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Fenbufen Pretreatment Potentiates the Anticonvulsant Activity of CPPene and NBQX in DBA/2 Mice

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Abstract—The anticonvulsant activity of 3-((±)-2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (CPPene) and 2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxoline (NBQX), two excitatory amino acid antagonists, was studied against audiogenic seizures in DBA/2 mice, following intraperitoneal (i.p.) or intracerebroventricular (i.c.v.) administration. Maximal anticonvulsant protection was observed 15–30 min following NBQX and 45–180 min after CPPene. Coadministration with fenbufen (20 mg kg^{-1}, i.p.), a non-steroidal anti-inflammatory agent, enhanced and prolonged the anticonvulsant actions of CPPene and NBQX and also potentiated and prolonged the impairment of rotarod performance. The enhancement of the anticonvulsant activity and the prolonged impairment of rotarod performance suggests that fenbufen may have some pharmacokinetic interactions with CPPene and NBQX and that fenbufen is able to increase the brain levels of these excitatory amino acid antagonists. In particular, fenbufen was able to exert a major degree of potentiation of effects of NBQX rather than those of CPPene, suggesting that the chemical structures of these excitatory amino acid antagonists are responsible for the different degree of interactions between CPPene or NBQX and fenbufen. NBQX appears to have a notable similarity with quinolones whilst CPPene does not. Additionally fenbufen may displace CPPene and NBQX from plasma binding sites or inhibit the renal excretion. The present data are also consistent with previous studies showing pharmacokinetic interactions between fenbufen and quinolones.

The excitatory amino acids, aspartate and glutamate, are the major excitatory neurotransmitters in the central nervous system. Compounds acting as selective *N*-methyl-D-aspartic acid (NMDA) antagonists have been shown to have anticonvulsant properties. The 3-((±)-2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (CPPene) and some other analogues have been shown to exhibit anticonvulsant activity in several models of experimental epilepsy (Chapman et al 1987, 1990; Nevins & Arnolde 1989; Patel et al 1990; De Sarro & De Sarro 1992, 1993). The discovery of quinoxalinediones and their analogues has opened new dimensions in studying the mechanisms mediated by non-NMDA receptors in the central nervous system (Honoré et al 1988; Sheardown et al 1990). NBQX (2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxoline) possesses two advantages compared with CNQX (6-cyano-7-nitroquinoxoline-2,3-dione) and DNQX (dinitroquinoxoline-2,3-dione); it does not act as an NMDA antagonist (via the glycine site) and it is bioavailable after systemic administration to animals. This compound has neuroprotective effects in animal models of cerebral stroke (Sheardown et al 1990) as well as anticonvulsant activity in genetic seizure models (Chapman et al 1991; Smith et al 1991).

Fenbufen is one of the non-steroidal, anti-inflammatory, analgesic and antipyretic agents which belongs to the group of propionic acid derivatives (Chiccarelli et al 1980; Sloboda et al 1980). Recently, it has been reported that fenbufen increased serum and cerebrospinal fluid levels of ciprofloxacin, a quinolonecarboxylic acid (quinolone) with a broad spectrum of antibacterial activity (Naora et al 1991). We postulated that fenbufen, like other antipyretic agents, might be administered concomitantly with some new anticonvulsant drugs (i.e. CPPene and NBQX), and that some chemical similarities existing between quinolones and NBQX might be responsible for a major activity of these excitatory amino acid antagonists. The elucidation of the mechanism for potentiation of effects by the coadministration of fenbufen and CPPene or NBQX is very important for effective and rational anticonvulsant therapy. We report here that the anticonvulsant effects as well as the impairment of co-ordinated motor movements and other behavioural actions produced by CPPene and NBQX are enhanced and prolonged by pretreatment with fenbufen.

