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Effects of Extremely Low-Frequency Magnetic Fields on Blocked Sodium Channels

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Keywords

Hodgkin-Huxley; Sodium Channel; Magnetic; Field; Low-frequency.

A B S T R A C T

Ion channels in neurons and the transmitted signal between neurons are disrupted by drugs or poison. To have insight into the regulation of deformed neuron function by an extremely low-frequency magnetic field (ELF-MF), a theoretical model is presented which introduces ELF sinusoidal MF as an additive voltage input. The Hodgkin-Huxley neuronal model is exposed to an ELF-MF to suppress the blocking of the sodium ion channel. By analyzing the average spiking frequency and average spiking amplitude, it can be found that the effects of ELF-MF on neuronal activity will increase as the frequency $[0-400]$Hz and amplitude $[5-50]$mT of MF increase. It is shown that by blocking sodium channels, the amplitude and number of spikes of the action potential are decreased. Results show that an ELF-MF can increase INa which indicates that toxic ion channels can be modulated and their impaired function can be remedied.

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مقاله پژوهشی

اثرات میدانهای مغناطیسی با فرکانس بسیار پائین روی کانالهای سدیمی مسدود

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چکیده

کانال های یونی در نورون ها و سیگنال ارسالی بین نورون ها توسط دارو یا سم مختل می شوند. برای داشتن بینشی در مورد تنظیم عملکرد نورون تغییر شکل یافته توسط میدان مغناطیسی (MF) با فرکانس بسیار پایین(ELF) ، یک مدل تعمیم یافته ازهاجکین و هاکسلی ارائه میشود که ELF سینوسی MF را به عنوان ولتاژ ورودی افزایشی معرفی می‌کند. مدل عصبی هوچکین و هاکسلی در معرض ELF MF قرار می گیرد تا کانال یونی سدیم مسدود شده را سرکوب کند. با تجزیه و تحلیل میانگین اسپایکینگ فرکانس و میانگین اسپایکینگ دامنه، می توان دریافت که با افزایش فرکانس و دامنهMF ، اثرات ELF MF بر فعالیت عصبی افزایش می یابد. نشان داده میشود که با مسدود کردن کانال های سدیم، دامنه و تعداد اسپایک ها از پتانسیل عمل کاهش می یابد. نتایج نشان می‌دهند که یک ELF MF می‌تواند INa را افزایش دهد که نشان می‌دهد که کانال‌های یونی سمی را می‌توان تعدیل کرد و عملکرد مختل آنها را می‌توان اصلاح کرد.

کلیدواژه‌ها

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I. INTRODUCTION

In 1952, Hodgkin-Huxley (HH) presented an equivalent circuit describing the electrical be- havior of the membrane [Hodgkin AL and Huxley AF, 1952]. It is constructed of a membrane capacitor and several resistors that regulate the flow of ions. Channels are structures in the cell membrane to move ions in and out of the cells. The excitability mechanism of the chan- nel causes ions to pass through. On the other hand, one of the most specific methods of investigating the neuromodulatory effect is to use of magnetic stimulation. This approach can be made through various processes such as extremely low frequency (ELF) [Barker AT et al., 1985], and transcranial magnetic stimulation (TMS) [Modolo J et al., 2010]. Former is a non-invasive neuromodulation process and later is a nerve stimulation that is applied to small and limited areas of the brain. In the TMS procedure, a MF generator or "coil" is placed near the patient's head. Through electromagnetic induction, the coil generates a gen- tle electric current in the lower part of the brain. The coil is also connected to a pacemaker or actuator that conducts it to electricity.

