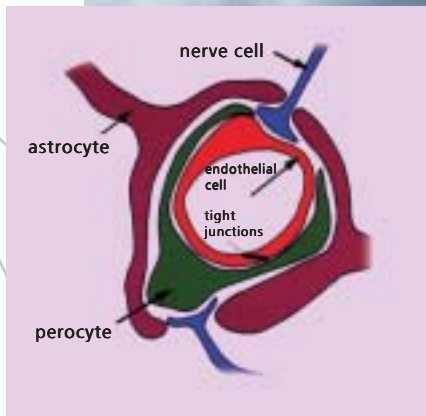


Edition Wissenschaft

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Prof. Dr. Florian Stögbauer

**Effects of electromagnetic
fields on the function
of the blood brain barrier**

Edition
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Dear readers:

After a break of about four years the Research Association for Radio Applications (FGF) is set to continue its publication series EDITION WISSENSCHAFT. The purpose of the series initiated in November 1995 has been to publicise and inform about results of investigation projects promoted by the Research Association. Up to the year 1998, in total 14 issues dealing with research projects of the FGF were published. EDITION WISSENSCHAFT is not a so-called peer-reviewed journal (i.e. scientific periodical in which submissions are reviewed and selected for publication by experts in the field).

As we all know, the scientific community primarily takes notice of papers made available by peer-reviewed magazines and journals acting as a forum for scientific debate. Hence, in the years since 1998 the Research Association focused on publishing research results there instead of in its own publications seeing it is indispensable for investigators to face critical scientific evaluation and thorough public discussion.

Still, that does not diminish the scientific value of previous or future publications within the EDITION WISSENSCHAFT series. We are fully convinced that continuing the series is rewarding for other reasons. So we have decided to revive the series EDITION WISSENSCHAFT in future focusing on publicising survey studies.

Often, it is necessary to first acquire a basic overall knowledge about a certain topic area before being able to deal with related single research subjects and projects. Therefore, the Research Association – besides meeting its central purpose of commissioning special research projects based upon precisely defined work hypotheses – will ask leading experts to draw up survey studies on research fields of interest. One of this studies now is presented in the here following issue of EDITION WISSENSCHAFT.

Subject of this study are interferences with the function of the blood brain barrier caused by electromagnetic fields (EMF). In his introduction to this topic, the author, Privatdozent Dr. Florian Stögbauer, under

special consideration of EMF effects elucidates the significance of the blood brain barrier as a structure being crucial for maintaining homeostasis (equilibrium) of the neural parenchyma (basal nervous tissue). The blood brain barrier has been found to prevent passage of certain substances, for example toxins, from blood capillaries to brain tissue.

The paper is completed by a comprehensive reference index. We think that this introduction to the topic provides a good overview of the current state of scientific knowledge about the blood brain barrier.

Best regards,
Gerd Friedrich

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Effects of electromagnetic fields on the function of the blood brain barrier

1 Introduction

In recent years, worldwide use of mobile communication systems has shown exponential growth. For this reason, general population increasingly voices doubts and uncertainties towards the effects of exposure to electromagnetic fields (EMF) on the human organism and in particular on brain functions. Because of the immediate vicinity of mobile phoning devices to the head, as compared to the rest of the body, the brain is exposed to relatively higher specific absorption rates (SAR) (1). One of the most important variables in health risk assessment of mobile telecommunications is the whole-body averaged SAR limit value above which a noticeable increase of body core temperature would occur. Based on these thermoregulatory limit values and an additional safety interval, a whole-body averaged SAR of 0.4 W/kg is generally accepted (2). As the limit value for thermal effects in the

human body lies above SAR values typically reached by mobile phones, immediate thermal effects of mobile communication seem to be highly unlikely.

Presently, there are no consistent epidemiological studies providing evidence for an association between EMF exposure and malignant tumor incidence. This includes different tumor entities like malignant glial brain tumors and leukemias (3-5). But, apart from potential cancerigenous effects, exposure to EMF can also lead to molecular and biophysical alterations of the central nervous system (CNS) and/or single cellular systems (6). In the past few years, a great number of studies has dealt with such potential effects on different cellular systems of the CNS. These studies were performed in various experimental models. In vivo tests in animals were carried through aimed at finding evidence for neurophysiological effects (evoked potentials, EEG) (7, 8), metabolic and genetic effects (9, 10)

or influences on various neurotransmitter systems (11). In cultures of different cellular components of the CNS, tests on possible alterations of single cell membrane potentials (12) or of secretion of different ions serving as signal transducers were performed (13).

Because of its immediate vicinity to exposure sources, experimental studies very early focused on the blood brain barrier (BBB).

2 The blood brain barrier (BBB)

The BBB is the central structure for maintaining homeostasis of the neural parenchyma (14). Thus, it is of essential significance for normal CNS functioning. The BBB protects the neuropil against neurotoxic components, against the considerable variations of blood composition, and helps to maintain concentration gradients between

blood and CNS. The barrier, on one side consisting of the endothelial BBB, on the other side separates blood from cerebrospinal fluid. To the main part, the barrier function of the BBB is guaranteed by highly complex and very tight intercellular adhesion structures located between specialised brain capillary endothelials, the so-called *tight junctions* (15). The controlled and directed transport of ions and molecules required for maintaining concentration gradients between blood and CNS is supported by specific transport systems expressed in the endothelials. The crucial pathophysiological significance of the BBB as a basis for CNS functioning becomes obvious during the course of neurological diseases being associated with a function decrease or function loss of the BBB. To these belong extremely serious diseases like meningitis, intracerebral ab-

cesses, brain tumors and ischemic strokes.

