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اثر افزایشی میدان الکترومغناطیسی بر بیان فاکتور رونویسی الیگودندروسیت ۱ و ۲ (Olig1/2) در کورتکس مغز موش

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چکیده. Olig1 و Olig2 دو فاکتور کپی برداری است که نقش تنظیم کنندگی در تمایز و اختصاصی شدن سلول‌های اجدادی اولیگودندروسیت بازی می‌کنند. در این مطالعه اثر میدان الکترومغناطیسی بر غلظت کل پروتئین و بیان Olig1 و Olig2 در کورتکس مغز موش بررسی شد. بیست و یک موش نژاد Balb/c به سه گروه کنترل، تیمار و شم (تعداد ۷ موش برای هر گروه) تقسیم شدند. موش‌های گروه تیمار درون بوبین (سولنوئید) بطور روزانه در معرض میدان ۵۰ هرتز /۱ میلی‌تسلا برای ۶ ساعت در هر روز و به مدت ۱۰ روز قرار داده شد. گروه شم درون همان بوبین ولی بدون میدان الکترومغناطیس قرار داده شد. بعد از اتمام این مدت موش‌ها بیهوش شده و کورتکس مغز آنها برای آنالیزهای بعدی جدا گردید. غلظت کل پروتئین و بیان Olig1 و Olig2 به ترتیب توسط اندازه‌گیری پروتئین Bio-Rad و وسترن بلات بررسی شد. تفاوت معنی داری در غلظت کل پروتئین در کورتکس مغز گروه تیمار در مقایسه با گروه‌های شم و کنترل دیده نشد. همچنین نشان داده شد که بیان Olig1 و Olig2 در کورتکس مغز موش گروه تیمار در مقایسه با گروه‌های شم و کنترل بیشتر است. نتیجه‌گیری می‌شود که میدان الکترومغناطیسی باعث افزایش بیان Olig1 و Olig2 در کورتکس مغز موش میشود. به علاوه چون Olig1 و Olig2 نقش مهمی در تکوین سلولهای اجدادی اولیگودندروسیت بازی می‌کند، نتیجه‌گیری می‌شود که EMF ممکن است با افزایش بیان Olig1 و Olig2 در تمایز سلول‌های اجدادی اولیگودندروسیت نقش داشته باشد. مطالعه بیشتر برای تایید اثر میدان الکترومغناطیسی بر تمایز اولیگودندروسیت ضروری است.

واژه‌های کلیدی. بیان ژن، پرتو مغناطیسی، کورتکس، گلیوژنز، وسترن بلات

The enhancing effect of electromagnetic field on the expression of Oligodendrocyte transcription factor 1 and 2 (Olig1/2) in the mice cerebral cortex

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Abstract. Olig1 and Olig2, two transcription factors, play regulatory function in the differentiation and specification of oligodendrocyte progenitor cells (OPCs). In this study the effects of electromagnetic fields (EMF) on total protein concentration (TPC) and Olig1 and Olig2 expression in the cerebral cortex of mouse was examined. Twenty-one Balb/c mice were separated into three groups: control, EMF and Sham groups (n=7 for each group). The mice were placed inside the solenoid for a daily EMF exposure of 50 Hz, 1 mT for 6 h/day, 7 days/week for 10 days. The Sham group was also located in the same coil with no exposure. Mice were anesthetized after the final exposure session and their cerebral cortex were collected. TPC and the expression of Olig 1 and Olig2 were studied by Bio-Rad protein assay and western blot, respectively. The cerebral cortex samples were removed for further analysis. There was no significant difference in TPC in the EMF treated cortical samples as compared with those from the SHAM and control groups. It was also shown that the expression of Olig1 and Olig2 was increased in the EMF treated cortical extracts as compared with those in controls and SHAM groups. Therefore, it could be concluded that EMF enhances Olig1 and Olig2 expression in the mice cerebral cortex. Moreover, as Olig1 and Olig2 plays important role in the development of oligodendrocyte progenitor cells, it can be deduced that EMF may affect OPC differentiation by increasing the expression of Olig1 and Olig2. Further studies are needed to clarify the extent of EMF impact on oligodendrocyte differentiation.

