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Electroencephalographic Effects of Chlorpromazine in Rats

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The effects of an antipsychotic, chlorpromazine, on the electroencephalogram (EEG) were observed while rats were awake but immobile. The time course and the dose-dependency of the EEG changes were examined. The method of the power spectrum analysis was used to examine the EEG changes by the drug. The bands were divided into delta (1~3.5 Hz), theta (3.5~8 Hz), alpha (8~13 Hz), beta1 (13~21 Hz), beta2 (21~30 Hz) and gamma (30~50 Hz). In rats, the low dose of chlropromazine (1 mg/kg, i.p.) produced a significant increase in the power of the beta1 band. The higher doses (5, 10 mg/kg, i.p.) produced a significant increase in the power of the delta, theta, alpha and beta1 bands, and the decrease in the power of the gamma band. The powers of the bands changed dose-dependently. Then, the authors discussed whether the EEG effects produced by a drug are associated with the accompanying behavioral changes specifically.

Key Words: Antipsychotic, Chlorpromazine, Electroencephalography, EEG, Power, Spectrum, Rat

INTRODUCTION

The beginnings of quantitative evaluations of the EEG in the human date back the 1930s, but comparable animal studies have been rare. Quantitative electroencephalography has gained a considerable importance in the characterization of psychotropic drug effects in the human (Künkel et al, 1976; Fink, 1977; Herrmann, 1982; Itil, 1982; Herrmann & Irrgang, 1983). Also, the use of quantitative EEG for drug monitoring purposes in various animals has been widely recognized (Fairchild et al, 1980; Depoortere & Granger, 1982; Glatt et al, 1983; Krijzer et al, 1983). The quantitative analysis of cerebral field potentials, when conducted in a way similar to that of quantitative EEG analysis has proved to be a very sensitive indicator of drug action in the rat (Dimpfel & Decker, 1984, 1985).

Our previous report (Park et al, 1996) showed that the effects of diazepam on the cortical EEG altered depending on the behavioral states such as walking, awake immobility, or sleep. This shows how important is the control of the behavioral state during the experiment the effects of the drug on EEG when examining the effects of centrally acting drugs. So we kept the rats in the immobile awake state throughout the experiment.

The aim of this study is to disclose what changes in the EEG spectral pattern are induced by an antipsychotic drug, chlorpromazine (CPZ). Also discussed was whether the EEG effects of a drug are associated with behavioral changes.

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METHODS

Animals and preparation

The total of eight Sprague-Dawley rats (body weight 300~400 g) were used for the experiment. They were housed in standard facilities with free access to food and water and at a 12-hour day and night cycle. They were anesthetized with pentobarbital (25 mg/kg, i.p.) and urethane (0.5 g/kg i.p.) and were operated in a stereotaxic apparatus. Four or two cortical electrodes (gold-plated screws, tip diameter 1 mm) were implanted over bilateral frontal

(AP 2.5 mm, ML 2.5 mm) cortex (Paxinos & Watson, 1982). Two screws driven into the bone above cerebellum served as indifferent and ground electrodes. The electrodes and screws with connecting pins were installed over the skull with dental acrylic. The rats were allowed to recover for at least 2 days prior to the recording session.

EEG recording and analysis

The EEG from the screw electrodes over bilateral frontal cortices was recorded monopolarly with respect to the indifferent screw electrode via a bioelectric amplifier (A-M Systems, Inc., USA). The signals were amplified by 1000x and filtered at the range of 1 to 500 Hz. They were sampled by the A/D converter (DigiData 1200A, Axon Instrument, Inc., USA) at a sampling frequency of 1 KHz. The 1 or 2-min EEG recording was carried out before and 10, 20, 30, 40, 50, 60 min after CPZ administration while the animal was neither sleeping nor walking.

