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Daytime 50 Hz magnetic field exposure and plasma melatonin and urinary 6-sulfatoxymelatonin concentration profiles in humans

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Abstract: Concern about the health effects of extremely low frequency (ELF) magnetic fields (MF) has been raised by epidemiological studies indicating an association between certain cancers and living near power lines or working in high electric field environments. Alterations in pineal function have been proposed as a mechanism through which power-frequency MFs may interact with living organisms. A double blind laboratory study was performed to evaluate daytime exposure effects of 100 μT root mean square (rms) 50 Hz MF. Three head exposure sessions of 30 min each were performed: sham, continuous, and intermittent (15 s on/off cycles) MFs were presented to each subject in early or late afternoon (13:30 or 16:30 hr). Twenty-one healthy male volunteers (20–27 yr old) participated in these 3-weekly experimental conditions. Blood samples were drawn for serum melatonin measurement, hourly at night (from 20:00 to 07:00 hr) under controlled environmental conditions. Urinary excretion of 6-sulfatoxymelatonin (aMT6s), the main melatonin metabolite, was measured for a 17 hr period, by means of urine samples taken at 19:00 hr (14:00–19:00 hr "afternoon period"), 23:00 hr (19:00–23:00 hr "evening period"), and 07:00 hr, day 2 (23:00–07:00 hr day 2 "night-time period"). There were no significant differences in either plasma melatonin or in aMT6s excretion profiles in the three experimental conditions. However, a tendency for a smaller increase of night-time urinary aMT6s after continuous MF exposure was found ($P = 0.08$) particularly in men with the lower excretion rate of aMT6s ("Low Group") ($P = 0.07$). We conclude that this study does not indicate that daytime acute MF exposure influences either melatonin secretion or aMT6s excretion. Inter-individual differences in pineal production of melatonin, however, have to be taken into account in further studies.

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Introduction

For nearly 20 yrs, there has been concern about the health effects of extremely low frequency (ELF) magnetic fields (MF), raised by epidemiological studies indicating an association between certain cancers and living near power lines or working in a high electric field environment [Portier and Wolfe, 1999]. Most studies have reported a relatively small risk, but the extensive use of electric power could result in substantial consequences for public health. Stevens in 1987, and later Stevens et al. [1992, 1997], and Stevens and Scott [1996] formulated the melatonin hypothesis which assumes that MF and electric fields may act to suppress the pineal melatonin production of melatonin which, in turn, influences breast carcinogenesis.

Wilson [1988] postulated that if long-term exposure to ELF fields causes pineal dysfunction in human beings, the changes may contribute to the onset of depression or exacerbate existing depressive disorders. The melatonin hypothesis currently represents one of the most well cited plausible

mechanisms by which EMF exposure could lead to several outcomes [Crasson et al., 1992; Reiter 1993, 1995; Lambrozo et al., 1996; Stevens et al., 1997; Reiter 1998]. Physiological and/or pharmacological levels of melatonin have been shown to modulate a variety of biological processes which are related to the regulation of circadian rhythms, seasonal reproduction, sleep, free radical scavenging, metabolism, immunity, and neoplasia [Brzenzinski, 1997]. Weak power-frequency MFs (60 Hz in the US, 50 Hz in most other countries) have also been implicated in reducing or time-shifting pineal melatonin production, its metabolite or pineal N-acetyltransferase activity in some animals. However, this was not found in all studies and depends on the species (rodents, dairy cows, lambs, or in non-human primates) and experimental protocol [review in Portier and Wolfe, 1998]. Only two animal studies describe a significant increase in serum melatonin concentration or in urinary 6-sulfatoxymelatonin (aMT6s) excretion after MF exposure, and this is explained as rebound phenomenon [Bakos et al., 1997; Niehaus et al., 1997]. A few studies have been conducted using humans. MF exposure in these experiments generally ranged from 1 to 30 μT root mean square (rms) and was presented at night-time. The first study of the Midwest Research Institute indicated a significant suppression of night-time melatonin levels with intermittent 60 Hz MF exposure in a sub-group of subjects whose melatonin secretion was lower than normal. However, these results were not replicated in a follow-up study [Graham et al., 1996] nor in the recent study [Graham et al., 2000] or in a study where men were exposed to MF continuously, rather than intermittently throughout the night [Graham et al., 1997]. Likewise, Selmaoui et al. [1996] found no difference in serum melatonin levels or in 6-hydroxymelatonin sulfate (6-OHMS) excretion in exposed men compared with control subjects during night-time continuous or intermittent 50 Hz linearly polarized MF of 10 μTrms. Only one study indicated changes in plasma melatonin profiles, when exposure preceded onset of the rise in melatonin concentration [Wood et al., 1998].