The study of MF effects on neurons is one of the exciting topics for researchers. Roth and Basser have presented a model that is introduced to illustrate the physics of nerve stim- ulation by EM field induction [Roth BJ and Basser PJ, 1990]. Furthermore, an analysis of magnetic stimulation presented by Nagarajan et.al at a finite length neuronal using com- puter modeling [Nagarajan SS et al., 1993]. They described the effects of the spatial and temporal distribution of the MF-induced EF on finite neural structures. Moreover, Pashut et.al calculated the induced current in a nerve cell membrane using an external MF, by introducing a numerical and simulation method [Pashut T et al., 2011]. They studied the mechanisms of magnetic stimulation of central nervous system neurons with this outline. In this way, Jiang Xiu-Yu et.al showed that an ELF-MF is able to advance neuronal spike timing, as well as delay spike timing [Xiu-Yu, Jiang, et al., 2012]. Similarly, Jiajia Yang et.al found that the effect of the MF improved their depressive behavior and cognitive dysfunction effectively, by experiments on alpha mice [Yang, Jiajia, et al., 2019].

On the other hand, ionic channels are sometimes blocked by external agents such as drugs and toxins. There are many blockers that interfere with the function of ion channels, sometimes leading to their destruction [Kushnarev et al., 2020]. In this regard, tetrodotoxin (TTX) is a potent blocker of the voltage-gated sodium channels [Narahashi et al., 1964] in the nanomolar range. This was later verified on systems such as squid giant axon, eel elec- tric organ, and frog myelinated axons [Nakamura et al., 1965; HILLE, B, 1966]. A class of drugs acts by inhibition of sodium influx through cell membranes [Dokken et al., 2020]. The blockade of sodium channels slows the rate and amplitude of initial rapid depolarization, reduces cell excitability, and reduces conduction velocity. The most commonly used drugs in this group include Propafenan, Quinidine, Procainamide, Mexiletine, Lidocaine, and Fle- cainide [Trujilloand et al., 2000]. Experimental and simulations show that EMF changes the biological properties of the brain cells membrane [Ramundo-Orlando A et al., 2000]. These modifications include increasing permeability to carbonic anhydrase, and stimulating the activity of potassium ion-dependent channels by increasing ion concentration [Pall ML,2013]. Furthermore, by applying an external magnetic field, the concentration of arachidonic acid increases, which causes the activation of the sodium channels of cerebellar granular cells [He YL et al., 2013]. These works motivated us to examine how an ELF-MF affects closed sodium channels. For this purpose, first, the HH model is developed by including an ELF- MF, and then the effects of the magnetic field are considered on blocked sodium channels by the simulation process. Furthermore, it is analyzed how the nervous system responds to changes at different amplitudes and frequencies.

II. Materials and Methods

HH Model

The HH model is based on the assumption that the electrical properties of a portion of a cell membrane can be determined by an equivalent circuit [Hodgkin AL and Huxley AF,1952]. By arising the stimulus current sodium ion channels open, and an influx of sodium ions flows through the cell. The sodium ion channels closed and the potassium ion channels opened until the action potential had passed further down the cell axon. According to this mechanism of ions flowing across the cell membrane with sodium (N a) and potassium (K)(with any ion leakage L), the membrane potential is described by:

$$C_m = \frac{dV(t)}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{app} \quad (1)$$

with gL being a constant that is experimentally established and Cm is the membrane capacity. The model breaks down if the values of gK and gNa are both kept constant. The membrane conductance of sodium and potassium is given by:

$$g_{Na} = \bar{g}_{Na} m^3 h, \; g_K = \bar{g}_K n^4 \quad (2)$$

in which $\bar{g}_{Na}$ and $\bar{g}_K$ are also experimentally constants, m and h indicate the activation and deactivation gates of the sodium ion and n being the potassium ion diffusion gates. Both m and h are functions of time and obey the two differential equations as follows

$$\frac{dm(t)}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m, \quad (3)$$

$$\frac{dh(t)}{dt} = \alpha_h(V)(1 - h - \beta_h(V)h, \quad (4)$$

where the coefficients $\alpha m(V)$, $\beta m(V)$, $\alpha h(V)$, and $\beta h(V)$ are voltage functions calculated experimentally [Hodgkin AL and Huxley AF, 1952]. Similarly, for potassium ion gate (n) one gets:

$$\frac{dn(t)}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n, \quad (5)$$

where the coefficients $\alpha n(V)$ and $\beta n(V)$ are also functions of voltage determined by experi- mental results. Accordingly, the stimulated cell membrane's behavior is described by a set of four differential equations of the HH model as follows:

$$C_m = \frac{dV(t)}{dt} = -g_k n^4(V - V_K) - \bar{g}_{Na} m^3 h (V - V_{Na}) - g_L(V - V_L) + I_{app} \quad (6)$$

$$\frac{dm(t)}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m, \quad (7)$$

$$\frac{dh(t)}{dt} = \alpha_h(V)(1 - h - \beta_h(V)h, \quad (8)$$

$$\frac{dn(t)}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n, \quad (9)$$

