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Extremely low-frequency electromagnetic field exposure during chronic morphine treatment strengthens downregulation of dopamine D2 receptors in rat dorsal hippocampus after morphine withdrawal

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Abstract

The aim of this study was to investigate the effect of extremely low-frequency electromagnetic field (ELF-EMF) exposure during morphine treatment on dopamine D2 receptor (D2R) density in the rat dorsal hippocampus following withdrawal. Rats were exposed to ELF-EMF (20 Hz, 14 mT) or sham exposed for 1 h per day before injection of morphine (10 mg/kg, i.p.) once daily for 12 days. The saline control group was sham exposed for the same period. Immunohistochemistry was used to detect the density of D2Rs on the 1st, 3rd and 5th morphine withdrawal days. The results showed that the density of D2Rs in sham-exposed morphine-treated rats on the 1st and 3rd days of morphine withdrawal was significantly lower than that of the saline control group. The ELF-EMF-exposed morphine group also exhibited a significantly lower density of D2Rs on the 1st and 3rd withdrawal days relative to the sham-exposed morphine group. However, the D2R density in both groups tended to recover as morphine withdrawal days increased. The results suggest that dorsal hippocampal D2Rs are sensitive to morphine withdrawal and that this is potentiated by ELF-EMF pre-exposure during morphine treatment.

Keywords: D2 receptors; Electromagnetic field; Immunohistochemistry; Dorsal hippocampus; Morphine; Rats

Repeated opioid administration leads to tolerance, dependence and withdrawal syndrome once the drug is removed. Opiate withdrawal promotes further drug-seeking behavior by inducing an aversive subjective state [7]. This aversive state is suggested to be associated with a decrease of dopaminergic neuronal activity in the ventral tegmental area (VTA) and of dopamine D2 receptors (D2Rs) in the dorsal striatum [6,32]. Some research has shown that there is a reduction in the number of striatal D2Rs after chronic morphine treatment [20]. D2Rs in the nucleus accumbens (NAc) have been implicated in the somatic expression of naloxone-precipitated morphine withdrawal syndrome [13]. Moreover, spontaneous withdrawal from chronic morphine treatment has been reported to be associated with a down regulation of accumbens D2Rs [12].

The hippocampus has been suggested to play an important role in the reward effects of opiates [2,10,21] and in drug-seeking behavior [9,33]. Neurochemical and neuroanatomical studies have shown that the hippocampus contains all five types of dopamine receptors [14,19]. Recently, Rezayof and co-workers demonstrated that D1 and D2 receptors in the dorsal hippocampus might be involved in morphine reward [26]. A few studies

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have investigated the effects of chronic morphine treatment on D2Rs in the hippocampus but with inconsistent results. Reddy et al. found that chronic morphine treatment for 1 week, followed by a 0 h or 18 h abstinence did not alter the density of hippocampal D2Rs compared with placebo-treated controls [25]. By comparison, other investigators examining the effects of repeated morphine administration after 1 h abstinence on D2R density showed an increase [8]. Therefore, the effects of chronic morphine exposure and, especially, withdrawal on D2Rs density in the hippocampus need to be clarified.

Our previous experiments demonstrated that exposure to a 20 Hz electromagnetic field (EMF) substantially enhances and prolongs morphine-induced conditioned place preferences (CPP) during morphine withdrawal [17]. The CPP paradigm is considered to be an animal model of drug-seeking behavior [31]. Extremely low-frequency (ELF)-EMF exposure may, therefore, exacerbate the aversive state induced by morphine withdrawal and this may be associated with changes in dopamine receptor levels in the hippocampus. Chronic ELF-EMF exposure has been found to alter the function of the dopamine and serotonin systems [27,28]. Moreover, while a previous study observed that chronic ELF-EMF exposure to adult drug-naïve rats did not alter D2R density, it increased the number of μ-opioid receptors in some brain regions [35].

Therefore, in the present work, we attempted to examine whether spontaneous withdrawal is associated with an alteration of D2R density in the dorsal hippocampus after chronic morphine administration, and to investigate whether ELF-EMF combined with chronic morphine treatment strengthens the withdrawal-induced alteration of D2R density in this region.

