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The New Competitive NMDA Receptor Antagonist CGP 40116 Inhibits Pilocarpine-Induced Limbic Motor Seizures and Unconditioned Motor Behaviour in the Mouse

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STARR, M. S. AND B. S. STARR. *The new competitive NMDA receptor antagonist CGP 40116 inhibits pilocarpine-induced limbic motor seizures and unconditioned motor behaviour in the mouse.* PHARMACOL BIOCHEM BEHAV 47(1) 127–131, 1994. — The biologically active enantiomer (CGP 40116) of the new competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist CGP 37849 was investigated for its effects on pilocarpine-induced limbic motor seizures and unconditioned motor behaviour in the mouse. CGP 40116 (1–8 mg/kg IP) reduced the incidence and severity of pilocarpine-induced motor seizures, although the overall effect was weak. In contrast to the noncompetitive NMDA antagonist MK 801, there were no signs of CGP 40116 producing a proconvulsant response in this model. In the nonhabituated mouse, MK 801 promoted hyperlocomotion at low doses and hypolocomotion and ataxia at high doses, while CGP 40116 dose-dependently suppressed motor behaviour. Because CGP 40116 and MK 801 exert opposite effects on the seizure threshold to pilocarpine and differentially alter species-typical behaviours in the mouse, it is suggested that different populations of NMDA receptors may mediate their effects. The indivisibility of seizure suppression and motor impairment noted previously with noncompetitive NMDA antagonists such as MK 801 appears also to apply to the new generation competitive NMDA antagonist CGP 40116.

NMDA antagonist CGP 40116 MK 801 Mouse Epilepsy Motor behaviour

GLUTAMATE is held to be the most abundant excitatory neurotransmitter in the central nervous system, and as such is acknowledged to be involved in the initiation of seizures and their propagation (5). Drugs which prevent the neuroexcitatory actions of glutamate at its various receptors (*N*-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA], and kainate) are consequently being evaluated as novel and therapeutically useful anticonvulsants. In particular, NMDA antagonists have proved effective against convulsions induced by electroshock and pentylenetetrazol (20) and in genetically epilepsy-prone animals (13,20), but less so against kindling (4,10,15,17). The latter test is considered predictive of drugs with potential anticonvulsant activity against secondarily generalized complex partial seizures in man, a condition that is traditionally accepted to be the most difficult to control with currently available treatments.

Thus, whereas the noncompetitive NMDA antagonist MK 801 (3) has been reported to attenuate the severity of fully amygdala-kindled seizures in rats (6,15), Löscher and Hönack (10) indicated this anticonvulsant activity only occurred at the expense of severe motor impairment, reflecting the importance also of glutamate systems in brain regions concerned with motor behaviour (27). Conversely, some authors have shown that MK 801 can have the opposite effect and exacerbate hippocampus-kindled seizures (7), in line with other literature reports of NMDA antagonists being proconvulsant rather than anticonvulsant (2,9,10).

As an alternative to electrical kindling, a readily produced and quantifiable limbic motor seizure can also be elicited in rodents with the cholinomimetic pilocarpine. Turski's group (25,26) has extensively characterized this type of seizure and reviewed the utility of the pilocarpine model for investigating novel anticonvulsant drugs (21). The electrographic characteristics and neuropathology of the seizures produced by pilocar-

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pine are similar in many respects to temporal lobe epilepsy in man, leading Turski and colleagues to propose the pilocarpine-treated rodent as a simple model of this human condition (21, 25). The effects of NMDA antagonists on pilocarpine-induced seizures have received little attention, though interestingly MK 801 has once again been found to increase rather than decrease the animal's sensitivity to the seizure stimulus (14,19).

The purpose of this study was to determine the anticonvulsant potency of the new competitive NMDA antagonist CGP 40116 (16) in the pilocarpine-treated mouse (1,25). CGP 40116 is the newly prepared biologically active enantiomer of CGP 37849, a novel compound with enhanced bioavailability in the brain which has already been shown to have anticonvulsant activity against kindled seizures (4,10,15,17). The behavioural properties of CGP 40116 are currently being evaluated to determine if it offers any advantages over the racemic mixture in the treatment of epilepsy. Because motor disabilities have proved to be a major factor limiting the usefulness of NMDA antagonists as anticonvulsants in other seizure models, a principal goal of this study was to determine if this was also true of CGP 40116.