Effects of ELF-MF on Action Potential

According to Faraday's theorem, the magnetic waves cause the electrical field E in the tissue as follows

$$\nabla \times E = -\frac{\partial B}{\partial t} \quad (10)$$

We consider the radius r coil positioned in the x − y plane at z = 0 (Fig. 1). The generated electrical field E can be measured along with the closed-loop L. For this situation, membrane depolarization voltage ΔV induced by a stable EF satisfies the following differential equation [Modolo J. et al., 2010]:

$$\Delta V + \tau \frac{d\Delta V}{dt} - \lambda E = 0. \quad (11)$$

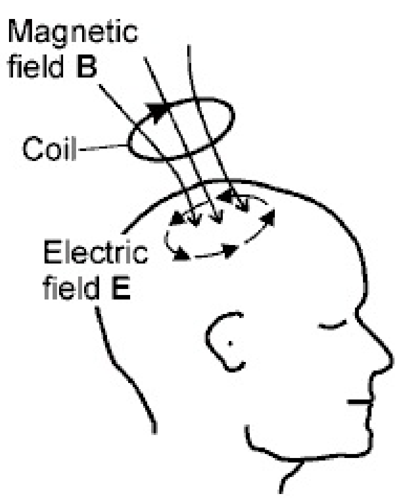


Figure 1

Here τ indicates the time constant of Maxwell-Wagner. For a sinusoidal form of external MF as $B = B_0 \sin(2\pi f t)$, relation (10) leads to

$$E(t) = r\pi f B_0 \cos(2\pi f t) \quad (12)$$

where B_0 is constant and f represents frequency. For this EF one can easily show that ΔV is given by

$$\Delta V(t) = \lambda r B_0 \pi f \left(\frac{\cos(2\pi f t) + 2\pi f \tau \sin(2\pi f t)}{1 + (2\pi f \tau)2}\right. \quad (13)$$

which can be used to find the field-induced membrane depolarization at any time. For this purpose, it is appropriate to define a parameter called the "polarization length". This pa- rameter is used to consider the cell's shape from its geometrically and polarizability aspects. In fact, the electric field induced by an external magnetic field causes charges to accumulate on parts of the cell membrane, which leads to further membrane depolarization [Radman et al., 2009]. In the present model, the polarization length, time constant of Maxwell-Wagner and the radius of exposure are assumed λ = 0.5 × 10−3m, τ = 10−4s and r = 0.1m respec- tively [C. Bedard, et al., 2006]. These values are chosen because of the hypothetical area of the part of the brain that is stimulated by the external electromagnetic field.

Effects of Extremely Low-Frequency Magnetic Field

We can take a commonly used approach to explain the interactions between neuronal behav- ior and applied MF to depict applied MF action as a cellular level perturbation of membrane voltage

[Yi, Guosheng, et al., 2014]. MF exposure can also be modeled over physiological membrane potential as an additive concept ΔV [J. Modolo et al., 2010; T. Y. Tsong and R. D. Astumian, 1987; K. R. Foster and H. P. Schwan, 1986; M. Giann'I et al., 2006]. So, it is possible to express the equations of the modified HH model representing the dynamics of a neuron exposed to ELF sinusoidal MF by:

$$C \frac{d(V + \Delta V)}{dt} = I_{app} - J \times \bar{g}_{Na} m^3 h (V + \Delta V - V_{Na}) - \bar{g}_K n^4 (V + \Delta V - V_K) - g_L (V + \Delta V - V_L) \quad (14)$$

Here, the $J = \frac{j}{N_{Na}}$ factor is the non-blocked ion channels relative to the total sodium N_{Na} ion channels, the j factor represents non-blocked channels, and N_{Na} indicates all sodium ion channels [Xu, Ying et al., 2018].

