

Exposure to Extremely Low Frequency Magnetic Fields Induces Fos-Related Antigen-Immunoreactivity Via Activation of Dopaminergic D1 Receptor

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We previously demonstrated that repeated exposure to extremely low frequency magnetic fields (ELF-MF) increases locomotor activity via stimulation of dopaminergic D1 receptor (*J. Pharmacol. Sci.*, 2007;105:367-371). Since it has been demonstrated that activator protein-1 (AP-1) transcription factors, especially 35-kDa fos-related antigen (FRA), play a key role in the neuronal and behavioral adaptation in response to various stimuli, we examined whether repeated ELF-MF exposure induces FRA-immunoreactivity (FRA-IR) in the striatum and nucleus accumbens (striatal complex) of the mice. Repeated exposure to ELF-MF (0.3 or 2.4 mT, 1 h/day, for consecutive fourteen days) significantly induced hyperlocomotor activity and FRA-IR in the striatal complex in a field intensity-dependent manner. ELF-MF-induced FRA-IR lasted for at least 1 year, while locomotor activity returned near control level 3 months after the final exposure to ELF-MF. Pretreatment with SCH23390, a dopaminergic D1 receptor antagonist, but not with sulpiride, a dopaminergic D2 receptor antagonist, significantly attenuated hyperlocomotor activity and FRA-IR induced by ELF-MF. Our results suggest that repeated exposure to ELF-MF leads to prolonged locomotor stimulation and long-term expression of FRA in the striatal complex of the mice via stimulation of dopaminergic D1 receptor.

Key words: extremely low frequency magnetic fields, Fos-related antigen, locomotor activity, dopaminergic D1 receptor, striatal complex

INTRODUCTION

Numerous studies have suggested that exposure to magnetic fields affects various physiological and pathological processes. For instance, magnetic fields have been considered as a “possible

risk factor” for childhood leukemia, brain tumor or breast cancer (Floderus et al., 1993; Forssén et al., 2000; World Health Organization, 2007; Kheifets et al., 2010). On the other hand, therapeutic intervention with repetitive transcranial magnetic stimulation has shown to be beneficial for improving symptoms of Parkinson’s disease (Fregni et al., 2005; Epstein et al., 2007) or several psychiatric diseases (George et al., 1995; Post and Keck, 2001).

The activator protein-1 (AP-1) transcription factors are composed of Fos and Jun proteins in a Fos/Jun heterodimeric or Jun/Jun homodimeric complex that recognize and bind to specific

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DNA sequences (5'-TGAGTCA-3') in the promoter regions of a number of genes (Pennypacker et al., 1994; Karin et al., 1997). Temporal expression profiles of each member of the Fos family, including c-Fos (Young et al., 1991; Rosen et al., 1994; Hsieh et al., 2002), FosB (Chen et al., 1995; Doucet et al., 1996; Bing et al., 1997a), Δ FosB (Chen et al., 1995; Doucet et al., 1996) and fos-related antigen (FRA) (Young et al., 1991; Rosen et al., 1994; Bing et al., 1997a and 1997b; Pennypacker et al., 2000; Hsieh et al., 2002) have been characterized in various *in vivo* animal models. In particular, a 35-kDa FRA have shown long-lasting expression pattern in response to chronic drug treatment or chronic neuronal stimulation (Rosen et al., 1994; Bing et al., 1997a and 1997b; Hsieh et al., 2002), suggesting that prolonged induction of 35-kDa FRA is important for regulating genes related to neuronal adaptation (Pennypacker et al., 1994; Pennypacker et al., 1995; Foletta, 1996; Bing et al., 1997b). We also have demonstrated the induction of 35-kDa FRA after treatment with kainic acid (Kim et al., 1996; Kim et al., 1998), cocaine (Jhoo et al., 2000; Kim et al., 2001), or methamphetamine (Shin et al., 2005).

Magnetic fields have shown to affect behavioral profiles regulated by dopaminergic system (Wilson, 1988; Choleris et al., 2001; Sieroń et al., 2004; Janać et al., 2005; Shin et al., 2007; Liu et al., 2008) in rodents. In the previous study, we demonstrated that exposure to extremely low frequency magnetic fields (ELF-MF) increases striatal dopamine levels (Lee et al., 2001), and that ELF-MF induces hyperlocomotor activity via dopaminergic D1 receptor stimulation (Shin et al., 2007).

