn et al. [2003] showed that despite the huge interindividual differences, melatonin production remains constant in the same individual during childhood and adolescence (from age 3 to 18). The authors attribute other reports of a decrease in plasma melatonin in the young to an increase in body size rather than to decreasing pineal secretion.

Mechanisms of EMF Interaction With Melatonin

While there is evidence that chronic exposure to magnetic and/or electric fields associated with the electricity supply disrupts melatonin in humans, the detailed steps involved have not been established. In animal species, some experiments suggest retinal involvement in responding to magnetic fields, while others also suggest involvement of the pineal itself [Semm et al., 1980; Raybourn, 1983; Reuss et al., 1983; Welker et al., 1983; Olcese et al., 1985]. In general, pulsed, static, and time-varying magnetic fields have been shown to reduce various parameters of melatonin production in the mammalian pineal gland and, in some reports, circulating levels of melatonin in the blood, but in a rather inconsistent way.

Those aspects of melatonin biosynthesis which have been reported to be influenced by magnetic fields include a reduction in the activity of the rate-limiting enzyme in melatonin production, that is, *N*-acetyltransferase (NAT), and a suppression in the activity of the melatonin-forming enzyme, hydroxyindole-*O*-methyltransferase (HIOMT) (Fig. 1). Additionally, the ser-

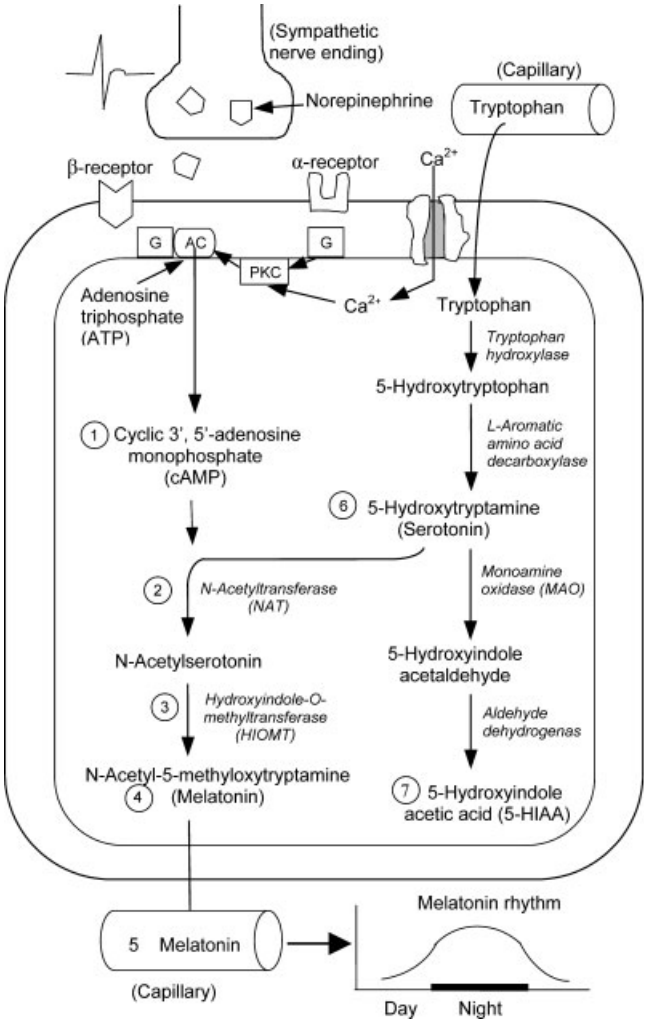

Fig. 1. Interactions of the post-ganglionic sympathetic neuron with the pinealocyte and the synthesis of melatonin. Each of the numbered sites has been reported to be influenced by magnetic fields; 1–5 are reportedly reduced and 6 and 7 are increased.

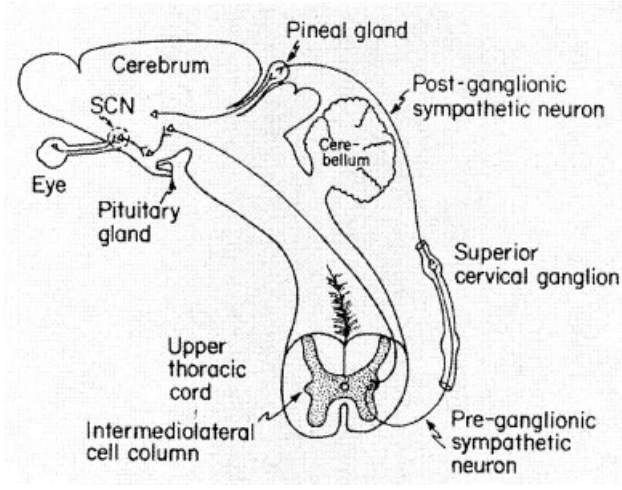

Fig. 2. Neural connections between the eyes and the pineal gland. Magnetic fields could interact with cells at any of these sites. SCN, suprachiasmatic nuclei (biological clock).

