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Failure of carbamazepine to prevent behavioural and histopathological sequels of experimentally induced status epilepticus

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Abstract

Sustained electrical stimulation of the perforant pathway was used to induce long-lasting hippocampal seizures in conscious rats. One hour prior to stimulation, rats were given i.p. injections of either saline or a commonly used antiepileptic drug, carbamazepine (5*H*-dibenz[*b*,*f*]azepine-5-carboxamide; CBZ; 20 mg/kg). When tested 2 weeks later in a water maze, both the saline- and the carbamazepine-pretreated rats showed similarly a severe impairment in spatial learning compared to non-stimulated controls. Histological evaluation revealed that the pyramidal cell damage was ($P < 0.05$) milder in the carbamazepine-pretreated group in the CA1, but not the CA3c subfield. However, the number of somatostatin-immunoreactive neurons in both stimulated groups was reduced equally. Thus, at the dose of 20 mg/kg, which is a usual anticonvulsive dose in humans, carbamazepine seems to offer only partial protection against pyramidal cell damage, but no protection against the hilar somatostatin-immunoreactive neuron loss or the spatial learning deficit after perforant pathway stimulation in rats. The result clearly differs from that obtained either with a GABA (γ-aminobutyric acid)-enhancing drug and a novel antiepileptic, vigabatrin (4-amino-hex-5-enoic acid) or with a competitive NMDA (*N*-methyl-D-aspartate) receptor antagonist, CGP 39551 (DL-[*E*]-2-amino-4-methyl-5-phosphono-3-pentenoic acid carboxyethylester) in the same test situation.

Keywords: Hippocampus; Seizure; Cell death; Learning disorder; (Rat)

1. Introduction

Learning and memory deficits associated with epilepsy have been thought to arise primarily from the hippocampal cell damage occurring in both epileptic patients and some animal models of epilepsy (Zola-Morgan et al., 1986; Ylinen et al., 1991b). Furthermore, epileptiform neuronal activity (Bridgman et al., 1989; Knowlton et al., 1989) or antiepileptic medication (Trimble, 1987) on their own have been suggested to partly account for the cognitive decline.

Carbamazepine (5*H*-dibenz[*b*,*f*]azepine-5-carboxamide), a tricyclic compound, is widely used for the treatment of seizures and some other disorders such as trigeminal neuralgia and manic-depressive illness (see Schmutz, 1985). Although the exact mechanism underlying the action of carbamazepine in nervous tissue is not clear, the therapeutic effect of the drug is obviously based on its inhibitory action on Na^+ and Ca^{2+} conductances. The effects of carbamazepine on cognitive functions in epileptic patients have been reported to be moderate (Trimble, 1987; Gillham et al., 1990; Reinvang et al., 1991). However, in healthy volunteers as well as in patients with newly diagnosed epilepsy, distinct cognitive impairment due to carbamazepine treatment has been reported (Forsythe et al., 1991; Meador et al., 1993; Kälviäinen et al., 1995).

In experimental epilepsy, sustained stimulation of the rat perforant pathway has been used for inducing long-lasting seizures (Sloviter, 1983; Freund et al., 1991; Ylinen et al., 1991a, b, c). This experimental model mimics the situation in humans after repeated seizures or status epilepticus. In addition, it induces cell degeneration in the hippocampus comparable to that found in human epileptic brain: pyramidal cells in the CA1 and CA3c regions as well as somatostatin-immunoreactive interneurons in the hilus of the dentate gyrus selectively degenerate (Dam, 1980; De Lanerolle et al., 1989; Freund et al., 1991;

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Ylinen et al., 1991a, b). In addition, binding to NMDA (*N*-methyl-D-aspartate) receptors decreases (Lahtinen et al., 1993c). These various changes are associated with learning and memory deficits, assessed in water maze tasks for spatial learning (Ylinen et al., 1991a, b; Lahtinen et al., 1993c) and a passive avoidance test for conditional learning (Rogers et al., 1989).

