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MINI-REVIEW ARTICLE

Low Intensity Electromagnetic Fields Act *via* Voltage-Gated Calcium Channel (VGCC) Activation to Cause Very Early Onset Alzheimer's Disease: 18 Distinct Types of Evidence

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Abstract: Electronically generated electromagnetic fields (EMFs), including those used in wireless communication such as cell phones, Wi-Fi and smart meters, are coherent, producing very high electric and magnetic forces, which act on the voltage sensor of voltage-gated calcium channels to produce increases in intracellular calcium $[Ca^{2+}]i$. The calcium hypothesis of Alzheimer's disease (AD) has shown that each of the important AD-specific and nonspecific causal elements is produced by excessive $[Ca^{2+}]i$. $[Ca^{2+}]i$ acts in AD *via* excessive calcium signaling and the peroxynitrite/oxidative stress/inflammation pathway, which are each elevated by EMFs.An apparent vicious cycle in AD involves amyloid-beta protein (Aβ) and $[Ca^{2+}]i$. Three types of epidemiology suggest EMF causation of AD, including early onset AD. Extensive animal model studies show that low intensity EMFs cause neurodegeneration, including AD, with AD animals having elevated levels of Aβ, amyloid precursor protein and BACE1. Rats exposed to pulsed EMFs every day are reported to develop universal or near universal very early onset neurodegeneration, including AD; these findings are superficially similar to humans with digital dementia. EMFs producing modest increases in $[Ca^{2+}]i$ can also produce protective, therapeutic effects. The therapeutic pathway and peroxynitrite pathway inhibit each other. A summary of 18 different findings is provided, which collectively provide powerful evidence for EMF causation of AD. The author is concerned that smarter, more highly pulsed "smart" wireless communication may cause widespread very, very early onset AD in human populations.

Keywords: Calcium hypothesis of Alzheimer's disease, non-thermal electromagnetic field effects, the voltage sensor as the direct target of electromagnetic fields, animal models of Alzheimer's disease, EMF safety guideline failure, apoptotic and autophagic cell death, Aβ and $[Ca^{2+}]i$ vicious cycle.

1. INTRODUCTION

The confluence of two important findings is the origin of this paper. One of those findings is that increased intracellular calcium $[Ca^{2+}]i$ may be both central and essential to the causation of Alzheimer's disease (AD) and that increased $[Ca^{2+}]i$ in the cells of the brain produces elevated levels of the amyloid-beta (Aβ) protein whose protein aggregates have specific and essential roles in causing AD. This has been called the calcium hypothesis of AD.

The second important finding is that diverse low intensity electromagnetic fields (EMFs) activate voltage-gated calcium channels (VGCCs) and that such EMFs act *via* increases in $[Ca^{2+}]i$ to produce biological effects. The two most important pathways of action by which such EMFs produce effects following $[Ca^{2+}]i$ elevation are the excessive calcium signaling pathway and the elevated peroxynitrite/free radical/oxidative stress/NF-kappaB activation/inflammation pathway. While these are among the most important findings providing a rationale for this paper, there are 17 additional types of findings; each provides important evidence for the AD/EMF causal connection. Each of the 19 such findings is summarized at the end of this paper. It is not the contention here that EMFs are the sole initiating causal factor of AD. Other initiating causal factors include diverse chemicals and head trauma, each of which can act *via* excessive NMDA activity to produce excessive $[Ca^{2+}]i$.

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2. THE IMPORTANCE OF EXCESSIVE $[Ca^{2+}]i$ IN AD CAUSATION

Fifteen reviews are cited here [1-15], each providing large amounts of evidence and opinion on the importance of excessive $[Ca^{2+}]i$ in AD causation. Twelve of these reviews [1-5, 9-15] use the term "calcium hypothesis of Alzheimer's disease" to describe their view that excessive $[Ca^{2+}]i$ has both essential and central roles in AD causation.

Each of these reviews [1-15] discuss the roles of excessive calcium signaling in AD. They also discuss various

types of evidence showing that excessive $[Ca^{2+}]i$ causes both specific and non-specific aspects of AD. These include excessive amyloid beta (Aβ) protein [3, 4, 6, 8, 10, 14, 15], hyperphosphorylated tau protein and consequent neurofibrillary tangles [3, 4, 6, 14], oxidative stress [6, 8], increased cell death *via* apoptotic or autophagic mechanisms [5-7, 9] and lowered memory function *via* synaptic changes, including increased long-term depression and loss of dendritic spines [1, 2, 4, 8, 9, 10, 15]. Aβ levels can both be increased by $[Ca^{2+}]i$ and Aβ can act, in turn, to produce increases in $[Ca^{2+}]i$ [1, 2, 3, 5], suggesting a possible vicious cycle mechanism.

3. THE PRIMARY MECHANISM OF ACTION OF LOW INTENSITY EMFs IN PRODUCING BIOLOGICAL EFFECTS IS ACTIVATION OF VOLTAGE-GATED CALCIUM CHANNELS (VGCCs)

The most important type of evidence for the EMF action *via* activation of the voltage gated calcium channel (VGCC) mechanism is that effects produced by EMF exposures can be blocked or greatly lowered by calcium channel blockers, drugs that are specific for blocking voltage-gated calcium channels (VGCCs) [16-20]. Five different types of calcium channel blockers have been used in these studies, each of which is thought to be highly specific for blocking VGCCs [16]. Diverse EMFs produce effects that are blocked or greatly lowered by the calcium channel blockers, ranging from millimeter wave frequencies, microwave, radiofrequencies, intermediate frequencies, extremely low frequencies (including 50 and 60 Hz), all the way down to static electrical fields and even static magnetic fields [16, 19]. Following EMF exposure, the exposed cells and tissues have large, rapid increases in calcium signaling [16-19], produced by increases in intracellular calcium $[Ca^{2+}]i$ levels. This overall interpretation has been confirmed by patch-clamp studies, studies using calcium-free medium, and studies measuring $[Ca^{2+}]i$ levels [19].

When one effect produced by EMFs was blocked or greatly lowered by a calcium channel blocker, each other tested effect was also blocked or greatly lowered by the calcium channel blocker [16-20]. These findings argue that most EMF effects are produced *via* VGCC activation. An additional study on this is discussed below, where 11 different measured EMF effects involved in producing neurodegeneration in rats were all greatly lowered by the calcium channel blocker amlodipine.