Some studies have been undertaken in real life conditions, among electric utility workers [Burch et al., 1998, 1999], Swiss railway workers [Pfluger and Minder, 1996], video display unit workers [Arnetz and Berg, 1996] or among nightly electric blanket users [Wilson et al., 1990]. They indicate slight alterations in the urinary excretion of the melatonin metabolite after daytime exposure to MF; however, the perturbations were not consistent across studies, which were subjected to confounding bias like differential light exposure. More recently, Juutilainen et al. [2000] undertook a study to determine if daytime occupational exposure to MF alters nocturnal melatonin production in humans. They showed lower average 6-hydroxymelatonin sulfate (6-OHMS) among garment industry workers than in the reference group.

Although no theoretical or biophysical rationale is provided for why or how brief head exposure, when melatonin is almost non-existent in the circulation, could influence subsequent night-time secretion of this hormone that is released from the pineal into the circulation almost as quickly as it is produced, laboratory study has been conducted to test power-frequency daytime exposure in humans. In the present report, we describe the results of a double blind human study designed to determine whether daytime exposure to 100 μTrms 50 Hz MF can affect melatonin secretion and urinary aMT6s excretion in healthy humans. The question of intermittent vs. continuous exposure to MF has not been resolved [Graham et al., 1996, 1997], so the study population was subjected to three different head exposures, one sham condition and two real MF exposures: continuous (field on for 30 min) and intermittent (field 15 s on/off for 30 min). We chose a field-strength (100 μTrms) similar to that in the proximity of some household and industrial electrical appliances. Other parameters were assessed in this study (psychological and psychophysiological) and are described elsewhere [Crasson et al., 1999].

Material and methods

Subjects

Twenty-nine male subjects were recruited for this study. They were aged from 20 to 35 yrs old and most of them were local university students or local residents, a region centred around 50°50′. Each was offered a complete and accurate description of the aims, risks, and benefits of the study and was submitted to psychological (self-reported scales) and physical (medical and biological) examinations. Four subjects were excluded because of biological abnormalities (blood analysis) and one because of psychophysiological recording difficulties in the pre-tests. One discontinued after the first exposure session because of anticipated anxiety and subjective complaints of concentration difficulties, hypersomnia and excessive fatigue feelings attributed to the presumed MF exposure. Upon opening of the exposure order codes, the subject had been sham exposed. The data of two

subjects were deleted from the analysis when equipment problems invalidated 1 day of the experiment.

The remaining 21 subjects met all requirements for the study: good general health, normal weight, no history of chronic disease or neurologic or psychiatric illness, no medication use, no alcohol, drug or tobacco (< 20 cigarettes/day) abuse and no metal intra-cranial prosthesis or implant. They were instructed to eat balanced meals and were not allowed to drink alcohol or caffeine 12 hr before and after each experimental day.

The mean age was 23 ± 2 (range, 20–27 yr). The Institutional Ethics Board approved this study, and informed consent was obtained from all subjects.

Exposure facility and study design

The exposure facility has been described previously [Crasson et al., 1999]. In summary, the sinusoidally MFs linearly polarized, were generated by a "magnetic helmet" specifically designed and constructed for this experiment by the Department of Applied Electricity (University of Liège, Belgium, W. Legros and P. Scarpa) to expose the human head to maximally reduced electric fields and homogeneous 50 Hz MF. It is a cubic structure formed by six Helmoltz coils, 35 cm in diameter, distributed in the three orthogonal directions allowing human cephalic exposure. Each axis of the MF can be independently energized from an adjustable transformer. For both real exposure sessions (continuous and intermittent), two pairs of coils were energized, in phase, to produce a uniform oblique 100 μTrms 50 Hz MF which, because of the physical installation of the apparatus, was parallel to the direction of the local geomagnetic field.

For the intermittent exposure, an automatic time switch operated the temporal cycle. A relay was operated every 15 s without consideration of voltage or current zero crossing. Therefore, some transients existed in the generated MF, although their magnitude was limited by the, mainly, inductive electrical circuit.

