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Original Article

Antimuscarinic-Induced Convulsions in Fasted Rats after Food Intake: EEG Patterns of Fasting, Scopolamine Treatment, and Convulsions

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Abstract

Objective: Antimuscarinic treatment in fasted mice and rats causes clonic convulsion soon after food intake. This study was designed to evaluate the electrophysiological markers of these convulsions and fasting in electrocorticograms in rats.

Methods: Male Wistar albino rats were stereotaxically implanted with 10 cortical electrodes, and baseline electroencephalogram recordings were taken for 10 minutes. After weighing, rats were deprived of food for 52 hours. At the 24th and 52nd hours of deprivation, continuous electroencephalogram recordings were repeated. After the deprivation period, animals were treated with saline or scopolamine (3 mg/kg). Twenty minutes after injections, animals were given food pellets. After eating food, electroencephalogram recordings were taken for 60 minutes and all animals were observed simultaneously to determine the incidence and onset of convulsions.

Results: These results show that food deprivation for 52 hours decreased the amplitude of the gamma band when compared to basal (P <.05) and 24 hours (P <.008) food deprivation. And the amplitude of the beta band in the 52nd hour decreased when compared to the 24th hour of food deprivation (P <.05). The treatment with scopolamine changes the effects of food deprivation on the electroencephalogram. As a typical epileptiform manifestation, refeeding after scopolamine treatment caused a series of high-voltage polyspikes and synchronized spikes with a predominant frequency in the 1-3 Hz range.

Conclusions: It was revealed that the behavioral patterns of rats and the electroencephalogram properties in these convulsions are in accordance with each other.

Keywords: Antimuscarinic, convulsion, EEG, fasting, rat

INTRODUCTION

Fasted mice and rats, treated with antimuscarinic drugs such as atropine and scopolamine, develop convulsion soon after food intake.[1-3] Deprivation for 6, 12, 18, and 24 hours causes these convulsions in antimuscarinic treated and refed mice and rats.[4,5] These findings suggest that the food deprivation itself causes convulsions but not the duration of the fasting period or weight loss. Hypoglycemia does not contribute to the occurrence of these convulsions because prevention of hypoglycemia development by water containing glucose intake during fasting has no preventive effect on the development of convulsions.[6,7] Refeeding with solid food eating induces convulsions while liquid food intake orally or gastric gavage does not cause convulsions.[8] It could be argued that antimuscarinic treatment and refeeding with solid food have essential roles in the occurrences of these convulsions. These convulsions could not be suppressed with conventional and new antiepileptic drugs.[9] In addition to these findings, it was shown that pretreatments with MK-801 (noncompetitive *N*-methyl-D-aspartate antagonist), clonidine and tizanidine (alfa-2 agonists), chlorpromazine, and haloperidol (dopaminergic antagonists) prevent or suppress these antimuscarinic-induced convulsions in mice and rats.[6,7,10]

[3*H*]glutamate-binding kinetics in the brain change when animals are deprived of food for 48 hours,[6] also M1 and M2 receptors increase in the frontal cortex and hippocampus, respectively, at the fasting period.[11] These findings indicate that neuroadaptive changes occur when animals are fasted. However, both mice and rats that are two different species of rodents, treated with antimuscarinic drugs after fasting, develop clonic convulsions soon after refeeding, the characteristics of the seizure stages differ somewhat between mice and rats. Gustatory movements and forelimb clonus are more profound in mice, whereas buccal movements with opening the mouth and putting out the tongue are being strongly marked in rats.

Neck spasms with head in backward position and tonic activity of trunk are also clearly observed seizure stages in rats. On the other hand, rats, but not mice, exhibit repetitive myoclonus of hindlimbs starting before or after food intake. An interesting point of these differences was that some rats in the saline given control group developed stage 1 and stage 2 activities with tongue protrusion and neck spasm after food intake.[2]

The electroencephalogram (EEG) patterns of seizures in experimental models correlate with paroxysmal, stereotypical behavior.[12] With cortical electroencephalography recordings, typical epileptiform discharges were shown in mice with antimuscarinic-induced convulsions.[13] But, the electroencephalographic properties of antimuscarinic-induced convulsions in fasted rats were not described yet. EEG findings of eating epilepsy have been investigated in humans and animals. Seizures triggered by food intake and EEG patterns vary between patients.[14,15] Although scopolamine-induced convulsions are known to be triggered with solid food intake, the changes in food deprivation and effects of refeeding on EEG were not defined either. In the light of the above-mentioned information, this study was designed to evaluate electroencephalographic patterns of antimuscarinic-induced convulsions in fasted rats after food intake.

METHODS

Animals

Inbred male Wistar albino rats weighing 250-300 g (n = 20) were used in this study. All animals were housed under standard laboratory conditions for at least 7 days until the experiment. They were allowed to access food and water *ad libitum*. All studies were approved by Marmara University's Animal Experiment Local Ethics Committee (32.2002.mar) and in accordance with the guidelines outlined in Interdisciplinary Principles and Guidelines for the Use of Animals in Research and Education from the New York Academy of Sciences.

Electrode Implantation

Rats were anesthetized with thiopental sodium (50 mg/kg i.p) and placed in a stereotaxic instrument. The handmade EEG electrodes were constructed from insulated stainless steel wire (200 μm diameter) with insulation removed at the end to form the contact. Ten holes were drilled through the skull, and bilaterally electrodes were placed to contact the dura of the frontoparietal (FP1-2), frontal (F1-2), central (C1-2), parietal (P1-2), and occipital (O1-2) locations referenced to an electrode implanted over the cerebellum. Electrodes were fixed on the skull with dental acrylic cement. After electrode implantation ceftriaxone (75 mg/kg, i.m.), as an antibiotic agent, was given for one dose.

EEG Recordings

The experiment was performed 8 days after the operation. All rats were individually placed in a plexiglass EEG recording cage. Continuous EEG recordings were taken for 10 minutes with neuroscan (SynAmps Model 5083, USA) from all rats. A control EEG sample was recorded as a baseline value before the experiments. These records were used to compare all subsequent EEG recordings for each animal. All animals were observed during the EEG recording session.

EEG signals were recorded with a bandpass of 0.30-70 Hz digitally with a sampling frequency of 1000 Hz. After giving foods, EEG was recorded for 60 minutes, properties of EEG were specified, and power spectrum analyses were made for different stages. The frequency band of 0-3.4 Hz was expressed as delta, 3.5-7.4 Hz as theta, 7.5-12.4 Hz as alpha, 12.5-20.4 Hz as beta, and 20.5-45 Hz as gamma.

Experimental Groups

Baseline EEG recordings were taken from all animals on the 8th day after the operation. A group of rats (n = 6) were moved to clean cages, administered with scopolamine (3 mg/kg i.p.), and allowed to eat. Twenty minutes after injections, 10 minutes of EEG recordings were retaken.

Another group of animals (n = 14) were deprived of food for 52 hours after baseline recordings. EEG recordings were retaken at the 24th and 52nd hours of their food deprivation periods. After 52 hours, animals were treated with saline (n = 6) or scopolamine (n = 8) and were given food pellets 20 minutes later. All animals had free access to water during the fasting period. The experimental design of the study is shown in Figure 1.