The direct target of the EMFs is the voltage-sensor which, in the normal physiology, controls the opening of the VGCCs in response to electrical changes across the plasma membrane. Four distinct classes of VGCCs are activated in response to low level EMF exposures, L-type, T-type, N-type and P/Q-type VGCCs [16]. Voltage-gated sodium, potassium, and chloride channels are also activated by low intensity EMF exposures, although these have relatively minor roles in causing effects compared with those of VGCC-produced $[Ca^{2+}]i$ elevation [19]. Plant TPC channel activation, a channel controlled by a similar voltage sensor, produces plant calcium-dependent EMF effects [21].

The forces produced by even weak electronically generated EMFs on each of the 20 positive charges in the VGCC voltage sensor are thought to be very strong for each of three distinct reasons: 1. Electronically generated EMFs are highly coherent, being emitted with a specific frequency, in a specific vector direction, with a specific phase and specific polarity [22]. This high level coherence causes the electrical and time varying magnetic forces produced by such EMFs to be vastly higher than forces produced by incoherent natural EMFs [22]. 2. The electrical forces on the charges in the voltage sensor are thought to be approximately 120 times higher than forces in the aqueous phases of our cells and bodies, due to Coulomb's law [17, 19]. 3. The electrical forces on these charges in the voltage sensor are thought to be amplified approximately 3000 times because of the high electrical resistance of the plasma membrane [17, 19]. These three factors, acting multiplicatively, help us to understand how VGCCs and other voltage-gated ion channels can be activated by what are considered to be very weak EMFs. One puzzle which was discussed in a two studies [16, 22] is how can static magnetic fields activate the VGCCs when it is well established that static magnetic fields cannot put forces on static electrical charges. The previously discussed answer [16, 22] is that plasma membranes where the VGCCs are located, are constantly moving and therefore, static magnetic fields can put forces on the moving voltage-sensor charges controlling VGCC and other voltage-gated ion channel activation. It is thought that both millimeter wave and lower microwave frequency EMFs produce highly penetrating effects in our bodies largely *via* the highly penetrating time-varying magnetic fields acting *via* two distinct mechanisms to put forces on the charges of the voltage sensor [22].

How then does EMF-produced VGCC activation produce biological effects? Our best understanding of this is outlined in Fig. (**1**). The main pathophysiological effects seen going to the bottom of (Fig. **1**) are produced through excessive calcium signaling produced by $[Ca^{2+}]i$ elevation and by the peroxynitrite pathway, with the latter involving increases in reactive free radicals, oxidative stress, NF-kappaB activity and inflammatory cytokine levels and also causing mitochondrial dysfunction. Citations [1-15], as discussed above, each provide evidence that excessive calcium signaling in AD. The role of the peroxynitrite pathway in AD is documented below.

4. DECREASING AGE OF ONSET OF AD

There has been a rapid drop in the age of onset of Alzheimer's disease (AD) and other neurological diseases in recent years [23-27]. As a consequence of that, people circa age 30 have been coming down with AD – these cases are still relatively rare, but they were unheard of until recently. One study [26] suggests EMF causation of such early onset.

There have been large increases in microwave frequency pulse modulated EMF exposures, starting in the mid-1990s with cordless phones and satellite phones followed by cell (mobile) phones and cell phone tower (mobile phone base station) radiation, smart meters, digital power supplies and digital inverters, increased civilian radar usage, and of course, increased amount of modulating pulsation going from 2G to 3G to 4G and to 5G. The timing of the recent decreasing age of onset of AD corresponds, at least roughly,

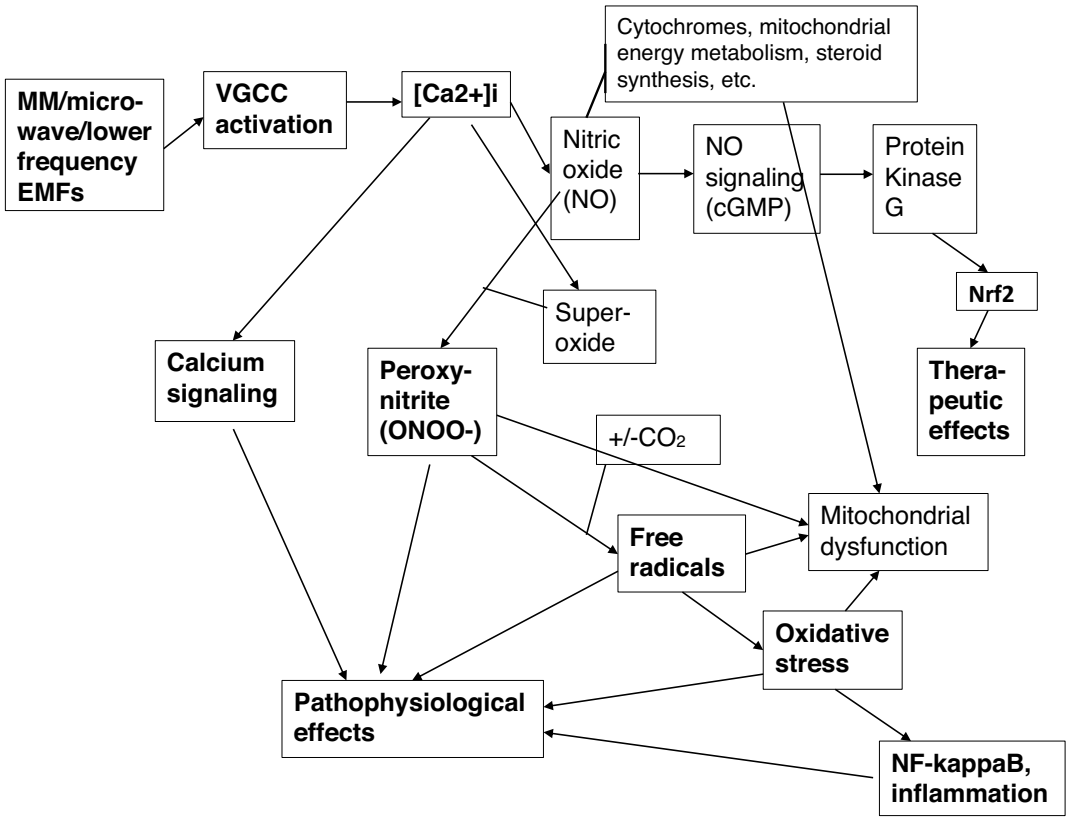

Fig. (1). EMF pathways of action produced *via* VGCC activation.
There are four pathways of action each starting from excessive intracellular calcium [Ca^{2+}]i. They are excessive calcium signaling and excessive peroxynitrite, reactive free radicals, oxidative stress and NF-kappaB/inflammatory cytokines with these two pathways responsible for most of the pathophysiological effects. The nitric oxide signaling/Nrf2 pathway is responsible for most therapeutic effects. And the nitric oxide binding and inhibiting various cytochromes which can contribute to pathophysiological effects as well. Taken from [19] with permission.

to increases in such EMF exposure, suggesting but not proving possible EMF causation.