In our previous studies we had found that pretreatment with vigabatrin (4-amino-hex-5-enoic acid) (Ylinen et al., 1991b, c), an irreversible inhibitor of GABA (γ-aminobutyric acid) transaminase, and CGP 39551 (DL-[*E*]-2-amino-4-methyl-5-phosphono-3-pentenoic acid carboxyethylester) (Ylinen et al., 1991a; Lahtinen et al., 1993c), a competitive and orally active NMDA receptor antagonist, protected from both hippocampal cell damage and cognitive deficits after stimulation of the rat perforant pathway. While no comparable studies are available about generally used older antiepileptics, the aim of the present study was to investigate the neuroprotective effect of carbamazepine in the same test situation. Moreover, since carbamazepine is a commonly used antiepileptic in the treatment of partial seizures as well as tonic-clonic convulsions in adults and children, it was of importance to investigate its effectiveness, particularly in a model that allows cognitive testing.

2. Materials and methods

2.1. Animals

Male Han:Wistar rats bred in the National Animal Center at the University of Kuopio (Finland) and initially weighing 250–300 g were used in this study. They were housed in a standard temperature- (20 ± 1°C), humidity- (50–60%) and light-controlled (light period 07:00–21:00 h) environment with ad libitum access to food and water. Operated animals as well as their non-operated controls were separated at the time of surgery and housed singly in Makrolon Plexiglas cages.

2.2. Surgical procedures

For stimulation of the perforant pathway, the animals were anesthetized with Equithesin (chlornembutal, 3.0 ml/kg i.p.) and placed in a stereotaxic frame with bregma and lambda on the same horizontal level. For EEG recording, pairs of insulated stainless steel electrodes (1.0-mm separation) were implanted bilaterally into the hippocampus (4.1 mm posterior, 2.6 mm lateral and 3.6 mm ventral to the bregma) with the upper tip in the pyramidal cell layer of the CA1 area and the lower tip in the granular cell layer of the dentate gyrus. A similar pair of electrodes (but with a 0.5-mm tip separation) was implanted in the angular bundle (7.0 mm posterior, 4.5 mm lateral, 4.1 mm ventral to the bregma) for stimulating the perforant pathway. Two stainless steel watch screws were attached as indifferent and ground electrodes to the occipital skull above the cerebellum. The electrodes were fixed with dental acrylate.

2.3. Perforant pathway stimulation and EEG recording

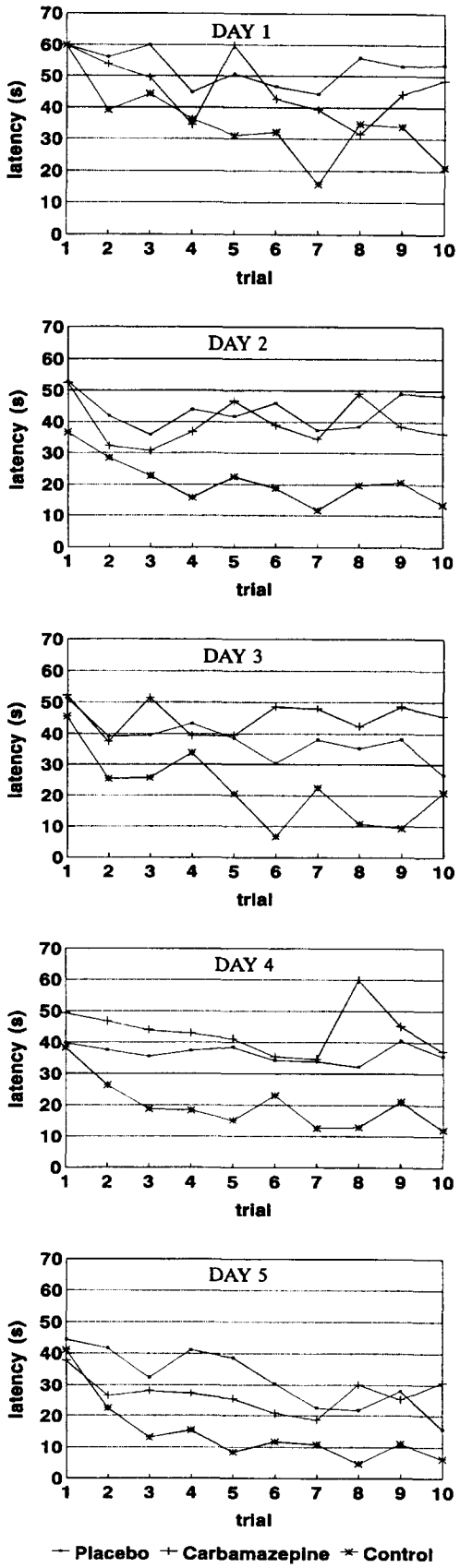
Two weeks later, hippocampal baseline EEGs were recorded with a polygraph (Grass 78, 7P511 amplifiers) and evoked potentials were stored on a hard disk. Only those rats showing evoked population spikes in the dentate gyrus were chosen for perforant pathway stimulation, the others were included as controls. Rats with acceptable population spikes ($n = 11$) were divided randomly into two groups: the first group received an injection of carbamazepine (5*H*-dibenz(*b*,*f*)azepine-5-carboxamide, 20 mg/kg i.p. dissolved in propylene glycol; Ciba-Geigy, Basel, Switzerland) and the others received physiological saline solution 1 h before stimulation. A Grass 88 stimulator was used to stimulate the rats unilaterally in the angular bundle, using a modified method of Sloviter (Sloviter, 1983; Ylinen et al., 1991a) (i.e. 60-min sustained stimulation with 20-Hz train of 0.1-ms duration and 2-mA pulses). During the entire stimulation session, evoked responses of the hippocampus were monitored with an oscilloscope. After completion of the stimulation, the behavior of the rats was observed for 3–4 h including occasional recordings of the EEG. If the seizures continued during this follow-up period, the animals received an i.p. injection of 100–200 μl Diapam (diazepam, 1–2 mg/kg) 30 min after completion of the stimulation period to stop seizure activity. The need for this treatment was independent of the pretreatment with either saline or carbamazepine.

