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ORIGINAL ARTICLE

**Barbara Griefahn · Christa Künemund
Meinolf Blaszkewicz · Klaus Golka · Gisela Degen**

Experiments on effects of an intermittent 16.7-Hz magnetic field on salivary melatonin concentrations, rectal temperature, and heart rate in humans

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Abstract ***Objectives***: The present experiments concerned the hypothesis that an intermittent, strong and extremely low frequency magnetic field reduces salivary melatonin levels and delays consecutively the nadirs of rectal temperature and heart rate. ***Methods***: Twelve healthy young men (18–25 years) participated in three randomly permuted sessions, which were performed as constant routines. The participants kept a strict bed rest over 26 h, air temperature was 20 °C, illumination < 30 lx, and sound level < 50 dBA. Salivary melatonin levels were determined hourly, rectal temperature and heart rate were registered continuously throughout. An intermittent magnetic field was administered in one session from 6 p.m. to 2 a.m. at 16.7 Hz, 0.2 mT and alternating on/off-periods of 15 s. This situation was compared with a control session without any additional stress. Another session was performed to determine the participants' ability to respond to a well-known melatonin-suppressing stress, namely bright light (1,500 lx, 10 p.m.–2 a.m.). ***Results***: Bright light inhibited melatonin synthesis in all 12 participants and delayed the nadirs of rectal temperature and heart rate. The only significant alteration that was associated with exposure to the magnetic field was a delay in the heart rate nadir, which was not mediated by an accordingly altered melatonin profile. ***Conclusion***: The fact that the circadian rhythm of only the heart rate was altered indicates an internal dissociation which might constitute a health risk in the long run and needs to be investigated more extensively.

Keywords Salivary melatonin concentrations · Rectal temperature · Heart rate · Circadian rhythm

B. Griefahn (✉) · C. Künemund · M. Blaszkewicz
K. Golka · G. Degen
Institute for Occupational Physiology,
University of Dortmund, Ardeystrasse 67,
44139 Dortmund, Germany
E-mail: griefahn@arb-phys.uni-dortmund.de
Tel.: +49-231-1084221
Fax: +49-231-1084400

Introduction and objectives

It has been repeatedly shown that bright light suppresses melatonin production in animals and in humans (e.g., Boivin and Czeisler 1998; Lewy et al. 1980). Similar though far smaller effects have been ascertained for nocturnally active small animals exposed to extremely low frequency magnetic fields [reviewed by Brainard et al. (1999)] but they are debatable for humans and the few experiments executed so far revealed contradictory results, which might be ascribed to the mode and the time of exposure as well as to the strength of the field. If applied continuously, neither weak nor strong magnetic fields affected melatonin synthesis or other physiological functions [Åkerstedt et al. 1999 (1 μT), Graham et al. 1996a (20 μT), Griefahn et al. 2001 (200 μT)], but there is some evidence that intermittent fields might evoke changes. Graham et al. (1996b) registered reduced plasma melatonin concentrations in persons with habitually low levels (60 Hz, 20 μT, 15-s on/off-periods) and Wood et al. (1998) observed a partial inhibition of melatonin synthesis, but, however, only if they administered the field (50 Hz, 20 μT, 15-s on/off-periods) during the usual onset and rise of nocturnally elevated melatonin synthesis. Concerning the field strength, it is well known that humans need much higher illumination levels than animals for melatonin suppression (Lewy et al. 1980) and this might also be true for magnetic fields and the reason for the lack of effects in previous studies.

The present study was performed to prove the accordingly derived hypothesis that an intermittent, very strong, and extremely low frequency magnetic field (16.7 Hz, 200 μT, 15-s on/off-periods) affects melatonin synthesis if applied during the sensitive period where nocturnally elevated melatonin production starts and rises. As melatonin is assumed to mediate the circadian rhythm of physiological functions, consecutive delays of the nadirs of rectal temperature and of heart rate were expected as well (Cagnacci 1997).

The study concerns 16.7-Hz magnetic fields that are emitted by railways in several countries, to which many persons are regularly and frequently exposed, namely residents living beside railway tracks, commuters, and the employees of railway companies.

Material and methods

Participants

The study was approved by the local ethics committee. Twelve healthy young men, whose data are listed in Table 1 were selected on the basis of a questionnaire on health, particularly on symptoms and diseases concerning the central nervous system. They were informed about the goal and the procedure of the study and gave their written consent. They could withdraw at any time.