Evaluation of Scopolamine-Induced Convulsions in Fasted Rats

EEG recordings of scopolamine-treated fasted rats were taken simultaneously for 60 minutes. During this time, all animals were observed to determine the incidence and onset of convulsions. Stages of seizure activity are scaled as: (stage 0) no difference; (stage 1) freezing; (stage 2) tongue protrusion and neck spasms; (stage2+) repeated (at least 2 times) buccal movements with opening the mouth and putting out the tongue with neck spasms; (stage 3) forelimb clonus; (stage 4) forelimb clonus and tonic activity in the upper part of the body with rearing and/or falling; (stage 5) generalized convulsions with rearing, falling, and jumping.[2] The animals were also observed for myoclonus of hindlimbs. Stages 2+, 3, 4, and 5 were assessed as a convulsive response, and incidence of convulsions was expressed as the percentage of animals displaying either stage 2+, 3, 4, or 5 activity. The onset of convulsions was defined as the time passed before an animal displays stage 2+ activity after starting to eat.

All experiments were carried out between 12:00 PM and 3:00 PM in a temperature-controlled (21 ± 2ºC) quiet room. Observers were blind to the treatments.

Drugs

Scopolamine hydrobromide (Sigma, St. Louis, Mo, USA), thiopental sodium (Sigma), and ceftriaxone (Ibrahim Ethem Ulagay) were used in this study. Scopolamine and thiopental sodium were dissolved in saline and given intraperitoneally (i.p.) in a volume of 3 mL/kg body weight. Ceftriaxone was dissolved in 1% lidocaine and given intramuscularly in a volume of 2 mL/kg body weight.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 20.0. (IBM SPSS Corp.; Armonk, NY, USA) Fisher's exact test (n < 20) was used to evaluate the frequency of the incidence of convulsions. The onset of convulsions was evaluated with Student's *t*-test. Continuous EEG recordings were divided into 2-second epochs and epochs with movement artifacts (i.e., exceeding 500 μV) and were extracted automatically. Then epochs were analyzed by averaged frequency spectra. The part from 0 to 52 Hz was normalized (was equalized to 100). Moving averages were calculated for 5 points. A repeated-measures analysis of variance followed by the Bonferroni test was used for the evaluation of frequency bands in fasted rats. A series of point-to-point two-tail paired Student's *t*-test was applied for each channel for the values of basal and for the values that were recorded at the 24th and 52nd hours of fasting and scopolamine treatments. A *P*-value less than.05 was considered statistically significant.

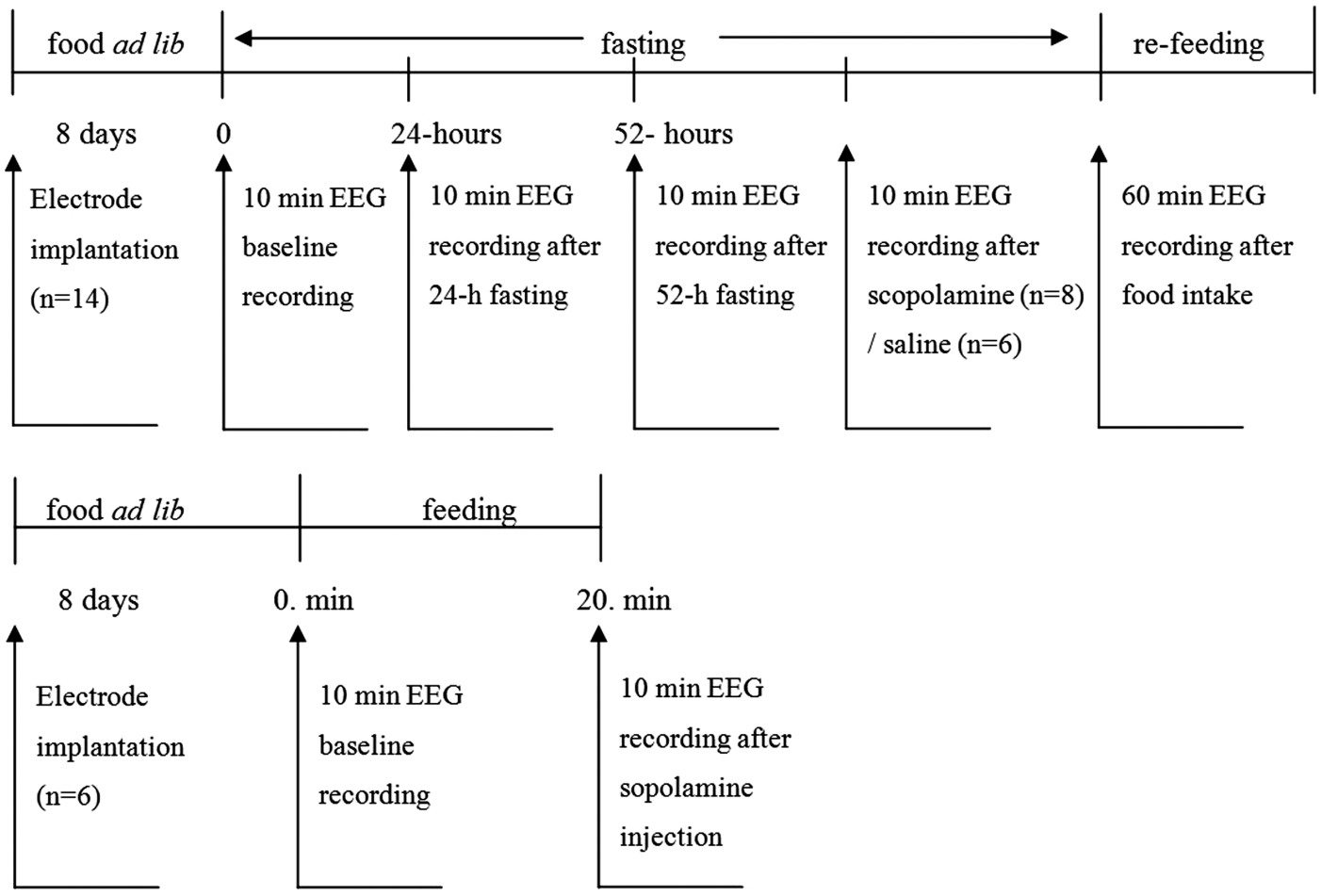

Figure 1 Schematic flowchart of the experimental design.

RESULTS

After fasting for 24 and 52 hours, the body weights of the rats fell to approximately 95% and 89% of the initial body weights, respectively. All channel comparisons between consecutive recordings of fasted rats showed a difference in gamma ($F(2,26) = 7.194$, $P < .005$) and beta ($F(2,26) = 4.767$, $P < .02$) frequency bands. There was a significant decrease in the gamma band in recordings of the 52nd-hour fasted rats when compared to basal recordings ($P < .05$) and 24th-hour EEG recordings ($P < .008$). Beta frequency band of fasted rats in the 52nd hour was significantly lower than the 24th hour recording ($P < .05$). The changes of the amplitudes in the frequency bands in basal, 24th, and 52nd hour fasted rats could be seen in Figure 2.