The EEG was analyzed by modifying the methods that were described in our earlier reports (Lee et al, 1992; Kim et al, 1996). The 1-min segment of EEG data from the frontal recording electrodes at every time point was divided into 5-sec epochs. Each epoch was converted to the amplitude spectrum of frequency domain by Fast Fourier Tranform algorithm and then calculated to the power spectrum. An absolute spectrum at one state and one condition of the animal was averaged from 8 or more noise-free epochs. A standardized spectrum was calculated from the division of the absolute spectrum by the normalized total power (total power/number of frequency points) of the spectrum at normal condition. Smoothing procedure (1 Hz window), which reduces the normalized standard error (Bendat & Piersol, 1971), was applied to the standardized spectrum. Each animal had its own control spectrum derived from un-drugged normal condition (awake immobile). Also, we calculated the power of the frequency bands (delta 1~3.5; theta 3.5~8; alpha 8~13; beta1 13~21; beta2 21~30; and gamma 30~50 Hz). Using paired t-test, significant differences in the power of each frequency (range 1 to 50 Hz) of the spectrum between pre-(normal) and post-drug administration were evaluated with p-value ($p<0.005$).

Drugs

Chlorpromazine (RBI, USA), pentobarbital (Hanlim Pharm. Inc., Korea) and urethane (Wako Chemical Co., Japan) were used in this study.

RESULTS

Provided there was a standardized behavioral state and a standard electrode implantation, the normal EEG power spectra are proved to be fairly constant in animals (Popken et al, 1983). The power spectra recorded during the awake immobile state were fairly constant between animals as well as within animal (Fig. 1C). The pattern of the power spectra showed larger variability when rats were moving or their tails were stimulated (Fig. 1D). Movement or tail stimulation increased the power of the theta and gamma frequency bands (Fig. 1B). Then, to examine the drug effects on the EEG power spectra, we used the data recorded during the awake, but immobile state only.

The time course of the power change of each band after intraperitoneal administration of CPZ (5 mg/kg, i.p.) was observed (Fig. 2). After the drug administration, the powers of the delta, theta, alpha and beta1 bands increased but the power of the gamma band decreased gradually. The total power was increased. Changes appeared in the alpha, theta and the beta1 band as early as 10 min after the drug administration, and approached the maximum after 30 min. Fifty min after the administration, the powers of all the delta, theta, alpha and beta1 reached their maximum level.

The power spectrum at 60 min after each dose of CPZ (1, 5, 10 mg/kg, i.p.) was calculated, and the power of each band was compared with that in the awake immobile state before the drug administration. In general, the activity of the slower wave than the beta2 band was increased and the activity of the faster wave was decreased (Fig. 3). To examine the changes of the power of each band by CPZ, the power value at 60 min after each dose of the drug was calculated, and the results showed the dose-dependent changes (Fig. 4). At the dose of 1 mg/kg CPZ, the power of the beta1 band significantly increased. The powers of the delta and alpha bands were significantly increased at the dose of 5 and 10 mg/kg CPZ. The total power also increased at the same dose. In contrast, the power of the gamma band significantly decreased at the

