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Contingent Tolerance to Carbamazepine is Not Affected by Calcium-Channel or NMDA Receptor Blockers

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WEISS, S. R. B., R. M. POST, P. ANTHONY AND J. FERRER. *Contingent tolerance to carbamazepine is not affected by calcium-channel or NMDA receptor blockers.* PHARMACOL BIOCHEM BEHAV 45(2) 439–443, 1993.—We previously demonstrated that tolerance to carbamazepine's anticonvulsant effects occurs only with contingent presentation of the drug relative to the seizure (i.e., drug administration before but not after the seizure). Moreover, this tolerance can be reversed by altering the contingencies of drug administration (e.g., giving the drug after the seizure has occurred) without discontinuation of drug treatment. These findings imply an associative component to tolerance development in this model. Thus, we evaluated the effects on contingent tolerance development of two agents that have been shown to affect rate of tolerance development and acquisition or retention in other learning paradigms. Rats were electrically kindled in the amygdala until they reliably experienced seizures with each stimulation. In three separate studies, MK-801 (0.3 and 0.15 mg/kg), an NMDA receptor antagonist, and nimodipine (20 mg/kg), an L-type calcium channel blocker, were coadministered with carbamazepine prior to each kindling stimulation to evaluate the rate of tolerance development compared to controls. No effect of either drug was seen on the rate of contingent tolerance development to carbamazepine, suggesting that neither NMDA receptors nor L-type calcium channels are critically involved in this type of tolerance. The contingent tolerance paradigm may, however, prove useful in elucidating novel biochemical mechanisms of associative learning that might ultimately be explored in clinical situations where tolerance is a problem.

Contingent tolerance NMDA receptors Calcium channels Nimodipine MK-801 Carbamazepine Kindling

KINDLING is a process in which a previously subconvulsant stimulus comes to elicit a convulsant response following repeated, intermittent administration (17). The kindling stimulus can be direct electrical stimulation of the brain or can involve systemic or intracerebral administration of certain drugs [e.g., local anesthetics (32), opiates (7)]. Electrical stimulation of the amygdala is a rapid way of producing kindled seizures in which approximately 10–15 stimulations are required for full-blown seizures to develop and become reliably induceable.

Carbamazepine is a tricyclic iminostilbene derivative used to treat seizure disorders (8,37), trigeminal neuralgia (5), and manic-depressive illness (33–35). Carbamazepine is also highly effective in the suppression of completed amygdala-kindled seizures (1,2,43), decreasing seizure intensity, duration, and focal afterdischarge activity in the amygdala. However, repeated once-daily administration of carbamazepine prior to each kindling stimulation results in the rapid development of tolerance to its anticonvulsant effects (44). Tolerance in this model was a contingent process because it only occurred when rats were given carbamazepine prior to the kindled seizure. Animals given the same dosage of carbamazepine, but after the kindled seizure occurred, were not tolerant when they were tested with carbamazepine administration before the kindling stimulation. Moreover, once an animal had been made tolerant to carbamazepine a reversal of this tolerance could be induced by 5 days or more of kindled seizures without drug or with drug given after the kindled seizures. Tolerance in this model is associative, or conditional upon the temporal sequence of drug and kindling stimulation, and is not based upon pharmacokinetic alterations (45).

The current study was designed to determine whether contingent tolerance to carbamazepine might be affected by agents that have previously been shown to affect tolerance development and associative learning in other paradigms. MK-801 is a noncompetitive NMDA antagonist (46). Antago-

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nists of this receptor can disrupt acquisition or retention of discrimination performance in a number of paradigms (10, 27,28,31), long-term potentiation (20,29), and opiate tolerance development (41). Nimodipine is one of several dihydropyridine calcium channel antagonists. Drugs from this class have been shown to produce cognitive enhancing effects in several behavioral paradigms (11-13,23,38,39) but to block tolerance development to opiates (9) and alcohol (16).

