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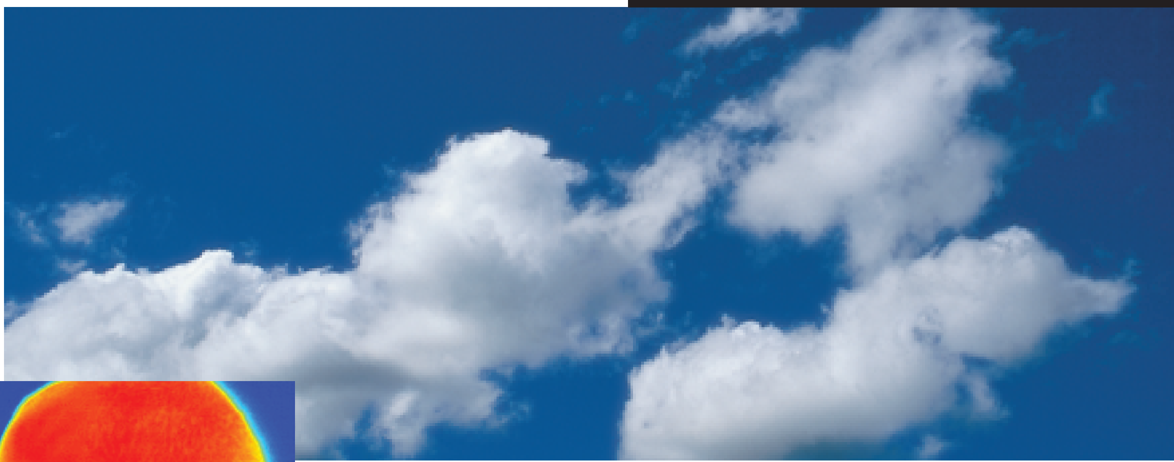
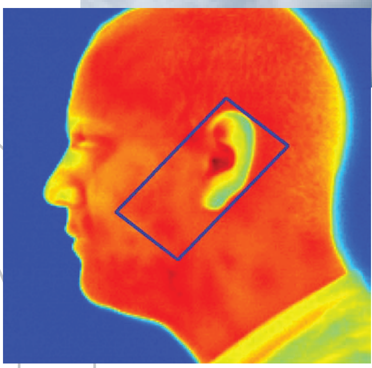




Roland Glaser

Are thermoreceptors responsible for „non-thermal“ effects of RF fields?

Forschungsgemeinschaft Funk

Dear readers,

as "Edition Wissenschaft Nr. 21" the Forschungsgemeinschaft Funk likes to present you at the end of the year 2005 an very interesting article of Prof. Dr. Roland Glaser, Humboldt University, Berlin about the question: "Are thermoreceptors responsible for "non-thermal" effects of RF fields?". This should be a valuable contribution to the still open discussion, whether there are reliable existing evidences for "non-thermal" effects far under the limits of the ICNIRP recommendations.
During the last years Prof. Roland Glaser had taken several times the opportunity to aim on clarification of the burning question, which biophysical mechanism can contribute to "non-thermal" or "athermal" effects. This question is not new. Neither there was a reliable commonly accepted reproducible effect, nor an unanimously accepted definition for the usage of the terms "non-thermal" or "athermal". Very often in discussions the scientific community even could not be brought on the same level of understanding of underlying mechanism or processes in cells. On different occasions this study question was hotly discussed. We have reported about several FGF- and COST 281- Workshops in the "FGF Newsletter". During the last four years a special group of scientists with the support of MMF and FGF have donated much time to look for concepts to understand the issue. We are eager to look at the output of this task force and we will inform you immediately after the presentations of the results.
Till today it can be stated, that there is a lack of knowledge concerning research on cellular and molecular mechanisms. And that lack of knowledge has to be filled under the consideration, that without solid basic research of that study issue the question will be still remain open. This will underline the necessity of that kind of research: "to look for mechanism under the condition of very small energy input in biological systems like it is with EMF energy emission of modern radio communication systems"
If one is speculating that may be one of the results of further epidemiological research will be: „no clear cancer evidence", the results of human and animal studies will getting more and more important. Sometimes the result of studies is like that following statement: „there are some effects, but probably non dangerous and possibly subtle-thermal". Then the old stereotype questions arise: „but what will be with other conditions or other frequencies or pulsations?..." These questions can only be answered on the basis of a known mechanism. That exactly underlines the main points of further research needs.
It is absolutely correct, that: „*The only established mechanisms that relate to health consequences are caused by temperature elevation ...*" but: excitation of molecular vibrations and protein conformations can be the result of this, not only by radical pair mechanism (which, as already known, is not relevant for weak RF-fields!). This is in accordance with the statement in the WHO research agenda that: „*Microdosimetry research (i.e., at the cellular or subcellular levels) that may yield new insights concerning biologically relevant targets of RF".*
This exactly should be the start point for high priority research. Including the recent results of thermosensible molecules (TRP-receptors, GrpE, as „riboswitches" for HSP-expression etc.) one really could understand the so called „non-thermal" effects of weak RF-fields. The papers of Ken Foster and Earl Prohofsky are important steps to find the answer of this question, but they did not include these new results of thermoreception. FGF recently have organized a workshop "Subtle Thermal Effects of RF-Fields *in vitro* and *in vivo*", which exactly tackle this point (Stuttgart, Nov. 2005).
Only knowing the theoretical background of possible molecular absorption and heat-dissipation of RF-energy at molecular and supramolecular level, predictions could be made on frequency dependence, pulsation etc. Furthermore, these results can indicate, what really does the term „dose" mean, and what kind of "dosimetry" we really need (SAR, SAR* Time, W*m^{-2} ...).
To realize this kind of research, experiments should be performed in cooperation with specialists of thermoreception on RF-field effects on established models of molecular and cellular thermoreceptors. These sorts of experiments are much faster and cheaper than animal studies. They easily can realize conditions of frequency dependence or pulsations and can produce data, which leads to new insights in to molecular mechanisms. So, let us try to set this kind of research in force. Glaser´s contribution in this edition is just one step. Other studies have to follow.

