FK960 [N-(4-Acetyl-1-piperazinyl)-p-fluorobenzamide Monohydrate], a Novel Potential Antidementia Drug, Improves Visual Recognition Memory in Rhesus Monkeys: Comparison with Physostigmine

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ABSTRACT

Our previous studies demonstrated that FK960 [N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate], a novel antide mentia piperazine derivative, exerts beneficial effects on memory deficits in various rodent models of amnesia, through activation of the somatostatin neuronal system. To extend the antiamnesic action of FK960 to nonhuman primates, FK960 was evaluated for its ability to reverse the deficits in visual recognition memory produced by muscarinic cholinergic receptor blockade by scopolamine or N-methyl-D-aspartate receptor blockade by dizocilpine (MK-801) in four rhesus monkeys performing a computer-automated version of delayed nonmatching to sample, with a list length of 20 trial-unique graphic symbols. Furthermore, the effects of FK960 were compared with those of physostigmine, a cholinesterase inhibitor. Doses of FK960 (1, 3.2, 10, 32, 100, 320 or 1000 μg/kg) injected i.m. 30 min before testing minimally affected visual recognition memory when administered alone. FK960 (1, 3.2, 10 or 32 μg/kg) significantly antagonized the deficits in visual recognition memory produced by scopolamine (10 μg/kg); the same doses of the drug minimally affected the deficits produced by dizocilpine (32 μg/kg). Similarly, physostigmine (3.2, 10 or 32 μg/kg) significantly and dose-dependently restored the visual recognition memory deficits produced by scopolamine (10 μg/kg) but not those produced by dizocilpine (32 μg/kg). From these results, we conclude that FK960 improves deficits in recognition memory associated with central cholinergic hypo function in nonhuman primates, and we suggest that the therapeutic potential of this drug for patients with dementia should be evaluated.

Central cholinergic systems have been repeatedly shown to play an important role in learning and memory. Lesions of the basal forebrain cholinergic nuclei produce cognitive impairments in various animal models (e.g., Aigner et al., 1991; Dunnett and Fibiger, 1993). Degeneration of these areas has also been associated with the cause of senile dementia of AD, a disorder in which impaired memory is the hallmark (Davies and Maloney, 1976; Perry et al., 1978; Coyle et al., 1983). A considerable body of pharmacological evidence also supports the important role of cholinergic systems in mnemonic function. For example, scopolamine, a muscarinic receptor antagonist, has been shown to impair learning and memory under a variety of testing conditions in rodents (Haroutunian et al., 1985; Flood and Cherkin, 1986), primates (Aigner and Mishkin, 1986; Rupniak et al., 1989) and humans (Petersen, 1977; Sitaram, 1984); some of these impairments reflect neuropsychological similarities with the demented states in patients with AD (Molchan et al., 1992).

In addition to the central cholinergic system, NMDA receptors, which are a subclass of glutamate receptors in the brain (Nakanishi, 1992), are now thought to participate in regulating cognitive processes (Collingridge and Lester, 1989; McEntee and Crook, 1993). NMDA receptor activation has been shown to be a necessary component for the induction of LTP, a proposed synaptic mechanism of memory (Teysler and Discenna, 1984; Bliss and Collingridge, 1993), in certain synaptic pathways in the hippocampus; blockade of this receptor prevents induction of LTP (Collingridge et al., 1983; Morris et al., 1986). Both competitive and noncompetitive NMDA antagonists produce consistent impairments in a wide variety of memory-related tasks in rodents (Whishaw and Auer, 1989; Ylinen et al., 1991; Bischoff and Tiedtke, 1992) and monkeys (Ogura and Aigner, 1993).

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ABBREVIATIONS: AD, Alzheimer’s disease; ANOVA, analysis of variance; DNMS, delayed nonmatching-to-sample; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate.
In addition to these neurotransmitters, certain peptidergic systems may contribute to normal cognitive processing. For example, it has been demonstrated that the brain somatostatinergic system is one of the most severely affected in patients with AD (Davies et al., 1980), suggesting another possible mechanism for the memory deficits observed in this disease. Somatostatin is currently believed to be an important neurotransmitter in the central nervous system for several reasons (Epelbaum, 1986; Epelbaum et al., 1994). This peptide is highly concentrated in the cerebral cortex and the hippocampus (Johansson et al., 1984), and several lines of evidence have confirmed that somatostatin affects neuronal activity in these brain regions (Matsuoka et al., 1991). In experimental animals, somatostatin enhances memory (Matsuoka et al., 1994), whereas cysteamine, a depletor of somatostatin (Sagar et al., 1982), produces the opposite effect (Matsuoka et al., 1995). These results, taken together, favor the view that brain somatostatin also plays a pivotal role in mnemonic processing.