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Materials and Methods

Animals

DBA/2 mice (6–12 g, 21–26 days old) and Swiss mice (20–30 g, 42–48 days old) were purchased from Charles River (Calco, Como, Italy). The animals were housed 8–10 per cage under stable conditions of humidity (60 ± 5%) and temperature (22 ± 2°C) and allowed free access to food and water until the time of the experiment.

Anticonvulsant activity

DBA/2 mice were exposed to auditory stimulation, at several times following intraperitoneal (i.p.) or intracerebroventricular (i.c.v.) administration of vehicle or drugs (CPPene alone, NBQX alone or concomitantly with fenbufen). To examine the inhibition of audiogenic seizures the mice were exposed to a 12–16 kHz, sinusoidal tone at 109 dB in an emispheric box (58 cm diam.). Seizure response as previously reported (De Sarro et al 1984) was assessed on

the following scale: 0 = no response, 1 = wild running, 2 = clonus, 3 = tonus, 4 = respiratory arrest. The maximum response was recorded for each animal. Rectal temperature was recorded immediately before auditory testing using an Elektrolaboratoriet thermometer type T.E.3.

Effects on motor movements

Behavioural changes and their onset and duration were recorded after drug injection until the time of rotarod test. In particular, two independent observers followed gross behavioural changes consisting of locomotor activity, ataxia, squatting posture and possible piloerection. These behavioural changes were noted but not statistically analysed.

Groups of 10 male Swiss mice, 20–30 g, were trained to do co-ordinated motor movements continuously for 2 min on a rotarod 3-cm diameter 8 rev min^{-1} (U. Basile, Comerio, Varese, Italy). Impairment of co-ordinated motor movements was defined as inability of the mice to remain on the rotarod for a 2-min test period (Dunham & Miya 1957). The ability of the mice to remain on the rotarod was tested at various times after administration of CPPene or NBQX alone or after the combined treatment with fenbufen +CPPene or fenbufen + NBQX.

Statistical analysis

Statistical comparisons among groups of concurrent control and drug-treated animals were made using Fisher's exact probability test (incidence of the seizure phases or impairment of motor performance) or analysis of variance and Dunnett's *t*-test (rectal temperatures). A Kruskall–Wallis analysis of variance was first carried out and if this was significant, a Mann-Whitney *U*-test was used to compare the seizure response among two concurrent groups. The percentage incidence of each phase of the audiogenic seizure was determined for each dose of compound administered and log dose-response curves were fitted using linear regression analysis of probit-transformed percentage response. ED50 values (with 95% confidence limits) for each compound and each phase of seizure response were estimated using the method of probit analysis (Finney 1978); the relative convulsant activities were determined by comparison of respective ED50 values. The dose which induced 50% of mice to fall from the rotarod (TD50 with 95% confidence limits) for each compound was estimated using the method of probit analysis (Finney 1978); the relative activities were determined by comparison of respective TD50 values.

Table 1. The effect of intraperitoneal administration of CPPene or NBQX in combination with saline or fenbufen in DBA/2 mice.