Kindest regards
Gerd Friedrich

Contents

Roland Glaser

Are thermoreceptors responsible for „non-thermal“ effects of RF fields?

Introduction: What does „non-thermal“ mean?

In contrast to ELF, the fields in the frequency range of mobile phones do not excite nerve and muscle cells. Therefore, the only obvious effect of RF and MW fields on biological systems is heating potentially bringing about the consequences of temperature increases. Although interactions of high frequency fields were investigated already in the thirties of the last century [Rajewsky, 1938], the question whether there exist additional “non-thermal“ effects that would have to be considered in defining safety limits, still remains controversial. The reason for this are publications claiming to have found such “non-thermal“ effects in *in vitro* experiments with cells, as well as in experiments with animals or human volunteers.

What do the terms “thermal“ and “non-thermal“ (or “athermal“) really mean? This question can be answered either from a biophysical perspective, considering possible mechanisms of interaction, or just empirically, based on experimental setups. From the empirical point of view, effects usually are called “non-thermal“:

- if irradiation intensity in the experiment is so low that changes in temperature are unlikely to occur physically [Geletyuk et al., 1995; Kwee et al., 2001; Phillips et al., 1998; Preece et al., 1999; Weisbrot et al., 2003];
- if, during irradiation, no significant change in temperature has been measured in the body or in the experimental vessel, or if water jacketing, etc., has been part of the experimental setup warranting a constant temperature during exposure [Bohr and Bohr, 2000; Byus et al., 1988; Leszczynski et al., 2002; Markkanen et al., 2004];
- if, in comparison, a temperature increase caused by conventional heating does not show effects similar to those induced by RF exposure [Cao et al., 1995; de Pomerai et al., 2000; Peinnequin et al., 2000; Velizarov et al., 1999], or if, due to a normal temperature increase, an opposite effect is expected related to RF exposure [Allis et al., 1987].

In general, in these papers an effect is considered “non-thermal“ if it is not accompanied by a predictable or measurable temperature increase, or if it does not correspond to effects occurring after conventional heating of the same amount.

Contrary to this, the biophysical definition is based on the types of mechanisms of field interaction. Concomitant heating is not considered in this approach. Consequently, a mechanism is seen as non-thermal if the interaction of the electrical (or magnetic) vector of the RF field with charges or dipoles of molecules in the living system directly leads to specific effects other than heating. Fröhlich [1982] already pointed out that: “An effect is non-thermal when, under the influence of a field, the system changes its properties in a way that can not be achieved by heating, i.e. when its response is non-linear“. His calculations made clear that extremely strong fields would be necessary to move molecular dipoles.

Non-thermal effects in this sense actually are well known, as for example in dielectrophoreses or electrorotation of cells [Fuhr and Hagedorn, 1996; Fuhr et al., 1996; Gimsa, 1991; Glaser and Fuhr, 1987; Glaser, 2000]. To induce them, however, electric field strengths are required which are many magnitudes above those which are used by normal telecommunications systems. Consequently, dielectrophoresis and electrorotation are accompanied by considerable heat production. According to the „empirical“ definition, they should therefore be classified as “thermal“. They are of particular interest regarding biotechnological applications, but irrelevant to the issue of safety limits as discussed in this paper.

Thus, the use of the empirical versus the biophysical definition of the term "non-thermal" sometimes leads to rather contradictory evaluations. It would probably make sense to introduce the terms "quasi-non-thermal" or "subtle thermal" to make the empirical definition of "non-thermal" more precise. For simplifying matters, however, in the following we will enclose the term "non-thermal" in quotation marks when referring to the empirical definition in the sense of "so-called non-thermal" effects.
In this context, the question arises: Are effects that are called "non-thermal" in the above mentioned empirical sense of the word "subtle thermal" effects, or do non-thermal effects, according to the biophysical definition, really occur also at weak RF field exposure? At first glance, this question may seem sophistical, but in fact it is crucial where safety aspects, i.e. the setting of exposure limits, are concerned. If such responses to weak RF fields found in some experiments are just that: "subtle temperature" effects – meaning that they simply activate common reactions of the biological system to a very low and probably only locally detectable degree of heating – they are harmless and can be neglected. Such effects can be treated similarly to those caused by temperature influences to which the organism is exposed on a daily basis and under various environmental conditions. If, on the other hand, particular interaction mechanisms of weak RF or MW fields do exist that are not identical with those of normal heating, they should be carefully investigated considering potential health consequences, and should also taken into account when defining exposure limits.

This paper is an attempt to verify hypotheses claiming that "non-thermal" effects of RF fields, at least those found in experiments performed under well-controlled conditions, ultimately are the result of thermoreceptor activation. Possibly only single molecules or thermosensitive cells were stimulated that triggered various reactions of the highly complicated system of thermoregulation without involving conscious perception of test volunteers, or behavioural consequences in animals. Temperature elevation gains and the size of the heated volume may be so small that measurement is technically impossible (this aspect was already discussed in detail by Stern et al. [1979]).

