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Reduction of Dizocilpine and Scopolamine-Induced Deficits in Avoidance Responding by SCH 54388, a Metabolite of Felbamate

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SMITH, R. D., M. E. GRZELAK AND V. L. COFFIN. *Reduction of dizocilpine and scopolamine-induced deficits in avoidance responding by SCH 54388, a metabolite of felbamate.* PHARMACOL BIOCHEM BEHAV **58**(3) 657–664, 1997.— Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a novel antiepileptic agent with a unique structure and mechanism of action, possibly involving binding sites at the *N*-methyl-D-aspartate receptor (NMDA) complex. A monocarbamate metabolite of felbamate (SCH 54388) was compared to felbamate using a mouse passive-avoidance paradigm (PAR). SCH 54388 was markedly free of toxic side effects up to doses of 300 mg/kg, sc. SCH 54388 reduced the deficit-producing effects of either scopolamine, a cholinergic antagonist, or dizocilpine (MK-801), an NMDA receptor channel blocker, in a dose-dependent manner. The effective dose range of SCH 54388 was between 0.01 and 10 mg/kg, sc. SCH 54388 was also orally active at doses between 0.1 and 10 mg/kg. Felbamate also reduced scopolamine and dizocilpine antagonism, but was less potent than SCH 54388, reducing scopolamine-induced deficits at 1 to 3 mg/kg, sc in a dose-dependent manner and reducing deficits induced by dizocilpine at doses of 0.1 and 3 mg/kg, SC. The reduction of dizocilpine-induced deficits by felbamate was not dose dependent. These results suggest that SCH 54388 has a mechanism of action involving either directly or indirectly, glutaminergic and cholinergic central neuronal systems. © 1997 Elsevier Science Inc.

Felbamate Dizocilpine Passive-avoidance responding Scopolamine

FELBAMATE (FBM, Felbatol, Taloxa, 2-phenyl-1,3-propanediol dicarbamate; Fig. 1) is a novel antiepileptic agent that has therapeutic efficacy in the treatment of partial onset seizures in adults and in childhood epileptic seizures associated with Lennox-Gastaut syndrome. Although the mechanism by which FBM inhibits seizure has not been fully elucidated, the pharmacological profile for FBM determined in animal models of epilepsy suggests a blockade of NMDA receptors (2,26), enhancement of GABAergic transmission (22), blockade of voltage-sensitive Ca^{2+} channels (12), and possibly the blockade of Na^{+} channels as indicated by the inhibition of pentylentetrazol-induced convulsions (3). In addition, radioligand binding studies (13,21), reversal of NMDA/glycine-stimulated increases in intracellular Ca^{2+} (23), whole cell, and direct single-channel recordings (15,21) collectively indicate that FBM can function as a low-affinity antagonist at the NMDA receptor. Physiological studies using whole-cell recordings have confirmed the role of FBM enhancement of GABA transmission by demonstrating a potentiation of $GABA_A$-receptor Cl^{-} current in the presence of FBM (15).

FBM may also act as a ligand for the strychnine-insensitive site at the NMDA receptor. The NMDA receptor is actually a complex of modulatory sites associated with ion-gated channel activity. A neuromodulatory role for FBM at the NMDA receptor has been suggested by the displacement of 5,7-[^{3}H]dichlorokynurenic acid ([^{3}H]DCKA). DCKA is a ligand for the strychnine-insensitve glycine site that is thought to act as an allosteric modulator of the NMDA ionophore. This evidence was provided both from in vitro studies (13) and from investigations in human postmortem tissue (25). In support of these findings, when glycine was given to mice the protective effects of FBM on NMDA and electroshock-induced seizures

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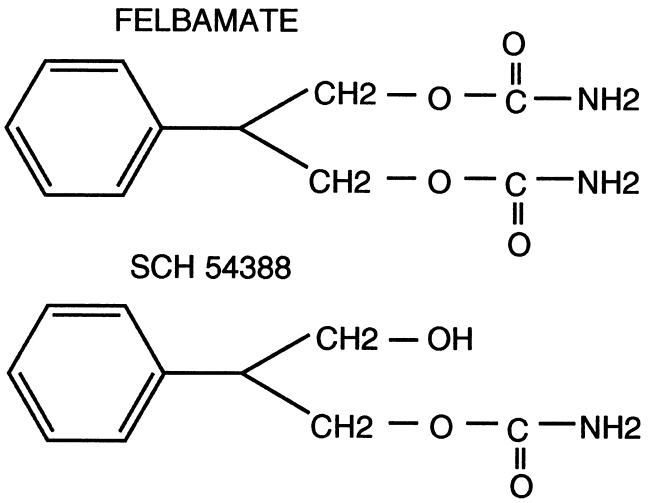

FIG. 1. The structure of Felbamate and SCH 54388.

were attenuated (2). In contrast, Subramaniam et al. (21), using an in vitro binding assay, found that FBM could not displace the binding of [^{3}H]DCKA. However, FBM displaced [^{3}H]dizocilpine binding at the NMDA receptor ionophore, where at higher concentrations the maximal saturation binding of [^{3}H]dizocilpine could be reduced by FBM (21). This finding suggests the presence of allosteric activity at the NMDA receptor. Thus, taken together, these data indicate that FBM binds at the NMDA receptor complex and could have a unique neuromodulatory mechanism of action.

