From: Ppsi Ppsi [mailto:ppsi@aol.com]
Sent: Friday, January 08, 2016 4:42 PM
To: Nambiar, Madhusoodana
Cc: jeanbowler@greenswan.org; jmm@berkeley.edu
Subject: FDA citizens petition on Cell Phones, Docket #FDA-2013-P-1374,

Madhusoodana Nambiar
Regulations Staff
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Dear Mr. Nambiar:

Please add the following emails/articles to our FDA Citizens Petition on Cell Phones, Docket # FDA-2013-P-1374,

Thanks for all your past assistance and Happy New Year.

Best,

Fred

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New York Times article January 2016

http://www.saferemr.com/2016/01/new-york-times-expose-of-cdcs.html

Effect of electromagnetic field on cyclic adenosine monophosphate (cAMP) in a human mu-opioid receptor cell model

Ross CL, Teli T, Harrison BS. Effect of electromagnetic field on cyclic adenosine monophosphate (cAMP) in a human mu-opioid receptor cell model. Electromagn Biol Med. 2015 Dec 29:1-8. [Epub ahead of print]

Abstract

During the cell communication process, endogenous and exogenous signaling affect normal as well as pathological developmental conditions. Exogenous influences such as extra-low-frequency electromagnetic field (EMF) have been shown to effect pain and inflammation by modulating G-protein receptors, down-regulating cyclooxygenase-2 activity, and affecting the calcium/calmodulin/nitric oxide

pathway. Investigators have reported changes in opioid receptors and second messengers, such as cyclic adenosine monophosphate (cAMP), in opiate tolerance and dependence by showing how repeated exposure to morphine decreases adenylate cyclase activity causing cAMP to return to control levels in the tolerant state, and increase above control levels during withdrawal. Resonance responses to biological systems using exogenous EMF signals suggest that frequency response characteristics of the target can determine the EMF biological response. In our past research we found significant down regulation of inflammatory markers tumor necrosis factor alpha (TNF-α) and nuclear factor kappa B (NFκB) using 5 Hz EMF frequency.

In this study cAMP was stimulated in Chinese Hamster Ovary (CHO) cells transfected with human mu-opioid receptors, then exposed to 5 Hz EMF, and outcomes were compared with morphine treatment. Results showed a 23% greater inhibition of cAMP-treating cells with EMF than with morphine. In order to test our results for frequency specific effects, we ran identical experiments using 13 Hz EMF, which produced results similar to controls.

This study suggests the use of EMF as a complementary or alternative treatment to morphine that could both reduce pain and enhance patient quality of life without the side-effects of opiates.

http://1.usa.gov/1RyCNA1

Excerpts

Tissue injury results in the production of inflammatory mediators, several of which sensitize primary afferent nociceptors (Davis et al., 1993; Reuff and Dray, 1993), resulting in hyperalgesic pain (Ferreira, 1981; Fierreira et al., 1978). Hyperalgesic pain is often associated with inflammatory pain (Schultz et al., 2003). The largest family of receptors for pharmaceutical agents is the G-protein-coupled receptors (GPCRs), whose signal transduction pathway is well understood. For example, Gαs (stimulating) subunit increases adenylate cyclase (AC) activity, thereby stimulating the production of cyclic adenosine monophosphate (cAMP); whereas the Gαi (inhibitory) subunit decreases AC activity and inhibits the production of cAMP. The second messenger cAMP activates a specific number of tissue-specific cAMP-dependent protein kinases, ultimately affecting intracellular processes such as ion channel activity, release of neurotransmitters, regulation of transcription factors, and numerous other processes. GPCRs determine ligand binding and selectivity (Karlsmark et al., 2003). A number of ligands inhibit the function of specific enzymes by competitive or non-competitive inhibition (Sen et al., 2009). A ligand that binds to the same active catalytic site as the endogenous substrate is a competitive inhibitor. Ligands that bind at different sites on the enzyme, alter the shape of the molecule, and reduce its catalytic activity, are called non-competitive inhibitors. Extracellular environments, and to some extent transmembrane regions, determine ligand binding (Brenner and Steven, 2010). A substantial amount of literature suggest that hyperalgesia induced by tissue damage is initiated by the activation of AC – cAMP – protein kinase A (PKA) second messenger cascade, activated at the mu-opioid receptor (MOR) site (England et al., 1996; Khasar et al., 1995; Malmberg et al., 1997; Taiwo and Levine, 1989, 1990, 1991, 1992). Agents that inhibit AC- and cAMP-dependent PKA prevent induction of hyperalgesia by prostaglandin E2 (PGE2) and other inflammatory mediators....