Thermoregulatory response to IR versus RF energy absorption

The concept of radiofrequency (RF) and microwave (MW) fields activating the thermoregulatory system is not new. Recently, Eleanor R. Adair and D. R. Black summarized related investigations in a diligent review [Adair and Black, 2003]. First detailed experiments investigating the activation of human thermoreceptors by GHz fields in comparison to infrared (IR) irradiation were already performed by Hendler and Hardy [1960]. In the seventies, a number of related studies followed, summarized in the book "Microwaves and Thermoregulation" that was edited by Eleanor A. Adair [1983]. Blick at al. [1997] repeated and extended investigations using experiments with advanced dosimetry, and at an extended frequency range. Thresholds for microwave-evoked skin sensations of warmth at frequencies of 2.45, 7.5, 10, 35, and 94 GHz were measured and compared to warmth evoked by infrared radiation (IR). These findings are generally consistent with those reported by earlier investigators indicating dependency on frequency which corresponds to the depth of tissue penetration of radiation. Sensitivity monotonically increased with increasing frequency throughout the range of microwave frequencies tested. When irridiating an area of 327 cm^2 for 10 seconds, the threshold at 94 GHz (4.5 $\pm$ 0.6 mW/cm^2) was more than an order of magnitude below that at 2.45 GHz (63.1 $\pm$ 6.7 mW/cm^2), and was comparable to the threshold for IR (5.34 $\pm$ 1.07 mW/cm^2) (Tab. 1). These differences were due to the effectivity of the absorbed radiation in attaining a defined temperature elevation across the regions where thermoreceptors are located. The energy absorbed by other regions is dissipated without any effect on the thermoregulatory system. Thermoreceptors of the skin located in the outer 0.6 mm skin layer are primarily activated [Adair and Black, 2003]. Riu et al. [1997] calculated the temperature profiles generated by these frequencies after 3 and 10 seconds of skin exposure and found corresponding thresholds of temperature sensation of about 0.07°C. The thresholds found in these experiments therefore clearly exceed the exposure limits recommended by the ICNIRP and prescribed by official regulations. Furthermore, they are above the level of exposure at which "non-thermal" effects have sometimes been found. Does this mean that thermosensors can be ignored in such low level experiments?

Subject	Author	Radiation	Threshold mW/cm^2
Human volunteers (skin sensations of warmth in the middle of the back)	Blick et al. 1997	2.45 GHz	63.1 ± 6.7
		7.5 GHz	19.5 ± 2.9
		10 GHz	19,6 ± 2.9
		35 GHz	8.8 ± 1.3
		94 GHz	4.5 ± 0.6
		Infrared	5.34 ± 1.1
Boa constrictor	De Cock Buning 1983	Infrared	0.177
Python reticulaturs		Infrared	0.059
Agkistrodon rhodostoma (pit viper)		Infrared	0.011
Fire beetle *(Melanophila acuminata)*	Evans 1964	Infrared	0.06

Tab. 1: Sensitivity threshold of humans and various animals to MW-, and infrared radiation.

Limitations of behavioural experiments performed in animals and human volunteers

The above mentioned experiments testing the warmth sensation of human volunteers or the behaviour of animals are of relevance when investigating the basic problem of RF field influence on the system of thermoregulation, but cannot exclude the possibility of thermosensory activation in general. This is already made evident by two circumstances which were observed in these experiments: (I) The threshold of activation depends not only on what region of the body is exposed to the field, but also on what area of the skin is irradiated. This means that a response was detected only if a minimum number of singular thermoreceptors were activated. The observed intensity does therefore not reflect the threshold of a single thermoreceptor cell. (II) The time constant of the sensation is >1 s. The sensitivity to thermal stimulation was found to increase with exposure time ranging from 3 s up to 10 s [Riu et al., 1997]. This indicates that the reaction was not determined by the primary response of thermosensors but by the time constant of the heating of the tissue surrounding the thermoreceptors and by subsequent neuronal processes.

In fact, warmth sensation does not simply reflect the activation of thermoreceptors in a specific region of the body, but is a result of the subsequent information processing in the hypothalamus and cortex (see: Fig. 1). Thermoreceptors of warm-blooded animals are located on the surface as well as in many other parts of the body, including the brain and the spinal cord. Whilst thermoreceptors in the skin measure the environmental temperature, internal thermoreceptors are responsible for controlling blood temperature. They are all part of a complicated network transmitting information to the center of temperature control: the preoptic area of the anterior hypothalamus. Conscious warmth sensation, therefore, is the result of processing the information provided by all these sensors, including a lot of other physiological conditions.

In the last years our knowledge on molecular and cellular mechanisms of thermoreception has remarkably increased. So it was shown that not only nerve endings and dendrids are responsible for thermoreception, but thermosensitive ion channels are also found in keratinocytes, ovary cells [Peier et al., 2002 a, b] and aorta endothelial cells [Watanabe et al., 2002]. These investigations must be taken into consideration to understand the results of experiments on "non-thermal" reactions of RF-fields.