Treatment	Dose (μmol)	% Response				Mean response	Rectal temperature (°C) (mean ± s.e.m.)	n
		Wild running	Clonus	Tonus	Respiratory arrest			
Saline + CPPene	Vehicle	100	100	100	50	3·5	37·8 ± 0·18	10
	0·33	100	100	70	30	3·0	37·6 ± 0·22	10
	1·0	100	80	50*	10**	2·4	37·4 ± 0·19	10
	2·15	90	40**	30**	10**	1·7	37·4 ± 0·24	10
	3·3	70	20**	10**	0**	1·0	37·2 ± 0·25	10
	6·6	50*	0**	0**	0**	0·5	37·1 ± 0·18	10
	10·0	0**	0**	0**	0**	0	37·0 ± 0·22	10
Saline + NBQX	Vehicle	100	100	100	50	3·5	37·9 ± 0·24	10
	3·3	100	90	80	30	3·0	37·8 ± 0·19	10
	10·0	100	60	60	10**	2·3	37·9 ± 0·21	10
	33·3	70	50*	30**	0**	1·4	37·8 ± 0·23	10
	66·6	20**	20**	0**	0**	0·4	37·6 ± 0·18	10
	100·0	0**	0**	0**	0**	0	37·7 ± 0·22	10
Fenbufen	Vehicle	100	100	100	50	3·5	37·8 ± 0·22	10
	10	100	100	100	40	3·4	37·7 ± 0·19	10
	20	100	100	100	40	3·4	37·7 ± 0·21	10
Fenbufen + CPPene	Vehicle	100	100	100	50	3·5	37·8 ± 0·18	10
	0·33	90	70	50	20	2·3	37·5 ± 0·20	10
	1·0	70	40+	30	0	1·4	37·3 ± 0·21	10
	2·15	50	20+	10+	0	0·8	37·2 ± 0·22	10
	3·3	40	10+	0	0	0·5	37·1 ± 0·19	10
	6·6	20+	0	0	0	0·2	37·0 ± 0·23	10
	10·0	0	0	0	0	0	36·8 ± 0·24++	10
Fenbufen + NBQX	Vehicle	100	100	100	50	3·5	37·9 ± 0·24	10
	3·3	90	50	40+	10	1·9	37·8 ± 0·18	10
	10·0	70	30+	20++	0	1·2	37·7 ± 0·22	10
	33·3	30++	20++	0++	0	0·5	37·6 ± 0·20	10
	66·6	0+	0+	0	0	0	37·5 ± 0·19	10
	100·0	0	0	0	0	0	37·4 ± 0·21	10

Groups of DBA/2 mice were injected intraperitoneally with the stated doses of the drugs or vehicle and exposed to auditory stimulation 45 min after CPPene or fenbufen injection or 30 min after NBQX administration. Incidence of each seizure phase is expressed as the percentage of mice in each group displaying that phase. Significant differences in the incidence of seizure phases between concurrent saline + anticonvulsant-, and fenbufen + anticonvulsant-treated groups are denoted by $^{++}P < 0{\cdot}01$. The mean response is the arithmetic mean of the maximum individual responses for each animal in the group. Significant differences between rectal temperature in drug-treated and control groups are denoted by $^{+}P < 0{\cdot}05$; $^{++}P < 0{\cdot}01$. Significant changes between control (vehicle) and drug-treated (CCPene or NBQX) are denoted by $^{*}P < 0{\cdot}05$; $^{**}P < 0{\cdot}01$.

Drugs

3-((±)-2-Carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (CPPene) was kindly supplied by Dr P. L. Herrling (Sandoz Ltd, Berne, Switzerland). 2,3-Dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxoline (NBQX) was kindly supplied by Dr T. Honoré (Novo-Nordisk A/S, Soeborg, Denmark). Fenbufen was purchased from Sigma (St Louis, MO, USA). For systemic administration, all compounds were dissolved in sterile saline and administered intraperitonally (0·1 mL/(10 g body weight)). For intracerebroventricular administration, all compounds were dissolved in 67 mM sodium phosphate buffer and injected (10 μL/animal) by a Hamilton microsyringe under light ethyl ether anaesthesia as previously described (De Sarro et al 1988).

Results

Anticonvulsant activity of excitatory amino acid antagonists in DBA/2 mice

The anticonvulsant activity of CPPene and NBQX against audiogenic seizures in DBA/2 mice pretreated with saline are reported in Table 1. Fenbufen (20 mg kg^{-1}, i.p.) in DBA/2 mice, had no anticonvulsant activity against audiogenic seizures (Table 1). However, when animals were pretreated, 15 min before, with fenbufen (20 mg kg^{-1}, i.p.) and then received NBQX or CCPene the anticonvulsant as well as the impairment of co-ordinated motor movements produced by NBQX or CPPene were enhanced and prolonged (Table 1, Fig. 1). The excitatory amino acid antagonists CCPene and NBQX were also administered intracerebroventricularly in DBA/mice after pretreatment (30 min before) with vehicle or fenbufen (20 mg kg^{-1}, i.p.). As is reported in Table 2, pretreatment with fenbufen was unable to modify significantly the anticonvulsant or the behavioural effects elicited by the following intracerebroventricular injection of CCPene or NBQX. ED50 values against clonic and tonic seizures and for the impairment of co-ordinated motor movements are reported in Table 3.