Clearly, from Eq. (14), MF exposure can stimulate an added substance to perturbation

ΔV in the membrane potential based on the HH model. This perturbation does not change the fundamental structure of the neuron model. Rather it adds nonlinear potential (ΔV) to the membrane potential (V) and leads to an extra current $C = \frac{d(\Delta V)}{dt}$ The perturbation ΔV affects the operation of ionic channels depending on the amount of voltage value.

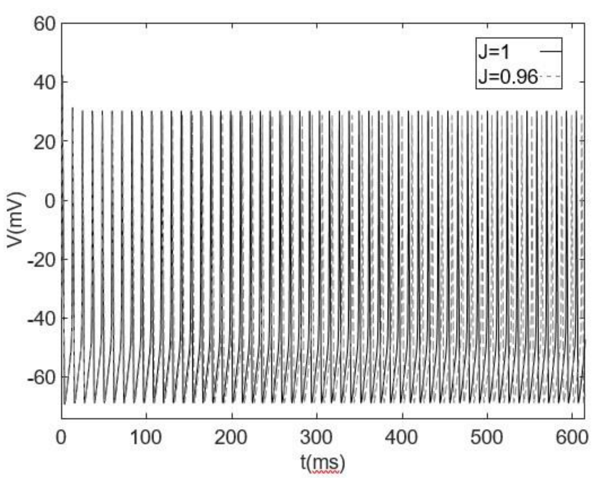
Table 1: Parameters values related to Eq. (14) [Hodgkin AL and Huxley AF, 1952].

Parameters	Values
C	1µF/cm2
Iapp	20µA/cm2
gNa	120mS/cm2
VNa	55mV
$\bar{g}$K	36mS/cm2
VK	−72mV
gL	0.3mS/cm2
VL	−50mV

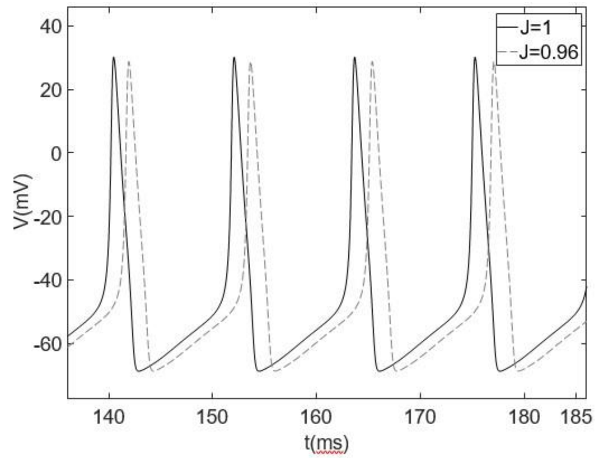
Discussion

In this investigation, a numerical model was proposed to study the behavior of neurons in response to blocked sodium ion channels as well as the effect of an ELF-MF on them. Fur- thermore, a generalized HH biological model was used to consider the behavior of neurons for blocked sodium ion channels. In this way, we consider a small area of the brain amount 10cm under the influence of the magnetic field with the amplitude (5 − 50) mT and fre- quency (0 − 400)Hz ranges. The reaction of a single neuron exposed to an external ELF-MF with differing frequencies and amplitudes is analyzed using simulation. This procedure was carried out using a fourth-order Runge-Kutta process with a random time step of [0.01, 0.02] ms. The simulation experiment lasts 10000 ms, to achieve the steady-state situation for each period. First, the neuron function is stimulated for both a) without blocked sodium channels, and b) with blocked sodium channels without exposure to MF. In the absence of a magnetic field, the constant stimulated current Iapp = 20µA/cm2 was applied to the cell and simulation was performed for J = 1 in the situation with non-blocked sodium channels; and for J = 0.96 in which some of the sodium channels are blocked. According to figure 2, am- plitude and duration of spike occurrence were changed for J = 0.96 and spikes occurred with lower magnitude and time delay compared with the non-blocked sodium channels J = 1. Furthermore, the number of spikes is reduced from 862 (for J=1) to 854 (for J=0.96) in comparison with the non-blocked channel. At the same time, the amount of interspike in- terval (ISI) for the poisoned cell (J = 0.96) was increased from 0.0202 to 0.0211 relative to a healthy cell (J = 1). It is also evident that the distance between the occurrences of spikes in the poisoned cell was increased compared to the healthy cell, which obviously indicates the pattern of the spikes in the two cells is different (Fig. 2).