In addition to its inhibitory effects on seizure activity, FBM has been evaluated for its effects on retention (19). The possibility that FBM may affect retention has been investigated in this context due to indications that antagonists of excitatory amino acid transmitters for the NMDA receptor can impair learning and memory processes (1,4,14), possibly through interference with long-term potentiation (5,24). Although the NMDA channel-blocker dizocilpine was found to produce dose-dependent deficits in retention in rodents, FBM did not produce retention deficits even up to doses as high as 1000 mg/kg (19). This suggests that although FBM may displace dizocilpine at the NMDA ionophore (21), the compound does not produce retention deficits by interacting with the ionophore in a manner similar to dizocilpine.

The evidence compiled, demonstrating a relationship between retention and the glutaminergic system, suggests that a drug capable of acting at an NMDA modulatory site, rather than directly at the NMDA ionophore or at the aspartate binding site, may provide a specific therapeutic indication for agents capable of reversing cognitive decline. Drugs acting directly at the NMDA receptor or ionophore have been associated with a variety of side effects. Thus, an allosteric modulation of the NMDA ionophore through a glycine binding site may provide a pathway for compounds active at the NMDA receptor that would produce less toxicity. Through an ongoing search for such agents, we decided to evaluate the in vivo pharmacological effects of the monocarbamate form of FBM. The biotransformation of FBM in the dog, rabbit, and rat (27), has previously resulted in the identification of three major metabolites. From preliminary studies we determined that one of the three metabolites, 2-phenyl-1,3-propanediol monocarbamate (SCH 54388; Fig. 1) had biological activity in CF-1 mice, both in models of seizure (3) and in the passive-avoidance response (PAR), a standard model of retention. Based on this information, and the recent finding that FBM can reverse the effects of muscarinic and glutamatergic agonists (12), we evaluated SCH 54388 against the deficit-inducing effects by the cholinergic antagonist scopolamine and the noncompetitive NMDA channel blocker dizocilpine in mouse passive-avoidance responding. The PAR was considered to be a useful model of retention in these studies because scopolamine has been well established as an amnesic agent in tests of retention in humans as well as in rodent passive avoidance.

METHODS

Subjects

Two strains of male Charles River CF-1 and BALB mice (25–30 g) were used in these studies. Mice were acclimated to a 12-h light/dark cycle (lights on at 0600 h) at a room temperature at 22–23 for at least 5 days prior to the day of experimentation. The animals were housed five per hanging polycarbonite cage (45 × 24 × 20 cm). Previous in-house work has indicated that CF-1 mice are optimally sensitive to the amnesia-producing effects of dizocilpine in the PAR, whereas BALB mice are more sensitive to the amnesia-producing effects of scopolamine in the PAR. A total of 300 CF-1 and 200 BALB mice were used in seven passive-avoidance experiments, and an additional 20 CF-1 mice were used for assessment of behavioral side effects to SCH 54388. The animals were given standard mouse chow and water ad lib. All experiments were conducted between 0900–1200 or 1300–1500 h.

These studies were carried out in accordance with the NIH guide to the care and use of laboratory animals and the Animal Welfare Act in an AAALAC-accredited program.

Passive-Avoidance Procedure

The PAR procedure was modified from Jarvik and Essman (11) and has been used routinely in our laboratories to establish the cognitive potential for different drugs under standard behavioral assay conditions as described in Smith et al. (18). Briefly, the PAR apparatus was constructed of dark and light Plexiglas chambers (20 × 20 × 24 cm) connected by a semielliptical doorway (height = 6 cm × base width = 9 cm). A grid floor in the dark chamber was attached to a pulse generator (Coulbourn Instruments). During training, mice were initially positioned into the light chamber facing away from the entrance to the dark chamber. After entering the dark chamber, a guillotine door was closed and a 1 mA scrambled foot shock was administered for 1 s. The animal was immediately removed from the apparatus and returned to its home cage. The animals were placed back into the light chamber 1 h later. The latency for a full reentry into the dark chamber was recorded. The animals were removed from the apparatus upon entry into the dark chamber or at the end of 180 s. A reduction of drug-induced deficits in avoidance performance was defined as a statistically significant increase in entry time to the dark chamber for animals treated with either vehicle alone or test drug, when compared to animals treated with either dizocilpine or scopolamine alone.