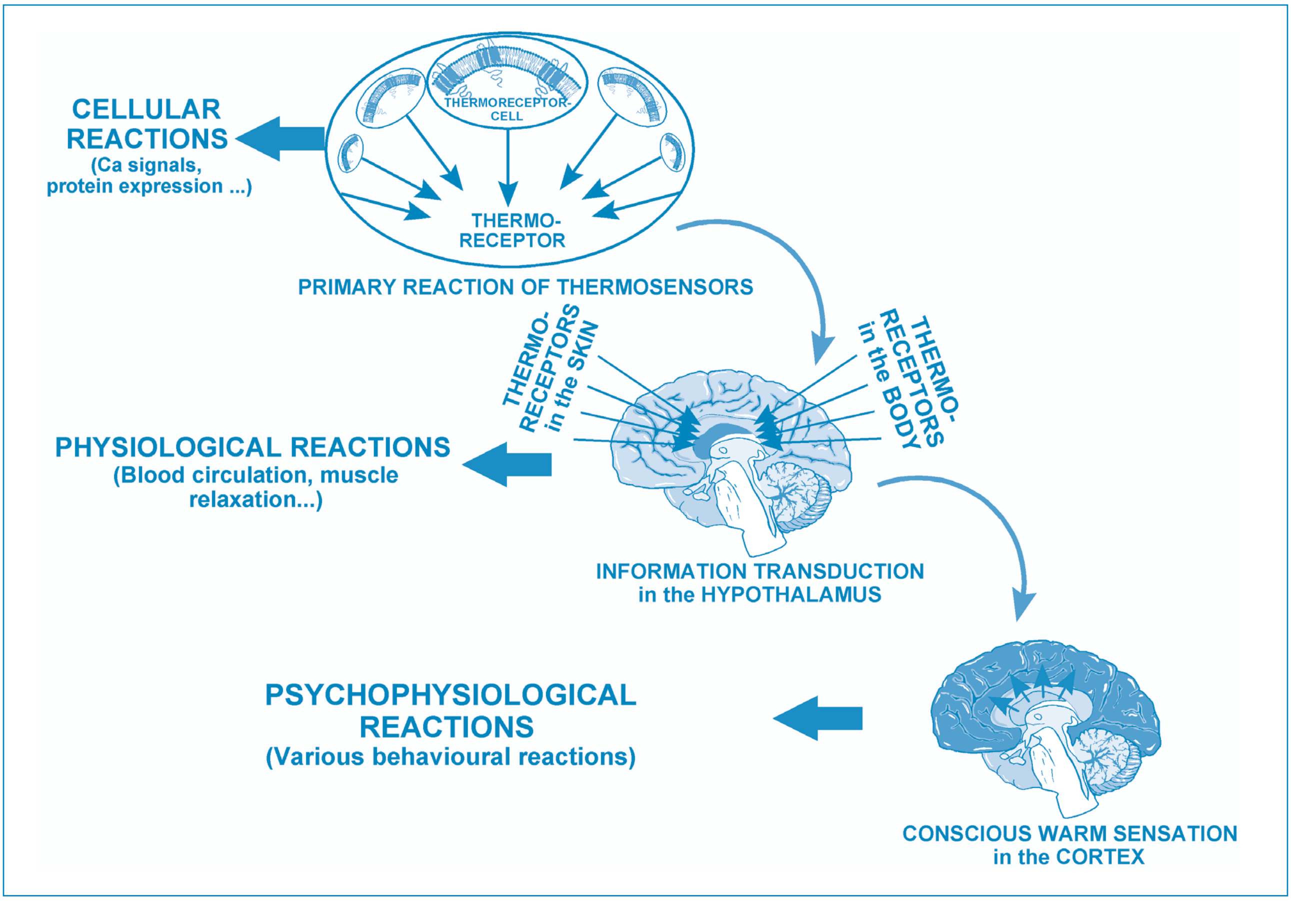
What do we know about the physiology of specialized thermoreceptors in animals?

Provided that many processes in living nature are similar across organisms of different organizational levels, it makes sense firstly to take a look at the highly specialized thermoreceptors of various animals and insects, aiding them in hunting, feeding and overall survival. Boas, pythons and pit vipers are known to use IR radiation emanated by warm-blooded animals. Their pit organs are radiant heat detectors helping them to locate an IR source with an angle resolution of few degrees [Campbell et al., 2002; de Cock Buning, 1983; Neuweiler, 2003]. A similarly functioning pit organ is found in vampire bats, as for example in *Desmodus rotundus* [Kürten and Schmidt, 1982]. Many insects also are equipped with IR and thermal sensors of different sensitivity and function. The larvae of the Australian "fire beetle", for example, can only develop in freshly burnt wood. The IR receptor of these beetles enables them to detect forest fires from a distance of 60 to100 miles [Campbell et al., 2002]. Other insects just feel the temperature of their surroundings with high sensitivity.

For all these IR sensors, absorption systems were found which transform IR radiation into heat. It is generally accepted that not the quantum energy of radiation – as for the visual system – but heat, resp. the temperature change induced by IR absorption, is sensed [Campbell et al., 2002; Gingl and Tichy, 2001; Harris and Gamow 1971, 1972; Neuweiler, 2003; Schmitz et al., 2000, 2002, 2003].

In contrast to mammalian skin sensors, where the sensation requires the heating of a thick layer of tissue, masses absorbing radiation and transforming it into temperature elevation are much smaller in these animals. In the pit organ of snakes, a 15 micrometer thick, heavily innervated membrane is responsible for IR reception. It measures 30 mm^2 and is thermally isolated by air layers on both sides [Neuweiler, 2003]; additionally, a rich capillary network acts as an effective heat sink [Pappas et al. 2004]. In the fire beetle, the IR radiation is absorbed by a 30 micrometer thin disk with a diameter of about 120 micrometer. This disk is located in an air-filled space inside a hemispherical invagination, and held in place by a small cuticular stalk [Schmitz et al., 2002]. In Drosophila, thermoreceptors are located at the third antennal segment [Liu et al., 2003]. Consequently, all these receptors, in contrast to those of mammals, exhibit extremely short time constants.

