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# Profile of ucb L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats

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The novel anticonvulsant drug ucb L059 ((S)-α-ethyl-2-oxo-1-pyrrolidineacetamide) was evaluated in several rodent models of partial and generalized seizures. Ucb L059 (27–108 mg/kg i.p.) increased the thresholds for tonic electroconvulsions and myoclonic and clonic seizures induced by timed i.v. infusion of pentylenetetrazol (PTZ), but was ineffective in the traditional maximal electroshock seizure and s.c. PTZ seizure tests in mice and rats in doses up to 500 mg/kg. The anticonvulsant potency of ucb L059 in seizure threshold tests was similar to that of standard drugs, such as valproate. In amygdala-kindled rats, ucb L059 exerted potent anticonvulsant activity against both focal and secondarily generalized seizures at doses of 13–108 mg/kg. The adverse effects of ucb L059 were quantitated in the open field and in standard tests for motor impairment, such as the rotarod and chimney tests. Ucb L059 exerted only minimal effects on behaviour, e.g. slight hyperactivity, and did not impair muscle activity in the rotarod test in doses up to 1700 mg/kg i.p. The data indicate that ucb L059 is an interesting new anticonvulsant agent with a broad spectrum of activity and high therapeutic index.

Ucb L059; Seizures; Epilepsy; Piracetam; Valproate; Anticonvulsant drugs

## 1. Introduction

Nootropic drugs, such as piracetam (2-oxo-1-pyrrolidineacetamide), are used clinically as cognition-enhancing agents in the elderly (Rosenberg et al., 1990; Sarter, 1991). The mechanism of action of these drugs is unknown, but some evidence suggests that effects on energy metabolism and neuronal excitability might be involved (Rosenberg et al., 1990; Sarter, 1991). More recently, piracetam and other nootropic drugs were reported to exert anticonvulsant effects in different seizure models, including chemical kindling in rats (Schmidt, 1990; Fischer et al., 1991; Keller, 1991). Piracetam has also been reported to lessen cognitive disturbances and to improve seizure protection in epileptic patients receiving carbamazepine (Chaudhry et al., 1991). Since many epileptic patients have memory disturbances, either due to the disease itself or to the chronic treatment with standard antiepileptic drugs (Trimble, 1991), an anticonvulsant drug with cognition-enhancing activity would offer important advantages for the treatment of epilepsy. However, most nootropic drugs, including piracetam have to be administered at very high doses in order to achieve anticonvulsant activity (Schmidt, 1990; Fischer et al., 1991; Keller, 1991).

More recently, ucb L059 ((S)-α-ethyl-2-oxo-1-pyrrolidineacetamide), an ethyl analogue of piracetam (fig. 1), was shown to exert potent anticonvulsant effects at relatively low doses (5–30 mg/kg) in various models of generalized seizures in rats and mice (Gower et al., 1992). The novel drug appeared to be more potent against tonic seizures than against clonic seizures, which would be similar to standard antiepileptic drugs, such as phenytoin and carbamazepine. Models of partial epilepsy, such as amygdala-kindling (McNamara, 1984), were not included in the study of Gower et al. (1992).

In the present study, we examined the anticonvulsant profile of ucb L059 in a battery of seizure models previously proposed for the evaluation of new anticonvulsant drugs in mice and rats (Löscher and Schmidt, 1988). The seizure tests included models with threshold as well as suprathreshold induction of seizures in order to ensure that effects of ucb L059 against specific seizure types were not missed. Furthermore, amygdala-kindled rats were used as a model to evaluate drug activity against complex partial seizures (Löscher and Schmidt, 1988). The selectivity of the anticonvulsant effects produced by ucb L059 was examined by using

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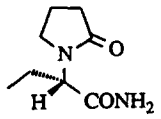

Fig. 1. Chemical structure of ucb L059 ((S)-α-ethyl-2-oxo-1-pyrrolidineacetamide).

models for quantitative determination of 'minimal neurotoxicity', such as the rotarod and chimney tests. All tests were used in a standardized manner as recently described (Löscher et al., 1990, 1991a, b; Löscher and Nolting, 1991).