Time course of anticonvulsant and ataxia effects of combined treatment with fenbufen and NBQX or CPPene in mice

Following the intraperitoneal administration of saline and CPPene (3·3 μmol kg^{-1}), maximum protection was observed at 45–180 min, with subsequent return to control seizure response at 300 min (Fig. 1). When DBA/2 mice were pretreated, 15 min before, with fenbufen (20 mg kg^{-1}, i.p.) and then received CPPene (3.3 μmol kg^{-1}, i.p.) the maximum protection was observed at 45–180 min with subsequent return to control seizure response at 360 min (Fig. 1). Although fenbufen alone did not cause ataxia, it was able to enhance and prolong the impairment of co-ordinated motor movements assessed by rotarod (Fig. 1). In particular, impairment of co-ordinated motor movements was not evident 150 min following intraperitoneal administration of saline + CPPene (20 μmol kg^{-1}) whilst it was shown by 20% mice in the group treated with fenbufen + CPPene (20 μmol kg^{-1}) (Fig. 1).

Following the intraperitoneal injection of saline and NBQX (66.6 μmol kg^{-1}) maximum protection was observed at 15–30 min, with subsequent return to control seizure response at 120 min (Fig. 2). When DBA/2 mice were pretreated, 15 min before, with fenbufen (20 mg kg^{-1}, i.p.) and then received NBQX (66.6 μmol kg^{-1}, i.p.) the maximum protection was observed at 15–30 min, with subsequent return to control seizure response at 150 min (Fig. 2). The impairment of co-ordinated motor movements was present for 30 min in mice receiving saline + NBQX which was significantly ($P < 0.01$) more evident and lasted for 90 min in animals treated with fenbufen + NBQX (Fig. 2). In addition, fenbufen pretreatment (20 mg kg^{-1}, i.p.) 30 min before did not enhance or prolong the anticonvulsant or the impairment of co-ordinated motor movements induced by intracerebroventricular administration of these excitatory amino acid antagonists (Table 2). Squatting posture and mild piloerection were observed after the intraperitoneal or intracerebroventricular administration of the highest dose of both CPPene and NBQX when they were given in combination with vehicle or fenbufen.