Opioid dependence has been reported to be associated with changes in the cAMP systems in experiments in vitro. For example, in neuroblastoma cells, acute treatments with morphine and other opiates inhibit adenylate cyclase (AC) activity resulting in a decrease of cAMP levels (Sharma et al., 1975; Traber et al., 1975); however, after repeated exposure to morphine, the AC activity and cAMP levels return to control levels in the tolerant state and increased above control levels during withdrawal (Benalal and Bachrach, 1985; Sharma et al., 1975; Traber et al., 1975). These findings are the basis for cAMP as the mechanism of action for the development of morphine dependence (Mamiya et al., 2001). An increase in AC activity and cAMP levels in the brain represent biochemical associations of morphine dependence (Collier, 1980; Kuriyama et al., 1978), whereby cAMP levels are regulated by AC and phosphodiesterases (PDEs) (Thompson, 1991). It has been substantiated that 3-isobutyl-1-methylxanthine (IBMX)-modulated forskolin induces behavior that resembles morphine withdrawal syndrome in naïve rats and increases naloxone-precipitated morphine withdrawal syndrome in morphine

dependent rats (Collier and Francis, 1975; Rasmussen et al., 1990).

In humans, electromagnetic field (EMF) therapy has proven to be a safe, non-invasive, easy-to-use method to treat the source of pain and inflammation (Markov, 2007; Ross and Harrison, 2013). Research has shown that therapeutic applications at extra-low frequency (ELF) EMF (1–100 Hz) levels stimulate the immune system by suppressing inflammatory responses at the cell-membrane level (O'Connor et al., 1990). Double-blind, placebo-controlled clinical trials (Stiller et al., 1992) report EMF passes through the skin into the body's conductive tissue (Hannan et al., 1994; Stiller et al., 1992; Traina et al., 1998), reducing pain and the onset of edema shortly after trauma (Chalidis et al., 2011; Rohde et al., 2009). In one such study low-frequency pulsed EMF (PEMF) therapy at 0.1 to 64 Hz was reported to improve mobility, and reduce pain and fatigue in fibromyalgia patients (Sutbeyaz et al., 2009). Both human and in vitro studies report EMF to be effective in the treatment of pain and inflammation in osteoarthritis (OA) (Li et al., 2013; Sadoghi et al., 2013), without the addictive side-effects of opiates. It has been proposed that charge receptors or other kinds of sensors at the extracellular membrane could recognize EMF by their ability to resonate with varying frequencies (Funk and Monsees, 2006).

In this study we hypothesize that an EMF at certain frequencies can be therapeutic, therefore we are looking for a similar down regulatory effect of EMF on cAMP as would be seen in morphine treatment. EMF has a number of well-documented therapeutic effects on cells and tissues afflicted with inflammatory pain (Ross and Harrison, 2013). Reports of resonance frequency responses of biological systems to exogenous EMF signals suggest the frequency response characteristics of the tissue can determine the EMF response (Bawin et al., 1975; Markov, 1981). EMF parameters such as frequency, field strength, and time of exposure, all account for the mechanistic pathway affecting inflammatory pain mediators. Oscillating EMF exerts forces on free ions present on both sides of the plasma membrane which move across the cell surface through the transmembrane proteins creating a forced intracellular vibration. This force is responsible for phenomena such as the influx of extracellular calcium and the binding affinity of calmodulin (CaM) – the primary transduction pathway to second messengers such as cAMP. Because of the important ramifications for treating inflammatory pain, we investigated the effect of EMF on the cAMP second messenger pathway, which contributes to maintenance as well as the initiation of hyperalgesia.

Six individual groups were used in this experiment: (1) μ-CHO cells only (baseline) [positive control]; (2) μ-CHO cells + forskolin/IBMX stimulant [F only]; (3) μ-CHO cells + forskolin/IBMX stimulant + 0.1 mM morphine [F + M]; (4) μ-CHO cells + forskolin/IBMX stimulant + EMF treatment [F + E]; (5) μ-CHO cells + forskolin/IBMX stimulant + 0.1 mM morphine + EMF treatment [F + M + E]; and (6) CHO-K1 [negative control]. In the F + M + EMF group, morphine was added immediately before cells were exposed to EMF.

... The [F + E] and [F + M + E] groups were exposed to a 5 Hz EMF for 15 min to determine treatment effect on cAMP. The time point of 15 min was selected as it is the amount of time needed for cAMP accumulation levels to be maintained fully until the end of the incubation period. The EMF coils were driven by an alternating current power supply with adjustable frequency and amplitude. From the coil center the uniform field strength was measured to be approximately 1.5 μT (see flux density schematic in Figure 1a). Each coil carried a 50% duty sine wave in the same direction (Figure 1b) .... The EMF exposed cells were kept in a warm bath to ensure a consistent 37 °C temperature during these experiments. Background EMF was measured and averaged the same as Earth's (~0.5 Gauss).