Rat Behavioral Evaluations

A side-effect profile for SCH 54388 was done in CF-1 mice using a modification of the method of Irwin (8). The tests for side effects were comprised of 14 different measurements of behavior, autonomic, or neurological function. Quantitation

of the measurements was done by assigning a "0" to normal behaviors such as alertness, spontaneous locomotor activity, etc. Scores of +1, +2, or +3 were assigned to indicate slight, moderate, or severe increases from normality, or scores of −1, −2, or −3 to indicate decreases from normality. A test was considered abnormal if a score of 2 or greater was recorded for at least 50% of the animals in a particular treatment group.

Five animals per treatment group were used in these studies. The mice were given a single, subcutaneous injection of either 30, 100, 300, or 1000 mg/kg SCH 54388. The drug was dissolved in water and administered at a volume of 5 ml/kg. Scores were assessed 1 h after injection, and lethality was checked at 24 h.

Finally, a separate group of mice was used to assess the analgesic potential of SCH 54388 using a standard hot-plate procedure. These animals were given SCH 54388 30 min before being placed on a heated metal surface (55°C), and were removed immediately upon an initial jump or at the end of 120 s. The latency to the escape jump response was taken for animals given vehicle, 0.1, 1, 10, or 100 mg/kg SCH54388, subcutaneously.

Data Analysis

For each experiment, statistical calculations were done using the Dunnett *t*-test to determine differences between an individual control group treated with either scopolamine or dizocilpine, and a group treated with vehicle alone, or groups that were treated with different doses of either FBM, SCH 54388, or its enantiomers, SCH 56645(+) or SCH 56643(−). Means were calculated for each treatment group for reentry into the dark chamber on the test day. All experiments used 10 animals per treatment group. For graphic comparison, the data was plotted using mean latency times ± standard error of the mean (SEM).

Drugs

SCH 54388 was synthesized at Schering-Plough laboratories. Scopolamine and dizocilpine were obtained from Research Biochemicals, Inc. All drugs were given a total of 30 min before the animals were placed in the PAR apparatus. The animals were given subcutaneous injections of either 3 mg/kg scopolamine or 0.3 mg/kg dizocilpine to produce amnesia, followed in 20 min by different doses of either FBM, SCH 54388, SCH 56645, or SCH 56643. With the exception of one experiment to assess oral bioavailability, the test drugs were given subcutaneously in all other experiments. The doses of scopolamine and dizocilpine chosen to produce amnesia in the PAR were based on findings from previous studies (18,19). The drugs were dissolved in 0.4% methylcellulose vehicle and administered in a volume of 5 ml/kg. The range of doses were from 0.001 to 1000 mg/kg, expressed in base form.

RESULTS

Subcutaneous SCH 54388 reduced the deficit-producing effects of both scopolamine and dizocilpine on the mouse PAR in a dose-dependent manner. Figure 2 illustrates the dose-dependent reduction of subcutaneous SCH 54388 on a PAR deficit induced by 3 mg/kg scopolamine. The main effect produced by SCH 54388 given with scopolamine was statistically significant at $F(8, 111) = 11.53$, $p < 0.0001$. BALB mice treated with with scopolamine alone had significantly lower response latencies than mice treated with vehicle alone, $t(8) = 7.27$, $p < 0.05$). Doses of 0.1, 1.0, and 10 mg/kg SCH 54388 enhanced mean reentry latencies that were greater than that produced by scopolamine alone, $t(8) = 3.1$, 4.43, and 2.78, respectively; $p < 0.05$). Similarly, SCH 54388 reduced the deficit-inducing effects of dizocilpine on the PAR. The main effect of SCH 54388, $F(6, 132) = 18.34$, $p < 0.0001$, to reduce deficits induced with dizocilpine is illustrated in Fig. 3. Mice treated with 0.3 mg/kg dizocilpine alone had lower mean response times, $t(6) = 6.79$, $p < 0.0001$, than vehicle-treated animals. Subcutaneous doses of SCH 54388 at 0.01 and 0.1 mg/kg produced mean latency times that were greater than those obtained for dizocilpine alone, $t(6) = 3.48$ and 2.85, respectively; $p < 0.05$. In addition, the effects of SCH 54388 when given alone were evaluated on the PAR to determine whether the compound was associated with intrinsic deficit-inducing effects. In this study a range of doses up to 100 mg/kg, sc did not produce deficits in the avoidance response (data not shown).

