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# Electromagnetic fields instantaneously modulate nitric oxide signaling in challenged biological systems

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ABSTRACT

This study shows that a non-thermal pulse-modulated RF signal (PRF), configured to modulate calmodulin (CaM) activation via acceleration of $Ca^{2+}$ binding kinetics, produced an immediate nearly 3-fold increase in nitric oxide (NO) from dopaminergic MN9D cultures ($P < 0.001$). NO was measured electrochemically in real-time using a NO selective membrane electrode, which showed the PRF effect occurred within the first seconds after lipopolysaccharide (LPS) challenge. Further support that the site of action of PRF involves CaM is provided in human fibroblast cultures challenged with low serum and exposed for 15 min to the identical PRF signal. In this case a CaM antagonist W-7 could be added to the culture 3 h prior to PRF exposure. Those results showed the PRF signal produced nearly a two-fold increase in NO, which could be blocked by W-7 ($P < 0.001$). To the authors' knowledge this is the first report of a real-time effect of non-thermal electromagnetic fields (EMF) on NO release from challenged cells. The results provide mechanistic support for the many reported bioeffects of EMF in which NO plays a role. Thus, in a typical clinical application for acute post operative pain, or chronic pain from, e.g., osteoarthritis, EMF therapy could be employed to modulate the dynamics of NO via Ca/CaM-dependent constitutive nitric oxide synthase (cNOS) in the target tissue. This, in turn, would modulate the dynamics of the signaling pathways the body uses in response to the various phases of healing after physical or chemical insult or injury.

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## 1. Introduction

Many studies have shown that NO plays a role in biological responses to weak non-thermal electromagnetic fields (EMF) [1–6]. Recently, it has been proposed that EMF can be configured to modulate the rate of calmodulin (CaM) activation when intracellular $Ca^{2+}$ increases after insult or injury [7]. This, in turn, modulates the activation of Ca/CaM-dependent cNOS and, therefore, the dynamics of NO in the target cells/tissues. The Ca/CaM-dependent NO cascade is an important and early response to physical, chemical or thermal injury [8]. Several cellular, animal and clinical studies, using EMF signals configured *a priori* to affect CaM-dependent signaling [9,10], have reported significant EMF effects [7,9–16]. It follows that EMF which can be configured to modulate CaM-dependent signaling should directly modulate the rate of $Ca^{2+}$-dependent NO release from a challenged cell. This study will show that a non-thermal pulse-modulated radio frequency (RF) signal, used clinically [14–16], approximately tripled NO release from a dopaminergic cell (MN9D) challenged acutely with a non-toxic concentration of lipopolysaccharide (LPS) within seconds, as measured electrochemically in real-time. In a parallel experiment, designed to further elucidate the EMF target, the same RF signal applied for 15 min to human fibroblast cultures challenged long-term with low serum, as is typical for clinical applications [14–16], increased NO in conditioned medium by approximately two-fold. A CaM antagonist, N-(6-Aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride (W-7), blocked the EMF effect on NO, supporting Ca/CaM as the EMF target.

## 2. Materials and methods

### 2.1. Neuronal cells

The MN9D cell line, a fusion of embryonic ventral mesencephalic and neuroblastoma cells used extensively as a model of dopamine neurons, was a gift from Dr. Alfred Heller (University of Chicago). Cells were plated at 250,000 per 35 mm culture dish in Dulbecco's Modified Eagle's medium (DMEM) containing 10% fetal calf serum and 1 mM dibutryl cyclic adenosine monophosphate ($Bt_2$cAMP), which enhances differentiation [17]. Cells were grown for 5 days to approximately 70% confluent with well developed dendritic outgrowth. NO from these cells was determined electrochemically in real-time (see 2.4).

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### 2.2. Human fibroblasts

Normal human fibroblasts (Clonetics, Walkersville, MD) were plated in 35 mm culture plates with DMEM containing 0.1% fetal calf serum, a challenge known to increase cytosolic $Ca^{2+}$ [18]. A previous study determined 0.1% calf-serum would allow cells to adhere, form a monolayer, and remain viable when cultured for up to four days [6]. Fibroblasts were grown for 24 h before EMF exposure and were stressed for the entire experiment. W-7 (EMD Biosciences, San Diego, CA) was added three hours prior to EMF exposure at concentrations ranging from 16 to 150 μM to establish a dose response. NO from these cells was determined after a single 15 min EMF dose in conditioned medium using the Griess assay. Nitrate was reduced to nitrite by saturating the Griess assay mixture with vanadium(III) chloride [19].