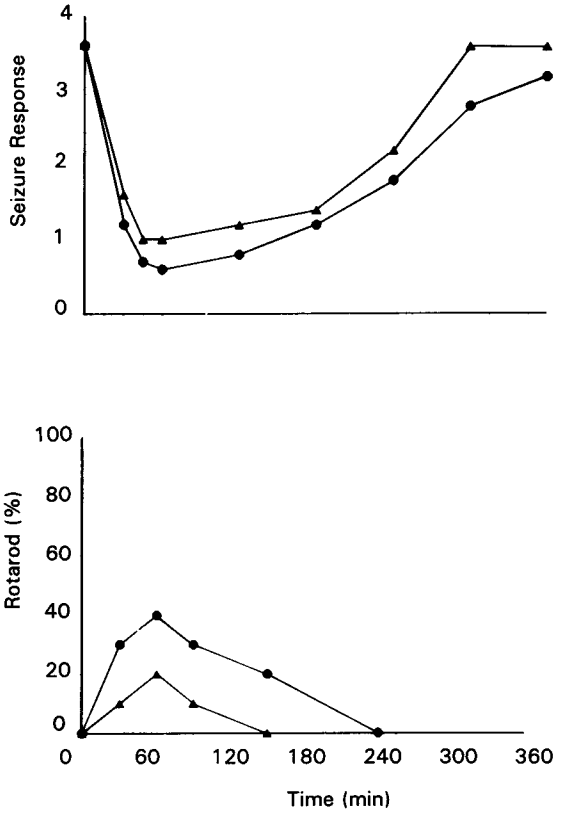

FIG. 1. Anticonvulsant effects of CPPene (3·3 μmol kg^{-1}, i.p.) alone or in combination with fenbufen against audiogenic seizures in DBA/2 mice. Ordinate shows seizure score. Abscissa shows the time after drug administration in min. For the determination of each point (mean seizure score ± interquartile range) eight animals were used. Data are from groups of 10 mice each and represent the percentage of animals which did not pass the test.

Discussion

The present results confirm that CPPene and NBQX possess an anticonvulsant activity as previously reported in various seizure models. In addition, we demonstrated that pretreatment with fenbufen was able to potentiate and prolong the

Table 2. The effect of intracerebroventricular administration of CPPene or NBQX in combination with vehicle or fenbufen in DBA/2 mice.

Treatment	Dose (μmol)	Wild running	% Response			Mean response	Rectal temperature (°C) (mean ± s.e.m.)	n
			Clonus	Tonus	Respiratory arrest			
Vehicle + CPPene	Vehicle	100	100	100	60	3·6	37·7 ± 0·31	10
	0·033	100	100	100	40	3·4	37·6 ± 0·34	10
	0·066	100	100	100	20**	3·2	37.4 ± 0·28	10
	0·1	100	70	50*	10**	2·3	37·2 ± 0·33	10
	0·33	90	40**	30**	10**	1·7	37·0 ± 0·24	10
	0·66	20**	0**	0**	0**	0·2	36·9 ± 0·26†	10
Vehicle + NBQX	Vehicle	100	100	100	50	3·5	37·9 ± 0·24	10
	0·33	100	100	90	30	3·2	37·8 ± 0·25	10
	0·66	100	70	60	20**	2·5	37·9 ± 0·22	10
	1·0	80	50*	40**	0**	1·7	37·8 ± 0·23	10
	3·3	40**	20**	0**	0**	0·6	37·7 ± 0·25	10
	6·6	10**	0**	0**	0**	0·1	37·7 ± 0·21	10
Fenbufen + CPPene	Vehicle	100	100	100	50	3·5	37·8 ± 0·28	10
	0·01	100	100	150	30	3·3	37·5 ± 0·21	10
	0·033	100	80	80	40	3·0	37·4 ± 0·27	10
	0·066	100	60	40**	20**	2·2	37·1 ± 0·25	10
	0·1	90	40**	30**	20**	1·8	37·0 ± 0·23	10
	0·33	20**	10**	0**	0**	0·3	36·9 ± 0·25†	10
Fenbufen + NBQX	Vehicle	100	100	100	50	3·5	37·9 ± 0·20	10
	0·33	100	90	70	30	2·9	37·8 ± 0·21	10
	0·66	100	70	50*	10**	2·3	37·7 ± 0·23	10
	1·0	80	40**	20**	0**	1·4	37·6 ± 0·25	10
	3·3	30**	20**	10**	0**	0·6	37·5 ± 0·18	10
	6·6	0**	0**	0**	0**	0	37·4 ± 0·21	10

Groups of DBA/2 mice were injected intracerebroventricularly with the stated doses of the vehicle + drugs, or fenbufen + CPPene, or fenbufen + NBQX and exposed to auditory stimulation 30 min after the administration of CPPene or NBQX. Incidence of each seizure phase is expressed as the percentage of mice in each group displaying that phase. Significant differences in the incidence of seizure phases between concurrent vehicle* and anticonvulsant-treated groups are denoted by *$P < 0.05$; **$P < 0.01$. The mean response is the arithmetic mean of the maximum individual responses for each animal in the group. †Significant differences ($P < 0.05$) between rectal temperature in drug-treated and control groups.