Experimental design

The monitoring of melatonin synthesis and of rectal temperature determined the experimental design and procedure. The highly reproducible diurnal pattern of melatonin synthesis in the same individual and the great inter-individual differences (Shanahan and Czeisler 1991; Shanahan et al. 1997) required within-subject comparisons between control and exposure sessions, which were performed by identical protocols.

Each subject participated at weekly intervals in three randomly permuted 26-h sessions. An intermittent magnetic field (16.7 Hz, 0.2 mT, 15-s on/off-periods) was applied from 6 p.m. to 2 a.m. (Central European Time) in one session which was compared with a control session without any additional stress. Bright light (1,500 lx, 10 p.m.–2 a.m.) was applied in another session to determine the ability of the individuals to respond to a well-known melatonin-suppressive stress.

Technical equipment

The experiments were performed in two rooms. The equipment was computer-controlled and the physical and physiological data were monitored on screens in rooms which were not directly connected with the test rooms and to which only the technical personnel had access.

Magnetic field

The control session and the exposure to the magnetic field took place in the same sound-attenuated room. We presupposed that the participants were unable to perceive the field consciously and thus did not know the date and the time of field exposure. The bed, which contained no metal, was located between two Helmholtz-coils with a diameter of 1.80 m each and an inter-coil distance of 92 cm. Homogeneity of the horizontally oriented field was assessed with measurements at 14 grid points in up-down direction and 12 points each in back-front and in left-right directions. The results revealed a minor decrease in the intensity at the margins of the field (up–down (mean/SD): 0.171/0.030 mT; back–front: 0.177/0.022 mT; left–right: 0.217/0.011 mT).

An extremely low frequency magnetic field (16.7 Hz) was applied from 6 p.m. to 2 a.m. with a flux density of 200 μT. Intermittency was achieved by alternating on-and-off periods every 15 s, thus resulting in 960 presentations overall. The predefined field strength and the off condition were reached within 0.3 s. The hum from the coils was not audible. The coils were not energized during the control session.

Table 1 Personal data of the 12 male participants. Means, standard deviations (*SD*), minima and maxima

Variable	12 Male participants	
	Mean ± SD	Min–max
Age (years)	22.4 ± 2.2	18.0–25.0
Weight (kg)	74.1 ± 12.0	60.6–102.6
Height (cm)	181.7 ± 7.6	172.0–194.0
BMI	22.4 ± 2.6	17.7–28.1

Bright light

Exposure to bright light was performed in a climatic chamber where the entire ceiling was covered with fluorescent tubes which provided white light (OSRAM L58 W/12, Lumilux de Luxe, daylight, 12–950). Flickering was prevented by a special device (Professional QTP 2*58/230–240). The tubes were separately controlled and the illumination level was adjusted from 10 p.m. to 2 a.m. to 1,500 lx for the gaze directed towards the light source.

Experimental procedure

Prior to each session, the participants stated their actual health state, well being and consumption of alcohol or drugs. Based on the answers, none of the experiments was postponed. After the application of the thermistors for rectal temperature and the electrodes for the electrocardiogram the participants went to bed, and the constant routine protocol was started. This protocol was developed to minimize masking influences on core body temperature (Czeisler et al. 1985). It consisted of a strict 26-h bed rest (10 a.m. to 12 p.m. the next day), where air temperature was adjusted to 20 °C, illumination to < 30 lx and sound level to < 50 dBA and where the participants were unaware of the time. After giving saliva samples every full hour they received snacks (200–400 kJ) and water or herbal tea ad libitum. The remains were removed half an hour later. Thus, the experimenters entered the test rooms every 30 min. In the meantime, the participants were allowed to read, write or sleep. Apart from the application of the physical stress, the procedure was the same during the exposure sessions.

As melatonin levels decrease in the supine posture and rise in the erect posture (Deacon and Arendt 1994) and reach steady states after about 20 min, the participants left the bed only to use the bathroom soon after saliva sampling.

Melatonin concentration

Saliva samples were collected every full hour using the Salivette (Sarstedt, Nuembrecht, Germany), a cotton wool swab which was moved within the mouth until soaked with saliva. The swabs were immediately centrifuged and the saliva was then stored at –20 °C until required for assay. Melatonin concentrations were determined by means of a commercial competitive radioimmunoassay (RIA, IBL, Hamburg, Germany) with ^{125}I-labeled melatonin which was registered by γ-counting and finally analyzed with a standard curve. The limit of detection was about 0.8 pg/ml saliva. Most samples were analyzed in duplicate. The within and between variabilities were 11.5% and 2.6%, respectively, compared with a reference value of 11.1 pg/ml.