FK960 [N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate] (fig. 1) was recently discovered as a novel cognitive enhancer in rats tested in passive avoidance, water maze and eight-arm radial maze tasks (Yamazaki et al., 1996). This compound was originally identified as possessing indirect cholinergic activating properties in the hippocampus (Maeda et al., 1994). FK960 reversed scopolamine-induced memory impairment not only in experiments with normal rats but also in tests with aged rats and rats with lesions of the nucleus basalis magnocellularis; in these tests acetylcholinesterase inhibitors such as physostigmine had no effect. In addition to these cholinergic properties, it was recently shown that FK960 indirectly stimulates somatostatinergic neurons in the brain (Yamazaki et al., 1996; N. Matsuoka, unpublished observations). The purpose of the present study was to determine whether FK960 would reverse the visual recognition memory deficits produced by pharmacological blockade of muscarinic or NMDA receptors. We also compared the actions of FK960 with those of physostigmine, a cholinesterase inhibitor that has been tested for therapy of AD.

Materials and Methods

Subjects. This study was conducted under a protocol approved by the National Institute of Mental Health Animal Care and Use Committee and was in accordance with the Guide for the Care and Use of Laboratory Animals adopted by the National Institutes of Health. Four rhesus monkeys (Macaca mulatta), three males (11–12 years of age, weighing 7.8–9.0 kg at the beginning of testing) and one female (12 years of age, 5.2 kg), were used. All animals had prior behavioral testing experience. Food intake was restricted to the amount earned during each daily session plus a regular afternoon feeding of monkey chow (Purina, St. Louis, MO) provided at least 4 h after testing was completed. Fresh fruits were given daily and water was freely available in the home cage.

Apparatus. The apparatus used in the present study was a darkened cubicle (120 × 60 × 100 cm) that was sound-attenuated by means of an exhaust fan located on the ceiling. A color monitor fitted with a touch-sensitive screen (Microtouch, Wilmington, MA) was located on a shelf on one wall of the cubicle. The monkey sat in a primate chair positioned directly in front of and within easy reach of the monitor. Rewards were banana-flavored pellets (190 mg; Noyes Co., Lancaster, NJ), which were delivered from a dispenser (BRS/LVE, Greenbelt, MD), located outside the cubicle, into a receptacle in front of the animal.

Behavioral procedure. The task was a computer-automated version of a DNMS task that has been described previously (Ogura and Aigner, 1993; Matsuoka and Aigner, 1996b). The stimuli were trial-unique graphic symbols, each occupying an area of approximately 50 cm². The symbols for each session were selected from a file of 1200 different letters and numbers that were combinations of 69 ASCII characters, seven colors and four angles of rotation (0, 90, 180 and 270 degrees). These characters had been randomly divided into 60 sets of 20 symbols each. The sets were used in sequence, four sets for each session, so that an animal saw a particular symbol no more often than once during testing. In the sample phase of the task, the 20 symbols were displayed one at a time in the center of the color monitor. Each time the monkey touched the symbol on the screen, it earned a banana pellet. After all 20 had been presented, the sample symbols were re-presented in the same order as before but were paired with an unfamiliar symbol for the choice phase. The symbols were presented on the left and right segments of the monitor (approximately 10 cm apart); the positions of the old and new symbols varied pseudorandomly. The animal was rewarded with a pellet for touching the unfamiliar symbol in this choice phase. Thirty seconds elapsed between symbol presentations in both the sample and choice phases. Thus, an interval of 10 min elapsed from the time a given symbol in the list was shown initially as the sample until it was paired with a novel symbol in the choice phase. Two sets, or lists, of 20 symbols each comprised a daily 40-trial, 40-min session. Testing was conducted 5 days per week. Drug tests began when day-to-day performance was stable for all of the monkeys. Percent correct, response latency and response bias measures were automatically calculated at the end of the session. Response bias was determined using index Y (Sahgal, 1987), a measure developed specifically for memory studies, which is the absolute difference between the two right and left alternative hit frequencies divided by the sum of the frequencies.