Anatomically, the BBB of vertebrates is located at the specialised endothelial cells of brain capillaries. These capillaries consist of overlapping endothelial cells showing multiple points of contact with astrocyte end feet on the side of the brain (fig. 1). Endothelial cells of brain capillaries are different from those of other organs in two respects. These differences are the basis for the BBB's ability to prevent many molecules from passing across the barrier.

(I) In contrast to peripheral endothelial cells being either fenestrated or showing low-resistance *tight junctions* (0.5 W/cm^2), brain endothelial cells are connected by *tight junctions* of an extremely high resistance (1000 W/cm^2). These specialised *tight junctions* effectively act as a

barrier even against single ions.

(II) Peripheral endothelial cells allow different types of transcellular movement of single molecules. In contrast, in brain endothelial cells such transport processes have not been found. Here, fluid-phase endocytosis as well as receptor-mediated endocytosis, as found in peripheral endothelial cells, are lacking. Molecule transport via the BBB as a rule is regulated by active transport systems available for different molecular blood components.

At morphological and molecular level, the strong tightness of the BBB is based on the above mentioned specific molecule transport systems preventing free diffusion as well as on *tight junction* expression which very effectively and tightly connect single brain capillary endothelial cells. Morphologically, these *tight junctions* can be visualised by electron microscopy done on freeze-fracturing and ultrathin frozen sections (16). Physiologically, their function is measured by determining paracellular permeability and transendothelial impedance. In principle, the molecular structure of *tight junctions* is similar across all barrier systems; however, there are significant differences between epithelial and endothelial *tight junctions* on the one side, and between those of peripheral endothelials and of brain capillary endothelials of the BBB on the other side. There is conclusive evidence for *tight junctions* being formed by different sub-structures one of

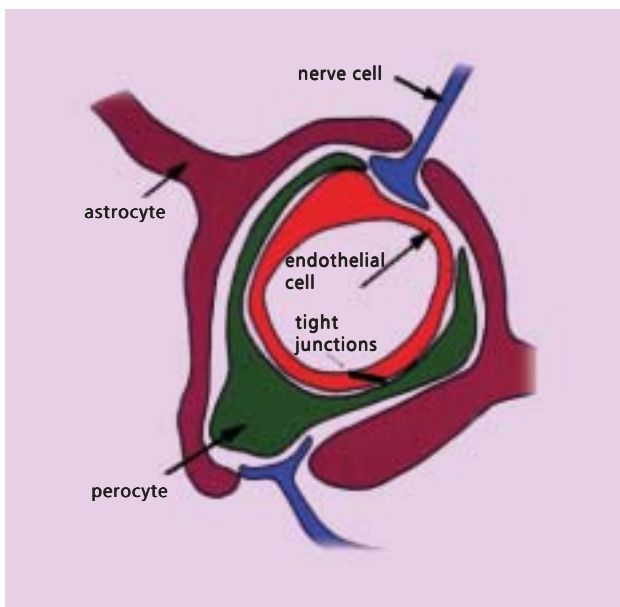


Figure 1: Schematic of the cellular structure of the BBB. Endothelial cells connected by tight junctions and pointing to the BBB's vascular side play an essential role. Astrocytes are located at the side of the brain showing points of contact with endothelials.

