Arch. Pharm. Res. Vol.18, No.3, pp. 146-152, 1995

Alterations in Motor Activity Induced by High Dose Oral Administration of Dextromethorphan Throughout two Consecutive Generations in Mice.

Hyoung-Chun Kim and Wang-Kee Jhoo

College of Pharmacy, Kangwon National University, Chuncheon, 200-701, Korea.

(Received December 28, 1994)

To achieve a better understanding of the effects on behavioral safety caused by possible neuroprotective doses (50 mg/kg, p.o.) of dextromethorphan HBr (DM), several motor activity measures were monitored in two generations of mice through a long-term period of ten months. Adult male mice (G1), in the presence of DM, developed behavioral tolerance after an initial suppression period. Prenatally exposed, second generation (G2) mice formed two groups, prenatal exposure alone (G2C) and prenatally exposed with additional postnatal exposure (G2T). In the presence of DM, group G2T was characterized by significant behavioral impairment; while G2C exhibited behavioral activation. These results suggest that more attention should be given to the prenatal effects of DM on a developing organism.

Key words : Dextromethorphan, Neuroprotective dose, Behavioral tolerance, Prenatal exposure, Behavioral impairment.

INTRODUCTION

Dextromethorphan, (DM), D-3-methoxy-N-methylmorphinan, is a nonprescription antitussive agent with surprisingly novel and complex pharmacology. Recently, DM has been shown to be an N-methyl-D-aspartate (NMDA) antagonist capable of attenuating several types of brain damage (Tortella *et al.,* 1988; Kim *et al.,* in press). The primary metabolite of DM, dextrorphan, is also an NMDA antagonist with neuroprotective properties in the animal study (Rockhold *et al.,* 1992; Tortella *et al.,* 1988). However, to block an NMDA-mediated response, the DM dosage required is higher than that used for antitussive effects (Feeser *et al.,* 1988; Finnegan *et al.,* 1991; Karler *et al.,* 1992).

After consumption of doses approximately 10 times higher than the antitussive dose of DM, patients presented signs of sedative hypnotic effect, sensory distortion, slurred speech, drunkeness, and euphoria (Jasinski *et al.,* 1971). Ironically, although the dextrorotatory morphinans are indeed devoid of morphine-like effects, they induced a striking PCP-like syndrome of effects at supra-antitussive doses. Abuses of cough suppressants, including DM, and their toxic effects are well recognized (Dodds *et al.,* 1967; Fleming, 1986; France *et al.,* 1989; Jhoo and Kim, 1990; Katona *et al.,* 1986; Orrell *et al.,* 1986; Shaul *et al.,* 1977). It is possible that the anticonvulsive and/or neuroprotective doses of DM in rodents may correspond to abusive doses in human as reflected by toxicological basis. Furthermore, high doses of some NMDA antagonist can induce neuronal vacuolation in the retrosplenial and cingulate cortices of experimental animals (Olney *et al.,* 1989). Recently, clinical evaluation of NMDA antagonists, including DM, is proceeding cautiously due to a number of safety concerns (Albers, 1990).

It is important to investigate the behavioral safety and tolerance of higher doses of DM before a clinical study can be done. Little has been reported in the literature on the chronic effects of higher doses of DM on the spontaneous behavior in rodents. In light of this safety concern, as a first step, the current study was performed to evaluate the behavioral ontogeny induced by a high dose of DM (50 mg/kg p.o.) for 10 months. Motor activities were observed after 1, 5, and 10 months of DM insults, respectively.

MATERIALS AND METHODS

Animals and breeding

Six weeks old male and nulliparous female ICR mice, weighing 20~26 g, were utilized for the experiment. Laboratory rodent chow and water were available *ad libitum.* The animal room was maintained at 22± 1°C, with 45± 5% relative humidity, and a 12

Correspondence to: H. C. Kim, College of Pharmacy, Kangwon National University, Chuncheon 200-701, Korea.

hour light/dark cycle.