METHOD

Kindling Procedure

Subjects were 46 male Sprague-Dawley rats, purchased from Taconic Farms, weighing 300-350 g at the beginning of the experiment. Rats were individually housed with a 12-h alternating light-dark cycle and free access to food and water. Rats were anesthetized with chloral hydrate for surgical implantation of a bipolar electrode in the left amygdala [5.7 mm anterior, 4.5 mm lateral, 2.0 mm dorsal to interaural zero (21)]. Following at least 1 week of recovery, animals were stimulated once daily using the following parameters: 800-μA peak-to-peak intensity, 60-Hz, biphasic square waves, 1-s train duration. Afterdischarge duration, seizure stage, and seizure duration were evaluated. Seizure stage was rated according to the five-point scale formulated by Racine (36), which ranges from behavioral arrest and facial twitching (1-2) to unilateral forepaw clonus (3) to bilateral forepaw clonus (4) with rearing and falling (5). Seizure duration was rated if a generalized motor seizure was observed (i.e., seizure stage of 3 or greater) and afterdischarge duration was assessed by the presence of EEG spiking at a frequency of at least once per second. Rats were kindled until reliable major motor seizures could be elicited by each kindling stimulation. When this was achieved, rats were evaluated for acute anticonvulsant responsiveness to MK-801 (Research Biochemicals Inc., Natick, MA; 0.5 mg/kg) and nimodipine (gift from Miles Pharmaceuticals; 10 and 20 mg/kg). A minimum of 2 days of kindling without drug separated each drug test. MK-801 was dissolved in saline in a concentration that would yield a 1-ml/kg injection. Nimodipine was suspended in saline with a few drops of Tween-80, sonicated, and kept in a light-tight container at a concentration of 5 mg/ml. No acute anticonvulsant effects were observed using MK-801 (0.5 mg/kg; $n = 17$), although animals were severely ataxic. Because the ataxia interfered with the behavioral manifestation of the seizures (e.g., animals were unable to rear), we lowered the dose of MK-801 for the contingent tolerance studies to 0.3 and 0.15 mg/kg. A slight anticonvulsant effect was seen at both doses of nimodipine ($n = 5$) on seizure duration; however, no effect was seen on seizure stage or afterdischarge duration.

Seizure Threshold Determination

In a previous study, we found that seizure thresholds were a determinant of the rate of tolerance development to carbamazepine in our paradigm. For this reason, in each of the following studies rats were divided into two groups matched for generalized seizure thresholds and number of kindled seizures. Thresholds were determined by stimulating rats at progressively increasing currents, beginning at 50 μA and incrementing in 50-μA steps. Stimulations were spaced at least 20 min apart, which we have found necessary for producing reliable seizure threshold measures. The seizure threshold was the lowest current that elicited a major motor seizure (stage 3 or greater). The seizure thresholds in kindled animals did not differ from their afterdischarge thresholds, that is, the current required to elicit an afterdischarge was sufficient to also produce a motor seizure. After we initially determined the threshold, we repeated the threshold test on a second day beginning at a current level two steps down from the previously determined threshold. If there was any discrepancy between the two measures, we began the procedure again. In almost all cases, the thresholds were reliable from the first to the second determination.

Contingent Tolerance Development

Each drug study was conducted independently using different groups of kindled animals matched for seizure thresholds. MK-801 (0.3 mg/kg, $n = 7$; and 0.15 mg/kg, $n = 6$) or nimodipine (20 mg/kg, $n = 9$) or their respective vehicles ($n = 7$, 7, and 10, respectively) were administered 30 min prior to kindling stimulation and carbamazepine was administered 15 min prior to kindling. This procedure was followed once/day until tolerance to carbamazepine's anticonvulsant effects was observed in each group. The criterion for tolerance was the occurrence of a major motor seizure (stage 3 or greater) in response to kindling stimulation in the presence of carbamazepine (+ MK-801, nimodipine, or vehicle). The studies continued, however, until all animals in the control group (treated with carbamazepine and vehicle) had experienced two seizures within a 3-day period.

Carbamazepine (15 mg/kg) was administered in a vehicle of 10% EtOH, 40% propylene glycol, and 50% saline at a concentration of 7 mg/ml. A 25-mg/kg dose of carbamazepine (10 mg/ml) was used in the high-dose MK-801 study (0.3 mg/kg) because rats did not show an initial complete anticonvulsant response to carbamazepine at 15 mg/kg. The 25-mg/kg dose inhibited seizures in all kindled animals. We found that tolerance develops to this dose of carbamazepine at about the same rate as to the lower dose (44). The high dose of MK-801 (0.3 mg/kg) was used initially because this dose was shown to inhibit opiate tolerance development. However, we also examined the effect of a lower dose of MK-801 (0.15 mg/kg) on the rate of tolerance development because of our concern that side effects, such as ataxia, observed at the 0.3-mg/kg dose could have affected the seizure measures. The dose of nimodipine that we chose was a compromise between what is required for anticonvulsant activity (50-100 mg/kg) vs. effects in learning and memory paradigms (1-10 mg/kg).