METHOD

Animals and Seizure Induction

Male albino mice (TO strain, Tuck, Southend-on-sea, UK) weighing 30–36 g (approx. six to eight weeks) were housed in groups of 22 at 22 ± 1°C under fluorescent lighting from 0700 to 1700 and allowed free access to food and water. Limbic seizures were induced by systemic injection of pilocarpine (400 mg/kg IP) after first protecting the mice against the peripheral autonomic effects of the cholinomimetic by injecting methylscopolamine bromide (1 mg/kg IP) 30 min beforehand (1,25). The glutamate antagonist CGP 40116 (1–8 mg/kg IP) and saline (controls) were administered 120 min prior to seizure induction, this being the optimal latency for the anticonvulsant action of CGP 37849 (17). The mice were then observed for 3 h for overt signs of seizure activity, which was quantified according to the following rating scale: 0 = *no seizure activity*; 1 = *head bobbing, body tremor*; 2 = *rearing and falling, occasional forepaw myoclonus*; 3 = *continuous myoclonic seizure*; 4 = *tonic seizure*; 5 = *respiratory arrest.* We also noted the time each animal took to exhibit a full tonic/clonic motor seizure (seizure latency) and the incidence of such seizures. In a separate experiment the convulsant potential of CGP 40116 was determined by challenging the mice with a subconvulsant dose of pilocarpine (100 mg/kg IP) (1,25).

Assessment of Species-Typical Behaviours

Motor behaviours were measured over a 10-min period after placing the mice individually onto the floor of a Perspex container (30 × 35 × 25 cm high), without prior acclimatisation. Horizontal locomotor movements were recorded automatically by underfloor sensors using a Panlab model 0603 detector unit (18). The number of rears, in which both forepaws were lifted off the floor, and time spent grooming (s) were recorded by an experienced observer using a hand-held counter and stopwatch, respectively. The effects of 120 min pretreatment with CGP 40116 (0.25–8 mg/kg IP) or 30 min pretreatment with MK 801 [0.1–1.6 mg/kg IP; see (14)] on these motor parameters were investigated.

Data Analysis

The incidence of seizures in control and drug-treated groups was compared by Fisher exact probability test. Seizure latencies were analysed by one-way analysis of variance (ANOVA) and by Mann-Whitney *U* test, and seizure severi-

TABLE 1

EFFECTS OF CGP 40116 ON PILOCARPINE-INDUCED MOTOR SEIZURES IN THE MOUSE

Treatment (mg/kg)	Number Convulsing	Latency to Convulsion (s)	Seizure Severity
Pilocarpine 100 mg/kg challenge			
CGP 40116 (0)	0/27	–	–
CGP 40116 (1)	0/10	–	–
CGP 40116 (2)	0/10	–	–
CGP 40116 (4)	0/10	–	–
CGP 40116 (8)	0/10	–	–
Pilocarpine 400 mg/kg challenge			
CGP 40116 (0)	20/20	10.9 ± 0.4	4.40 ± 0.14
CGP 40116 (1)	15/20*	24.4 ± 4.0*	3.11 ± 0.09
CGP 40116 (2)	7/10*	33.9 ± 6.0*	2.89 ± 0.50
CGP 40116 (4)	4/10*	24.8 ± 3.1*	3.00 ± 0.45
CGP 40116 (8)	6/10*	24.3 ± 1.0	1.82 ± 0.45

All animals received methylscopolamine bromide (1 mg/kg) 30 min, plus the treatments shown 120 min before pilocarpine. All drugs were administered IP and the mice observed for 3 h. Seizure intensity was quantified according to the following rating scale: 0 = *no seizure activity*; 1 = *head bobbing, body tremor*; 2 = *rearing and falling, occasional forepaw myoclonus*; 3 = *continuous myoclonic seizure*; 4 = *tonic seizure*; 5 = *respiratory arrest*. *$P < 0.05$ vs. controls by Fisher exact probability test (number convulsing), or Mann-Whitney *U* test (seizure latency). All doses of CGP 40116 significantly reduced seizure severity in mice challenged with 400 mg/kg pilocarpine (Kruskal-Wallis $H = 13.10$, $P = 0.01$).

ties by Kruskal-Wallis test. Motor behaviours were analysed by ANOVA with post hoc comparisons by Dunnett's t test.