In contrast to experiments in mammals, these receptors can be examined by direct electrophysiological recording using microelectrodes. Thus, a direct investigation of threshold values is possible, without any interference of subsequent information processing in the CNS. The maximum sensitivity of pit vipers (*Agkistrodon rhodostoma*) has been found at 0.011 mW/cm^2, for *Python reticulatus* at 0.059 mW/cm^2, and for *Boa constrictor* at 0.177 mW/cm^2 [de Cock Buning, 1983] (Tab. 1). In these experiments, the head of the respective snake was exposed to infrared radiation emitted by the black painted surface of a copper



block with a temperature warmer by 10°C than the environment, at distances of 16.4 to 66.6 cm. Recordings were conducted at heat-sensitive neurons in the brain. The Australian fire beetle *Melanophila acuminata* shows a maximum sensitivity at 0.06 mW/cm^2 [Evans 1964].

The real temperature increase of the receptor sides in these experiments are not measurable. Calculations of the corresponding temperature elevations, however, led to estimated values between 0.003 and 0.01 K. This is below the sensitivity of conventional technical thermosensors. By the way – from the use of the empirical definition it would follow that the infrared sensation of these animals is based on "non-thermal" effects!

The time constants of these thermoreceptors were limited not so much by the heating of the absorber – as is the case in humans, monkeys and rats – as by the time constants and the firing frequency of nerves. So the response to a stepwise increased irradiation was below 20 ms [Schmitz et al., 2000; Gingl and Tichy, 2001].

Unfortunately, there are no detailed experiments on the sensibility of these thermoreceptors to RF-fields. Only Harris and Gamow [1972] tested the response of the pit organs of boas to 10.7 GHz microwave radiation. They found a response to pulses of about 11.1 mW/cm^2, at a distance of 4 cm from the horn antenna "making an accurate measurement of the power density nearly impossible". The aim of this paper was just to demonstrate that it is not a specific infrared effect that is responsible for this reaction, but an unspecific temperature elevation.

By exceeding the scope of biological objects and including those specialized for thermosensation to better focus on the primary reactions as occur in mammals, thermoreceptors with extremely low thresholds and short time constants were found. Even such neurophysiological experiments, however, fail to reflect the real time constant of the primary reaction, because they nevertheless include a time delay for nerve reactions. A closer look at the molecular mechanisms is necessary to obtain information about the real data of this reaction, and also on the probable sensitivity of single thermosensitive cells in mammals.

Molecular mechanisms of thermoreception

Over the last years a number of detailed investigations of the thermoregulation processes of procaryotic and eucaryotic cells have been published. These investigations provided new insight into the molecular mechanisms of thermosensation of various cells, and reveal the ambivalence of their functions. The implication of cells in the neuronal system of thermosensation just reflects one special case in this diversity. Thermosensitive molecules are responsible for various cellular functions, such as the protection against physiologically adverse temperatures, or even for the activation of cells in the case of favorable temperatures [Chowdhury et al., 2003]. Some of them are temperature dependent RNA molecules, a special kind of the so-called „riboswitches" [Lai, 2003]. Bacteria and cells of many other organisms regulate their phase transition of membrane lipids in response to temperature by controlling the fatty acid composition of lipids. In *B. subtilis*, for example, this is done by a temperature dependent expression of oxygen-dependent saturase, in *E. coli* activating enzymes for synthesizing new phospholipids [Mansilla et al., 2004]. The expression of heat-shock proteins in procaryotes such as *E. coli* is controlled by temperature dependent structural alterations of the nucleotide exchange factor GrpE exhibiting "non-Arrhenius" behaviour. This means there is an increasing activity in one, and a decreasing activity in another temperature region [Gelinas et al., 2003; Grimshaw et al., 2003].

Although these kinds of cellular thermoregulation seem to be important too, sine they explain some other "non-thermal" cellular effects, we will focuse here on neuronal thermosensors. A growing number of so called TRPV-transport proteins in membranes of various cells has been found over the last years, some of them showing a high degree of temperature dependence of their function (TRP stands for "transient receptor potential", V indicates a vallinoid sensitive subfamily) [Tominaga et al., 2004]. In mammals, TRPV3 and TRPV4 are the most important channels responding at temperatures in the physiological range [Benham et al., 2003]. Notably, they do not only occur in neurons but are also found in a number of other cells. TRPV4 channels, for example, occur in a HEK293 cell expression system and in native mouse aorta endothelial cells [Watanabe et al., 2002]. Gating mechanisms of these channels, at a specific temperature interval, show a much larger sensitivity to temperature elevation than standard biochemical reactions. At

