Korean J Physiol Pharmacol
Vol 9: 17–22, February, 2005

Differential Effects of Typical and Atypical Antipsychotics on MK-801-induced EEG Changes in Rats

Jee Sook Kwon[1], Ki Min Kim[1], Su Min Chang[1], Choong-Young Kim[1], Tai Ho Chung[2], Byung-Ju Choi[3], and Maan Gee Lee[1]

[1]Department of Pharmacology, School of Medicine, [2]WHO Collaboration Viral Hepatitis Center, [3]Department of Dental Pharmacology, School of Dentistry, Kyungpook National University, Daegu 700-422, Korea

We examined whether the abnormal EEG state by NMDA receptor blocker MK-801 can be reversed by typical and atypical antipsychotics differentially by comparing their spectral profiles after drug treatment in rats. The spectral profiles produced by typical antipsychotics chlorpromazine (5 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.) were differ from that by atypical antipsychotic clozapine (5 mg/kg, i.p.) in the rats treated with or without MK-801 treatment (0.2 mg/kg, i.p.) which produce behavioral abnormalities like hyperlocomotion and stereotypy. The dissimilarity between the states produced by antipsychotics and the control state was examined with the distance of the location of the canonical variables calculated by stepwise discriminant analysis with the relative band powers as input variables. Although clozapine produced more different state from normal state than typical antipsychotics, clozapine could reverse the abnormal schizophrenic state induced by MK-801 to the state closer to the normal state than the typical antipsychotics. The results suggest that atypical anesthetic can reverse the abnormal schizophrenic state with negative symptom to the normal state better than typical antipsychotic. The results indicate that the multivariate discriminant analysis using the spectral parameters can help differentiate the antipsychotics with different actions.

Key Words: Schizophrenia, MK-801, Antipsychotics, EEG, Power spectral analysis, Linear discriminant analysis

INTRODUCTION

Preclinical test is focused to screen the novel compounds with potential antipsychotic actions which block the MK-801-induced hyperlocomotion and stereotypy (Tiedtke et al, 1990) or the PCP-induced social withdrawal (Sams-Dodd, 1999) in the schizophrenic animal model produced by non-competitive NMDA receptor blocker. Traditionally, it is supposed that schizophrenic symptoms may result from the hyperfunctional state of dopamine and then the schizophrenic animal model produced by injection of the dopaminergic agents such as amphetamine and apomorphine, that represent the positive symptoms of the paranoid schizophrenia in humans, has been used for screening potential antipsychotic agents. In contrast, the schizophrenic model produced by administration of NMDA receptor blockers may represent both the positive and the negative symptoms (Javitt and Zukin, 1991).

The hyperlocomotion and social withdrawal produced by NMDA receptor blockers are selectively suppressed by atypical antipsychotic clozapine but not by typical antipsychotic chlorpromazine and haloperidol (Corbett et al, 1995). A typical antipsychotics but not typical antipsychotics blocked the MK-801-induced hyperlocomotion (Ninan and Kulkarni, 1998), discriminative stimulus effect of MK- 801 (Goudie and Smith, 1999), and pre-pulse inhibition of startle response (Varty and Higgins, 1995) and pre-pulse inhibition of electrical stimulation of hippocampus (Zhang et al, 1999). The clozapine preferentially potentiates NMDA receptor- mediated transmission, whereas haloperidol depresses the non-NMDA receptor-mediated response (Arvanov et al, 1997; Arvanov and Wang, 1999). Then, the schizophrenic behavioral model which is produced by NMDA receptor blockers has been used for screening novel atypical antipsychotic like clozapine (Goudie and Smith, 1999; Smith et al, 1999; Deutsch et al, 2002).

