

Exposure to wireless phone emissions and serum β -trace protein

LENNART HARDELL¹, FREDRIK SÖDERQVIST¹, MICHAEL CARLBERG¹,
HENRIK ZETTERBERG² and KJELL HANSSON MILD³

¹Department of Oncology, University Hospital, SE-701 85 Örebro; ²Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital/Mölndal, SE-431 80 Mölndal; ³Department of Radiation Sciences, Umeå University, SE-901 87 Umeå, Sweden

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Abstract. The lipocalin type of prostaglandin D synthase or β -trace protein is synthesized in the choroid plexus, leptomeninges and oligodendrocytes of the central nervous system and is secreted into the cerebrospinal fluid. β -trace protein is the key enzyme in the synthesis of prostaglandin D₂, an endogenous sleep-promoting neurohormone in the brain. Electromagnetic fields (EMF) in the radio frequency (RF) range have in some studies been associated with disturbed sleep. We studied the concentration of β -trace protein in blood in relation to emissions from wireless phones. This study included 62 persons aged 18-30 years. The concentration of β -trace protein decreased with increasing number of years of use of a wireless phone yielding a negative β coefficient = -0.32, 95% confidence interval -0.60 to -0.04. Also cumulative use in hours gave a negative β coefficient, although not statistically significant. Of the 62 persons, 40 participated in an experimental study with 30 min exposure to an 890-MHz GSM signal. No statistically significant change of β -trace protein was found. In a similar study of the remaining 22 participants with no exposure, β -trace protein increased significantly over time, probably due to a relaxed situation. EMF emissions may down-regulate the synthesis of β -trace protein. This mechanism might be involved in sleep disturbances reported in persons exposed to RF fields. The results must be interpreted with caution since use of mobile and cordless phones were self-reported. Awareness of exposure condition in the experimental study may have influenced β -trace protein concentrations.

Introduction

The lipocalin type of prostaglandin D synthase (L-PGDS) plays a crucial role in sleep promotion. L-PGDS is mainly synthesized in the choroid plexus, leptomeninges (pia-arachnoid

membrane) and oligodendrocytes of the central nervous system (CNS). It is secreted into the cerebrospinal fluid (CSF) as β -trace (1,2). L-PGDS purified from human CSF and β -trace are structurally, enzymatically and immunologically identical (3).

β -trace is the second most abundant protein in CSF after albumin, representing 8% of all CSF protein (2). The concentration in CSF is 32-times higher than in serum, which indicates that serum β -trace originates predominantly from CNS (4). Small quantities of β -trace are found in closed compartments outside the brain, such as testis, retina and cochlea, but can not influence serum β -trace (5). There is a continuous release of β -trace into CSF and by the CSF flow into the blood stream. The half-life time has been calculated to 4 h in the blood (6).

β -trace has a circadian pattern, increasing in the evening with the highest concentration at night, and regulates sleep through the prostaglandin D system (7). Prostaglandin D₂ (PGD₂) is present in relatively high concentration in the brain. β -trace is the key enzyme in the synthesis of PGD₂, which is an endogenous sleep-promoting neurohormone (8). The action of PGD₂ is mediated by a specific prostanoid receptor, the DP receptor. This receptor is localized in the chemosensory region of the ventromedial surface of the rostral basal forebrain (9). The signal to initiate sleep is initiated via adenosine A2A receptive neurons (10). This results in the activation of a cluster of neurons in the sleep center within the ventrolateral preoptic area (11).

During recent years the prevalence of disturbed sleep has increased in the Swedish population. Thus, sleep problems were twice as common in 2003 compared with 1993, increasing from 10-12% to 20-24% of the population. Among adolescents in Sweden it was three to four times more common in 2003 compared with 1993. The reasons for this are unknown, although life style, school- and work-related factors probably are involved with increasing demands on the individual (12-14).