## 2. Materials and methods

### 2.1. Animals

Male NMRI-mice were obtained from a commercial breeder (Winkelmann Versuchtstierzucht GmbH, Borchen, F.R.G.) at the age of 4 weeks (body weight 19–27 g) and were allowed to adapt to the laboratory for 1 week before the experiments were started. All experiments with drug injections were then carried out within the next week to minimize the effect of increasing age on drug susceptibility. Each mouse was used for only one experiment.

Female Wistar rats (Winkelmann) were bougth at an age of 11–12 weeks (body weight 180–200 g) and were used after at least 1 week of adaptation to the laboratory. Female rats were used because they are known to eliminate drugs less rapidly than male rats, which was thought to be an advantage for the drug potency studies. Furthermore, at the age used, the female rats had almost reached their final body weight and, in contrast to adult male rats, could be kept in groups of 10 (or more) in one cage, which is an advantage for large scale studies.

Mice and rats were kept in groups of 10 in plastic cages at controlled temperature (25°C) and humidity (about 40%) with a 12-h light cycle beginning at 7 a.m. They received standard diet (Altromin, Lage, F.R.G.) and tap water ad libitum. All drug injections were given in the forenoon at an ambient temperature of 23–25°C.

### 2.2. Tests used to evaluate anticonvulsant activity against generalized seizures

The threshold for seizures induced by maximal (tonic hindlimb extension) electroshock in mice was determined via transauricular electrodes (i.e. copper electrodes introduced bilaterally into the ears) by means of a stimulator (BMT Medizintechnik GmbH, Berlin, F.R.G.) which delivered a constant current (adjustable from 1 to 200 mA regardless of the impedance of the test object; self-adjusting stimulus voltage maximally 7000 V) with sinusoidal pulses (50/s) for 0.2 s. The stimulus intensity was varied by an up-and-down method in which the current was lowered or raised in 0.1-log intervals if the preceding animal did or did not show hind limb extension, respectively. The data thus generated in groups of 20 mice were used to calculate the threshold current for inducing hind limb extension in 50% of the mice ($CC_{50}$ with confidence limits for 95% probability), using the method of Kimball et al. (1957). Each group of animals was used for only one threshold determination. Control groups, which received the vehicle used for drug administration, were tested together with the drug-treated animals, using the same pretreatment time at which the drug was tested. In additional experiments with ucb L059, the threshold for tonic electroconvulsions was determined with transauricular electrodes in rats (20 animals per group), using 0.6-log intervals for the up-and-down method instead of the 0.1-log intervals used for mice.

The maximal (tonic hindlimb extension) electroshock seizure (MES) test with supramaximal stimulation was carried out with corneal copper electrodes and with apparatus described above, using a fixed current of 50 mA in mice and 150 mA in rats with a pulse frequency of 50/s for 0.2 s. The tonic extension of the hind limbs was used as endpoint in both species. Ten animals were used per group. In several control groups (with or without vehicle injection) of mice and rats tested prior to the drug experiments, all animals of a group exhibited tonic extension of hindlimbs so that, in contrast to the threshold test, daily control groups were not necessary for experiments with the MES test.

The threshold for different types of pentylenetetrazol (PTZ)-induced seizures was determined by infusing a 1% solution of PTZ into the tail vein of unrestrained freely moving mice at a rate of 0.3 ml/min with an infusion pump (Perfusor-E, Braun Melsungen, F.R.G.). Groups of 10–12 mice were used per threshold determination. In untreated control mice, the following seizure types occurred during PTZ infusion (described in order of appearance): (1) one or more generalized myoclonic twitches of the whole body, (2) repeated clonic seizures of fore- and/or hindlimbs without loss of righting reflexes, (3) a generalized clonus with repeated clonic seizures of fore- and hindlimbs, during which animals fell onto their side, i.e. exhibited loss of righting reflexes, (4) clonic seizures with loss of righting reflexes followed by backward extension of forelimbs (forelimb tonus), often but not always followed by (5) tonic hindlimb extension. In the experiments with ucb L059, the following endpoints were used for quantification of drug effects: (1) the initial myoclonic twitch, (2)