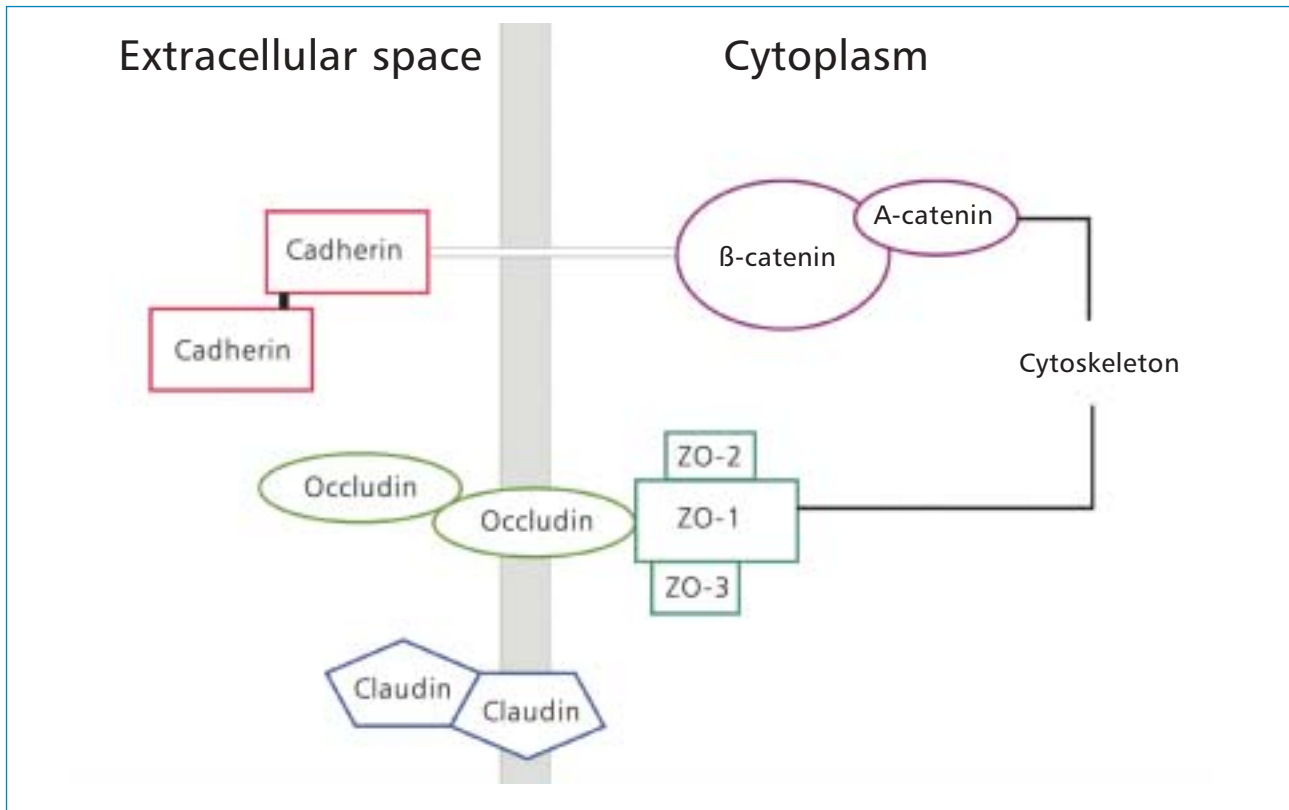


Figure 2: Protein structures of the tight junctions

which is of lipid character, the other one consisting of proteins. A final integration model of *tight junction* structure is not yet available. To date, a number of proteins could be identified being associated with *tight junctions*. To these belong the transmembrane proteins occludin and claudin (fig. 2).

By overlapping the intercellular space between two endothelial cells these transmembrane proteins participate in the formation of *tight junctions*. At intracellular level, they are connected with the *zona occludens* proteins ZO-1 to ZO-3 which again make direct contact with

cytoskeleton proteins thus promoting transmembrane protein attachment. There is a direct connection between junction tightness and the level of expression of these transmembrane proteins as well as cytoplasmatic proteins and their aggregation state at the plasma membrane. Apart from these original *tight junction* proteins, adherence proteins were identified which also contribute to binding tightness of endothelial cells. These mainly consist of cadherins indirectly attached to the membrane and also making contact with the cytoskeleton via intracellular association (fig. 2).

3 Methods for investigating the BBB in vivo and in vitro

'Classical' studies investigating BBB functions did so by applying in vivo experiments. Generally, these experiments are based on providing direct or indirect evidence for physiologically non-BBB-transgressing molecules in the brain of test animals. One well-used approach shows permeability of the BBB for normal blood components like f.e. albumin or fibrinogen by applying immunocytochemical methods.

Methods

Further, for demonstrating permeability dyes like, for example Evans Blue, are used which bind with albumin, or enzymes, which subsequently can be visualised in brain sections with simple color development reactions like, for example, horseradish peroxidase (HRP). Moreover, dyes are transferred via the specific ferritin transporter of the BBB, subsequently made visible in the brain sections. Radioactively marked molecules like ^{14}C -saccharosis or ^{14}C -inulin are used to this end, too. Both substances penetrate the BBB only to an extremely small extent and may be identified on brain sections by simple autoradiography.

All above mentioned methods of in vivo investigation of the BBB require sacrificing the animal after experiment in order to provide quantitative evidence for indicator substances in consecutive brain sections by applying different dying methods. This is one of the basic limitations of these methods, since there is no possibility to perform dynamical tests. For this reason, in recent years tests have been developed that can also be used in living animals without requiring histological analysis for evaluation. The applied technique is microdialysis which is able to provide a quantitative and dynamic investigation of BBB function as well as of substance

transport across the BBB. The local substance concentration in the extracellular brain fluid is measured. All in vivo methods show fundamental limitations in experiment considerably decreasing replicability and validity of single experiments. On the one hand, replicability of exposure conditions must be provided for, since even minimum alterations of the experimental setup can lead to changed results. So, for example, increased strain during exposure is related to an increased release of glucocorticoids from the adrenal cortex resulting in an increase of BBB tightness. And it is extremely difficult to control potential thermal effects of EMF exposure