The use of wireless phones has become an essential part of modern life. There is a general concern about potential health effects of exposure to electromagnetic fields (EMF) in the radiofrequency (RF) range from these devices, both mobile phones and cordless desktop phones (DECT). Since the phones are used in close proximity to the head, EMF emitted from these phones result in considerably higher exposure to the brain than to other organs (15). An increased risk for brain

Correspondence to: Professor Lennart Hardell, University Hospital, SE-701 85 Örebro, Sweden
E-mail: lennart.hardell@orebroll.se

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tumours has been indicated in some studies, for overview see Hardell *et al.* (16). Self-reported symptoms include e.g. headache, fatigue, dizziness, skin sensations, cognitive symptoms and sleep-disturbances (17,18).

Exposure to pulse-modulated EMF affected human EEG in several studies according to the Independent Expert Group of the Swedish Radiation Safety Authority (19). It also affected the sleep EEG during night-time sleep (20) and prior to daytime sleep (21). In a follow-up study pulse-modulated EMF altered waking regional cerebral blood flow. Also waking and sleep EEG was changed, and pulse modulation of EMF was necessary to induce these effects (22). A GSM-handset-like signal affected non-REM sleep EEG in a dose-response relation with the applied SAR ranging from 0.2 to 5 W/kg (23). Additionally, components of sleep were affected in an experimental study of 884 MHz GSM wireless communication signals. After 3 h average 1.4 W/kg exposure there was a prolonged latency to reach the first cycle of deep sleep (stage 3) and the amount of stage 4 sleep was decreased (24). In another experimental study the 'talk-mode' signals of a GSM 900 mobile phone delayed EEG-determined sleep onset (25). This has been reviewed elsewhere (26,27). Additionally, sleep disturbances have been reported among inhabitants around mobile phone base stations (28,29).

Since EMF emissions from mobile phones might affect sleep and β -trace is a sleep-promoting neurohormone it was of interest to also analyse that protein in our experimental study on exposure to a GSM signal (30). The study was approved by the regional ethics committee.

Materials and methods

In the first part of this study 44 volunteers aged 18-30 years were recruited from the municipality of Umeå, Sweden (30). Of these, 35 were randomly recruited from the population registry and 9 by personal invitation at the Department of Radiation Sciences, Umeå University, Sweden. They were asked to answer a questionnaire on e.g. use of mobile phones and cordless phones and some health and life-style related factors. The final sample consisted of 40 persons since one woman was excluded because of pregnancy, another due to loss of blood pressure during blood sampling and a third and a fourth could not participate for technical reasons in the statistical pair-wise analyses. Exposure was to an 890 MHz GSM signal as described previously (30,31). A specific absorption rate (SAR_{1g}) of 1.0 Watt/kg to the temporal area was applied.

Blood was drawn on four occasions; the first 10-15 min after arrival to the hospital, the second after 30 min rest including study information and just before the mobile phone exposure, the third immediately after 30 min exposure, and the fourth 60 min after ending of the exposure. Serum was frozen for later analysis.

Additionally 22 volunteers, 11 of each sex, 18-30 years of age were recruited separately and the pre-analytical stability of β -trace was tested in that group. They were all inhabitants of the municipality of Örebro in Sweden. All answered the same questionnaire as the 40 subjects in the experimental study. This was not intended to be part of the experimental study as a control group, but to analyse the stability of the

investigated proteins in relation to time to freezing of the blood sample. No microwave exposure was given during this stability test, although all other conditions were similar to the real exposure situation. Blood was drawn at the same time intervals as in the exposure study, but two samples instead of one were taken on the first two occasions. One sample (the a-sample) was handled in the same way as in the exposed material, while the other was centrifuged and frozen immediately after blood was drawn (the b-sample). There was no statistically significant difference of the results for the a- and b-samples, so in the following analyses the a-samples were used. All participating persons were healthy with no use of drugs. Informed consent including storing of the blood in a Biobank was given by all subjects.

Analysis. β -trace protein was determined by an immunonephelometric assay on a BN ProSpec (Dade Behring Marburg GmbH, Marburg, Germany) according to the instruction manual. All subjects were assigned a code number so that no personal identification was known during the analyses that were performed at the Neurochemistry Laboratory, Sahlgrenska University Hospital/Mölnadal, in Sweden. All results are expressed in mg/l.

