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Is melatonin the hormonal missing link between magnetic field effects and human diseases?

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Abstract The disruption of melatonin secretion has been largely studied since it could provide the missing link between the exposure to 50/60-Hz electric and magnetic fields (EMF) and the occurrence of possible health effects as the ''melatonin hypothesis''. We analysed the current experimental data from animal (rodents) where contradictory results have been observed, and from human studies conducted with volunteers or with workers in various conditions of exposure, biological endpoints and metrics. In humans, even in long lasting exposures, the overall results of these studies do not support the ''melatonin hypothesis''. It is unlikely that malignancies or mood disorders reported by people exposed to 50/60-Hz EMF could be related to the disruption of the melatonin levels.

Keywords Melatonin · Melatonin hypothesis · Electric and magnetic fields (EMF) · Human · Animal

Introduction

The last century has seen an extraordinary growth of electric power use in industrialized countries. It was necessarily accompanied by a parallel increase of environmental exposure to electromagnetic fields (EMF) superimposed to the earth's geomagnetic field. To various degrees (domestic, professional), the human population of technologically advanced nations has been increasingly exposed to two groups of radiations: fields in relation with the electric current (50 Hz in Europe, 60 Hz in the USA) which are in the extremely low frequency (ELF) range and more recently those resulting from the use of cellular phone systems (radio frequencies 900 and 1800 MHz). Therefore, the biological effects of EMF and their possible consequences upon human health began to raise more and more scientific attention and became a recurrent subject of public debate.

This public concern was stimulated by a number of epidemiologic studies reporting a possible relation between magnetic fields and human diseases among which leukemia [1–4] and depression [5, 6] although the controversy soon developed [7, 8]. In search for a way in which EMF would affect animals and humans, both possible relations with cancers and behavioral diseases may be associated with effects on melatonin [9, 10]. Indeed the secretion of melatonin is known to be inhibited by light [11, 12] which is the visible part of the EMF, its oncostatic properties have been described [13–15] and so was its association with some depressive disorders [16] and with troubles of the circadian rhythmicity shown to generate neurobehavioral disturbances [17, 18]; thus arose a ''melatonin hypothesis'' as a tentative explanation for the occurrence of clinical disorders possibly related to exposure to EMF [19].

Effects in animals

Great care must be given when comparing data obtained in different animal species, even within a group as rodents. Indeed differences have been described between rodent species and even between pigmented and albino breeds.

Since Yellon [20] first reported a reduction of pineal and plasma melatonin peaks in Djungarian hamsters with a short

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exposure (15 min, 2 h before darkness onset) to a sinusoidal 100 μT magnetic field, many studies were carried on. The same team also obtained these results in this species with various photoperiodic conditions [21]. The same changes, also in Djungarian hamsters, were described by Wilson et al. [22] who in addition reported an increase of the concentration of norepinephrine in the area of the suprachiasmatic nuclei, the brain central rhythm-generating system.

In search for similar effects in other species, Kato et al. [23] exposed albino male Wistar-King rats for 6 weeks to a 50 Hz circularly polarized sinusoidal magnetic field with 1, 5, 50 and 250 μT intensities and also observed a drop in pineal and plasma melatonin concentrations but could not put in evidence a dose–response relationship. The same team repeated the experiment with 0.02 and 1 μT intensities in the same strain of rat and with the same protocol of exposure but with a horizontal or vertical instead of a circularly polarized magnetic field [24] and failed to find an effect on melatonin levels. Suspecting a possible interference of pigmentation Kato et al. [25] then documented in Long–Evans rats the same 0.02 and 1 μT intensities of a circularly polarized magnetic field and did indeed show a reduction of pineal and plasma melatonin concentrations.

Thus both the characteristics of the magnetic field (linear or circular polarization) the animal species and, within a species, the strain appear to determine the biologic response obtained. Bakos et al. [26] have documented the influence of the duration of exposure on male and female Wistar rats using a vertical magnetic field of 5 and 500 μT for 24 h without finding any effect upon urinary 6-sulphatoxymelatonin concentrations.

In order to compare short-term and long-term exposure effects, Selmaoui and Touitou [27] used male Wistar rats. The animals housed in a 12:12 light:dark schedule were submitted to a 50 Hz sinusoidal magnetic field of 1, 10 or 100 μT intensity, either once for 12 h or repeatedly 18 h per day for 30 days. While a single 12 h exposure to a 1 or 10 μT magnetic field had no effect on plasma melatonin levels or *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase pineal activities, a 100 μT exposure significantly decreased 30% plasma concentrations of melatonin and depressed 23% pineal NAT activity (HIOMT activity unchanged) when compared to sham-exposed rats. In turn, the 30 days repeated exposure found that while the 1 μT intensity showed no effects on pineal function, both 10 μT and 100 μT intensities resulted in an approximately 42% decrease of plasma melatonin levels, NAT activity was also decreased and HIOMT activity remained unchanged. This study showed that a sinusoidal magnetic field alters plasma melatonin levels and pineal NAT activity without modifying HIOMT activity and that the sensitivity threshold varies with the duration of exposure, thus suggesting that magnetic fields may have a cumulative effect upon pineal function.