One week after arrival, the mating period was initialized by placing each female into each male's cage. The female subsequently were inspected twice daily at 9 a.m. and 8 p.m. for the presence of a vaginal plug. The presence of the vaginal plug was designated pregnancy day 0. After conception, the studs were transfered to the other cages and were assigned randomly to a DM or saline control gruop. Gravid mice received DM (50 mg/kg p.o.) daily through the entire gestation period.

On postnatal day 21, the pups were weaned and examined for distinguishing gender characteristics. The female were discarded. This prevented any female which were incorrectly sexed at birth from entering the experimental paradigm. Although, an attempt was made to randomize the choice of which individuals were culled, neonates appearing to have a low chance of survival were selectively eliminated.

To get the age-matched condition corresponding to the adult/first generation (G1) group, the male pups/second generation (G2) were housed separately until behavioral testing commenced. DM (50 mg/kg p.o.) or the same volume saline was administered to both the first generation (G1) and second generation (G2) of 50-day old male mice five times a week by gastric intubation throughout the 10 month period. This study was done by following 4 experimental groups; G 1C: prolonged administration of saline (saline alone); G1T: prolonged administration of DM (DM alone); G 2C: prolonged saline administration following initial exposure to DM throughout the gestation period; and G2T: prolonged DM administration (re-exposure) following initial exposure to DM throughout the gestation period.

Drug

Dextromethorphan hydrobromide (Sigma, Co.) 5 mg dissolved in 1 ml of normal saline was administered 0.1 ml/10g of body weight by gavage. Each control mice received the same volume of normal saline solution.

Apparatus and measurement of spontaneous activity

The testing for the ontogeny of locomotor activity was carried out using the Automated Activity Monitoring System (Omnitech Electronics, Inc., Columbus, OH) in a plexiglas box (40×40×30.5 cm) with both horizontal and vertical sensors. Data were collected and analyzed by a Digiscan Analyzer (Omn-itech Model DCM), which in turn transmitted the data to an Apple II Plus computer for storage. The plexiglas boxes were thoroughly washed each session.

On the days of testing, the mice individually were placed in the activity boxes and permitted to habituate for 30 minutes. Each animal then received a DM challenge (50 mg/kg p.o.) and waited for an additional 30 minutes prior to the beginning of the testing phase. The testing phase with data collection lasted one hour. All testing was completed between 13:00 and 17:00 hours.

Five different measures were utilized in this investigation. Horizontal Activity was the total number of beam interruptions for the lower bank of sensors. Total Distance was the distance travelled by an animal in meters. Movement Times was the numbers of seconds the animal was in motion during the given time sample. Perimeter Walking was the number of times the animal made a complete trip (clockwise and anticlockwise) around the wall of the chamber; and Vertical Activity was the total number of beam interruptions for the upper bank of infrared beams.

Data were compared among the group using a Simple Effects Analysis of Variance (ANOVA) for each parameter test.

RESULTS

Body weights

No external malformation or stillborns were evident in the offspring (G2). Between 5 months and 10 months of DM treatment, five adult (G1) mice died ($P<0.05$, X^2-test); whereas all control mice survived to the completion of this study. Mean body weights for the DM treated adults (G1) were 25.4 ± 0.8 g at the beginning of drug administration and 48.9 ± 4.8 g at the end of the treatment ten months later (n=14, excluding mice that died during treatment). Corresponding weights for the G1 control mice were 23.9 ± 1.0 g at the beginning and 54.8 ± 4.2 g at the conclusion (n=9). After seven months of treatment, six animals in the G2 DM treated group died, while two control animals died. Mean body weights for the DM treated group were 25.3 ± 1.3 g at the initial dosing and 47.8 ± 6.2 g at the end of the treatment (n=9, excluding mice that died during treatment). Corresponding body weights for the control mice were 23.2 ± 1.2 g at the beginning and 56.0 ± 5.8 g at the completion (n=7). No significant differences in body weight were found among all corresponding groups. No surviving DM-treated mice appeared to be debilitated (Table I).

Each figure illustrates motor system tests for each 60 minute period, including horizontal activity, total distance, perimeter walking, movement time and vertical activity of mice treated with DM or saline throughout the two generations.

