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RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

The effects of typical and atypical antipsychotics on the electrical activity of the brain in a rat model

Rat modelinde tipik ve atipik antipsikotik ilaçların beyin elektriksel aktivitesi üzerine etkileri

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ABSTRACT

Objective: Antipsychotic drugs are known to have strong effect on the bioelectric activity in the brain. However, some studies addressing the changes on electroencephalography (EEG) caused by typical and atypical antipsychotic drugs are conflicting. We aimed to compare the effects of typical and atypical antipsychotics on the electrical activity in the brain via EEG recordings in a rat model.

Methods: Thirty-two Sprague Dawley adult male rats were used in the study. The rats were divided into five groups, randomly (n=7, for each group). The first group was used as control group and administered 1 ml/kg saline intraperitoneally (IP). Haloperidol (1 mg/kg) (group 2), chlorpromazine (5 mg/kg) (group 3), olanzapine (1 mg/kg) (group 4), ziprasidone (1 mg/ kg) (group 5) were injected IP for five consecutive days. Then, EEG recordings of each group were taken for 30 minutes.

Results: The percentages of delta and theta waves in haloperidol, chlorpromazine, olanzapine and ziprasidone groups were found to have a highly significant difference compared with the saline administration group ($p<0.001$). The theta waves in the olanzapine and ziprasidone groups were increased compared with haloperidol and chlorpromazine groups ($p<0.05$).

Conclusion: The typical and atypical antipsychotic drugs may be risk factor for EEG abnormalities. This study shows that antipsychotic drugs should be used with caution. *J Clin Exp Invest 2013; 4 (3): 279-284*

Key words: Haloperidol, chlorpromazine, olanzapine, ziprasidone, EEG, rat

ÖZET

Amaç: Antipsikotik ilaçların beyinde güçlü biyoelektrik aktivite etkilerinin olduğu bilinmektedir. Fakat tipik ve atipik antipsikotik ilaçlara bağlı olan elektroensefalografi (EEG) değişikliklerinin karşılaştırmalı çalışmaları tartışmalıdır. Biz bir rat modelinde tipik ve atipik antipsikotik ilaçların beyinde elektriksel aktivitesi üzerine olan etkilerini EEG ile karşılaştırmayı amaçladık.

Yöntemler: Bu çalışmada, 35 adet erişkin erkek Sprague Dawley cinsi rat kullanıldı. Herbiri 7 adet rat içeren 5 adet grup oluşturuldu. Birinci grup kontrol grubu olarak kullanıldı ve intraperitoneal yolla 1 ml/kg salin verildi. Beş gün boyunca intraperitoneal olarak haloperidol (1 mg/kg) (grup 2), klorpromazin (5 mg/kg) (grup 3), olanzapin (1 mg/kg) (grup 4) ve ziprasidon (1 mg/kg) (grup 5) verildi. Beşinci günün sonunda bütün grupların 30 dakika EEG kaydı alındı.

Bulgular: Haloperidol, klorpromazin, olanzapin ve ziprasidon gruplarında delta ve teta dalga yüzdelerinin salin verilen gruba göre anlamlı düzeyde yüksek olduğu görüldü ($p<0.001$). Olanzapin ve ziprosidon gruplarındaki teta dalgaları haloperidol ve klorpromazin grubuyla karşılaştırıldığında anlamlı düzeyde artmış olarak saptandı ($p<0,05$).

Sonuç: Olanzapin ve ziprasidon tipik antipsikotik ilaçlara göre EEG de daha az yavaş aktiviteye neden olabilir. Bu çalışma antipsikotik ilaçlarin dikkatli kullanılması gerektiğini gösteriyor.

Anahtar kelimeler: Haloperidol, klorpromazin, olanzapin, ziprasidon, EEG, rat

INTRODUCTION

Antipsychotic drugs are more often used in the treatment of psychosis, impulse control disorders and other psychiatric conditions [1,2].