5. THE HIGH LEVEL IMPORTANCE OF EMF PULSATION

Wireless communication devices, with the exception of FM radio, communicate *via* modulating pulsation such that the more information they communicate per second, the more they pulse. Pulsations also act *via* VGCC activation, so the target is the same as for non-pulsed EMFs, but the effectiveness in activating the target can be greatly increased [17, 19]. There are 10 different previously cited reviews [19] that have each shown that pulse-modulated EMFs are, in most cases, much more biologically active than are non-pulsed EMFs of the same average intensity. Because all "safety guidelines" are based on intensities averaged over 6 minutes or 30 minutes and are all based on the 1998 ICNIRP "safety guidelines" [28], these findings show that "safety guidelines" do not predict biological effects and therefore safety. Because allowable levels are all based on specific absorption rates (SAR) [28], a measure of heating, they can only protect us from thermal effects and not from the activation of the VGCCs or any other non-thermal effect.

There are at least 100 nanosecond pulse studies where such pulses produce biological effects in the EMF-Portal database. Nanosecond pulses are defined as pure pulses, not modulating pulses, between 1 nanosecond and 1 microsecond in length. Four of those nanosecond pulse studies, where the pulses were shown to produce effects *via* VGCC activation, are cited here [29-32]. If you take a typical, let us say 40 nanosecond pulse and average it over 6 minutes, approximately 10 billion times longer, as the "safety guidelines" do [28], the average intensity drops by a factor of circa 10 billion. Consequently, the "safety guidelines" predict there cannot be any effects because the average intensities are too low, but there are some [33]. It makes no sense to take a pulse that only takes 40 nanoseconds to produce effects and average it over circa 10 billion times longer.

The modulated pulsation findings are especially important for 5G radiation, where any full-fledged 5G system communicating with "the internet of things" will expose us to trillions extremely short modulating and many billions of paired pulses of identical polarity. The pulsations of 5G radiation are modulating pulses, not the pure pulses of these nanosecond pulses. Because both types of pulses act *via* VGCC activation, they may each be expected to produce similar effects on the cells of our bodies. Pulsation may also be of great importance for other highly pulsed radiation, such as 4G or smart meter radiation. It is essential, therefore, that each of these be biologically tested for safety before they irradiate the unsuspecting public, but no such safety testing has been done.

6. THE IMPORTANCE OF THE PEROXYNITRITE PATHWAY ELEMENTS AS WELL AS CALCIUM SIGNALING IN AD CAUSATION

The two main pathways producing pathophysiological effects following EMF exposures, the calcium signaling pathway and the peroxynitrite/free/radical oxidative stress/NF-kappaB/inflammation pathway (Fig. **1**), have essential roles in AD causation. The importance of calcium signaling in AD was documented in each of the AD reviews cited above [1-15]. Calcium/calmodulin kinase II (CaMKII) [4, 14, 15] and the calcium-dependent protein phosphatase, calcineurin [4, 9, 10], have important roles in AD causation and there are other calcium-dependent regulatory mechanisms, including calpains and protein kinase C, which also have AD roles.

Other pathophysiological downstream effects produced by $[Ca^{2+}]i$ come from the peroxynitrite/free radical/oxidative/NF-kappaB elevation/inflammatory cytokine pathway, as well as the mitochondrial dysfunction that is produced largely due to this pathway, as shown in Fig. (**1**). The role of each of the elements of this pathway in AD is documented in Table **1**.

7. ROLE OF VGCCs IN AD

This section considers studies specifically implicating elevated VGCC activity in AD causation. It includes genetic studies and also calcium channel blocker studies.

Villela *et al.* [34] reviewed studies showing that copy number mutations producing extra copies of three VGCC genes are reported to increase the prevalence of AD.

Novotny *et al.* [35] reviewed studies of calcium channel blockers in the treatment of AD. They report that the dihydropyridine blocker nitrendipine, appears to be substantially more active in AD treatment than most other blockers, including other dihydropyridine blockers. These included studies finding that nitrendipine can produce substantial improvements in AD patients. Novotny *et al.* discuss [35] "extremely positive and preventive effects of nitrendipine therapy."

Anekonda *et al.* [36] reviewed earlier studies showing that elevated VGCC activity can occur in AD models and that calcium channel blockers may be useful in lowering AD-related changes. They provide evidence [36] that the dihydropyridine calcium channel blocker, isradipine, may be particularly useful in lowering AD-related changes. When isradipine was compared with nitredipine for AD treatment, nitredipine was found to be the more active of the two [35]. Tan *et al.* [37] reviewed studies showing that four dihydropyridines, diltiazem and verapamil blockers were each effective in the treatment of AD animal models and/or cell culture models.

Gholamipour-Badie *et al.* [38] showed that AD-related pathophysiological changes in animals produced by injection of the Aβ protein into the brain, including delayed memory acquisition, could be largely reversed by using isradipine or nimodipine calcium channel blockers. Other studies, not discussed here, have shown that small Aβ protein aggregates raise $[Ca^{2+}]i$ *via* several mechanisms, including increased VGCC activity and Aβ protein aggregates acting as plasma membrane calcium channels. Copenhaver *et al.* [39] proposed isradipine as a candidate drug for AD treatment.

Three recent genetic studies implicate CACNA1C (the Cav1.2 channel) in causation of different aspects of the pathophysiology of AD [40-42].

Before leaving this issue of VGCC activity in AD, it is important to note that while VGCC production of increased $[Ca^{2+}]i$ is the main consequence of VGCC activation, it is not the only consequence. Striessnig *et al.* [43] showed that activated L-type VGCC proteins can directly interact and therefore regulate three protein activities in cells, AKAP-MAP2B, AKAP-15 and AKAP-79/150 each of which regulate the neuronal dendrites and dendritic spines, such that some of the AD changes in synapse structure and activity may be produced by direct VGGC-protein regulatory interaction rather than *via* excessive $[Ca^{2+}]i$ effects.

In summary, the findings in this section implicate elevated VGCC activity in both the causation of AD and also in the exacerbation of already existing cases of AD. The consequence of the exacerbation of AD raises an issue that has not been discussed above – namely whether lowering EMF exposures of AD patients either by improving their existing environment or moving them to a low EMF environment may produce substantial improvements or slow down the progression of AD.