Keywords. cortex, gene expression, gliogenesis, magnetic radiation, Western Blot

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INTRODUCTION

Oligodendrocytes (OLs) are responsible for myelin production in the central nervous system (CNS). Several transcription factors, including Olig 1, Olig 2 and Sox10, have been shown to regulate the development of oligodendrocyte progenitor cells (OPCs) (Kim et al., 2011). It was shown that the expression of Sox10 and Olig2 in the pluripotent stem cells promote OPCs production and oligodendrocyte (OL) terminal differentiation (Li et al., 2016; Muth et al., 2016). Olig 1 and Olig 2 belong to the large family of basic helix-loop-helix (bHLH) transcription factors that play important role in cellular differentiation and development (Wegner, 2008). Olig 1 plays a key role in OL myelin synthesis and in remyelination after experimentally induced CNS demyelination (Arnett et al., 2004). Olig 2 was shown to regulate Purkinje cell generation in the developing brain of mice and is essential for primary motor neuron and OL development (Ju et al., 2016; Park et al., 2002). It was demonstrated that the proper regulation of the Olig gene family is essential for the formation of oligodendrocytes, astrocytes and neural crest (Choudhury, 2019). The mechanism by which Olig1/2 increase the oligodendrocyte maturation is not clear. The state of olig2 phosphorylation might be another important step in the promotion of oligodendrocyte development (Sun et al., 2011). The differentiation of OPCs expressing Olig2 into oligodendrocytes as observed in Cuprizone-induced demyelinated lesions showing that Olig1 and Olig2 are needed for oligodendrocyte differentiation and remyelination (Fancy et al., 2004). Moreover, it was shown that the upregulation of Olig1 and/or Olig2 transcription factors in OPCs leads to myelination (Maire et al., 2010).

Environmental factors including nutrition were shown to be important in Olig1 expression in the cerebral cortex (Semnani et al., 2016). Leukemia inhibitory factor (LIF) was demonstrated to increase Opalin expression, which was shown to be the marker of oligodendrocyte maturity (Mashayekhi et al., 2015). It was documented that electromagnetic field (EMF) potentiates proliferation and migration of neural stem cells and increases the repair of myelin in demyelinating conditions (Sherafat et al., 2012). EMF was shown to induce hippocampal proteome and transcriptome changes that may explain the brain proteome changes (Fragopoulou et al., 2018). EMF has been shown to play important role in the neural cell migration by increasing reelin and Dab1 expression in the developing Brain (Hemmati et al., 2014). EMF therapy was shown to be useful in MS patients with weakness (Haase et al., 2011). Exposure to EMF increases neurogenesis in the adult brain (Cuccurazzu et al., 2010). EMF decreases symptoms in some patients with MS and utilization of extremely low frequency (ELF) magnetic fields can improve symptoms of MS (Lappin et al., 2003). It has been shown that EMF stimulation promotes re-myelination of demyelinated MS plaques, enhances the number of sub-ventricular proliferating cells and reduces the extent of demyelinated plaques in animal models of MS (Sherafat et al., 2012). EMF exposure potentially affects the gene and protein expression *in vitro* and *in vivo* (Frisch et al., 2013; Faass et al., 2009). It was suggested that chronic exposure to RF-EMF for 8 months may be associated with the increases in neurogenesis-related signals in the hippocampus of C57BL/6 mice (Jeong et al., 2020). The aim of this study was to demonstrate the effects of EMF on Olig1 and Olig2 expression in the Balb/c mice cerebral cortex.

