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Short communication

Convulsant and anticonvulsant effects of bupropion in mice

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Abstract

This study demonstrated that bupropion hydrochloride, an effective antidepressant and a commonly used smoking cessation aid, dose-dependently caused clonic convulsions in mice, with the CD_{50} (convulsive $dose_{50}$, i.e., the dose producing convulsions in 50% of mice) at 119.7 mg kg^{-1}. An evaluation for anticonvulsant effects showed that bupropion in the doses of 15–30 mg kg^{-1} protected against convulsions induced by maximal electroshock with the ED_{50} (effective $dose_{50}$, i.e., the dose protected 50% of mice against convulsions) being 19.4 mg kg^{-1}. Bupropion had no effect on pentylenetetrazole- and kainic acid-induced convulsions. It is possible that the anticonvulsant activity of bupropion may be exploited for use in the treatment of epilepsy but it requires further investigations.

Keywords: Bupropion; Seizure; Antidepressant drug; Smoking cessation; Epilepsy

1. Introduction

Originally approved as an antidepressant, bupropion hydrochloride is recommended for first-line pharmacotherapy for tobacco dependence (JAMA, 2000). Clinical observations have shown that bupropion, like many other antidepressant drugs, may produce seizures after an accidental or intentional massive overdose or even in the doses considered to be therapeutic (Van Wyck Fleet et al., 1983; Johnston et al., 1991; Pesola and Avasarala, 2002). However, the mechanism of the bupropion convulsant effect still remains unknown.

Since experimental evidence for bupropion contribution to the induction and propagation of seizures is very limited, there is a need for detailed animal studies on the issue. Therefore, in the present study we examined whether bupropion, similarly to humans, had convulsant activity in mice. In the second part of the experiments, we investigated an effect of lower doses of bupropion on electrically and chemically induced convulsions.

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2. Materials and methods

2.1. Animals

The experiments were performed on male Swiss mice weighing 20–25 g. The animals were acclimatized for 1 week and housed in standard laboratory conditions, on a natural light-day cycle, in colony cages with free access to chow pellets and tap water. The experimental groups, consisting of eight animals, were chosen by means of a randomized schedule. All testing procedures were performed between 12:00 a.m. and 6:00 p.m. The experimental protocol was approved by the Medical University of Lublin Ethics Committee for the use of experimental animals.

2.2. Drugs

Bupropion hydrochloride (Zyban; Glaxo-Wellcome, Greenford, Middlesex, UK) was suspended in a 1% solution of Tween 81 (Loba Chemie, Vienna, Austria) and administered intraperitoneally (i.p.) in a volume of 10 ml kg^{-1} of body weight. Kainic acid and pentylenetetrazole (both from

Sigma, St. Louis, MO, USA) were dissolved in sterile saline to be administered i.p. and subcutaneously (s.c.), respectively. Control mice received sterile saline.

2.3. Convulsant activity of bupropion

Four groups of mice were injected i.p. with various doses of bupropion (100–160 mg kg^{-1}). Then, mice were observed for 60 min and the number of convulsing out of the total number of mice tested was noted for each treatment condition. Clonic convulsion, defined as clonus of all four limbs with loss of righting reflex for at least 5 s, was the endpoint. The bupropion convulsant activity was evaluated as the CD_{50} and CD_{97} (convulsive $doses_{50}$ and $_{97}$, i.e., the doses of bupropion producing convulsions in 50% and 97% of mice, respectively). The CD_{50} and CD_{97} were calculated from dose–response curve of four data points.

2.4. Effects of bupropion on maximal electroshock-, kainic acid-, and pentylenetetrazole-induced convulsions and lethality

Electroconvulsions were produced according to Swinyard et al. (1952) with the use of ear-clip electrodes and alternating current generator (Hugo Sachs type 221, Freiburg, Germany; stimulus duration 0.2 s, 50 Hz). Tonic extension of hind limbs was the criterion for convulsant activity. Mice were treated with different doses of bupropion 30 min before maximal electroshock. The ED_{50} (effective dose 50, i.e., the dose of bupropion protecting 50% of mice against convulsions) value was determined on the basis of the percentage of protected mice. To estimate the ED_{50}, five groups of mice were used.

In the pentylenetetrazole or kainic acid models of epilepsy, following the pentylenetetrazole or kainic acid injection, each mouse was placed into a separate Plexiglass transparent cage and observed for 30 min and 1 h, respectively. The abolition of the clonus lasting at least 5 s was chosen as the endpoint. Latency until convulsant activity occurred was determined. Again, the ED_{50} values of pentylenetetrazole and kainic acid were estimated. Lethality was assessed 2 h after pentylenetetrazole or kainic acid administration.

