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1. Microwave electromagnetic fields act by activating voltage-gated calcium channels: why the current international safety standards do not predict biological hazard

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Abstract. Microwave and other low frequency electromagnetic fields (EMFs) have been shown to act by activating voltage-gated calcium channels (VGCCs) with most biological effects being due to elevated intracellular calcium, consequent nitric oxide (NO) elevation and either peroxynitrite or NO signaling. This, the role of excessive intracellular calcium in microwave effects and some 20,000 papers on microwave biological effects show that the current international safety standards do not predict biological hazard. Such standards are based on the false assumption that the predominant effects of microwave and other low frequency EMF exposures are due to heating. A whole series of biological changes reportedly produced by microwave exposures can now be explained in terms of this new paradigm of EMF action via VGCC activation, including: oxidative stress; single and double stranded breaks in cellular DNA; therapeutic effects; blood-brain barrier breakdown; greatly depressed melatonin levels and sleep disruption; cancer; male and

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female infertility; immune dysfunction; neurological dysfunction; cardiac dysfunction including tachycardia, arrhythmia and sudden cardiac death. A two-phase program for greatly improving EMF safety standards is proposed.

There have been demonstrations by "activists" in many parts of the world against what they consider to be unsafe exposures to microwave frequency electromagnetic fields (EMFs). Such exposures have increased by large amounts in recent years. Such demonstrations have been met with assertions by government organizations and by industry that these exposures are well within international and national safety standards and therefore can be assumed to be safe. They are correct that these are well within safety standards. A central question being examined here is whether these standards are based on well documented science such that if they are, we should be assured of safety.

Current U.S. and International safety standards are based on the assumption that the only important thing that microwave and other low frequency EMFs can do biologically is to heat things (1-5), like heating things in a microwave oven. Based on that assumption, safety standards are based on heating (1-5) and the reasonable inference, *if that assumption is correct*, is that levels of exposures which only produce insignificant heating have no biological impact and therefore are "safe." In fact advocates for current standards argue that current safety standards are about 100 times more stringent than is needed (1), because even exposure levels 100 times higher than allowed by current safety standards produce only slight heating.

However, over 20,000 publications in the scientific literature have reported substantial biological effects of at exposures well within safety standards, such that none of these should be possible if current safety standards are scientifically based. These include some 4000 studies on therapeutic effects of microwave EMFs, effects that are well known to be non-thermal (6).

It should be noted that there is a reasonable basis for the heating assumption underlying current safety standards. The photons that make up microwave frequency and other low frequency fields are very low energy photons, without insufficient energy to individually change the chemistry of our bodies. That is they are different from ionizing radiation or even ultraviolet or visible radiation, where individual photons have sufficient energy to produce chemical changes. How, then can we understand the thousands of studies showing well-documented non-thermal biological effects of microwave frequency and other low frequency EMFs?

EMFs act via stimulation of voltage-gated calcium channels (VGCCs)

The author showed in a recent review (7), that in 2 dozen studies, EMF effects on cells and organisms could be blocked by calcium channel blockers, agents that block voltage-gated calcium channels (VGCCs; also known as voltage-operated, voltage-dependent or voltage-regulated calcium channels). In each of these two dozen studies, all of the measured effects were greatly lowered by the calcium channel blockers, suggesting that activation of these channels is responsible for most if not all of the EMF effects (7). In most but not all cases, it was L-type VGCCs that were primarily involved.

Activation of these channels is thought to produce most biological effects through increases in intracellular calcium levels.

In these studies, the EMFs studied were of various types, including extremely low frequency fields such as coming from the 50 or 60 cycle electrical wiring, microwave frequency EMFs, very short nanosecond pulses, and even static electric or magnetic fields. The findings for microwave EMFs create the most concerns, however, because our exposures have increased so quickly in recent years, and new technologies involving new exposures are becoming available at an ever increasing rate. The action of such microwave exposures via VGCC activation is also supported by a large number of studies, reviewed earlier (8,9), showing that elevated intracellular calcium levels were found following low level microwave EMF exposures, leading to changes in calcium signaling. This mode of action is also supported by two studies by Panagopoulos et al (10,11) who predicted that EMFs, including microwave EMFs can act by influencing the charged amino acid residues that control voltage-gated ion channels, to activate some of those channels. These were biophysical modeling studies and they not only support these VGCC findings, they also argue that the activation of these channels by microwave and other low frequency EMFs is biophysically plausible.