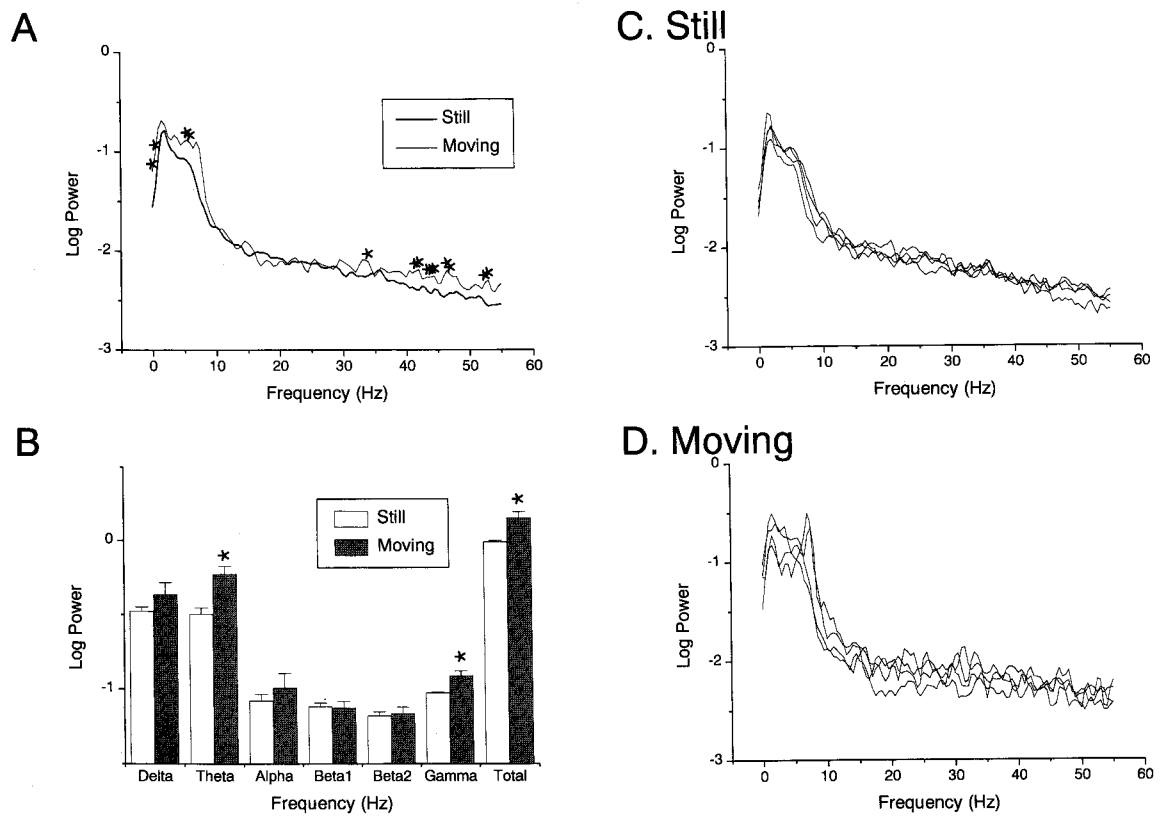

Fig. 1. A. Average power spectra of the frontal EEG of 4 rats during the awake immobile and moving or tail tactile stimulation. B. The power of each band and total band. C. Superimposed power spectra of the frontal EEG from 4 rats at immobile awake state. D. Superimposed power spectra of the frontal EEG from 4 rats during moving or tail tactile stimulation. The power is calculated as the relative value to the total power of the EEG recorded from each rat at immobile awake state.

same dose. The power of the theta band significantly increased only at the dose of 10 mg/kg CPZ.

DISCUSSION

This study was to examine the changes of the power of the EEG induced by CPZ in awake immobile rats. CPZ increased the powers of the delta (1～3.5 Hz), theta (3.5～8 Hz), alpha (8～13 Hz), and beta1 (13～21 Hz) bands, but it decreased that of the gamma (30～50 Hz) band dose-dependently. These results indicate a shift of the power distribution to the lower frequency, and they are similar, in part, to the report that CPZ increases the power of EEG over the whole range of frequency band (1～30 Hz) in rats (Dimpfel & Decker, 1984) and in rabbits (Yamamoto, 1997). In this study, the power of the gamma band was also decreased. The overall changes in the power spectrum indicate the EEG slowing, which may result from the sedation (Bo et al, 1988). They also suggest a decrease in the high frequency wave, which may result from the decreased perception of external stimulus (Kim et al, 1996).

In the present experiment, the total power was increased by CPZ, which is different from other report with regard to rats (Dimpfel & Decker, 1984). In that report, the total power was decreased by CPZ. One of the most important differences between these two set of reports is that monopolar electrodes with the reference electrode over the cerebellum were used in this study, while bipolar electrodes were used in the study by Dimpfel and Decker, which recorded the differences in electrical activities in a small restricted area.