Data Analyses

A paired t-test was used to evaluate the acute anticonvulsant effects of nimodipine and MK-801 on kindled seizure and afterdischarge duration. The Wilcoxon matched-pairs signed-ranks test was used for seizure stage. For the contingent tolerance studies, a two-way repeated-measures analysis of variance (ANOVA) was used to compare the drug effects on afterdischarge and seizure duration. Student's t-test was used to assess drug effects on the number of days until the first major motor seizure occurred on carbamazepine ($\pm$ MK-801 or nimodipine).

RESULTS

A significant loss of anticonvulsant efficacy was observed for carbamazepine following repeated administration before each electrical stimulation [Figs. 1 and 2; $F(9) = 4.14$, $p <$

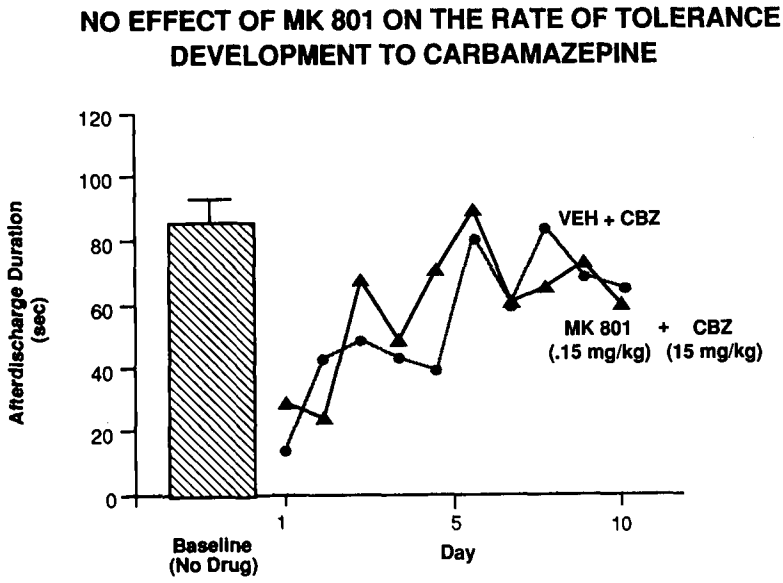

FIG. 1. Tolerance development to carbamazepine with or without MK-801 (0.15 mg/kg) cotreatment. The group mean afterdischarge duration (±SEM) is plotted for the 2 days prior to initiation of the study (left; hatched bar) and for the two treatment groups receiving daily carbamazepine administration (line graphs). An initial anticonvulsant effect is illustrated that becomes attenuated over several days. No significant difference was seen in animals cotreated with MK-801 compared to vehicle, $F(1, 11) = 0.019$, n.s.

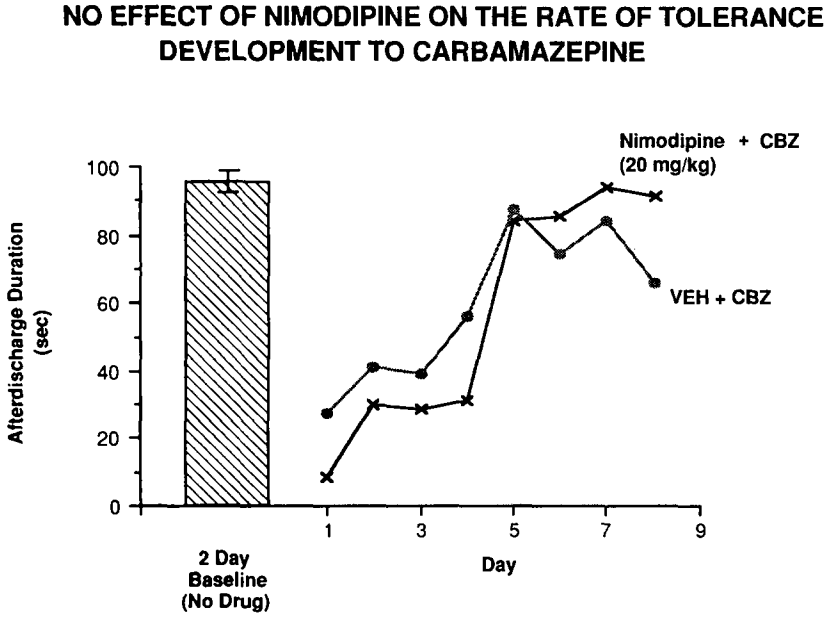

FIG. 2. Tolerance development to carbamazepine with or without nimodipine (20 mg/kg) cotreatment. The group mean afterdischarge duration (±SEM) is plotted for the 2 days prior to initiation of the study (left; hatched bar) and for the two treatment groups receiving daily carbamazepine administration (line graphs). An initial anticonvulsant effect is illustrated that becomes attenuated over several days. No difference was observed in animals cotreated with nimodipine compared to vehicle, $F(1, 17) = 0.159$, n.s.

