Summaries and assessments of selected studies

In the period from end of July to early November 2017, 95 new publications have been identified, and 11 of these were discussed in depth by BERENIS. Based on the selection criteria, four of these publications were selected as the most relevant ones. Their summaries and assessments are provided below. In this issue, special attention is paid to the role of cryptochrome as a magnetic field receptor.

1) Experimental animal and cell studies

New insights into the role of cryptochrome as a magnetic field receptor (Muheim et al. 2016 and other publications on the subject)

In recent years, several studies investigating the perception of static and extremely low frequency magnetic fields by cryptochrome (CRY) have been published. CRY is a photoreceptor, i.e. a protein that reacts to blue light, and that requires light on order to perform its functions. CRY was first discovered in plants in the 1990s. In the meantime, numerous publications report the existence of these CRY proteins in flies, rodents, birds and also in mammals. Precursors of CRY in bacteria are light-activated enzymes involved in DNA repair. This function is not present in organisms with a nucleus.

In plants and animals, CRY are important for the circadian rhythm. Fruit flies can sense the geomagnetic field and use it for navigation. Exposure of these flies to an alternating magnetic field of 3 and 50 Hz (0.3 and 1 mT) changed the sleep-wake cycle as well as the movement activity of the fruit flies (see Newsletter Nr. 2, June 2015). In many animals, CRY are thus responsible for the perception of the geomagnetic field, while the importance of CRY in mammals is still largely unknown. Scientists from the University of Oldenburg/Germany detected CRY proteins in the retina of the eye of migratory birds (Niessner *et al.* 2016). There is growing evidence that CRY is the molecule that is magneto-sensory, controlling the perception of magnetic fields and allowing birds to use the geomagnetic field for orientation. CRY proteins are thus part of the magnetic compass of certain animals. This circumstance is remarkable because it shows the existence of a magnetic field sensor in the realm of biology, although so far this only applies to the static magnetic field (geomagnetic field).

Interestingly, this "magnetic sense" can be disturbed by an alternating magnetic field under certain conditions, and it can even be lost completely. Interferences were generated with noise-like radiofrequency electromagnetic fields and with specific effective frequencies ("Larmor frequency"). On the one hand, this leads to a loss of orientation, on the other hand, it can change the movement activity.

Current research focuses on elucidating the molecular mechanism for this magnetic field detection and its perturbation, using animal experimental approaches and theoretical models. Molecular properties that selectively respond to a magnetic field and its spatial orientation are of particular interest, as well as subsequent biochemical reactions that enhance the initial "stimulus". The main focus is on the radical pair hypothesis, which assumes that the life span and chemical reactivity of short-lived intermediates of CRY are affected by an external magnetic field in a photochemical reaction. This would imply that CRY together with light and the subsequent reactions represent the sensory organ for magnetic fields.

Recent studies with zebra finches have shown interactions between polarised light and the magnetic compass (natural light is polarised, with the polarisation depending on the weather and the position of the sun). The spatial orientation of the birds in a labyrinth was dependent on the relative alignment of the polarized light axis to the magnetic field. When the polarised light axis was aligned perpendicular to the magnetic field, the birds became disoriented. For the first time, it was shown that the relative alignment of directed physical quantities (polarization of the light and direction of the static magnetic field) influences the magnetic compass and thus the spatial orientation of animals (Muheim et al. 2016). Continuous illumination amplifies the magnetic compass, which is caused by delayed termination of the radical pair reaction (Kattnig et al. 2016).

For fruit flies, studies have reported other CRY-mediated behaviours that depend on magnetic fields including locomotor activity, increased neuronal activity and convulsions. The latter could be prevented by antiepileptic drugs (Marley et al. 2014). This raises the question how the signal transduction to the brain occurs, which leads to increased neuronal activity through a combination of light and magnetic field. In general, such signal amplification processes are known. Many of these signalling cascades involve so-called G-proteins, which can cause a signal amplification of more than 1 million. This allows biological organisms to detect extremely weak signals. At the end of such signalling cascades, ion channels are often involved (Hore & Mouritsen 2016). Sodium channels are ion channels responsible for the development and transmission of action potentials and thus neuronal excitation. Many antiepileptic drugs activate the GABA (gamma-aminobutyric acid) receptor, which is also an ion channel. Such interactions of CRY with signalling proteins and the transmission of this information in the brain are yet unknown.