We are, therefore, in a situation where the old paradigm of such EMF action, where only heating effects were considered plausible and real (1-5), is replaced by a a new paradigm where VGCC activation by microwave and other EMFs is both plausible and real and provides an explanation for over 20,000 papers in the scientific literature that are inexplicable by the old paradigm.

That does not mean that there may not be other biological actions of EMFs, not involving VGCCs, through their actions on various charged

chemical groups including amino acid residues in proteins. Pilla reviewed two studies in which microwave EMFs increased calmodulin activation (6). Calmodulin is regulated by intracellular calcium such that its activation may act along with VGCC activation in two related pathways of action discussed below.

Two related pathways of action that can be activated by VGCC activation

VGCC activation is thought to act, to a great extent by increasing intracellular calcium levels. This is especially true for activation of the L-type VGCCs where the channels stay open relatively long periods of time. Whereas most other ion channels tend to stay open for only perhaps 1 or a few milliseconds, L-type VGCCs tend to stay open typically for a hundred milliseconds or more. Consequently their activation can easily produce a substantial impact on the levels of intracellular calcium.

While other effects of intracellular calcium are also likely to occur following VGCC activation, much of the effect of elevated intracellular calcium has been shown to be produced by calcium/calmodulin stimulation of the two calcium/calmodulin-dependent nitric oxide synthases, nNOS and eNOS (see Fig. 1, below), leading to large increases in nitric oxide (NO). NO can act along two pathways, as indicated in Fig. 1 below, to either stimulate NO signaling along the NO/cGMP, G kinase pathway which is

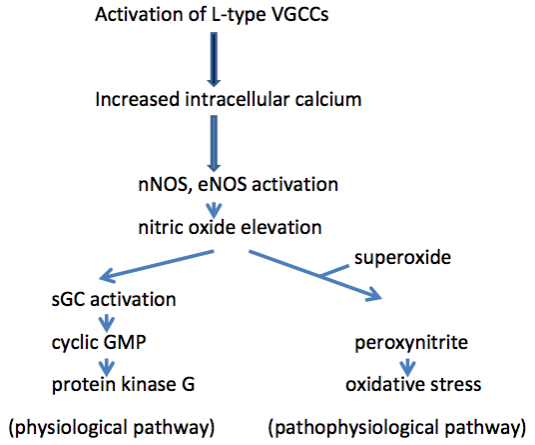

Figure 1. Possible pattern of action of VGCCs via nitric oxide (NO).

thought to be the main pathway of action of NO in producing normal physiological responses. This is thought to be the pathway involved in producing therapeutic effects of EMFs (6,7). In contrast, the pathway leading from NO to peroxynitrite and oxidative stress is thought to be the main pathway of action in pathophysiological responses to EMFs (7); it is the likely pathway of action of EMFs in producing single strand breaks in cellular DNA (7,15). So immediately we can see plausible mechanisms of action for some EMF effects, effects that were inexplicable by the old heating paradigm.

Other well-documented responses to microwave EMFs can also be produced via plausible mechanisms via VGCC activation

It can be seen from the previous section that three well-documented responses to microwave EMFs, namely therapeutic effects, single stranded breaks in cellular DNA and oxidative stress, can each be explained as being plausible consequences of VGCC activation by such EMFs. What about other such well-documented effects?

Double strand breaks in DNA, which are detected through the accumulation of micronuclei in cells after microwave and other EMF exposures, can be generated through the same mechanism as single stranded breaks.

Cancer is now well-established to be caused by weak microwave radiation exposures (reviewed in: 12-14). Adey many years ago showed that calcium effects were involved in cancer causation by such weak EMFs (9). It is known that cancer can be produced by a combination of single and double stranded breaks and other changes in DNA produced by peroxynitrite and its radical breakdown products. This NO/peroxynitrite pathway of action has been implicated in what is called inflammatory carcinogenesis (15-17) and provides, therefore a plausible mechanism of action for EMF/VGCC carcinogenesis.