Rectal temperature and heart rate

Rectal temperature was measured continuously with thermistors (YSI 401 Yellow Springs) 10 cm beyond the sphincter. Heart rate was calculated from the continuously recorded ECG (the leads were not disturbed by the magnetic field).

Statistics

The temporal and the quantitative parameters of melatonin synthesis, rectal temperature and heart rate were determined from fitted curves. Two models were applied to the courses of melatonin synthesis. The model proposed by Brown et al. (1997) gives a fairly good estimation of the individual onset and offset. The acrophase was estimated from the model provided by Lerchl and Partsch (1994). The correlation between observed and predicted melatonin levels was sufficiently high, and the correlation coefficient was lower than 0.8 in five out of 36 cases and above 0.9 in 24 cases.

The analysis of rectal temperature and heart rate rhythms was based on the "harmonic regression plus correlated noise" model proposed by Brown and Czeisler (1992). This model was adjusted, insofar as the periodic signal was described by a three-harmonic regression model and the correlated noise in the data was assumed to be a first-order autoregressive process. The model parameters were estimated by a maximum likelihood procedure. The models fitted very well to the recorded data. In each case the correlation between observed and predicted values was above 0.9 in 89% of the sessions (including exposure sessions).

With rectal temperature and heart rate showing steady initial declines in all test persons (due to physical inactivity), values for the first 2 h were excluded from the overall assessment. The remaining data were then averaged over every consecutive 10-min interval for rectal temperature and 8-min interval for heart rate. For the parameter estimation in the harmonic-regression model the circadian period was assumed to be constant at 24 h.

Results

The courses of melatonin levels, rectal temperature, and heart rate

Figures 1, 2 and 3 present the courses of salivary melatonin concentration, rectal temperature, and heart rate as averaged over the individually fitted curves of the 12 men, separately for the three conditions. During control, melatonin concentrations (Fig. 1) exceeded daytime levels at about 9 p.m.; they rose until 2 a.m, and then declined, first slowly and then rapidly to reach the baseline between 9 a.m. and 10 a.m. The corresponding course ascertained under exposure to the magnetic field was almost identical, though the maximum was somewhat higher. Exposure to bright light resulted in a biphasic curve. After an initial increase at exactly the same time as during both the other sessions, melatonin levels declined under the influence of bright light to daytime levels, but synthesis was immediately resumed upon return to dim light and increased steeply to reach the maximum between 5 a.m. and 7 a.m. The maxima were somewhat lower than during the other sessions, but actual concentrations were in the same range as those monitored at the same time during the other two conditions.

The courses of rectal temperature (Fig. 2) were almost identical during the control and the field conditions. Exposure to bright light caused a less-steep decline after 10 p.m. and a delay in the nadir. The courses of heart rate (Fig. 3) during exposure to both bright light and magnetic field revealed a moderate shift of the nadir. (The slightly higher heart rate in the bright-light condition had already been found at the beginning and was, therefore, not determined by light).

The effects of bright light and of the magnetic fields

Several temporal and quantitative parameters were derived from the individually fitted curves of the melatonin profile [onset, acrophase, offset, duration, maximum, area under the curve (AUC), density (AUC/duration)] as well as of the curves of rectal temperature and heart rate (acrophase, nadir, maximum, minimum, mesor, amplitude). The differences between control and exposure conditions are listed in Tables 2 and 3 together with the corresponding P values as determined by the nonparametric Wilcoxon test (2-tailed). As the curves in