Little is known about the role of magnetic fields in modulations of AP-1 transcription factors *in vivo*, although magnetic fields-induced up-regulations in AP-1 transcription factors have demonstrated *in vitro* (Lin et al., 1998; Hirai et al., 2002). Since FRA is the most important factor of the AP-1 modulation of genes necessary for neuronal adaptation (Pennypacker et al., 1995; Bing et al., 1996; Bing et al., 1997b), we examined FRA-immunoreactivity (FRA-IR) in the striatum and nucleus accumbens (striatal complex) after ELF-MF exposure, and we evaluated whether dopaminergic receptors are involved in the induction of FRA by applying dopaminergic D1 receptor antagonist, SCH 233390 and dopaminergic D2 receptor antagonist, sulpiride. Unexpectedly, we observed that FRA-IR lasted for at least 1 year after final exposure to ELF-MF. This long-lasting FRA-IR requires activation of dopaminergic D1 receptor.

MATERIALS AND METHODS

Animals and treatments

All mice were handled in accordance with the US National

Institute of Health guidelines for the humane care of laboratory animals and the Institutional Animal Care and Use Committee of Kangwon National University. Male adult C57BL/6 mice (Orient Bio Inc., Charles River Technology, Gapyung-Gun, Gyeonggi-Do, Korea), weighing 25 ± 2 g, were maintained on a 12:12 h light:dark cycle, with food and water available *ad libitum*. The ambient conditions were maintained at $20 \pm 2^\circ\text{C}$. Mice were adapted to these conditions for 2 weeks before the experiments.

The ELF-MF was generated with three Helmholtz coils, set parallel to each other, in a wooden frame (Lee et al., 2001; Shin et al., 2007). The ELF-MF consisted of 60-Hz time-varying fields and the magnetic flux density was 0.3 or 2.4 mT. Animals were exposed to ELF-MF for 1 h/day for fourteen days. As seven days' exposure to ELF-MF was not fully enough for locomotor stimulation (Shin et al., 2007), we extended exposure period by fourteen days in this study. Thirty minutes before the animals were exposed to ELF-MF, mice were treated with SCH23390 hydrochloride (SCH, D1 antagonist; Tocris Co., Ellisville, MO, USA) at 0.03 or 0.1 mg/kg, i.p. or (RS)-(\pm) sulpiride (Sulp, D2 antagonist; Tocris Co.) at 10 or 20 mg/kg, i.p. (Shin et al., 2007). Locomotor activity was measured 0 hour, 1 day, 1 week, 3 months or 1 year after the final ELF-MF exposure using an automated video-tracking system (Noldus Information Technology, Wagenin, The Netherlands). Eight test boxes (40×40×30 cm high) were operated simultaneously by a computer. Animals were studied individually during locomotion in the test box. A printout for each session showed the pattern of ambulatory movements in the test box. The distance traveled (in cm) was analyzed for 30 min. Data were collected and analyzed between 9:00 and 17:00 h. Animals were sacrificed for immunohistochemical analyses 90 min after measurement of locomotor activity.

Immunohistochemistry

Sections containing the nucleus accumbens and striatum were processed for FRA immunohistochemistry. Prior to incubation with the primary antibody, sections were preincubated in PBS containing 0.2% Triton X-100 and 4% normal goat serum for 20 min. After 48-h incubation with the primary antibody against FRA (1 : 2,000, Young et al., 1991; Bing et al., 1996; Kim et al., 2001) at 4°C , sections were incubated with the secondary biotinylated anti-rabbit IgG (1 : 1,000; Vector Laboratories, Inc., Burlingame, CA, USA) for 1 h, and immersed in avidin-biotin-peroxidase complex (ABC Kits; Vector Laboratories, Inc.) for 1 h. 3,3'-Diaminobenzidine was used as the chromogen. Digital images of FRA-immunoreactive neurons were acquired on an Olympus microscope (Tokyo, Japan), using an attached digital microscope camera (Olympus, Tokyo, Japan) and a personal

computer. A region of interest (ROI), having an area of 0.1 mm^2 , was created using Optimas (version 6.51; Media Cybernetics, Inc., Silver Spring, MD, USA). Cell counting was performed blindly by two investigators and their results were averaged. Results are indicated as the number of FRA-immunoreactive cells/ 0.1 mm^2 .