MATERIALS AND METHODS

Animals

Balb/c mice were purchased from Pasteur Institute (Karaj, Iran) and kept under a 12-h light/dark cycle in individual ventilated cages and maintained in a specific pathogen-free grade environment. They were kept in 40×40×30 cm (H×L×W) cages at a constant temperature of 20–22°C with unrestricted access to laboratory food pellets (Pars Company, Tehran, Iran) and water. All animal experiments were carried out in accordance with the Animals (Scientific Procedure) Act, 1986. This project has been accepted by the university of Guilan (Ref: 96- 4927).

Design and Description of EMF emitter set

The solenoid (EMF producer) was designed to produce an EMF with 50Hz frequency and 0.5mT intensity by means of an urban electric line adaptor (220v-10A). The calibration of the exposure facility was carried out to confirm the constant distribution of the magnetic field intensity in the experiment area, where the mice were kept (Valberg et al., 1995).

EMF exposure

A total of 21 mice were separated into three groups: control, EMF and SHAM groups (n=7 for each group). The mice were placed inside the solenoid for a daily EMF exposure of 6h/day, 7 days/week for 10 days. The SHAM group was also located in the same coil with no exposure. Mice were sacrificed after the final exposure session by excessive dose of anesthetic (sodium pentobarbitone) Sigma-Aldrich, Dorset, UK), the cortex were removed in order to study the effects of EMF on total protein concentration (TPC), Olig1 and Olig2 expression. The temperature and humidity were checked continuously through the experiments. This ensures that all the mice were kept in similar condition.

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Cell extract

Tissue samples (cerebral cortex, 10 mg each) were cut into small pieces and suspended in 0.5 ml of protein lysis buffer (140 mM NaCl, 1.0% NP40, 20 mM Tris (pH 7.5), 6 mM EDTA, and Complete Mini protease inhibitor cocktail (Roche Diagnostics, West Sussex, UK)) and then mechanically homogenized by sonication. After centrifugation, the protein extracts were collected and stored at the temperature of -70°C for further analysis.

Total protein concentration (TPC) and Olig1 and Olig2 expression

TPC was determined in cortical extract by means of Bio-Rad protein assay based on the Bradford dye procedure. For Western blotting, the extracts (40 µg/lane) were loaded on 10% SDS-polyacrylamide gel and transferred to a polyvinylidene difluoride membrane (Bio-Rad Laboratories, Hertfordshire, UK). The membranes were blocked with phosphate buffered saline (PBS) containing 0.05% Tween 20 and 5% dry milk and probed either with monoclonal mouse anti-Olig1 (ab24908) and anti-Olig2 (ab109186) antibodies (Abcam, Cambridge, UK) (1:5000 dilution) or a mouse monoclonal anti- β-tubulin antibody (loading control) (Abcam, Cambridge, UK) (1: 5000 dilution) and then treated with the appropriate horseradish peroxidase-conjugated secondary antibody. Immunoreactive protein was visualized using the Enhanced Chemiluminescence Western blotting detection system (Bio-Rad Laboratories, Hertfordshire, UK). Densitometry analysis was done by scanning immunoblots and quantitating protein bands using an image analyzer (Metaview Software, version 4.0, West Chester, PA).

Statistical analysis

All data presented are expressed as mean ± standard error of the mean (SEM). Statistical analysis was done by means of one-way ANOVA to test the differences among the groups, and only values with $P \leq 0.05$ were considered as significant.

RESULTS

Total protein concentration

The TPC in the cortical extracts obtained from EMF exposed, SHAM and control groups was determined by Bio-Rad protein assay based on the Bradford dye mixture. The total protein content of EMF exposed, SHAM and control groups were 0.92±0.02, 0.90±0.04 and 0.90±0.05 (g/l), respectively. There was no significant difference in the TPC of EMF exposed samples as compared with those from either the SHAM or control groups ($P>0.05$) (Fig. 1).