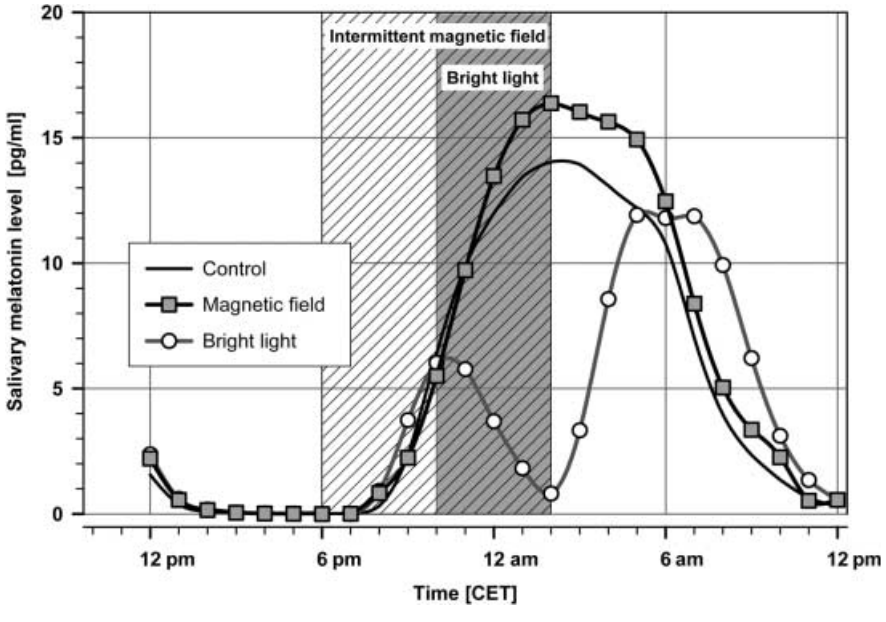

Fig. 1 Averaged courses of hourly determined salivary melatonin levels in 12 healthy young men during control, with a 4-h exposure to bright light (1,500 lx) and an 8-h exposure to an intermittent magnetic field (16.7 Hz, 200 μT, 15-s on/off-periods)

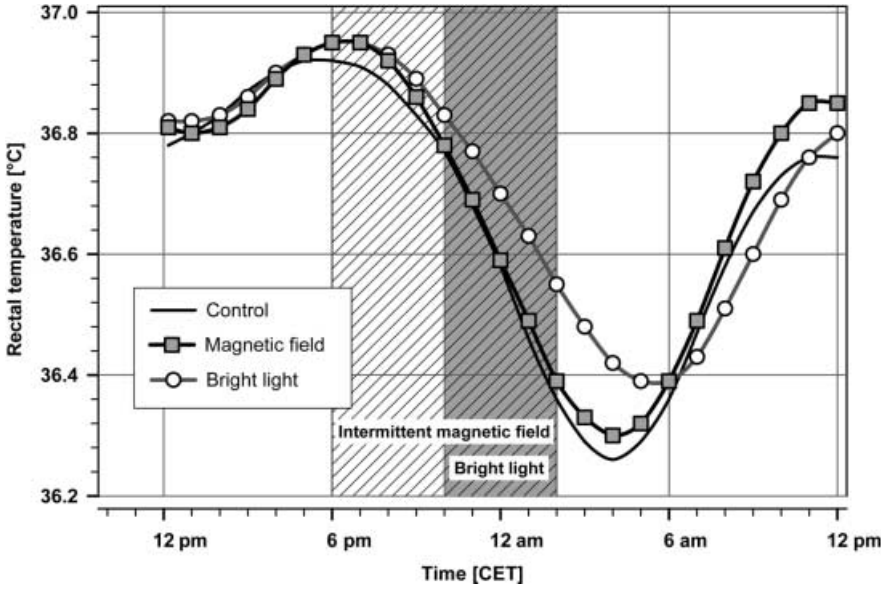

Fig. 2 Averaged courses of rectal temperature in 12 healthy young men during control, with a 4-h exposure to bright light (1,500 lx) and an 8-h exposure to an intermittent magnetic field (16.7 Hz, 200 μT, 15-s on/off-periods)