Statistics

Data were analyzed using analysis of variance (ANOVA) and *Post-hoc* Fisher's PLSD test was followed for the comparison among groups. A *p* value less than 0.05 was deemed to be statistically significant.

RESULTS

Experimental schedules are shown in Fig. 1. Control mice showed a basal locomotor activity (Fig. 2). Locomotor activity was significantly increased immediately after the final exposure to ELF-MF in a field intensity-dependent manner, and it remains elevated 1 week later (0 hour and 1 day: Saline+0.3 or 2.4 mT vs. Saline+Control, $p < 0.05$ or $p < 0.01$; 1 week: Saline+2.4 mT vs. Saline+Control, $p < 0.05$). However, locomotor activity returned near control level 3 months after the final exposure to ELF-MF. ELF-MF-induced hyperlocomotor activity was significantly attenuated by treatment with SCH23390, a dopaminergic D1 receptor antagonist in a dose-related manner [0 hour: SCH23390 (0.1 mg/kg)+2.4 mT vs. Saline+2.4 mT, $p < 0.01$; 1 day: SCH23390 (0.03 or 0.1 mg/kg)+2.4 mT vs. Saline+2.4 mT, $p < 0.05$ or $p < 0.01$; 1 week: SCH23390 (0.1 mg/kg)+2.4 mT vs. Saline+2.4 mT, $p < 0.05$]. However, dopaminergic D2 receptor antagonist, sulpiride did not significantly alter hyperlocomotor activity induced by ELF-MF (Fig. 2).

FRA-immunoreactive cells were barely observed in the striatal complex of the control (Fig. 3 and 4). Repeated exposure to ELF-MF significantly increased FRA-IR in the striatal complex 2 hours

after the final exposure in a field intensity-dependent manner, and this FRA induction lasted for 1 year (both of striatum and nucleus accumbens at 2 hours, 1 day, 1 week, 3 months and 1 year: Saline+0.3 or 2.4 mT vs. Saline+Control, $p < 0.01$). Treatment with SCH23390 (0.1 mg/kg, i.p.) significantly attenuated the ELF-MF-induced increase in FRA-IR in the striatum [0 hour, 1 day and 1 week: SCH23390+2.4 mT vs. Saline+2.4 mT, $p < 0.01$; 3 months and 1 year: SCH23390+2.4 mT vs. Saline+2.4 mT, $p < 0.05$] and nucleus accumbens [0 hour, 1 day, 1 week and 3 months: SCH23390+2.4 mT vs. Saline+2.4 mT, $p < 0.01$; 1 year: SCH23390+2.4 mT vs. Saline+2.4 mT, $p < 0.05$], while sulpiride (20 mg/kg, i.p.) did not significantly affect FRA-IR induced by ELF-

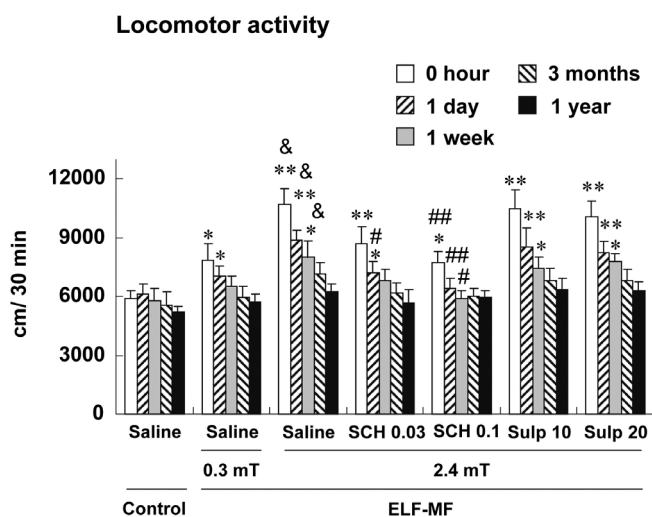


Fig. 2. Changes in locomotor activity after repeated exposure to extremely low frequency magnetic fields (ELF-MF) in the mice. Locomotor activity was measured 0 hour, 1 day, 1 week, 3 months and 1 year after the final ELF-MF exposure. SCH 0.03 or 0.1 = SCH 23390 at 0.03 or 0.1 mg/kg, i.p. Sulp 10 or 20 = sulpiride at 10 or 20 mg/kg, i.p. Each value is the mean \pm S.E.M. of 6 mice. * $p < 0.05$, ** $p < 0.01$ vs. Saline+Control, § $p < 0.05$ vs. Saline+0.3 mT ELF-MF, # $p < 0.05$, ## $p < 0.01$ vs. Saline+2.4 mT ELF-MF (One-way ANOVA followed by Fischer's PLSD test).