For the continuous exposure, the time switch was off and MF was presented without disconnection during the entire exposure session. In sham exposure, the field was off during the whole exposure session. Ambient alternative current (AC) field strength in the experimental room was checked using an EMDEX II (Enertech-EPRI) dosimeter and was ≤ 0.06 μTrms. Local geomagnetic field (DC field), measured with a Gaussmeter RFL912, was 40 μTrms at an inclination of 60° N.

The double blind strategy assumed that subjects were randomly assigned to exposure order, and the field generated by an operator not involved in the study nor present during the exposure and testing sessions. Each subject participated in three 30 min exposure sessions, spaced 1 wk apart. The experimental conditions consisted of one sham field condition and two real MF exposure conditions; one continuous (field on for 30 min) and one intermittent exposure (field 15 s on/off for 30 min). MF amplitude was set at 100 μTrms at 50 Hz. A preliminary study showed that the volunteers did not perceive the MF generated by the "magnetic helmet" [Crasson et al., 1993]. However, after each exposure session, subjects noted whether the fields were on or off and were asked upon which indices they had based their judgements. They noted their responses on a field detection questionnaire, a French adaptation of the Field Status Questionnaire (FSQ) [Cook et al., 1992].

Each of the 21 subjects participated in the 3-weekly experimental sessions. In order to test a maximum number of volunteers in the same season, two subjects were exposed each afternoon. Thus, from the 21 subjects, 10 were exposed at 13:30 hr and 11 at 16:30 hr. They arrived 30 min before the exposure session and remained in the hospital until the next morning. They went in their sleeping room at 19:00–07:00 hr for blood and urinary sample collection, in controlled lighting conditions. Between 20:00 and 23:00 hr, lighting was set at 50 lux to provide the opportunity to read or study. Subjects were not allowed to watch television to control for electromagnetic field exposure and lighting differences. Sleeping was allowed only while the lights were off, between 23:00 and 07:00 hr. During this time, a 5 lux light was kept on in the corridor to permit blood sampling without interfering with melatonin production.

Data collection and radioimmunoassay

Blood samples and urinary collections were performed in this study. At 19:50 hr, for blood sampling, an indwelling catheter was inserted into an antecubital vein. The intravenous line was kept patent with a slow drip of heparinized saline. Blood samples were drawn at hourly intervals over a 12 hr period from 20:00 to 07:00 hr. At every sampling, 5 ml of blood was collected through a three-way stopcock, immediately transferred to heparinized plastic tubes, and stored at 4°C before being centrifuged and stored at -20°C until analysis.

Urinary excretion of aMT6s, was measured for a 17 hr period, through urine samples provided at

19:00 (14:00–19:00 hr, "afternoon period"), 23:00 (19:00–23:00 hr, "evening period") and 07:00 hr day 2 (23:00–07:00 hr day 2, "night-time period"). Total urine volumes were measured for each sampling period. Each urine sample was immediately frozen at -20°C. All samples were collected from March to June.

Urine and blood samples were analysed by radioimmunoassay (RIA). Assays were done within 6 months after collection. A double blind procedure was installed and samples were coded so that personnel who conducted the RIAs were unaware of whether blood samples were from real or sham exposure days. All samples from a given participant were analysed in the same assay by RIA methods described previously [Claustrat et al., 1984; Harthé et al., 1991]. The sensitivity of the melatonin assay was 5 pg/mL. For 100 pg/mL melatonin, the intra- and inter-assay coefficients of variation (CV) were 4 and 10.5%, respectively ($n = 20$). Plasma melatonin concentrations are expressed in pg/mL. The maximum melatonin level was defined as the highest melatonin level recorded for a subject for the night (from 20:00 to 07:00 hr). The peak time was the time at which the maximum melatonin level occurred. For an aMT6s concentration of 300 pmol/L, the intra-assay CV was 8% and the inter-assay CV was 12%. aMT6s values are expressed by the average hourly excretion (ng/hr) for each sampling period (afternoon, evening and night-time periods).