Forty-two adult male Sprague–Dawley rats (250–280 g, 6–8 weeks old) were obtained from Kunming Medical School. Animals were adapted to housing in individual cages under controlled conditions (21–23 °C, 12 h light–12 h dark cycle) for at least 1 week before the experiment. Rats were allowed free access to food and water. Experiments were conducted in accordance with the guidelines for the National Care and Use of Animals approved by the Institutional Animal Care and Use Committee.

As described by Lei et al. previously [17], the sinusoidal electromagnetic field was generated by a single coil of four layers, each having 250 turns. Each layer was wrapped horizontally above the previous layer around a 70 cm × 40 cm × 43 cm (length × width × height) plastic frame. The coil was connected to an extremely low-frequency sinusoidal waveform generator (developed by the Bioelectromagnetic Laboratory, Institute of Electrical Engineering, Chinese Academy of Sciences, Beijing, China) for modulating the frequency and intensity of the electromagnetic field. The exposure area (60 cm × 30 cm × 43 cm, length × width × height) was inside the coil. We chose exposure parameters (20 Hz, 14 mT) according to previous studies [1,17]. During exposure, rats were placed in a non-metallic plastic box (50 cm × 25 cm × 25 cm, length × width × height), which was mechanically isolated from the magnet. The variation of the electromagnetic fields in the plastic box as determined by actual measurement was ±4.5% of the mean. The local geomagnetic field was approximately 0.038 mT. Fig. 1 shows the electromagnetic field system and the exposure area.

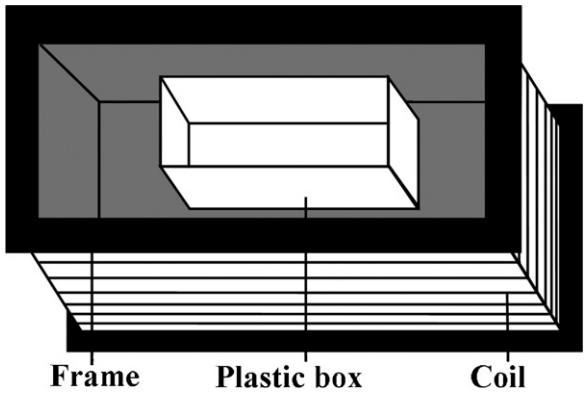

Fig. 1. Schematic diagram of electromagnetic field system and the exposure area. The coils are wrapped horizontally around the plastic frame and the inside of the coils is the exposure area. During exposure, rats were placed in a plastic box.

Rats were made morphine dependent by receiving an injection of morphine (10 mg/kg, i.p.) once daily for 12 consecutive days. This procedure has been shown to successfully produce psychological dependence of morphine [17]. Forty-two rats were randomly divided into three groups: ELF-EMF-exposed morphine group (EMF-Morph, $n = 18$), sham-exposed morphine group (Sham-Morph, $n = 18$) and sham-exposed saline control group (Sham-Sal, $n = 6$). For the EMF-Morph group, after receiving each injection of morphine, the rats were exposed to the 20 Hz electromagnetic field at a flux density of 14 mT for 1 h. The same procedure was applied to the Sham-Morph group but with no electromagnetic radiation (non-energized system); the Sham-Sal group received saline injection (0.5 ml, i.p) and no electromagnetic radiation. EMF-Morph and Sham-Morph rats were euthanized at day 1 ($n = 6$), day 3 ($n = 6$) and day 5 ($n = 6$) after morphine withdrawal. Sham-Sal rats were euthanized at day 1 after identical handling procedures as the EMF-Morph and Sham-Morph rats. Brains were immediately removed and fixed in 4% PFA in 0.1 M phosphate-buffered saline (PBS) for 48 h after the rats were euthanized. Then the dorsal hippocampus area, including the CA2 and CA1 regions approximately 3–4.3 mm posterior to Bregma [24], was verified and dissected out from the brain. Serial sections (15 μm thickness, three sections per rat) were cut on a cryostat and collected onto gelatin-coated slides and stored at −20 °C.