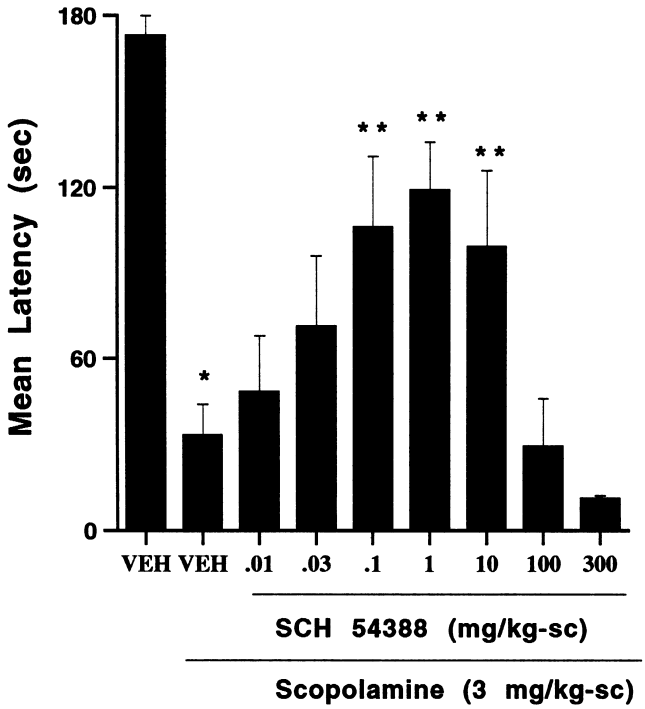

FIG. 2. The reentry latencies for BALB mice given vehicle alone, scopolamine alone, or scopolamine with different doses of SCH 54388. The single star represents the statistical difference from vehicle-treated animals, and double stars represent the statistical differences from animals treated with scopolamine alone as determined by the Dunnett *t*-test.

When SCH 54388 was tested for oral activity in the PAR, the deficit-producing effects of scopolamine were reduced in a dose-dependent manner. The overall effect of oral SCH 54388 in reversing 3 mg/kg scopolamine given subcutaneously was statistically significant, $F(5, 114) = 7.67$, $p < 0.0001$, illustrated in Fig. 4. The mean entry times were statistically higher than that for scopolamine alone at doses of 0.1, 1.0, and 10 mg/kg, $t(5) = 4.49$, 4.01, and 3.76, respectively; $p < 0.0001$.

Summary data for subsequent experiments with the enantiomers of SCH 54388, SCH 56645, and SCH 56643 are presented in Table 1. As in previous experiments, the evaluation of each enantiomer was done using reference groups treated

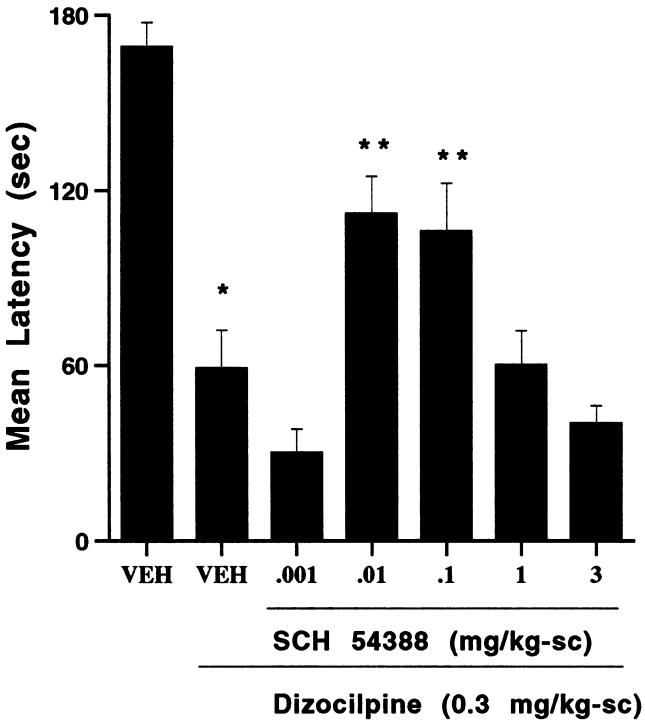

FIG. 3. The reentry latencies for CF-1 mice given vehicle alone, dizocilpine alone, or dizocilpine with different doses of SCH 54388. Statistical differences indicated by the stars as in Fig. 2, determined by the Dunnett *t*-test.