The therapeutic effects of low-frequency EMF have been reported for years; however, a mechanism of action has yet to be elucidated. Here we compared the effects of EMF on cAMP at both 5 Hz and 13 Hz. The 5 Hz frequency showed a stronger inhibitory effect in cAMP expression on [F + EMF] than the 13 Hz frequency. EMF appears to competitively inhibit cAMP as morphine does; however, EMF exposure does not have the addictive side-effects of morphine. If EMF changes the conformation of the MOR receptor, along with stabilizing Ca^{2+} flux, then it would explain the outcomes we observed. If EMF is able to induce homeostasis via the stabilization of Ca^{2+}, then it appears to be frequency specific as our study suggests.

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Top Stories in 2015 about Cell Phone and Wireless Radiation
http://bit.ly/saferemr2015

New York Times' Exposé of CDC's Retraction of Warnings about Cell Phone Radiation
http://bit.ly/NYTHakim

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My comments: The following study examines the risk of glioma, the most common form of brain cancer, among cell phone users. That this case-control study had relatively few subjects seriously limits its ability to find statistically significant effects. Hence the confidence intervals around the risk estimates are large.

Nonetheless, some risk estimates **suggest** that mobile phone use may increase glioma risk as much as three-fold among heavy users. Examples of increased glioma risk were found among (1) those who used analog mobile phones [OR = 1.83 (95% confidence interval = 0.63 - 5.26)]; (2) those who used both analog and digital mobile phones [OR = 1.89 (0.96 - 3.81)]; and (3) those who used mobile phones in urban areas [OR = 1.66 (0.86 - 3.22)]. Moreover, greater glioma risk was found on the same side of the head where the mobile phone was used (i.e., ipsilateral use) among (4) those who used the phones 900 or more hours in their lifetime [OR = 1.77 (0.32 - 1.84] and (5) those who averaged 10 or more calls per day [OR = 3.13 (0.83 - 11.3)].

To put this study in context, see my post, "Brain Tumor Rates Are Rising in the US: The Role of Cell Phone & Cordless Phone Use" (http://bit.ly/risingtumors).

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Mobile phone use and risk of glioma: a case-control study in Korea for 2002-2007

Yoon S, Choi JW, Lee E, Ahn H, Kim HS, Choi HD, Kim N. Mobile phone use and risk of glioma: a case-control study in Korea for 2002-2007. Environ Health Toxicol. 2015 Dec 21. doi: 10.5620/eht.e2015015. [Epub ahead of print]

Abstract

Objectives: There has been a growing concern about the possible carcinogenic effects of the electromagnetic radiofrequency fields emitted from mobile phones. The purpose of this study was to investigate the association between mobile phone use and the development of gliomas in Korea.

Methods: Our study methods were based on the International Interphone study that aimed to evaluate possible adverse effects of mobile phone use. This study included 285 histologically-confirmed Korean patients 15-69 years of age, with gliomas diagnosed between 2002 and 2007 in 9 hospitals. The 285 individually-matched controls were healthy individuals examined at the same hospitals for medical check-ups. Unconditional logistic regression was used to calculate the adjusted odds ratios (OR) and 95% confidence intervals (CIs) for use of mobile phones.

Results: For the entire group, there was no significant association between gliomas and regular use of mobile phones, type of mobile phone, lifetime years of use, monthly service fee, and the other exposure indices investigated. Analyses restricted to self-respondents showed similar results. However, in case that the body side for usual mobile phone use agreed with the location of a glioma (ipsilateral use) for all the respondents, the ORs (95% Cis) for the lifetime years of use and cumulative hours of use were 1.25 (0.55-2.88) and 1.77 (0.32-1.84), respectively. The contralateral users showed slightly lower risk than the ipsilateral users.

Conclusion: Our results do not support the hypothesis that the use of mobile phones increases the risk of gliomas in Koreans; however, we found a non-significant increase in risks among ipsilateral users. These findings warrant further evaluation for glioma risks among long-term mobile phone users.

http://1.usa.gov/1R9EGEO

Paper: http://e-eht.org/journal/view.php?doi=10.5620/eht.e2015015 or http://e-eht.org/upload/pdf/eht-e2015015-AOP.pdf

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***New York Times'* Exposé of CDC's Retraction of Warnings about Cell Phone Radiation**

See Dr. Neutra's January 2nd letter to the New York Times at http://bit.ly/NYTHakim.

Also see the link to Environmental Health Trust's post about the CDC retraction (January 4).

The 500 pages of documentation that the CDC released are available at http://bit.ly/CDCFOIA.

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