Influence of extremely low frequency magnetic fields on the epigenetic regulation associated with neurodegeneration (Consales et al. *2017)*

Consales *et al.* (2017) report a series of interesting observations that provide new insights and approaches with regard to the mode of action of ELF-MF on the functionality and viability of neurons. They performed experimentations with cultured neuronal cells; *i.e.* human neuroblastoma cells that were either undifferentiated or differentiated into dopamine-responsive neurons, and murine cortical neurons). Under blinded conditions, cells were exposed to a continuous magnetic field (50 Hz, 1 mT, 4 to 72 hours) and compared to the corresponding sham control. In control conditions, the authors found that the expression of two specific microRNA molecules (miR-34b/c) was continuously increasing over the course of three days of cultivation, while their expression remained relatively stable when exposed. As microRNA molecules play an important role in the epigenetic control of gene expression, the authors then investigated how this relative reduction in miR-34b/c expression affects the cells compared to the control condition. Computational analyses identified potential miR-34b/c-regulated genes, including a strikingly high number of proteins that play a role in the integrity and/or the oxidative balance of mitochondria. Through targeted regulation of miR-34b/c levels, indeed, it could then be shown that the MF-dependent reduction led to altered mitochondrial functionality, redox balance, and an increase in ROS. As these factors are linked to the function and degeneration of neurons, the authors postulate that miR-34b/c directly regulate some important neuronal proteins that play a role in neurodegeneration. For example, under MF exposure there is an increase of alpha-synuclein expression that, in turn, may lead to increased pathological aggregation, as seen in Parkinson's disease patients. This study is noteworthy because of the well-done technical and methodological approach, and the aspect that MF could act by influencing the epigenetic regulation, which would conceptually explain a variety of previously reported effects. In addition, this study

provides good mechanistic evidence how MF exposure could affect cells, indirectly leading to an increase in ROS, which is an often tested and observed experimental endpoint in EMF studies.

2) Human experimental studies

Salivary enzyme alpha-amylase and electromagnetic hypersensitivity (Andrianome et al. *2017)*

This study investigated whether salivary and urinary biomarkers for electromagnetic hypersensitivity (EHS) can be identified. There are no established biomarkers so far, so diagnosis is based solely on subjective information of affected individuals. Thirty persons who considered themselves as hypersensitive and a control group of 25 persons with similar age and sex distribution were examined. Cortisol is considered to be an indicator of hypothalamic-pituitary-adrenal axis activity and a stress indicator. The salivary enzyme alpha-amylase is considered as an indicator of autonomic nervous system changes and responds to psychosocial stressors, but is not correlated with other so-called stress markers such as cortisol, noradrenaline, and heart rate. Most markers of the immune system and circadian rhythms (e.g. cortisol) did not differ between the two groups. The salivary enzyme alpha-amylase, however, was increased in the EHS group. It is unclear whether this difference is due to EMF or whether it is a consequence of chronic stress in people with EHS. The statistical analysis raises concerns because the measured markers were tested individually, while no multivariate analysis was performed. It is also not clear how the control group was recruited. Nevertheless, the results are interesting and future studies will have to show if the differences in alpha-amylase are large enough to be suitable as specific markers for EHS.

3) Dosimetric studies

New head models of children and radiofrequency electromagnetic fields (Mohammed et al. *2017)*

Previous children's head exposure studies used scaled adult anatomical head models or head models based on MRI data of children above the age of three years. These models only considered changes in the external shape and size of the head, and the age dependence of the dielectric parameters. However, in reality, apart from the shape and size of the head, the spatial distribution of the various types of tissue also changes. In children up to the age of three years, the fontanelles are gradually decreasing in size, which must also be added to the model. The model used in this study considered three important age-related anatomical changes. Based on the model of a 7-year-old child, models of 3, 6, 12, 18, and 36-month-old infants were created by scaling. The age-related spatial distribution of white and gray matter of the brain was adapted, and the fontanelles were included into the model. Due to lack of measurement data of infant tissue parameters, the age-related changes were numerically extrapolated. It was considered that in infants, the volume fraction of extracellular fluid and the content of certain chemical elements are greater than in adults. Growth and the associated decrease of the water content in the tissue significantly change the tissue parameters. This causes a decrease of the dielectric constant, whereas the conductivity increases. These changes directly influence the radiation absorbed in the tissue. The different child and adult models were calculated for different exposure scenarios. For this purpose, a mobile phone was positioned at the ear, in front of the mouth and above the head. The situation of the mobile phone above the head is meant to mimic the scenario of an adult carrying a child and making a telephone call. The results of this study indicate a previous underestimation of the maximum SAR levels in the heads of children under the age of three years. For example, the maximum SAR values for the situation of the mobile phone at the ear are increased by 61% (700 MHz) and 78% (2.6 GHz) in three-months-old children compared to adults.

Higher SAR values than in adult models and in previous studies are also resulting for the other situations. Based on these results, an in-depth investigation of the influence of anatomical and dielectric differences between children and adults on maximal SAR levels and the power absorbed by the tissue would be desirable. There is also a certain amount of uncertainty in the numerical extrapolation of the tissue parameters, which needs to be checked more closely.

References

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BERENIS - Swiss expert group on electromagnetic fields and non-ionising radiation

List of abbreviations (pdf)