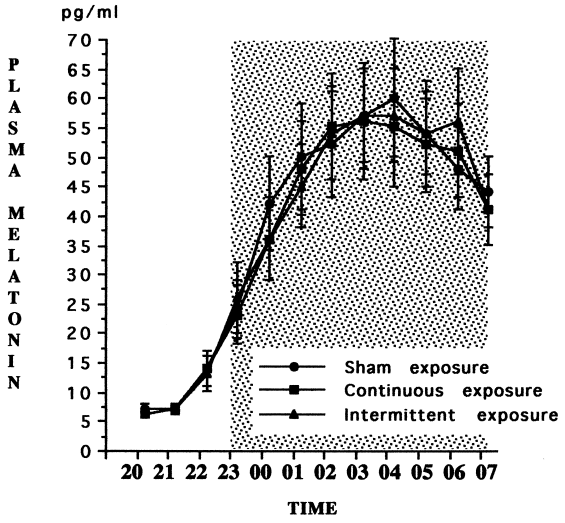

Fig. 1. Nocturnal plasma melatonin concentrations (pg/mL) after sham, continuous, and intermittent exposure sessions to a 50 Hz MF of 100 μTrms. Each time point is the mean and S.E.M. of the 21 subjects, from 20.00 to 07.00 hr. The shaded area represents the period of darkness (light ≤ 5 lux).

Statistical analysis

MF exposure effect was defined as the difference in urinary aMT6s or plasma melatonin concentrations measured after the sham and the two real MF exposures at any period of sampling. The differences were tested using a three-way repeated measure analysis of variance (ANOVA-R). ANOVA for repeated measurements was applied to reveal inter- and intra-individual differences in melatonin secretion and aMT6s excretion. Post-hoc analysis was conducted when significant results emerged to specifically determine between which conditions the statistical differences occurred. Exposure time (13:30 vs. 16:30 hr) was included in the analysis as a covariable. Additional ANOVAs were computed with the order level as between subject factors, therefore, checking the effectiveness of the counterbalancing procedure. All statistical hypotheses were tested at the *P*-value 0.05 level of significance. Results obtained were expressed as mean $\pm$ S.E.M. Regression analysis was used for plasma melatonin and urinary aMT6s correlation studies. The χ^2 non-parametric test was used to analyse FSQ data.

Results

The FSQ data indicated that subjects were unable to detect the presence of the MF in the helmet in the two experiments [Crasson et al., 1999].

The night-time melatonin plasma concentrations (from 22:00 to 06:00 hr) as well as the maximum melatonin level, are highly correlated with night-time urinary aMT6s levels (from 23:00 to 07:00 hr period), with the highest correlation coefficient at 02:00 hr; $r = 0.83$ ($P = 0.0001$, $F = 41.66$, d.f. $= 1.20$).

A total of 755 blood samples were collected from the 21 subjects exposed in the three experimental sessions. Only two sets of data are missing (20:00 hr sampling for two subjects in one condition).

Fig. 1 shows group average levels and S.E.M. of plasma melatonin concentrations every hour from 20:00 to 07:00 hr for sham condition, continuous, and intermittent MF exposures. The secretory profile shows that melatonin production increases in the evening, corresponding to the onset of darkness, peaks in the middle of the night (between 03:00 and 04:00 hr), and gradually falls during the second half of the night, in the three experimental conditions. Large inter-individual variations are exhibited compared with the intra-individual variations, as described in the literature [Bergiannaki et al., 1995]. The group exposed at 13:30 hr did

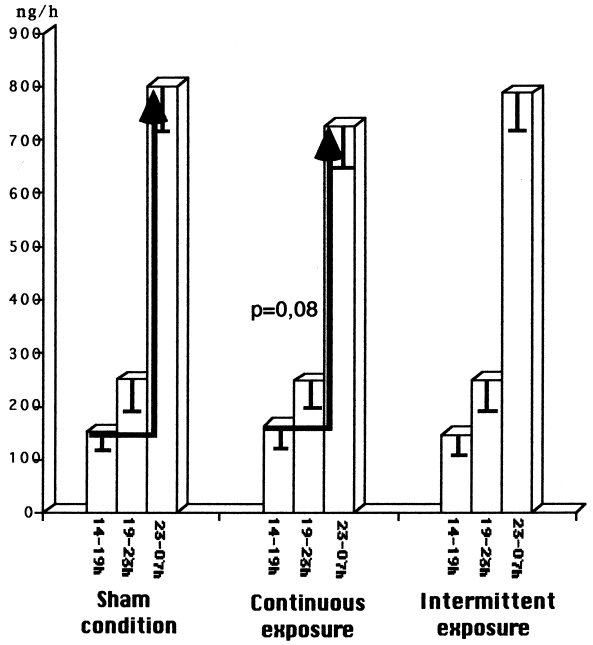

Fig. 2. Urinary concentrations of aMF6s (ng/hr) in the afternoon (14.00–19.00 hr), in the evening (19.00–23.00 hr) and in the night (23.00–07.00 hr) in the three exposure conditions: sham condition (left), continuous MF exposure (center) and intermittent MF exposure (right). Arrows indicate the nocturnal increase of aMT6s level from the afternoon levels.

not differ from the group exposed at 16:30 hr, based on their plasma melatonin values.