2.5. Statistics

The CD_{50}, CD_{97}, and ED_{50} values as well as statistical analysis of the data were estimated by computer probit analysis, according to Litchfield and Wilcoxon (1949). The index of probability of 0.05 or less ($P<0.05$) was considered significant in comparative analysis. The latency results were analyzed by Kruskal–Wallis non-parametric analysis of variance (ANOVA) test and expressed as median along with the minimum and maximum values (min−max).

3. Results

3.1. Convulsant activity of bupropion

Bupropion administered i.p. dose-dependently caused clonic convulsions, with the CD_{50} and CD_{97} being 119.7 (104.1–137.6) and 156.7 mg kg^{-1}, respectively (see Fig. 1). Initially, mice showed hyperactivity, chewing, head movements, followed by balance impairment and Straub tail. After a few minutes, clonus of forelimbs occurred, followed by loss of righting reflex and clonus of all four limbs. When bupropion was given at a full convulsant dose of 160 mg kg^{-1}, the median latency was 6.00 min (3.50–8.15). Tonic convulsions were observed occasionally (1 per 8 mice) only in the groups receiving bupropion at 140 or 160 mg kg^{-1}.

3.2. Effects of bupropion on maximal electroshock-, pentylenetetrazole- and kainic acid-induced convulsions and lethality

Bupropion in the doses of 15–30 mg kg^{-1} inhibited maximal electroshock-induced convulsions. The incidence of anticonvulsive protection in mice treated with bupropion in doses of 10, 15, 20, 25, and 30 mg kg^{-1} was 0%, 12.5%, 50%, 62.5% and 100%, respectively. The ED_{50} value of bupropion was 19.4 (16.8–22.5) mg kg^{-1} (Table 1).

As shown in Table 1, bupropion in the doses of 5–50 mg kg^{-1} (which per se did not produce convulsions) had no significant effect on the CD_{50} of pentylenetetrazole. The median latency for a group receiving pentylenetetrazole in the dose of 70 mg kg^{-1} was 6.03 min (3.05–30.00) and for the groups receiving both pentylenetetrazole (70 mg kg^{-1}) and bupropion in the doses of 5, 20, or 50 mg kg^{-1}, was 5.33 min (4.20–30.00), 7.33 min (4.35–30.00) and 4.53 min (3.00–30.00), respectively (not significant vs. pentylenetetrazole alone treated group).

No lethality among animals receiving pentylenetetrazole alone (70 mg kg^{-1}) or pentylenetetrazole (70 mg kg^{-1}) and bupropion in the doses of 5 or 20 mg kg^{-1} was observed. In

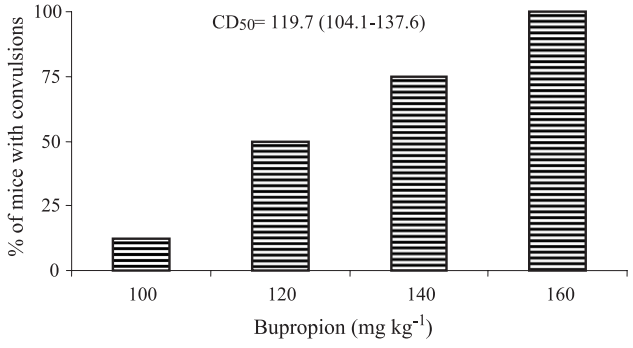

Fig. 1. Convulsant effect of bupropion in mice. The bars represent a percentage of animals with convulsions. To determine CD_{50} value, four groups consisting of eight mice were used.

Table 1
Influence of bupropion (BUP) on convulsions induced by maximal electroshock (MES), pentylenetetrazole (PTZ), and kainic acid (KA) in mice

Treatment (mg kg^{-1})		Convulsions	Lethality	
MES+Saline		8/8	0/8	
MES+BUP	10	8/8	0/8	
	15	7/8	0/8	
	20	4/8	0/8	ED_{50}=19.4 (16.8–22.5)
	25	3/8	0/8	
	30	0/8	0/8	
Saline+PTZ	40	1/8	0/8	
	50	4/8	0/8	CD_{50}=54.4 (46.6–63.4)
	60	5/8	0/8	
	70	6/8	0/8	
BUP 5+PTZ	50	1/8	0/8	
	60	5/8	0/8	CD_{50}=58.4 (50.7–67.2)
	70	7/8	0/8	
BUP 20+PTZ	50	2/8	0/8	
	60	4/8	0/8	CD_{50}=58.8 (52.2–66.2)
	70	5/8	0/8	
	80	8/8	3/8	
BUP 50+PTZ	40	0/8	0/8	
	50	2/8	1/8	CD_{50}=56.3 (50.6–62.6)
	60	6/8	2/8	
	70	7/8	3/8	
Saline+KA	30	0/8	0/8	
	40	3/8	0/8	CD_{50}=45.3 (39.5–51.8)
	50	6/8	3/8	
	60	7/8	7/8	
BUP 20+KA	30	0/8	0/8	
	35	3/8	1/8	CD_{50}=41.6 (36.7–47.3)
	40	4/8	1/8	
	50	6/8	5/8	
BUP 50+KA	30	0/8	0/8	
	35	1/8	1/8	CD_{50}=42.8 (38.1–48.1)
	40	4/8	4/8	
	50	6/8	4/8	