2.4. Spatial learning test

After a recovery period of 2 weeks, the rats ($n = 21$) were tested for 5 days in a water maze task using a modified Morris water maze apparatus (San Diego Instruments, San Diego, CA, USA), which has been described in detail previously (Riekkinen et al., 1990). The test consisted of 10 daily trials, in which the starting direction was changed continuously (north, east, south and west; in this order). The platform was in the same location during the first and second day, after which it was changed daily to another quadrant of the pool. The total swimming distances (units) and latencies (s) used for finding the platform were measured.

2.5. Histology

At the end of the experiment (18–20 days after stimulation), 13 of the rats were deeply anesthetized again and perfused transcardially, first with saline (3 min), then with a fixative (30 min) containing 4% paraformaldehyde, 0.05% glutaraldehyde and 0.02% picric acid in 0.1 M phosphate buffer (PB), pH 7.4 and finally with 10% sucrose in PB (3 min). The brains were removed from the



skull and blocks of the dorsal hippocampus with overlying neocortex were blocked and immersed in 20% sucrose. The blocks were then freeze-thawed in liquid nitrogen and sectioned coronally on a vibratome at 60 μm. Alternate sections were processed for silver impregnation (Gallyas et al., 1980) to evaluate the degeneration pattern of the hippocampus and for somatostatin immunocytochemistry (for detailed methodological description, see Lahtinen et al., 1993b) to estimate the number of somatostatin-immunoreactive cells in the dentate hilus. The remainder of the animals ($n = 8$), which were not used for immunocytochemistry, were decapitated. Their brains were quickly removed, mounted on a piece of cork with Tissue-Tek embedding medium, frozen immediately in isopentane and stored at -80°C until sectioned. 16-μm sections were cut coronally throughout the dorsal hippocampus on a cryostat and thaw-mounted onto gelatin-coated slides. Sections were stained with cresyl violet to evaluate the stimulation-induced degeneration of the hippocampal formation (compare Lahtinen et al., 1993a).

2.6. Data analysis

The difference between the two stimulated groups of animals as to seizure severity as well as incidence and duration of seizures during the stimulation session was analyzed using Fisher's exact test. Water maze data, escape latency and distance between groups were evaluated using an analysis of variance (ANOVA) with training trial as a covariate. The Mann-Whitney U-test was used to analyze the differences between groups as to the number of somatostatin-immunoreactive cells and in CA1 pyramidal cell damage.