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the first generalized clonus with loss of righting reflexes, and (3) the forelimb tonus. The threshold for each endpoint was calculated as the dose (mg/kg) of PTZ inducing this endpoint during infusion. The threshold for tonic hindlimb seizures could not be quantitated in all animals because the infusion was usually stopped after 2 min and not all animals exhibited tonic hindlimb seizures during this period. Increasing the infusion time did not resolve this problem, since several mice of a group died without showing hindlimb tonus. However, all animals showed forelimb tonus within 2 min, and this seizure type proved to be a more reliable endpoint with less variation than hindlimb tonus. All drug-treated groups were compared with vehicle-treated groups on each day.

For the s.c. PTZ seizure test, before evaluation of the anticonvulsant drugs, a dose-response curve for PTZ was determined in groups of 10 mice or rats. PTZ was injected s.c. in the back of the neck of the animals. The animals were then observed for 30 min after injection and the first generalized clonic seizure with loss of righting reflexes was used as the endpoint. In this way, the dose inducing this seizure type in 97% of the animals ($CD_{97}$) was calculated in mice (80 mg/kg) and rats (90 mg/kg) by the method of Litchfield and Wilcoxon (1949). After administration of these doses, the following seizure types were observed in untreated mice and rats (described in the order of appearance): (1) one or more generalized myoclonic twitches of the whole body, (2) repeated clonic seizures of fore- and/or hindlimbs without loss of righting reflexes (corresponding to the 'threshold seizure' proposed by Swinyard (1969) for anticonvulsant drug evaluation in the s.c. PTZ test), (3) a generalized clonic seizure of fore- and hindlimbs, during which animals fell onto their side, i.e. exhibited loss of righting reflexes, (4) loss of righting followed by tonic forelimb seizure, and/or (5) loss of righting with tonic fore- and hindlimb seizure. In the controls (with or without vehicle injection), endpoints 1, 2 and 3 were observed in 9–10 animals of a group. In contrast, especially in mice, the number of animals that also exhibited generalized tonic seizures (extension of hind- and/or forelimbs) after these doses varied.

For drug potency studies, PTZ was injected s.c. in groups of 10 animals at the time of the maximal anticonvulsant effect (see below) and the animals were observed for 30 min for the occurrence of seizures. None of the vehicles used during these experiments affected PTZ-induced seizures.

For the threshold models, the significance of differences between individual (vehicle-treated) control groups and drug-treated groups was calculated by Student's t-test. In case of significant drug effects, the doses increasing the MES or PTZ threshold by 20% ($TID_{20}$) were determined by log-linear regression analysis from dose response curves, using at least three doses per drug (for more details see Löscher et al., 1991a, b). For comparison with the anticonvulsant potency of ucb L059, $TID_{20}$ values of seven standard antiepileptic drugs were determined in the seizure threshold models. Swinyard et al. (1952) originally proposed the use of $TID_{20}$ values to compare the potency of anticonvulsant drugs, and $TID_{20}$ values have been used to compare GABA mimetic drugs in seizure threshold models (Löscher, 1982, 1985). In this respect, it is important to not that the $TID_{20}$ values of drugs such as vigabatrin are much closer to the doses effective in epileptic patients than the more commonly used $TID_{50}$ values (Löscher, 1982, 1985). Thus, in the case of drugs with relatively low potency, the concept of $TID_{20}$ measurements, as originally proposed by Swinyard et al. (1952), might yield predictive data in terms of clinical effectiveness.