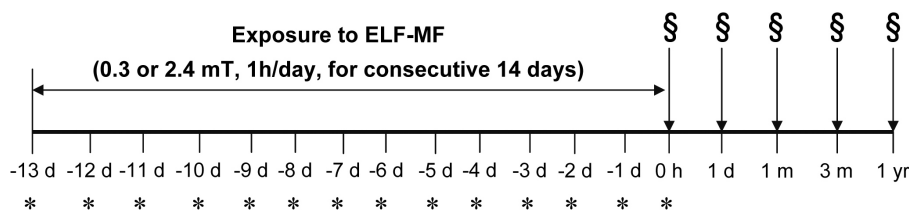


Fig. 1. Experimental schedule for evaluating effects of repeated exposure to extremely low frequency magnetic fields (ELF-MF) on the locomotor activity and fos-related antigen-immunoreactivity (FRA-IR) in the striatum and nucleus accumbens (striatal complex) of the mice. Animals were exposed to ELF-MF (0.3 or 2.4 mT, 1 hour/day) for consecutive 14 days. Thirty minutes before each exposure to ELF-MF, mice were treated with SCH23390 hydrochloride (a dopaminergic D1 antagonist; 0.03 or 0.1 mg/kg, i.p.) or sulpiride (a dopaminergic D2 antagonist; 10 or 20 mg/kg, i.p.). Locomotor activity was measured 0 hour, 1 day, 1 week, 3 months and 1 year after the final ELF-MF exposure using an automated video-tracking system. Mice were sacrificed for immunocytochemical evaluation 90 min after the measurement of locomotor activity. *SCH23390 (a dopaminergic D1 antagonist; 0.03 or 0.1 mg/kg, i.p.) or Sulpiride (a dopaminergic D2 antagonist; 10 or 20 mg/kg, i.p.) was injected 30 min prior to ELF-MF exposure. §Behavioral evaluation followed by immunocytochemical study.

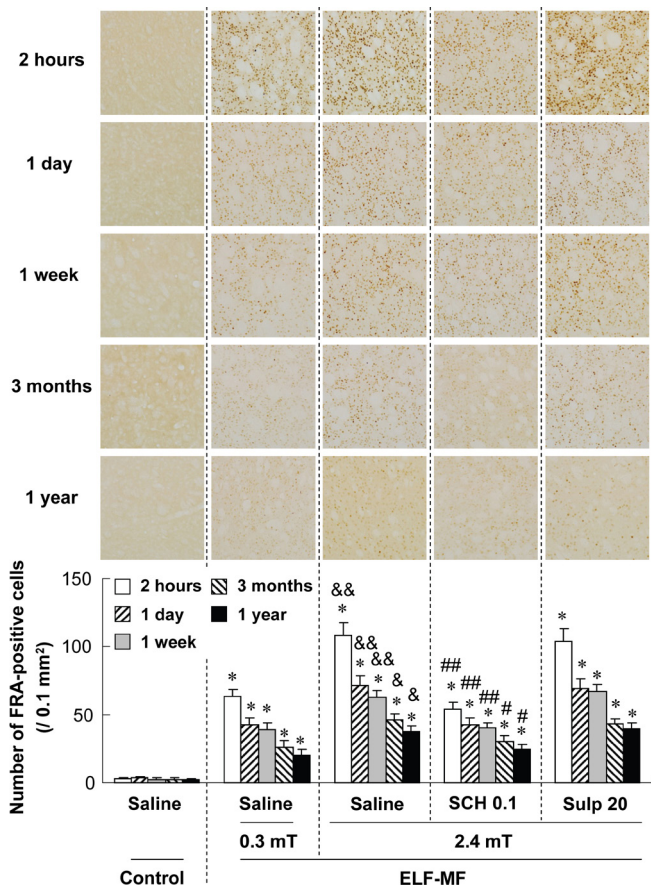


Fig. 3. Changes in fos-related antigen-immunoreactivity (FRA-IR) after repeated exposure to extremely low frequency magnetic fields (ELF-MF) in the striatum of the mice. SCH 0.1=SCH 23390 at 0.1 mg/kg, i.p. Sulp 20=sulpiride at 20 mg/kg, i.p. Each value is the mean±S.E.M. of 6 mice. *p<0.01 vs. Saline+Control, &p<0.05, &&p<0.01 vs. Saline+0.3 mT ELF-MF, #p<0.05, ##p<0.01 vs. Saline+2.4 mT ELF-MF (One-way ANOVA followed by Fischer's PLSD test).