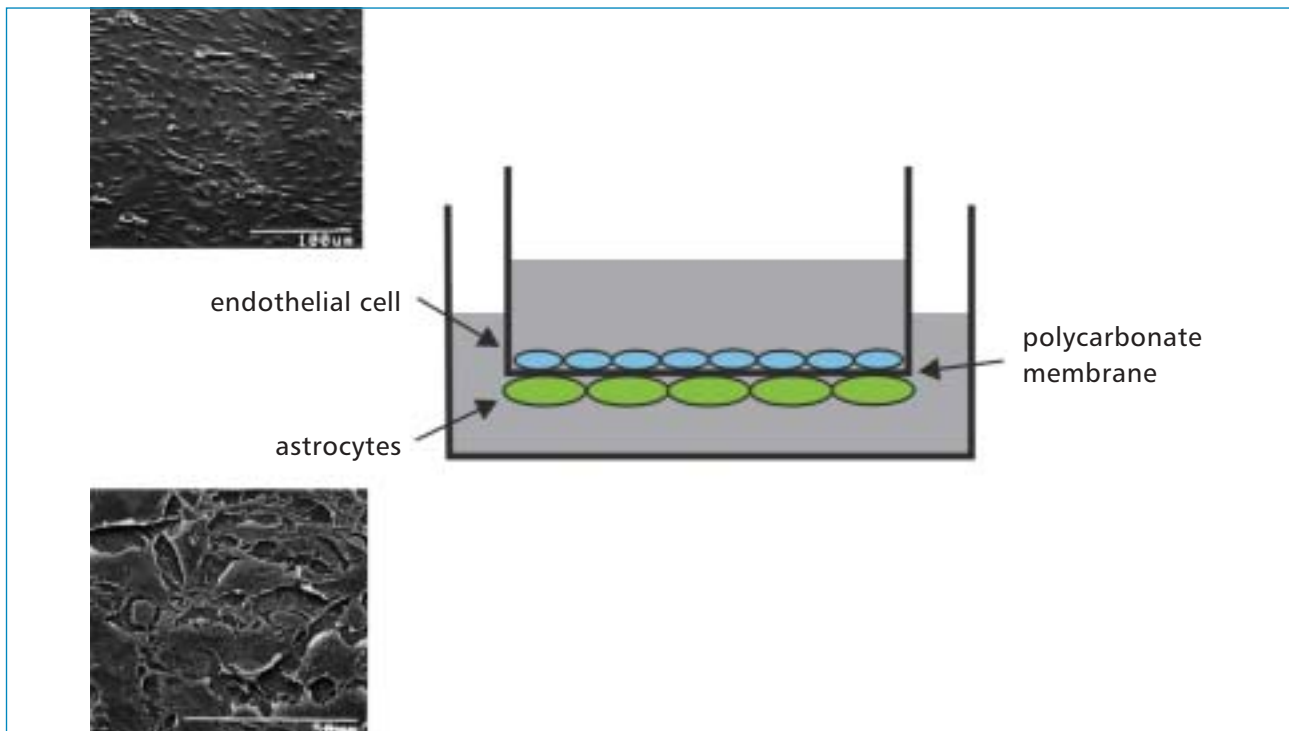


Figure 3: Coculture model of the BBB. On both sides of a polycarbonate membrane brain endothelial cells and astrocytes are cultivated. Both cell types primarily were propagated as monocultures to the monolayer. The electron microscopical images show both cell types being located at the membrane as a dense monolayer.

in the living test animals. In the last 20 years, the shortcomings of in vivo experiments resulted in different groups beginning to establish in vitro models of the BBB. Several of these technically different models now are worldwide established and accepted (17-20). An advantage of in vitro models is that they can be exposed under reproducible conditions. Further, possible temperature effects can be precisely measured. Of utmost importance, however, is the possibility to perform sophisticated morphological, biophysical and biomolecular experiments under cell culture conditions. Practically all to date developed in vitro BBB models are based on cultures of isolated brain capillary endothelial cells. In culture, these endothelial cells can be characterised via their typical morphology and the expression of the van-Willebrand factor. In addition, characterisation is made by showing evidence for typical BBB functions like *tight junction* expression, limited paracellular transport and expression of gamma-glutamyl-transpeptidase. Essentially, culture systems can be divided into monocultures consisting of brain capillary endothelial cells and cocultures containing neonatal astrocytes. It has been demonstrated that monolayers consisting of endothelial cells have a low barrier characteristic; in contrast, a coculture containing astrocytes significantly increases the transendothelial resistance particularly when cultivated in the immediate vicinity of endothelial cells (fig. 3) (20). Further, such

cocultures are far more resistant to substances leading to a decrease of the BBB's barrier characteristic, for example lipopolysaccharides. By adding substances like cyclic AMP or glucocorticoids, however, endothelial cell monocultures may develop a significantly increased tightness, too. But, on the whole, for the time being non-stimulated coculture systems seem to be most appropriate for functional tests in the BBB.

4 Effects of EMF on the BBB in vivo

Effects of EMF exposure on BBB permeability have been investigated by means of providing evidence for extravasation of external tracers or internal serum components. Several authors conclude that both continuous as well as pulsed EMF exposure increase BBB permeability. Besides, a number of studies have been performed aimed at reproducing single results. However, as a rule they did not succeed in confirming replicability (see table in the annex). Only few studies could show an enhanced permeability of the BBB exclusively at very high SAR values being connected to a temperature rise (21, 22). This led to the conclusion that earlier found increases of BBB permeability mainly were caused by thermal effects. But there are data, too, which confirm permeability increases under thermally controlled conditions (23). Few experiments give evidence for underlying possible mechanisms of

BBB permeability increases. Of interest are the studies of Neubauer et al. (1990) finding an increase of BBB permeability to rhodamine-ferritin. However, after pre-treatment with colchicine, there was no such effect. These results hint at an underlying mechanism similar to pinocytosis. Further evidence for this suggestion is that horseradish peroxidase could be detected in cytoplasm from brain capillary endothelials (24). Salford et al. (1984), however, found an increase of permeability to albumin, but not to fibrinogen. As albumin is of considerably smaller molecular weight than fibrinogen, this is to be seen as proof against a mechanism similar to pinocytosis, since pinocytosis is independent of molecular weight.

Regional temperature increases within the CNS can lead to alterations of membrane characteristics, among others of permeability or enzymatic activity. Thus activity of ornithine-decarboxylase in CNS capillary cells is heightened by a temperature-sensitive calcium influx. Interestingly, an activation of ornithine-decarboxylase after EMF exposure could be found (25). This activity increase led to a reversible permeability increase of the BBB (26).

Further, we have to consider that the strain test animals are exposed to during in vivo experiments may lead to alterations of the autonomic nervous system. These alterations, on the one hand, may result in a release of glucocorticoids from the

adrenal cortex ultimately leading to an increased tightness of the BBB. On the other hand, these autonomic alterations act as a trigger of transient blood pressure rises. Such hypertensive episodes regularly cause an increase of BBB permeability. Thus, in clinical everyday practice, we find regional brain edema following hypertensive crises. Consequently, Fritze et al. (1997) during performance of a test series with exposure of immobilised animals also succeeded in proving circumscribed extravasation of serum albumin in non-exposed animals.

