ELSEVIER

European Journal of Pharmacology 359 (1998) 27–32

ejp

PNU-151774E protects against kainate-induced status epilepticus and hippocampal lesions in the rat

Roberto Maj *, Ruggero G. Fariello, Giorgio Ukmar, Mario Varasi, Paolo Pevarello, Robert A. McArthur, Patricia Salvati

CNS Preclinical Research, Pharmacia and Upjohn SpA, Viale Pasteur 10, 20014 Nerviano, (MI), Italy

Received 12 February 1998; revised 15 July 1998; accepted 21 July 1998

Abstract

Kainic acid-induced multifocal status epilepticus in the rat is a model of medically intractable complex partial seizures and neurotoxicity. The exact mechanisms of kainic acid epileptogenic and neurotoxic effects are unknown, but enhanced glutamate release seems to be an important factor. PNU-151774E ((*S*)-(+)-2-(4-(3-fluorobenzyloxy) benzylamino) propanamide, methanesulfonate) is a broad-spectrum new anticonvulsant with Na^+ channel-blocking and glutamate release inhibiting properties. We have examined the effect of pretreatment with this compound on both seizure activity and hippocampal neuronal damage induced by systemic injection of kainic acid in rats. Lamotrigine, a recently developed anticonvulsant with similar glutamate release inhibitory properties, was tested for comparison, together with diazepam as reference standard, on the basis of its anticonvulsant and neuroprotectant properties in this animal model. PNU-151774E, lamotrigine (10, 30 mg/kg;i.p.) and diazepam (20 mg/kg; i.p.) were administered 15 min before kainic acid (10 mg/kg; i.p.). In the vehicle-treated group, kainic acid injection caused status epilepticus in 86% of animals. Hippocampal neuronal cell loss was 66% in the CA4 hippocampal area at 7 days after kainic acid administration. Diazepam inhibited both seizures and neurotoxicity. Lamotrigine reduced hippocampal neuronal cell loss at both doses, even when it did not protect from seizures, although it showed a trend toward protection. On the other hand PNU-151774E protected from both hippocampal neurodegeneration and status epilepticus. Thus, these data support the concept that seizure prevention and neuroprotection might not be tightly coupled. Glutamate release inhibition may play a major role in neuroprotection, but an additional mechanism(s) of action might be relevant for the anticonvulsant activity of PNU-151774E in this model.

Keywords: Seizure; Complex; Partial; Kainic acid; Status epilepticus; Neuroprotection

1. Introduction

Epilepsy is a collection of disease states currently affecting about 2 million people in the US and about 50 million people worldwide (Shorvon, 1990). Despite optimal use of available antiepileptic drugs, 20–30% of people suffering from epilepsy are resistant to treatment (Brodie and Dichter, 1996). Complex partial seizures, which originate from limbic structures are the most frequent type of epilepsy in humans (Gastaut et al., 1975) and are the seizure type with the highest percentage of drug resistance. About 70% of affected patients fail to experience seizure control with standard antiepileptic drugs (Löscher and Schmidt, 1994), and if not amenable to destructive surgery (Engel, 1996), become chronically invalid. Therefore the discovery of novel antiepileptic drugs with efficacy in drug-resistant patients is strongly needed.

Experimentally, kainic acid has been extensively used as a model of limbic seizures (McGeer and McGeer, 1988; Ben-Ari, 1985; Sperk, 1994). Kainic acid is a structural analogue of glutamic acid displaying potent neurotoxic properties (Coyle, 1983; Nadler, 1979). In addition to producing local cell death, kainic acid produces lesions in brain areas distant from the site of administration even when administered intracerebrally. The brain areas mainly affected by these distant lesions are the olfactory cortex, amygdaloid complex and hippocampus (Nadler et al., 1978; Lothman and Collins, 1981). In addition to neuronal dam-

* Corresponding author. CNS Preclinical Research, Pharmacia and Upjohn SpA, Via del Commercio, 63046 Marino del Tronto (AP), Italy. Tel.: +39-2-4838-8407; Fax: +39-2-4838-8263; E-mail: roberto.maj@eu.pnu.com

0014-2999/98/$ - see front matter
PII: S0014-2999(98)00554-8

age, kainic acid elicits a complex behavioural pattern of wet-dog shakes, convulsions and limbic automatisms accompanied by electroencephalographic (EEG) seizures and status epilepticus (Nadler, 1981). This syndrome is reproducible, albeit with some differences in pattern and sensitivity, between species and also between strains within the same species (Golden et al., 1991). The type of lesions, brain areas involved, and characteristics of the seizure/convulsive activity produced by kainic acid injection in the rat are bases for the validity of a model of medically intractable complex partial seizures (Ben-Ari, 1985), and multifocal limbic status epilepticus (Fariello and Golden, 1985).