times, this property is expressed by a Q_{10}-value, a change in the reaction rate resulting from a 10 °C temperature rise. For normal biochemical reactions as well as for normal ion channels, this value is a factor of 2, approximately. In the thermosensitive temperature range of these channels, however, it can be much larger. Between 24 and 36 °C, TRPV4 channels, for example, indicate a current increased by a Q_{10} of 19.1 [Watanabe et al., 2002]. Exposed in Chinese hamster ovary cells, TRPV3 channels showed a Q_{10} of 1.9±0.3 for lower temperatures, and a Q_{10} =17.3±3.0, after the temperature rose above 32 °C. Cells exposed to rapid heating typically exhibited a steep initial activation phase with Q_{10} =21.6±4.2 [Xu et al., 2002]. In keratinocytes, a TRPV3 channel was found that was activated at temperatures above 35 °C, showing a mean Q_{10} = 6.62 [Peier et al., 2002]. The reason for this extremely sensitive reactions in a narrow, specific temperature range are structural alterations of the molecule, a kind of molecular phase transition. As a result, for example, the TRPV4 channels transform temperature stimuli into electrophysiological responses of the cell connected by a calcium influx from outside of the cell [Güler et al., 2002].
Although TRPV1 to TRPV 4 channels have not been found yet in invertebrates, similar channels were detected in *Drosophila* and in the roundworm *Caenorhabditis elegans*. Another channel of the TRP family, the ANKTM1 protein is found in *Drosophila* as well as in vertebrates, and possibly is also involved in thermosensation [Viswanath et al., 2003]. Unfortunately, the channels which are responsible for the enormous sensibility of the pit organs of snakes have not yet been isolated. However the functional similarity of the corresponding membrane proteins with the TRPV1-channel has already been demonstrated [Pappas et al. 2004].
It seems important to note that the reaction of these temperature sensitive molecules depends on several conditions. The response of the TRPV3 channel, for example, increases with repeated stimulation at suprathreshold temperatures, indicating pronounced sensitization of this receptor by heat. Its responses increased at each subsequent stimulus so that current responses were enhanced about 10-fold over the course of the experiment [Benham et al., 2003]. This may be one molecular reason for the above mentioned dependence of the thermal reaction of humans and animals on the duration of IR irradiation, besides other reactions such as heating of the tissue etc. Furthermore, the sensitivity of the corresponding cells depends on the osmolarity of the medium, the lipid composition of the membrane and other conditions [Güler et al., 2002]. Consequently, these channels exhibit a surprising temperature dependence of their function, particularly at narrow temperature ranges. A single cell usually contains many copies of different types of such channels, each being responsible for a specific temperature region. The general response of this cell, i.e. the signal given by this cell to the thermoreceptor, therefore is the resulting average of the behavior of of a large number of proteins. Since thermoreceptors moreover represent the response of many cells, this is to be understood as a system of substantial noise suppression.
Unfortunately, at present we know only the temperature dependence of these molecules, but not the threshold of their response. A full analysis of the temperature threshold of these primary reactions cannot be given yet.

Conclusions: The system of thermoreception and its side reactions – a possible reason for „non-thermal" reactions of RF-fields

In Fig. 1 an attempt was made to roughly illustrate the system of thermosensation, from the primary reaction of the membrane proteins, the response of the cells, the transduction of nervous information to the hypothalamus up to the conscious warm sensation as a reaction of the cortex. Considering the properties of this system and its elements, as summarized in this paper, new insights into the issue of "non-thermal" RF field interaction become possible.
The extremely high sensitivity of thermoreceptors of several animals and insects, as listed in Tab. 1, shows that in general this system is able to react to temperature elevations below those measurable in experiments investigating RF- and microwave effects, as well as below calculated temperature elevations which usually occur in the skin and surface of the brain during the use of a mobile phone. Of course, the sensitivity of the specialized thermosensors in snakes or insects possibly is higher than those of mammals. As can be seen in many other cases, however, similar molecular systems are used conser-

vatively in nature, at different levels of evolution. There is a similarity, for example, with the molecules of the TRP-transporters, or thermosensitive RNA-systems. Therefore, a response of other cells at this level of temperature elevation cannot be excluded. The signal-to-noise ratio of thermoreception obviously is optimized by averaging and filtering at all information processing steps. Thermoreceptor cells average the information from many proteins; the thermosensors at the nerve endings use the information from many thermosensitive cells; in the hypothalamus, information from various thermosensors in the body is evaluated. The physiological evaluation of signals sent by thermoreceptors obviously depends on the number of activated thermoreceptors (i.e. the area of exposed skin), the duration of activation, but also on a number of general psychophysiological parameters.

The conscious warm sensation is therefore the endpoint of the system, the result of various neuronal processes, signaling the body there is a need of behavioral reactions, like moving away from a source etc. The absence of this sensation, however, does not mean that several less dramatic regulatory processes were initiated. EEG modifications as a result of weak RF-field exposure, for example, are understandable as being caused by locally modified circulation in the brain, even without a conscious warm sensation. The dependence of this reaction on a number of other physiological factors certainly explain why replications of these results in human volunteers sometimes were impossible [e.g.: Freude et al., 2000; Wagner et al., 2000]. Consequently, if „non-thermal" effects – at least those found in experiments using accurate exposure systems and exact dosimetry - really are based on the activation of the molecular or cellular system of thermosensors, they must be classified as 'everyday' responses without real consequences to health.

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Adair ER, Black DR 2003. Thermoregulatory responses to RF energy absorption. Bioelectromagnetics Supp. 6: S17-S38.

Adair ER (Edit.) 1983. Microwaves and Thermoregulations. Academic Press, New York.

Allis JW, Sinha-Robinson BL. 1987. Temperatur-specific inhibition of human red cell Na+/K+ATPase by 2,450-MHz microwave radiation. Bioelectromagnetics 8: 203-212.

Benham CD, Gunthorpe M J, Davis J B. 2003. TRPV channels as temperature sensors. Cell Calcium 33: 479-487.

Blick DW, Adair ER, Hurt WD, Sherry CJ, Walters TJ, Merritt JH. 1997. Thresholds of microwave-evoked warmth sensation in human skin. Bioelectromagnetics 18: 403-409.

Bohr H, Bohr J. 2000. Microwave enhanced kinetics observed in ORD studies of a protein. Bioelectromagnetics 21: 68-72.

Byus CV, Dartun K, Pieper S, Adey WR. 1988. Increased ornithine decarboxylase activity in cultured cells exposed to low energy modulated microwave fields and phorbol ester tumor promoters. Cancer Res. 48: 4222-4226.