5 Effects of EMF on the BBB in vitro

To date, there are only few studies available applying BBB in vitro models for investigating effects of EMF. Of interest are the studies of Neubauer et al. (1990) testing the absorption of the rhodamine-ferritin complex (Rh-F) through the use of cultivated brain capillary endothelial cells. A 15-min exposure interval was sufficient to discover a measurable absorption of the Rh-F complex by endothelial cells. From a quantitative point of view, there was an approximately two-fold absorption rate. As already mentioned in the last paragraph, the working group tried to trace effects back to the underlying mechanism. Either an opening of *tight junctions* between endothelial cells and thus an increased passive entering of the Rh-F complex or an activation of pinocytosis possibly

leading to facilitated transcellular transport were suggested. In subsequent experiments, the effect of added colchicine was tested. Colchicine is able to at least partially inhibit pinocytosis through binding to intracellular transport proteins. Parallely, after adding colchicine, a decrease in absorption of the Rh-F complex by endothelial cells was observed nearly reaching down to the baseline of experiments without exposure. From this observation the authors derive a mechanism similar to pinocytosis as a target point for the identified field effect. However, as already mentioned before, this assumption is disproved by data of Salford et al. (1984) who found an increase of permeability for low-molecular albumin, but not for the higher-molecular fibrinogen. If pinocytosis is the molecular mechanism responsible for the effect, molecule transport is independent of their molecular weight, since pinocytosis is independent of molecular weight. Neubauer et al. (1990) think that an alteration of the *tight junctions* is highly unlikely pointing to the papers of Williams et al. (1984) who did not find any alteration of *tight junction* structure in electron microscopically selected ultrathin BBB sections. However, these experiments cannot be regarded as fully valid from a technical point of view, since for precisely determining network formation, tightness and conformation of *tight junctions* freeze-fracturing techniques have to be applied showing *tight junction* figuration both at the

luminal as well as at the abluminal side of cell membranes.

In recent years, our working group has established one of the internationally renowned BBB coculture systems characterised by using physiological, biochemical and morphological criteria. In this model, transendothelial resistances as well as tightness values approximating physiological values are measured confirming the biological relevance of the model. As an indicator substance for BBB permeability sucrosis was selected. For this molecule, there is no specific mechanism for transport across the BBB. Moreover, sucrosis is a hydrophilic molecule of low molecular weight suggesting that its passage across the BBB very likely is based on paracellular flux. Our results proved a significant increase of BBB permeability for sucrosis at exposure to EMF (27). This permeability rise can be shown over several days. During subsequent experiments, we also could show a permeability rise for the hydrophobic molecule albumin that has a considerably higher molecular weight than sucrosis. There is neither a specific transport system for albumin; therefore, for the time being we are testing the hypothesis that enhanced BBB permeability after EMF exposure would be a result of an increase of the paracellular flux. A possible subcellular structure being responsible for the effect could be tight junctions primarily controlling paracellular tightness of brain capillary endothelial cells.

6 Prospects

As shown in detail in the paragraphs above, to date a great number of in vivo studies has been performed not being able to present a consistent result regarding the effects of EMF on BBB function. The reason for the indicated lack of replicability is to be found in the selected in vivo experimental approaches themselves where the control of experimental framework under identical exposure conditions in different laboratories is not guaranteed. In practically all areas of biochemistry, cell biology as well as molecular biology, this problem has led to investigators leaving behind in vivo models and replacing them by adequate in vitro models for in-depth experiments in the area of biochemistry and molecular biology. In such in vitro models, experiments on basic molecular mechanisms can be successfully performed under very well-replicable overall conditions even in different laboratories. For this reason, it seems conceivable and even likely that studies on the impact of EMF on BBB functions using in vitro models ultimately will lead to replicable and hence generally accepted results. As soon as there will be replicable proof of BBB function losses after EMF exposure, it will be possible to develop new approaches to the underlying molecular mechanisms which will be of particular interest for biological basic research.

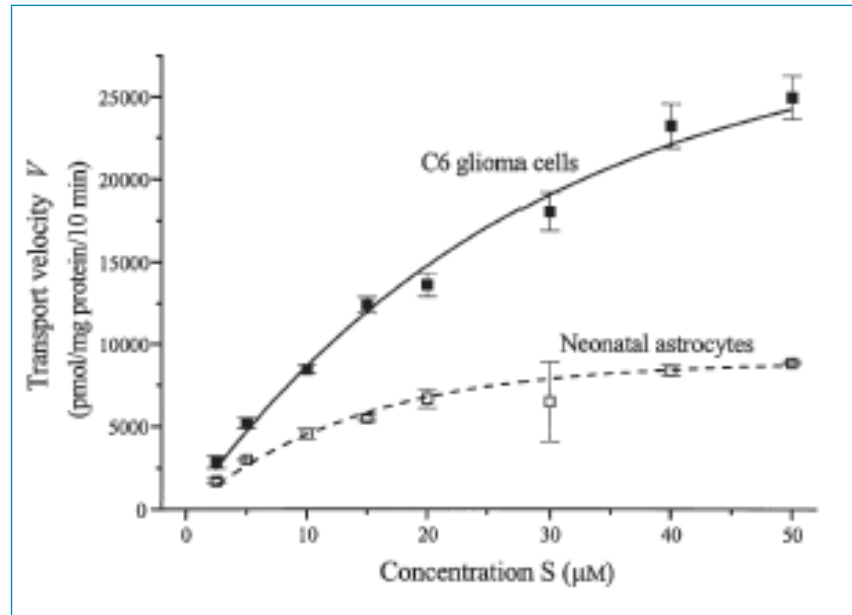


Figure 4: Example of determination of the Michaelis-Menten constant as well as the V_{max} of a specific carrier system for neutral amino acids at normal and malignant astrocytes. Activity discrepancies can be directly detected (28).