8. AD AND DIGITAL DEMENTIA ARE ASSOCIATED WITH EMF EXPOSURES

Most of this review is focused on what is known about the cellular and molecular etiology of AD, the cellular and molecular mechanism by which non-thermal electromagnetic fields (EMFs) act in the cells of our bodies and the confluence of these two areas of scientific study. However, epidemiological evidence regarding the possible causation of AD and other dementias by EMF exposures is also important. A large number of such epidemiological studies have shown a higher incidence of AD in human populations with higher EMF exposures [26, 43-52]. AD is thought to typically show a latency period of about 25 years from the time of initiation of the disease process *via* a stressor (such as head trauma) and the development of AD symptoms. However, many of these studies report increases in AD incidence in much shorter times, suggesting that EMF exposures may lower the latency period. For example, Rösli *et al.* [52] concludes that "this study suggests a link between exposure to ELF-MF and Alzheimer's disease and indicates that ELF-MF might act in later stages of the disease process". Most of our concerns with regard to EMF exposures have been for microwave and other higher frequency EMF exposures, but most of these epidemiological studies are for extremely low frequency EMFs such as 60 Hz or 50 Hz from our power wiring. However, 50/60Hz EMFs and microwave frequency EMFs each act *via* VGCC activation [16, 19]. Consequently, the 50/60 Hz epidemiological studies may well be relevant to higher frequency EMF effects.

Furthermore, such higher frequencies were involved in the apparent causation of what have been called digital dementias, where prolonged exposures to microwave fre-

Table 1. AD involvement of elements of the peroxynitrite pathway and excessive calcium signaling produced by EMF VGCC activation.

PubMed Central Search Terms	Numbers of Citation Hits
Alzheimer's disease and peroxynitrite	6403
Alzheimer's disease and oxidative stress	73,832
Alzheimer's disease and free radicals	23,888
Alzheimer's disease and (NF-kappaB or NF-kappa B)	29,636
Alzheimer's disease and inflammatory cytokine*	24,566
Alzheimer's disease and mitochondria*	40,231
Alzheimer's disease and (calcium signaling or CaMKII or calcineurin or calmodulin)	50,320

*Based on PubMed Central search dated April 24, 2021.

quency EMFs from Wi-Fi, tablets and/or heavy cell phone usage in young people, appear to be causing such dementias [53-57]. Unfortunately, there have been no studies on physiological changes in the brains of people with digital dementia to determine whether they suffer from brain changes similar to those found in AD.

These various studies [26, 43-57] suggest but do not prove EMF causation of AD and digital dementias. Such epidemiological studies are rarely definitive on their own. They need to be considered in conjunction with all of the other evidence on how EMFs act to produce effects in our bodies and all of the evidence linking those same downstream effects of EMFs acting *via* VGCC activation to both AD and the effects causing AD.

9. LOW-INTENSITY MICROWAVE FREQUENCY EMFs PRODUCE WIDESPREAD NEURODEGENERATION IN ANIMAL BRAINS: DO THESE INCLUDE AD?

Ahn *et al.* [58] discussed many animal models of AD, which closely resemble human AD in their pathophysiology and therefore give many important insights into AD causation. The discussions in this section are of the non-thermal EMF exposures reviewed by Tolgskaya and Gordon [59] and also of the much more recent rat study of Tolgskaya *et al.* [60], where there are neurodegenerative effects with similarities to AD but where no AD-specific changes have been measured. Then, in the next section, rat studies with more compelling similarities to human AD will be discussed.

Tolgskaya and Gordon [60], published in 1973, have a circa 75 page description of the changes in histological tissue structure of rodent tissue exposed to non-thermal microwave frequency EMFs. Their review findings were summarized in Table **2** of a study [18]. The nervous system, including the brain was the most sensitive organ in the body to EMF-caused histological changes followed by the heart and the testis, but with many other organs also being impacted. The changes in brain structure from such microwave frequency EMF exposures [59] are summarized in another study [18].

Nervous system regions impacted by non-thermal microwave and lower frequency fields include: cortex, diencephalon including the hypothalamus and thalamus, hippocampus, autonomic ganglia, sensory fibers, pituitary gland including neurohypophysis. AD typically impacts the frontal lobe, temporal lobe and parietal lobe of the cortex as well as the hippocampus. Those regions of the brain degenerate in rodents because of low intensity EMF exposure and it seems plausible that EMFs may cause AD-like effects as well as other neurodegenerative effects.

Relatively brief periods of exposure (typically for several weeks) produce modest histological and behavioral changes with cessation of exposure, leading to recovery pretty much to normal over a period of a few months in both structural changes in the brain and behavioral changes. However, longer periods of exposure, produced more severe histological and behavioral changes which appeared to be irreversible [59, 18]. It appears that cumulative effects produce genuine neurodegeneration, with one of the features reported being widespread increased numbers of dead cells.

The rodent neurodegeneration reviewed in Tolgskaya and Gordon [60] and human neurodegeneration each involve widespread loss of synaptic connections as well as deformed and losses of dendritic spines, which have essential roles in the formation of synaptic connections. These are both found to be produced by increased $[Ca^{2+}]i$ in AD as discussed above [1, 2, 4, 6, 8-10, 15]. The dendritic including dendritic spine changes are also produced by direct regulatory interactions of activated L-type VGCCs with three AKAP proteins, as discussed above in the section of VGCC roles in AD (see Table **3** in [42]).

One other type of observation of aberrant structure reviewed in Tolgskaya and Gordon [60] was the structurally aberrant and excessive numbers of boutons. These are presynaptic, axonal structures that have been shown to complex with hyperphosphorylated tau protein and may have some roles in generating the neurofibrillary tangles in AD [61]. While these aberrant boutons are not specific for AD, they may be specific for tauopathies, including AD [61].

Table 2. El-Swefy *et al.* [61] changes produced in rat brains by four weeks of EMF exposure, leading to severe neurodegeneration.

Measure or Observed Changes	Probable Mechanism Producing Change, Fig. (1)
Large increases in total brain calcium	Increased VGCC activity leading to large increases in $[Ca^{2+}]i$
Large increases in % of dead cells in brains, as shown by histology	Calcium-dependent increases in apoptotic and autophagic cell death [62,63].
Large increases in apoptotic index (% of cells undergoing apoptosis)	See above
Large increases in BAX expression, a protein involved in apoptosis	See above
Approximate 34% decrease in brain DNA, showing loss of circa 34% of cells	See above
Increases in superoxide	Calcium-dependent increases in NADPH oxidase; there may also be both direct and indirect effects increases superoxide generation in the mitochondrial electron transport chain
Increases in nitric oxide (NO)	Increased calcium/calmodulin-dependent nNOS and eNOS enzymatic activity
Increases in MDA (malondialdehyde) a marker of lipid peroxidation	Produced by elevated peroxynitrite and consequent lipid peroxidation
Decreased reduced glutathione (GSH)	See above
Increased TNFα	Produced by peroxynitrite/NF-kappaB/inflammatory pathway
Increased C reactive protein (CRP)	See above
Observed increased reddening or the eye)	Inflammatory response (see above)
Observed altered visual function	Neurological changes produced by VGCC activation and increased $[Ca^{2+}]i$
Observed increased aggressiveness	Possibly due to neuroinflammation and increased norepinephrine release
Observed increased hyperactivity	See above

Table 3. Jiang *et al.* [78] studies of 100, 1000 or 10,000 nanosecond pulses, given on one day to two month old rats, where AD-like effects were measured 18 months later (in 20 month old rats).