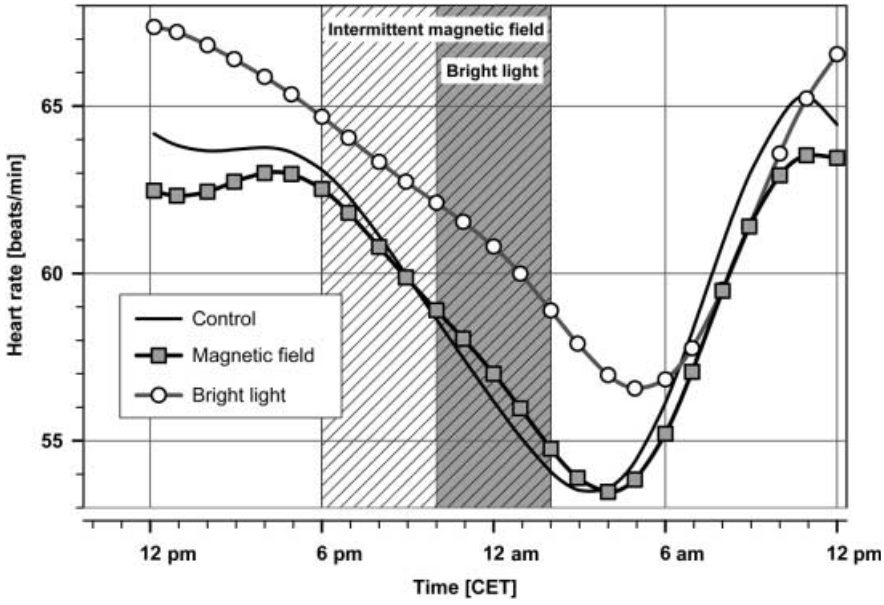

Fig. 3 Averaged courses of heart rate in 12 healthy young men during control, with a 4-h exposure to bright light (1,500 lx) and an 8-h exposure to an intermittent magnetic field (16.7 Hz, 200 μT, 15-s on/off-periods)

Figs. 1, 2 and 3 present averages, some moderate deviations between the data in the table and in the figures are unavoidable.

Compared with the control condition, none of the melatonin parameters was affected by the magnetic field, whereas bright light suppressed the synthesis soon after exposure onset in all the 12 subjects and caused significant delays in onsets, acrophases, and offsets of the major portion of nocturnally elevated melatonin levels (5 h 39 min, $P=0.001$; 3 h 02 min, $P=0.034$; 1 h 53 min, $P=0.002$). The duration of synthesis was reduced by 1 h 40 min ($P=0.014$) and the total amount (AUC) by 40% (45 pg/ml*h, $P=0.005$).

Apart from a significant delay in the nadir of heart rate under the influence of bright light and magnetic field (1 h 55 min, $P=0.005$; 59 min, $P=0.012$), no other changes could be ascertained for rectal temperature and for heart rate.

Discussion

It was hypothesized that an intermittent, very strong, and extremely low frequency magnetic field (16.7 Hz, 200 μT) reduces melatonin synthesis if administered during the period where nocturnally elevated melatonin production starts and rises, and that this mediates a delay in the nadirs of rectal temperature and heart rate.

A total of only 12 participants might be regarded as small, but it proved to be sufficient with respect to the statistical power, and is even higher than in similar experiments with constant routines. Deacon and Arendt

Table 2 Means of temporal and quantitative parameters of salivary melatonin concentrations, rectal temperature, and heart rate during control and during exposure sessions

Parameter	Control condition	Bright light condition	Magnetic field
Melatonin synthesis			
Onset (h:min)	20:32	2:11	21:30
Acrophase (h:min)	2:54	5:56	2:55
Offset (h:min)	5:20	7:13	5:10
Onset–acrophase (h:min)	5:18	3:50	5:44
Duration (h:min)	7:43	6:03	8:33
Maximum (pg/ml)	12.7	10.4	12.3
Area under curve (pg/ml*h)	75.0	45.0	96.0
Density (pg/ml/h)	9.8	7.2	12.3
Rectal temperature			
Acrophase (h:min)	18:48	18:19	18:39
Nadir (h:min)	4:38	5:16	3:44
Nadir–acrophase (h:min)	9:50	10:12	9:17
Maximum (°C)	36.99	37.01	37.01
Minimum (°C)	36.20	36.31	36.23
Mesor (°C)	36.66	36.71	36.69
Amplitude (°C)	0.39	0.35	0.39
Heart rate			
Acrophase (h:min)	11:49	12:25	12:08
Nadir (h:min)	3:05	5:00	4:04
Nadir–acrophase (h:min)	14:02	16:59	15:45
Maximum (bpm)	67.1	69.0	66.0
Minimum (bpm)	52.6	55.5	52.9
Mesor (bpm)	60.0	62.2	59.5
Amplitude (bpm)	7.3	6.7	6.5

Table 3 Temporal and quantitative parameters of salivary melatonin concentrations, rectal temperature and heart rate. Means of differences between control and exposure sessions, *P* values for Wilcoxon signed rank test

