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Low dose of bupropion significantly enhances the anticonvulsant activity of felbamate, lamotrigine and topiramate in mice

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ABSTRACT

Experimental evidence indicates that bupropion hydrochloride, an antidepressant and a first-line smoking cessation aid, exerts dose-dependently anticonvulsant and convulsant effects. In this study, chronic bupropion pretreatment intraperitoneally (i.p.) for 14 days in a dose of 5 mg/kg reduced the ED_{50} (i.e. the dose protecting 50% of mice against electroconvulsions) of lamotrigine, topiramate, and felbamate from 4.58, 60.95, and 48.79 (antiepileptic + vehicle) to 3.01, 41.68, and 37.28 mg/kg (antiepileptic + bupropion), respectively, against maximal electroshock-induced seizures in mice. Bupropion significantly increased the plasma and brain concentrations of lamotrigine. Plasma concentration of topiramate was elevated, however, the brain concentration of the drug was not affected. Neither plasma nor brain concentrations of felbamate were elevated by bupropion administration. Bupropion did not exacerbate motor coordination impairment caused by the antiepileptic drugs in the rotarod test. Chronic administration of bupropion significantly potentiates the protective activity of lamotrigine, topiramate, and felbamate against maximal electroshock-induced seizures. A pharmacokinetic interaction is responsible for the effect of bupropion co-administered with lamotrigine.

1. Introduction

Accumulating evidence indicates that depression represents the most frequent psychiatric comorbidity in epileptic patients (Seethalakshmi and Krishnamoorthy, 2007), and may appear in more than 60% of patients with epilepsy (Kanner and Palac, 2000). Nevertheless, neurologists typically focus on the adequate control and reduction of seizures in these patients. Underdiagnosed and largely untreated depression may lead to increased seizure frequency and can be deleterious to quality of life (Boylan et al., 2004).

Additionally, seizures may develop in patients with previously diagnosed depression. Many antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and atypical antidepressants like bupropion, may decrease seizure threshold and promote seizures (Montgomery, 2005; Unverir et al., 2006).

Bupropion was approved in the treatment of major depressive disorders and prevention of seasonal affective disorder (FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, 2008), as well as a first-line treatment of nicotine addiction (Nides, 2008).

The efficacy of bupropion in depression and smoking cessation has been attributed to its effects on monoaminergic neurotransmission. Although mechanism(s) of its action is(are) still not fully understood, it is believed to result from dopamine and norepinephrine reuptake inhibition, and, additionally, from antagonizing several subtypes of neuronal nicotinic acetylcholine receptors ($\alpha3\beta2$, $\alpha4\beta2$ and $\alpha7$) (Salminen et al., 2004; Rau et al., 2005). It has been shown that bupropion enhances dopaminergic and noradrenergic functions by blocking the dopamine and norepinephrine transporters (Learned-Coughlin et al., 2003; Argyelan et al., 2005), without binding to receptors (Ferris and Cooper, 1993).

Bupropion is generally well tolerated. Most dangerous adverse effect, however, is the increased incidence of seizures. A dose-dependent risk of convulsions has been reported in both animals (Tutka et al., 2004; Silverstone et al., 2008a,b) and humans (Johnston et al., 1991; Shepherd, 2005; Rissmiller and Campo, 2007).

Clinical reports indicate that bupropion accounts for 0.1–1.4% of the new-onset generalized seizures presenting to an emergency department (Johnston et al., 1991; Pesola and Avasarala, 2002), mainly as a result of accidental or intentional drug overdose (Shepherd, 2005;

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Morazin et al., 2007). Seizures may occur in patients taking bupropion not only in overdose, but also in doses considered to be therapeutic (Shepherd, 2005; Rissmiller and Campo, 2007). Nonetheless, there are reports suggesting that the risk of seizures associated with sustained-release bupropion is not higher than that in the general population (up to 0.1%) (Montgomery, 2005).

Surprisingly, bupropion was shown to have anticonvulsive activity in animal models of epilepsy. In lower doses, which per se did not produce convulsions, bupropion significantly protected against convulsions evoked by maximal electroshock which may serve as a model for human generalized tonic–clonic seizures. (Tutka et al., 2004). Slemmer et al. (2000) found that bupropion was effective in antagonizing nicotine-induced convulsions in mice. However, bupropion failed to block pentylenetetrazole- and kainic acid-induced convulsions (Tutka et al., 2004). Taken together, the results seem to indicate that the anticonvulsant effect of bupropion depends on the animal model of epilepsy.

There have been no published studies examining the influence of bupropion on the anticonvulsive activity of the antiepileptics. The aim of the study was, therefore, to evaluate whether chronic administration of bupropion affects the anticonvulsive action of three second-generation antiepileptic drugs, i.e. lamotrigine, topiramate, and felbamate on maximal electroshock-induced convulsions, which are thought to be an experimental model of human generalized tonic–clonic seizures in mice. Additionally, the effect of bupropion on motor impairment produced by the antiepileptic drugs was investigated in a rotarod test.