Number of Pulses Showing Statistically Significant Effects	Effect Studied and AD Importance
100, 1000, 10,000	Increased escape latency in Morris water maze escape test, a measure of lowered memory and behavioral function
100, 1000, 10,000	Large increases in Aβ protein oligomers in the hippocampus
1000, 10,000	Increases in the amyloid beta precursor protein (APP) in the hippocampus
1000, 10,000	Increased LC3-II in the hippocampus, a marker for autophagic cell death
100, 1000, 10,000	Lowered reduced glutathione (GSH) in the hippocampus, caused by and causing increased oxidative stress
Non-significant trend	Lowered superoxide dismutase (SOD) in the hippocampus, caused by and causing increased oxidative stress

Because pulses were given at 10 millisecond intervals, pulses were given within on second, 10 seconds or 100 seconds. Ten rats were used for each group measured.

The Tolgskaya and Gordon [60] reviewed studies included studies of both non-pulsed and pulsed modulated microwave frequency EMFs with the pulsed EMFs producing more rapid neurodegeneration. One of the neurons described [59] in one of the multi-month studies was a completely asynaptic neuron. Brain neurons typically have about 1000 synaptic connections with other neurons.

The only individual study that is described in detail in this section is El-Swefy, *et al.* [61], a paper published in

2008 that is, therefore, much more recent than the Tolgskaya and Gordon reviewed literature. I discovered this paper very recently by searching the EMF-Portal database for studies where microwave frequency EMF effects were blocked or greatly lowered by VGCC calcium channel blockers.

In that study, 4 to 5 month old male rats were exposed to very low intensity 3G mobile phone base station (in the US, often called cell phone tower) radiation [60]. The intensity used was the same level as that produced by a GSM cell phone 7 meters away from the cell phone. These are very low intensities, orders of magnitude below the allowable levels in the safety guidelines.

Where the rats were EMF exposed, they were exposed two hours per day. The rats were studied for their biochemical, structural and other changes in the brain after either one week or four weeks of such radiation. There were four different groups of rats studied:

1. Unexposed (sham exposed) rats.

2. Rats were given the VGCC calcium channel blocker amlodipine (20 mg/kg, once per day).

3. Rats exposed to the mobile phone base station radiation.

4. Rats exposed to the mobile phone base station radiation and given amlodipine.

These four week exposures were described as long term exposures, but four weeks is only about 2.6% of the typical lifespan of the rat (circa 36 months). Each of the 11 measured effects and four observed effects, each described in Table **2**, were greatly lowered by amlopidine. This clearly showed that each effect was produced largely or completely *via* VGCC activation. Furthermore, the effects can be produced *via* mechanisms described in Fig. (**1**), showing an excellent fit for the proposed mechanisms of action of EMFs [62-65].

Is it likely that mobile phone base station radiation may produce widespread neurodegeneration in humans? Examination of reviews [66-68] of effects on people living within 300 to 400 m of mobile phone base stations shows that such people do develop widespread neurological/neuropsychiatric effects. These findings clearly strongly suggest impacts of mobile phone base station radiation on the brains of humans, but are these caused by human neurodegeneration? The defining features of neurodegeneration are that effects are cumulative, that they become irreversible and that they are caused by irreversible changes in the structure of the nervous system. I know of no data on whether the neurological/neuropsychiatric changes when produced by mobile phone base station radiation are cumulative. However, there are data from human occupational exposure, which were studied when we had no other exposures in human populations so that exposures to specific occupational exposures could be studied in isolation of other EMF effects. Such studies show cumulative effects producing progressively more severe effects with the time of exposure to a specific occupational exposure [69-72]. Furthermore, the largest published review of such studies finds that while results were initially modest and reversible over time, subsequent exposures produced much more severe effects, which appeared to be irreversible [72]. Low intensity EMFs also produce changes in the electrical activity in the human brain as shown by EEG changes [18]. We have no data, to my knowledge on whether there are cumulative, irreversible changes in human brain structure from such EMF exposures. However, we do have very extensive studies showing cumulative brain structure changes are produced from low intensity EMFs in animals. How relevant are such animal studies to humans? While the answer to that question is not completely clear, the findings, discussed above, show that electronically generated coherent EMFs have highly penetrating time-varying magnetic fields components that produce highly penetrating effects [22], suggesting that animal studies are likely to be highly relevant to humans. Human larger body sizes may produce only minor changes in biological effects.

Now, let us consider EMF effects on causing what are clearly AD-like animal models, such as those discussed in Gołaszewska *et al.* [59].

EMF Exposures Cause AD-like Effects in Four Studies in Rat Models of AD Each Involving Increased or Apparent Increased Aβ

Four such animal AD studies are discussed here, in the approximate order in which they were published. The first two were published by Dr. Suleiman Dasdag's group in Turkey and the other two from a group of Dr. Guo and others in China.

The first of these published in 2012 [73] used non-pulsed 900 MHz exposures, 2 h per day for 10 months to irradiate Wistar rats. Seven rats were used in the sham groups and 10 rats in the irradiated group. The small numbers may be expected, of course, to possibly limit findings of statistical significance. Two markers of oxidative stress in the brain. elevated protein carbonyls and malondialdehyde, were each measured. Both showed apparent increases. The protein carbonyl increases were highly statistically significant, whereas the malondialdehyde apparent increases failed to reach statistical significance. They also reported an apparent increase in Aβ, which again failed to reach statistical significance [73]. The lack of statistical significance for two of these may be due to the small numbers studied or the lack of pulsations in the radiation or both.

The same research group's second paper used the same radiation described in the preceding paragraph, but for 3 h/day for 12 months [74]. They measured levels of several microRNAs in irradiated and sham male Wistar rats. Large statistically significant decreases were seen in miR107 in the rat brains following non-pulsed low intensity 900 MHz. miR107 lowering is thought to be highly relevant to AD causation [74]. miR107 prevents both the neurotoxic effects and memory impairment produced by Aβ in a mouse model of AD [75] and also regulates the levels of three proteins each of which are of importance in AD. miR107 lowers the levels of BACE1 and raises the level of BDNF [75,76] and also lowers the levels of one of the VGCCs in the brain [77] that was previously implicated in human AD in a copy number mutation study [34]. BACE1 is the rate limiting protease in the cleavage of APP to produce Aβ. BDNF has key roles in producing synaptic changes involved in memory and low-

ered BDNF has important roles in AD causation [78]. It follows that the EMF lowering of miR107 levels may be highly relevant to AD causation.