In all seizure tests, anticonvulsant potency was quantified at the time of the maximal anticonvulsant effect (Löscher et al., 1991a, b). For ucb L059, the time of the peak effect was determined for the electroconvulsive threshold in mice and for kindled seizures (see below) in rats.

### *2.3. Amygdala kindling*

For implantation of stimulation and recording electrodes, rats were anaesthesized with chloral hydrate (360 mg/kg i.p.) and a bipolar electrode was stereotaxically implanted in the right basolateral amygdala (according to the surgery methods described in the atlas of Paxinos and Watson (1986)). The coordinates for electrode implantation were AP—2.2, L–4.8, V–8.5, measured from the bregma. Skull screws served as the indifferent reference electrode. The electrode assembly was attached to the skull with dental acrylic cement. After a postoperative period of 2 weeks, constant current stimulations (500 $\mu$A, 1 ms, monophasic square-wave pulses, 50/s for 1 s) were delivered to the amygdala at intervals of 1 day until 10 stage 5 seizures were elicited. The electrical susceptibility of the stimulated region (threshold for induction of afterdischarges) was recorded on the first day of the experiment (initial afterdischarge threshold) as well as after kindling (with an interval of at least 4 days after the 10th stage 5 seizure), using an ascending stairstep procedure (Freeman and Jarvis, 1981). The initial current intensity was 10 $\mu$A, and the current intensity was increased in steps of about 20% of the previous current at intervals of 1 min until an afterdischarge lasting at least 3 s was elicited. Since almost all fully kindled animals exhibited generalized seizures (stage 4–5) at the afterdischarge threshold current, it was not necessary to determine the threshold for generalized seizures separately. In fully kindled rats, the afterdischarge threshold determined with interstimulation intervals of

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1 day was not different from the afterdischarge threshold values determined with interstimulation intervals of 1 min, thus demonstrating that the short interstimulation interval did not bias the afterdischarge threshold determinations. In addition to afterdischarge threshold, the following parameters of kindled seizures were measured in fully kindled rats after stimulation with either the afterdischarge threshold current or suprathreshold stimulation with 500 $\mu$A: seizure severity was classified according to Racine (1972): 1, immobility, eye closure, twitching of vibrissae, sniffing, facial clonus; 2, head nodding associated with more severe facial clonus; 3, clonus of one forelimb; 4, rearing, often accompanied by bilateral forelimb clonus; 5, rearing with loss of balance and falling accompanied by generalized clonic seizures. Seizure duration was the duration of limbic (stage 1–2) and/or motor seizures (stage 3–5); limbic seizure activity sometimes occurred *after* termination of stage 3–5 seizures but was not included in the seizure duration. Afterdischarge duration was the total time that spikes with a frequency of at least 1/s were present in the EEG, recorded from the site of stimulation.

The anticonvulsant effects of ucb L059 in fully kindled rats were determined in a group of eight rats with reproducible stage 5 seizures in two ways: (1) kindled seizures were evoked by suprathreshold stimulation with 500 $\mu$A after i.p. drug injection; (2) the focal seizure threshold (afterdischarge threshold) was determined after i.p. drug injection. The drug was injected 0.5 h, 1 or 2 h prior to stimulation. In the experiments with suprathreshold stimulation, control responses were determined 2–3 days before and after each drug administration, and the next drug experiment was only undertaken if all rats showed reproducible stage 5 seizures. Similarly, in the experiments for the determination of the afterdischarge threshold, the control focal seizure threshold was determined 2–3 days before and after drug treatment. For control determinations, rats received an i.p. injection of vehicle (saline) with the pretreatment time of the respective drug experiment (see below). For all drug experiments, at least 4 days were interposed between two drug injections in order to avoid changes in drug potency due to drug accumulation or tolerance.

The anticonvulsant activity of piracetam was evaluated in additional experiments with another group of fully kindled rats. Experiments were done at 500 $\mu$A as described above.