Loscher et al. [28] studied the effects of a 24 h/day, 7 days/week, and 3 months exposure to magnetic fields on female rats bearing DMBA-induced mammary tumors; the field intensities were similar to the domestic exposures recorded close to electric power facilities. Whereas a significant decrease of blood melatonin concentrations was observed with 1 μT, no influence on the development of the mammary tumors could be put in evidence.

No clear explanation exists for these various and contradictory results. A possible change in the spatial structure of the photoreceptor pigment rhodopsin due to the electric field induced by the magnetic field has been proposed. Magnetic fields might as well change either the electrical activity of the pinealocytes or their ability to produce melatonin or both.

Effects in humans

Most of the data gathered come from studies carried on rodents, which in majority are nocturnally active species, which is not the case in monkeys and humans. Moreover, the anatomical location of the pineal gland and the geometry of the skull of rodents are largely different from those in humans.

The results obtained after a short exposure to magnetic field (30 min to 72 h) in humans are also contradictory (Table 1). Most often published studies report a lack of effect of magnetic fields upon melatonin secretion in healthy volunteers submitted to an acute exposure [29–37, 39–42, 44]. However, it cannot be excluded that a chronic exposure might affect melatonin secretion or circadian rhythm or both, in human subjects.

Experimental chronic exposure of humans is, for obvious reasons, hardly feasible and therefore studies involving long period or high intensities of exposure necessarily deal with subjects continuously exposed either at home or at their working places (Table 2).

Wilson et al. [47] studied 6-sulphatoxymelatonin excretion in volunteers sleeping with conventional electric blankets and found no changes; when the blankets were replaced by continuous polymer-wire types generating a 50% greater magnetic field, 20% of the subjects had a decrease in 6-sulphatoxymelatonin excretion that ceased when the exposure was stopped. Graham et al. [48] exposed volunteers to a 20-μT magnetic field 1 h on/1 h off with the field switched on and off every 15 s and found a drop of serum melatonin only in subjects with a low basal level of the hormone. But a replicate experiment [49] could not repeat the originally reported results.

Selmaoui et al. [29] exposed once human volunteers for 9 h at night to either a continuous or pulsed (1 h on/1 h off with the field switched on and off every 15 s) 50 Hz, 10 μT magnetic field, and again, no differences were seen in serum melatonin levels or in urinary concentrations of

Table 1 The effects of short-term exposure (30 min to 72 h) to magnetic field on melatonin secretion in humans

Reference of the study	Subjects	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluids	Sampling time	Effect of MF on melatonin secretion
[29]	16 exposed 16 controls	M	20–30	50 Hz – 10 μT Continuous and intermittent Linear and circular	23 h–08 h	Pl Mel Ur 6SM	Circadian rhythm: every 2 h during daytime – hourly at night	No effect
[30]	47	NG	NG	1 day in front of video display unit (VDU)	1 day	Mel		Decrease but exposure not exclusively related to 50/60 Hz
[31]	11 exposed 1 μT 11 exposed 20 μT 11 controls	M	19–34	60 Hz – 1 and 20 μT Intermittent Circular sinusoidal	23 h–07 h	Pl Mel	Hourly at night	No effect – No replication of the suppression by MF of men with low basal melatonin
[32]	40	M	18–35	60 Hz continuous circular sinusoidal	23 h–07 h	Pl Mel	Hourly	No effect even in men with low basal melatonin
[33]	42 controls 66 locomotive engineers	M	NG	16.7 Hz – 1 μT 16.7 Hz – 20 μT	30 min – 4 h	Ur 6SM	Morning and evening samples	No effect on morning 6SM Evening 6 SM decreased
[34]	18	M, F	24–49	50 Hz – 1 μT Continuous Linear	23 h–07 h	Pl Mel	Hourly	No effect
[35]	203	F	20–74	Residential exposure	72 h	Ur 6SM	3 daily a.m. 6SM samples, 3–6 months apart	Higher MF: lower log – 6SM Effects stronger in summer and when taking drugs reducing melatonin
[36]	21 controls 8 factory workers 31 sewing machine operators	F	43.5	Professional exposure 21 < 1 μT 10>1 μT		Ur 6SM	6SM a.m. samples twice a week for 3 weeks	Lower a.m. 6SM in operators without relation to higher MF exposure. Recovery during the week-end
[37]	142 utility workers 57 controls 29 field generation 56 field distribution	M	20–60	60 Hz professional exposure intermittent or circular 1 μT 0.2 μT 0.1 μT	72 h	Ur 6SM	a.m. samples	No effect at work 6 SM decreases at home
[38]	15 exposed 15 controls	M	18–35	60 Hz – 28.3 μT Circular	23 h–07 h 4 nights exposure	Ur Mel Ur 6SM	First-void morning urine	No effect
[39]	22 exposed men 24 exposed women	M, F	40–60	60 Hz – 28.3 μT Circular sinusoidal	23 h–07 h	Ur Mel Ur 6SM	First-void morning urine	No effect even in subjects with low basal melatonin
[40]	24 exposed Each subject is his own control	M	19–34	60 Hz – 127.3 μT Circular polarized	23 h–07 h	Ur Mel Ur 6SM	First-void morning urine	No effect