The mechanisms of kainic acid epileptogenic and neurotoxic effects in the rat are multifactorial and include direct stimulation of kainic acid receptors, changes in metabolism, hypoxia, hypoglycaemia and oedema (Ben-Ari, 1985). However, enhanced neuronal excitation and/or reduced inhibitory control have a primary role (Ben-Ari, 1985). The glutamate-releasing property of kainic acid is considered to be an important contributing factor (Sperk, 1994). Consequently, compounds with glutamate release inhibiting properties such as the adenosine analogue, 2-chloroadenosine (Phillis and Wu, 1981), lamotrigine (Miller et al., 1986), and the $GABA_B$ receptor agonist, baclofen (Kato et al., 1982), have been shown to protect rats from kainic acid lesions (Arvin et al., 1988; McGeer and Zhu, 1990; Ault et al., 1986). However, both the 2-cloroadenosine and lamotrigine studies have been limited to histological and neurochemical features of kainic acid-induced neurotoxicity in the striatum. The anticonvulsant potential of lamotrigine in particular (Leach et al., 1991) was not considered in this model.

PNU-151774E ((*S*)-(+)-2-(4-(3-fluorobenzyloxy) benzylamino) propanamide, methanesulfonate, former FCE 26743) is a novel, broad spectrum anticonvulsant active in a variety of electrically and chemically induced seizures in mice and rats, with a high therapeutic safety window (Pevarello et al., 1998, Fariello et al., 1998). Among biochemical properties of PNU-151774E is inhibition of the release of glutamate evoked by the Na^+ channel activator, veratridine, as well as of the release induced by KCl in rat hippocampal slices (Vaghi et al., 1997). PNU-151774E has also shown potential for the treatment of complex partial seizures in the amygdala fully-kindled rat model (Maj et al., 1995) and electrically induced limbic after discharges in primates (Salvati et al., 1996).

The primary aims of this study were to assess the antiepileptic properties of PNU-151774E in the kainic acid model of complex partial seizures in the rat and to compare its effects to those of lamotrigine. A secondary aim of this study was to compare the effects of both PNU-151774E and lamotrigine on hippocampal neuronal damage induced by kainic acid administration. Diazepam was used as a reference positive control, as this compound has been shown to have both anticonvulsant and neuroprotectant properties in this model (Ben-Ari et al., 1979; Worms et al., 1981; Fuller and Olney, 1981).

2. Materials and methods

2.1. Experimental procedures

Male Wistar rats (Charles River, Italy) weighing 225–250 g were used. The rats were housed individually in plastic cages in a room with controlled temperature (21 ± 1°C) and relative humidity (60%). This room was illuminated on a 12-h light–dark cycle (lights on: 06:00 to 18:00 h).

Rats were anaesthetised with Na pentobarbital (50 mg/kg; i.p.). They were implanted extradurally with electrodes over the frontal and parietal cortex and with a reference electrode on the cerebellum. Caution was taken not to break the inner table of the diploe. All the electrodes were connected to plugs (U Danuso, Milan, Italy) and held to the skull with dental acrylic cement. At least 7 days after surgery, rats were treated with either saline, PNU-151774E (10, 30 mg/kg; i.p.), lamotrigine (10, 30 mg/kg; i.p.) or diazepam (20 mg/kg; i.p.), according to an independent-group design. Fifteen min later the animals received a single i.p. dose of kainic acid (10 mg/kg). The

Table 1
Effects of diazepam, lamotrigine and PNU-151774E on the onset and duration of EEG status epilepticus