Breakdown of the blood-brain barrier is another commonly reported response to microwave EMF exposure. Such breakdown occurs through peroxynitrite/oxidant product stimulation of the activation of matrix metalloproteinases (MMPs) (18-20), with the MMPs degrading the tight junctions between cells that are essential to maintain the blood-brain barrier (20,21). So again, we have a plausible mechanism leading from microwave EMF exposure to breakdown of the blood-brain barrier.

There are many studies showing that melatonin levels at night are greatly depressed in people exposed to microwave EMFs, with substantial sleep disruption as an apparent consequence. It has been shown that VGCCs and consequent intracellular calcium have effects on both the entrainment of the circadian rhythm which controls melatonin production as well as a more directly on melatonin production (22,23), providing simple explanations for this effect.

There has been much concern over the both male and female infertility in response to microwave EMF exposure. Such infertility may be caused by multiple effects of VGCC activation, including those produced through the peroxynitrite/oxidative stress pathway. Kesari et al (24) showed important roles of oxidative stress in cell-phone exposure caused male infertility. Double stranded breaks in the DNA of the gamete precursor cells, have been shown to have infertility roles (25). Such double stranded breaks in DNA produce a breakdown of the integrity of the genome and produces, therefore spontaneous early abortion and consequent infertility. However high levels of intracellular calcium can also induce apoptotic cell death through effects of elevated calcium in the mitochondria of those cells (26,27). In males, there may also be a breakdown of the blood-testis barrier via a mechanism identical to the breakdown of the blood-brain barrier, discussed above.

It can be seen from the above that 10 different well-documented microwave EMF effects can be easily explained as being a consequence of EMF VGCC activation: oxidative stress, elevated single and double strand breaks in DNA, therapeutic responses to such EMFs, breakdown of the blood-brain barrier, cancer, melatonin loss, sleep dysfunction, male infertility and female infertility.

This may be just the beginning

When one looks at what cell types carry functional VGCCs, there are many. Let's discuss a few of these where there has been substantial study. Most of the cells of the immune system carry VGCCs. O. Johansson (28) reviewed effects of microwave EMFs on the immune system and suggests that increases in allergies and inflammation may be produced by such EMFs.

VGCCs are found widely in the nervous system where almost every neurotransmitter is released in response to VGCC activation (29). There have been studies on the impact of cell phone or cordless phone use on various aspects of brain function but we are still in the very early stages in studying such effects. But given the widespread and important role of VGCCs in the central nervous system, one needs to carefully consider all

types of neuropsychiatric and neurodegenerative responses as to whether or not these may possibly be linked to microwave EMF exposure. There have been many studies showing various changes in neurological function and other brain changes following low level microwave EMF exposures (see for example, refs. 30-48).

Most of the hormones of the body are released under the control of mechanisms triggered by VGCC activation (29). What effects there may be of such possible linkage between EMFs and hormonal control is difficult to fathom. One hormone release system that has been studied in this context is the release of epinephrine/norepinephrine from the chromaffin cells of the adrenal gland. It has been shown in two studies that EMFs stimulate the release of these two hormones by chromaffin cells by a VGCC-dependent mechanism (7) as well as in many other EMF chromaffin cell studies where a VGCC role was not tested. These two hormones, when elevated produce major stress on the body, including psychological stress.

Another cell type where VGCCs have major roles are the pacemaker cells of the heart, endocrine system and central nervous system (29). These pacemaker cells have very high densities of VGCCs in them and may, therefore, be particularly susceptible to EMF activation. In the heart hyperactivity of the VGCCs produces tachycardia and arrhythmias, leading in some cases to sudden cardiac death (49,50). There are studies, in two cases going back to the 1960s (51,52), showing that isolated animal hearts exposed to microwave EMFs (again, well within current safety standards) developed tachycardia and arrhythmia and Havas has shown that some electromagnetic hypersensitive (EHS) individuals developed instantaneous tachycardia when unknowingly exposed to an activated cordless phone (53,54). We currently have an epidemic of tachycardia, arrhythmia and sudden cardiac death despite the fact that ischemic heart disease is decreasing. Could this be due to microwave EMF exposure? This is a possibility that cannot be ruled out at this point.