To consider the effects of the MF on the spiking pattern, in the following, the neuron activation is stimulated during ELF-MF exposure. For each intensity of the MF, simulations are performed ten times. The frequency range of the ELF-MF is [0, 400] Hz with steps of 1 Hz and the domain of intensity is B0 = [5 − 50] mT with steps of 5 mT .



(a)



(b)

Figure 2

Figure 3 indicates noises occurring at the threshold of the action potential, which can

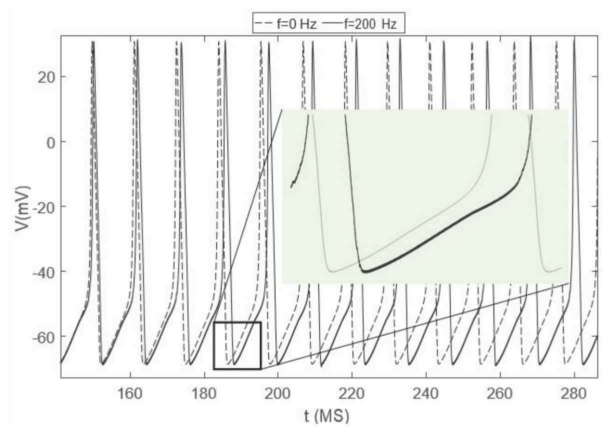


Figure 3

be explained by the inability of the ELF-MF to produce the induced current required to stimulate the cell to generate the action potential. Accordingly, induced currents of very low amplitude emerge as noise.

According to figure 4, up to 100 Hz, no significant change in the average amplitude of the spikes occurs, and by increasing frequency, the average amplitude of the action potential fluctuates.

Obviously, by increasing the MF, the average amplitude of the action potential increases and also by decreasing the MF, fluctuations start at higher frequencies.

In the absence of poisoning which all sodium channels are non-blocked, the number of spikes is N = 862 and the average action potential is V ≈ 30.2 mV . As shown in figure 5 for the case that J = 0.96 and domain ELF-MF in B = 5 mT, only in a few limited points is the number of spikes closer to the number of spikes in a healthy cell. Also, the average action potential of a poisoned cell in this range of the MF is much smaller than that of a healthy

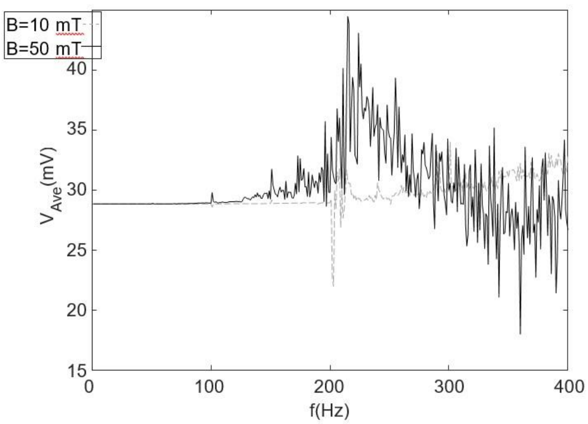


Figure 4

cell. Therefore, in this situation, no suitable frequency was found to observe the function of a healthy cell. By keeping the sodium channel blockade, the amplitude ELF-MF increased to find a suitable MF in which the average action potential and the number of spikes are close to a healthy cell. According to figure 6, under an ELF-MF with B0 = 45 mT amplitude and frequency in the range [150-155] Hz, the function of the nerve cell is modulated. Actually, the mean values of the action potential and the number of spikes of the poisoned cell are affected by the ELF-MF close to the values of the healthy cell (black dash line). It was also observed in this amplitude that in the higher frequency range, the deviation of the action potential values and the number of spikes of the poisoned cell increased compared to the healthy cell.