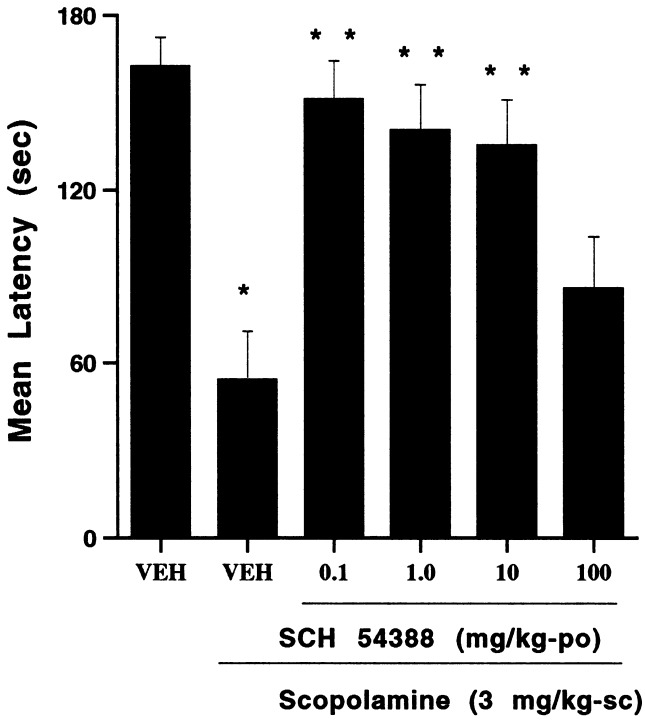

FIG. 4. The reentry latencies for BALB mice given scopolamine or SCH 54388 by oral administration.

with vehicle alone and groups treated only with the antagonist, scopolamine, or dizocilpine. The effects on reentry latency produced by the antagonists were statistically lower than the effects on reentry latency of the vehicle-treated animals (data not shown). To compare the effects of the enantiomers on the antagonists with each other, the minimum effective dose (MED) was used to determine the dose at which an antagonist was reversed. The MED refers to a threshold dose; i.e., the lowest dose at which reentry latencies occurred that were significantly greater from animals treated with either scopolamine or dizocilpine alone. The *p*-values in Table 1 represent the probability of rejection of the null hypothesis for each MED. From these experiments, both the enantiomers SCH 56645 and SCH 56643 were found to be equipotent, each reducing the effects of scopolamine at 0.01 mg/kg, and reducing the effects of 0.3 dizocilpine at 0.001 mg/kg, respectively.

Figure 5 illustrates the main effect of the parent compound for SCH 54388, FBM, tested against 3 mg/kg scopolamine, $F(5, 59) = 11.84$, $p < 0.0001$. A dose at 1 mg/kg produced latencies significantly different than latencies for animals treated with scopolamine alone, $t(5) = 2.09$ and 2.29, respectively; $p < 0.0001$. Finally, FBM was tested against 0.3 mg/kg dizocilpine. As illustrated in Fig. 6, dizocilpine produced a mean entry time that was statistically different from mean entry times that were produced with 0.1 and 1 mg/kg FBM, $t(5) = 2.03$ and 2.43, respectively; $p < 0.0001$.

The profile of side effects produced by SCH 54388 occurred in an all or none fashion; i.e., all mice given a particular dose either exhibited the same specific symptom, or conversely, all were uniformly free of symptoms. The side-effect profile of SCH 54388 is presented in schematic form in Table 2. Behavioral, neurological, and autonomic side-effects produced by SCH 54388 did not occur until 100 mg/kg, and were observed to be minimal. These effects included observed changes in limb position, gait, ptosis (eyelid closure) or miosis (pupillary contraction). Additional effects of SCH 54388 did not occur until 300 and 1000 mg/kg. Lethalities were not observed at any doses over a 24-h observational period. In the hot-plate test, doses of SCH 54388 at 10 and 100 mg/kg produced an enhanced latency to escape jumping (Fig. 7).

DISCUSSION

SCH 54388 the monocarbamate metabolite of FBM, exhibited a similar pharmacological profile when tested against either dizocilpine or scopolamine, but was slightly more potent against avoidance deficits induced by dizocilpine (0.01 vs. 0.1, respectively; Figs. 2 and 3). This may reflect a relatively higher binding affinity of SCH 54388 for receptors associated with the mouse glutaminergic system. For both antagonists, the amelioration of the avoidance deficit by subcutnaeous SCH 54388 was incomplete. As reported, there were statistical differences between the mean latency times exhibited when doses of SCH 54388 (0.01–10 mg/kg) were given in conjunction with dizocilpine or scopolamine, compared with means obtained when the antagonists were given alone. However, there were also statistical differences between mean latencies associated with the effective doses of SCH 54388 compared to the mean latencies found for animals treated with vehicle alone (statistical values not reported). This partial reversal effect may reflect the correspondence between the magnitude of the reduction of antagonist-induced deficit by SCH 54388 or FBM, and the magnitude of the deficit produced by the antagonists alone. An exception to this trend

TABLE 1

THE ISOMERS OF SCH 54388 AND REVERSAL OF THE DEFICIT-INDUCING EFFECTS OF SUBCUTANEOUSLY ADMINISTERED SCOPOLAMINE OR DIZOCILPINE ON THE MOUSE PAR

Enantiomer	Doses*	MED†	Antagonist	N‡	P§	Strain
SCH 56645 (+)	0.001-10	.01	scopolamine	70	.0168	BALB
SCH 56643 (−)	0.001-10	.01	scopolamine	80	.0008	BALB
SCH 56645 (+)	0.001-100	.001	dizocilpine	70	.0271	CF-1
SCH 56643 (−)	0.001-100	.001	dizocilpine	60	.0117	CF-1

*These values refer to the range of doses in mg/kg. The doses were administered by log units. There were five doses given in the experiments with scopolamine and six doses given in the experiments with dizocilpine.

