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Chronic administration of the Ca^{2+} channel blocker amlodipine facilitates learning and memory in mice

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Abstract

Acute administration of the Ca^{2+} channel antagonist amlodipine has been shown to facilitate memory for several types of learning in adult animals and to improve retention in aging mice. This study reports three experiments investigating the effect of chronic amlodipine treatment on retention in mice. In the first experiment, groups of mice were treated with either amlodipine or vehicle once a day for 14 days prior to training on a spatial discrimination task. Immediately after training, animals were given a single dose of amlodipine or the vehicle and tested for retention 24 h later. Both groups showed facilitated retention, thereby demonstrating that chronic amlodipine treatment did not produce desensitization to the facilitating effects of a post training treatment. In the second experiment, chronic treatments were administered once daily for 14 days beginning 24 h after training on one-way active avoidance and retention was tested on day 15. Results showed that chronic amlodipine attenuated spontaneous forgetting, but surprisingly, a similar enhancement could be achieved by a single treatment administered 1 day after training. In the third experiment, amlodipine was given either before or immediately after 10 daily training sessions in the one-way active avoidance task. Results showed that chronic treatment accelerated rate of learning. These findings confirm the memory facilitating properties of amlodipine under conditions of chronic drug administration.

Keywords: Ca^{2+} channel antagonist; Amlodipine; Memory enhancement; Maze learning; Active avoidance, mice; Chronic drug administration

1. Introduction

Amlodipine is a relatively new Ca^{2+} channel antagonist of the dihydropyridine class, which is different from other dihydropyridine-based antagonists by virtue of having a long side chain at the 2-carbon position of the dihydropyridine ring. As a result of this structural feature, more than 90% of the amlodipine molecules are ionized under physiologic conditions, and this is believed to account for its ability to penetrate the lipid bilayer (Nayler, 1994). Amlodipine has a slow rate of both association and dissociation with its receptor, which results in a gradual onset and long duration of action. In an earlier study (Quartermain et al., 1993), we reported experiments using young adult mice, which showed that this agent strongly facilitated retention of passive avoidance learning, appetitively motivated maze learning and Pavlovian fear conditioning, and that pre-training treatment accelerated rate of acquisition of a two-way active avoidance response. In addition, post-training administration completely reversed the deficit in retention of inhibitory avoidance exhibited by an 18-month-old mice.

Since this report was published, two studies have appeared which failed to find memory enhancement after treatment with amlodipine. In one study (Clements et al., 1995), amlodipine, nimodipine and nifedipine were administered before training in both passive avoidance and visual discrimination learning in young chicks. None of the dihydropyridines facilitated learning or retention. In the second study (Yamamoto et al., 1995), amlodipine, nimodipine, nicardipine and nilvadipine (0.3, 1.0 and 3.0 mg/kg) were administered daily for 3 weeks by gastric intubation to senescence-accelerated prone mice. Results showed that nimodipine, nicardipine and nilvadipine improved retention of passive avoidance learning, but amlodipine was without effect.

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Reasons for the failure of amlodipine to facilitate retention in these studies is not readily apparent. While there are many reports of memory enhancement in neurologically normal adult animals following treatment with Ca^{2+} channel antagonists (e.g. Isaacson et al., 1988; Deyo et al., 1990; Levy et al., 1991; McMonagle-Strucko and Fanelli, 1993; Deyo and Hittner, 1995; Quartermain et al., in press), several studies have failed to find facilitating effects (e.g., Isaacson et al., 1989; Vetulani et al., 1993) and some studies have reported memory impairments (e.g. Deyo et al., 1992; Nikolaev and Kaczmarek, 1994; Maurice et al., 1995). The inconsistency of these findings indicates that the variables, which determine the effect of calcium antagonists on learning and memory processes, have yet to be completely identified. Among the factors which may determine these effects include route of administration (central vs. peripheral), dosing schedule (acute vs. chronic administration), time of treatment (pre-training vs. post-training) and other variables related to the nature of the behavioral tasks employed to evaluate memory and learning.

The purpose of the present experiment was to attempt to confirm the memory-enhancing capability of amlodipine using chronic, rather than acute, drug administration. Relatively little preclinical research has investigated the effects of chronic administration of putative cognitive enhancers on retention, and it is therefore uncertain whether drugs, which facilitate retention when administered acutely will, in all instances, continue to do so under conditions of chronic administration. That the effects of chronic drug administration may not always be predicted from their acute effects is suggested by the results of two recent studies. One study showed that while acute propranolol treatment does not generally impair memory in mice, chronic (15 days) administration significantly disrupted retention of passive avoidance learning (Nielson et al., 1999). A second study, (Quartermain et al., 1994) showed that the partial NMDA receptor agonist D-cycloserine facilitated memory consolidation of maze learning when administered acutely immediately after training, but failed to do so in animals that had been pre-treated with D-cycloserine for 14 days. In the first experiment of the present study, we used a similar design to that employed in the D-cycloserine experiment cited above to determine whether chronic administration of amlodipine would alter the enhancing effects of a post-training treatment. Animals were pretreated with amlodipine or vehicle for 14 days, after which time they were trained in the linear maze and given a single acute post training injection of either amlodipine or vehicle. In the second experiment, amlodipine was administered for 14 days beginning 24 h after training in a one-way active avoidance task to determine whether chronic treatment could alleviate spontaneous forgetting. The third experiment explored the effects of daily pre- and post-training treatment on the acquisition of active avoidance learning.