Horizontal activity

Table I. The effect of Dextromethorphan (DM) on change of body weight and mortality in each experimental group

Experimental group	ANBT	Starting body weight	The periods (months) DM administered									ANET	Total No. of dead animals
			☆1m	2m	3.5m	☆5m	6m	7m	8m	9m	☆10m		
G1C	9	23.9±1.0	29.9±2.8	33.2±3.2	38.2±4.2	42.3±3.8	46.0±2.7	49.2±5.6	52.0±3.0	53.8±3.8	54.8±4.2	9	0
G1T	19	25.4±0.8	29.0±3.0	34.3±2.8	38.7±1.9	41.4±2.9 *1	44.3±3.0	46.3±4.9 *2	47.2±3.9 *1	48.2±5.9 *1	48.9±4.8	14	5*
G2C	9	23.2±1.2	28.2±1.7	36.8±2.9	41.9±3.7	45.6±3.9	48.4±4.9	53.8±6.9 *1	53.8±5.8	55.8±6.9	56.0±5.8 *1	7	2
G2T	15	25.3±1.3	29.1±2.9	24.7±3.2	36.6±3.9	39.8±4.0	42.3±5.0	45.2±6.0 *1	45.8±5.7 *3	47.9±5.4 *1	47.8±6.2 *1	9	6

Each body weight value shows mean± S. E. Dead animals were excluded from data of body weights. ANBT: animal number at the beginning of the treatment. ANET: animal numbet at the end of the treatment. DM 50 mg/kg was administered orally to each group in the absence (G1C) and/or in presence (G2) of prenatal DM exposure for 10 months. G1C: saline alone, G1T: DM alone, G2C: saline challenge following initial exposure to DM through the entire gestation period, G2T: DM challenge following initial exposure to DM through the entire gestation period. *, dead number at each time point; ☆, time point at which was measured motor activity; #, $p<0.05$ vs. G1C (X^2-test).

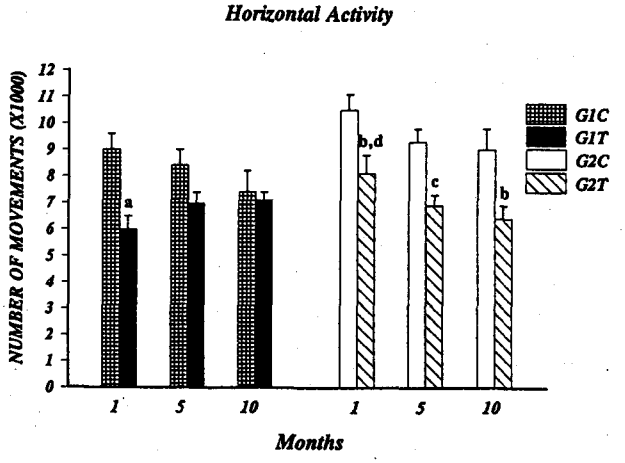

Fig. 1. Effects of chronic destomethorphan administration on horizontal activity in mice. Detailed explanation is described in Table I. Each value shows mean±S. E. of 7 to 14 experiments. a, P<0.001 vs. G1C; b, P<0.05 vs. G2C; C, P <0.01 vs. G2C; d, P<0.02 vs. G1T

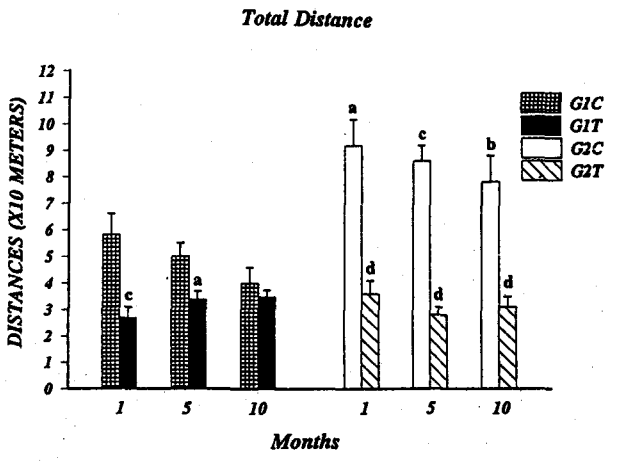

Fig. 2. Effects of chronic dextromethorphan administration on total distance of motor activity in mice. Detailed explanation is described in Table 1. Each value shows mean± S. E. of 7 to 14 experiments. a, P<0.01 vs. G1C; b, P<0.002 vs. G1C; c, P< 0.001 vs. G1C; d, P<0.001 vs. G2C