There are many attempts to develop more convenient procedures compare to the behavioral screening to screen drugs with specific central effects by electroencephalographic measure for many years (Herrmann, 1982). These electroencephalographic procedures have employed spectral analysis by FFT and derived spectral parameters like band powers. Because a specific central acting drug produces a specific spectral profile, newly synthesized chemical can be classified as a drug with a certain potential central effect by which its spectral profile is examined by comparison with the spectral profiles of already known drugs (Dimpfel and Otten, 1984; Dimpfel, 2003). This quantitative method is very sensitive to the functional state change produced by a drug. Therefore, the changes of spectral profile can

Corresponding to: Maan Gee Lee, Department of Pharmacology, School of Medicine, Kyungpook National University, Dong-In 2-101, Daegu 700-422, Korea. (Tel) 82-53-420-4832 (Fax) 82-53-426-4703, (E-mail) mglee@knu.ac.kr

ABBREVIATIONS: PCP, phencyclidine; NMDA, N-methyl-D-aspartate; FFt, fast fourier transform; EEG, electroencephalogram.

be used for objective quantification of drug effect. There are many spectral parameters which represent the functional state of the brain and the change can be estimated by combination of multivariate statistical technique with multiple parameters.

Typical antipsychotics such as chlorpromazine, haloperidol and sulpride produce increase of delta and theta power and decrease of alpha and fast beta, while atypical antipsychotics such as clozapine and olanzapine produce an increase in power over all frequencies in rats (Ahnaou et al, 2003). In human, typical or atypical agents produce different spectral profiles. Chlorpromazine and haloperidol increases the power of the low frequency ranges and decreased the power of the high frequency range in healthy volunteers (McClelland et al, 1990; Hughes et al, 1999) while clozapine induces increase the power over alpha and beta frequencies (Knott et al, 2001). It is supposed that the differences of spectral profiles reflect underlying action differences on the specific receptor. Series of studies done by Dimpfel and collegues (Dimpfel and Decker, 1985; Dimpfel et al, 1992) reported that the neuroleptic drugs show characteristic spectral profile which is different from other therapeutic groups and that drugs within the same therapeutic group show smaller difference in spectral profile. Then, they suggested that the therapeutic group of a central acting drug can be predicted by its spectral profile.

So far even though the drug action can be predicted by spectral characteristics in the normal animal, because this spectrum resulted from drug action on the normal brain state, this does not reflect drug's therapeutic action on the abnormal pathological state. The pathophysiological state of the brain such as schizophrenia is already different state from normal brain, then the spectrum of EEG recorded from the disease state is different from normal EEG spectrum (Knott et al, 2001). Schizophrenia state results from disordered functional state of dopamine/glutamate neurotransmission. Therapeutic potential of a drug can be examined by showing the potential to reverse the pathological state to the normal state. So the therapeutic potential of a drug can be examined by showing the potential to reverse the spectral profile of the pathological state to that of the normal state. Therefore, in this study, we examined whether the EEG spectrum of the schizophrenic state by NMDA receptor antagonist, MK-801 can be reversed by typical and/or atypical antipsychotic to the EEG spectrum of the control state. For this, we calculated the spectral parameters such as band powers of each drug and compared the parameters resulted from different drugs and examined grouping between typical and atypical drug by multivariate statistics such as the stepwise discriminant analysis.

METHODS

The experiments were carried out in 23 male adult Sprague-Dawley rats (250~350 g, SamTaco Inc., Korea). Animals were individually housed in stainless steel cages (20 cmW×35 cmD×17 cmH). They were maintained under controlled environmental conditions throughout the study: 21~25°C ambient temperature, 12:12 light-dark cycle (light on from 7:00 to 19:00) and standard laboratory food and tap water available ad lib. All animal procedures were approved by the institutional animal care and use committee.