First-generation antipsychotics (FGAs) such as haloperidol, chlorpromazine are lipophilic and having high protein and large volumes of distribution. In addition, they have role in severe problems such as reducing thinking, mood and behavior [3]. The typical agents often lead to extrapyramidal side effects including rigidity, bradykinesia, tremor, akathisia, and tardive dyskinesia [4]. Therefore, typical agents have more side effects than the second-generation

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antipsychotics (SGAs) such as olanzapine, ziprasidone. Besides, the general belief is that the SGAs are effective in terms of efficacy and safety in treatment of psychiatric disease [5]. There has not been many studies available comparing the adverse effects of antipsychotics in the brain. Some studies have reported that risk of epileptic seizure depending on the effect of antipsychotics in patients [6,7].

Electroencephalography (EEG) was introduced to study brain dysfunction. It is the gold standard for the diagnosis and treatment of epilepsy [9]. EEG not only provides information about epileptic activity but also generates rhythmic activity in several frequency ranges [10,11,15,16]. In previous studies, it was determined that EEG abnormalities have been found in schizophrenia and manic patients [17]. The antipsychotics are known to have a strong influence on the bioelectric activity in the brain [11]. EEG abnormalities during antipsychotic treatment are common and are also particularly dose-dependent [12,13]. Spectral analysis is a representation of the signal's amplitude as a function of frequency. Power spectral analysis (PSA) is one of the standard methods used for the quantification of EEG. The PSA can be used to accurately measure the frequency content and distribution of power over the frequencies [14]. It was found in approximately 10% of the cases on usage antipsychotic drugs that epileptic activity such as spikes, poly-spikes, and spike-wave complexes increased in slow-wave activity and high-voltage theta-delta groups.

Antipsychotics treatment is a risk factor for epilepsy. Epilepsy is a high risk factor for subsequent cognitive impairment, especially for early onset of seizures. Due to the treatment affects both the direct and indirect thresholds for epilepsy and cognitive functions, it is important that limited usage the antipsychotic drugs. Drugs to be used in schizophrenia patients with cognitive impairments should have the least negative effects on cognitive performance [4]. Despite the high utilization of EEG in psychotic patients with seizures, few studies examined the relationship between brain rhythms, as measured by EEG, and compared the effects of typical and atypical antipsychotics on the brain. In the study, we aimed to evaluate PSA using EEG in the treatment of typical and atypical antipsychotics on experimental rat models.

METHODS

The study was performed at the Electrophysiology Research Laboratory of the Department of Physiology, Faculty of Medicine, Ege University after obtaining Animal Ethics Committee approval. Thirty-five male Sprague Dawley rats at 8 weeks, weighing 450-500 g, were used for the study. The animals were fed ad libitum and housed in pairs in steel cages having a temperature-controlled environment (22±2°C) with 12-h light/dark cycles. The experimental procedures were approved by the Committee for Animal Research. All animal studies strictly conformed to the animal experiment guidelines of the Committee for Humane Care. Rats were anesthetized by combination of ketamine hydrochloride at a dose of 40 mg/kg (Alfamine®, Ege Vet, Alfasan International B.V. Holland) and 4 mg/kg of xylazine hydrochloric (Alfazyne®, Ege Vet, Alfasan International B.V. Holland) which was administered intraperitoneally (IP). One week before testing, the rats implanted, under anesthesia, with the outer parts of the isolated bipolar EEG electrodes (100 µm diameter) were placed in the basolateral amygdala with coordinates AP=2.8 mm, L=4.8 mm and V=8.5 mm (Paxinos). The electrodes were fixed in cranium using cold acrylic (numerous alloys are used in the making of dental restorations). The rats were divided randomly into five groups. The first group was used as control group and administered1 mL/kg saline. Haloperidol (1 mg/kg) (group 2), chlorpromazine (5 mg/kg) (group 3), olanzapine (1 mg/kg) (group 4), ziprasidone (1 mg/kg) (group 5) were injected IP for five consecutive days. Then, EEG recording of each group was taken 30 minutes. EEG recordings were taken in the range of 1-60 Hz band with 10.000 fold amplification. Recordings were taken by a Biopac MP30 amplifier and evaluated by PSA method. Delta waves=1-4 Hz, theta waves=4-8 Hz, alpha waves=8-12 Hz, beta waves=12-20 Hz were accepted and a percentage of the waves are evaluated in the EEG.