### 2.3. EMF exposure

The EMF signal used in these experiments consisted of a 27.12 MHz radio frequency (RF) carrier, pulse-modulated with a 2 ms burst repeating at 2 Hz, known commonly as a pulsed radio frequency (PRF) signal. The parameters of the RF signal used in this study were configured using a model which assumes $Ca^{2+}$ binding to CaM as the target pathway [7,9]. PRF signal parameters are within the range of those cleared by regulatory bodies worldwide for post-operative pain and edema relief, enhanced surgical healing, and for chronic wound healing. PRF was applied using a 20 cm circular single turn antenna (coil) either placed within an incubator equipped with a single plastic shelf for studies at 37 °C, or on a non-metallic laboratory bench for studies at 23 ± 1 °C. The peak magnetic field in the middle of a plane 1 cm from the surface of the coil was 2.5 μT, which resulted in a mean electric field of 41 ± 10 V/m in the layer of cells at the bottom of the 35 mm culture dish. PRF signal amplitude and configuration was verified with a calibrated 1 cm diameter field probe (model FCC-301-1-MR1, Fischer Custom Communications, Torrance, CA) connected to a calibrated 100-MHz oscilloscope (model 2358, Tektronix, Beaverton, OR). For real-time NO studies at room temperature with MN9D cells the PRF signal was turned on 2 min prior to the introduction of LPS in an active experiment. A single 15 min PRF exposure was employed for fibroblast cultures in a $CO_2$ incubator at 37 °C. The PRF signal was turned off for all control experiments.

### 2.4. Real-time NO measurement

NO was measured electrochemically [20–22] with a special three spoke NO selective membrane electrode, designed specifically to detect NO in cell cultures (amiNO-FLAT, Innovative Instruments, Tampa, FL), attached to an amperometric free radical analyzer (Apollo 4000, WPI, Sarasota, FL). Calibration of the NO electrode was performed using a calibration solution containing 0.1 M KI and 0.1 M $H_2SO_4$ to which graded concentrations of $KNO_2$ (0, 1, 2, 5, 10, 20, 50, 100 nM) were added to generate known NO concentrations [20]. In a typical experiment, one culture dish was removed from the incubator, placed on a non-metallic laboratory bench top, and the culture medium was replaced with phosphate-buffered saline (PBS) at pH 7.4 and at room temperature (23 ± 2 °C). This constitutes a depleted serum and heat shock challenge, both of which cause an immediate rise in cytosolic $Ca^{2+}$ [18,23]. The spoke electrode was reproducibly placed within 100 ± 50 μm of an adherent monolayer of MN9D cells. The electrode, stabilized in PBS, was in contact with cells for 3 min, allowing a reproducible partial recovery from heat shock and medium change (minimum slope proportional to residual NO from these challenges) to be obtained. At the end of 3 min an acute chemical challenge, consisting of 0.2 mL LPS (100 ng/mL), was pipetted into the culture making certain that the initial entry of LPS was directly above the electrode spokes. In control cultures there was an immediate (<5 s) peak increase of NO (2–5 nM), followed by a slow decay lasting up to 1 min. Only the peak NO response was considered as quantitatively proportional to the immediate activation of CaM as a result of the LPS insult. Introduction of 0.2 mL of pure PBS (blank) to the MN9D culture at room temperature provided a stirring correction.

### 2.5. Statistical analysis

Results were compared using the Student's *t* test, or one way ANOVA as required (Sigmastat 3.0, Systat, Chicago, IL) and are reported ±SD. Significance was accepted at $P \leq 0.05$.

## 3. Results

### 3.1. Neuronal cells

The mean peak NO in 5 PBS-only experiments corresponded to 1.4 ± 0.42 nM, which was used for blank stirring corrections. The mean peak NO in 10 control experiments corresponded to 1.45 ± 0.64 nM. In contrast, the mean peak NO in 10 PRF experiments corresponded to 4.32 ± 0.89 nM. These results, summarized in Fig. 1, show that a PRF signal, configured to modulate CaM-dependent signaling, increased immediate NO release from MN9D cells in response to an acute non-toxic LPS challenge by approximately three-fold vs. that from control samples ($P < 0.001$).

### 3.2. Human fibroblasts

The W-7 dose study revealed that 50 μM was sufficient and non-toxic for the 4 h duration necessary for this study. The results, summarized in Fig. 2, from a single 15 min exposure, typical in the clinical use of this PRF signal, show that NO was increased (via Griess assay for nitrite in conditioned media) by approximately two-fold ($P < 0.001$). The PRF effect was blocked by W-7, which had no effect on the nitrite levels already present in control cultures before its introduction because of the serum depletion challenge.