Compound	Dose (mg/kg; i.p.)	Number of rats treated	% of rats showing SE	SE latency (min)	SE duration (min)
Vehicle	–	29	86	104.8 ± 12.5	135.2 ± 12.5
Diazepam	20	16	19[b]	215.1 ± 13.8[d]	22.2 ± 15.3[d]
Lamotrigine	10	22	59	139.7 ± 18.5	98.3 ± 20.5
Lamotrigine	30	24	79	103.8 ± 16.9	136.2 ± 16.9
PNU-151774E	10	21	57[a]	149.3 ± 18.2	89.7 ± 17.8
PNU-151774E	30	21	47[b]	166.6 ± 16.6	70.4 ± 15.7[c]

Data are expressed as mean ± S.E.M.
[c] $P < 0.05$.
[d] $P < 0.01$ as compared to vehicle group (Dunnett's test).
Percentage data are analyzed by Fisher's exact test where [a] $P < 0.05$ and [b] $P < 0.01$.

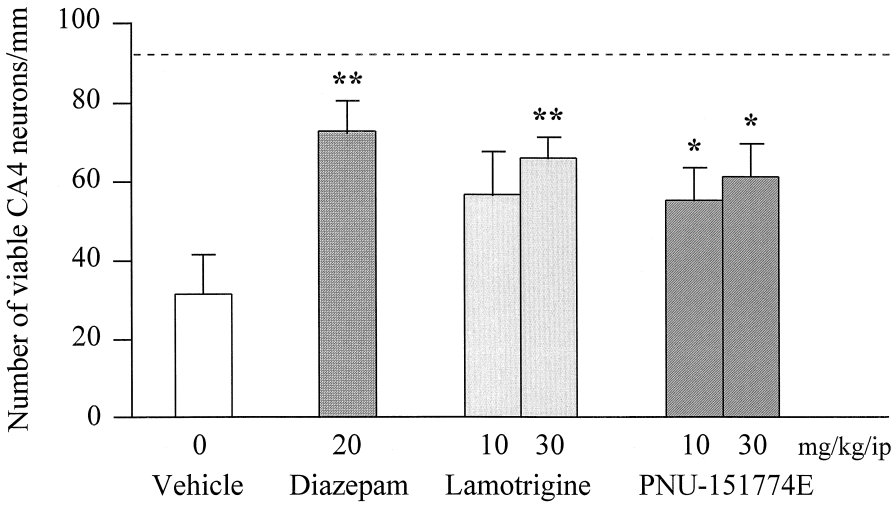

Fig. 1. Effects of PNU-151774E, lamotrigine and diazepam on kainic acid-induced damage in the CA4 hippocampal neurons. The dotted line represents the number of viable CA4 hippocampal neurons of non-treated rats. Data are means ± S.E.M.; $* P < 0.05$; $** P < 0.01$ as compared to vehicle group (Mann–Whitney non-parametric test).

EEG and behavioural observations lasted up to 240 min after kainic acid administration. The EEG tracing were reviewed by a blinded investigator, who assessed time of onset and duration of status epilepticus. Status epilepticus was defined as a sustained ictal EEG pattern lasting 20 min or longer without any interruption longer than 1 min (Fariello et al., 1989).

Seven days later, the animals were killed, the brains were removed and immersed for 48 h in 10% formalin (v/v) in 0.1 M phosphate buffer, pH 6.9. The brains were