effects of CPPene and NBQX. From the present findings it is assumed that fenbufen may possess pharmacokinetic interactions with CPPene and NBQX and such interactions may produce an elevation of brain concentration, as well as prolong the half-lives of CPPene and NBQX. Another acidic compound, probenecid, was also able to enhance the anticonvulsant effects and to prolong the half-life of NBQX by pharmacokinetic interactions (Taylor & Vartanian 1992). Previous experiments demonstrated that fenbufen administered concomitantly with some quinolones was able to induce a reduction in the body clearance of ofloxacin (Katagiri et al 1989), to prolong the half-lives of ciprofloxacin (Naora et al 1990b), norfloxacin (Katagiri et al 1989) and enoxacin (Naora et al 1990a). Furthermore, it was demonstrated that co-administered fenbufen tended to reduce the renal clearance of ciprofloxacin by about 20% (Naora et al 1990b). This effect was due to inhibition of the active secretion of ciprofloxacin at the renal proximal tubule by a metabolite of fenbufen (Naora et al 1992). A recent study demonstrated that fenbufen was unable to affect brain and cerebrospinal fluid concentration of sparfloxacin but fenbufen produced a slight decrease of protein binding of the latest quinolone (Naora et al 1992). The above reported data suggest that fenbufen might influence the pharmacokinetic parameters of quinolones and perhaps of CPPene and NBQX in a different manner. Both derivatives are acidic compounds and, therefore, fenbufen might affect their pharmacokinetic parameters thus increasing their anticonvulsant effects as well as their side-effects. The previous studies and the present results suggest that CPPene and

Table 3. ED50 and TD50 values (± 95% confidence limits) for anticonvulsant effects and impairment of co-ordinated motor movements following administration of CPPene or NBQX in combination with vehicle or fenbufen in DBA/2 mice.

Treatment	Time (min)	ED50		TD50
		Clonus	Tonus	Locomotor deficit
Vehicle + CPPene	45	1·76 (1·21–2·56)	0·79 (0·44–1·43)	> 33
Vehicle + NBQX	30	18·3 (9·45–35·3)	11·8 (6·15–22·5)	178 (114–278)
Fenbufen + CPPene	45	0·69 (0·35–1·38)*	0·4 (0·2–0·8)*	23·1 (14·9–35·6)
Fenbufen + NBQX	30	3·74 (1·16–12·1)*	2·65 (0·84–8·34)*	60 (39–92)*

Results are expressed as μmol kg^{-1} for antagonism of clonic or tonic phase of the audiogenic seizures or impairment of co-ordinated motor movements. Significant differences between the ED50 and TD50 of concurrent vehicle- and fenbufen-treated groups are denoted by *$P < 0.05$.

