

# Effect of Extremely Low Frequency Electromagnetic Field and/or GABAB Receptors on Foot Shock-induced Aggression in Rats

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## A B S T R A C T

**Introduction:** The present study investigated the interactive effect of GABAB receptors and extremely low frequency electromagnetic field (ELF-EMF) on foot shock-induced aggression in rats.

**Methods:** fifty adult male rats were randomly assigned into 10 groups. Groups 2, 4, 6, 8 and 10 were exposed to 50 Hz, 500  $\mu$ T ELF-EMF for 30 days 8h per day while the remaining groups (1, 3, 5, 7 and 9) were sham-exposed. At the end of this period, the animals in groups 1 and 2 received normal saline while groups 3 and 4 treated with 100 mg/kg (low dose) of CGP35348 and groups 5 and 6 injected with 200 mg/kg (high dose) of CGP35348. Groups 7 and 8 treated with 1.7 mg/kg (low dose) of Baclofen and groups 9 and 10 received 3 mg/kg (high dose) Baclofen by IP injections. Twenty min after the injection, the aggressive behavior was recorded in foot shock-induced aggression model. The number of lateral threat, lifted up threat, biting, attacking, chasing and approaching were considered as paradigms of aggressive behavior.

**Results:** ELF-EMF, Baclofen or CGP35348 alone had no significant effect on aggressive behavior. Except that rats exposed and treated with low dose of CGP35348 demonstrated significantly higher numbers of only one of the paradigms of aggressive behavior (lifted up threats), CGP35348 and Baclofen in both doses in combination with ELF-EMF exposure had no significant effect on aggression.

**Discussion:** GABAB receptors and ELF-EMFs had no effect (both enhancement and suppression) on aggressive behavior of rats in foot shock-induced model of aggression.

## Key Words:

Aggressive Behavior,  
Extremely Low Frequency  
Electromagnetic Field,  
GABAB Receptors,  
Rats.

## 1. Introduction

**E**xremely low frequency electromagnetic fields (ELF-EMFs) are present wherever electric power is used. They are emitted by power lines, televisions, hair driers, cellular phones, etc. (Karasek et al., 2004).

With regard to high possibility and extent for exposure to these fields, different investigations on health effects of ELF-EMFs accomplished in recent years resulting

contradictory and controversial findings in many cases. According to WHO fact sheet published on June 2007, there are established biological effects from acute exposure at high levels (well above 100  $\mu$ T) explained by recognized biophysical mechanisms. External ELF magnetic fields induce electric fields and currents in the body which, at very high field strengths, cause nerve and muscle stimulation and changes in nerve cell excitability in the central nervous system.

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Aggressive behavior is a clinical and social problem. Central neurotransmitters play a key role in modulation of aggression in all mammalian species. Specific neurotransmitter systems involved in mammalian aggression including serotonin, dopamine, norepinephrine,  $\gamma$ -aminobutyric acid (GABA) and neuro peptides such as vasopressin and oxytocin (Yanowitch and Coccaro, 2011).

As far as we know, the role of GABAB receptors along with exposure to ELF-EMFs on aggressive behavior has not been evaluated yet.

So, in the present study, the aggressive behavior of rats exposed to 50 hertz (Hz), 500  $\mu$ T ELF-EMF alone for 30 days 8h/day or concurrent with administration of Baclofen (a GABAB agonist) and CGP35348 (a GABAB antagonist) in high and low doses was evaluated in foot shock-induced aggression model.

## 2. Methods

### 2.1. The Exposure System

The magnetic field chamber used in the present study consisted of a 70 $\times$ 120 cm wooden cage with 30 cm height. Three coils of electrically insulated 1mm copper wire with 200 turns each were wound around the outer surface at equal distance. The coils were connected in parallel and sealed with adhesive bandage. The electrical source was an autotransformer with the input of 50 Hz and 220 V. The magnetic field inside the chamber was measured at different locations using a hand held Gauss/Tesla Meter. The field was homogenous in a zone with 21 cm distance from the transverse borders and 9 cm from the longitudinal borders. The cages were located inside this zone. The strength of the ELF-EMF was 500  $\mu$ T in the homogenous zone.