There were two papers published in 2013 and 2016 by Jiang *et al.* [79, 80] on rats which are each of great importance. In each paper, nanosecond pulses were given at 10 millisecond intervals, for a total of 100, 1000 or 10,000 such pulses; therefore, the 100 pulses were given within one second, the 1000 pulses within 10 seconds and the 10,000 pulses within 100 second. In the first paper [79], these pulses were only given once to 2 month old rats.

These produced (Table **3**) AD-specific increases in both Aβ and APP in the hippocampus, as well as AD-like changes in learning and behavior from the Morris water maze escape test and AD-like increases in hippocampal oxidative stress as measured by GSH decreases, and increases in hippocampal LC3-II.

Jiang *et al.* [79] produced still more striking evidence of EMF causation of very early onset AD (Table **4**). In another study [80], EMF pulse exposures started at 2 months of age and continued each day for eight months, such that AD-like effects were examined in 10 month old rats. Five distinct AD-like behavioral changes were found to occur. Seven additional AD-like biochemical changes occurred in the hippocampi of the exposed rats, with four of these being AD specific changes, each relating to the increases in Aβ. It should be noted that although Aβ increases in some other parts of the body are reported to occur in some non-AD diseases, hippocampal Aβ increases are thought to be AD-specific.

In comparing the two Jiang *et al.* [78, 79], there are several important findings:

1. Both of them had many statistically significant findings despite the very small numbers of animals in each group studied (n = 10 in [79] and n = 5 or 10 in another study [80]).
2. A study showed that giving each animal 100 or 1000 EMF pulses in 1 day (at 2 months of age) within 1 or 10 seconds of one day, produced universal or near universal AD in 20 month old rats [79]; another showed that giving these pulses once per day produced universal or near universal very, very, very early onset AD at 10 months of age.
3. Because rats have a lifespan of circa 36 months, the AD development [79] corresponds roughly to 42 year old humans and to 21 year old humans developing universal or near universal AD [80].
4. Up until circa 30 years ago, most cases of early onset human AD occurred in humans with a strong genetic predisposition to AD development; here, we are getting universal very, very, very early onset AD in rats with no apparent genetic predisposition, simply from EMF exposure.
5. It may be important to compare the two Jiang *et al.* studies [78, 79] with the El-Swefy *et al.* study [61] that was also conducted on rats. They both used pulsed EMFs, but Jiang *et al.* [78, 79] studied the effects of pure nanosecond pulses, whereas El-Swefy *et al.* [61] studied the ef-

Table 4. Jiang *et al.* [79] studies of 100, 1000, or 10,000 nanosecond pulses, given to rats on each day starting at two months of age, with effects measured eight months later (in 10 month old rats).

Number of Pulses Showing Statistically Significant Effects	Effect Studied and AD Importance
100, 1000, 10,000	Behavioral: Morris water maze navigation test*
100, 1000, 10,000	Behavioral: Morris water maze spatial recognition test*
1000, 10,000	Behavioral: Upright open field spontaneous exploration test*
100, 1000, 10,000	Behavioral: Error count in Y maze test*
100, 1000, 10,000	Behavioral: Elevated maze test, %of time spent in open arms*
1000, 10,000	Oxidative stress: Lowered GSH in hippocampus
1000, 10,000	Oxidative stress: Increased MDA in the hippocampus
Non-significant trend toward lower levels	Oxidative stress: Lowered hippocampal SOD activity
100, 1000, 10,000	Increased levels of hippocampal Aβ monomers**
1000, 10,000	Increased levels of hippocampal Aβ oligomers**
100, 1000, 10,000	Increased levels of hippocampal amyloid precursor protein (APP)**
100, 1000, 10,000	Increased levels of hippocampal BACE1 protease, the rate limiting protease in cleavage of APP into Aβ**
100, 1000, 10,000	Increased hippocampal LC3-II, marker of autophagic cell death

Behavioral tests were done with 10 rats in each group. Biochemical changes were done with 5 rats in each group. *AD-like behavioral changes. **AD-specific biochemical changes. Lowered Morris water maze spatial recognition test findings were found for all three pulsation numbers in rats after only four months of EMF exposure.

fects of highly pulse modulated low intensity mobile phone base station radiation similar or identical to radiation that many people are exposed to every day. El-Swefy *et al.* [61] did not measure any of the three AD-specific physiological changes, increased Aβ, APP and BACE1 that were measured in another study [79, 80] and consequently we do not know whether the effects seen in a study [61] included AD-specific effects. In the study by El-Swefy *et al.* [61], the rats developed severe neurodegeneration in four weeks of exposure, a much shorter time than the 8 months found in another study [80]; the neurodegeneration [61] was shown to be produced by VGCC activation because it was greatly lowered by the VGCC blocker amlodipine.

10. CAN EMF EXPOSURES PRODUCE THERAPEUTIC EFFECTS THAT LOWER INCIDENCE OF OR AMELIORATE AD?

Fig. (**1**), as discussed above, showed that EMF exposures can produce therapeutic effects mediated largely *via* nitric oxide (NO) signaling and elevated Nrf2 activity, as shown earlier [80, 81]. Patruno *et al.* [82] has shown that EMFs can raise Nrf2 activity. Such effects are thought to be produced when EMF-induced $[Ca^{2+}]i$ increases are relatively modest. There have been studies showing that EMF exposures can lower the incidence of or ameliorate AD in animal models and humans [83-85]. These do not argue against EMF AD causation, such as those shown in [72, 73, 78, 79] and elsewhere in this paper, because such causation occurs under different EMF conditions.

Two pathways of EMF action (Fig. **1**), the therapeutic NO signaling/Nrf2 pathway and the pathophysiologic peroxynitrite pathway, can each work to lower the other, such that EMFs under different conditions may produce opposite or almost opposite effects. Mechanistically, this can occur, in part, because each acts to down-regulate the other *via* multiple mechanisms described in Fig. (**2**) [86-89].

An example of opposite effects produced by different EMF exposures is that EMFs can produce both hypotension and hypertension.

There are many health-promoting factors, including but not limited to nutritional factors that raise Nrf2 and may be useful, therefore, in the prevention or treatment of AD [90,91].

