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Felbamate demonstrates low propensity for interaction with methylxanthines and Ca^{2+} channel modulators against experimental seizures in mice

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Abstract

The aim of this study was to determine the interaction potential of the new antiepileptic drug felbamate (2-phenyl-1,3-propanediol dicarbamate) with three Ca^{2+} channel blockers (nicardipine, nifedipine, and flunarizine), one Ca^{2+} channel activator (Bay K 8644; 1,4-dihydro-2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)-phenyl]-3-pyridine carboxylic acid), and two methylxanthines (caffeine and aminophylline (theophylline$_2$ · ethylenediamine)) which are all known to markedly change protective effects of conventional antiepileptic drugs. To do so, the maximal electroshock seizure test in mice (an experimental model predicting drug efficacy in the treatment of human generalized tonic–clonic seizures) was employed to (1) quantify changes in the protective efficacy and potency of felbamate produced by adjunct drugs and (2) assess the ability of aminophylline and caffeine to affect protective efficacy afforded by a submaximal protective dose of felbamate against maximal electroshock-induced seizures. Doses of adjunct drugs were selected based on their effects on the threshold for electroconvulsions and on appropriate literature. Nicardipine (10–30 mg/kg), nifedipine (5–20 mg/kg), flunarizine (2.5–10 mg/kg), Bay K 8644 (2.5–5 mg/kg), and aminophylline (50–75 mg/kg) did not change the protective efficacy and potency of felbamate against maximal electroshock-induced tonic convulsions. Aminophylline in the dose of 100 mg/kg, however, diminished the protective potency of felbamate as evidenced by a statistically significant increase in the protective ED_{50} value of felbamate (a dose, in mg/kg, predicted to protect 50% of mice against convulsive stimulus) from 79.6 to 118 mg/kg; $P < 0.05$). Aminophylline and caffeine only at high doses (100 and 161.7 mg/kg, respectively) significantly diminished the protective efficacy of felbamate (110 mg/kg) from 96% to 27% and 40% ($P < 0.05$), respectively. In conclusion, felbamate shows low interaction potential with Ca^{2+} channel modulators and methylxanthines. Such low interaction potential clearly differentiates felbamate from conventional antiepileptic drugs where protective effects are readily altered by the compounds tested in the present study.

Keywords: Felbamate; Nicardipine; Nifedipine; Flunarizine; Bay K 8644; Aminophylline; Caffeine; Convulsion; Drug interaction

1. Introduction

Studies on drug interactions in experimental models of epilepsy not only uncover their basic pharmacological properties (White, 1997), but also form rationales for either use or avoidance of certain drug combinations in clinical practice (Meinardi, 1995). As far as antiepileptic drugs are concerned, there are two main types of drug interaction. The first is when one antiepileptic drug is combined with another antiepileptic drug to achieve better control of seizures (Meinardi, 1995). The second occurs when an antiepileptic drug is co-administered with a non-antiepileptic drug due to general medical indication accompanying epilepsy (Parent and Aminoff, 1996). As experimental (see citations below) and clinical (Meinardi, 1995) studies reveal, the protective effectiveness of conventional antiepileptic drugs can be markedly changed by adding a non-antiepileptic adjunct drug. Examples of such drugs include specific methylxanthines and Ca^{2+} channel blockers, both frequently used in the management of clinical conditions requiring, respectively, bronchodilatation or vasodilatation (Fisher and Grotta, 1993; Serafin, 1996).

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Aminophylline (theophylline$_2$ · ethylenediamine) and caffeine can induce clonic–tonic seizures in doses above 200 mg/kg (Chu, 1981; Czuczwar et al., 1987a), whereas lower doses ($\leq$ 50 mg/kg) can markedly diminish the protective effects of all conventional antiepileptic drugs examined in experimental models of generalized (Czuczwar et al., 1986, 1987c, 1989, 1990b; Polc et al., 1986) and partial (Czuczwar et al., 1987b) seizures. Even at therapeutic doses in humans, theophylline and aminophylline have been reported to produce toxic symptoms including focal and generalized seizures (Zwillich et al., 1975; Goldberg et al., 1986; Shannon, 1993). As with animal models (Czuczwar et al., 1987a), methylxanthine-induced seizures in humans appear to be refractory to standard anticonvulsive treatments and may be fatal (Zwillich et al., 1975; Goldberg et al., 1986).