Drug testing. Solutions of FK960 (synthesized by Fujisawa Pharmaceutical Co., Osaka, Japan), physostigmine salicylate, scopolamine hydrobromide (Sigma Chemical Co., St. Louis, MO) and dizocilpine maleate [(+)-MK-801; Research Biochemicals International, Natick, MA) were prepared for i.m. injection immediately before each test session by dissolving the compound in sterile physiological saline. An injection volume of 0.1 ml/kg was maintained for all drugs, irrespective of dose. Each series of doses was tested once in ascending order. Saline control injections were also given before and after each series of drug tests. Injections were given no more often than twice per week, typically on Tuesdays and Fridays, and were made 30 min before the start of the session while the animal was seated in the primate chair. Combinations of FK960 or physostigmine with either scopolamine or dizocilpine were administered simultaneously 30 min before the start of testing.

Statistical analysis. All results were expressed as the mean ± S.E.M. The results for the dosages of FK960 and physostigmine were analyzed by one-way ANOVA with repeated measures, followed by post hoc paired Dunnett’s multiple-comparison test (two-tailed). For comparisons between saline and scopolamine-alone or dizocilpine-alone treatments, a paired Student’s t test was used. A P value of <.05 was considered statistically significant.

Fig. 1. Chemical structure of FK960 [N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate].
Results

Effects of scopolamine or dizocilpine on visual recognition memory. First, the dose-effect curves for scopolamine and dizocilpine effects on visual recognition memory in monkeys were determined. Scopolamine (0.32, 1, 3.2, 5.7 or 10 μg/kg) administered alone i.m. 30 min before testing produced a dose-dependent impairment in choice accuracy \( F(5,15) = 7.66, P < .001 \) by ANOVA, as shown in figure 2A. The 10 μg/kg dose of scopolamine significantly decreased the percentage of correct choices, compared with saline control (48.8 ± 2.2% vs. 76.3 ± 3.1%) \( (P < .01 \) by Dunnett’s multiple-comparison test). Scopolamine increased response latency in both the sample \( F(5,15) = 3.22, P < .05 \) and choice \( F(5,15) = 2.27, P = .10 \) phases; however, only the latency in the choice phase after scopolamine administration was significantly higher than saline control values \( (P < .05) \). Although administration of scopolamine tended to increase response bias (index Y), this change was not statistically significant (fig. 2C).

Similarly, dizocilpine (3.2, 10, 17.8 or 32 μg/kg) produced a dose-dependent impairment in DNMS \( F(4,12) = 4.15, P < .05 \). The 32 μg/kg dose of dizocilpine significantly impaired choice accuracy (60.6 ± 5.2%), compared with saline control (76.8 ± 3.7%) \( (P < .05) \) (fig. 3A). Unlike scopolamine, how-

![Figure 2](image1.png)

**Fig. 2.** Effects of single injections of scopolamine on visual recognition memory in monkeys \( (n = 4) \). Scores are group means \( (±\text{S.E.M.)} \) as a function of dose. Monkeys received saline or the indicated dose of scopolamine i.m. 30 min before testing. A, percentage of correct responses. B, response latency. C, response bias; index Y is the absolute difference between the left and right alternative hit frequencies divided by the sum of the frequencies (Sahgal, 1987). *\( P < .05 \), **\( P < .01 \), statistically significant, compared with the control group (by ANOVA followed by paired Dunnett’s multiple-comparison test).

![Figure 3](image2.png)

**Fig. 3.** Effects of single injections of dizocilpine on visual recognition memory in monkeys \( (n = 4) \). Scores are group means \( (±\text{S.E.M.)} \) as a function of dose. Monkeys received saline or the indicated dose of dizocilpine i.m. 30 min before testing. A, percentage of correct responses. B, response latency. C, response bias (index Y). *\( P < .05 \), **\( P < .01 \), statistically significant, compared with the control group (by ANOVA followed by paired Dunnett’s multiple-comparison test).
ever, dizocilpine only minimally affected response latencies ($F(4,12) = 1.79, P = .20$ in the sample phase; $F(4,12) = 1.22, P = .35$ in the choice phase) but significantly increased response bias, compared with saline treatment [$F(4,12) = 5.25, P < .05$].