Statistical analysis indicates that plasma melatonin levels were unaltered after MF exposure; sham, continuous, and intermittent MF exposure data were not significantly different from one another. No difference was found in maximum melatonin levels between exposure sessions, reaching 70 ± 10 (S.E.M.) pg/mL after sham condition, 65 ± 10 pg/mL after continuous and 65 ± 9 pg/mL after intermittent MF exposure. Finally, no difference was found in peak times between the three conditions. Moreover, maximum levels were very reproducible between conditions in the same individual (correlation coefficients between 0.83 and 0.91, $P = 0.0001$), indicating that the melatonin excretion profile within the same individual is rather stable.

The 189 urinary samples showed that aMT6s concentrations were low during the afternoon, increased in the evening and reached maximum values at night. The night-time aMT6s excretion values were significantly lower in the 13:30 hr group in each of the three experimental conditions: sham (mean $\pm$ S.E.M. $= 550.1 \pm 69.1$ vs. 1031.1 ± 145.1 ng/hr, $P = 0.01$, $F = 8.4$, d.f. $= 1,20$), continuous MF (542.4 ± 3.5 vs. 892.5 ± 122.1 ng/hr, $P = 0.04$, $F = 5.03$, d.f. $= 1,20$) and intermittent MF exposure (602.1 ± 70.6 vs. 953.6 ± 131.3 ng/hr, $P = 0.03$, $F = 5.2$, d.f. $= 1,20$).

The ANOVAs for repeated measures with period of exposure as a covariable, indicated that there were no differences in afternoon, evening, and night-time urinary averaged aMT6s concentrations between exposure conditions. However, the difference calculated between night-time and afternoon levels indicated a tendency for a smaller increase in night-time aMT6s concentration (23:00–07:00 hr) compared with the afternoon level (14:00–19:00 hr) ($P = 0.08$, $F = 2.47$, d.f. $= 2,38$). Post-hoc analysis indicated that this tendency differentiates continuous MF and sham conditions. Sixty-six percent ($n = 14/21$) of the subjects showed this smaller increase, which represents a difference mean of 85.6 ng/hr (Fig. 2). No field condition vs. period of exposure was seen in urinary pineal related parameters.

Based on previous work of Graham et al., we also tested the difference between individuals according to their melatonin secretion and aMT6s excretion. The plasma data of melatonin obtained under sham condition were divided at the median value into a "Low mel group" of 11 men with sham exposure maximum value less than 55 pg/mL and a "High mel group" of 10 men with sham exposure maximum value greater than 55 pg/mL. No significant difference was found involving exposure condition.

The urinary data of night-time aMT6s obtained under sham condition were divided at the median value into a "Low aMT6s group" of 11 men with sham exposure value less than 626 ng/hr and a "High aMT6s group" of 10 men with sham exposure greater than 626 ng/hr. No significant difference was found involving exposure condition. But, when ANOVAs were performed on the two subgroups separately, a tendency for a lower increase of aMT6s levels after continuous MF exposure from the afternoon to the night (night-time – afternoon measures) was seen in the low group only ($P = 0.07$, $F = 3.01$, d.f. $= 2,18$). The analysis showed that order level did not have any influence on plasma melatonin and aMT6s concentrations or any interaction with sham or real MF exposure.

Discussion

One frequently cited biological effect of animal exposure to electric fields and MFs is inhibition or phase shifting of the normal night-time levels of melatonin. The consequences of perturbed melatonin production in terms of cancer, depression, immunity and circadian rhythm disruption is of great interest in investigating whether or not MF

exposure may alter concentrations of this hormone in the pineal gland and blood [Wilson et al., 1989; Reiter, 1995; Ronco and Halberg, 1996; Stevens et al., 1997; Baldwin and Barrett, 1998]. Little is known, however, of the effective physical parameters and the mechanisms by which the fields act on the cells and/or the tissues [Schneider and Semm, 1992; Portier and Wolfe, 1998].