Parameter	Differences between control condition and exposure sessions			
	Bright light Mean difference	*P* value	Magnetic field Mean difference	*P* -value
Melatonin synthesis				
Onset (h:min)	–5:39	0.001	–0:58	0.966
Acrophase (h:min)	–3:02	0.034	–0:01	0.622
Offset (h:min)	–1:53	0.002	0:10	0.898
Onset–acrophase (h:min)	1:28	0.005	–0:26	0.831
Duration (h:min)	1:40	0.014	–0:50	0.413
Maximum (pg/ml)	2.3	0.064	0.4	0.518
Area under curve (pg/ml*h)	30.0	0.005	–21.0	0.123
Density (pg/ml/h)	2.6	0.014	–2.5	0.240
Rectal temperature				
Acrophase (h:min)	0:29	1.000	0:09	0.970
Nadir (h:min)	–0:38	0.519	0:54	0.129
Nadir–acrophase	–0:22	0.850	0:33	0.301
Maximum (°C)	–0.02	0.666	–0.02	0.648
Minimum (°C)	–0.11	0.265	–0.03	0.752
Mesor (°C)	–0.05	0.400	–0.03	0.522
Amplitude (°C)	0.04	0.294	0.00	0.977
Heart rate (h:min)				
Acrophase (h:min)	–0:36	0.677	–0:19	0.577
Nadir (h:min)	–1:55	0.005	–0:59	0.012
Nadir–acrophase (h:min)	–2:57	0.092	–1:43	0.622
Maximum (bpm)	–1.9	0.192	1.1	0.252
Minimum (bpm)	–2.9	0.023	–0.3	0.737
Mesor (bpm)	–2.2	0.067	0.5	0.532
Amplitude (bpm)	0.6	0.337	0.8	0.102

(1994), as well as Griefahn et al. (2001), for example, observed seven persons, and Wood et al. (1998) studied between four and 11 subjects per condition. Also, the age ranges within small limits (18–25 years), which is again not unusual for experimental studies, limits, on the other hand, generalization of the results.

As blood sampling is less acceptable for most people the present study concerned salivary melatonin levels instead of plasma concentrations, which is justified by the high correlation between salivary and plasma levels reported, e.g., by Deacon and Arendt (1994) and Kennaway and Voultsios (1998).

According to Trinder et al. (1996) and Wood et al. (1998) melatonin suppression is most easily achieved during the period just before the onset and during the rise of nocturnally elevated melatonin production. The magnetic field was therefore administered from 6 p.m. to 2 a.m. and the courses of melatonin concentrations ascertained during the control sessions have confirmed that each individual melatonin onset occurred during that period. Despite this and the confirmation that each individual was well able to respond to the melatonin suppressive stress of bright light, the participants did not respond to the field which was ten-times stronger than that applied by Wood et al. (1998) (50 Hz, 10 μT, 15-s on/off periods). This is in accordance with Brainard et al. (1999) who stated in their literature review that two-thirds of the laboratory studies with nocturnally active small animals have shown an effect on at least one element involved in the synthesis, secretion or metabolism of melatonin. Experiments with diurnally active larger animals and with human beings revealed, however, no statistical effect on circulating melatonin or on the urinary excretion of its major enzymatic metabolite 6-hydroxymelatonin sulfate (6-OHMS).

Field studies, however, ascertained consistently a reduced 6-OHMS excretion in persons who are occupationally exposed to magnetic fields, e.g., in railway workers (Pfluger and Minder 1996) or in electricy utility workers (Burch et al. 1998, 1999a, 1999b, 2000). This was determined as an acute effect in day and night workers where the post-shift urine was collected (Pfluger and Minder 1996; Burch et al. 1999b) as well as an after-effect where the urine of day workers was collected over the following night.

The reasons for the discrepancies between laboratory studies and the effects determined in occupational settings are numerous. Apart from the fact that occupational exposures are always accompanied by at least some light exposure, the most decisive factor might be the instability of the field. Occupational exposures are – at least due to the motions of the workers – characterized by permanent (relative) variations in the strength and direction of the field. These irregular occupational variations are even scarcely comparable with the periodic on/off-sequences as usually applied in the laboratory. Nonetheless, two studies gave some indications that intermittence might affect melatonin synthesis. Graham et al. (1996a) reported suppression in persons with habitually low melatonin levels (60 Hz, 20 μT, 15-s on/off-periods) and Wood et al. (1998) observed a reduction during the period of the usual onset and rise of melatonin production (50 Hz, 20 μT, 15-s on/off-periods). Both observations, however, were not replicated.