G1 animals treated with DM for one month exhibited significantly lowered activity, [F(1,21)=15.744, p <0.001]; however, activity increased to that of the control animals by the ten month period. The pup's control group (G2C) showed a tendency toward increased activity when compared to the adult control group, but did not reach statistical significance. In addition, the G2 group did exhibit a significant reduction in the presence of DM, [1 month, F(1,14)=5.565, p<0.05; 5 months, F(1,14)=12.513, p<0.01; and 10 months, F(1,14)=5.283, p<0.05]. The pup's group (G2T) was significantly more active than the adult's group (G1T) after one month of DM administration, [F(1,21)= 6.789, p<0.02]. Later time periods revealed no significant differences between either groups (Fig. 1).

Total distance

Chronic DM administration (G1T) of 1 month, [F(1, 21)=23.568, p<0.001], and 5 months, [F(1,21)=8.637, p<0.01], significantly decreased distance travelled; however, these differences progressively decreased and were close to that of the control levels by the tenth month. Significant increases were noted in the pup control group (G2C) as compared with the adult control group, [1 month, F(1,14)=9.296, p<0.01; 5 months, F(1,14)=19.840, p<0.001; and 10 months, F(1,14) =14.471, p<0.002]. The treatment group (G2T) showed significant decreases over the same time period, in comparison with the controls, [1 month, F(1,14)=37. 942, p<0.001; 5 months, F(1,14)=71.377, p<0.001; and 10 months, F(1,14)=22.343, p<0.001] (Fig. 2).

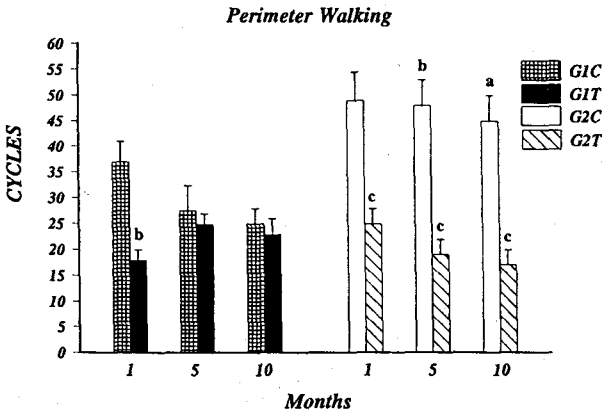

Fig. 3. Effects of chronic dextromethorphan administration on perimeter walking of motor activity in mice. Detailed explanation is described in Table I. Each value shows mean± S. E. of 7 to 14 experiments. a, P<0.01 vs. G1C; b, P<0.001 vs. G1C; c, p<0.001 vs. G2C.

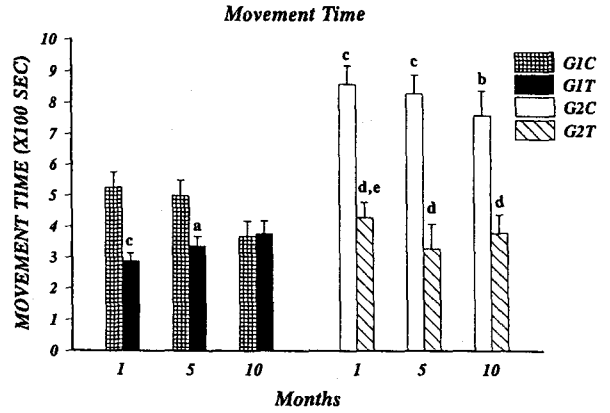

Fig. 4. Effects of chronic dextromethorphan administration on movement time of motor activity in mice. Detailed explanation is described in Table I. Each value shows mean± S. E. of 7 to 14 experiments. a, P<0.02 vs. G1C; b, P<0.002 vs. G1C; c, p<0.001 vs. G1C; d, P<0.001 vs. G2C; e, P<0.02 vs. G1T.