†The minimum-effective dose (MED) refers to the lowest dose at which reentry latency times were found to be significantly greater from animals treated with antagonist alone (see text).

‡The *N* refers to the total number of animals used in each experiment; there was a total *n* of 10 animals in each treatment group.

§The probability of rejection of the null hypothesis based on the Dunnett *t*-test.

was with orally administered SCH 54388 (Fig. 4). Generally, however, the reversal of dizocilpine and scopolamine antagonism by SCH 54388 can best be described in terms of a reduction of deficit.

SCH 54388 actively reduced the deficit-producing effects of dizocilpine or scopolamine when delivered either subcutaneously or orally, and was markedly free of significant behavioral, neurological, or autonomic side effects up to the relatively high doses of 100 to 1000 mg/kg. The dose-dependent manner in which the reduction of deficits produced by SCH 54388 does not indicate the presence of nonspecific side effects. The isomers of SCH 54388, SCH 56645(+), and SCH 56643(−), were included in these studies to assess stereospecificity. The ability to reduce avoidance deficits was not specific to either isomer of SCH 54388; both equally reduced the deficit-inducing effects of scopolamine or dizocilpine on the PAR. The therapeutic ratio for SCH 54388 (the difference between an effective dose and a dose that produces toxicity) results in a 1000 to 10,000-fold separation when based on an MED of 0.1 for scopolamine (Fig. 2 and 4) or 0.01 mg/kg for dizocilpine (Fig. 3), and compared to a 100 mg/kg side-effect dose, respectively.

The dose curves for SCH 54388 were all characterized by

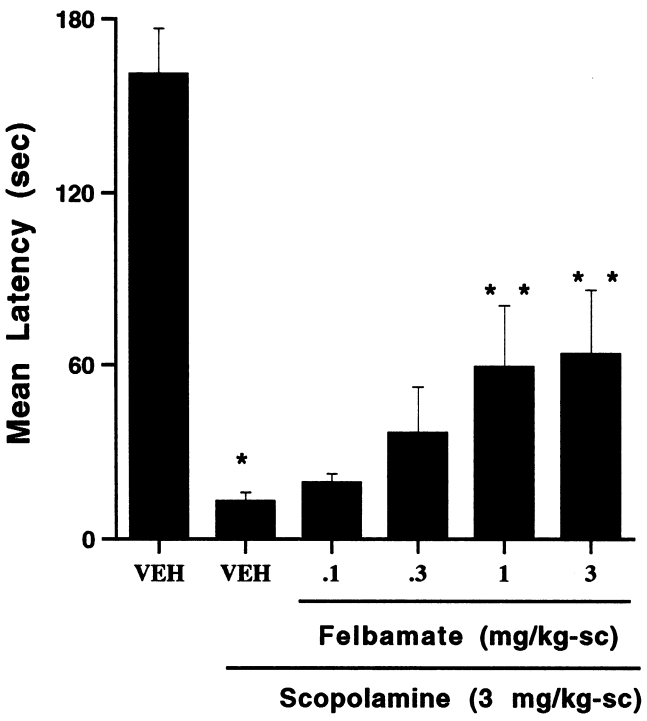

FIG. 5. The reentry latencies for BALB mice given vehicle alone, scopolamine alone, or scopolamine with different doses of FBM.