In contrast, different pharmacological effects may be expected when Ca^{2+} channel blockers are co-administered with antiepileptic drugs. Some Ca^{2+} channel blockers show anticonvulsive effectiveness per se (Shelton et al., 1987; De Sarro et al., 1988; Dolin et al., 1988; Czuczwar et al., 1990a,c Czuczwar et al., 1992; Palmer et al., 1993) and/or have the ability to potentiate the protective action of classical antiepileptic drugs (Czuczwar et al., 1990a,c, 1992; Gasior et al., 1996b) against a number of experimental models of seizures. Efficacy of flunarizine, nimodipine and nifedipine as additional therapy in patients with refractory epilepsy has also been documented in some cases (Binnie, 1989; Schmidt and Ried, 1989; Larkin et al., 1992).

Recently, several new antiepileptic drugs have been approved to improve the prognosis of epilepsy (Perucca, 1996). According to Perucca (1996), ''From a pharmacokinetic perspective, many of the newer drugs possess advantageous features.'' They also bear high interaction potential with other antiepileptic drugs and likely with non-antiepileptic drugs. However, the availability of data concerning interactions of newly developed antiepileptic drugs with non-antiepileptic drugs is limited. Thus, the aim of this study was to assess the propensity of the new antiepileptic drug felbamate (2-phenyl-1,3-propanediol dicarbamate) to interact with methylxanthines (aminophylline and caffeine), Ca^{2+} channel antagonists (nicardipine, nifedipine, flunarizine), and the Ca^{2+} channel activator Bay K 8644 against maximal electroshock-induced convulsions in mice. This measure stands as a recognized model predictive of drug efficacy in the treatment of generalized tonic–clonic convulsions in humans.

2. Materials and methods

2.1. General

Male Swiss mice weighing between 24 and 30 g were housed in colony cages with unlimited access to tap water and food. Standard laboratory conditions with a natural light–dark cycle were maintained throughout the housing. After animals adapted to laboratory conditions for 10 days, experimental group assignments (8 to 10 animals per group) were formed randomly. All experiments were performed between 09:00 and 14:00 on experimentally naive animals.

2.2. Drugs and administration regimens

The drugs used in this study included one antiepileptic drug felbamate (2-phenyl-1,3-propanediol dicarbamate; Wallace Laboratories, Cranbury, NJ, USA), two Ca^{2+} channel blockers of the dihydropyridine class nicardipine and nifedipine (both from Sigma, St. Louis, MO, USA), and one of the diphenylalkylamine class flunarizine (Polfa, Starogard, Poland), one Ca^{2+} channel activator (±)-Bay K 8644 (1,4-dihydro-2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)-phenyl]-3-pyridine carboxylic acid; RBI, Natick, MA, USA), two methylxanthines caffeine (Coffeinum Natrium benzoicum, Polfa, Łódź, Poland) and aminophylline (theophylline$_2$ · ethylenediamine; Polfa, Kraków, Poland). Felbamate and the Ca^{2+} channel modulators were suspended in a 1% solution of Tween 81 (Loba Chemie, Vienna, Austria). Methylxanthines, at doses referring to their free-base forms, were dissolved in sterile water. All solutions were freshly prepared and injected i.p. except for Bay K 8644 which was administered s.c. The injection volume was 0.1 ml per 10 g of body weight. Solutions of nicardipine, nifedipine and Bay K 8644 were handled in darkroom conditions. Pretreatment times for felbamate, Ca^{2+} channel blockers, methylxanthines, and Bay K 8644 were 60, 60, 30 and 15 min, respectively. When drug combinations were tested, mice were administered felbamate first and then with an adjunct drug at the times scheduled. Animals receiving appropriate vehicles served as control groups.

2.3. Electroconvulsive seizures and anticonvulsant testing

An alternating-current generator (Hugo Sachs Rodent Shocker, Type-221; Freiburg, Germany) was used to produce an electric stimulus of 0.2-s duration inducing seizures delivered via ear-clip electrodes in mice.