**Effects of FK960 on visual recognition memory.** The effects of FK960 on visual recognition memory are shown in figure 4. Doses of FK960 (1, 3.2, 10, 32, 100, 320 or 1000 µg/kg) administered alone i.m. 30 min before testing significantly affected the accuracy of DNMS performance [$F(7,21) = 2.94, P < .05$]. As shown in figure 4A, low doses of FK960 tended to produce a small enhancement of recognition memory, with an inverted U-shaped dose-effect curve; the higher doses had minimal effects. Overall analysis by ANOVA showed a statistically significant effect of FK960 treatment; however, post hoc tests revealed no statistically significant dose differences. FK960 had no effect on response latency in either the sample [$F(7,21) = 1.03, P = .439$] or choice [$F(7,21) = 0.67, P = .696$] phases, as shown in figure 4B. Also, FK960 showed only minor effects on response bias [$F(7,21) = 2.25, P = .071$] (fig. 4C).

**Effects of FK960 or physostigmine on visual recognition memory deficits produced by scopolamine.** Next, we evaluated the ability of FK960 to restore the memory deficits produced by cholinergic receptor blockade by scopolamine (fig. 5). The doses of FK960 (1–32 µg/kg) were chosen from the range that produced the inverted U-shaped curve for DNMS performance in the studies with single injections of FK960 (fig. 4). The dose of scopolamine (10 µg/kg) chosen induced significant memory deficits in the dose-response study (fig. 2). In agreement with those results, 10 µg/kg scopolamine again significantly decreased the percentage of correct choices ($47.5 \pm 3.1\%$), compared with saline control ($77.9 \pm 2.9\%$) ($P < .01$ by paired Student’s t-test). Scopolamine also significantly increased response latency in the choice phase ($P < .05$). Although administration of scopolamine tended to increase response bias, this change was not statistically significant (fig. 5C). Figure 5A shows that concomitant administration of FK960 (1, 3.2, 10 or 32 µg/kg) with scopolamine (10 µg/kg) significantly improved the cognitive impairment induced by scopolamine [$F(4,12) = 6.10, P < .01$]. The disruptive effects of scopolamine on performance were significantly reversed even by low doses of FK960 (1 and 3.2 µg/kg; $P < .05$), and a significant improvement was still observed at the highest dose of the drug. Combined administration of FK960 and scopolamine also showed a tendency to reverse the scopolamine-induced response latency increments in both the sample [$F(4,12) = 0.99, P = .452$] and choice [$F(4,12) = 3.19, P = .053$] phases. Similarly, FK960 tended to decrease response bias, although the differences again were not statistically significant [$F(4,12) = 2.08, P = .147$].

We then compared the ability of physostigmine to antagonize the memory deficits produced by scopolamine with that of FK960. Figure 6A shows that concomitant administration of physostigmine (3.2, 10 or 32 µg/kg) with scopolamine significantly and dose-dependently reversed these effects of scopolamine [$F(3,9) = 8.80, P < .01$]. The disruptive effects of scopolamine on performance were almost fully reversed by the higher doses of physostigmine (10 and 32 µg/kg); that is, the scores were significantly different from those obtained after treatment with scopolamine alone ($P < .05$) and were comparable to the performance after treatment with saline alone. Combined administration of physostigmine and scopolamine tended to decrease the response latency in both sample [$F(3,9) = 1.57, P = .264$] and choice [$F(3,9) = 1.24, P = .352$] phases, which were increased by the administration of scopolamine alone. Similarly, physostigmine tended to decrease the response bias, although there were no statistically significant changes between treatments [$F(3,9) = 2.09, P = .173$].

**Effects of FK960 or physostigmine on visual recognition memory deficits produced by dizocilpine.** In final sets of experiments, we evaluated the ability of FK960 or
physostigmine to reverse the memory deficits produced by NMDA receptor blockade with dizocilpine (fig. 7). The optimal dose of dizocilpine was selected from the dose-response study (fig. 3). In accordance with those results, 32 μg/kg dizocilpine markedly decreased the percentage of correct choices (60.6 ± 6.2%), compared with saline control (79.4 ± 3.8%) (P < .01), and significantly increased the response bias, compared with saline treatment (P < .05). Coadministration of FK960 (1, 3.2, 10 or 32 μg/kg) with dizocilpine did not significantly affect the cognitive impairment induced by dizocilpine (32 μg/kg) [F(4,12) = 1.61, P = .235] (fig. 7A). Concomitant administration of FK960 and dizocilpine only minimally affected response latencies in the sample [F(4,12) = 1.08, P = .409] and choice [F(4,12) = 1.10, P = .402] phases. FK960 also failed to attenuate the response bias [F(4,12) = 0.61, P = .665] that was significantly elevated by dizocilpine treatment (P < .05).
Lastly, the effects of physostigmine on the deficits in recognition memory produced by NMDA receptor blockade were determined. Dizocilpine (32 μg/kg) produced deficits in choice accuracy comparable to those seen in the previous experiment (fig. 7). Figure 8 shows that physostigmine (3.2, 10 or 32 μg/kg) failed to affect the cognitive impairment produced by dizocilpine (32 μg/kg) or the indicated dose of physostigmine i.m. 30 min before testing. A, percentage of correct responses. B, response latency. C, response bias (index Y). †P < .05, ††P < .01, statistically significant, compared with dizocilpine-alone control group (by paired Student’s t test).