In addition, it was observed that the presence of ELF-MF causes an increase in sodium

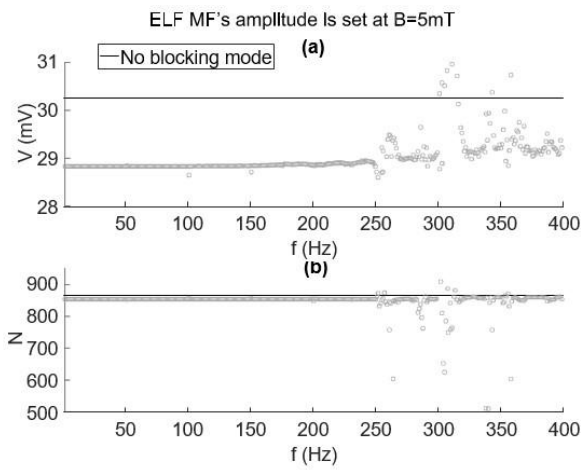


Figure 5

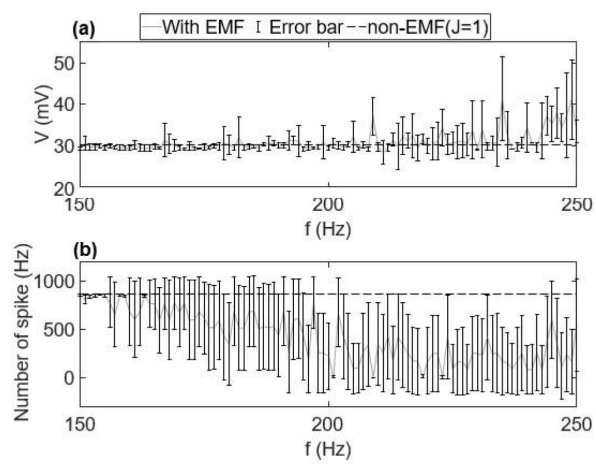


Figure 6

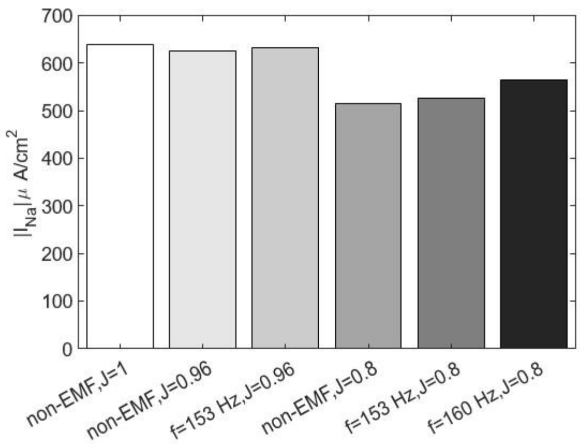


Figure 7

current. Two states J = 0.96 and J = 0.8 were considered with the same B0 = 45 mT amplitude and f = 153 Hz frequency and the results showed that the application of an external field increases the INa (Fig. 7). Furthermore, in state J = 0.8, the amount of sodium current increases with increasing frequency, and in general, the results obtained in figure 7 are consistent with experimental studies. Moreover, studies imply that INa and the average speaking potential increase with ELF-MF exposure significantly [He YL et al., 2013]. Also, figure 7 displays that the external electromagnetic field can increase the INa despite the blockage of sodium ion channels. By blocking the sodium channels, it was observed that the factor J, which represents the number of unblocked sodium channels relative to its total number, leads to the action potential with lower amplitude. Actually, blocking sodium channels causes defects in neural responses and consequently the message is not fully transmitted. In fact, blocking the sodium channel leads to the potential depolarization of the membrane in the new amplitude.