First, the convulsive threshold test was employed to identify any anticonvulsant or proconvulsant properties of drugs to be examined upon the protective action of felbamate in the maximal electroshock test. In the convulsive threshold test, drugs showing anticonvulsant or proconvulsant properties increased or diminished the threshold for electroconvulsions, respectively. The threshold for electroconvulsions is reflected by a CS_{50} value with 95% confidence limits. A CS_{50} value represents the current intensity (in mA) predicted to produce the tonic hindlimb extension in 50% of the mice challenged with electric shock. To calculate each CS_{50} value, at least three groups of mice

were challenged with electric shocks of increasing intensities in order to construct a full current intensity–response function. In the present study for each dose of drug, full current intensity–response functions were evaluated. Calculated CS_{50} values were then statistically compared with the CS_{50} value of vehicle-treated mice (control group). A drug that fails to alter the convulsive threshold is likely to show neither proconvulsive nor anticonvulsive actions in the maximal electroshock test (White et al., 1995). Thus, treatments which did not alter the CS_{50} value (the dose of 10 mg/kg of flunarizine was the only exception) were examined in combination with felbamate in the maximal electroshock test.

On completion of the convulsive threshold test, the anticonvulsant effects of felbamate alone and in combination with adjunct drugs were examined against maximal electroshock-induced seizures. Maximal electroshock-induced seizures were defined as tonic extension of the hindlimbs immediately after the electric shock of fixed intensity (25 mA; 4–5-fold higher than the CS_{50} value in untreated mice). This electric shock would produce tonic hindlimb extension in 100% of untreated mice. The anticonvulsant activity of a drug is reflected by the drug's ability to protect against maximal electroshock-induced tonic hindlimb extension. In the present study, the protective potency of felbamate in the maximal electroshock test was quantitatively expressed as an ED_{50} value (with 95% confidence limits) and reflected a dose of felbamate (in mg/kg) predicted to abolish tonic hindlimb extension in 50% of mice challenged with the fixed electric stimulus. To calculate each ED_{50} value, at least three groups of mice, after receiving progressive doses of felbamate alone or in combination with an adjunct drug, were examined against maximal electroshock-induced seizures and the number of mice protected was recorded. ED_{50} values of felbamate evaluated in mice treated with felbamate alone and in combination with adjunct drugs were statistically compared. Additionally, effects of methylxanthines on the protective efficacy of the submaximal protective doses of felbamate (110 mg/kg) were examined.

2.4. Statistical analysis

Calculations of CS_{50} and ED_{50} values (with lower–upper 95% confidence limits) and statistical comparisons were performed using linear regression analysis of quantal log dose–probit functions constructed from dose–effect data according to the method described by Litchfield and Wilcoxon (1949). Additionally, relative potencies of felbamate were calculated for drug combinations. The relative potency of felbamate, expressed as potency ratio with lower–upper 95% confidence limits, was obtained by dividing an ED_{50} value of felbamate + vehicle by a corresponding ED_{50} value of felbamate + adjunct. A potency ratio provided a quantitative and comparable measure of the shift of the dose–response function of felbamate produced by different adjuncts. For example, an increase in the ED_{50} value of felbamate and the potency ratio of less than 1, indicated a decrease in the protective potency of felbamate. Linear regression analysis was also used to calculate slopes (with ±95% confidence limits) of dose–response functions for drug combinations and were statistically compared for parallelism with corresponding control values (slope of the dose–response curve of felbamate + vehicle). Finally, when appropriate, Fisher's Exact Probability test was used for specific comparisons between treatments. A probability level, P, greater than or equal to 0.05 was considered nonsignificant. All calculations and

Table 1
Anticonvulsant potency of felbamate alone and in combination with adjunct drugs