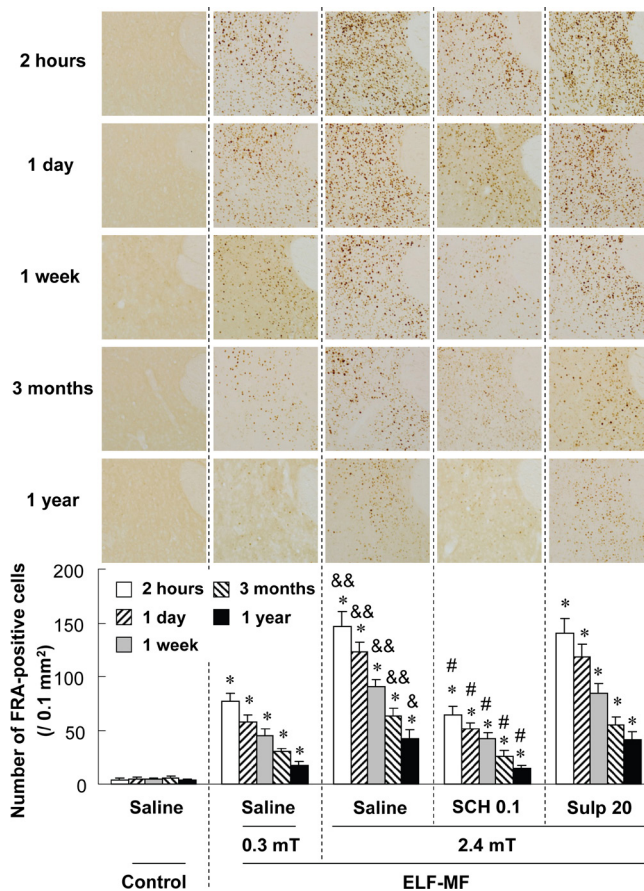


Fig. 4. Changes in fos-related antigen-immunoreactivity (FRA-IR) after repeated exposure to extremely low frequency magnetic fields (ELF-MF) in the nucleus accumbens of the mice. SCH 0.1=SCH 23390 at 0.1 mg/kg, i.p. Sulp 20=sulpiride at 20 mg/kg, i.p. Each value is the mean±S.E.M. of 6 mice. *p<0.01 vs. Saline+Control, &p<0.05, &&p<0.01 vs. Saline+0.3 mT ELF-MF, #p<0.05, ##p<0.01 vs. Saline+2.4 mT ELF-MF (One-way ANOVA followed by Fischer's PLSD test).

MF (Fig. 3 and 4).

DISCUSSION

To our knowledge, this is the first demonstration that repeated exposure to ELF-MF produces nearly permanent induction of FRA in the striatal complex *in vivo*. Elevated FRA-IR lasted for at least 1 year after final exposure to ELF-MF in the present study. A number of studies have suggested that transient and short-term expression of FRA proteins is a marker of extracellular stimuli (Nguyen et al., 1992; Bing et al., 1997b; Deutch et al., 1998), while long-term expression of FRA mediates neuronal adaptation through the persistent activation of the AP-1 binding site in the nucleus (Bing et al., 1996 and 1997b; Pennypacker et al., 2000). AP-1 binding sites are located in the promoter regions of various genes, including tyrosine hydroxylase, proenkephalin,