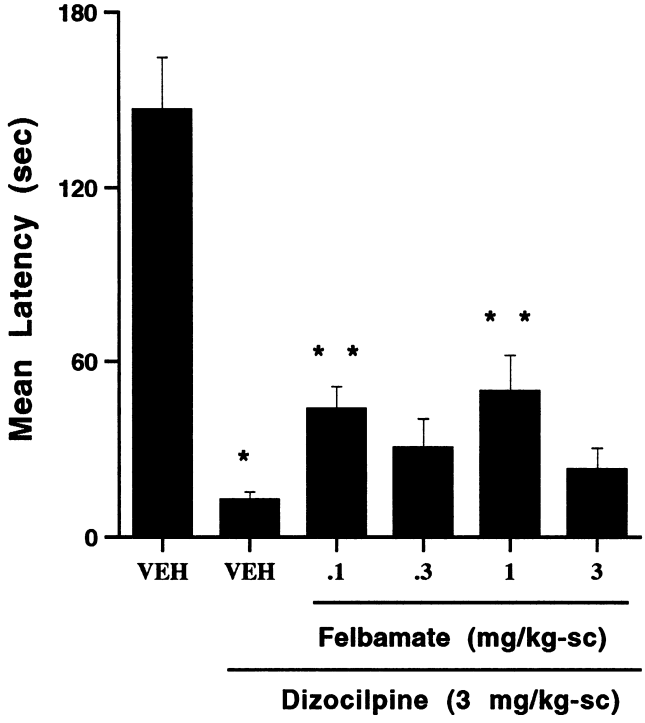

FIG. 6. The reentry latencies for BALB mice given vehicle alone, dizocilpine alone, or dizocilpine with different doses of FBM.

TABLE 2

EFFECTS OF HIGH DOSES OF SCH 54388 ON BEHAVIORAL, NEUROLOGICAL AND AUTONOMIC SIDE-EFFECTS IN CF-1 MICE AT 1 H POSTDRUG TREATMENT.

Side effect	30†	100	300	1000
Passivity			X	X
Stereotypy				X
Spontaneous activity			X	X
Body elevation			X	X
Limb position		X	X	X
Change in gait		X	X	X
Catalepsy			X	X
Ptosis		X	X	X
Miosis		X	X	X
Excretion				
Respiration			X	X
Tremors				
Convulsions				
Lethalities				

*Five animals were tested at each dose. The "X" areas indicate that all animals exhibited the specified symptom. The blank areas indicate that no animals were affected.

†All doses are in mg/kg.

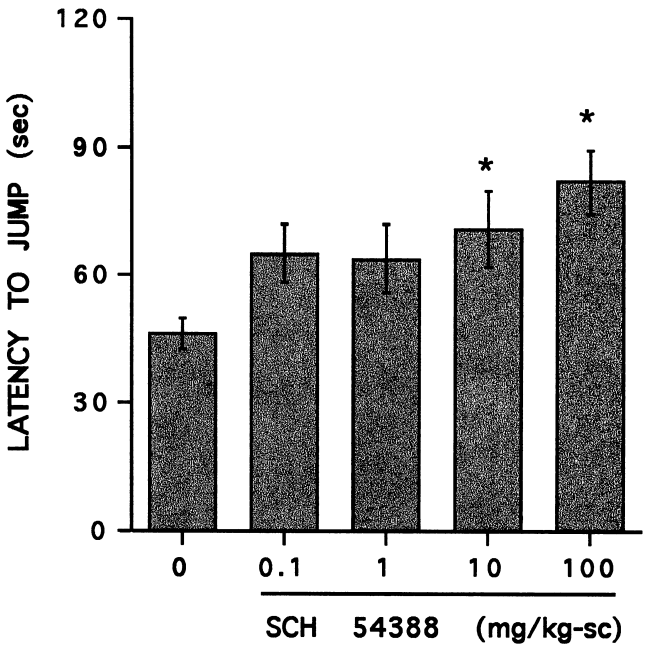

FIG. 7. The escape latencies for the hot-plate test in CD-1 mice given different doses of SCH 54388 is illustrated. There are 10 animals per treatment group. There is a statistically significant increase in mean (± SEM) escape latencies for animals given 10 and 100 mg/kg compared to the escape latency for the vehicle-treated animals ($p < 0.05$, Dunnett *t*-test).

an inverted "U" or bell shape; all dose curves had low entry times at either low or high doses, and high entry times defining a plateau in the curve at intermediate doses. This is a characteristic dose-dependency for many centrally active drugs, and is a direct consequence of probing for an optimal behavioral response with different doses of a test drug. Thus, with low doses of a drug, a low to moderate behavioral response indicates inadequate or ineffective concentrations of drug, whereas similar low to moderate behavioral responses that occur at high doses are generally a consequence of the negative effects that typically occur with excessive concentrations of drug. In the bell-shaped dose curve, intermediate doses typically produce the optimal response. The issue of bell-shaped dose curves for drugs producing cognitive effects is frequently reported (6,7,9,20) and the phenomenon has been reviewed by Seiden and Dykstra (16). In the present study, SCH 54388 was found to produce analgesia at doses of 10 and 100 mg/kg, using a standard hot-plate procedure. A therapeutic ratio of 100 and 1000-fold between the MED for the reversal of scopolamine or dizocilpine at 0.1 and 0.01, respectively, and 10 mg/kg SCH 54388 occurred. This separation indicates that lower concentrations of SCH 54388 were required to reduce the performance deficit in the PAR compared to the concentrations required to produce analgesia. The shock stimuli used in the training phase of the PAR procedure is presumably nociceptive. Thus, the decrease in latencies at the upper end of the dose curve may be attributed to higher doses of SCH 54388 through the production of antinociception that could either partially or completely obtund the aversive quality of the shock.