Treatment (mg/kg)	ED_{50} of felbamate	Potency ratio	Slope
Vehicle	77.5 (65.8–91.4)		1.19 (±1.01)
Nicardipine (10)	70.4 (57.5–86.2)	1.10 (0.85–1.43)	1.19 (±0.58)
Nicardipine (30)	68.0 (57.4–80.6)	1.14 (0.90–1.44)	1.06 (±0.33)
Vehicle	70.6 (61.8–80.6)		1.42 (±0.50)
Nifedipine (5)	61.4 (52.2–72.2)	1.15 (0.93–1.42)	1.19 (±0.80)
Nifedipine (10)	56.7 (47.0–68.5)	1.24 (0.99–1.57)	1.25 (±1.01)
Nifedipine (20)	66.5 (59.8–73.9)	1.06 (0.90–1.26)	1.27 (±0.30)
Vehicle	68.4 (59.5–78.6)		1.16 (±0.67)
Flunarizine (2.5)	59.5 (50.8–69.8)	1.15 (0.93–1.42)	1.22 (±1.37)
Flunarizine (5)	56.3 (48.0–66.0)	1.21 (0.98–1.50)	1.79 (±1.34)
Flunarizine (10)	67.6 (57.7–79.3)	1.01 (0.82–1.25)	1.33 (±0.33)
Vehicle	73.7 (64.4–84.3)		1.43 (±0.64)
Bay K 8644 (2.5)	70.1 (58.4–83.9)	1.05 (0.84–1.32)	1.40 (±0.53)
Bay K 8644 (5)	81.9 (72.2–93.0)	0.90 (0.75–1.08)	1.00 (±0.79)
Vehicle	79.6 (69.2–91.6)		1.14 (±0.50)
Aminophylline (50)	77.5 (66.8–89.9)	1.03 (0.84–1.26)	0.85 (±0.66)
Aminophylline (75)	94.6 (78.3–114)	0.84 (0.67–1.07)	1.47 (±0.98)
Aminophylline (100)	118[a] (99.5–139)	0.67[a] (0.54–0.84)	0.71 (±0.65)

Each ED_{50} value represents the protective potency of felbamate (in mg/kg; with upper–lower 95% confidence limits) predicted to protect 50% of mice against maximal electroshock-induced tonic seizures in (felbamate + vehicle)- and (felbamate + adjunct drug)-treated groups. See legend of Fig. 1 for other details.

Potency ratios (with upper–lower 95% confidence limits) were obtained by dividing a ED_{50} value of felbamate + vehicle by a corresponding ED_{50} value of felbamate + an adjunct drug (Tallarida and Murray, 1987). Slopes (with ±95% confidence limits) were calculated from regression lines constructed for each dose–response function and then compared for parallelism (Tallarida and Murray, 1987).

[a] $P < 0.05$ compared to vehicle treated group (Litchfield and Wilcoxon, 1949).

statistical analyses were performed using the software package accompanying the work of Tallarida and Murray (1987).

3. Results

3.1. Effects of Ca^{2+} channel modulators on the convulsive threshold and the anticonvulsant potency of felbamate

Of the three Ca^{2+} channel blockers tested, only nicardipine (10–30 mg/kg) failed to change the electroshock convulsive threshold. In contrast, both nifedipine (30–50 mg/kg) and flunarizine (10 and 15 mg/kg) significantly ($P < 0.05$) elevated the CS_{50} value for electroconvulsions by 20–24% and 28–60% above the base-line convulsive threshold ($CS_{50} = 5.3$ mA; 95% confidence limits: 4.6–6.0). Lower doses of nifedipine (5 to 20 mg/kg) and flunarizine (5 mg/kg) were ineffective. The treatments which did not alter the convulsive threshold (nicardipine: 10 and 30 mg/kg; nifedipine: 5, 10, 20 mg/kg; flunarizine: 2.5, 5 mg/kg) were examined in combination with felbamate in the maximal electroshock