The significance of differences between pre-drug control responses and responses after drug injection was calculated by the Wilcoxon signed rank test for paired replicates. The $ED_{50}$ for suppression of secondarily generalized (stage 4–5) seizures was calculated by the method of Litchfield and Wilcoxon (1949) as described previously (Löscher et al., 1986).

### *2.4. Tests used for quantification of adverse effects*

Groups of 10 mice or rats were used per dose of ucb L059. The animals were observed at various times up to 192 h after injection for adverse effects as described below. Groups of 10 mice or rats injected i.p. with vehicle (saline) were used as controls.

Minimal neurological deficit, such as sedation and impaired motor function, was quantitated with the rotarod test and the chimney test. In the chimney test, the animals had to climb backwards in a plastic tube of 25 cm length and 3 cm inner diameter in the case of mice and 50 cm length and 5.5 cm inner diameter in the case of rats. Neurological deficit was indicated by the inability of the animals to climb backwards up the tube within 30 s. Whereas untreated control mice were able to perform the test without previous training (normal mice climb backwards through the tube within less than 5–10 s), rats had to be trained (and data were then used as individual control) before drug administration.

The rotarod test was carried out with rods of different diameters, which were produced by inserting a metal rod into a rubber (mice) or foam rubber (rats) tube in order to provide traction. For mice, the rod had a diameter of 2.5 cm and rotated at 6 r.p.m., whereas for rats the rod had a diameter of 6 cm and rotated at 8 r.p.m. Neurological deficit was indicated by the inability of the animals to maintain their equilibrium for at least 1 min on the rotating rod. Untreated mice were able to remain on the rod for several min, whereas rats had to be trained before drug experiments. After drug treatment, mice or rats that were not able to maintain their equilibrium on the rod for 1 min were put on the rod twice. Only animals that were not able to remain on the rod at three subsequent 1-min attempts were considered to exhibit neurological deficit.

$TD_{50}$ was determined in the chimney test at the time of the maximum effect of ucb L059. $TD_{50}$ values with confidence limits for 95% probability were calculated by the method of Litchfield and Wilcoxon (1949), using a computer program (Pharm/PCS). For comparison with the $TD_{50}$ values of ucb L059, $TD_{50}$ values were determined in the same tests with seven standard antiepileptic drugs as described elsewhere (Löscher and Nolting, 1991).

In addition to these quantitative estimations of neurological deficit, behavioural alterations caused by ucb L059 were recorded in the animals' home cages and in an open field (90–100 cm in diameter). Muscle tone was estimated by palpation of the abdomen. The extent of sedation, ataxia and muscle relaxation after administration of ucb L059 was determined with a rating system as described previously (Löscher et al., 1987). In short, animals were taken out of cage, placed in an open field and observed for about 1 min; sedation and

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ataxia were rated separately (abdominal muscle tone was evaluated by palpation at the end of the observation period). Sedation: 1, slightly reduced forward locomotion; 2, reduced locomotion with rest periods in between (partly with closed eyes); 3, reduced locomotion with more frequent rest periods; 4, no forward locomotion, animal sits quietly with closed eyes. Ataxia: 1, slight ataxia in hindlegs (tottering of the hind quarters); 2, more pronounced ataxia with dragging of hind legs; 3, further increase in ataxia and more pronounced dragging of hind legs; 4, marked ataxia, animals lose balance during forward locomotion; 5, very marked ataxia with frequent loss of balance during forward locomotion. The same protocol for recording adverse effects was also used in kindled rats. Rectal body temperature was measured with an electronic thermometer. The weight of the animals was recorded daily, before and after drug injection. The significance of differences in body weight or body temperature between pre-drug and post-drug data determined in the same group of animals was calculated by using the Wilcoxon signed rank test for paired replicates.