3. Results

At the beginning of perforant pathway stimulation, all the rats immediately had evoked population spikes and had wet-dog shakes within 2 min. The rats showed spiking for more than 50% of the duration of the stimulation session, which was the primary criterion for successful stimulation. They also had partial as well as generalized seizures, which usually continued after stimulation (rated behaviourally from type I to V, Racine, 1972). Although

Fig. 1. Acquisition of the water maze task, expressed as escape latency(cies) for finding the submerged platform. Groups of rats ($n = 21$): (*) controls; (+) carbamazepine-pretreated rats (20 mg/kg i.p. injection 1 h before perforant pathway stimulation); (●) placebo rats (pretreatment with saline). The results are expressed as group means for the ten daily trials. Each day, both perforant pathway-stimulated groups showed a strikingly worse water maze performance compared to the controls (ANOVA, $P > 0.001$). The difference between the carbamazepine- and the saline-pretreated animals was not significant on any testing day (ANOVA, $P > 0.05$).

animals from both stimulated groups showed generalized seizures, none of the carbamazepine treated rats (0/5) showed the most severe (type V) seizures whereas almost all placebo animals (5/6) reached this stage at least once during the stimulation ($P = 0.013$, Fisher's exact test). The incidence and duration of seizures during the stimulation session appeared to be slightly lower due to the drug treatment, but the difference from the placebo group was statistically non-significant.

In the water maze task, the saline- ($n = 6$) and carbamazepine- ($n = 5$) pretreated, perforant pathway-stimulated rats showed a similar performance throughout the whole test (Fig. 1, swimming latencies). They differed significantly from each other only in speed, and due to this, in total distance during the first testing day: carbamazepine-pretreated animals swam faster (speed $F(1,107) = 11.3$, $P = 0.001$; total distance $F(1,107) = 11.8$, $P = 0.001$). During the rest of the test, no significant differences were found in either latencies, speed or total swimming distance between these two groups. However, on the third and fourth day, carbamazepine-treated rats tended to perform less well than the saline group. Both stimulated groups showed a significantly worse acquisition than the unstimulated controls ($n = 10$) during the whole test (both for latencies and total distances, $P < 0.001$ every day; see Fig. 1).

The degree of CA1 and CA3c pyramidal cell damage seen either with silver or Nissl staining was scored from 0 to 3 (0, normal; 1, < 10% of the neurons irreversibly damaged; 2, damage 10–50% and 3, damage > 50% (see Block and Pulsinelli, 1987). All six saline-treated rats showed grade 2–3 damage in either the CA1 or CA3c area (Table 1). One of these animals had grade 1 degeneration in CA1 but grade 3 degeneration in the CA3c subfield. Only two animals escaped the damage in the Ca3c subfield while showing degree 2–3 degeneration in the CA1 region. In carbamazepine-treated rats, the degree of cell damage varied between 0 and 2: one out of five animals had no damage in either subfield. One rat showed degree 2 degeneration only in the CA3c region. The other three showed damage, grade 2, in CA1 and grade 1–2 in CA3c. According to the Mann-Whitney U-test, saline-pretreated animals had significantly more severe degeneration in CA1 than the carbamazepine-pretreated animals ($P < 0.05$).

Table 1
Degree of hippocampal cell damage after sustained (60 min) perforant pathway stimulation in rats pretreated with either saline or carbamazepine (CBZ, 20 mg/kg)

Score		0	1	2	3
Placebo	CA1	0/6	1/6	1/6	4/6
($n = 6$)	CA3	2/6	0/6	0/6	4/6
CBZ	CA1	2/5	0/5	3/5	0/5
($n = 5$)	CA3	1/5	1/5	3/5	0/5

Scoring for cell damage: 0, normal; 1, damage < 10%; 2, damage 10–50%; 3, damage > 50%. n = number of animals. Statistically significant difference ($P < 0.05$) between the groups was found in the CA1 but not in the CA3 area (2-tail Mann-Whitney U-test).

Table 2
Number of somatostatin-immunoreactive neurons (cells/mm^2) in the dentate hilus of controls and perforant pathway-stimulated rats with saline or carbamazepine (CBZ, 20 mg/kg) pretreatment

Group	n	Mean for both sides	Ipsilateral side	Contralateral side
Control	5	209 ± 16		
Placebo	3	126 ± 16 [a]	114 ± 20 [a]	138 ± 6 [a]
CBZ	5	117 ± 19 [b]	93 ± 19 [b]	141 ± 13 [b]

Values are expressed as means ± S.E.M. n = number of animals. [a] $P < 0.05$ and [b] $P < 0.01$ compared to controls (2-tail Mann-Whitney U-test).

The number of somatostatin-immunoreactive neurons in the hilus of the dentate gyrus was significantly decreased in both stimulated groups (Table 2). Compared to the controls, however, carbamazepine-pretreated rats showed a more significant decrease on both the ipsilateral and the contralateral hilus ($P < 0.01$) than the saline-treated animals ($P < 0.05$).