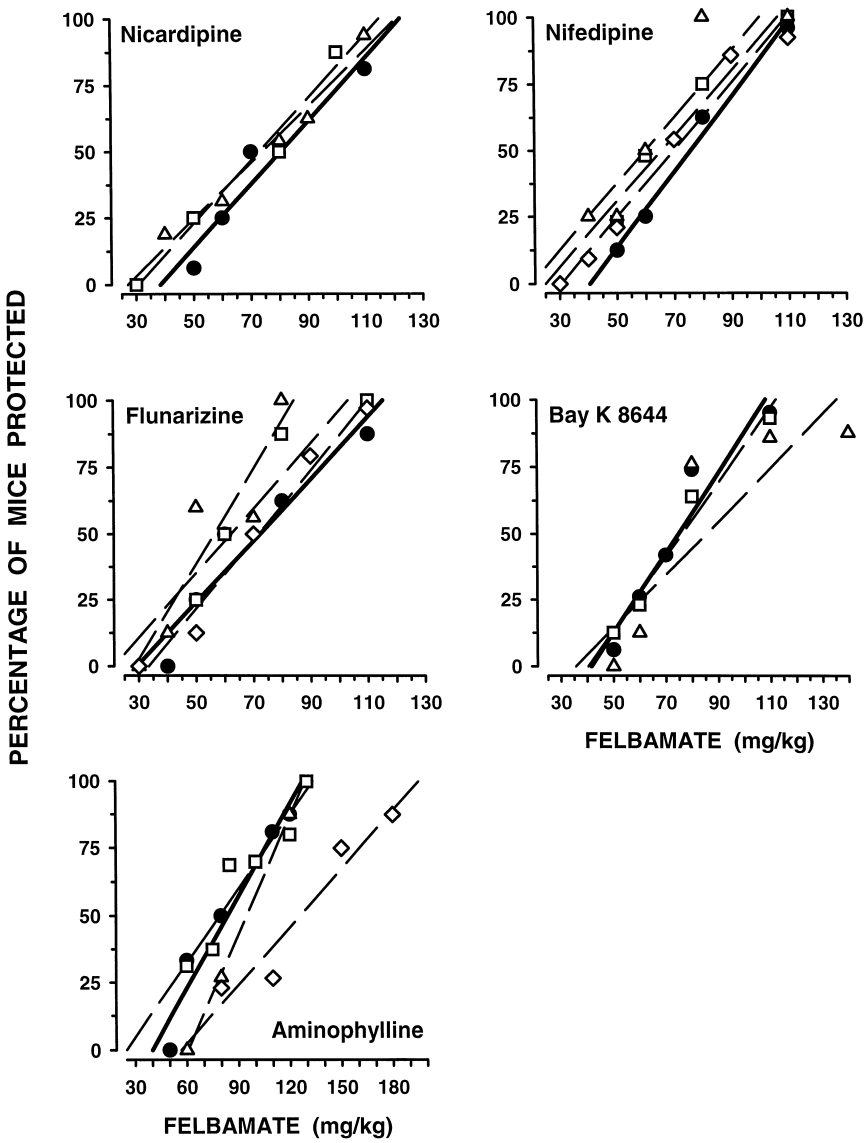

Fig. 1. Dose–response curves showing the protective effects of felbamate alone (● symbols) or in combination (open symbols) with nicardipine (top left plot), nifedipine (top right plot), flunarizine (middle left plot), Bay K 8644 (middle right plot), and aminophylline (bottom plot) against maximal electroshock-induced tonic convulsions. Felbamate was administered i.p. in increasing doses (doses on abscissa) 60 min before the test. Nicardipine (i.p.; 60 min before the test) was administered in doses of 10 (□) and 30 (△) mg/kg. Nifedipine (i.p.; 60 min) was administered in doses of 5 (□), 10 (△) and 20 (◇) mg/kg. Flunarizine (i.p.; 60 min) was administered in doses of 2.5 (□), 5 (△) and 10 (◇) mg/kg. Bay K 8644 (s.c.; 15 min) was administered in doses of 2.5 (□) and 5 (△) mg/kg. Aminophylline (i.p.; 30 min) was administered in doses of 50 (□), 75 (△) and 100 (◇) mg/kg. Each data point represents the percentage of mice protected ($n = 8$ to 21 mice per 1 data point). Computed linear regression lines were drawn for dose–response functions of felbamate alone (solid lines) and for felbamate in combination with adjunct drugs (dashed lines). See Table 1 for statistical comparison of slopes of regression lines and ED_{50} values.

test. The dose 10 mg/kg of flunarizine was the only exception. The Ca^{2+} channel activator Bay K 8644 was not tested for its effect on the convulsive threshold in this experiment as our previous experiments documented that Bay K 8644 at the dose of 5 mg/kg did not change the threshold for electroconvulsions or the overall behavior of the Swiss mice (Czuczwar et al., 1994; Gasior et al., 1995). Higher doses of Bay K 8644 (8 and 10 mg/kg), however, produced behavioral side-effects including convulsions (Gasior et al., 1995). Thus, the dose of 5 mg/kg of Bay K 8644 was selected as the highest dose to be tested in combination with felbamate in the maximal electroshock test.