Sections were immunostained using a streptavidin–biotin–peroxidase technique. Each section was immersed for 15 min in 0.01 M PBS, containing 3% hydrogen peroxide to block endogenous peroxidase, and then washed three times in 0.01 M PBS and pre-incubated for 15 min in 15 μl normal goat serum. Sections were then incubated overnight at 4 °C with a 1/50 solution of mouse anti-dopamine D2 receptor polyclonal antibody (Chemicon Int.) in 0.01 M PBS. After three washes in 0.01 M PBS, they were then incubated in the second antibody (biotin-conjugated goat anti-mouse IgG diluted 1/200, Fuzhou Maixin BioTechnologies Co. Ltd., Fujian, China) for 15 min. The reaction was visualized by incubating the sections in streptavidin-peroxidase

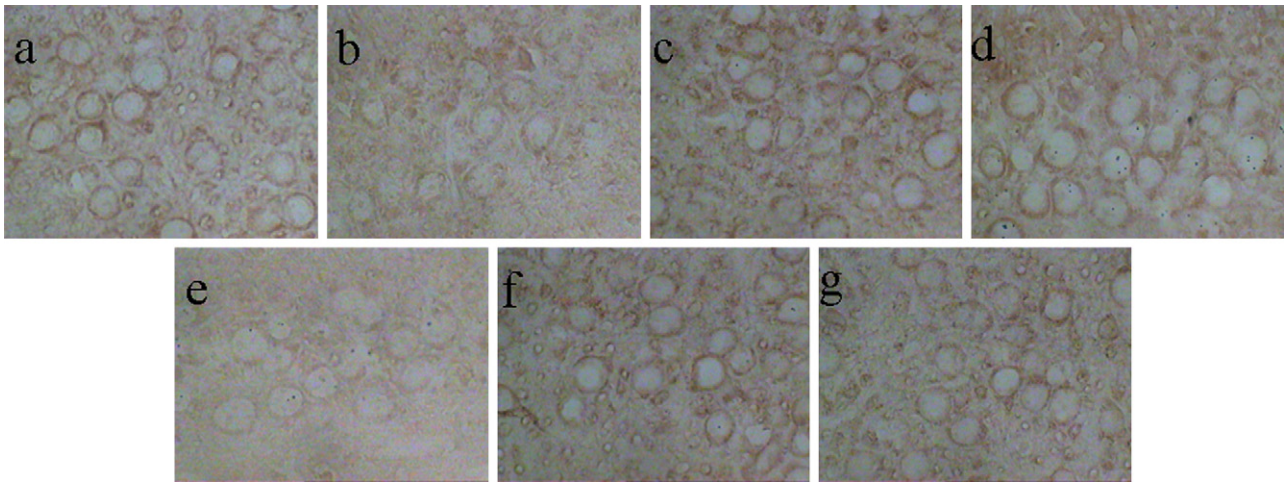

Fig. 2. Representative photomicrographs (×400) showing the expression of D2 receptors in the CA1 and CA2 of the dorsal hippocampus. (a) Sham-exposed saline group. (b–d) Sham-exposed morphine group. (b) Withdrawal 1st day. (c) Withdrawal 3rd day. (d) Withdrawal 5th day. (e–g) ELF-EMF-exposed morphine group. (e) Withdrawal 1st day. (f) Withdrawal 3rd day. (g) Withdrawal 5th day.

solution diluted 1/200 (15 μl) for 12 min. After washing in PBS three times, the tissue-bound peroxidase was developed by 3,3′-diaminobenzidine (DAB) solution (0.85 ml distilled water + 50 μl DAB buffer + 50 μl DAB substrate + 50 μl DAB chromogen, Fuzhou Maixin BioTechnologies Co. Ltd.) for 8 min. After staining, the sections were rinsed in distilled water for 3 min, and then dehydrated for a total of 20 min and coverslipped with neural gum. The specificity of the labeling was controlled by replacing the anti-dopamine D2 receptor polyclonal antibody with 0.01 M PBS in the first incubation bath. No residual immunoreactivity was found in this case.