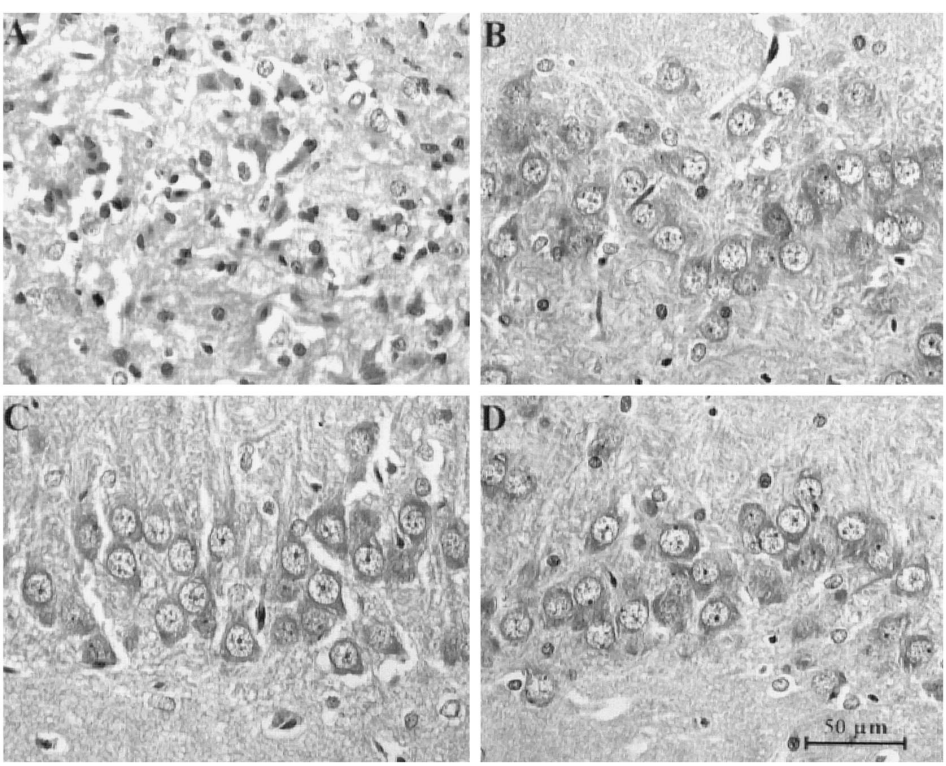

Fig. 2. Photomicrographs of hematoxylin-eosin-stained sections (4 μm) of the CA4 hippocampal region of representative rats treated with either vehicle (A), PNU-151774E 30 mg/kg (B), diazepam 20 mg/kg (C) and lamotrigine 30 mg/kg (D) 15 min before kainic acid (10 mg/kg) injection. Note the neuronal loss of the vehicle-pretreated rat, while rats pretreated with PNU-151774E, diazepam and lamotrigine show little evidence of damage, as witnessed by the abundance of normal healthy cells with clear cytoplasm.

then mounted on paraffin blocks and processed for histology. Coronal sections (4 μm) were cut with a RM2155 microtome (Leica, Milan, Italy), and stained with hematoxylin/eosin. Hippocampal injury was assessed by counting the number of histologically normal CA4 pyramidal neurons. Three sections per animal were examined and the neuronal counts averaged. All analysis were carried out by a blinded investigator.

2.2. Drugs

PNU-151774E was synthesised in the Medicinal Chemistry Dept. of Pharmacia and Upjohn (Nerviano, Italy). Lamotrigine isothionate was synthesised by Pharmacia and Upjohn according to the literature (Lee, 1996). Diazepam was obtained from Fabbrica Italiana Sintetici (Alte Montecchio, Italy). PNU-151774E and lamotrigine were dissolved in distilled water; diazepam was suspended in methocel.

2.3. Statistical analysis

The percentage of animals protected from status epilepticus was analysed using Fisher's exact test. For calculation of the latency to status epilepticus (min) and duration of status epilepticus (min), all animals were included regardless of whether they showed status epilepticus or not. The longest observation time (240 min) was assigned to the rats not showing status epilepticus. The data were evaluated by analysis of variance (ANOVA) followed by Dunnett's test. Neuronal counts were analysed using the Mann–Whitney non-parametric test. Levels of statistical significance are indicated as $* P < 0.05$ and $** P < 0.01$.

3. Results

In the vehicle-treated group, kainic acid induced the typical syndrome consisting of sustained seizures, status epilepticus and destruction of neural elements in different brain regions. In particular, status epilepticus was observed in 86% of kainic acid-treated rats. Mean status epilepticus latency was 104.8 min and mean status epilepticus duration was 135.2 min (Table 1). Pathological changes were seen 7 days after kainic acid injection in the hippocampus, prepyriform and pyriform cortex and amygdala. These changes included massive edematous swelling of glia and neuronal dendrites and either swelling or picnotic changes with necrosis of many of the neurons involved. In particular, we found 66% reduction of normal appearing neurons in the CA4 hippocampal area (Figs. 1 and 2).

Of the rats pretreated with diazepam (20 mg/kg; i.p.), 80% did not show status epilepticus ($P < 0.01$). This protection from status epilepticus was reflected by the increased latency as well as the shortened duration of status epilepticus (Table 1). Diazepam also showed neuroprotective effects by dramatically reducing the hippocampal CA4 cell loss induced by kainic acid systemic administration (Figs. 1 and 2).