11. SUMMARY, CONCLUSIONS AND PERSPECTIVES

The findings documented in this review are as follows:

1. The calcium hypothesis of Alzheimer's disease (AD) argues that increased intracellular calcium ($[Ca^{2+}]i$) is the central cause of AD.
2. The primary mechanism of action of EMFs is the activation of VGCCs, with such activation producing rapid, in some cases almost instantaneous, increases in $[Ca^{2+}]i$.
3. Excessive $[Ca^{2+}]i$ causes each of the following specific and nonspecific important AD effects: Elevated levels of Aβ; elevated levels of APP; hyperphosphorylated tau protein and consequent neurofibrillary tangles; lowered memory function produced in part by lowered synaptic activity, including the disappearance of dendritic spines; increased apoptotic and autophagic cell death.
4. AD may be caused, in part, by a vicious cycle with excessive $[Ca^{2+}]i$ causing excessive Aβ , which produces, in turn, excessive $[Ca^{2+}]i$.
5. EMF exposures in animal models of AD or neurodegeneration produce still additional changes that have roles in producing the changes described immediately above: lowered miR107, increased BACE1, elevated LC3-II, oxidative stress, deformed synaptic spines and bouton formation.
6. Genetic and pharmacological studies show that VGCC activity itself has important role in causing AD. VGCC activity may be important not only for producing excessive $[Ca^{2+}]i$ but also because of direct VGCC protein-protein interactions impacting synaptic function.
7. The two main pathways of action activated by $[Ca^{2+}]i$ producing pathophysiological effects, excessive calcium signaling and the peroxynitrite/free radical/oxidative stress/NF-kappaB/inflammation pathway each have essential roles in AD causation.
8. 12 different occupational exposure studies have each shown that people in occupations causing them to be exposed to substantial EMF exposures have a higher AD prevalence.
9. Very young people exposed to many hours per day of EMF exposures from Wi-Fi or cell phone usage develop digital dementia.
10. There has been a decrease in the age of onset of AD in humans over the past 20 years or so, which has been suggested to be caused by increases in human EMF exposures.
11. Studies reviewed by Tolgskaya and Gordon [60] showed that rodents develop over a period of months widespread neurodegeneration from low intensity microwave frequency EMF exposures which impact many regions of the brain including the cerebral cortex and hippocampus, regions that are heavily impacted in human AD patients. This EMF caused rodent neurodegeneration resembles human neurodegeneration in having high levels of brain cell death, changes in the structure brain synapses and massive loss of synaptic connection.
12. The El-Swefy *et al.* [61] study showed that very low intensity mobile phone base station radiation produced massive widespread neurodegeneration in 4 weeks. 11 measured changes and 4 observed changes in this EMF-caused neurodegenerative process were each greatly lowered by the VGCC blocker amlodipine. Among the changes documented were loss of approximately 34% of the brain cells, oxidative stress, high levels of apoptosis and inflammation. Excessive $[Ca^{2+}]i$ acts *via* excessive calcium signaling and the peroxynitrite pathway of action to produce each of the 11 measured changes neurodegenerative changes.