### 2.2. Animals and Experimental Design

Fifty adult male Sprague-Dawley rats with a mean body weight of 200g were randomly assigned into 10 experimental groups (n=5 each). Groups 2, 4, 6, 8 and 10 were exposed to 50 Hz, 500  $\mu$ T ELF-EMF for 30 days 8h per day while the remaining groups (1, 3, 5, 7 and 9) were sham-exposed. At the end of this period, the animals in groups 1 and 2 received normal saline while animals in groups 3 and 4 treated with 100 mg/kg (low dose) of CGP35348 (Sigma-Aldrich) and animals of groups 5 and 6 injected with 200 mg/kg (high dose) of CGP35348 (doses were in accordance with those used by Sahebgharani et al., 2006). Animals of groups 7 and

8 treated with 1.7 mg/kg (low dose) of Baclofen (sigma-Aldrich) and rats in groups 9 and 10 received 3 mg/kg (high dose) Baclofen (doses borrowed from Maccioni et al., 2005). All these treatments performed by IP injections and the volume of injection kept equal for rats with equal weights.

During the experiment, the animals had free access to commercial pellets and tap water. The environmental conditions included 12h light/12h dark cycles and temperature of about 22° C. All procedures performed in this study are in accordance with institutional guidelines of School of Veterinary Medicine, Shiraz University for using laboratory animals in scientific experiments.

### 2.3. Foot-shock-induced Aggression

Twenty min after the injection of normal saline or experimental agents, each rat paired with an untreated weight matched animal were placed in an aggressometer and subjected to 2 mA foot shocks for 5 minutes by 3 seconds intervals. The aggressive behavior was recorded during the next 20 minutes. Paradigms of aggressive behavior were considered, namely number of lateral threat, lifted up on the hind paws threat, biting, attacking, chasing and approaching. The procedure was adopted from Miczek (1979).

### 2.4. Statistical Analysis

All data presented as mean $\pm$ SEM. For multiple comparisons among different groups, one-way ANOVA method and Tukey's multiple comparison test as the post hoc were used.  $p < 0.05$  was considered as the significant level.

## 3. Results

Exposing rats to ELF-EMF alone had no significant effect on aggressive behaviors and rats of group 2 had statistically the same parameters as compared to sham-exposed animals of group 1 ( $p > 0.05$ ).

Although administration of CGP35348 alone in both doses had no effect on aggressive behavior, the rats of groups 4 exposed to ELF-EMF and treated with low dose of CGP35348, demonstrated significantly higher numbers of lifted up threats compared to non-treated exposed rats ( $p = 0.011$ ) as well as sham-exposed treated rats of group 3 ( $p < 0.001$ ). Baclofen in both doses alone or in combination with ELF-EMF exposure had no significant effect on any of the above mentioned parameters in comparison with rats of groups 1 and 2 ( $p > 0.05$ ). The data are summarized in table 1.

**Table 1.** Paradigms of aggressive behavior including number of lateral threat, lifted up threat, biting, attacking, chasing and approaching (mean±SEM).

Groups Paradigm	SE+NS	E+NS	SE+LC	E+LC	SE+HC	E+HC	SE+LB	E+LB	SE+HB	E+HB
Lateral threat	<sup>a</sup> 0.4±0.4	<sup>a</sup> 0.6±0.4	<sup>a</sup> 0	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0	<sup>a</sup> 0.8±0.5	<sup>a</sup> 0	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0
Lifted up threat	<sup>a</sup> 0.6±0.4	<sup>a</sup> 0.4±0.2	<sup>a</sup> 0	<sup>b</sup> 2.8±0.9	<sup>a</sup> 0.2±0.2	<sup>a,b</sup> 1.2±0.5	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.4±0.2	<sup>a</sup> 0	<sup>a</sup> 0.2±0.2
Biting	<sup>a</sup> 0.4±0.2	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.4±0.4	<sup>a</sup> 0.4±0.2	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.6±0.2	<sup>a</sup> 0	<sup>a</sup> 0.6±0.4	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.8±0.5
Attacking	<sup>a</sup> 0.4±0.2	<sup>a</sup> 0	<sup>a</sup> 0	<sup>a</sup> 0.8±1.7	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0.4±0.4	<sup>a</sup> 0.2±0.2	<sup>a</sup> 0	<sup>a</sup> 0	<sup>a</sup> 1±0.6
Chasing	<sup>a</sup> 5.8±2	<sup>a</sup> 2.6±0.9	<sup>a</sup> 4.8±1.8	<sup>a</sup> 2.6±1.7	<sup>a</sup> 2±0.7	<sup>a</sup> 3.4±1.8	<sup>a</sup> 0.4±0.4	<sup>a</sup> 3±1.5	<sup>a</sup> 3±1.5	<sup>a</sup> 3.6±1.1
Approaching	<sup>a</sup> 4.8±1.3	<sup>a</sup> 3.8±1.5	<sup>a</sup> 4.8±0.8	<sup>a</sup> 7.6±2.2	<sup>a</sup> 2.2±0.4	<sup>a</sup> 4.8±1.5	<sup>a</sup> 3.4±1.4	<sup>a</sup> 4.8±2.8	<sup>a</sup> 3.6±0.6	<sup>a</sup> 4.2±1.5