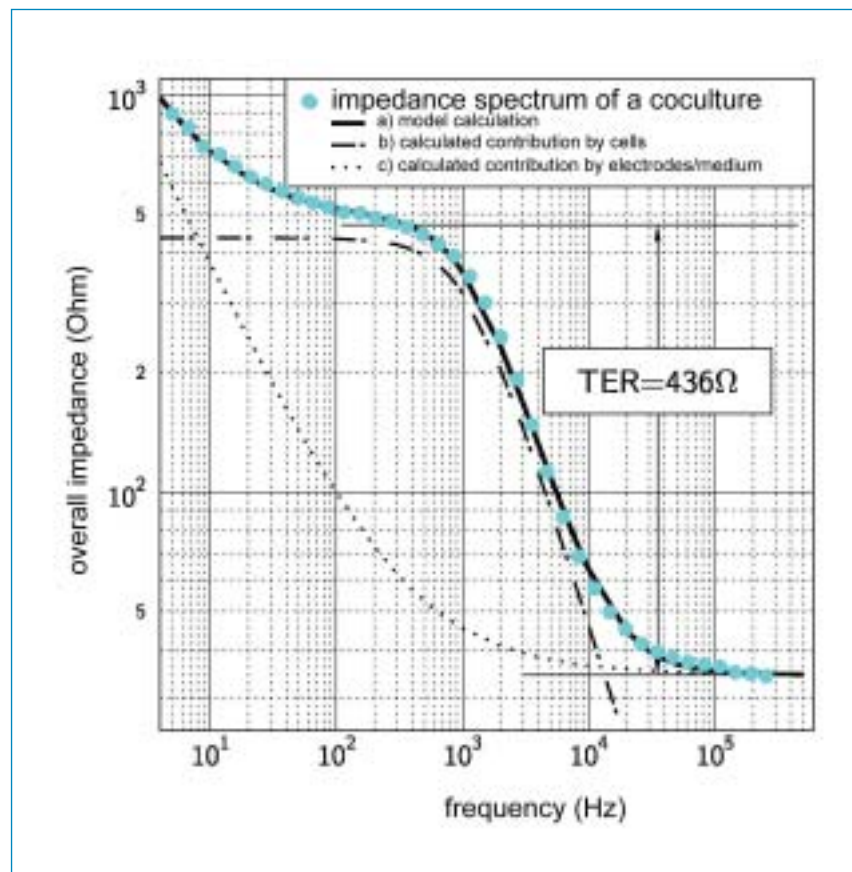


Figure 5: Determination of the transendothelial resistance from impedance spectra.

In the following, possible experimental approaches for a better understanding of fundamental issues at different levels using BBB coculture systems will be outlined.

(I) Activity of BBB-specific carrier systems. For practically all ion, sugar molecule and amino acid transports, the BBB possesses specific carrier systems. The specific Michaelis-Menten kinetics of these transport systems can exactly be determined in the cell culture system thus allowing detection of the Michaelis constant as well as of maximum transport rate (fig. 4). These parameters have sufficient sensitivity for reproducing even minimum kinetic alterations. Further, competitive assays can show the specificity of single effects. As specific model substances exist for competition of single transport systems, also large-scale studies are technologically possible.

(II) Biophysical experiments. Apart from the above described permeability measurements BBB function also can be detected by determining transendothelial resistance (fig. 5). By appropriate devices, this measurement quantity can be determined automatically. Thus, exact conclusions on time course, dose-dependency and reversibility of observed effects can be drawn. By combining impedance spectroscopy with high-resolution electron microscopic methods spatial determination of the observed permeability increase in the endothelial cell compound is made possible. Such experiments may provide essential evidence for underlying mechanisms.

(III) Ultrastructural description of tight junctions. Only in the cell culture model reproducible morphological conclusions on *tight junction*

quality can be drawn. To this end, generally freeze-fracturing electron microscopy is applied (fig. 6). This method allows the description of the complex network structure of *tight junctions* which is to be seen as direct evidence for BBB tightness.

(IV) Immunocytochemical studies. Single protein components of *tight junctions* can be dyed by specific antibodies, both regarding extracellular domains as well as intracellular domains (fig. 7). Configuration as well as subcellular distribution of these proteins provide immediate evidence for *tight junction* functioning. Such studies combined with ultramorphological studies may allow to draw sound conclusions on *tight junction* physiology before and after EMF exposure.

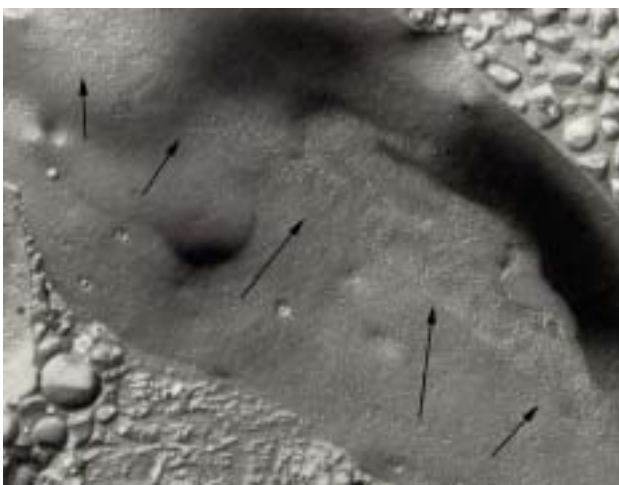


Figure 6: Typical electron microscopic image after freeze-fracturing preparation of the BBB in vitro. Tight junctions can be seen as pearlstring network formations (arrows). Network configuration allows drawing conclusions on junction tightness.