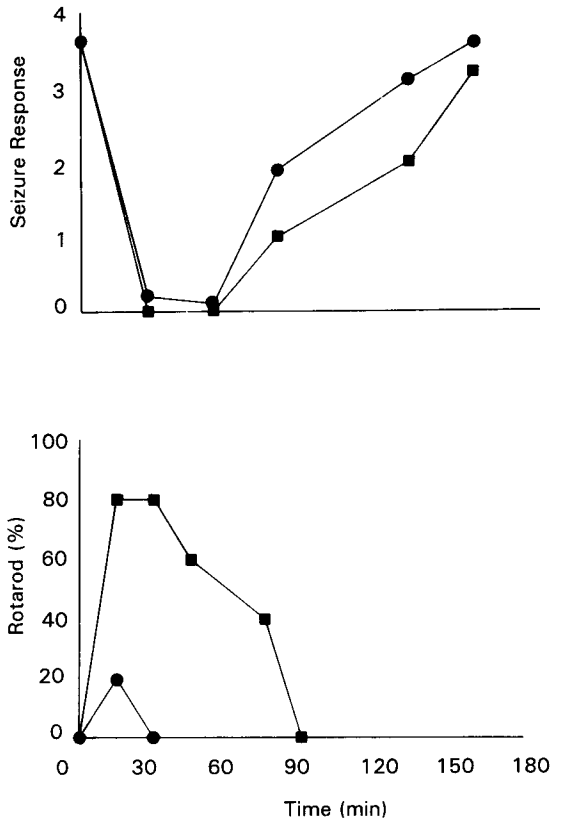

FIG. 2. Anticonvulsant effects of NBQX (66·6 μmol kg^{-1}, i.p.) alone or in association with fenbufen, against audiogenic seizures in DBA/2 mice. Ordinate shows seizure score. Abscissa shows the time after drug administration in min. For the determination of each point (mean seizure score ± interquartile range) eight animals were used. Data are from groups of 10 mice each and represent the percentage of animals which did not pass the test.

NBQX may be carried rapidly into the brain by a transporter mechanism sensitive to fenbufen and perhaps similar to that previously described for the probenecid (Taylor & Vartanian 1992). Alternatively or additionally, we may suppose that fenbufen inhibits the renal excretion of CPPene and NBQX or displaces both compounds from the plasma binding sites as already suggested for NBQX when it was administered concomitantly with probenecid (Taylor & Vartanian 1992). The data observed following intracerebroventricular administration of CPPene and NBQX also indicate that fenbufen did not induce an inhibition of the active efflux transport from the brain to the blood.

Neither CPPene nor NBQX produced marked impairment of co-ordinated motor movement at anticonvulsant doses when administered with saline, but these effects appeared more clearly or were potentiated following pretreatment with fenbufen. Although the effects of NBQX alone might be underestimated because of its rapid elimination, the same hypothesis might not hold for CPPene. In previous experiments we demonstrated that CPPene in genetically epilepsy-prone rats did not impair motor movements and did not show neurological side-effects at doses which had a good anticonvulsant activity (De Sarro & De Sarro 1992, 1993). The different degree of potentiation of the effects of CPPene and NBQX by fenbufen, observed in the present study, might be related to different chemical structures of these excitatory amino acid antagonists. NBQX, in fact, appears to have a notable similarity with quinolones whilst CPPene does not. However, we have also to consider that fenbufen did not increase the brain levels of all quinolones because of their different lipophilicity (Naora et al 1992). In addition, fenbufen might affect the protein binding or the renal tubular secretion of CPPene and NBQX to different extents. However, fenbufen may facilitate brain accumulation of these excitatory amino acid antagonists without decreasing the brain clearance. Finally, we conclude that the various pharmacokinetic interactions may result in the more evident anticonvulsant activity as well as impairment of co-ordinated motor movements observed when these excitatory amino acid antagonists and fenbufen are coadministered.

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References

Chapman, A. G., Meldrum, B. S., Nanji, N., Watkins, J. C. (1987) Anticonvulsant action and biochemical effects in DBA/2 mice of CPP (3-((±)-2-carboxypiperazin-4-yl)propyl-1-phosphonate), a novel *N*-methyl-D-aspartate antagonist. Eur. J. Pharmacol. 139: 91–96

Chapman, A. G., Graham, J. L., Meldrum, B. S. (1990) Potent oral anticonvulsant action of CPP and CPPene in DBA/2 mice. Eur. J. Pharmacol. 178: 97–99

Chapman, A. G., Smith, S. E., Meldrum, B. S. (1991) The anticonvulsant effect of the non-NMDA antagonists, NBQX and GYKI 52466 in mice. Epilepsy Res. 9: 92–96

Chiccarelli, F. S., Eisner, H. J., Van Leer, G. E. (1980) Metabolic and pharmacokinetic studies with fenbufen in man. Arzneim. Forsch. 30: 728–735

De Sarro, G. B., De Sarro, A. (1992) Anticonvulsant activity of competitive antagonists of NMDA receptor in genetically epilepsy prone rats. Eur. J. Pharmacol. 215: 221–229