The EEG changes produced by the drugs can be determined by their modulation of the neuronal activity of the brain. Synaptic activities occurring

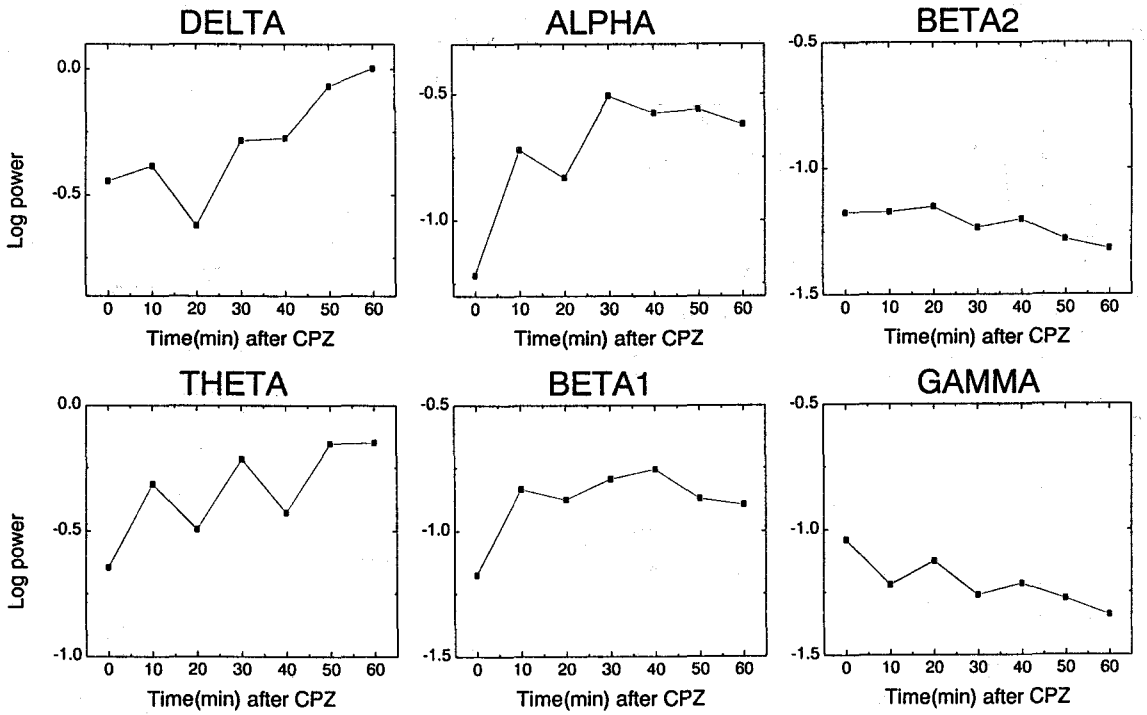

Fig. 2. The time course of the power changes of each band (delta (1~3.5 Hz), theta (3.5~8 Hz), alpha (8~13 Hz), beta1 (13~21 Hz), beta2 (21~30 Hz), and gamma (30~50 Hz)) after chlorpromazine (5 mg/kg, i.p.) administration.

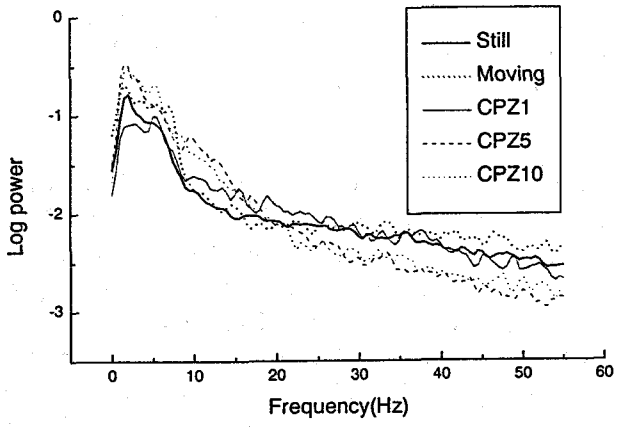

Fig. 3. The power spectra of the frontal EEG at 60 min after each dosage (1, 5, and 10 mg/kg, i.p.) of chlorpromazine.