Table 1 Continued

Reference of the study	Subjects	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluids	Sampling time	Effect of MF on melatonin secretion
[41]	21	M	20–27	50 Hz – 100 μT	30 min at	Pl Mel	Blood: hourly from 20 h to 07 h	No effect
				Circular sinusoidal Continuous and intermittent	13:30 and 16:30	Ur 6SM	Urine: 3 sample collection	May have an effect on those whose melatonin concentrations are low
[42]	11	M	23–43	Direct current 2–7 μT Static exposure	22 h–07 h	Ur 6SM	4 samples per 24 h	No effect
[43]	203	F	20–74	60 Hz residential exposure	Residential	Ur 6SM	Nighttime samples	Same subjects as study of Kaune et al. [35].
				Median exposure: 0.039 μT	72 h			Decrease in women using medications only during the summer

Pl Mel, plasma melatonin; Ur 6SM, urinary 6-sulfatoxymelatonin

Table 2 The effects of long-term exposure (3 weeks to 2 years) to magnetic fields on melatonin secretion in humans

Study reference	Subjects	Sex	Age (years)	Exposure characteristics	Timing of exposure	Fluids	Sampling time	Effect of MF on melatonin secretion
[44]	42	32 F	NG[a]	CPW Electric blanket	8 weeks	Ur 6SM	Urine voidings a.m. and p.m.	No effect.
		10 M		0.2–0.6 μT				6SM decreases in 7 of 28 CPW users in the last 3 weeks. Rebound effect
[45]	9	M	23–37	Head: 50 Hz – 0.7 μT	3 weeks preexposure	Ur 6SM	Urine voidings 5 times of day	No effect on urinary melatonin
				Feet: 3.5 μT	11 weeks of exposure at night			
[46]	15 exposed 15 controls	M	32–46	50 Hz Professional and residential exposure	1–20 years	Pl Mel Ur 6SM	Circadian study	No effect on plasma melatonin, urinary 6SM and melatonin circadian profile

[a] NG, Not given

6-sulphatoxymelatonin. Graham et al. [38] evaluated 30 healthy young volunteers in a double blind test protocol. They were exposed four consecutive nights to power frequency magnetic fields with a flux density of 28.3 μT: no effects were seen on the concentrations of melatonin and 6-sulphatoxymelatonin in daily morning urine samples compared to equivalent no exposure control conditions.

Due to the aforementioned reasons the effects of long-term exposure to EMF on melatonin secretion have been less extensively studied. Among the few studies carried on with chronic exposures, that of Burch et al. [50] reports data on 6-sulphatoxymelatonin excretion in 142 post-shift workers of an electric utility. The intensity of the magnetic field (geometric time weighted average) did not modify the urinary levels, but a reduction on the excretion of 6-sulphatoxymelatonin was related with a parameter corresponding to the temporal stability (standardized rate of change metric RCMS). This effect was predominantly observed in subjects with low workplace light exposure. Juutilainen et al. [51] documented 6-sulphatoxymelatonin excretion in 39 women working in a garment industry and exposed to 0.3–1 μt as average; the authors did observe a variation of the excretion of 6-sulphatoxymelatonin during workday but failed to put in evidence a correlation between exposure and effect. More recently Levallois et al. [52] studied the levels of 6-sulphatoxymelatonin in women living in the proximity of power lines with a residential exposure to magnetic field, compared to age-matched control women with a comparable light exposure, but living far from power lines. The intensity of exposure to magnetic fields was three times greater in the exposed group but the urinary levels were comparable to the low exposed group. Hong et al. [45] chose to expose nine male volunteers for 11 weeks to an electric sheet producing a 0.7 μT field at head level and did not find any change in urinary melatonin excretion.

Last, Touitou et al. [46] examined nighttime plasma melatonin profiles and 6-sulphatoxymelatonin excretion in 15 men exposed chronically and daily for 1–20 years in working places and at home, to a 50 Hz magnetic field. The weekly geometric mean of the subjects exposure ranged 0.1–2.6 μT as compared to a control group exposed to 0.0004–0.092 μT. No evidence of a change in mean level or time pattern of plasma melatonin could be found in the exposed group and no difference in the urinary excretion of the hormone was shown.

Conclusion

In view of all these data and especially of recently obtained results on long-term exposure it appears unlikely that the clinical signs (depression, mood and sleep disorders, malignant diseases, etc.) reported in some studies of people living or working near electric lines or substations are to be associated with a disturbance in their melatonin levels. It is possible that the difference observed in animals and humans in the effects on melatonin may be due to both the differences in anatomical location and configuration of the pineal gland and the difference in rest–activity rhythms between rodent and humans. A different sensitivity to magnetic fields between species could also be part of the explanation. A greater sensitivity to magnetic fields of some human subjects cannot be ruled out but is hardly demonstrable because of the very large interindividual variability of plasma melatonin concentrations.

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