Figure 3 presents the EEG findings in fasted rats. In order to show clearly the changes between basal and 24 hours of fasting data, differenced moving average amplitude spectra, that is. 24 hours of fasting-basal, were used. The amplitudes of 6.8-15 Hz increased in FP2, F1-2, C1, P1-2, and O1 locations.

Figure 4 shows the differences in EEG findings between 52 hours of fasting and 24 hours of fasting in all fasted rats. The amplitudes of 1.5-6.5 Hz bands were significantly decreased in F1, C2, P1, and O1 localizations. The amplitudes of 7.3-17 Hz bands were significantly increased in FP1-2, F1-2, C1-2, and P1-2 localizations, while the amplitudes of 23-45 Hz bands were significantly decreased in FP2, F2, C1, P1-2, and O2 localizations.

Figure 5 shows the differences in EEG findings between saline administrations and 52 hours of fasting in the control group. The amplitudes of 1.9-4.8 Hz bands were significantly decreased in F1 and C1 localizations. While the amplitudes of 9.7-15.1 Hz bands were significantly decreased in FP1-2, F1, C1, and P1-P2 localizations, the amplitudes of 20-45 Hz bands were significantly increased in FP1-2, F2, C1, P1, and O2 localizations.

Figure 6 presents the differences in EEG findings between scopolamine administrations and 52 hours of fasting in the scopolamine treatment group. Scopolamine administration was induced an increase in the amplitudes of 0-3 Hz bands, only in F1 localization. The amplitudes of 5-7.5 Hz bands were significantly increased in almost all localizations except F1 localization. The amplitudes of 9.2-13.1 Hz bands were significantly decreased in C1-2 and P2 localizations. The amplitudes of 18-19.5 Hz bands were significantly decreased only in F1 localization and the amplitudes of 22-38 Hz bands were significantly decreased in F1, C1-2, P1, and O2 localizations.

Figure 7 shows the differences in EEG findings between scopolamine treatment and basal value in the fed group. The amplitudes of 0.4-3.4 Hz bands were significantly increased in FP1-2, F1, C1, P1, and O2 localizations. The amplitudes of 5.8-7.4 Hz bands were significantly increased in FP1-2, F1, C1-2, P1-2, and O2 localizations, and the amplitudes of 7.5-13.2 Hz bands were significantly increased in FP1-2, F1, C1-2, P1, and O2 localizations. While the amplitudes of

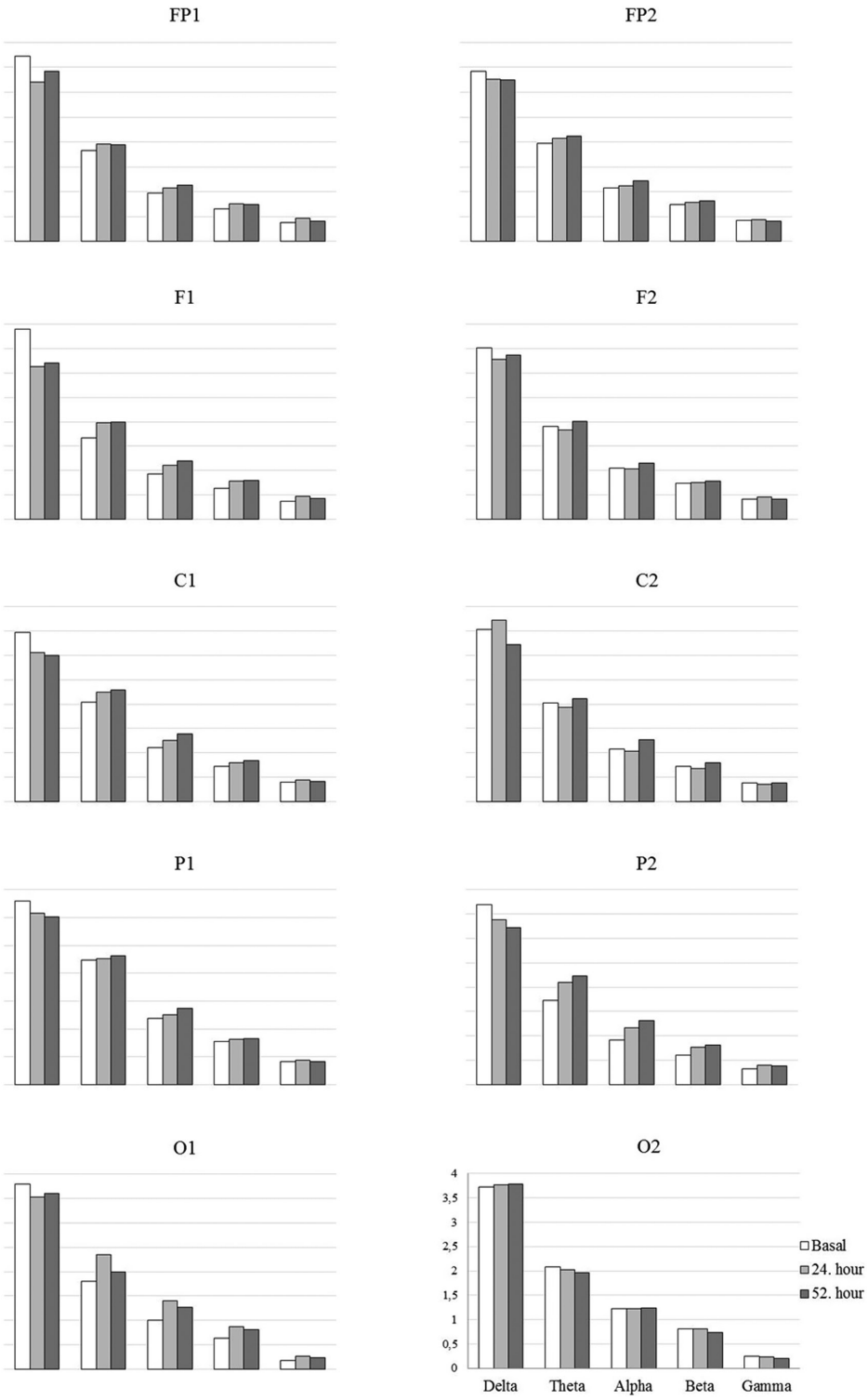

Figure 2 The changes of the amplitudes in the frequency bands between fasting periods.

20.5-45 Hz bands were significantly decreased in FP1-2, F1, C1-2, and P1-2 localizations.

The animals displayed normal EEG consisting of variable delta and theta activity. Isolated spike and sharp wave discharges were rarely standing out from the low amplitude and frequency of background activity in baseline EEG (Figure 8). At the 24th hour of fasting, the frequencies and amplitudes of spikes and sharp waves were increased according to the baseline value at the 52nd hour of fasting, the amplitude of spikes and the frequency of sharp waves were increased. Paroxysmal discharges for 3 seconds and sharp spikes were observed intensively in fast background activity occurred especially in the parietal cortex.