Drugs

Pilocarpine nitrate (Sigma, St. Louis), (−)-methylscopolamine bromide (Sigma), CGP 40116 (Ciba Geigy, Basel, Switzerland), and MK 801 (Research Biochemicals, Natick, MA) were dissolved in distilled water and delivered in a dose volume of 5 ml/kg.

RESULTS

In control mice, 100 mg/kg IP pilocarpine was confirmed to be a subconvulsant dose (Table 1). Pretreatment with CGP 40116, 1–8 mg/kg IP, did not lower the seizure threshold to pilocarpine.

Mice administered saline and challenged 30 min later with 400 mg/kg IP pilocarpine recorded a 100% seizure rate (20/20 convulsed tonically) with a mean latency of 10.9 ± 0.4 min and an average severity of 4.40 ± 0.14 (Table 1). CGP 40116 afforded significant protection across the whole dose range (1–8 mg/kg IP; Fisher P = 0.004 to 0.30). In addition, the competitive NMDA antagonist reduced the intensity of the seizures (Kruskal-Wallis H = 13.10, P = 0.01) and slightly, but significantly, delayed their onset, $F(4, 65)$ = 2.86, P = 0.029 by ANOVA.

Since the anticonvulsant action of CGP 40116 noted here was at variance with the proconvulsant response described for MK 801 in this model (14,19), in next examining the motoric effects of CGP 40116 we considered it appropriate to include a comparison with MK 801. Results for 30-min and 120-min saline-treated controls were not significantly different for the various behavioural parameters (not shown). In nonhabituated mice, 30 min pretreatment with MK 801 resulted in a significant dose-response effect on locomotion, $F(5, 42)$ = 12.76, P = 0.0002; MK 801 promoted locomotion in low doses (0.2–0.4 mg/kg IP, Dunnett's P = 0.012) but evoked severe hypokinesia and ataxia at high doses (1.6 mg/kg IP, Dunnett's P = 0.002; Fig. 1). The excitatory phase took the form of amphetamine-like darting about the test arena, whereas the inactive phase was characterised by a flattened posture, an unsteady gait, and pronounced hind limb abduction. CGP 40116, on the other hand, dose-dependently suppressed motor activity (1–8 mg/kg IP), $F(5, 51)$ = 13.66,

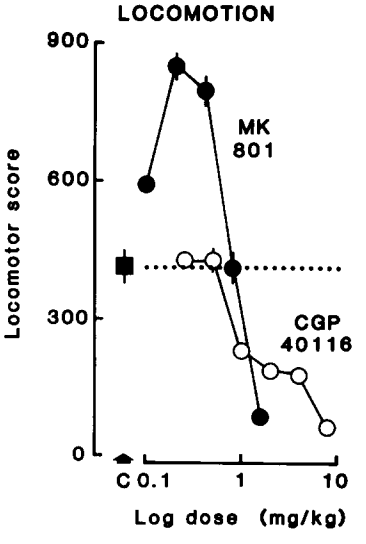

FIG. 1. Effects of MK 801 and CGP 40116 on locomotion in the nonhabituated mouse. Mice were injected with saline (controls, C; ■, 30 min before), MK 801 (●, 30 min before), or CGP 40116 (○, 120 min before) and returned to their home cage. They were subsequently transferred to a Perspex box, without prior acclimatization, and their locomotor activity was recorded automatically by underfloor sensors for a period of 10 min (see Method). Each point is the mean ± SE of at least six animals.