We are still in the early stages of studying many of these issues but safety standards should, of course, be genuinely tied to real safety, not simply to incomplete knowledge of extremely important potential and plausible hazards.

Are we going to jettison our false safety standards in favor of some that are at least somewhat biologically relevant?

Pulsed fields and different frequencies and intensities

It has been known for well over a quarter of a century that pulsed microwave fields are much more biologically active than are non-pulsed

fields. This is still another type of observation that is completely inconsistent with heating being the main effect. Pulsed fields are, of course, produced by any type of wireless communication device since it is the pattern of pulsations that conveys the information. However because different devices often use different types of pulsation patterns, we are left with the information that pulsations are important but we don't know how biologically active the different pulsation patterns are. So how can we rationally compare the dangers of one device vs another? The answer is we can't at this time because we don't have the required information.

Furthermore Barrie Trower, a retired military intelligence expert from the U.K. has stated that different wavelengths vary in their biological activities as well, but the specifics are all classified by multiple countries because of "national security." The problem of course is that this does not help the security of our bodies. However, this again says that we cannot compare different wireless communications devices with each other when they work on different wavelengths. Finally, it has been shown that there can be intensity "windows" where biological activity is greater than at intensities both higher and lower than the window intensity (55). This again argues against heating and also makes it impossible to currently predict biological activity without doing actual measurements of biological activity. While in general, lower intensities are safer than higher intensities, this "window" effect shows that there are some biologically important exceptions to this pattern.

Where do the threats come from and what can we do about them?

The threats come mainly but not solely from cordless communications devices, cell phones, cordless phones, cordless phone bases, Wi-Fi fields, Wi-Fi signaling from computers and tablets, cell phone and other microwave towers, radar units, microwave ovens, so called "smart meters" and all types of other cordless communications devices.

There are also concerns about extremely low frequency fields including 50/60 cycle fields coming from our wiring. In addition, essentially all such wiring nowadays, have various amounts of dirty electricity, which comes from high frequency transients in the electric wiring. These high frequency transients come from all types of digital devices. Digital power supplies, compact fluorescents and also digital inverter boxes used to convert photovoltaic energy from DC to AC and similar devices used in wind generated electricity may be particularly problematic. Dirty electricity can

move along the power lines and enter houses and other buildings from outside, so you have to deal with your own generation but also levels generated elsewhere in the vicinity. The biological effects of dirty electricity, as reported by Samuel Milham (56), Magda Havas and others are similar to those from microwave EMFs, so it seems likely that dirty electricity works, at least in part via VGCC activation, as well. I am not going to comment further on the dirty electricity problem here, although it is a substantial one.

The various types of devices listed in the first paragraph of this section, all put out pulsed fields with different patterns of pulsation from one device to another, making it impossible to currently predict biological effects of one device based on effects of another. Similarly since the different types of devices use different frequencies, they may differ from one another in biological impact in ways that cannot currently be predicted, given our current dearth of measurements of such effects by different devices. Accordingly, what is needed is a two-phase solution to this public health crisis:

1. Lowering exposures from current allowed levels, which use heating effects to compare different devices, by factors of 100 to 1000-fold. We know of, course, that this may be inadequate and that there may still be biological effects with many devices. But such lowering will produce a substantial improvement over current safety standards.
2. Use a series of biological response measures to compare biological responses to different devices to allow us to devise more biologically defensible safety standards in the future.

Lowering exposures by factors of 100 to 1000-fold

There are quite a number of things that can be easily done to improve the current situation. One can put shielding materials on the bottom of laptop computers and the back of tablets to lower exposures to our bodies. Wi-Fi fields are poorly designed with exposure levels of 1000 to 10,000 times that necessary for function when one is located near the Wi-Fi antenna. They can be redesigned to greatly lower such maximum exposures – the problem is that there has not been any focus on this issue. There are still problems using Wi-Fi in schools even if one does this, because a whole classroom of laptops communicating back to the Wi-Fi antenna still generates very high fields in a small space. My opinion is that it is better to go back to hard wiring computers in schools to completely avoid such unnecessary exposures.