### 2.5. Drugs

The drugs used in this study were kindly provided by the following companies: ucb L059 by UCB Pharmaceutical Sector (Braine l'Alleud, Belgium); phenobarbital (as sodium salt), valproate (as sodium salt), carbamazepine, phenytoin, and ethosuximide by Desitin Arzneimittel GmbH (Hamburg, F.R.G.); diazepam and clonazepam by Hoffmann-La Roche (Basle, Switzerland). PTZ was purchased from Caesar and Loretz (Hilden, F.R.G.) and piracetam from Sigma (Munich, F.R.G.).

Ucb L059 was dissolved in saline and injected i.p. at an injection volume of 10 ml/kg in mice and 2–4 ml/kg in rats. Piracetam, phenobarbital (as sodium salt), valproate (as sodium salt), phenytoin (by means of dilute NaOH), diazepam (by means of dilute HCl) and ethosuximide were freshly dissolved in saline and injected i.p. at a volume of 10 ml/kg in mice and 2–3 ml/kg in rats. Drugs, i.e. carbamazepine and clonazepam, which were insoluble in aqueous vehicles were dissolved by means of lipophilic vehicles. We used either warmed glycofurol (tetraglycol; tetrahydrofurfurylalcohol polyethylene glycol ether) or warmed polyethylene glycol 400 (PEG 400) to dissolve the drug and warmed saline was then added under continuous stirring. In order to avoid the possible effects of vehicle alone, maximum concentrations of 30% PEG 400 or 10% glycofurol were used; at these concentrations, the solvents do not alter the seizure thresholds or the behaviour of animals in the chimney and rotarod tests (Löscher et al., 1990). The injection volume was 10 ml/kg in mice and 2–10 ml/kg in rats.

All doses and concentrations of drugs given in this study refer to the free acid or base of the respective drug.

TABLE 1

Effect of ucb L059 on the threshold for tonic (hindlimb extension) electroshock seizures in mice and rats. The seizure threshold (stimulation via ear electrodes) was determined as $CC_{50}$ (with confidence limits for 95% probability) in groups of 20 animals per dose. For ucb L059, the effect of three different doses on the threshold is shown. Control groups (40 mice and 60 rats) received i.p. vehicle injection. Significant differences between controls and drug-treated groups are indicated ([a]$P < 0.001$). The dose which increased the threshold by 20% ($TID_{20}$) was calculated from the dose response curves for ucb L059 in mice and rats. For comparison, $TID_{20}$ values for standard antiepileptic drugs determined in the same model in mice are shown. All determinations were done at the times of the peak drug effects, i.e. 60 min (ucb L059 in mice and rats), 5 min (valproate), 15 min (diazepam, clonazepam), 30 min (phenobarbital, ethosuximide), and 120 min (phenytoin), respectively. Not effective is indicated by n.e., not determined by n.d.

| Drug | Dose (mg/kg i.p.) | Mice | | Rats | |
|---|---|---|---|---|---|
| | | Threshold ($CC_{50}$ in mA) | $TID_{20}$ (mg/kg i.p.) | Threshold ($CC_{50}$ in mA) | $TID_{20}$ (mg/kg i.p.) |
| Ucb L059 | 0 | 7.4 (6.8 – 8.0) | | 18.4 (17.4 – 20.0) | |
| | 27 | 8.3 (7.7 – 9.0) [a] | | 22.9 (20.8 – 25.2) [a] | |
| | 54 | 9.6 (8.9 – 10.3) [a] | | 22.4 (20.8 – 24.1) [a] | |
| | 108 | 9.6 (8.9 – 10.3) [a] | | 24.6 (22.1 – 27.2) [a] | |
| Ucb L059 | | | 40 | | 29 |
| Phenobarbital | | | 2.9 | | n.d. |
| Carbamazepine | | | 1.2 | | n.d. |
| Phenytoin | | | 4.9 | | n.d. |
| Valproate | | | 50 | | n.d. |
| Ethosuximide | | | n.e. | | n.d. |
| Diazepam | | | 1.6 | | n.d. |
| Clonazepam | | | 0.37 | | n.d. |

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