There have been too few studies on the 50–60 Hz electric field and MF effect on human melatonin concentration to conclude an ELF MF influence on pineal function. Moreover, in regard to the occupational studies, no laboratory research has been conducted to analyse the effect of 50 Hz MF daytime exposures on melatonin production in humans. The present study was undertaken to test the hypothesis that daytime exposure to MF results in a suppression of the pineal melatonin or its major urinary metabolite (aMT6s) in humans. We exposed healthy volunteers to 50 Hz MF of 100 μTrms for 30 min in the afternoon and measured their night-time plasma melatonin and urinary aMT6s concentration profiles. Each subject was submitted to three experimental conditions: one sham and two real MF exposures: a continuous one (field on during the 30 min of exposure) and an intermittent one (15 s on/off cycles) with a counterbalancing mode of presentation between subjects and 1 wk between each exposure session. Although there was no significant difference in urinary aMT6s level after exposure conditions, there was a tendency ($P = 0.08$) to a lesser night-time increase of aMT6s from afternoon level after continuous MF exposure related to the sham condition. Dividing men into two groups (''Low and High aMT6s Group'') according to their aMT6s night-time values, the same tendency ($P = 0.07$) was found in the ''Low aMT6s Group'' only.

There is no reliable evidence that inter-individual differences in the pineal production of melatonin have to be taken into account. However, it could be interesting to consider this known inter-individual difference observed in healthy subjects [Bergiannaki et al., 1995], according to the divergent results related to this issue [Graham et al., 1996; Karasek et al., 1998; Wood et al., 1998].

In this study, MF was set at 100 μTrms, a field strength similar to that in the proximity of some household and industrial electrical appliances or supply. It is also the limit recommended for general public exposure to 50–60 Hz on a continuous basis by the International Non-ionizing Radiation Committee of the International Radiation Protection Association [1998]. However, this study does not indicate if lower or upper field strength would be more or less effective in influencing pineal function. Other characteristics could be of importance in terms of pineal function including field direction, duration of exposure, single vs. chronic exposure, rate of change of the electromagnetic environment, exposure time, individual sensitivity to light, etc.

In a recent study, Karasek et al. [1998] showed that 40 Hz daytime MF exposure induced a significant depression in nocturnal melatonin rise of patients with low back pain syndrome, regardless of time of exposure (10:00 or 18:00 hr). It is the first study to show that daytime MF exposure can influence night-time production of melatonin in controlled conditions. Two main differences with our study should be underlined: the shape of the MF (square wave vs. sin wave) and the rate of exposure (chronic (3 wk, 20 mm/day, 5 days/wk) vs. single exposure). Again, the particular features of the experiments should be analysed in determining the most relevant parameters for pineal function changes. The latest study of Karasek et al. [2000] illustrates this assumption. With a MF exposure of 25–80 μTrms at 200 Hz, no changes in melatonin concentrations were observed either after 1 day or after 1 month following the MF daytime exposure in comparison with baseline.

Another question raised is why urinary aMT6s concentrations show results slightly differing from blood melatonin results, these two parameters being otherwise highly correlated? The correlation between night-time concentrations of melatonin in plasma and urinary aMT6s excretion indicate that a night-time urine sample is a good index of the endogenous production of melatonin in plasma, as previously described in literature [Markey et al., 1985; Bojklowski et al., 1987; Graham et al., 1998]. As melatonin has been reported to be secreted in discrete brief episodes superimposed on the baseline concentration in humans [Weitzman et al., 1978; Wetterberg, 1978; Vaughan et al., 1979], urinary samples also appear to be more informative than hourly blood values because they integrate the total production of melatonin [Wetterberg, 1978; Cook et al., 1997]. This explains why small differences could be revealed through total urine sampling or very close blood sampling.

In conclusion, the nocturnal plasma melatonin data from this study of 21 men, exposed to these MF presented continuously (without break) and intermittently (cycles 15 s on/off) relative to sham condition, do not support the hypothesis that daytime exposure to 50–60 Hz MFs alters melatonin secretion and aMT6s excretion. It is, however, too early to conclude that pineal function in humans is unaffected by MF exposure before further examining the MF effect with different experimental and technical characteristics of exposure.

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