Analysis of Olig1 and Olig2 expression

Western blot analysis was performed to quantitatively assess Olig1 and Olig2 expression in the cortical extracts. A western blot analysis using anti-Olig1 and anti-Olig2 antibodies as probes confirmed the presence of Olig1 and Olig2 in all the samples (Figs. 2A and 3A). An image analyzer was used to determine the intensities of the bands in the respective lanes. Quantification of the western blot bands showed that the expression of Olig1 and Olig2 was significantly increased in the EMF treated cortical extracts when compared with either SHAM or control groups ($P<0.0001$). The Olig1 expression in EMF exposed, SHAM and control groups were 40.11±6.50, 15.44±3.81 and 13.44±3.5, respectively. The Olig2 expression in EMF exposed, SHAM and control groups were 49.44±6.02, 24.55±7.39 and 22.55±5.74, respectively. However, no significant changes in the Olig1 and Olig2 expression in the cerebral cortical extract were seen between SHAM and control groups ($P>0.05$) (Figs. 2 B and 3 B).

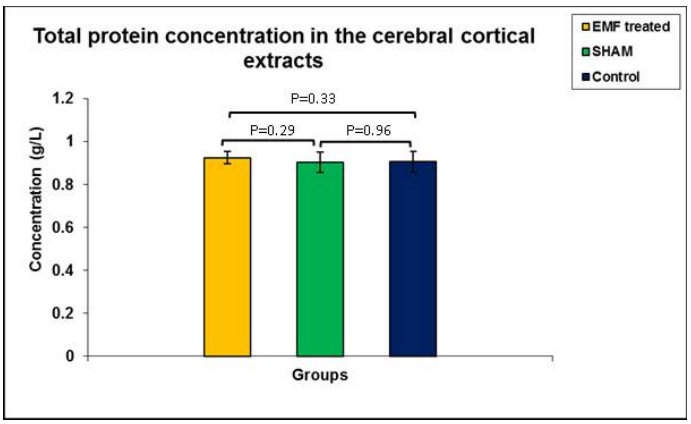

Figure 1. Total protein concentration in the cerebral cortex from EMF treated, SHAM and control groups (g/L). No significant difference was seen in total protein concentration among the groups ($P>0.05$).

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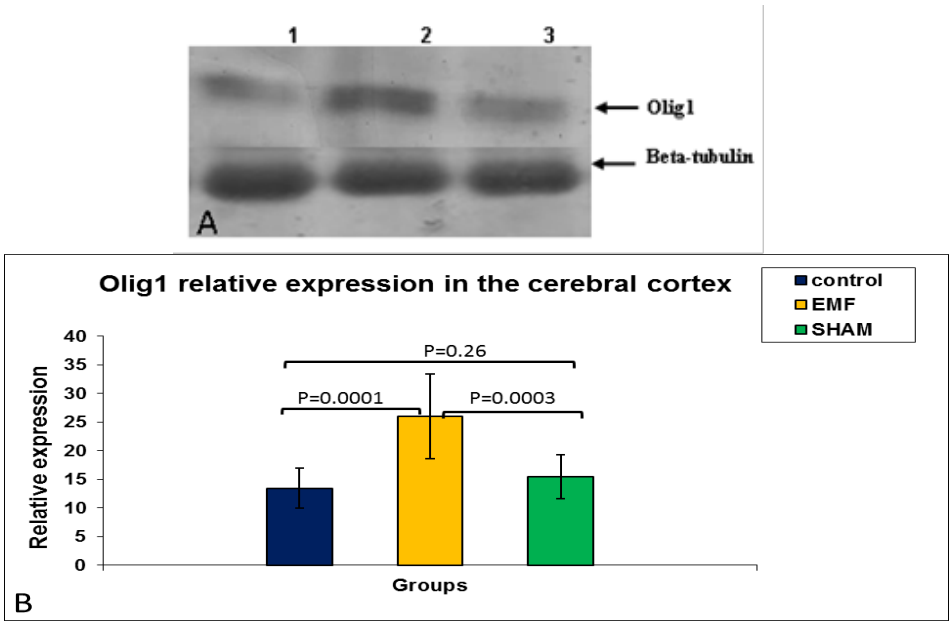