The administration of the parent compound of SCH 54388, FBM, resulted in reducing the avoidance deficits produced by the different antagonists. The overall potency of FBM was about 10-fold less than that of SCH 54388 (MED: 1.0 vs. 0.1 mg/kg, respectively, based on comparative dose–response curves in the scopolamine paradigm). FBM may reduce scopolamine or dizocilpine-induced deficits through the bioavailability of different metabolites, including SCH 54388. However, this possibility does not seem likely. In a study of FBM metabolism in the dog, rabbit, and rat (27), the monocarbamate was found to be only a minor metabolite in dog and rabbit urine, and was not observed in rat urine. FBM is a relatively stable compound and only small amounts of metabolite are recovered in plasma. In the study by Yang et al., (27) unchanged drug accounted for 72–100% of recovered plasma ^{14}C. However, as pointed out by these authors, the monocarbamate SCH 54388 may be further metabolized to monocarbamic acid (2-phenyl-3-carbamoyloxypropionic acid), as yet a tentatively identified metabolite. Thus, while SCH 54388 and its monocarbamate metabolite may account for the reduction in avoidance deficits observed when SCH 54388 is administered directly, given the high stability of FBM and low recovery of SCH 54388 as its metabolite, the monocarbamic acid of SCH 54388 may account for the essential neuroactive element involved in the defict-reducing effects of FBM.

Neither the mechanism of action for FBM or SCH 54388 is completely known. As described below, the present study, taken jointly with the available physiological and behavioral evidence, indicates that different mechanisms of action are associated with these compounds. First, FBM has been demonstrated to inhibit NMDA/glycine mediated influx of Ca^{2+} in cultured hippocampal neurons at an MED of 100 mM (23). In the same series of experiments, SCH 54388 at any dose, did not exhibit an effect on intracellular Ca^{2+} (Taylor, personal communication), indicating that SCH 54388, unlike FBM, does not act as a functional antagonist at the NMDA binding site of the receptor complex. Also, in animal models of seizure activity, SCH 54388 appears to involve a different mechanism of action than FBM. Subcutaneous SCH 54388 has been found

to be protective, with an MED of 1 mg/kg, against metrazol-induced convulsions in mice, whereas FBM was 100-fold less potent in this test (3). Interestingly, it has also been demonstrated that metrazol-induced seizure in mice can be reversed by certain carbamate agents exhibiting high-affinity for the γ-aminobutyric acid A/benzodiazepine receptor complex (10). Although structurally unrelated to the more complex carbamates synthesized by Jacobsen et al., the finding that certain carbamate compounds can exhibit GABAergic activity, taken with the GABAergic mechanism of action associated with the parent compound FBM (15), suggests that there may exist the potential within the structure of SCH 54388 to interact with the $GABA_A$ receptor. In this regard, SCH 54388 has been reported to be weakly active in the prevention of convulsions induced by NMDA and electroconvulsive shock in mice, whereas FBM exhibits protective effects in these models (3). Because potentiation of GABA currents has been demonstrated to occur in the presence of FBM in whole-cell recordings of hippocampal neurons (15), it may be that at least part of the anticonvulsive function associated with either FBM or SCH 54388 is a result of the enhancement of GABAergic neurotransmission. In this case, a convergence of function and mechanism of FBM and SCH 54388 may occur at the $GABA_A$ receptor.

The effect of SCH 54388 in the reduction of scopolamine or dizocilpine antagonism of PAR performance demonstrates that the compound is active in both cholingeric and glutaminergic neuronal systems. In addition, the potential for carbamate compounds to bind at $GABA_A$ receptors indicate that SCH 54388 has a range of cognitive-enhancing activity that may involve either directly or indirectly, GABAergic, cholinergic, and glutaminergic systems of neurotransmission. SCH 54388 was found to be active both subcutaneously and orally and to be markedly free of acute side-effect liability. Although the mechanism of action for SCH 54388 at this time is less clear than for FBM, as with FBM, SCH 54388 appears to exhibit a broad spectrum of neuronal activity. The doses of dizocilpine and scopolamine used in the present study to produce avoidance deficits are within a range consistent with doses used to produce similar avoidance deficits in mice over a 24-h period (18,19). Thus, further studies are needed to evaluate the kinetic/metabolic profile of SCH 54388 and how the drug may effect the way dizocilpine or scopolamine produce deficits associated with different components of retention, such as consolidation and retrieval. Overall however, the present pharmacological profile would suggest that as a prototype, SCH 54388 is favorable for the development of new, therapeutic agents capable of reversing cognitive decline.

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