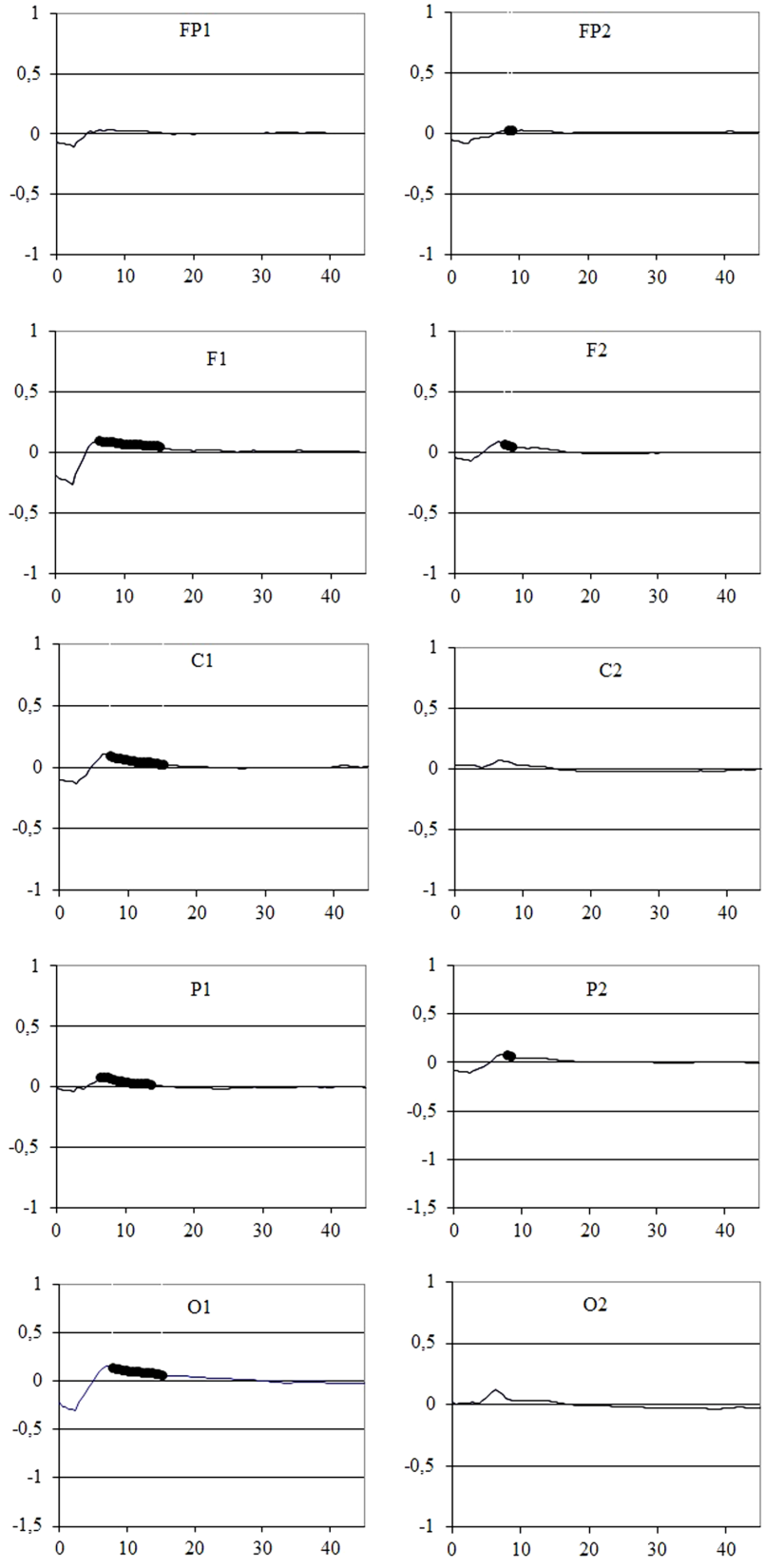

Figure 3 Presents difference between 24 hours of fasting and basal data. All fasted animals, moving averaged amplitude spectra of 24 hours of fasting values compared with basal values. The dots show statistically significant amplitude differences ($P < .05$).

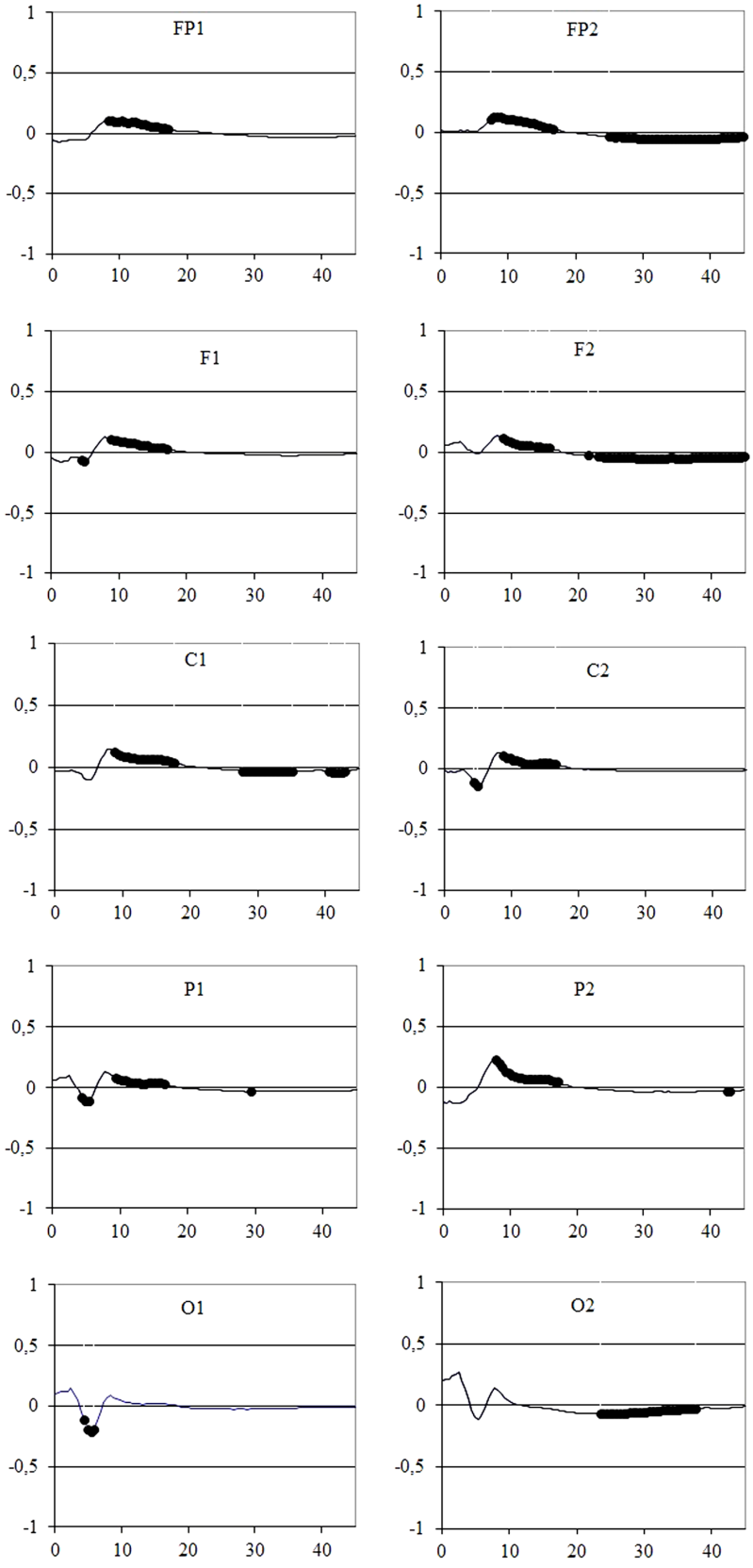

Figure 4 Presents a difference between 52 hours of fasting and 24 hours of fasting data. All fasted animals, moving averaged amplitude spectra of 52 hours of fasting values compared with 24 hours of fasting values. The dots show statistically significant amplitude differences (P <.05).