Perimeter walking

Significant decreases were noted for the DM one month treatment period for the adult treatment group (G1T), [F(1,21)=22.617, p<0.001] as compared to the control group, but progressive increases followed for the 5 and 10 month periods to that of the corresponding control levels (G1C). Comparison of the pup's control group (G2C) with that of the adult control group (G1C) at the one month period revealed no significant difference, [F(1,14)=3.536, p=0.08, ns]; however, significant differences were noted between the two groups at both the 5 and 10 month mark, [5 month, F(1,14)=16.988, p<0.001, and 10 months, F(1,14) =11.772, p<0.01]. The pup's (G2T) activity was dropped significantly by chronic DM administration at all three time periods, [1 month, F(1,14)=16.742, p<0.001; 5 months, F(1,14)=36.489, p<0.001; and 10 months, F(1,14)=23.905, p<0.001] (Fig. 3).

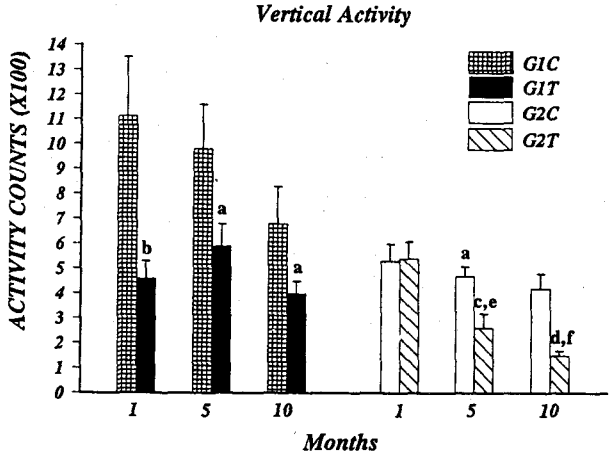

Fig. 5. Effects of chronic dextromethorphan administration on vertical activity in mice. Detailed explanation is described in Table I. Each value shows mean±S. E. of 7 to 14 experiments. a, P<0.05 vs. G1C; b, P<0.01 vs. G1C; c, p<0.05 vs. G2C; d, P<0.001 vs. G2C; e, P<0.05 vs. G1T; f, P<0.001. G1T.

Movement time

In the presence of DM, G1T movement time was reduced during the first two time periods, [1 month, F (1,21)=24.129, p<0.001; 5 months, F(1,21)=7.053, p <0.02]; however, these differences disappeared and the score at the 10 month period equalled that of the control level (G1C). The pup's control group (G2C) exhibited significant increases over time when compared with the adult control group (G1C), [1 month, F(1,14)=20.104, p<0.001; 5 months, F(1,14)=17.521, p<0.001; and 10 months, F(1,14)=15.334, p<0.002]. Chronic DM administration, however, resulted in activity decreases in G2T, [1 month, F(1,14)=27.995, p <0.001; 5 months, F(1,14)=56.171, p<0.001; and 10 months, F(1,14)=12.894, p<0.01]. The pup's group (G 2T) was more active, [F(1,21)=7.142, p<0.02], than the adult's group (G1T) after one month of treatment, but both DM treated groups showed the same levels of performance over time (Fig. 4).

Vertical activity

Chronic DM insults in the adult's group resulted in marked decrease, [1 month, F(1,21)=9.506, p<0.01; 5 months, F(1,21)=4.407, p<0.05; and 10 months, F(1, 21)=4.500, p<0.05], in vertical score throughout all observed periods as compared to corresponding controls. G2C at 5 months period presented striking reduction, [F(1,14)=5.475, p<0.05], even though reductions at the one month and 10 month period did not reach statistical significance compared with G1C. The DM challenge at the one month mark did not influence G2C's vertical score; however, the activities

at the 5 and 10 month mark decreased significantly, [5 months, $F(1,14)=5.697$, $p<0.05$; and 10 months, $F(1,14)=20.133$, $p<0.001$], compared to their respective controls. In addition, G2T exhibited significantly lowered activity at the 5 month, [$F(1,21)=5.770$, $p<0.05$], and 10 month, [$F(1,21)=18.677$, $p<0.001$], mark in comparison to their corresponding adult group (G 1T) (Fig. 5).