Cell phones can be used with headsets or on speakerphone, both of which substantially lower exposures. Headsets should be given to anyone purchasing or otherwise receiving a cell phone, to encourage use. Cell phones can be carried in pouches shielded on one side, so by carrying the cell phone near the body with the shielded side towards the body, exposures can be greatly lowered.

Cordless (DECT) phones in the U.S. and many other countries are poorly designed, having bases which broadcast 24 hours per day. There are cordless phones available in Europe where the bases only broadcast when the phone is in use – this type of design should be standardized. Most cordless phones are designed so that they can be used circa 200 ft (60 m) away from the base. Most people do not need such long distance usage. By lowering the signal, cutting the distance to 20 ft (6 m), one can cut exposures from the phone 100-fold; redesigning antennae and other properties in such phones could, no doubt, produce further improvements. Changing the design of the phone antennae in either cordless phones or cell phones could lower exposures to the head when these are used without headsets or on speakerphone.

"Smart meters" should be abolished because they use short high-intensity pulses of microwave radiation. We know from the nanosecond pulse studies can be very damaging and act via VGCC activation, with activation continuing long after the pulse has ceased (7). It has been known for over 30 years that short microwave pulses can cause massive cellular damage (57). Until we have some biological measures of "smart meter" effects, it is foolhardy in my view to continue using them.

Cell phone and other microwave towers can be redesigned to lower maximum exposures near the tower. Austria has done such redesigns, lowering such exposures by 1000-fold and there is no reason that similar redesigns cannot be done elsewhere.

Microwave ovens also put out pulsed fields, pulsing with the alternating current that runs them. Exposures from microwave ovens can easily be lowered 100-fold or more through simple redesigning, including putting finer grounded metal mesh over windows.

We had, in the U.S., a huge shift in automobile safety from the 1950's and 60's to the 1980's when safety became a big marketing issue, so companies were competing based on safety, not just style and performance. We need a similar shift in the electronics industry. It can be done if the public knowledge is such that the public demands it, but probably not otherwise.

Biological testing

Hardell and Sage (58) argued for biologically based EMF safety standards before the VGCC central mechanism of action was realized. It is possible, of course, that EMF action may occur via other mechanisms, not just VGCC activation, but until such alternatives are identified, they cannot be easily assessed. Because we know that VGCC activation occurs and is very important biologically, this must be the current focus of biological testing. There are 10 types of VGCCs, including four types of L-type channels and also four other types of VGCCs (N-type, P/Q-type, R-type, T-type), with T-types having three forms. These 10 VGCCs differ from one another in their properties and may therefore differ from one another in how easily they become activated by various EMFs. These channels are also subject to multiple forms of biological regulation which may also produce still more heterogeneity in terms of biological responses to EMFs. In general then, cells differ from one another in whether they have VGCCs or not (most but not all do), the types of VGCCs found in specific cell types and the density of the different VGCCs in the plasma membrane and how these VGCCs are regulated in specific cells under specific conditions.

It is highly desirable to test EMF effects using diverse biological responses, to lower the probability of missing important responses to specific types of EMF exposures.

The proposal here is to use three types of biological response tests. Our discussion here is on these three general approaches, but does not provide detailed descriptions of each.

1. Cell culture tests: Should use cells known to be sensitive to EMFs. Probably the simplest way to measure responses is to use a nitric oxide electrode positioned in the gas phase over the cells in culture to measure increases in nitric oxide production, as shown earlier by Pilla (59).
2. Specific biological effects measured in experimental animals: Some effects that should be considered are:
   Tachycardia and other changes in heart beat in experimental animals
   Increased levels of epinephrine/norepinephrine in the blood
   Changes in neurological function, such as those reported during cell phone or cordless phone use
3. Whole animal studies can be done, by measuring whole body nitric oxide production. Nitric oxide is unstable in the body and it is typically measured through nitrate/nitrite in the blood.

We very much need to get started with such studies which are essential in order to approach genuine safety instead of the fictional safety we have now.

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