Surgery was performed under anesthesia with cocktail (70 mg ketamine and 4 mg xylazine in 10 ml saline solution) 2 ml/kg i.p. After the rats had been placed in a stereotaxic apparatus, the midline of the scalp skin was injected with lidocaine and epinephrine solution and incised and the periosteum and the skull surface were cleaned. Four stainless screws were inserted into the frontal (2.5 mm anterior and 2.5 mm lateral from bregma) and the parietal (2.5 mm posterior and 2.5 mm lateral from bregma) bone bilaterally, without perforating the dura and four screws (tip diameter 1 mm) were threaded into the holes. Additional reference and ground screws were implanted into interparietal bone above cerebellum which served as indifferent and ground electrodes. The screw electrodes with connecting pins which were arranged 6x2 matrices were fixed over the skull with dental acrylic altogether. The rat was allowed to recover for at least 2 days prior to start the first recording session.

The animals were divided into 4 groups. Each group was started with 12 rats. The animals were allowed for 30 min in the recording cage for adaptation before the recording EEG. The rats were treated with 0.9% 1 ml/kg saline (group 's'), 5 mg/kg chlorpromazine (group 'c'), 0.5 mg/kg haloperidol (group 'h') or 10 mg/kg clozapine (group 'z') and were recorded for 60 min and then were treated with MK-801 injection (0.2 mg/kg, i.p., group 'sm', 'cm', 'hm', or 'zm') and were recorded for 60 min. The final number of animals used for analysis in group 's', 'c', 'h' and 'z' was 4, 12, 12 and 8, respectively.

The EEG from the electrodes over bilateral frontal and parietal cortices was recorded monopolarly with respect to the indifferent screw electrode via a bioelectric amplifier (Model 1700, A-M Systems, Inc., USA and CyberAmp 380, Axon Instruments, Inc., USA). The signals were amplified with ×10,000 and filtered with the range of 1 to 60 Hz. They were sampled by the AD converter (DigiData 1200A, Axon Instruments Inc., USA) at a sampling rate of 200 Hz. The EEG was analyzed according to the method descibed in our ealier paper (Lim et al, 2000). Briefly, The 60 min EEG recording after antipsychotic treatment and the 60 min EEG recording after MK-801 treatment were divided into 10-min segment of EEG signals. Overlapping 600 epochs of 2 sec epochs (1-sec overlap) were converted to power spectra by FFT algorithm and then averaged to power spectra. This represents the spectra of a 10 min segment. The power spectra were cut into 8 frequency ranges (D1, 1~2.5 Hz; D2, 2.5~4 Hz; T1, 4~6 Hz; T2, 6~8 Hz; AL, 8~13 Hz; B1, 13~20 Hz; B2, 20~30 Hz; and GA, 30~50 Hz) and whole frequency ranges (T, 1~50 Hz). The relative power of each frequency band were calculated from the absolute power of each frequency divided by total power.

The absolute powers or relative powers of all 8 frequency bands obtained from EEG recorded from 30 to 50 min after drug injection were used as input variables for a stepwise discriminant analysis.

RESULTS

Only the frontal EEG has been examined here because the power spectral profiles over the frequencies were not different between the frontal and the parietal EEGs although the EEG was recorded from both the frontal cortex and the parietal cortex.