Statistical Analysis

Data analyses were performed using Statistical Package for the Social Sciences version 15.0 for windows (SPSS Inc., Chicago, IL, USA) statistical package program. The groups of parametric variables were compared by Student's t-test and analysis of variance (ANOVA). The groups of nonparametric variables were compared by Mann Whitney U test. Shapiro-Wilk test was used to parametric-nonparametric differentiation. Results were given as mean±standard error of mean (SEM). A value of $p<0.05$ was accepted as statistically significant. $p<0.001$ was accepted as statistically highly significant.

RESULTS

The percentages of delta waves in groups including haloperidol, chlorpromazine, olanzapine, and ziprasidone were highly significant difference comparison to control group ($p<0.001$) (Figure 1). Increased delta waves in fourth and fifth groups were lower than second and third groups ($p<0.05$).

The percentages of theta waves in the second, third, fourth and fifth groups were significantly decreased compared with control group ($p<0.001$) (Figure 2). The decreased theta waves in fourth and fifth groups were lower than the chlorpromazine group ($p<0.05$).

The percentages of alpha waves in haloperidol, chlorpromazine, olanzapine and ziprasidone groups were significantly different compared with the control group ($p<0.001$) (Figure 3). The alpha waves in olanzapine and ziprasidone groups were decreased compared with haloperidol and chlorpromazine groups ($p<0.05$).

The beta waves were significantly increased in haloperidol, chlorpromazine and olanzapine groups compared with control group ($p<0.05$) (Figure 4). There were no significant differences in the ziprasidone group compared with the control group.

Table 1. The percentages of delta, theta, alpha and beta waves in groups.

Groups	Delta waves	Theta waves	Alpha waves	Beta waves
Controls	5.77±1.12	85.55±2.77	2±0.52	2.11±1.11
Haloperidol group	21.22 ± 2.78**	54.11 ± 5.50**	10.11 ± 1.61*	6.66 ± 0.89*
Chlorpromazine group	22.88±2.13**	52.33±5.08**	9.66±1.46**	7.11±1.34*
Olanzapine group	15.33±2.67**	69.33±4.95**	6.55±1.11*	7.77±2.50*
Ziprasidone group	16.44±1.90**	67.33±3.22**	5.94±0.99*	3.5±0.82

*p<0.05 compared with control group, **p<0.001 compared with control group

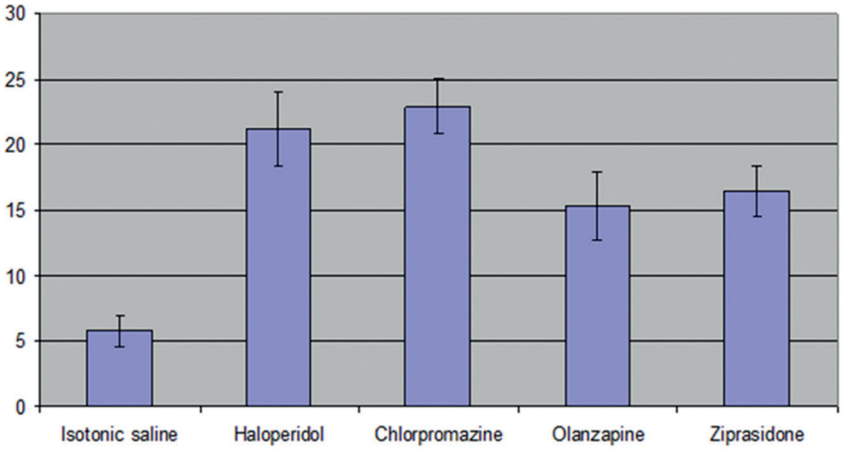

Figure 1. The analysis of power spectral ratio (percentages) of delta wave in basolateral amygdala