DISCUSSION

The purpose of this study was to evaluate the behavioral safety associated with chronic administration a neuroprotective dose (Finnegan *et al.,* 1991; Karler *et al.,* 1992) of dextromethorphan (50 mg/kg) in the rodent. The most likely method of human ingestion, the oral route (p.o.), therefore, was examined.

Interestingly, phencyclidine (PCP)-like adverse behavioral symptoms are significantly more pronounced with the oral administration than with a subcutaneous injection of a much larger dose (240 mg/kg) of DM (Jasinski *et al.,* 1971). Since DM is rapidly metabolized in the liver to dextrorphan, it is likely that side effects produced by oral administration might have been mediated by dextrorphan acting on the PCP receptor site, rather than by DM.

Whether the behavioral side effects produced by both competitive and non-competitive NMDA blockade will be similar is currently unknown. However, several studies suggest that important differences may exist. Potentially neuroprotective doses of the noncompetitive NMDA antagonist MK801 can substitute for PCP or Ketamine in behavioral experiments in which primates are taughts to distinguish between an active drug and a placebo. The competitive antagonists D-2-amino-5-phosphonovaleric acid (AP5) and cis-4-phosphonomethyl-2-piperidine-carboxylic acid (CGS19755) do not appear, however, to substitute for PCP in these paradigms (France *et al.,* 1989).

In addition, the motor excitement sometimes seen in animals given PCP or MK801 is not typically seen with a competitive antagonists. These increases in motor activity consisted of an increase in Distance Travelled, Movement Time, Perimeter Walking (all automated measures), ataxia, and head movement (Bennett *et al.,* 1988; Boast *et al.,* 1987). The observation of this pattern of motor activity requires relatively high doses of these compounds.

In the present results, however, DM did not show similar motor increases, but rather indicated a suppressive effect on the pattern of motor activity. This suppression of the early phase (1 month) in the adult DM group was reduced over time, and behavioral tolerence was evidenced. Vertical activity, on the other hand, remained suppressed throughout the entire time period. It is possible that vertical activity required more coordination, balance and muscular effort than any of the other movement measures (Turski *et al.,* 1985). In the offspring prenatally exposed to PCP, delay in development of locomotor performance in Sprague-Dawley rats (Jordan *et al.,* 1979), and a greater number of instances of vertical score elevation in Cox Swiss mice have been observed (Goodwin *et al.,* 1980). However, Hutching *et al.* (1984) could not confirm the developmental toxicity of PCP by measuring motor ativity in Wister rats dose levels of 5 and 10 mg/kg (Hutchings *et al.,* 1984). Unexpectedly, the pup's control group, which received a prenatal DM challenge, revealed a marked increase in motor activities. This increase was significant in comparison with the effects of the adult's control group, which did not receive a prenatal challenge.

The noncompetitive antagonists are lipid soluble, readily cross the blood-brain barrier, and are concentrated in the brain (Albers, 1990). Nonetheless, the female pup's control under the same experimental condition did not exhibit hyperactivity (data not shown). Thus, oral DM is producing effects in offspring in mice that is extremely subtle.

Future assessments of the motor side effects of DM should include efforts to monitor the effects of dose-dependency in different animal models. Motor activities of offspring's treated groups in the presence of DM was significantly suppressed without a development of tolerance as seen in the adult's treated group. A excitatory neurotransmission could lead to CNS depression or sedation and should be at least partially resistant to selective NMDA antagonists, even though selective NMDA antagonists have been documented to cause sedation at doses in the range of those needed for neuroprotection (Michenfelder *et al.,* 1989).