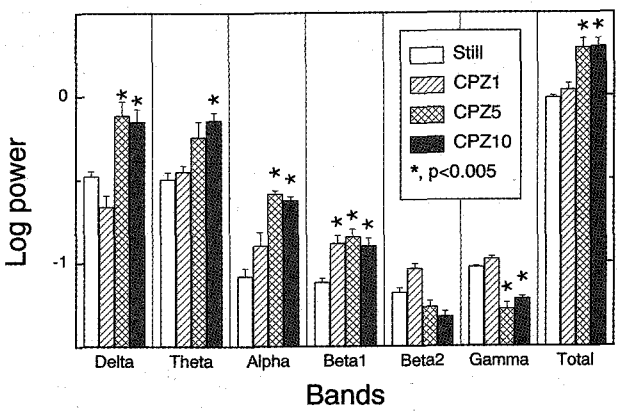

Fig. 4. The power of the bands at 60 min after each dosage (1, 5, and 10 mg/kg i.p.) of chlorpromazine.

from the interaction of the drugs and the neurotransmitters on the receptor sites lead to the generation of field potentials, which contribute to the EEG. Therefore, the EEG profile may have some characteristics related to the combinations of the actions on the specific receptor sites of the drug. As we know, the typical neuroleptics have an antagonistic effect on the dopamine D2 receptor and/or D1 receptor in several sites such as cholinergic, hitaminergic, and serotoninergic receptors (Hollister, 1995). Since the affinity to the dopamine D2 receptor of the neuroleptics is correlated well with the therapeutic dose of the neuroleptics used for treatment (Seeman, 1987), it is supposed that their EEG effect

is correlated with their action on the dopamine D2 receptor. In animal studies, however, a selective D2 antagonist antipsychotic remoxipride produces no significant changes in the EEG power spectrum in rabbit (Ongini et al, 1992), while CPZ and haloperidol which also have alpha-adrenergic action (Peroutka & Snyder, 1980), and clozapine which also has anticholinergic properties (Baldessarini, 1990). These antipsychotics except a selective D2 antagonist produce a significant EEG slowing and have a significant sedative action. The EEG changes such as the EEG slowing or the increase in the power of the lower frequency bands is associated with the action of neuroleptics other than the D2 receptor block. The slowings of EEG may be associated with behavioral sedation (Bo et al, 1988). In this study, the recording of EEG was conducted while rats were taking a posture indicating a constant arousal level, but the same posture dose not mean the same arousal level. Therefore, the result of the decrease in the low-frequency band power may be related with the sedation induced by CPZ. The neuroleptic, which has sedative action, may produce the EEG slowing.

In human studies, CPZ induces increase in the delta and theta activity and decrease in the alpha and beta activity (Small et al, 1987; McClelland et al, 1990). This result differs from our result and other animal studies. The spectral patterns between humans and animals (e.g., rats) in normal or no drug condition are different. There are genetically heritable charateristics in the background EEG (Van Baal et al, 1996). Thus, we can assume that the different pattern of the drug-induced EEG pattern as well as the background EEG is originated from the differences in the intrinsic circuitry of the brain. Sometimes, the arousal level of humans is controlled by experimenter during EEG recording (Small et al, 1996). This suppresses the EEG slowing that has to be produced by the sedative action of the antipsychotic agents, and then certain important EEG changes are missed. Likewise, diazepam, which has a sedative effect, induces some EEG changes, it increases the power over beta frequency band, which is associated with behavioral sedation of rats (Park et al, 1996). If the animal is aroused by sensory stimulus, the EEG changes would disappear. In addition, forcing the animal to be remained at a certain vigilance level rather reverses the EEG effects of diazepam (Glatt et al, 1983). Therefore, we suggest that the EEG changes induced by the antipsychotic CPZ occur with its accompanying behavioral changes of sedation.

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