2. Materials and methods

2.1. Animals

Male Swiss–Webster mice (Taconic, Germantown, NY), 6–8 weeks of age weighing between 25 and 30 g were the subjects for these experiments. Mice were housed five to a cage and were held in the vivarium for 7 days, prior to the start of the experiment. The procedures used in these experiments were approved by the institutional animal care and use committee of the New York University School of Medicine.

2.2. Drugs

Amlodipine Besylate (Pfizer) was administered chronically by subcutaneous injection at a dose of 5 mg/kg. This was chosen because previous research from this laboratory has shown that this dose was the lowest that reliably enhanced retention in several different tasks when administered acutely (Quartermain et al., 1993). Amlodipine was dissolved in distilled water and administered in a volume of 10 ml/kg body weight.

2.3. Behavioral tasks and apparatus

2.3.1. Linear maze learning

Thirsty mice were trained in a two-choice continuous spatial discrimination task previously described (Quartermain et al., 1994). In this learning task (see Fig. 1), mice are trained to obtain liquid reinforcement in each goal box by running down the unblocked alleyway. Mice shuttle continuously between the two goal boxes and are not handled by the experimenter during the training session. The apparatus, which consisted of two units, was constructed from wood and measured 75 cm long, 11.5 cm wide and 10 cm high. Each unit was 24 cm in length and contained a 15-cm long dividing partition with a 6-cm wall at each end to prevent the animal seeing the barrier from the choice point. Passageways were 5 cm wide. The goal boxes were 12-cm long with a 3.5-cm wide entrance with hinged end walls to facilitate removal of the mouse from the maze at the end of the session. The entire apparatus was covered with a clear Plexiglass lid. Reinforcement (0.05 ml of a 4% sucrose solution) was dispensed from a

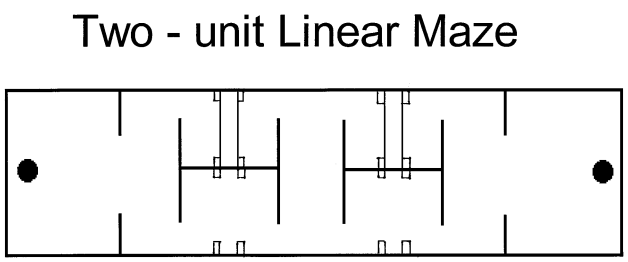

Fig. 1. Floor plan of the two-unit linear maze.

fluid delivery system, controlled by standard programming equipment.

Animals were initially familiarized with the apparatus in a 10-min session, in which they were permitted to drink in both goal boxes without barriers present in the alleys. On the training day, 24 h later, one of the alleys was blocked by placing a barrier in each unit. Training consisted of five trials, a trial being defined as a run in one direction. An error was recorded if any part of the animal's body entered a blocked alley or if the animal reversed direction. For half of the mice, the left alley was blocked and the right alley for the remaining half. Drug treatments were administered immediately after the fifth trial. Retention was tested 24 h later by determining the number of trials required to reach a criterion of four errorless runs in a block of five trials. Mice received access to water for 30 min in the home cage following both the adaptation and the training session.

2.3.2. One-way active avoidance

Apparatus was a two compartment chamber each 10-cm long, 10-cm wide and 20-cm deep, constructed from two aluminum plates bent at an angle of 45° to form a trough with a 5-cm gap at the bottom. A sliding door separated the two compartments. Foot shock (0.3 mA) was delivered to one compartment from a Grason Stadler Constant Current shock source. The apparatus was painted flat black and each compartment was covered with a hinged lid. Activation of a 10-s duration light attached to the lid on the shock compartment served as the CS. Mice were placed in the shock compartment, and after 5 s, the CS was initiated and the sliding door opened. After 10 s, the shock was automatically activated. The light and the shock were terminated and latency automatically recorded when the animal crossed into the safe compartment. The training session was terminated when the animal avoided shock on four of a block of five trials. Retention was tested by retraining to criterion.