A more serious class of problems might be lasting changes related to a disturbance of normal NMDA receptor function in excitatory synaptic plasticity. NMDA antagonists block some types of synaptic long term potentiation, and might, therefore, disrupt learning and memory function (Collingridge *et al.,* 1987). Activation of NMDA receptors has been shown to be important for the normal development of the visual system in tadpoles (Cline *et al.,* 1987), and kittens (Klinschmidt *et al.,* 1987), thus prolonged NMDA receptor antagonism during early development phases could have lasting adverse effects.

In conclusion, these test measures are simple automated behavioral recordings that partially reflect various behavioral parameters which differentiate between PCP-like compound/NMDA effects and nonspecific behavioral effects. The present findings suggest that neuroprotective doses of DM for the long-term period produced behavioral suppression follo-

wed by tolerance (G1T); whereas, their offspring's behavior, in the absence of postnatal DM loading (G 2C), remained behaviorally active, and the behavioral pattern, in the presence of postnatal DM (G2T), was characterized by marked depression/impairment. Therefore, it is possible that high-dose NMDA antagonists should be avoided until more is known about their effects on the developing nervous system. The key question will be whether doses in humans that are high enough to produce neuroprotective effects also will be accompanied by an acceptable level of side effects (Albers *et al.,* 1992).

ACKNOWLEDGEMENTS

Kim, H. C. was supported by Korea Science and Engineering Foundation (1992, post-doctoral program). With great appreciation to Dr. Schenk, S., Department of psychology, Texas A & M University, USA, for her helpful discussion and assistance.

REFERENCES CITED

Albers, G. W., Potential therapeutic uses of N-methyl-D-aspartate antagonists in cerebral ischemia. *Clinical Neuropharmacology,* 13, 177-197 (1990)

Albers, G.W., Saenz, R. and Moses Jr. J. A., Tolerability of oral Dextromethorphan in patient with a history of brain ischemia. *Clinical Neuropharmacology,* 15, 509-514 (1992).

Bennett, D. A., Bernard, P. S. and Amrick, C. L., A comparison of PCP-like compounds for NMDA antagonism in two *in vivo* models. *Life Sci.,* 42, 447-454 (1988).

Boast, C. A. and Pastor, G., Characterization of motor activity patterns induced by N-methyl-D-aspartate antagonists in gerbils. *Pharmacol. Biochem. Behav.,* 27, 553-557 (1987).

Bornstein, S., Czermak, M. and Postel, J., A propes of a case of voluntary drug poisoning with Dextromethorphan HBr. *Ann. Med. Psychol.,* 1, 447-451 (1968).

Cline, H. T., Debski, E. A. and Constantin-Paton, M., N-methyl-D-aspartate receptor antagonist desegregates eye-specific stripes. *Proc. Natl. Acad. Sci.* USA, 84, 4342-4345, (1987).

Collingridge, G. L. and Bliss, T. V., NMDA receptors-their role in long-term potentiation., *Trends in Neurosci.,* 10, 288-293 (1987).

Dodds, A. and Reval, E., Toxic psychosis due to Dextromethorphan. *Med. J. Aust.,* 2, 231 (1967).

Feeser, H. R., Kadis, J. D. and Prince, D. A., Dextromethrophan, a common antitussive, reduces kindled amygdala seizures in the rat. *Neurosci. Lett.,* 86, 340-345 (1988).

Finnegan, K. T., Kerr, J. T. and Langston, J. W., Dextromethorphan protects against the neurotoxic effects of p-chloroamphetamine in rats. *Brain Res.,* 558, 109-111 (1991).

Fleming, P. M., Dependence on Dextromethorphan HBr. *Br. Med. J.,* 293, 597 (1986).

France, C. P., Woods, J. H. and Ornstein, P., The competitive NMDA antagonist CGS 19755 attenuates the rate-decreasing effects of NMDA in rhesus monkeys without producing ketamine-like discrinative effects. *Eur. J. Pharmacol.,* 159, 133-139 (1989).