Absolute power of each band of the EEG produced by the

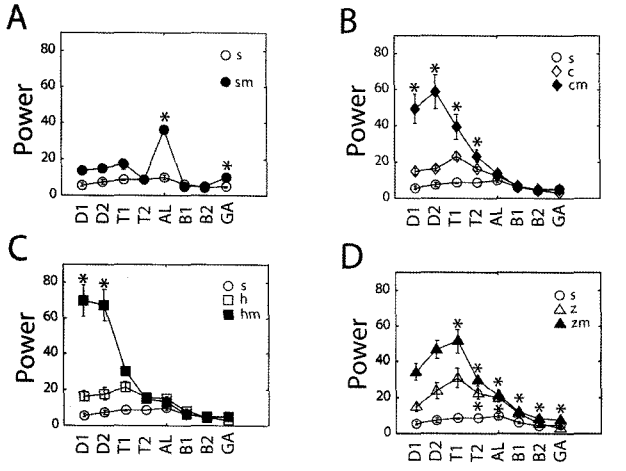

Fig. 1. The absolute power in the frequency bands of the parietal EEG. Each data point is plotted as a power +/− s.e.m. in each frequency band. The frequency bands are: D1, 1~2.5 Hz; D2, 2.5~4 Hz; T1, 4~6 Hz; T2, 6~8 Hz; AL, 8~13 Hz; B1, 13~20 Hz; B2, 20~30 Hz; and GA, 30~50 Hz. The power was calculated from the parietal EEG between 40~50 min after drug injection. The drug treatment groups are: A. 's', saline (1 ml/kg, i.p.) and 'sm', saline+MK-801 (0.2 mg/kg, i.p.) (n=4); B. 'c', chlorpromazine (5 mg/kg, i.p.) and 'cm', chlorpromazine+MK-801 (n=12); C. 'h', haloperidol (0.5 mg/kg, i.p.); 'hm', haloperidol+MK-801 (n=12); and D. 'z', clozapine (5 mg/kg, i.p.); and 'zm', clozapine+MK-801 (n=8). Significant differences of the treatment groups compared to the saline group ('s') are indicated with *($p<0.05$).

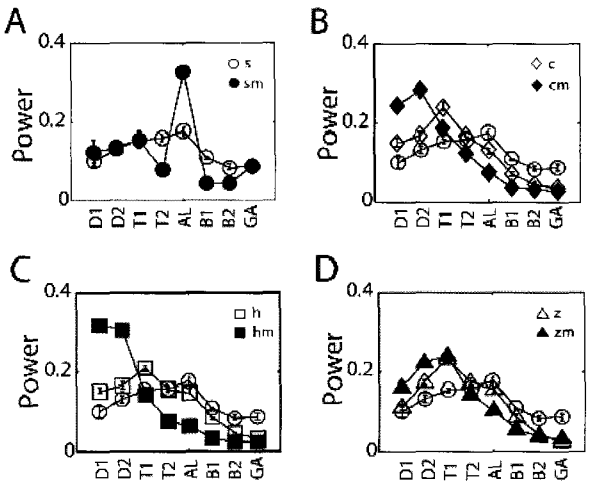

Fig. 2. The relative power in the frequency bands of the parietal EEG. Note the spectral profile over the frequency bands between the treatments of antipsychotic with and without MK-801. Refer to Fig. 1 for the description of the treatment groups and the frequency bands.

treatment of the antipsychotics chlorpromazine, haloperidol and clozapine with or without the NMDA receptor blocker MK-801, was compared to the saline-treated group (the group 's') that was injected with saline i.p. or the MK-801- treated group (the group 'sm') that was injected with MK-801 i.p. (Fig. 1). The typical antipsychotics chlorpromazine and haloperidol alone did not produce a significant change in the power of any band, while the atypical antipsychotic clozapine produced a significant increase of the power of the T2, AL and B1 bands (ANOVA and post-hoc Tukey test, $p<0.05$). MK-801 alone (the group 'sm') produced a significant increase of the power of the AL and GA bands compared to the group 's' ($p<0.05$). Administration of chlorpromazine or haloperidol with MK-801 produced a significant increase of the power of the lower frequency bands (the D1 and D2) and a significant decrease of the power of the AL and GA bands compared to the group 'sm'. In contrast, the administration of clozapine with MK-801 produced a significant increase of the power of the relatively high frequency bands (T1, B1 and B2) and a significant decrease of the power of the AL band compared to the group 'sm'. Both chlorpromazine and clozapine with MK-801 produced an increase of the power of the T2 bands compared to the group 'sm'.