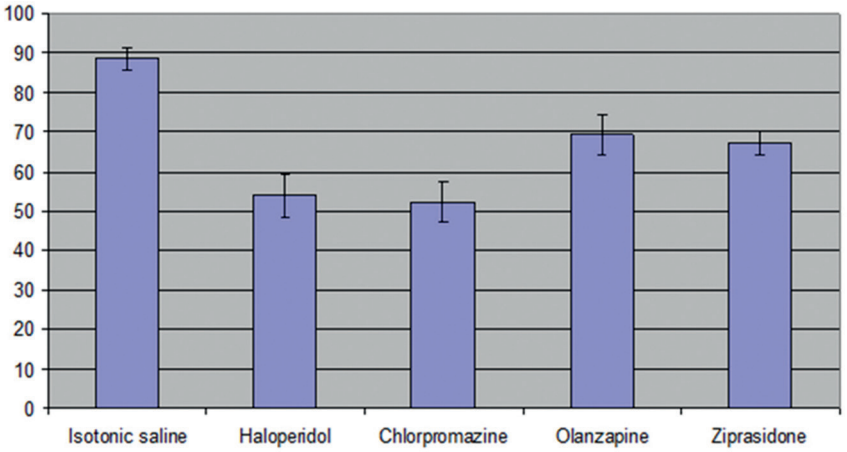

Figure 2. The analysis of power spectral ratio (percentages) of theta wave in basolateral amygdala

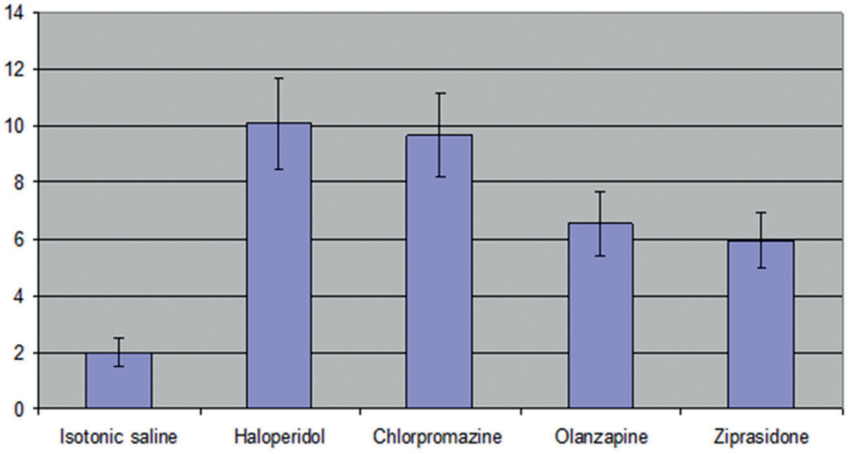

Figure 3. The analysis of power spectral ratio (percentages) of alpha wave in basolateral amygdala

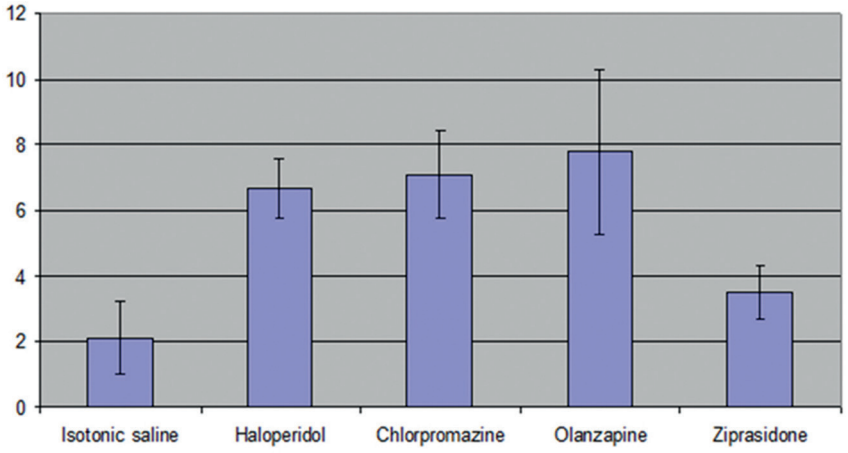

Figure 4. The analysis of power spectral ratio (percentages) of beta wave in basolateral amygdala

DISCUSSION

EEG abnormalities may be more common with typical antipsychotics than with atypical antipsychotics. In the current study, both typical and atypical antipsychotics drugs have been demonstrated to change the EEG rhythm; and contrary to popular belief, atypical antipsychotics drugs change the EEG rhythm less than typical antipsychotics drugs [21,22]. We investigated the changes caused by four different antipsychotic drugs on EEG. We used drugs such as chlorpromazine and ziprasidone, which have unknown effects on EEG, exactly.