Statistical methods. Frequency tables were produced and explanatory factors were analyzed by t-test and ANOVA. Linear regression, adjusted for age, was used to test an association between long-term trends in wireless phone use and serum concentrations of β -trace. For all these analyses the first serum sample (sample 1) was used, since the condition for drawing that blood sample was similar for all study subjects. Standardized β coefficients were used throughout.

The four blood samples in the exposure and stability studies were compared using repeated measures ANOVA with Huynh-Feldt correction followed by linear contrasts for pairwise comparisons between sample 1 and sample 2, sample 2 and sample 3, sample 3 and sample 4. Since these a priori chosen comparisons did not exceed the degrees of freedom between samples no multiple comparison adjustments were performed. All analyses were done using StataSE 10.1 (Stata/SE 10.1 for Windows; StataCorp., College Station, TX).

Results

No statistically significant difference of β -trace protein was found between men ($n=28$) and women ($n=34$), Table I. The median age was 24 years and somewhat higher concentration was found in the younger subjects ($P=0.049$). Regarding time for drawing blood (morning or afternoon), weekday or month no statistically significant differences were found.

A negative standardized β coefficient was calculated for cumulative use in hours of both mobile phones and cordless phones, however not statistically significant, Table II. Also for years since first use (latency) a negative coefficient was found, statistically significant for mobile and cordless phones combined ($P=0.03$).

In the exposure study there were no statistically significant differences between the different samples, Table III. However, in the stability study highest mean and median concentrations were found in samples 3 and 4, Table IV. The concentration

Table I. Descriptive data for β -trace protein (mg/l).

	n	Mean	Median	Min	Max	P-value ^a
β -trace sample 1, total	62	0.524	0.521	0.345	0.715	
Gender						0.74
Men	28	0.528	0.528	0.345	0.652	
Women	34	0.520	0.512	0.378	0.715	
Age (cut-point at median in the whole material)						0.049
≤ 24 years	33	0.543	0.542	0.345	0.715	
> 24 years	29	0.501	0.498	0.368	0.652	
Time (h) for drawing blood						0.34
08:00-12:00	35	0.533	0.532	0.384	0.649	
12:01-15:00	27	0.512	0.509	0.345	0.715	
Day for drawing blood						0.73
Monday	10	0.512	0.514	0.378	0.652	
Tuesday	17	0.505	0.498	0.368	0.609	
Wednesday	12	0.528	0.516	0.390	0.715	
Thursday	19	0.539	0.548	0.345	0.647	
Friday	4	0.549	0.524	0.498	0.649	
Month for drawing blood						0.20
March	9	0.504	0.527	0.390	0.588	
April	15	0.486	0.494	0.345	0.622	
May	16	0.552	0.551	0.400	0.715	
November	8	0.547	0.545	0.378	0.647	
December	14	0.531	0.516	0.437	0.652	

^at-test for gender, age and time (h) for drawing blood, ANOVA for day for drawing blood and month for drawing blood.

Table II. Linear regression analysis for serum β -trace, cumulative and latency and long-term use of wireless phone use adjusted for age.

Group	n	Standardized β coefficient	95% CI	P-value
Cumulative use (hours), mobile phone/DECT				
Mobile phones + DECT	62	-0.17	-0.41 to 0.07	0.16
Mobile phones	62	-0.18	-0.42 to 0.06	0.15
Analogue	2	-	-	-
Digital	62	-0.17	-0.41 to 0.07	0.17
UMTS	16	-0.38	-0.88 to 0.11	0.12
DECT	51	-0.08	-0.36 to 0.19	0.54
Years since first use, mobile phone/DECT				
Mobile phones + DECT	62	-0.32	-0.60 to -0.04	0.03
Mobile phones	62	-0.24	-0.54 to 0.06	0.11
Analogue	2	-	-	-
Digital	62	-0.21	-0.50 to 0.08	0.16
UMTS	16	-0.24	-0.79 to 0.32	0.38
DECT	51	-0.13	-0.42 to 0.16	0.38

Table III. Serum concentrations of β -trace (mg/l) for all the blood samples in the exposure study and linear contrasts for a priori pairwise comparisons (n=40).