The absolute and relative powers of the spectral bands of the EEGs from the experimental groups (the group 's', 'c', 'h', 'z', 'sm', 'cm', 'hm' and 'zm') were used as the multivariate input values for the stepwise discriminant analysis which can lead to evaluation of the differences among their spectral profiles statistically (Fig. 1 and Fig. 2). Because the result of the discriminant analysis did not differ whether either absolute or relative powers were used as the input values, we described here the results by using the relative powers of the bands as the input values. The degree of differences between groups can be represented by the distance on the canonical space which is resulted from the discriminant analysis (Fig. 3 and Table 1). The distances between the groups 'c' and 'h', 'c' and 'z' and 'h' and 'z' were 0.53, 1.98 and 1.84, respectively. Then, these results indicate that the EEG effects of the typical antipsychotic drugs are different from those of the atypical drug. The distances between the groups 'c', 'h', or 'z' and 's' were 6.21, 6.23 and 7.78, respectively. In MK-801-treated groups, the distance between the groups 'cm' and 'hm', 'cm' and 'zm' and 'hm' and 'zm' were 2.00, 3.55 and 5.12, respectively. These results indicate the similarity between the effects of typical agents is more than between the effects of the typical and the atypical drugs in the abnormal state as those in the normal state. The distances between the groups 'cm', 'hm' or 'zm' and 's' were 7.26, 7.87 and 5.54, respectively. The distance between the MK-801 treated group and the saline group was 18.18. All the antipsychotics recovered the abnormal state induced by MK-801 to the normal state which was evidenced by the distance between the groups.

DISCUSSION

In this study, we have shown two important findings by examining the EEG spectral profiles resulted from the treatment of the antipsychotic drugs in the saline-treated or in the MK-801-treated rats. First, the EEG effects of the typical antipsychotic were different from those of the atypical antipsychotic. Second, the atypical drug reversed more the abnormal state induced by MK-801 to the normal state than the typical drug did.

In a dose used in this study, the typical antipsychotics did not produce significant changes in all band powers, while the atypical drug produced significant increase of the power in the T2, AL and B1 bands. The significant increase

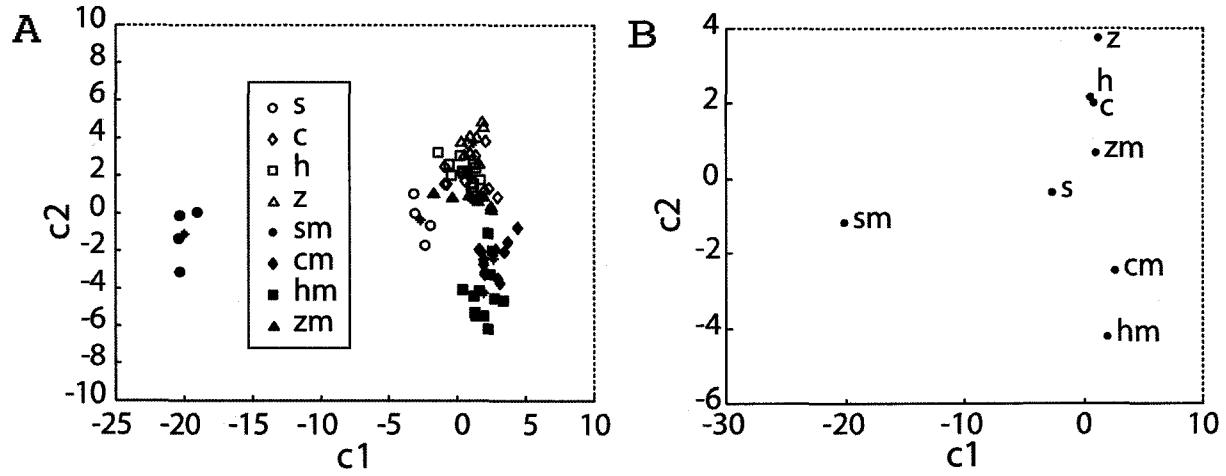

Fig. 3. Plot of single experiments (A) and group centroids (B) on the canonical space. The spectral profiles data which are same data used in Fig. 2. are used for obtaining the canonical variables (c1 and c2) by the stepwise discriminant analysis. Note that the distance between two points on the canonical space indicates the degree of dissimilarity between two spectral profiles.