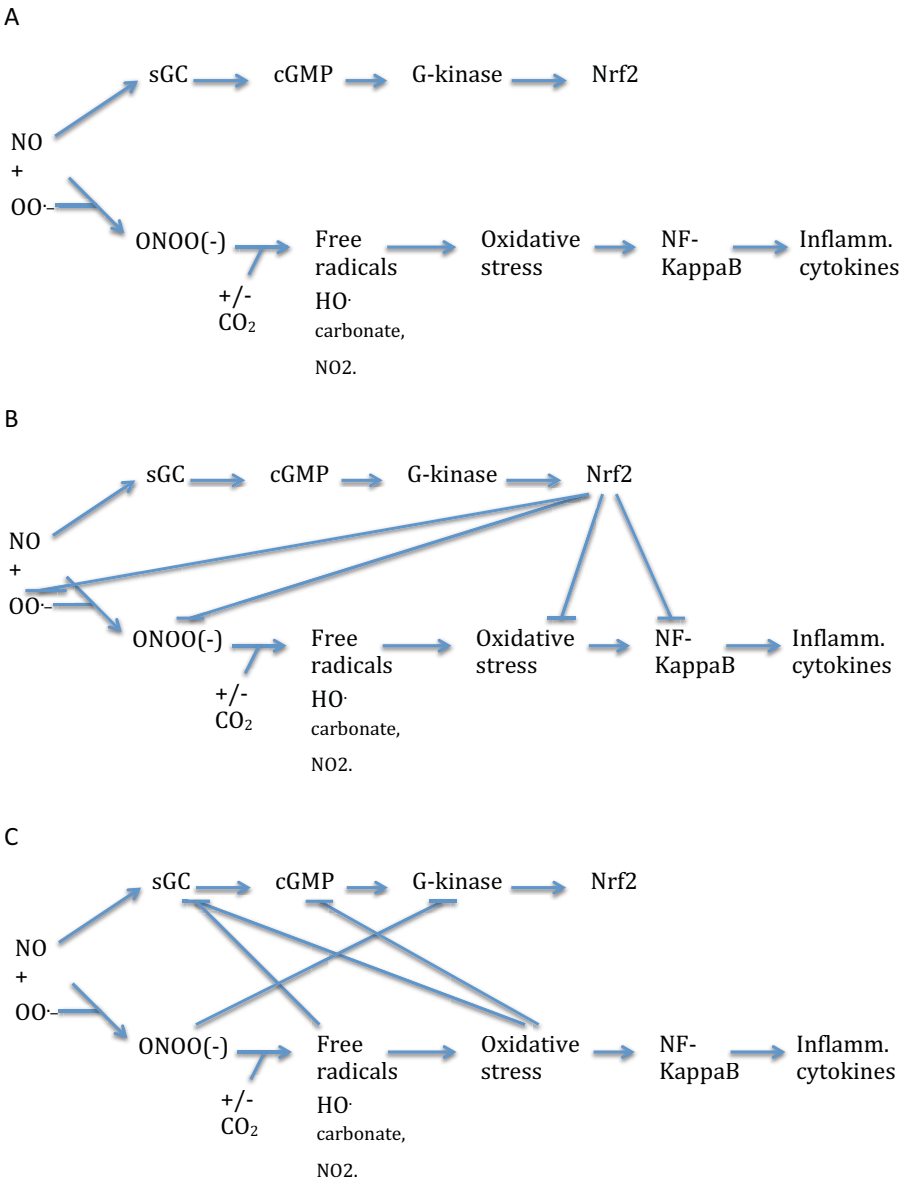

Fig. (2). The therapeutic pathway and the peroxynitrite/oxidative stress/inflammation pathway each inhibit the action of the other *via* multiple mechanisms. Pathways taken from Fig. (**1**). How almost opposite effects can be produced by EMFs. Fig. (**A**) shows the two pathways without any inhibitory influences shown. Fig. (**B**) shows multiple mechanisms by which raised Nrf2 in the therapeutic pathway inhibits multiple steps in the peroxynitrite pathway, including the following [86, 91]: 1.Raising Nrf2 raises the levels of both mitochondrial and cytoplasmic superoxide dismutases, lowering superoxide levels. 2. Raising Nrf2 raised the levels of redoxyredoxin-1 and -6, both of which scavenge peroxynitrite. 3. Raising the level of Nrf2 raises each of the two enzymes the synthesize reduced glutathione (GSH), raises the levels of glutathione reductase which is needed to reduce oxidized glutathione back to GSH, raises the levels of all 8 enzymes required to make the reductant for glutathione reductase, NADPH and raising Nrf2 raises the levels of the two glutathione peroxidases which used GSH to produce antioxidant effects. In summary, raising Nrf2 raises GSH-dependent antioxidant effects in a highly coordinated fashion by raising the levels of 13 different enzymes. 4. Raising Nrf2 lowers the levels of NF-kappaB, therefore lowering diverse inflammatory responses. Fig. (**C**) shows how multiple intermediates in the peroxynitrite pathway inhibit multiple steps in the therapeutic NO signaling pathway (pp. 22291-22292 in [91]).: 1. Raised oxidant levels in oxidative stress oxidizes the heme FeII iron in the sGC, labilizing the heme group which detaches from the protein, producing an enzymatically inactive protein. 2. A specific cysteine thiol group in sGC becomes oxidized to a thiyl group which becomes nitrosylated, producing an enzymatically inactive protein. 3. Tetrahydrobiopterin (BH4) prevents the formation of the thiyl group (immediately above) but BH4 is oxidized by ONOO(-) [88], lowering this preventive activity. 4. Phosphodiesterase 5 (PDE5) which hydrolyzes cGMP is produced in much greater amounts because of oxidative stress, thus lowering cGMP levels. 5. The G-kinase undergoes peroxynitrite-dependent tyrosine nitration, inactivating the G-kinase enzymatic activity. 6. An additional mechanism by which ONOO(-) lowers NO signaling, not diagrammed in Fig. (**2**). involving BH4 oxidation by ONOO(-) is that BH4 is a required cofactor for the nitric oxide synthases such that when the BH4 is oxidized, the NO synthases become uncoupled, synthesizing superoxide instead of nitric oxide [88]; BH4 depletion occurs in AD neurons [89].

13. While many of the studies on EMFs causing neurodegeneration in rodents did not measure any specific correlates of AD, four studies on EMFs causing AD in rats did measure such specific correlates. Two of these were discussed in detail [86, 87].
14. A series of nanosecond EMF pulses given to two-month old rats produced universal of near universal very early onset AD [78].
15. When these same pulses were started at 2 months of age and continued each subsequent day, universal or near universal AD was seen eight months after the first day of pulsation – that is in 8 month old rats [79]. Some signs of AD are seen after only four months after the beginning of irradiation. Because rats typically live to be 36 months old, these EMF pulses are causing universal or near universal very very very early onset AD. The El-Swefy *et al.* [61] findings are even worse – there irradiation started in 4 to 5 month old rats and massive neurodegeneration was evident after only 28 days of irradiation.
16. If humans were to succumb to very, very, very early onset AD at a similar fraction of the human life span as these rats do from EMF exposure [79], then we might expect humans to come down with EMF-caused AD at roughly 21 years of age.
17. The rat studies of EMF causation of AD [78, 79] clearly show that EMFs lower the latency period of AD and epidemiological studies suggest this is also true in humans.
18. The very early AD onset found in a study [78] and the very very very early onset AD or other neurodegeneration found in a few studies [61, 79] should be viewed as remarkable in another context. Up until 30 years ago, early onset AD in humans was caused mainly by relatively rare mutations that each have powerful causal roles in AD [23]. However, we see here universal or near universal very or very, very, very early onset AD being caused solely by EMF pulses.

These eighteen findings provide a specific type of evidence arguing that EMFs cause AD, possibly including very very very early onset AD in humans. These must be interpreted in conjunction with two other important findings:

Electronically generated EMFs are coherent, being emitted at a specific frequency, in a specific direction with a specific polarity and phase and for that reason, they generate vastly higher electrical forces and time varying magnetic forces than natural incoherent EMFs [22]. Those time varying magnetic forces are very highly penetrating and can act both directly and indirectly to place strong forces on the electrical charges on the VGCC voltage sensor to activate the channels [22]. They can, therefore, produce very highly penetrating effects deep in the human body even when they are present at millimeter wave frequencies where electric fields are largely absorbed in the outer 1 mm or so of the body. Five studies cited in another study [22] showed that non-pulsed MM-waves produced EEG changes in the human brain, with four of them also showing other neurological effects in the human brain, confirming the presence of penetrating effects.

Pulsations, both modulating pulses and pure nanosecond pulses produce much higher effects than non-pulsed EMFs of the same average intensity. Moreover, the entire telecommunications industry is in a big push towards greater and greater pulsation in order to carry larger and larger amounts of information. This includes, of course, 2G leading to 3G leading to 4G leading to 5G and, in addition, smart meters, smart cities and even smart highways, *etc.* This push for smarter, ever more highly pulsed devices may well be leading us to the ultimate disaster: universal or near universal very very very onset AD in human populations. Both animal and human studies, discussed above, show that EMFs can not only greatly increase the incidence of AD but can also decrease the latency period; the human latency of AD may decrease from about 25 years to perhaps 5 or 10 years. This means that it is possible that exposures we already have, 5G and possibly also 4G and smart meters, may have already caused the ultimate disaster, but we do not know it yet because we are still in the latency period.

The confluence of these changes of our understanding of EMFs put us at great risk of producing this ultimate disaster in the light of the 19 different findings regarding EMFs and AD listed above: the coherence of electronically generated EMFs, which produce vastly greater electrical and time varying magnetic forces than do natural incoherent EMFs [22]; the high level sensitivity of the voltage sensor controlling the VGCCs and other voltage gated ion channels to those forces; the importance of pulsation; and the push to faster and faster modulating pulsation in order to carry ever more information together put us at unprecedented risk.

CONCLUSION

Among the more important studies that should be done are studies of Aβ, hyperphosphorylated tau protein and other markers of AD in the cerebrospinal fluid [92] of digital dementia victims and others with greatly elevated pulsed EMF exposures. We also need good AD epidemiological studies on people with elevated pulsed EMF exposures.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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