2. Experimental procedures

2.1. Animals and experimental conditions

The experiments were carried out on adult male Swiss mice housed under controlled laboratory conditions (ambient temperature 20 ± 2 °C, relative humidity 55 ± 3% and natural light/dark cycle). The animals were kept in colony cages with a free access to chow pellets and tap water. The experiments started after at least 6 days of acclimatization of mice to the environmental conditions. The groups of mice consisted of 8–10 animals and were chosen by means of a randomized schedule and each animal was used once only. All the experimental procedures were carried out between 9 A.M. and 2 P.M. The control groups were always tested on the same day as the respective experimental groups. The experimental protocols and procedures were followed according to "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985), approved by the Medical University of Lublin Ethics Committee for the use of experimental animals and confirmed with the European Communities Council Directive (86/609/EEC).

2.2. Drugs

The following drugs were used in this study: bupropion hydrochloride (Zyban, GlaxoSmithKine Pharmaceuticals S.A., Poznan, Poland), felbamate (Felbamate, Tocris Bioscience, Bristol, United Kingdom), lamotrigine (Lamitrin, GlaxoSmithKline Pharmaceuticals S.A., Poznan, Poland), and topiramate (Topamax, Janssen Pharmaceutica N.V., Beerse, Belgium). All drugs were suspended in 1% solution of Tween 80 (Sigma, St. Loius, MO, USA) in sterile saline immediately before injection and administered intraperitoneally (i.p.) in a volume of 0.01 ml/g. Fresh drug suspensions were prepared *ex tempore* on each day of experimentation. Bupropion was administered every 12 h for 14 days, and only once on the 15th day, 30 min before the appropriate tests. The antiepileptics were injected on the 15th day, 60 min before tests and 30 min before the injection of bupropion. Pretreatment times of the drugs were based on information on their behavioral effects from the literature (Luszczki and Czuczwar, 2004) and confirmed in our pilot experiments. Control animals received adequate amounts of vehicle (1% solution of Tween 80 in sterile saline) in the same manner, i.e., every 12 h for 14 days.

2.3. Electrically-induced convulsions

Electroconvulsions were induced according to Swinyard et al. (1952) with the use of alternating current impulses (50 Hz, 0.2 s) delivered from a generator (Rodent Shocker, type 221, Hugo Sachs Elektronik, Freiburg, Germany) via ear-clip electrodes.

In the first part of the experiments, the electroconvulsive threshold for chronic (14 days) administration of bupropion was determined. For this purpose, CS_{50} value (i.e. median current strength in mA, necessary to induce tonic hind limbs extension in 50% of animals) was calculated. Three doses of bupropion were screened: 5, 7.5 and 10 mg/kg. Full tonic extension of the hind limbs was taken as the end point. In each case, at least four groups of mice consisting of eight animals received bupropion at the respective doses were used. Mice were subjected to current stimulation with different intensities (5–13 mA) and, depending on the number of convulsing animals, an intensity–response curve was calculated according to Litchfield and Wilcoxon method (1949). The control group of mice received the adequate amount of vehicle.

In the second part of the experiments, the maximal electroshock model was applied to evaluate the protective efficacy of chronic administration of bupropion. For this purpose, bupropion was administered in a previously determined subthreshold dose of 5 mg/kg, i.e., the highest dose that did not significantly change electroconvulsive threshold in previous experiments. Again, minimum four groups of mice consisting of eight animals were used and challenged with set current intensity of 25 mA and 0.2 s stimulus duration. Complete protection against tonic convulsions during 1 min observation was taken as the end point. The study groups received progressive doses of antiepileptic drug in combination with bupropion (5 mg/kg) and control groups received progressive doses of antiepileptic drug and vehicle. The antiepileptic drugs were administered in the following doses: felbamate — 20–60, lamotrigine — 2–6, and topiramate — 30–80 mg/kg. Anticonvulsant activity of the antiepileptic drugs was determined as ED_{50} values (i.e., doses of the drugs in mg/kg, protecting 50% of animals against maximal electroshock-induced convulsions). Depending on the number of protected animals, a dose–response curve for each antiepileptic drug was calculated according to Litchfield and Wilcoxon method (1949). The ED_{50} of the antiepileptic drug for mice pretreated with bupropion were compared with the respective ED_{50} of the antiepileptic drug administered separately (+vehicle).

2.4. The rotarod test

The rotarod test was applied to assess the influence of chronic administration of bupropion on motor coordination impairment caused by antiepileptic drugs. The experiments were performed on the rotating track BD-5 type (COTM, Bialystok, Poland) according to Dunham and Miya (1957). Each animal was placed on a 3-cm diameter, 10-cm long wooden rod, rotating with constant speed of 1.25 cm/s (8 rpm). Impairment of motor coordination was defined as inability of mice to remain on the rotating rod for a 180 s test period. Experimentally naïve animals were pretrained on the rotating track 24 h before the proper test, and all mice that had fallen off the rod were excluded from further experiments. Dose–response curve calculated according to Litchfield and Wilcoxon method (1949) and the respective TD_{50} values (i.e., doses of the antiepileptics which caused impairment of motor coordination in 50% of animals) were determined. In each case, TD_{50} for the study group of mice (antiepileptic drug + bupropion) was compared with TD_{50} for the respective control group (antiepileptic drug + vehicle).