Table 1. Canonical space distance between two groups among all drug treatment groups.

	's'	'c'	'h'	'z'	'cm'	'hm'	'zm'	'sm'
's'	0.00							
'c'	6.21*	0.00						
'h'	6.23*	0.53	0.00					
'z'	7.78*	1.98	1.84	0.00				
'cm'	7.26*	4.77*	5.10*	6.43*	0.00			
'hm'	7.87*	6.34*	6.58*	8.03*	2.00*	0.00		
'zm'	5.54*	1.42	1.77	3.38*	3.55*	5.12*	0.00	
'sm'	18.18*	21.21*	20.80*	21.78*	22.70*	22.16*	21.21*	0.00

They are 's', saline (1 ml/kg, i.p.) and 'sm', saline+MK-801 (0.2 mg/kg, i.p.) (n=4); 'c', chlorpromazine (5 mg/kg, i.p.) and 'cm', chlorpromazine+MK-801 (n=12); 'h', haloperidol (0.5 mg/kg, i.p.); 'hm', haloperidol+MK-801 (n=12); and 'z', clozapine (5 mg/kg, i.p.); and 'zm', clozapine+MK-801 (n=8).

*$p<0.05$, a distance between two groups is significant.

in the delta and theta power by chlorpromazine and haloperidol was reported in previous studies (Yun and Lee, 1999). Not significan changes in this study may result from dosage used. Although the typical antipsychotics could not produce any significant changes in band powers in this study, the tendency of power increase in low frequency bands is similar to the previous reports that chlorpromazine produces increase in low frequency band powers (Yun and Lee, 1999). These increases may be related to its action on the dopamine D2 receptor with D1 receptors (Bo et al, 1988) and also related to its sedative action via other antiadrenergic or anticholinergic activity (Hollister, 1995). In contrast to typical drugs, clozapine produced significant increase of T2, AL, B1 band powers. This difference may result from the action of clozapine on the D1, D4 receptors (Seeman et al, 1997) and 5-HT2A receptors (Martin et al, 1997; Seeman et al, 1997) which is not influenced by the typical antipsychotics.

The NMDA receptor blockers such as MK-801 and phencyclidine induce positive and negative symptoms resembling schizophrenia in human and potentiate the preexisting symptoms in schizophrenic patients (Javitt and Zukin, 1991). These drugs administered in subanesthetic doses produce abnormal behaviors such as hyperlocomotion, head-weaving and ataxia in animals (Koek et al, 1988). These behavioral abnormalities have been considered as a good schizophrenic animal model, which differ from the schizophrenic model produced by dopaminergic agonists apomorphine. Some behavioral abnormalities like hyperlocomotion and social withdrawal produced by NMDA receptor blockers can be blocked by atypical antipsychotics but not by typical antipsychotics. So the model has been used to screen the novel atypical antipsychotic like clozapine. In this study, it is considered that we can differentiate the action of the atypical drug from the action of the typical drug by comparing the EEG spectral profiles so that the study of EEG spectral profiles of some new compound will show its potential efficacy on the schizophrenia treatment. Because it is hypothesized that a spectral profile reflects a certain state of brain activity, the EEG spectral profile produced by the NMDA receptor blocker may represent the schizophrenic behavioral state with the negative symptom as well as positive symptom. Thus, we hypothesized that a certain drug which can block the EEG effects produced by NMDA receptor blockers may be a potential antipsychotic for the treatment of negative symptom as well as positive symptom in schizophrenia. In this study, alpha and gamma band powers were increased and behavioral abnormalities head weaving and hyperlocomotion were induced by NMDA-receptor blockers. The behavioral effects were blocked by atypical antipsychotic but all the EEG effects were not blocked by the antipsychotic. Typical drugs reversed the increase of alpha and gamma power but massively increased the delta powers. Atypical drug only blocked the alpha power. The reversal of alpha power was common in the treatments of both types of antipsychotics, so it is suggested that the increase of the alpha band may represent the abnormal brain state in schizophrenia, which is corresponding to the hyperlocomotion by NMDA receptor blocker. Prominent increase in delta power by typical antipsychotic in MK-801 treated animals reflect the synergistic

action of antipsychotic sedative and MK-801 cataleptic action. These effects may be related to the sedative side effect during typical antipsychotic treatment.