De Sarro, G. B., De Sarro, A. (1993) Anticonvulsant properties of non-competitive antagonists of the *N*-methyl-D-aspartate receptor in genetically epilepsy-prone rats: comparison with CPPene. Neuropharmacology 32: 51–58

De Sarro, G. B., Croucher, M. J., Meldrum, B. S. (1984) Anticonvulsant action of DS 103–282: pharmacological studies in rodents and the baboon, *Papio-papio*. Neuropharmacology 23: 326–530

De Sarro, G. B., Meldrum, B. S., Nisticò, G. (1988) Anticonvulsant effects of some calcium entry blockers in DBA/2 mice. Br. J. Pharmacol. 93: 247–256

Dunham, N. W., Miya, T. S. (1957) A note on a simple apparatus for detecting neurological deficit in rats and mice. J. Am. Pharm. Assoc. 46: 208–209

Finney, D. J. (1978) Statistical Methods in Biological Assay. Charles Griffen, London

Honoré, T., Davies, S. N., Drejer, J., Fletcher, E. J., Jacobsen, P., Lodge, D., Nielsen, F. E. (1988) Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. Science 241: 701–703

Katagiri, Y., Naora, K., Ichikawa, N., Hayashibara, M., Iwamoto, K. (1989) Absence of pharmacokinetic interaction between ofloxacin and fenbufen in rats. J. Pharm. Pharmacol. 41: 717–719

Naora, K., Katagiri, Y., Ichigawa, N., Hayashibara, M., Iwamoto, K. (1990a) A minor possibility of pharmacokinetic interaction between enoxacin and fenbufen in rats. J. Pharmacobiodyn. 13: 90–96

Naora, K., Katagiri, Y., Ichikawa, N., Hayashibara, M., Iwamoto, K. (1990b) A possible reduction in the renal clearance of ciprofloxacin by fenbufen in rats. J. Pharm. Pharmacol. 42: 704–707

Naora, K., Katagiri, Y., Ichikawa, N., Hayashibara, M., Iwamoto, K. (1991) Enhanced entry of ciprofloxacin into the rat central nervous system induced by fenbufen. J. Pharmacol. Exp. Ther. 258: 1033–1037

Naora, K., Katagiri, Y., Iwamoto, K., Yamaguchi, K., Sekine, Y. (1992) Effect of fenbufen on the pharmacokinetics of sparfloxacin in rats. J. Antimicrob. Chemother. 30: 673–683

Nevins, M. E., Arnolde, S. M. (1989) A comparison of the anticonvulsant effects of competitive and non-competitive antagonists of the *N*-methyl-D-aspartate receptor. Brain Res. 503: 1–4

Patel, S., Chapman, A. G., Graham, J. L., Meldrum, B. S., Frey, P. (1990) Anticonvulsant activity of the NMDA antagonists, D(−) 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (D-CPP) and D(−)(E)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid (D-CPPene) in a rodent and a primate model of reflex epilepsy. Epilepsy Res. 7: 3–10

Sheardown, M. J., Nielsen, E. O., Hansen, A. J., Jacobsen, P., Honoré, T. (1990) 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline: a neuroprotectant for cerebral ischemia. Science 247: 571–574

Sloboda, A. E., Tolman, E. L., Osterberg, A. C., Panagides, J. (1980) The pharmacological properties of fenbufen. Arzneim. Forsch. 30: 716–721

Smith, S. E., Durmuller, N., Meldrum, B. S. (1991) The non-*N*-methyl-D-aspartate receptor antagonists. GYKI 52466 and NBQX are anticonvulsant in two animal models of reflex epilepsy. Eur. J. Pharmacol. 201: 179–183

Taylor, C. P., Vartanian, M. G. (1992) Probenecid pretreatment enhances anticonvulsant action of NBQX in mice. Eur. J. Pharmacol. 213: 151–153