Discussion

The most important finding in the present study is that FK960, a novel putative cognitive enhancer of piperazine derivation, partially but significantly reversed the visual recognition memory deficits produced by scopolamine administration in rhesus monkeys, without affecting their basal performance. We interpret these findings to indicate that FK960
specifically affected the deficits associated with cholinergic hypofunction. This evidence extends our previous findings in rodents, where FK960 markedly reversed the memory impairments in rats induced by central cholinergic blockade with scopolamine treatment, lesions of the nucleus basalis magnocellularis or aging (Yamazaki et al., 1996). The ability of FK960 to reverse the scopolamine-induced memory impairments in monkeys in the present study was 10- to 100-fold more potent than the effect of the drug in rats; the magnitude of the shift in the effective doses of FK960 was comparable to that of the relative scopolamine doses in the two species (the optimal amnesic dose of scopolamine was 500-1000 µg/kg in rats). This finding suggests that rhesus monkeys may be more sensitive to pharmacological manipulations of central cholinergic systems. Taken together, the present results in primates, which have more complex cognitive processing capabilities and more relevance to human pathology than do rodents (Ridley and Baker, 1991; Wenk, 1993), strengthen the view that FK960 may have therapeutic potential in dementia-producing disorders such as AD.

Administration of physostigmine, an indirect cholinergic agonist, dose-dependently and significantly restored the memory deficits that were produced by systemic administration of scopolamine, providing additional evidence that cholinergic hypofunction was primarily involved in the memory deficits after scopolamine administration and thus confirming earlier findings by others in primates (Aigner et al., 1987; Rupniak et al., 1989). In the present studies, FK960 improved the memory deficits produced by scopolamine but also showed a tendency to attenuate the other behavioral measures (response latency and response bias) that were increased by scopolamine administration. Given this evidence, FK960 may exert its memory-improving action on the scopolamine-induced impairment via an indirect stimulation of central cholinergic system activity. However, the finding that the dose-response relationship for FK960 in the scopolamine model was different from that for physostigmine may imply that the neural mechanisms of cholinergic enhancement produced by FK960 differ from those of physostigmine. Additionally, physostigmine facilitated recognition memory in this paradigm with a bell-shaped dose-response curve when administered alone (Ogura and Aigner, 1993), which differs from the effects of FK960 in the present study. This also suggests a different mechanism of memory improvement by FK960, compared with that of physostigmine. In fact, FK960 has little direct action on acetylcholinesterase activity and no binding affinity for muscarinic cholinergic receptors at concentrations up to 10 µM (N. Matsuoka, unpublished observations).

FK960 has recently been shown to exert cognitive enhancing actions in rats tested in a variety of memory tasks, such as passive avoidance, water maze and eight-arm radial maze (Yamazaki et al., 1996). The dose-response curves in these studies were equally bell-shaped, and their maximal effects were observed constantly at the dose of 1 to 3.2 mg/kg. Of additional interest is that FK960, like its predecessor FR121196 (Matsuoka et al., 1992), induces penile erection in rats, which is a sign of hippocampal activation, and facilitates the development of LTP of population spikes in the mossy fiber-CA3 system in guinea pig hippocampal slices with similar bell-shaped dose-response curves (N. Matsuoka, unpublished observations). The bell-shaped dose-response curve is common with most drugs that have been reported to exert cognitive property-enhancing actions, such as cholinergic stimulants and nootropic drugs; the precise mechanisms of this remain to be established. FK960 appears to activate at least two neuronal mechanisms, depending on the doses used; smaller doses stimulate cognitive function, whereas larger doses mask it via an unknown mechanism. In the present study, FK960 significantly improved scopolamine-induced recognition memory deficits with a relatively flat dose-response function. Additional studies in monkeys with FK960, using a wider range of dosages, are required to address this issue.