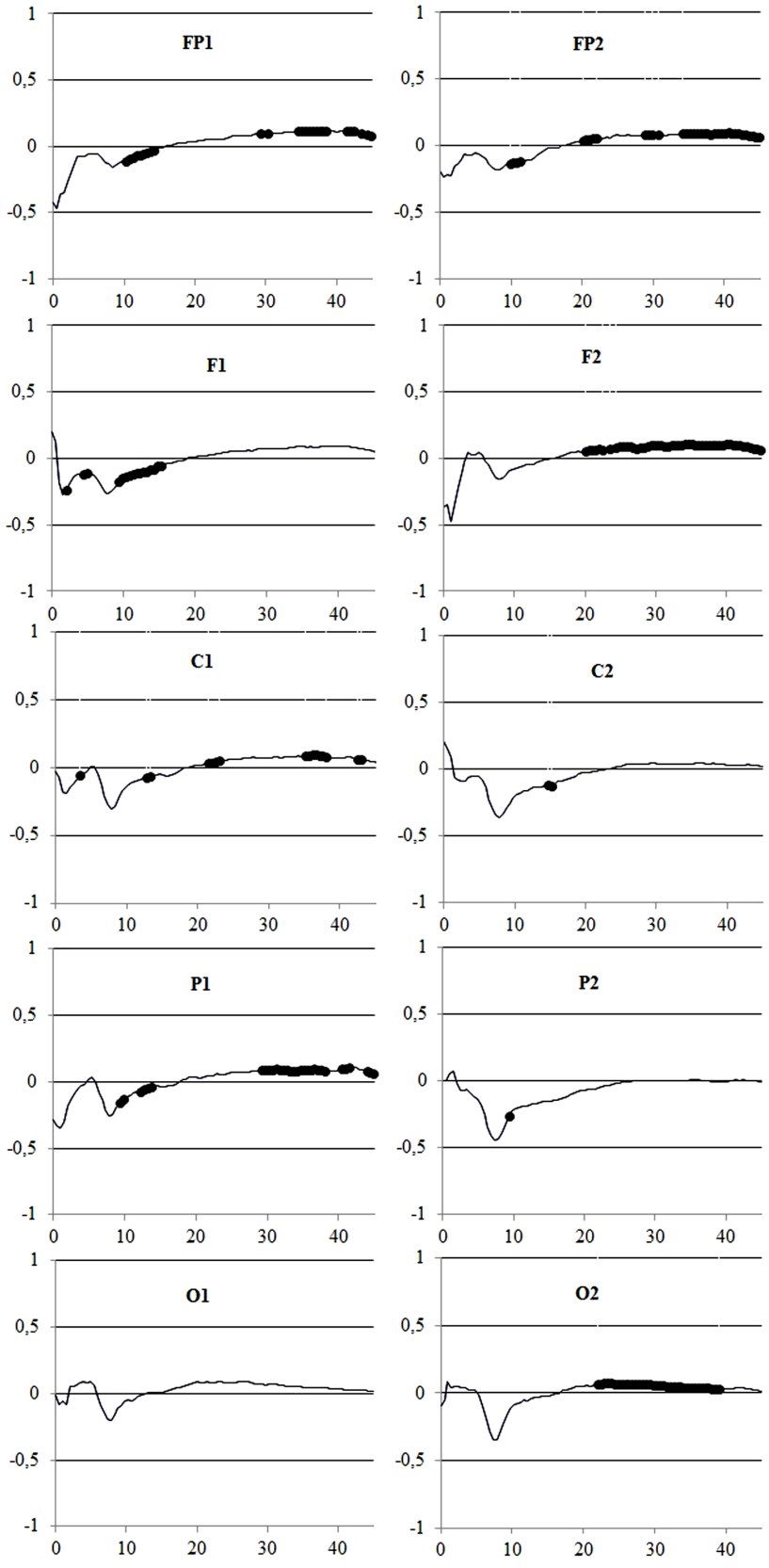

Figure 5 Presents a difference between saline treatment and 52 hours of fasting data. All fasted animals, moving averaged amplitude spectra saline treatment values compared with 52 hours of fasting values. The dots show statistically significant amplitude differences (P <.05).