Data are expressed as a number of convulsing (convulsion study) or dead (lethality study) animals in relation to the total number of animals tested in the single experiment.
The ED_{50} of BUP and CD_{50} of PTZ or KA with 95% confidence limits in parentheses were calculated and compared according to the method elaborated by Litchfield and Wilcoxon (1949). BUP was administered i.p. 30 min before s.c. PTZ injection, i.p. KA injection or MES. For more details, see Materials and methods.

a group treated with pentylenetetrazole (70 mg kg^{-1}) and bupropion in the dose of 50 mg kg^{-1}, 37.5% of mice died.

Bupropion in the doses of 20 or 50 mg kg^{-1} did not change significantly the CD_{50} of kainic acid (Table 1). The median latency for a group receiving kainic acid alone in the dose of 50 mg kg^{-1} was 18.00 (12.10–60.00) min and for the groups receiving both kainic acid (50 mg kg^{-1}) and bupropion (20 or 50 mg kg^{-1}) was 16.23 (8.45–60.00) and 23.00 (7.10–60.00) min, respectively (not significant vs. kainic acid alone treated group).

When kainic acid was administered in the dose of 50 mg kg^{-1}, the lethality was 37.5%, while in the groups receiving both kainic acid (50 mg kg^{-1}) and bupropion in the doses of 20 or 50 mg kg^{-1}, was 12.5% and 50%, respectively.

4. Discussion

Seizures are uncommon, but serious, adverse effects of antidepressant drugs (Peck et al., 1983; Dailey and Naritoku, 1996). This study showed that the monocyclic antidepressant bupropion, an inhibitor of the neuronal reuptake of dopamine and norepinephrine, commonly used as a unique non-nicotine smoking cessation aid, caused clonic convulsions in mice. Similarly to humans seizures (Davidson, 1989), the occurrence of convulsions in mice was dose-dependent.

So far, the treatment of bupropion-induced seizures in humans has been empirical (Belson and Kelley, 2002; Pesola and Avasarala, 2002). Our results indicate that mice can be a good model for studying pharmacological mechanism(s) of bupropion-induced convulsions and for preclinical evaluation of the effectiveness of antiepileptic drugs in these convulsions.

On the other hand, bupropion in lower doses, which per se did not produce convulsions, significantly protected against convulsions evoked by maximal electroshock which may serve as a model for human generalized tonic–clonic seizures. Both clinical and experimental data show that many antidepressant drugs have anticonvulsant activity. Imipramine blocked maximal electroshock-induced convulsions while exerting little or no effect on pentylenetetrazole-induced convulsions in mice (Lange et al., 1976). Fluoxetine suppressed behavioral and electrographic seizure activity in convulsions induced by focal intracerebral application of bicuculline in rats (Prendiville and Gale, 1993). Recently, Slemmer et al. (2000) found that bupropion was effective in antagonizing nicotine-induced convulsions in mice. In our experiments, however, bupropion, showing protection against maximal electroshock-induced convulsions, failed to block pentylenetetrazole- and kainic acid-induced convulsions. Pentylenetetrazole may serve as a model for human myoclonic seizures (Löscher and Schmidt, 1988) and kainic acid has been extensively used as a model of complex partial seizures and/or status epilepticus (Ben-Ari, 1985; Sperk, 1994). Taken together, our results seem to

indicate that the anticonvulsant effect of bupropion depends on the animal model of epilepsy.

In summary, the present findings support and extend previous observations of other investigators who showed that antidepressant drugs have biphasic effects in experimental models of epilepsy and may both prevent and cause convulsions. Bupropion has been well known to produce seizures in humans. However, this study demonstrates that bupropion has also anticonvulsant properties. It is possible that the anticonvulsant activity of bupropion may be exploited for use in the treatment of generalized tonic–clonic seizures but it requires further investigations.

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