Campbell A L, Naik R R, Sowards L, Stone MO. 2002. Biological infrared imaging and sensing. Micron 33: 211-225.

Cao G, Liu L-M, Cleary SF. 1995. Cell cycle alterations induced by isothermal 27 MHz radio-frequency radiation exposure. Bioelectrochem. Bioenerg. 37: 131-140.

Chowdhury S, Ragaz C, Kreuger, E, Narberhaus, F. 2003. Temperature-controlled structural alterations of an RNA thermometer. J. Biol. Chem. 278: 47915-47921.

de Cock Buning TJ. 1983. Thresholds of infrared sensitive tectal neurons in *Pyton reticulatus, Boa constrictor* and *Agkistrodon rhodostoma.* J. Comp. Physiol. 151: 461-467.

de Pomerai D, Daniells C, David H, et al. 2000. Non-thermal heat-shock response to microwaves. Nature 405: 417-418.

Evans, W. G. 1964. Infrared receptors in Melanophila acuminata De Geer. Nature; 202, 211

Freude G, Ullsperger P, Eggert S, Ruppe I. 2000. Microwaves emitted by cellular telephones affect human slow brain potentials. Eur. J. Appl. Physiol. 81: 18-27.

Fröhlich H. 1982. What are non-thermal electric biological effects? Bioelectromagnetics 3: 45-46.

Fuhr G, Hagedorn R. 1996. Cell Electrorotation. In: Lynch, P. T., M. R. Davey (Edrs.): Electrical Manipulation of Cells. Chapman & Hall, New York 38-70.

Fuhr G, Zimmermann U, Shirley SG. 1996. Cell motion in time-varying fields: principles and potential. in: U. Zimmermann, G. Neil (Edit.) Electromanipulation of cells. CRC Press INC, Boca Raton 259-328.

Geletyuk VI, Kazachenko VN, Chemeris NK, Fesenko EE. 1995. Dual effects of microwaves on single Ca2+-activated K+ channels in cultured kidney cells vero. FEBS Letters 359: 85-88.
Gelinas AD, Toth J, Bethoney KA, Langsetmo K, Stafford WF, Harrison CJ. 2003. Thermodynamic linkage in the GrpE nucleotide exchange factor, a molecular thermosensor. Biochemistry 42: 9050-9059.

Gimsa J, Marszalek P, Loewe U, Tsong TY. 1991. Dielectrophoresis and electrorotation of neurospora slime and murine myeloma cells. Biophys. J. 60: 749-760.

Gingl E, Tichy H. 2001. Infrared sensitivity of thermoreceptors. J. Comp. Physiol. 187: 467-475.

Glaser R. 2000. Biophysics. Springer, Berlin Heidelberg New York.

Glaser R, Fuhr G. 1987. Electrorotation – The spin of cells in rotating high frequency electric fields. In: M. Blank and E. Findl (eds.); Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems; Plenum Press, New York 271-289.

Grimshaw JPA, Jelesarov I, Siegenthaler RK, Christen P. 2003. Thermosensor action of GrpE - The DnaK chaperone system at heat shock temperatures. J.Biol. Chem. 278: 19048-19053.

Güler AD, Lee HS, Iida T, Shimizu I, Tominaga M, Caterina M. 2002. Heat-evoked activation of the ion channel TRPV4. J. Neuroscience 22: 6408-6414.

Harris JF, Gamow RI. 1971. Snake infrared receptors. Thermal or photochemical mechanisms? Science 172: 1252-1253.

Harris JF, Gamow RI. 1972. An analysis of heat receptors by means of microwave radiation. Biol. Med. Sci. Instrument. 9: 187-190.

Hendler E, Hardy JD. 1960. Infrared and microwave effects on skin heating and temperature sensation. IRE Trans. Med. Electronics 7: 143-152.

Kürten L, Schmidt U. 1982. Thermoreception in the common vampire bat (*Desmodus rotundus*). J. Comp. Physiol. A 146: 223-228.

Kwee, S., Raskmark, P., Velizarov, S. 2001. Changes in cellular proteins due to environmental non-ionizing radiation. I. Heat-shock proteins. Electro and Magnetobiology 20: 141-152.

Lai, EC. 2003. RNA sensors and riboswitches. Self-regulating messages. Current Biology 2003; 13: R285-R291.

Leszczynski D, Joenvaara S, Reivinen J, Kuokka R. 2002. Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: Molecular mechanism for cancer- and blood-brain barrier-related effects. Differentiation 70: 120-129.

Liu L, Yermolaieva O, Johnson WA, Abboud FM, Welsh M J. 2003. Identification and function of thermosensory neurons in Drosophila larvae. Nature Neuroscience 6: 267-273.

Mansilla, MC, Cybulski, LE, Albanesi, D., deMendoza, D. 2004. Control of membrane lipid fluidity by molecular thermosensors. J. Bacteriol. 186: 6681-6688

Markkanen A, Penttinen P, Naarala J, Pelkonen J, Sihvonen AP, and Juutilainen J. 2004. Apoptosis induced by ultraviolet radiation is enhanced by amplitude modulated radiofrequency radiation in mutant yeast cells. Bioelectromagnetics 25: 127-133.

Neuweiler G. 2003. Neuro- und Sinnesphysiologie - 3. Temperaturempfindlichkeit. In: G. Heldmaier u. G. Neuweiler: Vergleichende Tierphysiologie, Springer-Verlag Berlin 1: 89-96.

Pappas, TC, Motamedi, M., and Christensen, BN 2004. Unique temperature-activated neurons from pit viper thermosensors. Am. J. Physiol. Cell Physiology 287: C1219-C1228.