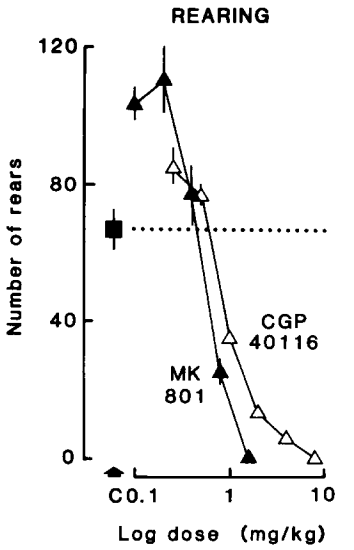

FIG. 2. Effects of MK 801 and CGP 40116 on rearing in the nonhabituated mouse. Mice were injected with saline (controls, C; ■, 30 min before), MK 801 (▲, 30 min before), or CGP 40116 (△, 120 min before) and 10-min rearing scores determined. Each point is the mean ± SE of at least six animals.

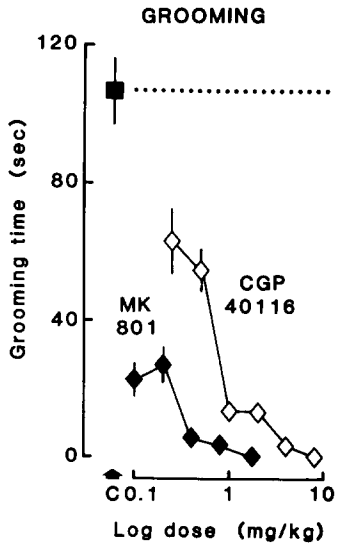

FIG. 3. Effects of MK 801 and CGP 40116 on grooming in the nonhabituated mouse. Mice were injected with saline (controls, C; ■, 30 min before), MK 801 (♦, 30 min before), or CGP 40116 (◇, 120 min before) and 10-min grooming scores determined. Each point is the mean ± SE of at least six animals.

$P = 0.0001$, with no signs of an excitatory phase at lower doses (0.25–0.5 mg/kg IP). At the middle doses of CGP 40116 (1–2 mg/kg IP), the animals looked little different from normal, except for longer periods of quiescence after an initial burst of exploratory activity. With higher doses (4–8 mg/kg IP), however, mice showed signs of postural abnormalities and ataxia. Rearing was similarly altered bimodally by MK 801, (ANOVA) $F(5, 42) = 3.92$, $P = 0.02$, and monomodally by CGP 40116, $F(5, 51) = 125.2$, $P = 0.001$ (Fig. 2). Grooming, however, was inhibited by both drugs at all doses tested, (ANOVA) $F(5, 42) = 9.37$, $P = 0.0007$ for MK 801; $F(5, 51) = 5.34$, $P = 0.005$ for CGP 40116 (Fig. 3).

DISCUSSION

The results of this study indicate that CGP 40116 exerts a weak, though distinct anticonvulsant effect against the intractable limbic motor seizures induced by pilocarpine in the mouse (1,25). CGP 40116 is the biologically active enantiomer of CGP 37849 (16), a novel compound which blocks the NMDA receptor by competing with glutamate for its recognition site (17). If this is its mechanism of action in the present experiments, then we may conclude that glutamate is one of the neurotransmitters involved in the genesis and/or propagation of pilocarpine-induced seizures, which are believed to originate through the excessive stimulation of cholinergic receptors in the hippocampus, before generalizing to other parts of the brain (21,25). This finding is in keeping with the modest anticonvulsant actions of CGP 37849 and CGP 40116 versus limbic kindling (4,10,15,17). On the other hand, the two competitive NMDA antagonists are much more effective against maximal electroshock-induced seizures (16), suggesting the therapeutic potential of this class of drug lies in the treatment of tonic-clonic generalised seizures rather than in the alleviation of complex partial seizures.

Another antagonist of the NMDA receptor that has been widely investigated for its anticonvulsant properties is MK 801, which works instead by gaining entry to, and blocking noncompetitively, the associated cation channel (3). Acutely, MK 801 has been variously described as inhibiting (6,15) or having little effect upon (10) kindled seizures, whilst chronic treatment with MK 801 has been reported to sensitise rats to the effects of kindling (7). Interestingly, a paradoxical lowering of the seizure threshold by acutely administered MK 801 has also been noted with the pilocarpine model of limbic epilepsy. Ormandy et al. (14) found MK 801 pretreatment significantly hastened the onset of electrographic seizures following systemic administration of pilocarpine to rats. Similarly, results from our laboratory showed MK 801 induced behavioural seizures in mice injected with a normally subconvulsant dose of the cholinomimetic (19). The contrasting effects of CGP 40116 and MK 801 against seizures of limbic origin, whether initiated by electrical kindling or by cholinergic stimulation, makes it unlikely that the two classes of NMDA antagonist act by occluding the same population of glutamate receptors.