The spectral profiles of EEG were plotted to the 3- dimensional space of canonical variables derived from a multivariate statistical analysis, the stepwise discriminant analysis. The distance on the canonical space between groups indicates the differences of spectral profiles or the brain states between groups. The absolute band powers or the relative band powers of FC or PC were used for input variables for the discriminant analysis. They resulted in similar discrimination between groups. The largest separation among groups resulted from the relative band power of PC. Then, we discussed with this result. In control animals, the distance between two typical antipsychotics in canonical space was closer than that between typical and atypical antipsychotics. But atypical antipsychotic indicated more distant from normal state than the typical antipsychotic did. These indicate the atypical antipsychotic may produces an abnormal state from normal more than typical antipsychotics may do so. In this study, we focused whether the abnormal sate of schizophrenia induced by NMDA receptor blockers can be reversed by antipsychotics. Actually, the location of MK-801 induced state on the canonical space was farthest from the control state. This indicates that the state induced by MK-801 is quite abnormal schizophrenic brain state. Typical antipsychotics, chlorpromazine and haloperidol reduced the distance from the control state while atypical antipsychotic reduced the distance from the control state, i.e. moved the state more close to the normal state. Given the distance between the location on the canonical space represent the difference of the state produced by a certain drug, it can be concluded that in reversing the abnormal schizophrenic state by NMDA receptor blockers, the atypical antipsychotic is more effective than the typical antipsychotic.

When both absolute band power or relative band power was used for the input variables for the discriminant analysis, the separation among groups was similar. This indicates that the absolute value of the power did not influence much on the representation of the states by the discriminant analysis. Then, the use of relative power values can give two possible advantage compared to the use of absolute power values. First, the amplification setting during signal acquisition does not affect the result of the discriminant analysis. Second, it is no necessarry to record the control state for comparison of the drug state.

ACKNOWLEDGEMENT

The research was supported by a grant from the IDR Labs (2001).

REFERENCES

Ahnaou A, Megens AA, Drinkenburg WH. The atypical antipsychotics risperidone, clozapine and olanzapine differ regarding their sedative potency in rats. *Neuropsychobiology* 48: 47–54, 2003

Arvanov VL, Wang RY. Clozapine, but not haloperidol, prevents the functional hyperactivity of N-methyl-D-aspartate receptors in rat cortical neurons induced by subchronic administration of phencyclidine. *J Pharmacol Exp Ther* 289: 1000–1006, 1999

Arvanov VL, Liang X, Schwartz J, Grossman S, Wang RY. Clozapine and haloperidol modulate N-methyl-D-aspartate- and non-N-methyl-D-aspartate receptor-mediated neurotransmission in rat prefrontal cortical neurons in vitro. *J Pharmacol Exp Ther* 283: 226–234, 1997

Bo P, Ongini E, Giorgetti A, Savoldi F. Synchronization of the EEG and sedation induced by neuroleptics depend upon blockade of both D1 and D2 dopamine receptors. *Neuropharmacology* 27: 799–805, 1988

Corbett R, Camacho F, Woods AT, Kerman LL, Fishkin RJ, Brooks K, Dunn RW. Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. *Psychopharmacology (Berl)* 120: 67–74, 1995

Deutsch SI, Rosse RB, Billingslea EN, Bellack AS, Mastropaolo J. Topiramate antagonizes MK-801 in an animal model of schizophrenia. *Eur J Pharmacol* 449: 121–125, 2002

Dimpfel W. Preclinical data base of pharmaco-specific rat EEG fingerprints (tele-stereo-EEG). *Eur J Med Res* 8: 199–207, 2003