Neither the anticonvulsant potency (Table 1) nor efficacy (Fig. 1) of felbamate against maximal electroshock-induced seizures changed as a result of co-administration of Ca^{2+} channel antagonists. Potency ratios of the drug combinations ranged from 1.01- to 1.24-fold greater than felbamate alone, however, none reached statistical significance (Table 1). Furthermore, the overall dose–response curves for felbamate in combination with adjunct drugs did not differ ($P > 0.05$) from that of felbamate + vehicle (Fig. 1 and Table 1). Similarly, Bay K 8644 in doses of 2.5 and 5 mg/kg failed to alter the protective potency and efficacy of felbamate ($P > 0.05$ vs. control value).

3.2. Effect of aminophylline on the convulsive threshold and the anticonvulsant potency of felbamate

Aminophylline up to 100 mg/kg failed to alter the threshold for electroconvulsions (5.4 mA (5.2–5.7) vs. 5.1 mA (4.5–5.7) and Czuczwar et al., 1987c).

Aminophylline in doses 50 and 75 mg/kg did not change the protective potency or the dose–response function of felbamate against maximal electroshock-induced convulsions (Table 1). In contrast, the anticonvulsant action of felbamate was markedly impaired when aminophylline was administered in the dose of 100 mg/kg. The latter effect was reflected by a statistically significant decrease in the protective potency of felbamate. Felbamate now produced 50% protection at 118 mg/kg, as opposed to 79.6 mg/kg ($P < 0.05$; Table 1). Further, aminophylline (100 mg/kg) produced a parallel rightward shift of the full dose–response function of felbamate (Fig. 1) as indicated by no differences ($P > 0.05$) in the slopes of the dose–response functions for felbamate alone and in combination with 100 mg/kg of aminophylline (Table 1).

3.3. Changes in the protective efficacy of felbamate produced by aminophylline and caffeine

Fig. 2 shows the effects of increasing doses of aminophylline and caffeine on the protective efficacy of the submaximal dose of felbamate against maximal electroshock-induced convulsions. For comparative purpose, caffeine and aminophylline were administered in equimolar doses (Fig. 2). When administered in the dose of 110 mg/kg, felbamate suppressed the tonic hindlimb extension in 96% of mice challenged with the maximal electroshock stimulus. No mice were protected without treatment. Aminophylline in doses of 0.238 mmol/kg (50 mg/kg) and 0.357 mmol/kg (75 mg/kg), failed to diminish the

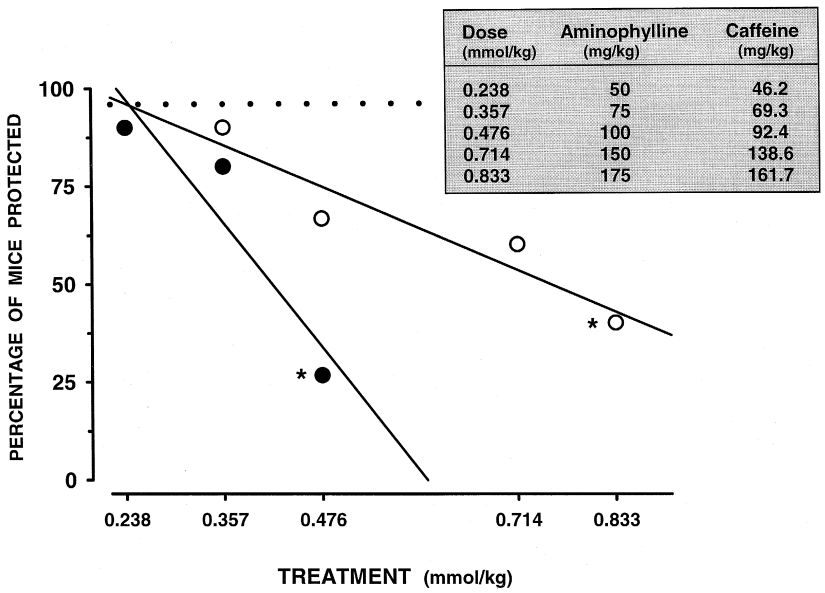

Fig. 2. Effect of aminophylline (● symbols) and caffeine (○ symbols) on the protective effectiveness of felbamate (110 mg/kg) expressed as a percentage of mice protected against maximal electroshock-induced tonic convulsions. Doses of aminophylline and caffeine are expressed in mmol/kg on abscissa (the table lists corresponding doses in mg/kg). The dotted line at 96% reflects the protection offered by 110 mg/kg felbamate + vehicle (25 out of 26 mice protected). The solid lines represent linear regressions calculated from dose–effect functions of aminophylline and caffeine. To evaluate each data point at least 10 mice were used. Felbamate, aminophylline and caffeine were administered i.p. 60, 30, and 30 min before the test, respectively. $* P < 0.05$ compared to 110 mg/kg felbamate alone (Fisher's Exact Probability test).