SE: Sham-Exposed; NS: Normal Saline; LC: Low dose CGP35348; HC: High dose CGP35348; LB: Low dose Baclofen and HB: High dose Baclofen.

Different superscript letters are used to demonstrate significant difference ( $p < 0.05$ ) in a row.

#### 4. Discussion

ELF-EMFs such as those originating from residentially proximate power lines, household electrical wiring and medical devices, have been reported to produce a variety of biological effects and may interfere with the activity of the brain to generate behavioral and cognitive disturbances (Mostafa et al., 2002).

Aggressive outbursts that result in harm and injury present a major problem for the public health and criminal justice systems, but there are no adequate treatment options (Miczek et al., 2002). GABA is one of the major neurotransmitter systems implicated in the pathogenesis of aggressive behavior (Comai et al., 2012). This study aimed to evaluate the effect of ELF-EMFs accompanied by administration of GABAB agonist and antagonist on aggressive behavior in rats.

As stated previously in the text, short-term repeated exposure of rats to a 500  $\mu$ T ELF-EMF had no significant effect on aggressive behavior. Very few studies are available about the effects of ELF-EMFs on aggressive behaviors. In 1996, the influence of exposing rats to 50 Hz, 46 mT ELF-EMF was evaluated by Lyskov et al. In Lyskov study, it was declared that the exposure to the field decreases aggression and sociability in rats which is dependent on the level of DC field. St-Pierre et al., (1998), demonstrated that group aggression in rats can be increased or decreased as a function of the temporal characteristics and morphology (shape) of the applied magnetic field. In general, it seems that different factors such as the strength of the field and/or duration of exposure may play a role in the final outcome, which may explain the controversies observed in above mentioned studies.

The results of the studies about the effect of GABAB receptors on aggressive behavior are inconsistent and contradictory, too. Rudissaar et al. (2000) observed that IP administration of Baclofen (8 mg/kg) attenuates the apomorphine-induced aggressive behavior in rats. Takahashi et al. (2010) demonstrated that pharmacological activation of GABAB, but not GABAA receptors in the dorsal raphé nucleus increases aggressive behaviors in resident-intruder test in male mice. Two years later (2012), Takahashi group showed that to increase aggression by Baclofen, specific stimulation (male intruder) and tonic level of serotonin (dark cycle) are required (Takahashi et al., 2012). In our study, IP administration of GABAB agonist or antagonist in both doses had no significant effect on aggressive behavior on foot shock-induced aggression in rats. The discrepancies may be related to the use of different models of aggression, different route of administration or even different doses of the same drug when used by the same route (1.7 or 3 mg/kg in the present study vs. 8 mg/kg of Baclofen in the study performed by Rudissaar et al.).

In our study, Baclofen in both doses in combination with ELF-EMF exposure had no significant effect on aggression. This was also true about CGP35348, except that rats exposed to ELF-EMF and treated with low dose of CGP35348, demonstrated significantly higher numbers of only one of the paradigms of aggressive behavior (lifted up threats) compared to non-treated exposed rats as well as sham-exposed treated rats. Regarding the diversity of paradigms used to evaluate the aggressive behavior in this study, a change in one of them may not be considered biologically significant. Since there is little information about the combined effects of ELF-EMFs and GABAergic system on aggressive behavior, we can-

not compare our results with the previous works and this subject needs to be more clarified in future studies.

In conclusion, we demonstrated that GABAB receptors and ELF-EMFs have no effect (both enhancement and suppression) on aggressive behavior of rats in foot shock-induced model of aggression.

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