prodynorphin, and glial fibrillary acidic protein (Pennypacker et al., 1994; Nakashima et al., 2003). Among these genes, proenkephalin- and prodynorphin-gene expressions have shown temporal correlation with long-lasting expressions of 35-kDa FRA induced by psychostimulants (Bronstein et al., 1996; Shin et al., 2005) or kainate (Bing et al, 1997b; Kim et al., 1998). Enkephalin and dynorphin, which are derived from proenkephalin precursor and prodynorphin precursor, respectively, have been suggested to play an important role in the neuroadaptive responses related to behavioral sensitization, drug reward, drug withdrawal, or recovery of motor function via modulating post-synaptic dopaminergic receptor sensitivity or pre-synaptic dopamine release (Steiner and Gerfen, 1998; Bruijnzeel, 2009). Moreover, it has been reported that exposure to magnetic fields increases prodynorphin gene expression (Ventura et al., 2000) and regulates the activity of opioid receptors (Thomas et al., 1997). Therefore,

it may be possible that proenkephalin- and prodynorphin-genes may be involved in the neuroadaptive responses mediated by long-term FRA expression in response to ELF-MF, although the role and physiological significance of the long-term expression of FRA induced by ELF-MF remain to be further clarified.

In the present study, ELF-MF-induced long-lasting FRA expression in the striatal complex was attenuated by SCH23390, a dopaminergic D1 antagonist, but not by sulpiride, a dopaminergic D2 antagonist, suggesting that ELF-MF induces long-lasting FRA-IR via stimulation of dopaminergic D1 receptor. These results are in line with previous findings showing that direct stimulation of D1 receptor with specific agonist (Wirtshafter, 2007) or indirect stimulation of D1 receptor with psychostimulants (Young et al., 1991; Bronstein et al., 1996; Zhang et al., 2002) augments FRA expression in the striatal complex. Especially, it has been suggested that dopaminergic D1 receptor-mediated adenylate cyclase signaling pathway, but not phospholipase C pathway, is necessary for inducing FRA in the striatum (Wirtshafter, 2007). Although it is not clear how ELF-MF stimulates dopaminergic D1 receptor, it has been reported that ELF-MF exposure alters intracellular Ca^{2+} levels and facilitates releases of neurotransmitters (Blackman et al., 1991; Sandyk, 1994). Thus, there is a possibility that ELF-MF might increase dopamine release into the synaptic cleft through the modulation of Ca^{2+} influxes. In addition, elevation in dopamine level in the striatum after repeated exposure to ELF-MF has reported (Lee et al., 2001; Sieroń et al., 2004). However, Janáč et al. (2009) indicated that ELF-MF does not change the affinity and density of striatal dopaminergic receptor. In their study (Janáč et al., 2009), rats were fully exposed to ELF-MF for up to 7 days, whereas mice were exposed to ELF-MF for consecutive 14 days in our present study. Since it has been suggested that ELF-MF-induced change in neuronal activity and behaviors may be affected by exposing schedule (Lyskov et al., 1993), it requires further study to achieve better understanding on the discrepancy between Janáč et al. (2009) and current finding.

In the behavioral evaluation, locomotor activity was increased after repeated exposure to ELF-MF, and it returned near control level 3 months later. ELF-MF-induced hyperlocomotor activity was also attenuated by dopaminergic D1 antagonist, SCH23390. Although locomotor activity can not fully support time-dependent pattern in FRA in the striatal complex, we raise the possibility that FRA expression modulates, at least in part, behavioral responses to repeated ELF-MF exposure. It has been reported that induction of 35-kDa FRA is accompanied with behavioral changes during repeated treatment with psychostimulants, such as cocaine (Rosen et al., 1994; Hiroi et al., 1997) or amphetamine (Turgeon et al., 1997). Striatal expression of 35-kDa FRA and hyperlocomotor

activity after repeated treatment with cocaine or amphetamine have shown to be more pronounced than those after single injection (Hiroi et al., 1997; Turgeon et al., 1997), suggesting that 35-kDa FRA plays a key role in repeated neuronal stimulation. In addition, Hsieh et al. (2002) reported that elevated 35-kDa FRA expression, but not c-Fos expression, is sustained for at least 40 days after withdrawal from repeated amphetamine administration, while locomotor activity returned near control level 10 days after withdrawal, suggesting that 35-kDa FRA plays a certain role in neurobehavioral adaptation.

Our results suggest that repeated exposure to ELF-MF induces prolonged locomotor stimulation and long-term expression of FRA in the striatal complex via stimulation of dopaminergic D1 receptor. Finally, we raise the possibility that ELF-MF-mediated dopaminergic activations can be one of the therapeutic interventions for improving Parkinson's symptoms.

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