otonin concentrations within the pineal gland have been found to be elevated. These combined changes are consistent with a reduction in the conversion of serotonin to melatonin [Reiter, 1993]. While each of these observations have been reported, these parameters have not been measured in a single experiment and different outcomes have been achieved in different studies [Warman et al., 2003a]. The findings are further confounded by the fact that, as indicated above, melatonin synthesis occurs in a number of organs in addition to the pineal gland, including in the bone marrow which gives rise to leukocytes. Also, melatonin in an organism is not in equilibrium; thus, much higher levels of melatonin are found in some bodily fluids, for example, in cerebrospinal fluid and bile. Whether these levels are influenced by magnetic fields has not been tested. Finally, how magnetic fields mechanistically influence the conversion of serotonin to melatonin within the pineal gland has never been adequately determined.

Several theoretical explanations have been advanced, including (a) magnetic fields are detected by photoreceptors in the eye and interpreted as ''light'' with the resultant inhibition of melatonin; (b) an action of the fields at the level of the biological clock, that is, the suprachiasmatic nuclei, which causes it to send an appropriate signal to the pineal gland thereby either reducing the amount of melatonin or altering its rhythm; and (c) a direct interaction of the magnetic fields with the melatonin synthetic machinery in the pinealocytes themselves (Fig. 2).

More recently, another potential mechanism has been proposed which involves the generation of free radicals by magnetic fields, thereby reducing melatonin levels due to the fact that the indole is more rapidly used as it scavenges radicals. This would lead to a depression in blood and tissue melatonin levels without interfering with its synthesis [Reiter, 1998]. Of additional interest, birds are know to be able to detect very small changes in the Earth's DC magnetic field, and Ritz et al. [2004] have shown that robins can detect fields as low as 0.084 μT, consistent with a resonance effect on singlet-triplet transitions in a radical pair reaction.

While each of these above proposed mechanisms may be logical, experimental support for any one of them in humans is incomplete.

If, in fact, melatonin levels or free radical generation are altered by magnetic fields, a potential

relationship between these fields and cancer, including leukemia, would be possible. A reduction in melatonin has been linked to cancer initiation as well as to cancer progression. As an antioxidant, in many studies melatonin has been shown to protect DNA from oxidative damage; once damaged, DNA may mutate and carcinogenesis may occur. With depressed melatonin levels this possibility is enhanced. Likewise, lower than normal melatonin levels may exaggerate the growth of tumors since (a) melatonin inhibits the uptake of fatty acid growth factors by cancer cells; (b) melatonin inhibits telomerase activity in cancer cells thereby reducing telomere length and increasing the likelihood of cancer cells undergoing apoptosis [Leon-Blanco et al., 2004]; and (c) melatonin inhibits synthesis of endothelin-1, a potent angiogenic factor which promotes blood vessel growth in tumors [Bagnato and Natal, 2004]. While all these explanations are possibilities, no studies have established a definitive link between magnetic field exposure, melatonin, and cancer, including leukemia. Overall, therefore, the hypothesis that magnetic fields cause increased risk of childhood leukemia via melatonin disruption is plausible but key aspects remain to be tested.

FUTURE EPIDEMIOLOGICAL AND LABORATORY INVESTIGATIONS

Many of the aspects of the hypothesis presented here can be investigated either epidemiologically or in experimental laboratory studies. It is clear from Table 1 that there is scope for further human studies of melatonin disruption in populations exposed to both electric and magnetic fields. The noninvasive nature of the 6-OHMS assay is such that it could be applied specifically to children. At the same time it would be useful to probe in more detail the role of melatonin in the fetus and neonate.

Following the work of Vijayalaxmi et al. [1996, 1998, 1999] and Ishido et al. [2001] cited above, experiments could be carried out using cells of the human haemopoietic system in the presence of both melatonin and magnetic fields. This would test whether magnetic fields act directly in inhibiting the protectiveness of melatonin on the haemopoietic system.

Finally, the incidence of childhood leukemia has increased steadily in recent decades in most developed countries [Steliarova-Foucher et al., 2004]. The causes of childhood leukemia are largely unknown. However, if magnetic fields cause increased risk via melatonin disruption, then certainly exposure to light-at-night should do likewise. While previously unconsidered, the latter could then turn out to be an important factor in the aetiology of the disease.

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