Figure 7: Immunocytochemical proof of ZO-1 in cultivated brain capillary endothelials. Expression height as well as protein distribution correlate with the markedness of BBB characteristics.

7 Summary

We have shown that the BBB is an adequate physiological system for investigating possible effects of EMF on functional systems of the CNS. As in vivo studies in the past did not lead to replicable results because of the above mentioned difficult-to-control framework conditions, it is necessary to apply cell culture systems. In scientific literature, these cell culture systems long since are established and can be installed in different laboratories under identical conditions thus providing for result replication. Further, cell culture systems open up the unique possibility to more closely examine cellular, biochemical and biomolecular mechanisms of observed effects and to describe them more exactly. Primarily, experiments in cell culture systems, however, serve to describe basic biological mechanisms. For the assessment of potential health risks well-targeted specific in vivo experiments have to follow.

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Table survey of the most important in vivo studies

reference	model	method/substance	exposure	result
Fritze et al., 1997	rat	albumin	900 MHz 0.3-7.5 W/kg	extravasation only at 7.5 W/kg, not at lower SAR values
Salford et al., 1994	rat	albumin, fibrinogen	915 MHz 0.016-5 W/kg	increased permeability for albumin, not for fibrinogen
Persson et al., 1992	rat	Evans Blue, albumin, fibrinogen	915 MHz 2.35 T (MRI)	permeability increase
Lange et al., 1991	mouse	Japanese Encephalitis Virus (JEV)	2.45 GHz 10-50 mW/cm ²	increased mortality because of facilitated virus passage, dose-dependent effect
Neubauer et al., 1990	rat and CEC	rhodamin-ferritin complex	2.45 GHz 2 W/kg	increased absorption, blocked by colchicine
Quock et al., 1987	rat and CEC	HRP in cells and in tissue	2.45 GHz 24 W/kg	increased permeability and absorption in endothelials
Ward et al., 1985	rat	saccharosis, inulin	1.7 GHz 0.1 W/kg	no permeability increase
Goldman et al., 1984	rat	⁸⁶ Rb	2.45 GHz 240 W/kg	increased permeability and temperature rise
Lin et al., 1982	rat	Evans Blue, fluorescein	2.45 GHz 0,08-240 W/kg	increased permeability only at 240 W/kg
Gruenau et al., 1982	rat	saccharosis	2.8 GHz 1-40 W/kg	no permeability increase
Ward et al., 1982	rat	saccharosis, inulin	2.45 GHz 2-6 W/kg	no permeability increase
Albert et al., 1981	hamster	HRP	2.45 GHz 2.5 W/kg	increased permeability
Preston et al., 1979	rat	sucrose	2.45 GHz 0.1-30 mW/cm ²	no permeability increase
Merritt et al., 1978	rat	mannitol	1.3 GHz 2-75 mW/cm ²	no permeability increase at constant temperature
Oscar et al., 1977	rat	mannitol, inulin, dextran	1.3 GHz 0.3-2 mW/cm ²	increased permeability for mannitol and inulin, not for dextran

Interferences with Blood Brain Barrier Functions caused by Electromagnetic Fields

To date a great number of in vivo investigations on effects of electromagnetic fields (EMF) on the function of the blood brain barrier (BBB) have been performed, however, without leading to consistent results. The reason for this obvious lack of replicability is found in the selected experimental in vivo approaches themselves. Control of identical experimental framework conditions can not be guaranteed for by different laboratories. Therefore, in nearly all fields of biochemistry, cell biology and molecular biology, scientists left behind in vivo models replacing them by adequate in vitro models for in-depth investigations of associations between EMF and the BBB. The use of in vitro models enables us to perform experiments on basic molecular mechanisms under very well-reproducible conditions in different laboratories. Cell culture systems used in this context are well-established in scientific literature for many years now offering the opportunity to better understand cellular, biochemical, and biomolecular mechanisms of observed effects and allowing a more exact description. However, experiments using cell culture systems primarily serve to describe general biological mechanisms.

Though, for possible health risk estimations specific well-targeted in vivo experiments have to follow. As a consequence, it seems conceivable and even probable that studies applying in vitro models for investigating effects of EMF on the BBB function ultimately will lead to replicable and hence commonly accepted results. Further, in case there will be reproducible evidence for function losses of the BBB after EMF exposure, it will be possible to gain more knowledge about underlying molecular mechanisms. This would be of great interest for basic research in biology.

We have shown that the BBB is a well-tested physiological system appropriate for investigations into possible EMF effects on functional systems of the central nervous system.

Abluminal

On the side away from the lumen, toward the outside (f.e. in hollow organs or blood vessels)

Adherence proteins

Proteins being able to attach to other biological tissue

Albumin

Proteins from the group of plasma proteins; serving among others as transport and reserve proteins

Astrocytes

Star-shaped support cells in the brain; subgroup of glia cells; making up one layer of the barrier between brain tissue and blood vessels

Autoradiography

Imaging method for localisation of radioactively marked substances in a sample; the sample (f.e. thin tissue slices) is brought into direct contact with a film dyed black at the sites of radioactive decay; this technique is also used for localisation of DNA fragments radioactively marked after gel-electrophoresis

Blood brain barrier

Selectively permeable barrier between the blood and the brain substance actively and passively controlling substance exchange with the central nervous system; the blood brain barrier is made up by the lining of brain capillaries (endothelial cells) and the endfeet of special glia cells (astrocytes) surrounding nerve cells.