On the other hand, according to figure 3, noises have appeared at the threshold of the action potential, which can be attributed to the inability of the ELF-MF to produce an in- duced current to stimulate the cell for generating the action potential. Therefore, inductions of induced current with a very weak amplitude appear as noise. Also, experimental studies have shown that toxic substances such as astrodotoxin and tetraethyl ammonium can act as ion channel blockers and disrupt their function usually. Actually, they cause a pertur- bation in the conduction of channels and cause drastic changes in the behavior of neurons [T. Narahashi et al., 1964; Hagiwara, So, and N. Saito, 1959]. Some research also indicates that drugs can be used to reduce neuropathic pain based on blocking ion channels properties [Wood, John N., and James Boorman, 2005; Kalso, Eija, 2005]. Since an external source with an appropriate frequency and amplitude of magnetic field can reopen blocked channels, but it can also damage healthy cells, a simulation was performed for 10 s to find a suitable external magnetic source. On the other hand, using chemical drugs to open the blockage of ion channels has side effects. Therefore, use of suitable ELF-MF with a low amplitude and frequency prevents damage to organs adjacent to the target tissue. By choosing an appro- priate ELF-MF with 45 mT amplitude and a suitable frequency in the range [150 − 155] Hz, the cause of poisoning and its effect on neuronal behavior was eliminated. Also, the defective nerve cell was modified and the spiking was modulated to healthy cells.

Conclusions

In this paper we investigated the consequences of neuronal activation through exposure to ELF-MF with the blocking of sodium channels along the axon, in the framework of the HH model. When the axon is injured or ion channels are blocked by drugs, signal transmission can be blocked and signal signaling between neurons can be disturbed. It was seen that ELF-MF could improve the performance of blocked sodium ion channels, by analyzing neural average spiking frequency and amplitude exposed to ELF-MF and choosing an appropriate amplitude and frequency. It was also shown that ELF-MF modulates neuronal spiking rhythms of blocked sodium ion channels by evaluating the neural average spiking frequency and amplitude exposed to ELF-MF with distinct amplitude and frequency. Furthermore, the fluctuations of MF on neuronal function increase as the frequency and amplitude of MF rise. For the study of blocked signals, the heterogeneity or local injury is generated by blocking sodium channels. When the sodium channels are blocked, it is found that the amplitude and number of spikes of the action potential are decreased. As the amplitude of the external magnetic field increases, while the frequency is set for specific amplitudes in the range of [0−400] Hz, the amplitude and number of spikes grow. Studies that have been done following experimental work have displayed that the ELF-MF field can modulate channels and currents of sodium ions. The present model and its results can contribute to exploring the mechanism and therapeutic application of magnetic brain stimulation techniques and the treatment of localized neurological disorders caused by ion channel blockage.

Figure Captions Page

Figure 1: The TMS device induces electric field E near the patient's head through a coil that generates magnetic field B [Sack, Alexander T., and David EJ Linden, 2003].

Figure 2: a) Membrane potential Vs. time. b)Membrane potential Vs. time at $J = 0.96$ and $J = 1$ for a small time interval.

Figure 3: The action potential of neurons with and without ELF-MF exposure. Figure 4: Function of ELF-MF exposure in neuronal average spiking amplitude.

Figure 5: a) The average value of the neuron membrane potential as a function of ELF- MF exposure with frequency f and intensity $B = 5$ mT . The solid black line is the action potential of a neuron without an ELF-MF exposure and the black circles show the membrane potentials of the poisoned neuron with ELF-MF exposure. b) The number of spikes Vs. fre- quency of ELF-MF exposure. For $J = 1$ black line shows the number of spikes of neurons without ELF-MF exposure. Also, black circles indicate the number of spikes of poisoned neurons during exposure to ELF-MFs with different frequency and $B = 5$ mT

Figure 6: Evolutions of a) membrane potential and b) number of spikes Vs. frequency at $B = 45$ mT for $J = 0.96$. The black dash line in both figures indicates the values of V (mV) and N in the non-ELF and $J = 1$ state.

Figure 7: Frequency-dependent increase in INa exposure to ELF-MF (B = 45mT).

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