After lamotrigine pretreatment (10 mg/kg) the number of animals entering status epilepticus was reduced (59%) and latency was slightly increased, without the effect reaching statistical significance (Table 1). Unexpectedly, the higher dose (30 mg/kg) produced results not dissimilar from those for the controls. In contrast, lamotrigine reduced hippocampal CA4 cell loss at both doses, although statistical significance ($P < 0.01$) was reached only at 30 mg/kg (Figs. 1 and 2).

Both doses of PNU-151774E significantly decreased the percentage of rats showing status epilepticus (57% and 47% at 10 and 30 mg/kg, respectively) (Table 1). Moreover, PNU-151774E significantly increased the latency of status epilepticus) at 30 mg/kg. The increase in latency was paralleled by a significantly shorter duration of status epilepticus. The protective effects of PNU-151774E were also evident in terms of hippocampal neuron survival after kainic acid administration (Figs. 1 and 2). Both doses of PNU-151774E significantly ($P < 0.05$) protected neurons in the CA4 hippocampal region.

4. Discussion

Kainic acid-induced convulsions is a model of excitotoxin-induced complex partial seizures and status epilepticus. We used this model to examine the effects of PNU-151774E because it allows the advantage of simultaneous assessment of the effects of a potential anticonvulsant compound on both occurrence of seizures and histological damage. We now compared the effects of pretreatment with PNU-151774E to those obtained with diazepam and lamotrigine. The results can be summarized as follows: (1) both PNU-151774E and diazepam were able to inhibit kainic acid-induced status epilepticus; (2) both PNU-151774E and diazepam reduced the hippocampal neuronal loss induced by kainic acid; (3) lamotrigine was able to reduce hippocampal neuronal death, but did not significantly alter either the latency or the duration of status epilepticus.

The ability of PNU-151774E to reduce status epilepticus in this model of complex partial seizures suggests clinical efficacy in the treatment of this type of epilepsy (Fariello and Golden, 1985). Indeed, drugs considered as first choice in the treatment of complex partial seizures, such as carbamazepine and phenobarbital (Mattson, 1992; Bruni and Albright, 1984), are also active in the kainic acid model. Carbamazepine, for example, antagonizes intrahippocampal kainic acid-induced seizures in rats (Zaczek et al., 1978). Similar effects are observed with phenobarbital (Clifford et al., 1982). Phenytoin, another first line antiepileptic drugs for complex partial seizures, is generally incapable of suppressing seizure activity or convul-

sions induced by kainic acid in vivo (Zaczek et al., 1978; Turski et al., 1980; Stone and Javid, 1980; Clifford et al., 1982). Phenytoin, however, has been shown to suppress kainic acid-induced paroxysms in vitro (Clifford et al., 1982). Lamotrigine, clinically effective for the treatment of complex partial seizures (Stolarek et al., 1994), was not active in the present study. The anticonvulsant activity of lamotrigine has not been, to the best of our knowledge, previously studied in the kainic acid model; however, lamotrigine is inactive in a model of status epilepticus in rats lesioned with cortical cobalt lesions precipitated by homocysteine thiolactone, another dicarboxylic excitotoxin (Walton et al., 1996). On the other hand lamotrigine was found active in the rat kindling model of complex partial seizures (Dalby and Nielsen, 1997).