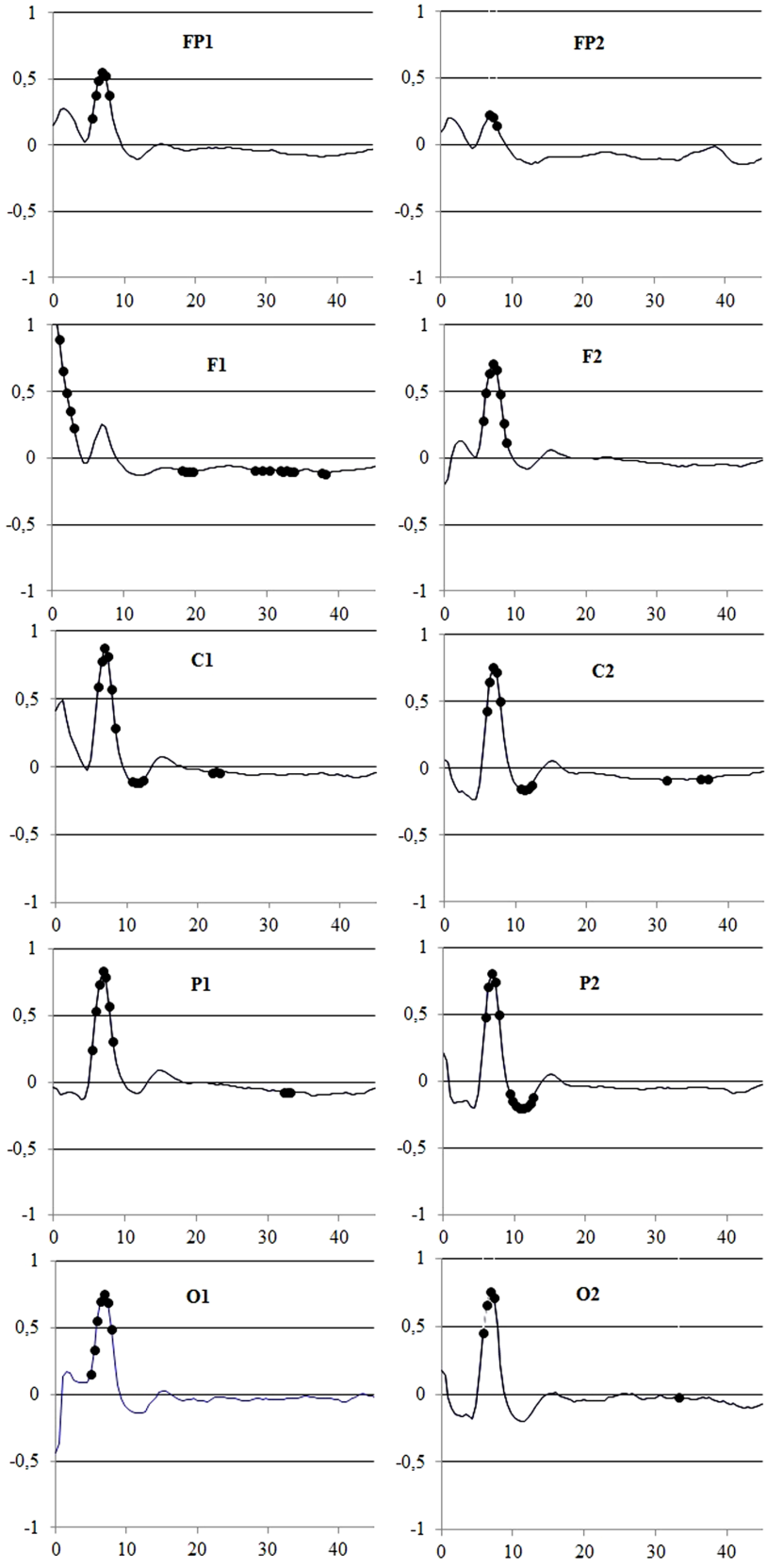

Figure 6 Presents a difference between scopolamine treatment and 52 hours of fasting data. All fasted animals, moving averaged amplitude spectra scopolamine treatment values compared with 52 hours of fasting values. The dots show statistically significant amplitude differences ($P < .05$).

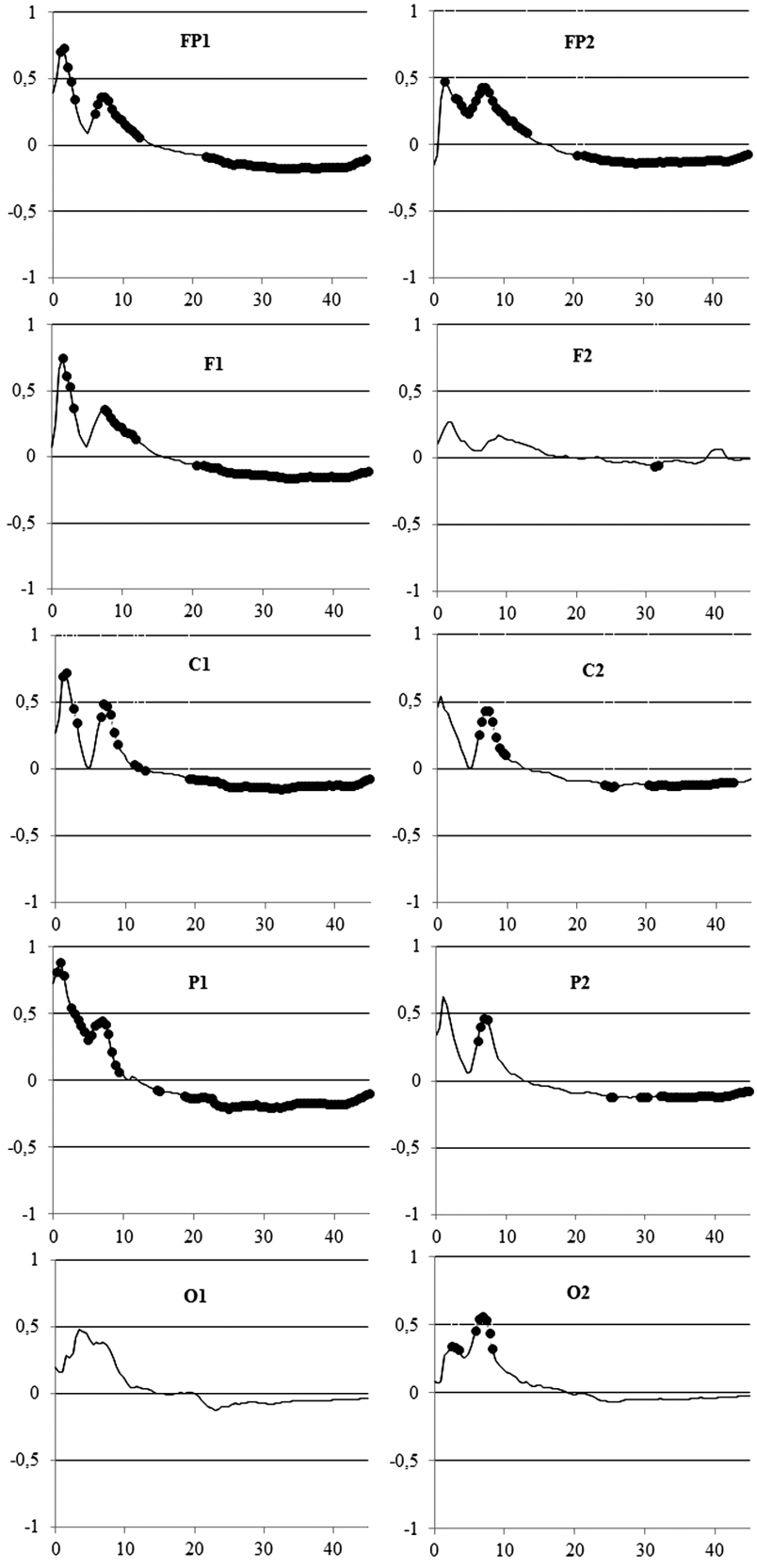

Figure 7 Presents a difference between scopolamine treatment and basal data. All fed animals, moving averaged amplitude spectra of scopolamine treatment values compared with basal values. The dots show statistically significant amplitude differences ($P < .05$).