protective efficacy of 110 mg/kg felbamate. The 0.476 mmol/kg (100 mg/kg) of aminophylline lessened the protective efficacy of felbamate in this test by reducing the number of protected mice from 96.15% to 27% ($P < 0.05$). Relative to equimolar doses, caffeine was both less effective and potent than aminophylline (Fig. 2). The statistically significant reduction of the protective efficacy of felbamate was minimal when caffeine was administered in the dose of 0.833 mmol/kg (161.7 mg/kg). Regardless, 40% of mice still remained protected (Fig. 2). Higher doses of caffeine were not tested because behavioral side-effects, such as locomotor activity depression and myorelaxation, were observed with 0.833 mmol/kg caffeine + 110 mg/kg felbamate. As a whole, aminophylline and caffeine diminished the protective efficacy of the submaximal dose of felbamate with potencies of 0.417 mmol (ED_{50} = 87.2 mg/kg; 95% confidence limits = 73.9–102 mg/kg) and 0.742 mmol (ED_{50} = 144 mg/kg; 105–196 mg/kg), respectively.

4. Discussion

This study revealed a low propensity for felbamate to interact with both Ca^{2+} channel modulators and methylxanthines. Specifically, none of the Ca^{2+} channel blockers altered the protective potency of felbamate against maximal electroshock-induced tonic convulsions. Flunarizine, even in the dose of 10 mg/kg which elevated the convulsive threshold, had no effect upon the protective potency of felbamate against maximal electroshock-induced convulsions. Moreover, the Ca^{2+} channel activator Bay K 8644 also failed to change the anticonvulsive potency of felbamate. Likewise, aminophylline in doses of 50–75 mg/kg did not effect the protective ED_{50} value of felbamate. Only 100 mg/kg aminophylline diminished the protective potency of felbamate as evidenced by a statistically significant increase in the protective ED_{50} value of felbamate. This was revealed by the rightward shift of the dose–response curve of felbamate against maximal electroshock-induced tonic convulsions. Further, relatively high doses of aminophylline and caffeine (100 and 161.7 mg/kg, respectively) were needed to markedly diminish the efficacy of the submaximal protective dose of felbamate (110 mg/kg) against maximal electroshock-induced tonic convulsions.