Aditionally, the field strength applied in the laboratory is often much lower than in many occupational settings. Åkerstedt et al. (1999), whose subjects slept under the influence of a magnetic field (50 Hz, 1 μT), found a decrease in total sleep time, sleep efficiency, and deep sleep but no alteration in circulating melatonin levels. The latter could scarcely be expected, after Selmaoui et al. (1996) had already failed to evoke an effect with a ten-times stronger field (50 Hz, 10 μT), and even the 20-times stronger and intermittently applied field in the present study was ineffective.

The most important reason for the diverging effects between the field and the laboratory is probably that occupational exposures are repeated daily, whereas the subjects in the laboratory are – as a rule – exposed only once for a few hours. The only study which took that into account was performed by Graham et al. (2000a) who exposed 30 healthy young men for four consecutive nights to intermittent magnetic fields of 28.3 μT. They determined a slight instability in excreted 6-OHMS over time, which might indicate a possible cumulative effect. A definite alteration in melatonin presupposes certainly more repetitions, as, for instance, in the study performed by Wilson et al. (1990) who reported reduced excretion of 6-OHMS in subjects sleeping under electrically heated blankets, or in the study of Karasek et al. (1998) who found lower melatonin levels in 12 men whom they treated with strong magnetic fields (daily repeated 20-min exposures to a 40-Hz field of 2.9 mT for 3 weeks).

Juutilainen et al. (2000) determined in female workers exposed to flux densities of up to 2.5 μT the same 6-OHMS excretion at the end of a week and at the end of a free weekend. The authors interpreted this as a lack of recovery during the weekend and therefore a chronic effect. It is, however, also conceivable to assume a threshold of flux density above 2.5 μT for repetitive exposures in the field.

The only significant alteration associated with exposure to the magnetic field was a delayed nadir of heart rate. This was actually expected but as a consequence of a delayed melatonin synthesis which did not take place. The isolated effect of magnetic fields (and of bright light) on cardiac function is, however, supported by Sastre et al. (1998) who have analyzed the heart rate variability from three experiments with magnetic fields (that were primarily executed to demonstrate an effect on melatonin synthesis). For intermittent exposures (60 Hz, 20 μT, 15-s on/off-periods) these authors determined a significantly reduced heart rate variability in the lower spectral band which is associated with temperature and blood pressure control mechanisms and an increased variability in the spectral band associated with respiration control.

The power reduction in the low-frequency band is obviously a consistent effect which was also observed in similar experiments with 40 to 60-year-old men (Graham et al. 2000b). As this effect is thought to be mediated by an alteration of the neural activity in the central nervous system, Sastre et al. (2000) supposed that stimuli within the range of EEG frequencies would cause stronger effects. They verified this with nine subjects whom they exposed to an intermittent magnetic field of 16 Hz, which is within the beta band of the EEG. Whether the assumed pathway is correct remains, however,

uncertain, as the authors did not record the EEG, and in view of an experiment executed by Bröde et al. (2001). These researchers exposed ten young persons in three separate sessions to electromagnetic fields of either 4, 8, or 16.7 Hz with a flux density of 200 μT. They expected an increase of the relative power in the frequency range of the stimulus applied, but found confirmation of their hypothesis only for the 4-Hz stimulus.

Apart from that, it can be hypothesized that cardiac function is particularly prone to the influence of magnetic fields. The possible effects on the circadian and/or the ultradian rhythm will need to be investigated in specifically designed studies.

The delay in the nadir without a corresponding shift in melatonin synthesis and rectal temperature might indicate an internal dissociation which typically occurs during nightshifts and which is assumed to cause a health hazard in the long run (Czeisler et al. 1980; Folkard and Monk 1981; Tenkanen et al. 1998).

The results of the present study confirm the view of Brainard et al. (1999) and Graham et al. (2000a) that melatonin synthesis is unlikely to be affected by single exposures to intermittently applied strong and extremely low-frequency magnetic fields. Changes are expected only as cumulative effects after repeated (occupational) exposures. Further studies must be designed from this point of view.

On the other hand, in accordance with the observations of Sastre et al. (1998, 2000), the circadian and ultradian rhythms of cardiac function seem to be the most likely to be affected. As these changes may cause a health risk in the long run, accordingly designed studies are required to investigate this assumption.

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