## 4. Discussion

The results presented here show that a pulse-modulated RF signal, which was configured, *a priori*, to modulate CaM activation

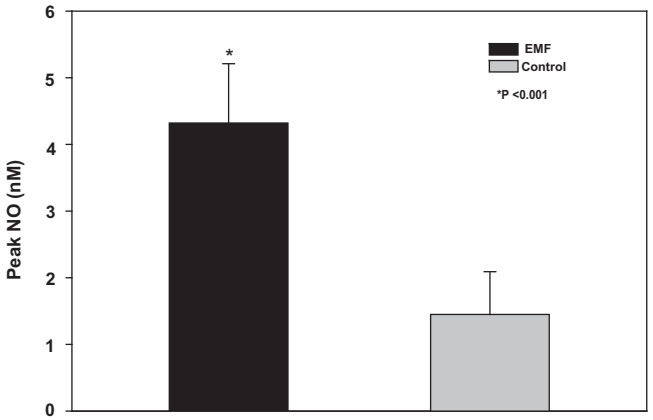


**Fig. 1.** Effect of a non-thermal pulse-modulated RF signal on peak NO release from MN9D dopaminergic cells during challenge with LPS (100 ng/mL). NO was measured in real-time with a NO selective electrode. Results show EMF produced an immediate (<5 s) three-fold increase in peak NO.

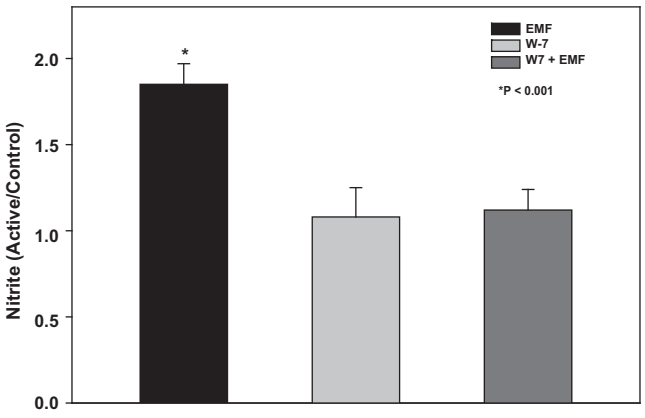


**Fig. 2.** Effect of 15 min exposure to the identical RF signal on NO in conditioned medium from human fibroblasts. The RF signal increased NO (via Griess determination of nitrite) about two-fold. The CaM antagonist W-7 blocked the EMF effect, but had no effect on baseline NO already present from the serum depletion challenge.

when intracellular $Ca^{2+}$ increases above homeostasis [7,9], produced nearly a three-fold increase in NO from MN9D neuronal cells challenged in real-time with LPS. This EMF effect could also be measured in real-time using a NO selective electrode, which showed that response to EMF was immediate. The parallel experiment with human fibroblasts in depleted serum showed that exposure to the same PRF signal for 15 min, typical for clinical applications, caused NO to be increased by approximately two-fold in conditioned medium. Importantly, the PRF effect on NO could be blocked with W-7, indicating that CaM is involved in the initial cellular response to non-thermal EMF. It has been shown elsewhere in human articular chondrocytes that an EMF effect on NO from a single 30 min exposure translates to an effect on DNA synthesis 72 h later, which could be blocked with W-7 [6].

To the author's knowledge, this is the first report of a real-time effect of non-thermal EMF on NO release from challenged cells. It is tempting to suggest that these results provide support for a recent model which proposed that EMF could act as a first messenger in the CaM-dependent signaling pathways that orchestrate the release of cytokines and growth factors in normal cellular responses to physical and/or chemical insults. One such pathway is the Ca/CaM-dependent NO signaling pathway, which involves CaM activation of cNOS, which in turn catalyzes l-arginine to produce NO. As a gaseous free radical with an in situ half-life of about 5 s, NO diffuses locally through membranes and organelles and acts on molecular targets at distances up to about 200 μm, well within the distance the electrode could be placed in proximity to the MN9D cells in this experiment. Low transient concentrations of NO can activate soluble guanylyl cyclase (sGC), which catalyzes the synthesis of cyclic guanosine monophosphate (cGMP). The CaM/NO/cGMP signaling pathway is a rapid response cascade which can modulate peripheral and cardiac blood flow in response to normal physiologic demands, as well as to inflammation and ischemia. This same pathway also modulates the release of cytokines, such as interleukin-1beta (IL-1β) and growth factors such as basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) which are important for angiogenesis, a necessary component of tissue repair.