The low interaction potential of felbamate with Ca^{2+} channel modulators and methylxanthine obtained in this study was somewhat surprising for several reasons. Felbamate has been demonstrated to readily interact with conventional antiepileptic drugs such that the ineffective doses of phenytoin, carbamazepine, valproate, and phenobarbital significantly (1.43- to 3.3-fold) enhanced the protective potency of felbamate against maximal electroshock-induced convulsions in mice (Gordon et al., 1993). The potentiation of the protective potency of felbamate was not accompanied by significant changes in plasma levels of drugs tested, thus indicating a pharmacodynamic origin of these interactions (Gordon et al., 1993). Moreover, this study (Gordon et al., 1993) provides straightforward evidence that the protective action of felbamate can be pharmacologically modulated by adjunct drugs administered in doses that are ineffective alone against maximal electroshock-induced seizures and that such interactions can be quantitatively and qualitatively evaluated by means of the maximal electroshock model of seizures in mice. Therefore, the failure of the Ca^{2+} channel modulators to effect the protective potency and efficacy of felbamate against maximal electroshock-induced tonic convulsions in the present study is unlikely due to inappropriate experimental procedure. It also cannot be attributed to an inherent inability of the Ca^{2+} channel modulators to augment the protective action of antiepileptic drugs against maximal electroshock-induced seizures. The latter conclusion is justified by demonstration that Ca^{2+} channel blockers, such as flunarizine, nifedipine, nicardipine, nimodipine and diltiazem, significantly potentiated the protective effects of the conventional antiepileptic drugs in doses that were devoid of any protective activity in this test and, further, without affecting the antiepileptic drugs' plasma levels (Czuczwar et al., 1990a, 1992). Also, in the maximal electroshock test in mice, the Ca^{2+} channel activator Bay K 8644, in doses of 1 and 5 mg/kg, markedly reduced the protective potency of carbamazepine, phenytoin, and phenobarbital without changing the antiepileptic drugs' plasma levels (Gasior et al., 1995). Thus, felbamate clearly differed from the conventional antiepileptic drugs in terms of interaction potential with Ca^{2+} channel modulators. Further, felbamate revealed a lower propensity for interactions with methylxanthines in the maximal electroshock model of seizures than conventional antiepileptic drugs. Aminophylline, up to 75 mg/kg, failed to diminish the anticonvulsant potency of felbamate against maximal electroshock-induced seizures (Table 1), whereas aminophylline at doses of 50 mg/kg or lower significantly diminished the protective potencies (1.29- to 1.89-fold; $P < 0.05$) of carbamazepine, phenobarbital, phenytoin, and valproate in the same seizure model (Czuczwar et al., 1987c). In our experiment, significant reduction (1.48-fold) of the protective potency of felbamate was observed after 100 mg/kg aminophylline. Further, aminophylline up to 75 mg/kg did not change the anticonvulsant efficacy of the submaximal protective dose of felbamate (Fig. 2). In contrast, 50 mg/kg of aminophylline significantly diminished the anticonvulsant effectiveness of the submaximal protective doses of carbamazepine, phenobarbital, phenytoin, and valproate (Czuczwar et al., 1989). The same trend was observed when caffeine was co-administered with felbamate. The present study required a 3.5-fold higher dose of caffeine to diminish the protective action of felbamate than Czuczwar found with conventional

antiepileptic drugs (Czuczwar et al., 1990b). Experimental settings used in cited experiments (e.g., pretreatment times, routes of administration, criteria for selection of doses, etc.) were similar to those in the current experiment with felbamate. Further, having previously established a marginal role of the pharmacokinetic interactions in the alterations of the protective action of the conventional antiepileptic drugs by the Ca^{2+} channel modulators (Czuczwar et al., 1990a, 1992; Gasior et al., 1995) or by methylxanthines (Czuczwar et al., 1989, 1990b) in the maximal electroshock test, we may assume that pharmacokinetic interactions were unlikely to play a critical role in this experiment.

Felbamate, unlike conventional antiepileptic drugs (Rogawski and Porter, 1990), shows a dual anticonvulsant action ascribed to the inhibition and potentiation of the glutamatergic and GABAergic neurotransmission systems, respectively, (McCabe et al., 1993; Sofia, 1995). The unique pharmacological profile of felbamate, however, does not immediately explain the low interaction propensity of felbamate. Recently we reported that the protective action of antagonists of the NMDA receptor complex can be significantly potentiated (CGP 40116, CGP 43487, LY 235959) by nicardipine, nifedipine, and flunarizine (Gasior et al., 1996a, 1997) or diminished (CGP 37849, D-CPP-ene) by Bay K 8644 (Czuczwar et al., 1994). Moreover, aminophylline, likewise, when combined with conventional antiepileptic drugs, significantly reduced the anticonvulsive effectiveness of the NMDA receptor antagonist D-CPP-ene with the potency of $ED_{50} = 55.7$ mg/kg against maximal electroshock-induced seizures (Tutka et al., 1996). In contrast, aminophylline appeared to be significantly less potent ($ED_{50} = 82.2$ mg/kg) in decreasing the anticonvulsive effectiveness of felbamate in the same test.

In conclusion, by demonstrating a low interaction potential with Ca^{2+} channel modulators and methylxanthines, felbamate clearly differs from the conventional antiepileptic drugs. The nature of this phenomenon awaits to be explained as well as the extent to which other recently approved antiepileptic drugs are similar to felbamate or conventional antiepileptic drugs in their interaction propensity. From a clinical perspective, our finding suggests that felbamate might be used to acutely control seizures in those patients who require intensive pharmacological treatment due to co-existing (other than epilepsy) medical conditions (e.g., status asthmaticus or malignant hypertension).

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