Peier AM, Moqrich A, Hergarden AC, et al. 2002. A TRP channel that senses cold stimuli and menthol. Cell 108: 705-715.

Peier AM, Reeve AJ, Andersson EA, et al. 2002. A heat-sensitive TRP channel expressed in keratinocytes. Science 296: 2046-2049.

Peinnequin A, Piriou A, Mathieu J, Dabouis V, Sebbah C, Malabiau R, Debouzy JC. 2000. Non-thermal effects of continuous 2.45 GHz microwaves on Fas-induced apoptosis in human Jurkat T-cell line. Bioelectrochem. Bioenerg. 51: 157-161.

Phillips JL, Ivaschuk O, IshidaJones T, Jones RA, CampbellBeachler M, Haggren W. 1998. DNA damage in Molt-4 T-lymphoblastoid cells exposed to cellular telephone radiofrequency fields in vitro. Bioelectrochem. Bioenerg. 45: 103-110.

Preece AW, Iwi G, DaviesSmith A, Wesnes K, Butler S, Lim E, Varey A. 1999. Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. Int. J. Radiat. Biol. 75: 447-456.

Rajewsky B. 1938. Biophysikalische Grundlagen der Ultrakurzwellen-Wirkung im lebenden Gewebe. in: B. Rajewsky (Hrsg.) Ultrakurzwellen in ihren medizinischen-biologischen Anwendungen, G. Thieme, Leipzig.

Riu PJ, Foster KR, Blick DW, Adair ERA. 1997. Thermal model for human thresholds of microwave-evoked warmth sensations. Bioelectromagnetics 18: 578-583.

Schmitz H, Schmitz A, Bleckmann H. 2000. A new type of infrared organ in the Australian „fire-beetle“ Merimna atrata (Coleoptera: Buprestidae). Naturwissenschaften 87: 542-545.

Schmitz H, Schmitz A, Trenner S, Bleckmann H. 2002. A new type of insect infrared organ of low thermal mass. Naturwissenschaften 89: 226-229.

Schmitz H, Trenner S. 2003. Electrophysiological characterization of the multipolar thermoreceptors in the ''fire-beetle'' Merimna atrata and comparison with the infrared sensilla of Melanophila acuminata (Both Coleoptera, Buprestidae). J. Compar. Physiology A Neuroethology Sensory Neural and Behavioral Physiology 189: 715-722.

Stern S, Margolin L, Weiss B, Lu ST, Michaelson SM. 1979. Microwaves: Effect on thermoregulatory behavior in rats. Science 206: 1198-1201.

Tominaga, M., Caterina, M J. 2004. Thermosensation and pain. J. Neurobiology 6: 3-11

Velizarov S. 1999. Electric and magnetic fields in microbial biotechnology: Possibilities, limitations, and perspectives. Electro and Magnetobiology 18: 185-212.

Viswanath V, Story GM, Peier AM, Petrus MJ, Hwang SW, Patapoutian A, Jegla T. 2003. Ion channels – Opposite thermosensor in fruitfly and mouse. Nature 423: 822-823.

Wagner P, Röschke J, Mann K, Fell J, Hiller W, Frank C, Grozinger M. 2000. Human sleep EEG under the influence of pulsed radio frequency electromagnetic fields – Results from polysomnographies using submaximal high power flux densities. Neuropsychobiology 42: 207-212.

Watanabe H, Vriens SH, Suh SH, Benham CD, Droogmans G, Nilius B. 2002. Heat-evoked activation of TRPV4 channels in a HEK293 cell expression system and in native mouse aorta endothelial cells. J. Biol. Chem. 277: 47044-47051.

Weisbrot D, Lin H, Ye L, Blank M., and Goodman R.2003. Effects of mobile phone radiation on reproduction and development in Drosophila melanogaster. J. Cell. Biochem.; 89: 48-55

Xu HX, Ramsey IS, Kotecha SA, et al. 2002. TRPV3 is a calcium permeable temperature-sensitive cation channel. Nature 418: 181-186.

Abstract

The existence of "non-thermal" effects of weak RF-fields has been discussed again and again. In these papers the expression "non-thermal" is mostly not related to the biophysical mechanism, but used in a empirical sense. Usually, an effect is considered "non-thermal" if it is not accompanied by a predictable or measurable temperature increase, or if it does not correspond to effects occurring after conventional heating of a similar degree. This approach does not take into consideration the real system of thermoregulation, its ambivalence, and its high sensitivity. Recently, a specialized class of transport proteins have been found functioning as thermosensors in cell membranes not only in cells of specialized organs, but also in normal keratinocytes and other cells. The signal-to-noise ratio in this system of thermoreception is optimized by averaging the response of many proteins and cells and many steps of information processing with various time constants from below microseconds for the primary reactions of the membrane proteins, milliseconds for nerve excitations, and eventually, tenths of seconds or even minutes for behavioral consequences. The threshold of this system can be lower than the sensitivity of our technical devices for measuring or controlling temperature in experiments. Considering this, the effects found in experiments with weak RF-fields in fact could be "quasi-thermal" or "subtle thermal" reactions of the biological system of thermosensation and thermoregulation. A number of reactions is conceivable, occurring at temperature elevations that are not high enough to be registered by the central nervous system. Protein expression, influences on local blood circulation, or other effects could be the the result of thermal stimulation, even if there is no measurable temperature increase and no behavioral consequences or conscious "warm" sensations. If "non-thermal" effects, at least those found in experiments using accurate exposure systems and exact dosimetry, really are based on the activation of the molecular system of thermosensors, they consequently must be classified as 'everyday' responses without real significance to health.

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