An animal experimental model was used in the study because of the criticism received by previous studies conducted on human subjects for not comparing pre- and post-treatment EEG, not considering the stage of the disease, and not investigating the drug levels in the blood. A remarkable EEG slowing was observed when the drugs reached a stable blood plasma concentration [14,22]. Slow waves were found to occur less with olanzapine, unlike in previous studies, and ziprasidone. Olanzapine might have caused fewer slow waves on EEG compared to typical neuroleptic drugs in our study due to the use of healthy animals instead of patients [23]. In other words, there are methodological differences between this study and previous studies in the literature.

High drug dosages, co-morbidity, and the use of multiple drugs in combination were all implicated in causing epileptic seizures related to antipsychotics. For example, in one case, epileptic seizures developed during transition from haloperidol to olanzapine. The changes in EEGs caused by antipsychotics are correlated with the concentrations of the drugs in the blood and to their anticholinergic features [24]. The authors reported that EEG abnormality risk may vary widely among antipsychotics. However, it is reported that antipsychotics not only cause changes on EEGs, but can also cause epileptic seizures and affect cognitive functions causing sleep disturbance [20,25]. Gunther et al. reported that clozapine caused both EEG abnormalities and epileptic seizures more often compared to neuroleptics [13].

It was recommended that the dose of antipsychotics be adjusted based on the extent of EEG slowing and the drug levels in the blood. However, EEG slowing occurs with most antipsychotics and after electroconvulsive therapy patients with psychosis, without causing seizures, which suggests that the therapeutics provide benefits to the patients by slowing down the electrical activity. Therefore, incomplete EEG slowing does not seem desirable [26,27]. Nevertheless, any EEG abnormalities were observed for any of the 12 patients treated with quetiapine in a study by Wetzel et al., which demonstrates that antipsychotics do not provide benefits solely when EEG slowing occurs [22]. Antipsychotics are known to have strong effects on bioelectric activity in the brain and to cause changes on EEG. However, comparative studies of changes on EEG caused by typical and atypical antipsychotics are still insufficient. It was reported that treatment of clozapine caused slowed down the EEG in half of the patients, and epileptiform disorders occurred in more than 10% of the patients [18,19]. Although quetiapine chemically resembles clozapine, it is less effective on EEG [18]. Olanzapine, another atypical antipsychotic, is also reported to cause EEG slowdown to a lesser extent compared to clozapine [19].

Previous studies showed that EEG abnormalities and seizures were more common with atypical antipsychotics than with typical antipsychotics [20]. Despite the importance of the current findings, a limitation must be mentioned. The effects of antipsychotics on the brain cannot be evaluated based solely on the slowing of electrical activity observed using EEG, and cognitive tests should also be used in combination with EEG. Non-comparison of the groups with cognitive tests may be considered as a weakness of this study. Here, conducting tests aimed at understanding whether antipsychotics cause cognitive impairment in rats would have been better. However, while the conduct of existing clinical studies on patients with psychosis and despite the fact that the changes in EEG may be due to both the effects of the psychosis and the antipsychotics are the shortcomings of this study, our study aimed to experimentally observe potential changes on healthy individuals and rats following administration of antipsychotics to normal rats.

In conclusion, these data obtained from this study suggested that most slow waves on EEG were in the haloperidol and chlorpromazine groups. The present data justifies carefully-controlled treatment with antipsychotic drugs. The typical and atypical antipsychotic drugs may be risk factor for EEG abnormalities. This study shows that antipsychotic drugs should be used with caution.

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