While phenobarbital was shown to be active in this kainic acid model (Clifford et al., 1982), its activity was only seen at high doses, out of the therapeutic range (40–200 mg/kg;i.v.). Even though the clinically effective dose of PNU-151774E has yet to be established, PNU-151774E reduced status epilepticus at doses comparable to those seen to antagonize seizures in classical anticonvulsant tests such as the maximal electroshock seizure test (ED_{50} = 6.9 mg/kg, i.p.), and well below doses producing psychomotor impairment (TD_{50} = 626 mg/kg, p.o.; Fariello et al., 1998). The differences between therapeutic and active doses in various models are important features, especially when considering that most of the clinically used antiepileptic drugs have undesirable side-effects, in particular when therapeutic plasma concentrations are exceeded (Dodrill, 1975; Thompson and Trimble, 1983). Diazepam, for example, is also active to reduce status epilepticus in the kainic acid model, as shown by the present data and literature reports (Ben-Ari et al., 1979; Worms et al., 1981; Fuller and Olney, 1981). However, its effects appear at a very high dose (10–20 mg/kg), roughly 10–20 fold higher than that required to suppress maximal electroshock-induced convulsions (Fariello et al., 1998) and much higher than those causing behavioural impairment (Kalynchuk and Beck, 1992; Fariello et al., 1998). Benzodiazepines in general, and other direct or indirect GABA receptor agonists (Fariello et al., 1982; Clifford et al., 1982) have been the first antiepileptic drugs to be proven effective against kainic acid seizures. However, as pointed out above, the doses required are well in the toxic range. PNU-151774E has shown a very wide therapeutic index in both electrical and chemical seizure models. This compound has also a low potential to induce psychomotor side-effects (Fariello et al., 1998). This profile of PNU-151774E as well as its ability to antagonize amygdala-kindled seizures, another model of complex partial seizures (Maj et al., 1995) at doses similar to those used in this study, further supports the hypothesis of clinical efficacy. However, only clinical testing can definitely establish the efficacy and tolerability of a new anticonvulsant agent in a defined epilepsy syndrome.

The second major result of this study was that PNU 151774E shows neuroprotective properties, in that it was able to counteract excitotoxin-induced hippocampal neuronal death. A similar neuroprotective effect was observed after diazepam administration, which is consistent with the effect found by other investigators (Ben-Ari et al., 1979; Fuller and Olney, 1981; Worms et al., 1981). The size of the difference between doses that are neuroprotective and the toxic doses for PNU-151774E and diazepam is clearly in favour of PNU-151774E.

Notwithstanding lamotrigine's slight and not statistically significant anti-seizure activity, we found it to be highly neuroprotective in this model. These results confirm and extend the observation that lamotrigine prevents kainic acid-induced striatal neuronal degeneration (McGeer and Zhu, 1990). Even if neuroprotection may be a consequence of antiseizure activity, these results also indicate a possible dissociation between hippocampal neurodegeneration and seizure activity, as previously reported by Fariello et al. (1989), who used MK-801 in the kainic acid model in rats. In that study, suppression of the kainic acid-induced behavioural seizures and reduction of neuronal damage were not accompanied by reduced EEG seizure activity after MK-801 treatment. PNU-151774E and lamotrigine may therefore differ in their mechanism of anticonvulsant action, while showing similar neuroprotective properties.

In conclusion, these results show that PNU-151774E has anticonvulsant activity in a model of intractable seizures and status epilepticus, associated with neuroprotective activity. PNU-151774E appears to prevent seizures, their maintenance and spread. Lamotrigine, on the other hand, showed only a trend toward prevention from status epilepticus, in spite of providing neuroprotection. While glutamate release inhibition may play a major role in neuroprotection, an additional mechanism(s) of action seems to be related to the anticonvulsant activity of PNU-151774E. Further studies are needed in order to elucidate this point.

Acknowledgements

The authors acknowledge the technical help of Marzia Breda for help in carrying out the surgical procedures, data compilation and analysis.

References

Ault, B., Gruenthal, M., Armstrong, D.R., Nadler, J.V., 1986. Efficacy of baclofen and phenobarbital against the kainic acid limbic seizure-brain damage syndrome. J. Pharmacol. Exp. Ther. 239, 612–617.

Arvin, B., Neville, L.F., Roberts, P.J., 1988. 2-Chloroadenosine prevents kainic acid-induced toxicity in rat striatum. Neurosci. Lett. 93, 336–340.

Ben-Ari, Y., 1985. Limbic seizure and brain damage produced by kainic acid: mechanisms and relevance to human temporal lobe epilepsy. Neuroscience 14, 375–403.

Ben-Ari, Y., Tremblay, E., Ottersen, O.P., Naquet, R., 1979. Evidence suggesting secondary epileptogenic lesion after kainic acid: pretreatment with diazepam reduces distant but not local brain damage. Brain Res. 165, 362–365.

Brodie, M.J., Dichter, M.A., 1996. Antiepileptic drugs. New Engl. J. Med. 334, 168–175.

Bruni, J., Albright, P.S., 1984. The clinical pharmacology of antiepileptic drugs. Clin. Neuropharmacol. 7, 1–34.