Figure 2. A. Expression of Olig1 in the cerebral cortex from control (lane 1), EMF treated (lane 2) and SHAM (lane 3) groups. ß-tubulin (50 kDa) expression was used as a protein loading control. **B.** Relative Olig1 expression. Signal intensities from control, EMF treated and SHAM immunoblotting experiments were determined by densitometric analysis. The bars represent standard error of the mean. There was significant difference in the Olig1 expression in EMF treated cortical extracts when compared with either SHAM or control group (P=0.0003 and 0.0001, respectively).There was no significant difference in the Olig1 expression between SHAM and control groups (P=0.26).

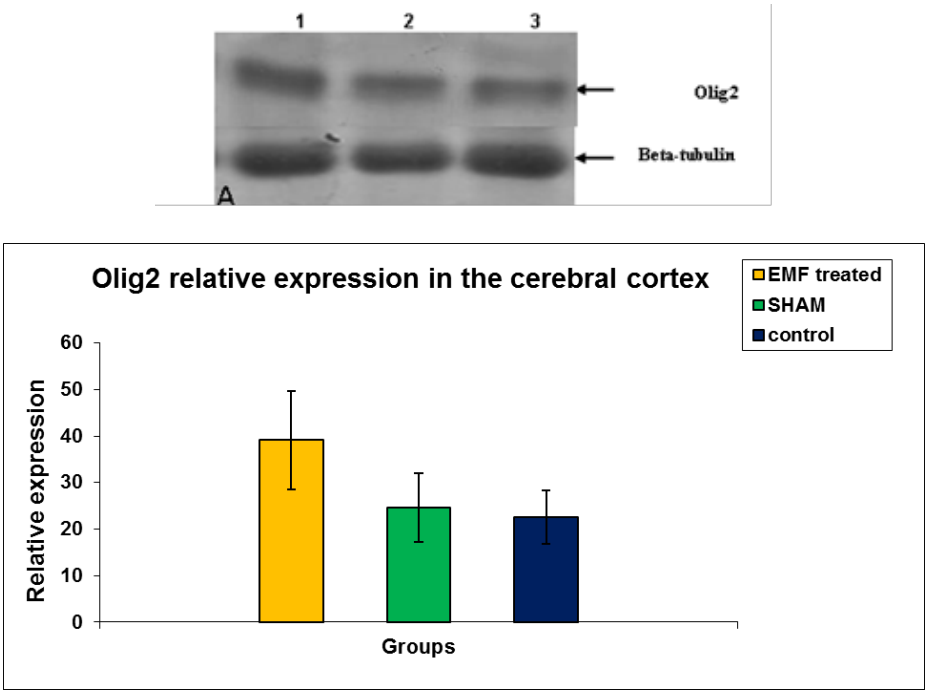

Figure 3. A. Expression of Olig2 in the cortex from EMF treated (lane 1), SHAM (lane 2) and control (lane 3) groups. ß-tubulin (50 kDa) expression was used as a protein loading control. **B.** Relative Olig2 expression. Signal intensities from control, SHAM and EMF treated immunoblotting experiments were determined by densitometry analysis. The bars represent standard error of the mean. There was significant difference in the Olig2 expression in EMF treated extracts when compared with either SHAM or control group (P=0.003 and P=0.0008, respectively). There was no significant difference in the Olig2 expression between SHAM and control groups (P=0.52).