The non-thermal PRF signal utilized in this study was configured using the assumption that the kinetics of $Ca^{2+}$ binding to CaM could be modulated if its frequency components had sufficient amplitude within the bandpass of known $Ca^{2+}$ binding kinetics to be detectable above thermal noise [7,9]. Any challenge which causes a rise in cytosolic $Ca^{2+}$ will produce a cascade characterized by $Ca^{2+}$ activation of CaM followed by CaM-dependent enzyme activation. The several steps in this initial signaling cascade result in asymmetrical $Ca^{2+}$ binding kinetics, with dissociation significantly slower than binding [7]. Kinetic asymmetry is the reason high frequency RF, or any other EMF signal for which pulse duration or period is significantly shorter than bound time (better part of a second for Ca/CaM), can increase bound $Ca^{2+}$ concentration. All of this suggests CaM as a likely EMF target. Thus, EMF could act upon either the $Ca^{2+}$ binding step, the most logical because the target pathway must be voltage dependent to respond to induced electric fields, and $Ca^{2+}$ is an ion with binding time constant in the ms range, or upon the binding of CaM to its target enzyme (e.g., cNOS). The latter is unlikely, due to the much lower charge/mass ratio of CaM in comparison to that of $Ca^{2+}$, i.e., CaM/cNOS binding is not voltage-dependent in the range applied by the weak signals considered here. In addition, EMF signals configured for Ca/CaM binding will not have sufficient amplitude in the extremely low frequency range that would be required by CaM/enzyme binding. Certainly, evidence that the pulse-modulated RF signal, as configured here, can directly affect $Ca^{2+}$ binding to CaM under normal physiological conditions is not yet available. Nonetheless, several reports have shown that EMF effects on signaling and downstream cascades can be blocked by CaM antagonists. [3,5–7], providing strong support that Ca/CaM binding is the most likely pathway through which the many reported biological effects of EMF occur.

The experimental results reported in this study provide support for Ca/CaM-dependent NO production as an important mediator of EMF signaling that may explain the observed effects of EMF on tissue repair, angiogenesis, pain, and inflammation in animal models and clinical studies. The actions of NO upon healing or regenerating tissue include the reduction of inflammation by blood and lymph vessel dilation via activation of soluble guanylyl cyclase, its primary target; down-regulating iNOS activity by inhibiting nuclear factor-kappa B in a negative feed-back mechanism [24]. This blocks the further production of destructive levels of NO and decreases the availability of pro-inflammatory cytokines, such as IL-1β. As the inflammatory phase of wound repair subsides, cGMP production via NO from $Ca^{2+}$-dependent cNOS can upregulate growth factors, such as FGF-2 for angiogenesis, and modulate fibroblast proliferation. NO from cNOS can also modulate cAMP production, which can accelerate differentiation and increase survival [25]. EMF mediated NO signaling could also be the common transduction mechanism in studies which report up and down regulation of anti-inflammatory genes [26,27], and modulation of adenosine pathways [28–30].

It is important to emphasize that the EMF transduction mechanism as presented here applies both to in situ electric field effects on the voltage-dependent ion-binding step in biological signaling processes, and to direct magnetic field effects for which the induced electric field is non-existant, or too small to be detected above thermal noise, on the same pathway. In the latter case, modulation of the trajectory of a bound charged ion via the Lorentz force has been proposed to affect reactivity by enhancing or inhibiting the dissociation (exit) kinetics of the target ion with weak DC and certain combinations of weak AC/DC magnetic fields [31]. Thus, overall reaction rate could be affected by manipulating dissociation kinetics, even in the presence of thermal noise. In the particular case of CaM, $Ca^{2+}$ remains bound for the better part of a second, which allows very low frequency, and even static, magnetic fields of very low amplitude ($\ll$1 G) to be employed. Application of a Lorentz force model, *a posteriori*, to CaM-dependent myosin phosphorylation [32] provides support that weak magnetic fields could also affect biological signaling and, therefore produce bioeffects [4,5,33,34] similar to those from electric fields configured to modulate Ca/CaM binding kinetics.

Recent animal and clinical studies have reported that the same PRF signal utilized here acted immediately to significantly

accelerate acute post-op pain reduction with a concomitant reduction in post-op narcotic requirements, as well as to significantly reduce IL-1β in the wound bed post-surgery [15], and in cerebral spinal fluid after traumatic brain injury [13]. PRF also significantly reduced chronic pain in knee osteoarthritis within 2 days [16]. It is tempting to unify all of these results via a PRF effect on NO signaling, however many further studies are required to establish a clear and firm relationship between EMF effects on NO signaling and clinical outcomes.

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