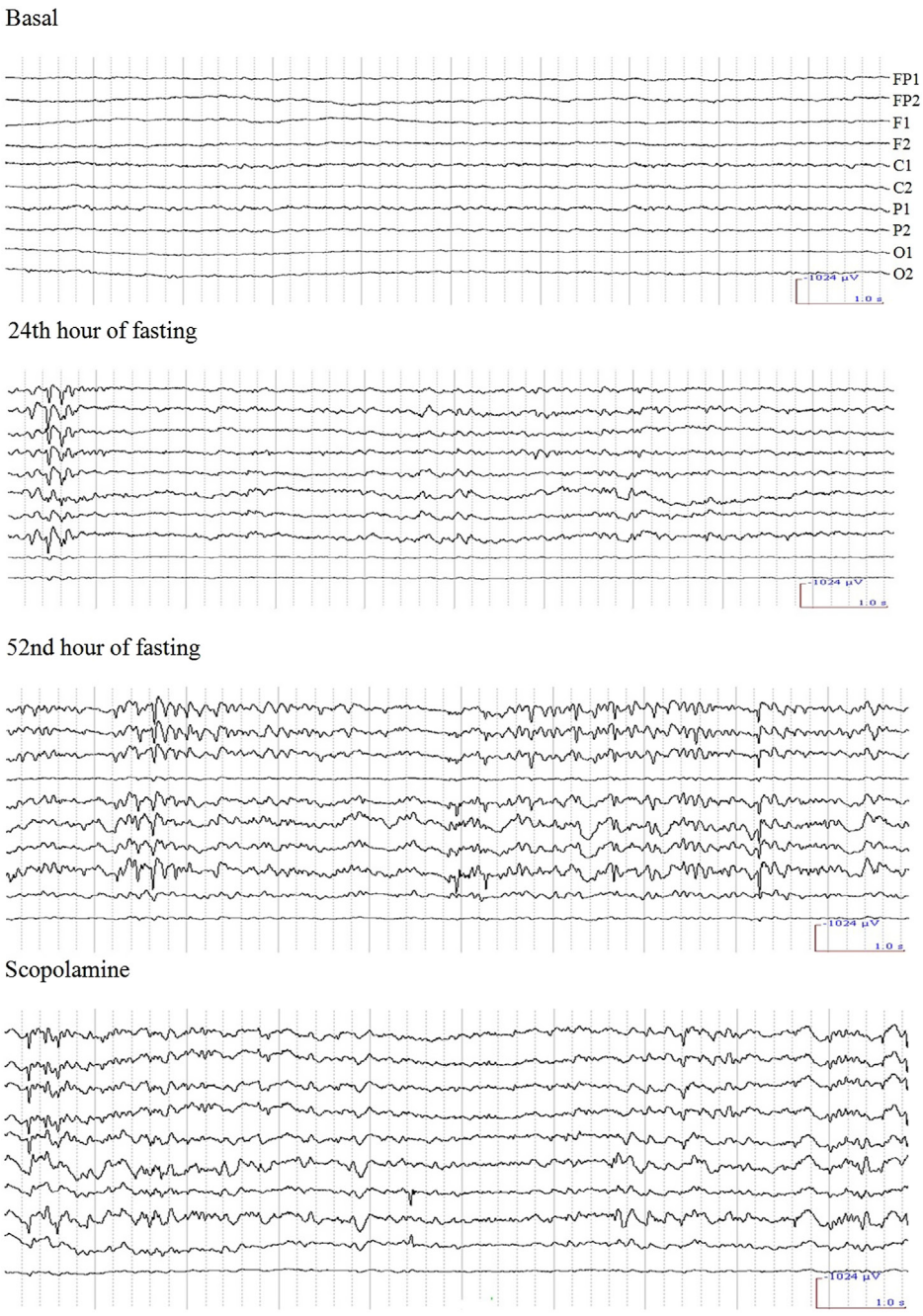

Figure 8 Electroencephalographic changes in fasting periods and after scopolamine treatment.

Scopolamine treatment induced an increase in both theta activity and the amplitudes of sharp spikes and spike-waves according to the 52nd hour values (Figure 8).

Scopolamine treatment caused convulsions in fasted rats, after food intake. This effect was statistically significant ($P < .01$) when compared to saline-treated control group (Table 1). In the saline-treated group, only 1 of 6 animals had stage 2 convulsion. In the scopolamine-treated group, 1 of 8 animals was excluded from the experiment, because it did not eat during the experiment. Two of the remaining 7 animals had stage 2, the other 2 had stage 2+, the other 2 had stage 3, and the last animal had stage 4 convulsions in the 60-minute observation time (Table 2).

No behavioral epileptic signs or EEG changes due to eating were observed in the saline-treated control animals except 1 animal. In 1 animal that had stage 2 convulsion, behavioral epileptic signs and EEG changes were like scopolamine treatments group. In the scopolamine treatment group, changes in EEG began a few minutes after eating. Eating caused initial EEG changes as an increase in the amplitude and frequency of sharp waves, especially in parietal cortex localizations. Figure 9 shows the EEG activity of different stages of convulsions. In

Table 1. Effect of Scopolamine on the Induction of Convulsions in Fasted Rats after Food Intake[a]

	Convulsions	
Groups (n)	**Incidence (%)**	**Time of Onset (min) (Mean ± SE)[b]**
Control (6)	0	-
Scopolamine (7)	71*	4.1 ± 1.1

n is the number of animals.
[a]Rats fasted for 52 hours were injected with saline, 3 mg/kg scopolamine, and were given free access to food 20 minutes later.
[b]Calculated from seizing animals.
*P <.01, significantly different from the control (saline) group, Fisher's exact test.

Table 2. Number of Animals Showing Seizure Stages and Myoclonus of Hindlimbs in Each Group

Groups (n)	Stage 0	Stage 1	Stage 2	Stage 2+	Stage 3	Stage 4	Stage 5	Myoclonus of Hindlimbs
Control (6)	5	-	1	-	-	-	-	-
Scopolamine (7)	-	-	2	2	2	1	-	6