Cadherin

Transmembrane protein controlled by calcium ions; responsible for tight binding between cells

Cerebrospinal fluid

A clear, colorless fluid filling free spaces in the brain and the spinal cord channel; protecting brain and spinal cord against blows and serving as a medium for substance exchange; this fluid contains small amounts of glucose and proteins and only few white blood cells

Competitive assays

Method for investigating transport systems (here, within or across cells in culture) using well-measurable model substances replacing normally transported substances (i.e. 'competing' with them for transport)

Cyclic AMP

Cyclic adenosine monophosphate; messenger substance within the cells

Cytoskeleton

Network of filament-forming proteins within the cell serving for tightening, for transport processes within the cell as well as for movement within the cell and cell movement itself; parts of the cytoskeleton f.e. are responsible for muscle cell movement and cell division

Endothelial

One-layer lining consisting of plate-shaped cells forming the inner walls of blood vessels; responsible for substance exchange with adjacent tissue in blood capillaries

Endocytosis

Absorption of substances (larger molecules and particles) by the inner cell via formation of small membrane vesicles (endocytosis vesicles)

Extravasation

Leakage of substances or fluid from a blood vessel into the surrounding tissue

Ferritin

Body-inherent iron-protein-binding with important storage and transport function for iron within the organism; in laboratory used as a marker for investigating transport processes within the cell

Fibrinogen

Factor I of blood clotting; water-soluble plasma protein released from the liver into the blood; pre-stage of fibrin that during blood clotting forms a connected network via its molecules (polymer)

Glia

Enveloping and supporting tissue of the central nervous system filling the spaces between nerve cells, their extensions and blood vessels; glia cells partially themselves develop long cell extensions

Glucocorticoids

One of three groups of steroid hormones developed in the adrenal cortex; other steroid hormones are cortisone and sexual hormones

Histology

Science of body tissues; in laboratory, histological test methods are used for investigating tissue or cell preparations – often as thin section preparations

Horseradish-peroxidase (HRP)

Enzyme catalysing oxidation responses; in microscopy used for color development reactions resulting in dark tainting

Hypersensitive

Hypertension; f.e. heightened blood pressure

Impedance spectroscopy

Measurement and interpretation of frequency-dependent electrical impedance, here of impedance across the artificially grown endothelial cell layer

In vivo

In Latin 'in life', i.e. in the organism; denotes experiments in living animals

Intracerebral

Within the cerebrum

Ischemia

Decrease or disruption of the blood circulation within an organ/part of an organ or tissue because of a lack of arterial blood supply

Lipopolysaccharide

Water-soluble molecule consisting of fatty substance and sugar chain components; lipopolysaccharides are a characteristic component of outer cell membranes playing a crucial role in immunoresponses

Luminal

Toward the inner space (f.e. in hollow organs or blood vesicles)

Malignant

Opposite of benign (f.e. cancerous tumors)

Meningitis

Inflammation of the hard or soft brain meninges

Michaelis(-Menten) constant (K_m)

In enzyme responses used as a term for concentrations of the original substance to be processed (substrate) reaching half the maximum response velocity (50% of the enzyme form the enzyme-substrate complex); thus the K_m provides a measure for the enzyme's tendency to respond to its specific substrate (enzyme affinity)

Monolayer

Single stratum, layer, film with a thickness of only one molecule or one cell, f.e. as a monolayer of polar lipids at water surface or as cell lawn in a petri dish

Morphology

Science of structure and shape of living entities and their organs

Neurotransmitter

Messenger substance serving for conduction of electrical impulses between nerve cells and synapses; some neurotransmitters are acetylcholine, adrenaline, noradrenaline, and serotonin

Ornithine-decarboxylase

Key enzyme for the formation of polyamines in cells; polyamines are able to – among others – increase BBB permeability

Permeability

Porosity of, for example, membranes or cell layers dependent of pore size, chemical structure, electric charges, and, in cell layers, of the contact between cells and of transport processes across cells, respectively

Pinocytosis

Absorption of small quantities of external fluid into cells with the help of endocytic vesicles; special type of endocytosis

Signal transducer

Signal-transporting substances

Specific absorption rate (SAR)

Term denoting the power which is absorbed per kilogram body weight (and/or biological matter) (W/kg), if the body is exposed to a high-frequency electromagnetic field; may be applied locally (for example during use of a mobile phone) or across the whole body (f.e. in a far-field of a base station); limit values in Germany: whole body: 0.08 W/kg; body parts: 2 W/kg (averaged across 10 g body tissue)

Tight junctions

Binding site between cells with particularly tight cell-to-cell contact of adjacent cell membranes (also see 'zona occludens')

Tracer

Artificial or specifically marked physiological substance, after insertion into living organs allowing or facilitating different tests without affecting natural body functions; leaves measurable traces in metabolism turnover and transport processes in the body, or in laboratory preparations

Transient

Short-term, temporary, fleeting

von-Willebrand factor

Subunit of a molecule playing a part in blood clotting; in laboratory, in this context used for clearly identifying endothelial cells in cell cultures

Zona occludens

Bar-shaped contact site between cell membranes, electron microscopically seeming so small as if membranes would have melted into one (see also 'tight junctions')

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