	Mean	Median	Min	Max	P-value
Repeated-measures ANOVA ²					0.17
Sample 1	0.516	0.521	0.345	0.715	
Sample 2	0.521	0.513	0.370	0.696	
Sample 3	0.537	0.543	0.217	0.808	
Sample 4	0.523	0.521	0.323	0.685	
Linear contrasts					
Sample 1 vs. Sample 2					0.65
Sample 2 vs. Sample 3					0.10
Sample 3 vs. Sample 4					0.15
Mean, sample 1+2 vs. mean, sample 3+4					0.09

²Huynh-Feldt correction.

Table IV. Serum concentrations of β -trace (mg/l) for all the blood samples from stability data and linear contrasts for a priori pairwise comparisons (n=22).

	Mean	Median	Min	Max	P-value
Repeated-measures ANOVA ³					0.0003
Sample 1	0.537	0.521	0.378	0.652	
Sample 2	0.554	0.541	0.365	0.689	
Sample 3	0.564	0.566	0.384	0.679	
Sample 4	0.557	0.545	0.378	0.701	
Linear contrasts					
Sample 1 vs. Sample 2					0.006
Sample 2 vs. Sample 3					0.07
Sample 3 vs. Sample 4					0.24
Mean, sample 1+2 vs. mean, sample 3+4					0.0003

³Huynh-Feldt correction.

increased from sample 1 to sample 2 (P=0.006) and increased further from sample 2 to sample 3 (P=0.07). The mean and median concentrations were higher in sample 4 than in sample 1 and sample 2, although not statistically significantly different from sample 3 (P=0.24).

We lumped together samples 1 and 2 and compared with samples 3 and 4 together. In the exposure study no statistically significant difference was found, mean sample 1 and 2=0.519, mean sample 3 and 4=0.530 (P=0.09). In the stability study mean concentration was in samples 1 and 2=0.545 and in samples 3 and 4=0.561 (P=0.0003) (Table IV).

Discussion

The main finding of this study was that the more years a mobile or a cordless phone had been used, the lower β -trace protein concentration in blood was found. The decrease of the concentration was statistically significant when use of

mobile and cordless phones was analysed together. Also cumulative use in hours yielded decreased concentration of β -trace with a negative β coefficient, although not statistically significant.

In the exposure study no statistically significant differences were found between the different samples. This was in contrast to the stability study where highest concentrations of β -trace protein were found in the last two samples. This difference was statistically significant. In both parts of the study highest concentrations were found in sample 3, but in the stability study also mean and median concentrations in sample 4 were higher than in samples 1 and 2.

These results may indicate that emissions from wireless phones affect the release of β -trace protein in the brain, primarily from the choroid plexus and the leptomeninges. Especially the leptomeninges that surround the brain close to the bone of the skull, are highly exposed to RF fields during the use of wireless phones.

The results for long-term use and cumulative use indicate a chronic effect on the concentration of β -trace, possibly by a down-regulation of the gene. Results from the exposure study indicate that an acute effect might also be involved. After the initial insertion of a needle for the blood samples and information about the study the persons were seated in a chair and looked at a film. All persons viewed the same film on nature without any emotional stress. During this relaxation time β -trace increased statistically significantly in the stability study in contrast to the exposure study.

There are, however, some limitations in the study. First, the number of participants was rather low, especially in the stability study. Furthermore, the persons in the exposure study were aware of exposure due to the noise from the equipment during the 30 min exposure. In the stability study no exposure was given, so these persons might have had a more relaxed and comfortable situation compared to the exposed group. Blood was drawn at the same intervals and with the same procedure in the both groups, so it is unlikely that the differences in the results were due to blood sampling.