Goodwin, P. J., Perez, V. J., Eatwell, J. C. Palet, J. C. and Jaworski, M. T., Phencyclidine : Effects of chronic administration in the female mouse on gestation, maternal behavior and the neonates. *Psychopharmacol.,* 69, 63-67 (1980).

Hiramatsu, M., Cho, A. K. and Nabeshima, T., Comparison of the behavior and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. *Eur. J. Pharmacol.,* 166, 359-366 (1989).

Hutchings, D. E., Bodnarenko, S. R. and Diaz-Deleon, R., Phencycline during pregnancy in the rat : Effects on locomotor activity in the offspring. *Pharmacol. Biochem. Behav.,* 20, 251-254 (1984).

Jasinski, D. R., Martin, W. R. and Manski, P. A., Progress report on the assessment of the antagonist nalbuphine and GPA-2087 for abuse potential and studies of the effects of Dextromethorphan in man. *National Academy of Science/National Research Council.,* 1, 143-178 (1971).

Jhoo, W. K. and Kim, H. C., Drug abuse among korean adolescents. *The international congress of applied psychology* (Kyoto, Japan). 22, 330 (1990).

Jordan, R. L., Young, T. R., Pinwiddie, S. H. and Harry, G. J., Phencyclidine induced morphological and behavioral alterations in the neonatal rat. *Pharmacol. Biochem. Behav. Suppl.,* 11, 39-45 (1979).

Karler, R. and Calder, L. D., Excitatory amino acids and the actions of cocaine. *Brain Res.,* 582, 143-146 (1992).

Katona, B. and Wason, S., Dextromethorphan danger. *New Eng. J. Med.,* 314, 993 (1986).

Kim, H. C., Pennypacker, K. Bing, G., Bronstein, D., McMillian, M. and Hong, J., The effects of Dextromethorphan on kainic acid-induced seizures in the rat. *Neurotoxicol.,* in press.

Kim, H. C., Kwon, M. S. and Jhoo, W. K., Influence of chronic dextromethorphan administration on cellular immune response in mice. *The 43rd Convention of the Pharmaceutical Society of Korea.,* (1994).

Klinschmidt, A., Bear, M. F. and Singer, W., Blockade of NMDA receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science,* 238, 355-357 (1987).

Michenfelder, J. D., Lanier, W. R., Scheithauer, B. W., Perkins, W. J., Shearman, G. T. and Milde, J. H., Evaluation of the glutamate antagonist Mk-801 on neurologic outcome in a canine model of complete cerebral ischemia: Correlation with hippocampal histopathology. *Brain Res.*, 481, 228-234 (1989).

Musacchio, J. M., Klain, M. and Canoll, D., Dextromethorphan and sigma ligands: Common sites but diverse effects. *Life Sci.*, 45, 1721-1732 (1989).

Olney, J. W., Labruyere, J. and Price, M. T., Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science*, 244, 1360-1362 (1989).

Orrell, M. and Campbell, P. G., Dependence on Dextromethorphan HBr. *Br. Med. J.*, 293, 1242-1243 (1986).

Rockhold, R. W., Surrett, R. S., Oden, G., Acuff, C. G., Farley, J. M., Zhang, T., Hoskins, B. and Ho, I. K., Inhibition of cocaine intoxification by excitatory amino acid receptor antagonists. *Ann N.Y. Acad.*, 648, 335-337 (1992).

Shaul, W. M., Wandell, M. and Robertson, W. O., Dextromethorphan toxicity: Reversal by Naloxone. *Pediatrics*, 59, 117-119 (1977).

Tortella, F. C., Ferkany, J. W. and Pontecorbo, M. J., Anticonvulsant effects of dextrorphan in rats: Possible involvement in dextromethorphan-induced seizure protection. *Life Sci.*, 42, 2509-2514 (1988).

Tortella, F. C., Pellicano, M. and Bowery, N. G., Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends in Pharmacol. Sci.*, 10, 501-507 (1989).

Turski, L. Schwarz, M., Turski, W. A., Klockgether, T., Sontag, K. and Collins, J. F., Muscle relaxant action of excitatory amino acid antagonists. *Neurosci. Lett.*, 53, 321-326 (1985).