Whether this means that MK 801 and CGP 40116 occlude different populations of the same NMDA receptor, or different types of NMDA receptor, remains to be determined. There are certainly strong hints that multiple NMDA receptors exist in the brain, with different regional distributions (28), but until these have been cloned it is impossible to say what the relevance of any such subgrouping to epilepsy mechanisms might be. We do know, however, that NMDA receptors in different parts of the brain can influence epileptogenesis in opposite ways. For instance, when NMDA is injected intracerebroventricularly, it strongly initiates seizures (23), but if it is applied focally to the caudate-putamen (22) or the substantia nigra pars compacta (24), NMDA actively prevents the development of seizures in response to systemic pilocarpine. It is quite conceivable, therefore, that MK 801 and CGP 40116 compromise these pro- and anticonvulsant NMDA receptors unequally, resulting in a net facilitation of seizures by MK 801 and vice versa for CGP 40116. This suggestion gains support from the observation that CGP 37849 is much more potent as an anticonvulsant when it is administered stereotaxically into the seizure focus than when it is given systemically (4). Cotterell et al. (4) interpreted this result to mean that insufficient levels of CGP 37849 are attained in the brain, and more especially at the focus of seizure activity, following systemic injection of the drug. However, the alternative explanation, that the anticonvulsant action of CGP 37849 at the focus (as with CGP 40116 in the present study) is countered by a facilitatory action of the drug elsewhere in the brain, would seem equally plausible.

A further distinction between the behavioural actions of CGP 40116 and MK 801 was apparent in the way these two compounds modified species-typical unconditioned behaviours in the mouse. As noticed by Löscher and Hönack (10,12), MK 801 caused the animals to become hyperexcitable at low doses, yet immobilised them at higher doses. The mobilisation of stores of monoamines (e.g., dopamine, 5-HT) throughout the brain (8) undoubtedly contributes to the motor stimulation elicited by MK 801, since the behavioural response can be attenuated by antagonists of monoamine receptors [(e.g., D_2, alpha-1, and 5-HT_{1A}; see (12)]. The absence of any such hyperactivity with CGP 40116 in the present experiments suggests this compound does not increase monoamine turnover in normal animals, unlike MK 801. However, we have to be careful when considering the actions of NMDA antagonists in epileptic animals, for Löscher and Hönack (11) have pointed out that the sensitising effects of kindling not only predispose animals to epilepsy, but also heighten their responsiveness to the motor excitatory actions of NMDA blockers. In the kindled brain, then, the racemic mixture CGP 37849 does promote hyperactivity, which is behaviourally and pharmacologically indistinguishable from the phencyclidine-like response observed with MK 801, although this only occurs at doses which are considerably greater than those affording protection against maximal electroshock (11). Nevertheless, if we accept that kindling more closely resembles the condition of epilepsy in man, the worsening of behavioural side effects of NMDA antagonists under these conditions makes their antiepileptic potential look even less attractive.

Except for CGP 40116 being two to three times more potent than CGP 37849, we have found that both compounds have virtually identical behavioural and anticonvulsant profiles in the mouse (unpublished observations). Thus, the resolution of CGP 37849 into its R- and S-enantiomers confers no apparent advantages as far as the separation of desirable anticonvulsant and unwanted motor properties is concerned. Given that the latter may be exacerbated in epilepsy-prone individuals (11), we may have to accept that the use of NMDA antagonists as anticonvulsants will necessarily be limited by their propensity to cause intolerable motor impairment and psychostimulation. The new competitive NMDA antagonists CGP 37849 and CGP 40116 appear to be little better in this regard than the noncompetitive drugs.

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