Clifford, D.B., Lothman, E.W., Dodson, W.E., Ferrendelli, J.A., 1982. Effect of anticonvulsant drugs on kainic acid-induced epileptiform activity. Exp. Neurol. 76, 156–167.

Coyle, J.T., 1983. Neurotoxic action of kainic acid. J. Neurochem. 41, 1–11.

Dodrill, C.B., 1975. Diphenylhydantoin serum levels, toxicity, and neuropsychological performance in patients with epilepsy. Epilepsia 16, 593–600.

Dalby, N.O., Nielsen, E.B., 1997. Comparison of preclinical anticonvulsant profiles of tiagabine, lamotrigine, gabapentin and vigabatrin. Epilepsy Res. 28 (1), 63–72.

Engel Jr., J., 1996. Surgery for seizures. New Engl. J. Med. 334, 647–652.

Fariello, R.G., Golden, G.T., 1985. Electroencephalographic models of epilepsy. In: Bartholini et al. (Eds.), Epilepsy and GABA Receptor Agonists: Basic Therapeutic Research. Raven Press, New York, NY, pp. 139–147.

Fariello, R.G., Golden, G.T., Pisa, M., 1982. Homotaurine (3 aminopropanesulfonic acid; 3APS) protects from the convulsant and cytotoxic effect of systemically administered kainic acid. Neurology 32, 241–245.

Fariello, R.G., Golden, G.T., Smith, G.G., Reyes, P.F., 1989. Potentiation of kainic acid epileptogenicity and sparing from neuronal damage by an NMDA receptor antagonist. Epilepsy Res. 3, 206–213.

Fariello, R.G., McArthur, R.A., Bonsignori, A., Cervini, M.A., Maj, R., Marrari, P., Pevarello, P., Wolf, H.H., Woodhead, J.W., White, H.S., Varasi, M., Salvati, P., Post, C., 1998. Preclinical evaluation of PNU-151774E as a novel anticonvulsant. J. Pharmacol. Exp. Ther. 285, 397–403.

Fuller, T.A., Olney, J.W., 1981. Only certain anticonvulsants protect against kainate neurotoxicity. Neurobehav. Toxicol. Teratol. 3, 355–361.

Gastaut, H., Gastaut, J.L., Goncalves, E., Silva, G.E., Fernandez Sanchez, G.R., 1975. Relative frequency of different types of epilepsy: a study employing the classification of epileptic seizures. Epilepsia 16, 457–461.

Golden, G.T., Smith, G.G., Ferraro, T.N., Reyes, P.F., Kulp, J.K., Fariello, R.G., 1991. Strain differences in convulsive response to the excitotoxin kainic acid. NeuroReport 2, 141–144.

Kalynchuk, L.E., Beck, C.H., 1992. Behavioral analysis of diazepam-induced memory deficits: evidence for sedation-like effects. Psychopharmacology 106, 297–302.

Kato, K., Goto, M., Fukuda, H., 1982. Baclofen: inhibition of the release of L-3Hglutamate and L-3Haspartate from rat whole brain synaptosomaximal electroshock test. Gen. Pharmacol. 13, 445–447.

Leach, M.J., Baxter, M.G., Critchley, M.A.E., 1991. Neurochemical and behavioral aspects of lamotrigine. Epilepsia 32 (Suppl. 2), S4–S8.

Lee, G.R., 1996. Preparation of lamotrigine. WO 9620935. Chem. Abstr. 125, 195693.

Löscher, W., Schmidt, D., 1994. Strategies on antiepileptic drug developmen: is rational drug design superior to random screening and structural variation?. Epilepsy Res. 17, 95–134.

Lothman, E.W., Collins, R.C., 1981. Kainic acid induced limbic seizures: metabolic, behavioral, electroencephalographic and neuropathological correlates. Brain Res. 218, 299–318.

Maj, R., Breda, M., Antongiovanni, V., Bonsignori, A., Varasi, M., McArthur, R.A., 1995. Anticonvulsant activity of FCE 26743 in the kindling model of epilepsy. Pharmacol. Res. 31 (Suppl.), 346.

Mattson, R.H., 1992. Drug treatment of uncontrolled seizures. Epilepsy Res. 5 (Suppl.), 29–35.