The results for long-term use of mobile and cordless phones were based on questionnaire data for these 62 persons in total. The questionnaires were answered before the study subjects were included in the study. It was of vital importance to assess information on potential confounders for all of the proteins analysed in this study (30). Thus, all study persons were healthy without e.g. hypertension, neurological diseases, kidney disorders, heart diseases such as angina or stenosis and thyroid dysfunction. That is diseases that may affect serum β -trace protein concentrations (32). For that reason it was of advantage to include only young persons aged 18-30 years. One disadvantage is, however, that the results can not be generalised to other age groups.

In the descriptive analysis only age predicted serum β -trace concentrations with higher concentrations in the youngest age group. The results for long-term use were consequently adjusted for age. The concentration of β -trace protein has a circadian rhythm coupled to the sleep - awake cycle with highest concentrations during night (32). We did not find any statistically significant differences if the first blood sample was taken in the morning or in the afternoon. Changes of the circadian rhythm with alterations of the prostaglandin D system has been shown in several diseases with hypersomnia such as African sleeping sickness (33), systemic mastocytosis (34), and severe obstructive sleep apnea syndrome (7).

Reduction of β -trace protein is a significant biological event involved in the malignant progression of astrocytoma and is predictive of poor survival (35). Significant reduction in cell proliferation and viability in the A172 glioblastoma cell line was found when PGD₂ was exogenously supplied. Our findings in this study of decreased concentration of β -trace protein in serum among long-term users of wireless phones might be of interest in relation to our previous results of increased risk for astrocytoma, especially high grade, among long-term users of mobile and cordless phones (36,37).

β -trace is the most common protein in liquor next to albumin. There is a high gradient to the blood since the concentration in liquor is 32 times higher. Small quantities are found in other compartments but they are closed to the blood and can not contribute to serum concentration to any substantial

degree. Thus, determining serum concentrations of β -trace in relation to exposure to RF-fields is feasible to further study potential effects on sleep by such exposure.

Several studies have indicated sleep disturbances by exposure to mobile phone emissions. As discussed above both short-term effect such as EEG (21,22) and latency to reach first cycle of deep sleep (24) as well as possible long-term effects e.g. sleep disturbances from emissions from base stations have been reported (28). The results in our study indicate a biological mechanism for these findings, possibly down regulation of the synthesis of β -trace protein.

Regarding long-term use our results were based on self-reporting of wireless phone use. We were not able to get verification of such use from records from different phone operators. A prospective study with individual measurement of emissions for a shorter time period would be one possibility to improve the study design. Of course a larger study sample would be worthwhile. Regarding long-term use a statistically significant negative β -coefficient was found for years since first use. It is most probable that reporting of the first year for use of mobile or cordless phone is more valid than cumulative exposure in hours over the years. The subjects were asked to report their average use in minutes per day over all years, but such use may differ from time to time. Years since first use was based on the reported first year of use of a wireless phone. For errors in recall to bias the results, such error would have to associate with β -trace levels. So, if the results suffer from recall error it is most likely non-systematic, which would dilute any association. A negative β -coefficient was also found for cumulative use, that is, the more the wireless phone was used the lower serum concentration of β -trace was found.

In respect to the exposure and stability studies each person served as his or her own control in the pairwise statistical analysis. The number of individuals especially in the stability study was low and a better study design is desirable with a randomised crossover study including sham exposure. As discussed it can not be excluded that the knowledge of being exposed made the persons in the exposure study less relaxed than in the stability study, which might have influenced β -trace concentration. Of interest is anyhow that the results in that part of our investigation support the findings in the study of long-term use among the same persons.

In summary, this study showed a negative trend of β -trace protein concentration in serum for long-term use of wireless phones. These results might be supported by the results in our study on exposure with an 890 MHz GSM signal that showed no statistically significant change of β -trace. This was in contrast to the results in a similar study with no exposure where β -trace increased significantly over time, probably due to a relaxed situation. However, in the exposure study the awareness of exposure might have biased the results although the two studies were otherwise performed under similar circumstances.

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