With each section, five microscopic fields were randomly selected to analyze the positive expression of the D2Rs. The cells showing positive expression of D2Rs were viewed with an Olympus microscope and images were captured. Gray values were recorded using an HPIAS 1000 Image Analysis System (High Resolution Pathological Image & Word Analysis System) and then transformed into optical density (OD) values, representing the density of D2Rs [18].

Data are represented as the mean ± S.E.M. Comparisons between Sham-Morph and Sham-Sal groups were analyzed with between-subjects one-way ANOVA followed by post hoc Dunnett *t*-tests. For the comparison of OD values between EMF-Morph and Sham-Morph groups, two-way ANOVA was used with day and treatment as between-subjects factors. Statistical analysis was conducted using the SPSS 10.0 Statistical Package. Differences were considered significant at the level of $p < 0.05$.

Fig. 2 shows immunolabeled D2Rs in the dorsal hippocampus during withdrawal days for rats in each group. The images were analyzed using an HPIAS 1000 Image Analysis System and OD values were obtained. As shown in Fig. 3, the D2R density in the Sham-Morph group significantly reduced compared to the Sham-Sal group at 1 and 3 days after morphine withdrawal ($F_{(3, 20)} = 8.49$, $p < 0.001$. Dunnett *t*-tests: 1st day, $p < 0.001$, 62% decrease; 3rd day, $p = 0.001$, 40% decrease; 5th day, $p = 0.09$, 20% decrease). Furthermore, the D2R density was significantly reduced in the EMF-Morph group compared to the Sham-Morph group during the withdrawal period (ANOVA effect of treatment, $F_{(1, 30)} = 14.49$, $p = 0.001$; 50% reduction for 1st day, $p = 0.042$; 32% reduction for 3rd day, $p = 0.026$), but there was no significant difference on the 5th withdrawal day (independent *t* test, $p = 0.14$). The D2R density in both the EMF-Morph and Sham-Morph groups tended to normalize as withdrawal days increased (ANOVA effect of day, $F_{(2, 30)} = 39.12$, $p < 0.001$). A treatment × day interaction did not reach significance (ANOVA effect of treatment × day, $F_{(2, 30)} = 0.38$, $p = 0.69$).

In summary, the results showed that there was a marked decrease of D2Rs in the dorsal hippocampus during the early

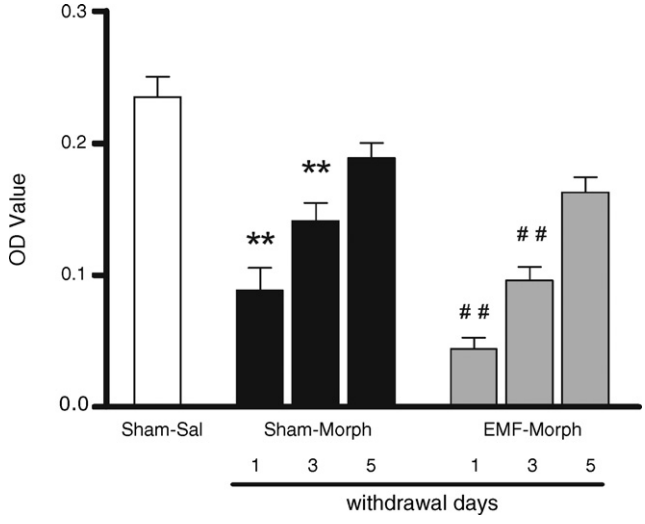

Fig. 3. Optical density (OD) values of dopamine D2 receptor expression. OD value is proportional to the density of D2 receptors. Data are represented as mean ± S.E.M. Sham-Sal: sham-exposed saline group; Sham-Morph: sham-exposed morphine group; EMF-Morph: ELF-EMF-exposed morphine group. (**) $p < 0.01$ vs. Sham-Sal; (##) $p < 0.01$ vs. Sham-Morph at the corresponding withdrawal day.

withdrawal period after chronic morphine treatment, and exposure to ELF-EMF potentiated this downregulation. In addition, the D2R density tended to normalize as morphine withdrawal days increased under the present experimental conditions.