McGeer, E.G., McGeer, P.L., 1988. Excitotoxin animal models of human disease. In: Galli, C.L., Manzo, L., Spencer, P.S. (Eds.), Recent Advances in Nervous System Toxicology. Plenum, New York, NY, pp. 107–131.

McGeer, E.G., Zhu, S.G., 1990. Lamotrigine protects against kainate but not ibotenate lesion in rat striatum. Neurosci. Lett. 112, 348–351.

Miller, A.A., Sawyer, D.A., Roth, B., Peck, A.W., Leach, M.J., Wheatley, P.L., Parsons, D.N., Morgan, R.J.I., 1986. Lamotrigine. In: Meldrum, B.S., Porter, R.J. (Eds.), New Anticonvulsant Drugs. John Libbey, London, pp. 165–177.

Nadler, J.V., 1979. Kainic acid: neurophysiological and neurotoxic actions. Life Sci. 24, 289–300.

Nadler, J.V., 1981. Kainic acid as a tool for the study of temporal lobe epilepsy. Life Sci. 29, 2031–2042.

Nadler, J.V., Perry, B.W., Cotman, C.W., 1978. Intraventricular kainic acid preferentially destroys hippocampal pyramidal cells. Nature 217, 676–677.

Pevarello, P., Bonsignori, A., Dostert, P., Heidempergher, F., McArthur, R.A., Pinciroli, V., Colombo, M., Fariello, R.G., Salvati, P., Post, C., Varasi, M., 1998. Synthesis and anticonvulsant activity of a new class of 2-[(Arylalkyl)amino] alkanamide derivatives. J. Med. Chem. 41, 579–590.

Phillis, J.W., Wu, P.H., 1981. The role of adenosine and its nucleotides in central synaptic transmission. Prog. Neurobiol. 16, 187–239.

Salvati, P., Algate, C., Beard, D., Bonsignori, A., Cervini, M.A., McArthur, R.A., Maj, R., Pevarello, P., Varasi, M., Fariello, R.G., Post, C., 1996. Anticonvulsant profile of FCE 26743A, a novel 2-aminopropionamide derivative. Soc. Neurosci. Abstr. 22, 2109.

Shorvon, S.D., 1990. Epidemiology, classification, natural history, and genetics of epilepsy. Lancet 336, 93–96.

Sperk, G., 1994. Kainic acid seizures in the rat. Prog. Neurobiol. 42, 1–32.

Stolarek, I., Blacklaw, J., Forrest, G., Brodie, M.J., 1994. Vigabatrin and lamotrigine in refractory epilepsy. J. Neurol. Neurosurg. Psychiatry 57, 921–924.

Stone, W.E., Javid, M.J., 1980. Effects of anticonvulsants and glutamate antagonists on the convulsive action of kainic acid. Arch. Int. Pharmacodyn. 243, 56–65.

Thompson, P.J., Trimble, M.R., 1983. Anticonvulsant serum levels: relationship to impairments of cognitive functioning. J. Neurol. Neurosurg. Psychiatry 46, 227–233.

Turski, L., Niemann, W., Stephens, D.N., 1980. Differential effects of antiepileptic drugs and β-carbolines on seizures induced by excitatory amino acids. Neuroscience 39, 799–807.

Vaghi, F., Maj, R., Rosa, B., Ukmar, G., Lamberti, E., McArthur, R.A., Varasi, M., Salvati, P., Post, C., 1997. Neuroprotective effect of PNU-151774E, a new anticonvulsant compound, in the model of global ischaemia in gerbils. Soc. Neurosci. Abstr. 23, 545.

Walton, N.Y., Jaing, Q., Hyun, B., Treiman, D.M., 1996. Lamotrigine vs. phenytoin for treatment of status epilepticus: comparison in an experimental model. Epilepsy Res. 24, 19–28.

Worms, P., Willigens, M.T., Lloyd, K.G., 1981. The behavioural effects of systemically administered kainic acid: a pharmacological analysis. Life Sci. 29, 2215–2225.

Zaczek, R., Nelson, M.F., Coyle, J.T., 1978. Effects of anaesthetics and anticonvulsants on the action of kainic acid in the rat hippocampus. Eur. J. Pharmacol. 52, 323–327.