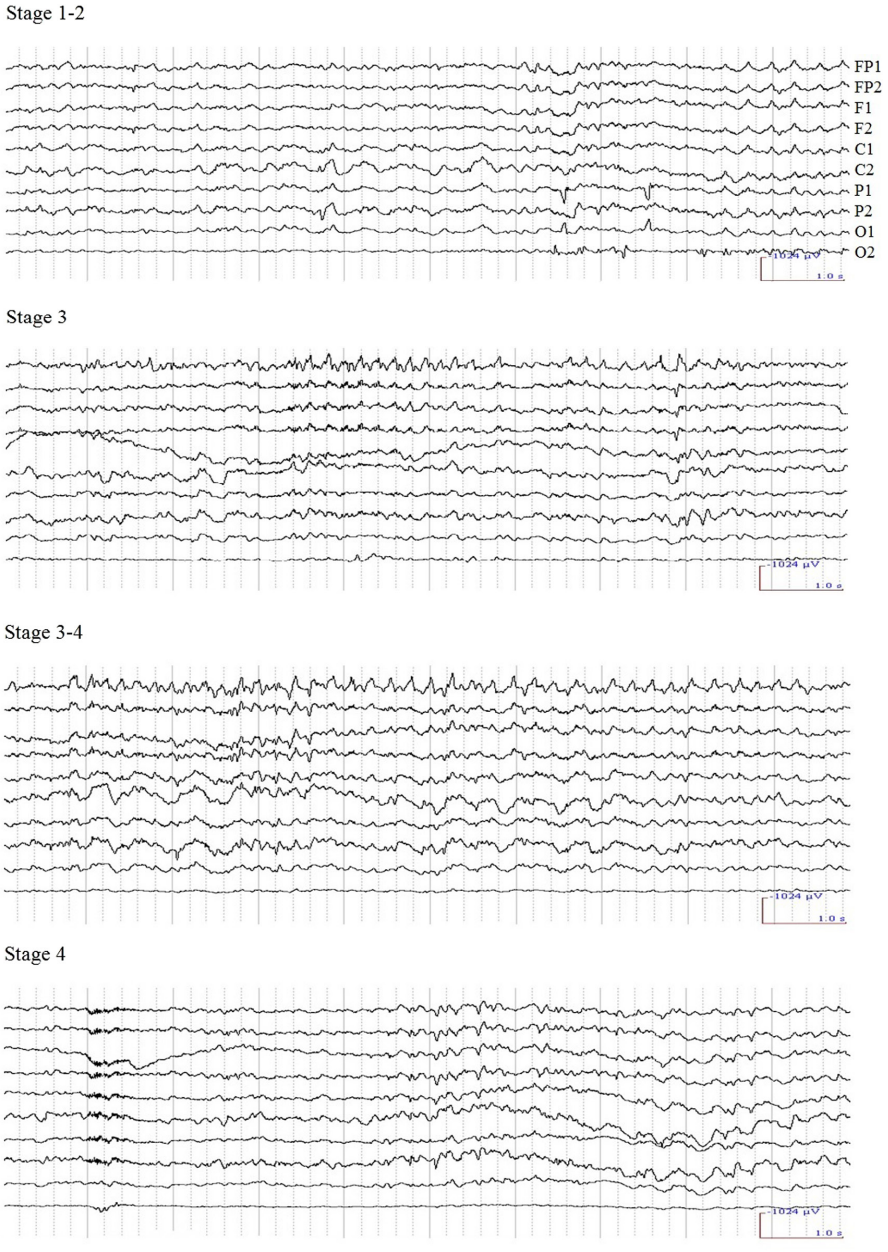

Figure 9 EEG activity of different convulsion stages of scopolamine-induced convulsions. EEG, electroencephalogram.

stages 1-2, slow EEG activity, increased amplitude, intermittent spike-wave discharges, and synchronized spikes were observed in all locations. During the tongue protrusion and neck spasms, theta background activity, sharp spikes, followed by spike-wave discharge were seen in the frontal location. In stage 3, high frequency, small amplitude, and rhythmic waves were observed. EEG alterations consisted of isolated sharp waves, spike or polyspike discharges standing out from the theta background activity were observed. Between stage 3 and stage 4 activities, EEG alterations were most pronounced and consisted of bursts of high-amplitude (poly) spike discharges (often >100 μV), spike-wave, or polyspike-wave complexes.

In all animals, the first of these paroxysmal patterns occurred around 5 minutes after eating. Episodes of high-amplitude rhythmic (poly) spike-wave complexes occurred per minute, each episode lasting 2-4 seconds, up to 10 seconds. EEG was showing high-frequency, high-amplitude discharges during myoclonic jerks.

DISCUSSION

This study supported the findings that antimuscarinic treatment in 52 hours fasted rats causes convulsions after food intake.[2,5] While convulsions were never observed when fasted mice were administered saline and then allowed to eat,[2,4,6,7] rats in saline given control group developed stage 1, and 1 animal was observed showing stage 2 activity with tongue protrusion and neck spasm after food intake. The most important difference between these convulsions occurring in rats and mice was that convulsions were seen in the saline-treated rats, albeit with a low stage. Also, rats seem less prone to develop convulsions with shorter periods of fasting in comparison with mice because 6 hours of fasting was required to reach the convulsive endpoint (stage 2+, 3, 4, or 5 activity).[5]

Repeated pretreatment with scopolamine sensitizes rats to make vacuous jaw movements induced by pilocarpine. The density of muscarinic receptors of these animals has also been shown to increase in the lateral striatum.[16] It is also known that food deprivation and refeeding cause changes in cortical and hippocampal M1 and M2 receptor expressions.[11] The lateral striatum implicates a role in producing the motor activity of eating behavior. Increased muscarinic receptor density may have caused potentiation of convulsions in animals. These findings thought that the role of fasting and antimuscarinic-dependent changes in muscarinic receptor expressed the possible underlying mechanism in the occurrence of convulsions in scopolamine-treated refed animals. Atropine as an antimuscarinic drug regulates the seizure pattern, as changing the continuous rapid spiking pattern of status epilepticus to periodic discharges.[17] Atropine infusions in the perirhinal cortex cause generalized seizures and induce spike activity.[18] Quantitative EEG studies with scopolamine have revealed slowing of spontaneous cortical activity, which manifests itself in decreased alpha[19,20] and beta[21] power and increased theta[22] and delta[19,20,21] power in humans. It is shown that scopolamine may produce synchronized cortical oscillations.[22] In addition, topical administration of high concentrations of scopolamine to the cerebral cortex has been shown to induce convulsive activity.[24] All these findings suggest that the muscarinic cholinergic system affects seizure development.

This study shows that EEG activity changes according to fasting periods. It is seen that fasting for 24 hours increased the amplitudes of the alpha and gamma frequency bands and decreased the amplitudes of the beta frequency band in the EEG. When the fasting period is prolonged to 52 hours, a decrement in the amplitudes of delta and theta frequencies is added to the findings at 24 hours. Scopolamine treatment shifted the peak point in the 13 Hz frequency band caused by fasting to the 7 Hz frequency band. The peak point of amplitude differences shifted from 13 to 7 Hz, and the amplitudes of theta activity increased significantly in parietal, occipital, and frontal localizations, respectively. Based on this rapid and obvious change in theta frequency band caused by the application of scopolamine, it can be argued that eating behavior causes the development of convulsions.

It seems that scopolamine treatment leads to the development of convulsions due to its effect on the frequency characteristics caused by fasting. In addition, the increase in the number of spike and sharp waves, which are rare in the basal period, during fasting confirms the increased excitability of the cerebrum.

The burst of uncontrolled electrical activity is the main factor in the initiation of seizures.[25] Also, exogenous factors such as repeatedly chewing movement could generate seizures and characterize as reflex epilepsy.[15,26] Eating epilepsy starts after food intake and could trigger an epileptic network. Also, in a recent study, food intake is associated with seizures and suggested as exogenous modifiers of brain excitability in humans.[27] In another study on eating epilepsy, it has been also shown that seizures were triggered by different mechanisms during eating. Although a combination of several stimuli may be involved in reflex epilepsy, chewing movement is the most common trigger causing seizures.[28] It is thought that seizure behavior originated from mastication muscles and the trigeminal nerve's motor and sensory nuclei. Thus, it may be speculated that the stimulation of excitatory pathways in the amygdala and associated regions with eating may be initiating convulsions.

Limitations

One of the limitations of this study was the risk of death of animals during the experiment. Also, the possibility of not eating was another limitation, since it was one of the main conditions for animals to eat food pellets for the development of convulsions.

CONCLUSIONS

In summary, we can conclude that the EEG properties of scopolamine-treated fasted rats and the behavioral patterns of these convulsions are in accordance with each other. However, further studies are needed to understand the underlying mechanisms of these convulsions and clarify the effects of fasting, refeeding, and antimuscarinic treatment on electroencephalographic patterns.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Marmara University (Date: September 23, 2002, Decision No: 32.02002mar).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.K., A.N.; Design - A.Z.T., A.N., B.Ö.E., S.K.; Supervision - A.N., İ.K., S.K.; Materials - A.Z.T., İ.Ö., B.Ö.E.; Data Collection and/or Processing - B.Ö.E., İ.Ö., A.Z.T.; Analysis and/or Interpretation - A.Z.T., A.N.; Literature Review - A.Z.T., A.N.; Writing - A.Z.T., A.N., S.K.; Critical Review - A.N., S.K., İ.K.

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