The D2R population in the dorsal hippocampus on the 1st and 3rd days after morphine withdrawal was downregulated, but on the 5th day it had almost returned to the control level. By contrast, Reddy et al. [25] found that density of D2Rs were not changed after 18 h morphine withdrawal. Many factors may contribute to this discrepancy, including differences in technique, such as the pattern of drug administration, the daily morphine dose, the agent used for D2R binding and the length of the withdrawal period. However, based on the potential role of D2Rs in the aversive effects of morphine withdrawal [4], the results in the present work are consistent with our previous behavioral findings utilizing the CPP paradigm [31]. In that study, behavioral drug-craving faded significantly by the 5th day after morphine withdrawal, suggesting that the withdrawal effect is time-dependent.

The NAc is the main target of projections from dopaminergic neurons in the VTA [5]. Research has shown increased levels of dopamine release in the NAc during chronic morphine treatment [15,30], and decreased levels following morphine withdrawal [3,29]. Associated with these alterations in dopamine release, the expression of accumbens D2Rs is reduced during morphine dependence and returns to normal levels after withdrawal [12]. The hippocampus also receives dopaminergic afferents from the VTA [11]. Our previous electrophysiological studies provide indirect evidence for a decrease in dopamine neurotransmission following morphine withdrawal by showing that hippocampal N40 gating was normalized, and even enhanced [36]. Therefore, the recovery of D2R density over time following morphine withdrawal may compensate for an associated reduction of dopamine release in the dorsal hippocampus and could possibly play a role in preventing the aversive effects induced by withdrawal. However, the exact mechanism underlying this remains to be fully elucidated.

A number of biophysical mechanisms, such as the induced electrical fields model and the ion resonance model, have been proposed to explain the biological effects of EMF [16]. Changes in cell-surface receptors and in the level of ion binding to the membrane surface following exposure has been reported but are frequency-dependent [34]. It has been shown that 50 Hz EMF does not cause alterations of D2R density in some brain regions of drug-naïve rats [35]. However, in the present study, the combination of ELF-EMF exposure and morphine treatment resulted in a further decrease in dorsal hippocampal D2Rs compared with morphine treatment alone during the withdrawal period, and even on the 5th withdrawal day, the D2R density did not return to normal levels. To our knowledge, there are few previous studies which contrast with this result. It is unlikely to result from increased bioavailability of morphine as evidence shows that 50 Hz electromagnetic field exposure has no effect on blood–brain barrier permeability in animals [23]. Therefore, in the light of an increase of μ-opioid receptors induced by ELF-EMF exposure [35], ELF-EMF may indirectly strengthen the activity of VTA dopamine neurons that are activated by morphine and consequently enhance dopamine release in the dorsal hippocampus. In this view, it seems fitting that the hippocampal D2R density is further decreased after withdrawal when compared to morphine alone, but requires more work to confirm the hypothesis. However, it should be noted that the 20 Hz ELF-EMF at 14 mT had a weak effect for there was no difference between EMF-Morph and Sham-Morph groups on the 5th withdrawal day. The present results provide a possible neural mechanism underlying the potentiating effect of ELF-EMF exposure on morphine-induced CPP observed in our previous behavioral studies [17].

In conclusion, the present work suggests that morphine withdrawal may lead to a time-dependent decrease in the density of D2Rs in the dorsal hippocampus. These findings have implications for the possible contribution of the hippocampal dopamine system to the neuroadaptations that occur following exposure to drugs of abuse [22]. In addition, the current work is the first to explore the effects of ELF-EMF exposure during morphine treatment on dorsal hippocampal D2R density following withdrawal, indicating an involvement of ELF-EMF in the modulation of hippocampal dopamine neurotransmission during morphine treatment. However, the mechanisms by which ELF-EMF exposure exercises its biological effects remain unclear and need further study.

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