Dimpfel W, Otten U. Studies of gangliosides in diverse nerve cell cultures. *Adv Exp Med Biol* 174: 525–534, 1984

Dimpfel W, Decker H. Classification of sulpiride, clozapine and haloperidol by toposelective recording from different brain structures in the immobilized rat (stereo-EEG). *Neuropsychobiology* 14: 157–164, 1985

Dimpfel W, Spuler M, Wessel K. Different neuroleptics show common dose and time dependent effects in quantitative field potential analysis in freely moving rats. *Psychopharmacology (Berl)* 107: 195–202, 1992

Goudie AJ, Smith JA. Discriminative stimulus properties of antipsychotics. *Pharmacol Biochem Behav* 64: 193–201, 1999

Herrmann WM. Electroencephalography in drug research: *Gustav Fischer Verlag*, 1982

Hollister LE. Antipsychotic agents and lithium. In: Katzung BG ed, *Basic and Clinical Pharmacology*. 6th ed. Prentice Hall International, London, p 432–447, 1995

Hughes AM, Lynch P, Rhodes J, Ervine CM, Yates RA. Electroencephalographic and psychomotor effects of chlorpromazine and risperidone relative to placebo in normal healthy volunteers. *Br J Clin Pharmacol* 48: 323–330, 1999

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 148: 1301–1308, 1991

Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res* 50: 41–53, 2001

Koek W, Woods JH, Winger GD. MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. *J Pharmacol Exp Ther* 245: 969–974, 1988

Lim SH, Kwon JS, Kim KM, Park SJ, Park JS, Jeong SH, Lee MG. Basic requirements for spectrum analysis of electroencephalographic effects of central acting drugs. *J Appl Pharmacol* 8: 63–71, 2000

Martin P, Waters N, Carlsson A, Carlsson ML. The apparent antipsychotic action of the 5-HT2a receptor antagonist M100907 in a mouse model of schizophrenia is counteracted by ritanserin. (Rapid communication). *J Neural Transm* 104: 561–564, 1997

McClelland GR, Cooper SM, Pilgrim AJ. A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers. *Br J Clin Pharmacol* 30: 795–803, 1990

Ninan I, Kulkarni SK. Preferential blockade by clozapine of hyperlocomotion induced by non-competitive NMDA antagonist MK-801. *Indian J Physiol Pharmacol* 42: 375–382, 1998

Sams-Dodd F. Phencyclidine in the social interaction test: an animal model of schizophrenia with face and predictive validity. *Rev Neurosci* 10: 59–90, 1999

Seeman P, Corbett R, Van Tol HH. Atypical neuroleptics have low affinity for dopamine D2 receptors or are selective for D4 receptors. *Neuropsychopharmacology* 16: 93-110; discussion 111–135, 1997

Smith JA, Boyer-Millar C, Goudie AJ. Does MK-801 discrimination constitute an animal model of schizophrenia useful for detecting

atypical antipsychotics? *Pharmacol Biochem Behav* 64: 429–433, 1999

Tiedtke PI, Bischoff C, Schmidt WJ. MK-801-induced stereotypy and its antagonism by neuroleptic drugs. *J Neural Transm Gen Sect* 81: 173–182, 1990

Varty GB, Higgins GA. Examination of drug-induced and isolation-induced disruptions of prepulse inhibition as models to screen antipsychotic drugs. *Psychopharmacology (Berl)* 122: 15–26, 1995

Yun JE, Lee MG. Electroencephalographic effects of chlorpromazine in rats. *Kor J Physiol Pharmacol* 3: 245–250, 1999

Zhang W, Pouzet B, Jongen-Relo AL, Weiner I, Feldon J. Disruption of prepulse inhibition following N-methyl-D-aspartate infusion into the ventral hippocampus is antagonized by clozapine but not by haloperidol: a possible model for the screening of atypical antipsychotics. *Neuroreport* 10: 2533–2538, 1999