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DISCUSSION

Multiple sclerosis is the most commonly studied demyelination disease and causes neurological disability in humans. However, some repair is possible during early stages of MS, presumably in association with partial re-myelination. In animal models of demyelination, oligodendrocyte progenitor cells (OPC) proliferate and migrate into demyelinated areas (Redwine & Armsrong, 1998). Some OPCs have the ability to proliferate, migrate and differentiate into myelin-forming oligodendrocytes, but they fail to lead re-myelination because of inadequate number and efficiency of the OPCs. Growth factor expression could participate in the repair process of demyelinating disease by modulating the activity of microglia/macrophages, inducing the expression of other factors that can affect myelin regeneration, and also by directly stimulating the localized proliferation and/or regeneration of oligodendrocytes within lesion areas (Rosenberg et al., 2006).

It has been shown that EMF increases neurogenesis in young rats (Orendáčová et al., 2011). EMF has been shown to change miRNA in brain tissue (Erdal et al, 2018). In this study the effects of EMF on olig1 and olig2 expression in mice cerebral cortex was studied. It was shown that EMF therapy can positively influence the functional repair after a nerve injury (Beck-Broichsitter et al., 2014). EMF has been shown to promote remyelination of demyelinated MS plaques and also increased the number sub-ventricular zone (SVZ) proliferating cells and decreased the extent of demyelinated plaques in local model of MS (Sherafat et al., 2012). It was shown that olig2^{+} progenitors from mice proliferate and differentiate into oligodendrocyte more efficiently (Islam et al., 2009). It was also suggested that Olig1 and/or Olig2 up-regulation in the progenitor cells leads to myelination (Kim et al., 2011).

It was demonstrated that the majority of surviving Olig2 overexpressing neural progenitor cells differentiated into oligodendrocyte and eventually became re-myelinated axons in the brain of Cuprizone-induced demyelinated mice (Sher et al., 2009). Oligodendrocyte development in Olig1 knockout mice after demyelination shows this progenitor are not able to complete differentiation which show that Olig1 is a key regulator of oligodendrocyte myelinogenesis in brain (Xin et al., 2005).

It was demonstrated that heat-shock proteins (Hsp) and heat-shock transcription factors (Hsf) expression were meaningfully up-regulated in the brain after EMF exposure (Ohtani et al., 2016). Hemmati and colleagues (2014) showed that reelin and Dab1 expression increases in the EMF-treated developing cerebral cortex and they concluded that EMF may play an important role in the neural cell migration by increasing reelin and Dab1 expression in the developing cortex. Podda and colleagues (2014) suggested that extremely low-frequency electromagnetic fields decreases the expression of the pro-apoptotic protein Bax, and increased levels of the anti-apoptotic protein Bcl-2, in the hippocampi of mice as well as in hippocampal neural stem cell cultures. They suggested that EMF have clinical implications for the treatment of decreased neurogenesis related to neurodegenerative diseases (Podda et al., 2014). It was also documented that EMF stimulates BDNF-TrkB signaling pathways and increase in GFAP levels (sign of a potential gliosis) in the different rat brain areas (Ammari et al., 2010; Ma et al., 2013). It was shown that EMP exposure could activate microglia in rat brain and affects its secretory function and the p38 pathway plays key role in this process (Yang et al., 2016). It was also shown that EMF increases the Alpha-fetoprotein (AFP) expression in the amniotic fluid (AF). It is also suggested that EMF may change the AFP expression in the AF by altering the expression of genes, including AFP, and/or by affecting the permeability of blood barriers (Esmaeilnezhad & Mashayekhi, 2020).

The results of this study suggest that EMF increases Olig1 and Olig2 expression in the mouse cerebral cortex. As Olig1/2 plays an important role in the myelination (Cheng et al., 2015) and EMF potentiates the repair of myelin (Sherafat et al., 2012), the significant increase in the expression of Olig1/2 in our study in response to EMF stimulation may be important in the process of myelination and remyelination, which may be applied for the treatment of multiple sclerosis. Moreover, as Olig1 and Olig2 plays important role in the development of oligodendrocyte progenitor cells, it is concluded that EMF may be important in in OPC differentiation by increasing the expression of Olig1 and Olig2. The results of this study provide a cellular and molecular framework for understanding the effects of EMF on gene expression in the brain.

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