0.01; $F(7) = 14.32, p < 0.01$, respectively]. This occurred for all measures of the kindled seizure, although seizure duration and seizure stage are not illustrated.

Compared to vehicle, the rate of tolerance development did not differ in animals receiving either dose of MK-801 (0.15 mg/kg, Fig. 1; or 0.3 mg/kg, data not shown). This lack of effect of MK-801 was demonstrated for seizure and afterdischarge duration (Fig. 1) and for the mean number of days until the first seizure was observed on carbamazepine [8.3 ± 2.2 days for MK-801 (0.3 mg/kg) vs. 5.9 ± 0.9 days for vehicle; $t(12) = 1.04$, n.s.; and 4.8 ± 0.7 days for MK-801 (0.15 mg/kg) vs. 3.4 ± 0.8 days for vehicle; $t(11) = 1.32$, n.s.].

Nimodipine also did not affect the rate of tolerance development to carbamazepine on any of the seizure measures noted above (Fig. 2). The mean number of days until the first seizure was observed on carbamazepine was 4.1 ± 0.5 in nimodipine-treated animals compared to 4.1 ± 0.4 in vehicle-treated controls, $t(17) = 0.02$, n.s.].

DISCUSSION

NMDA antagonists have been demonstrated to interfere with associative learning in a number of studies (10,26–28,30,31) at doses similar to those that interfere with long-term potentiation in the CA1 region of the hippocampus (27,28). Thus, it has been suggested that the NMDA glutamate receptor system may be implicated, directly or indirectly, in many basic learning and memory mechanisms. MK-801 (0.3 and 0.1 mg/kg) has also been demonstrated to interfere with morphine tolerance and dependence (41), although the paradigm used by these investigators did not distinguish between associative and nonassociative tolerance development, leaving open the question of whether MK-801 affected adaptative mechanisms concerned with opiate function or with learning mechanisms related to drug-environment interactions.

The results of the current studies indicate that the rate of tolerance development to the anticonvulsant effects of carbamazepine on amygdala-kindled seizures was not affected by the noncompetitive NMDA receptor antagonist MK-801 at doses that have been shown to interfere with learning in other paradigms (18,26,30,31). These doses also do not have anticonvulsant effects of their own on kindled seizures (25), which would complicate interpretation of the data. Thus, the current studies suggest that contingent tolerance to carbamazepine, unlike associative learning in some other paradigms, is not dependent upon effects at the NMDA receptor.

Nimodipine, a dihydropyridine calcium channel antagonist, blocks L-type calcium channels, which have also been implicated in learning and memory paradigms, that is, calcium-activated potassium channel conductance is reduced following classic conditioning in *Aplysia* (19), hermissenda (3,4), and rabbits (14). Thus, nimodipine could alter the rate of conditioning through its blockade of calcium channels (13). Enhanced learning has been demonstrated with nimodipine treatment in young and aged animals (11,12,38) and in animals recovering from brain lesions (23). Yet, the development of tolerance or withdrawal symptomatology to morphine (9) and to ethanol (16,24) is inhibited by dihydropyridine calcium channel blockers, although again these studies did not distinguish between associative and nonassociative tolerance development. The current study did not show any effect of nimodipine on contingent tolerance development to the anticonvulsant effects of carbamazepine. The dose used in this study was relatively high for effects in learning paradigms [range = 1–10 mg/kg (11, 12,23,38)] but lower than that used in tests of anticonvulsant efficacy [range 50–100 mg/kg (15,40)]. Thus, while we cannot rule out an effect of nimodipine at other doses, our data do not suggest an involvement of L-type calcium channels in contingent tolerance development.

Effects of carbamazepine at NMDA glutamate receptors and on calcium channels are currently under investigation (6,22). Carbamazepine appears to have an NMDA antagonist profile in cerebellar granule cells in that it acutely displaces MK-801 binding and upregulates this system following chronic treatment (Chuang et al., unpublished observations). Carbamazepine also decreases NMDA-induced phosphotidyl inositol (PI) turnover and calcium influx [Hough and Chuang, unpublished observations; (6)]. Carbamazepine may also have effects at calcium channels because it can potentiate verapamil's antispiking effects in hippocampal slices and vice versa (42). Further study is required to determine the functional relevance of these systems to carbamazepine's anticonvulsant effects; however, the data from the current studies did not demonstrate an enhancement of carbamazepine's anticonvulsant effects on kindled seizures by either MK-801 or nimodipine (Figs. 1 and 2) and also did not indicate a prominent role of these systems in tolerance development.

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