The effects of FK960 on scopolamine-induced memory impairment in the passive avoidance and water maze tasks were abolished after central somatostatin depletion by cytoeamine in our rodents studies (Yamazaki et al., 1996). Facilitatory actions of FK960 on mossy fiber-CA3 LTP in hippocampal slices were also antagonized by scopolamine pretreatment and somatostatin depletion (Matsuoka et al., unpublished observations), suggesting that FK960 indirectly stimulates the cholinergic system, possibly in the hippocampus, via an activation of somatostatinergic neurons (Matsuoka et al., 1993, 1994). It is therefore tempting to speculate that FK960 could reverse the deficits associated with cholinergic blockade in monkeys as a consequence of somatostatin activation. Previous neurochemical evidence from Araujo et al. (1990), demonstrating that somatostatin stimulates the release of acetylcholine from cholinergic terminals in the hippocampus, supports this view. Such indirect cholinergic stimulation by FK960 via somatostatin may explain the difference in the efficacies of FK960 and physostigmine in restoration of scopolamine-induced memory deficits. Taken together, the present results may provide initial evidence that somatostatin modulates the deficits in visual recognition memory associated with cholinergic blockade in nonhuman primates.

Another important finding in this study is that both FK960 and physostigmine failed to affect the memory deficits observed after NMDA receptor blockade by dizocilpine in monkeys. This finding is quite different from their effects on scopolamine-induced memory deficits, although direct comparison of drug effects on scopolamine- and dizocilpine-induced amnesia, in which the magnitudes of the deficits were different, may not provide an accurate comparison. This is the first evidence, to our knowledge, that the memory impairments seen after NMDA receptor blockade are independent of those produced by muscarinic receptor blockade. We previously found that low doses of scopolamine and dizocilpine, which were ineffective when given alone, significantly impaired recognition memory of monkeys when given in combination, suggesting that interactions between cholinergic and glutamatergic systems play an important role in the regulation of visual recognition memory (Matsuoka and Aigner, 1996b). It is also interesting to compare the present findings with our previous results with the same memory task, in which NMDA receptor activation by d-cycloserine, a partial agonist of the glycine/NMDA site, significantly improved the recognition memory deficits produced not only by dizocilpine but also by scopolamine (Matsuoka and Aigner, 1996a). Although the precise mode of interaction between these two neuronal systems remains to be elucidated, the inability of cholinergic activation by physostigmine to restore
memory deficits produced by NMDA receptor blockade, combined with the results with d-cycloserine, led us to hypothesize that the two neurotransmitters may form a serial pathway and that the glutamatergic mechanism is distal to the cholinergic mechanism as a final mediator for visual recognition.

Anatomical and biochemical evidence suggests that there are both pre- and postsynaptic disruptions of glutamatergic systems in the brain of patients with AD (Greenamyre and Young, 1989), which may contribute to the memory loss. For instance, recent studies of postmortem brain tissue have shown that the coupling between strychnine-insensitive glycine recognition sites and NMDA binding sites is impaired in AD (Procter et al., 1989). Additional studies will be required to assess how the memory deficits produced by dizocilpine in this and previous studies (Ogura and Aigner, 1993; Matsuoka and Aigner, 1996b) relate to the memory loss seen clinically in patients with AD. Although it is speculative at this time, the hypofunction of the cholinergic and glutamatergic systems may be differentially involved in the progressive clinical stages of memory loss in patients with AD (Palmer and Gershon, 1990). This view may also explain the variable results of clinical trials of acetylcholinesterase inhibitors, such as physostigmine or tacrine for the treatment of amnesic symptoms in patients with AD (Fitten et al., 1990). The present results, showing that FK960 improved memory deficits induced by scopolamine but not by dizocilpine, suggest that FK960 may potentially improve the memory disturbance in amnesic patients where NMDA receptors are spared in the cortex and hippocampus. It is also tempting to speculate that the integrity of glutamatergic neurotransmission may be essential for FK960-induced memory improvement.

In conclusion, the present studies provide the first evidence that the novel cognitive enhancer FK960 ameliorated the deficits in visual recognition memory of monkeys after cholinergic blockade. FK960 has been shown so far to be much less toxic than direct cholinergic stimulants in single- and repeated-dose toxicity studies in animals and humans (phase I trials). Combined with our previous observations that FK960 is unique in its mechanisms of pharmacological actions, these findings strongly suggest that FK960 represses a feasible alternative to cholinergic agonists or cholinesterase inhibitors, which have proven to be less than optimal. Taken together, these results should encourage the clinical evaluation of FK960 in early and middle stages of dementia-producing disorders such as AD.

References


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