4. Discussion

The effectiveness of carbamazepine to prevent hippocampal cell damage and impairment in spatial learning after sustained electrical stimulation of the rat perforant pathway was tested in the present study. We found that carbamazepine (20 mg/kg, single administration of the therapeutic dose) protected slightly the hippocampal pyramidal cells: most of the carbamazepine-pretreated animals showed grade 2 degeneration (10–50%) in the CA1 or CA3c subfields, and only one animal escaped damage. Interestingly, in some animals, the CA3c region seemed to be even slightly more vulnerable than the CA1, which usually exhibits the greatest degeneration, with or without drug treatment (Freund et al., 1991; Ylinen et al., 1991a, b; Lahtinen et al., 1993c). On the other hand, the carbamazepine-pretreated animals showed an even more severe loss of somatostatin-immunoreactive neurons in the dentate hilus than the saline-treated animals. The hilar somatostatin neurons are thought to degenerate during the acute phase of stimulation-induced excitotoxic cell death, i.e. already during stimulation. This may indicate that carbamazepine is inefficient against or even may augment the acute phase of the excitotoxic cell death but is able to partially block the delayed excitotoxic cell death (see Olney et al., 1986 and Choi, 1992), seen as necrosis in the CA1 region. This partial protection by carbamazepine in the CA1 region may be based on blockade of the Na^+/Ca^{2+} influx through NMDA receptors, which is in agreement with the report of the ability of carbamazepine to block NMDA-activated currents in cultured spinal cord neurons (Lampe and Bigalke, 1990). In our earlier studies,

using pretreatment with vigabatrin (an irreversible inhibitor of GABA transaminase) and CGP 39551 (a competitive NMDA antagonist), the extent of the somatostatin neuron loss was less or equal to that of saline-pretreated animals (Ylinen et al., 1991a, b, c; Lahtinen et al., 1993c).

The most notable finding of the present study was, however, that carbamazepine pretreatment failed to alleviate the perforant pathway stimulation-induced spatial learning deficit measured 2 weeks after stimulation. This contrasts sharply with the results with vigabatrin and CGP 39551 which could dose dependently abolish the spatial learning disorder (Ylinen et al., 1991a, b; Lahtinen et al., 1993c). Furthermore, although the learning deficit was abolished totally due to the treatment with either of these two drugs, the CA1 pyramidal cells usually showed at least moderate degeneration. In the case of carbamazepine, the CA1 pyramidal cell degeneration, which varied in extent between 0–50%, was partially and significantly prevented. In spite of this, the spatial navigation ability of the animals was still on the level of that of the saline-pretreated animals, with more than 50% of the neurons damaged. Although this kind of spatial learning task involving components from both reference and working memory (the platform location was changed daily) has been suggested to be specific for hippocampal CA1 damage (Auer et al., 1989), the result of the present study does not favor this idea. One possibility might be that carbamazepine functioned through a mechanism that was detrimental to the recovery process of the animal after perforant pathway stimulation. Another possibility is that extrahippocampal cell damage may have played a significant role.

The most common side (toxic) effects of carbamazepine, i.e. ataxia, nystagmus and vertigo (see Schmutz, 1985), refer to the impaired cerebellar function. Recently, it was reported that long-term administration of carbamazepine induces toxicity in a cerebellar neuronal cell culture, which can be reversed by application of NMDA (Gao and Chuang, 1992). If this were typical of cerebellar neurons, the influence of carbamazepine on the cerebellum during the excitotoxin overflow at the moment of stimulation might have been opposite to that observed in the hippocampus. Thus, impaired motor function due to cerebellar damage could partly explain the poor spatial navigation of the carbamazepine-pretreated rats in the water maze task.

Our finding about the failure of carbamazepine to alleviate the learning deficit after experimentally induced status epilepticus is important from the clinical point of view. It is also in line with findings with healthy volunteers as well as patients with newly diagnosed epilepsy (Forsythe et al., 1991; Meador et al., 1993; Kälviäinen et al., 1995). After all, the major goal in the pharmacotherapy of epileptic patients is the prevention of seizures as well as of the seizure activity-induced progression of epilepsy. However, preservation of cognitive functions has a great impact on the quality of the patient's life, especially in the case of a child. This is why the possible neuroprotective effects of not only the new drugs but also the commonly used older antiepileptics should be studied systemically.

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