2.4. Behavioral procedures

2.4.1. Effect of 14-day amlodipine treatment before linear maze learning

Groups of mice were treated daily between 0900 and 1100 h for 14 days with either distilled water (vehicle) or amlodipine 5 mg/kg ($N = 24$ per group). All animals were water-deprived on day 13 and given a 10-min adaptation session on day 14. On day 15, the mice were trained as described above and after training, the two groups were subdivided and treated with either vehicle or amlodipine 5 mg/kg. These group assignments resulted in four treatment conditions viz.: chronic vehicle–acute vehicle; chronic vehicle–acute amlodipine; chronic amlodipine–acute vehicle; chronic amlodipine–acute amlodipine. Retention was tested 24 h after training.

2.4.2. Effect of 14-day amlodipine treatment after training

Mice were trained in the active avoidance task as described in Section 2. Twenty four hours after training, animals were divided into two groups ($N = 24$ per group) and treated with either vehicle or amlodipine. Half of the animals in each group were tested 24 h after treatment (48 h post-training), while the remainder were continued on the treatments for an additional 14 days. Retention was tested 24 h after the last injection. In order to compare the effects of daily treatments with acute treatments administered at different times during the 14 day interval, additional groups of mice ($N = 12$ per group) were given a single injection of amlodipine either 1, 3, 7 or 14 days after initial training and tested on day 14. The last group was treated 30 min before the test to examine the effects of amlodipine administration on memory retrieval processes.

2.4.3. Effect of amlodipine treatment on acquisition of active avoidance

Thirty six animals were given seven training trials per day for 10 consecutive days. One hour prior to each daily session, mice were treated with either vehicle ($N = 12$) or amlodipine ($N = 12$). A third group ($N = 12$), was injected with amlodipine immediately after each daily trial.

2.5. Statistical procedures

The data were analysed by analysis of variance (ANOVA), followed by post hoc Newman–Keuls tests.

3. Results

3.1. Effect of amlodipine administered chronically prior to training

3.1.1. Training data

Error scores for the animals treated with vehicle or amlodipine for 14 days are shown in Fig. 1. Analysis of

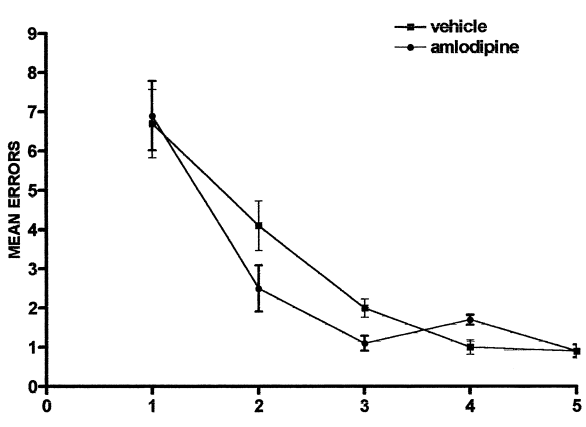

Fig. 2. Mean (+S.E.M) errors on linear maze training trials following 14 days treatment with vehicle or amlodipine (5 mg/kg).

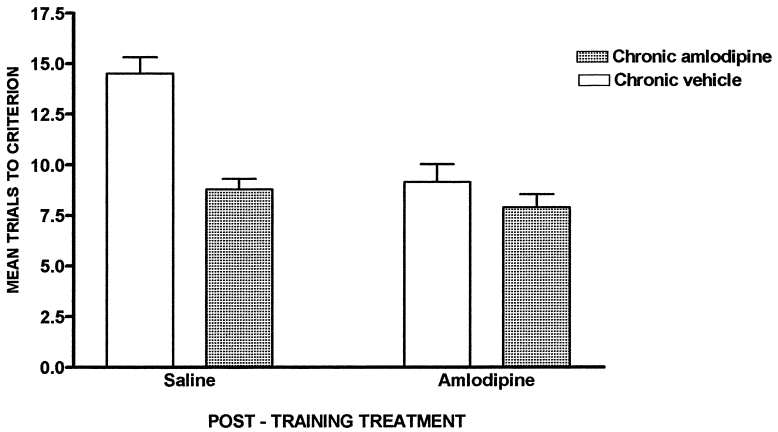

Fig. 3. Mean (+S.E.M) test trials to criterion for groups treated chronically with amlodipine or vehicle. Immediately after the training session, half of each group was injected with the vehicle and the other half with amlodipine (5 mg/kg). Retention was tested 24 h after training.

these data indicate no significant difference between the two treatments in rate of error reduction ($F = 0.78$).

3.1.2. Retention test data

These data are shown in Fig. 2. The results of a 2 (amlodipine or vehicle for 14 days pre-training) × 2 (amlodipine or vehicle immediately post training) ANOVA indicate a significant main effect for treatment pre-training ($F[1,44] = 19.23$; $p = < 0.001$) and a significant effect for post-training treatment ($F[1,44] = 23.44$; $p = < 0.001$). The interaction effect is also significant ($F[1,44] = 8.44$; $p = < 0.006$). These results show that mice, treated with amlodipine chronically before training, exhibit facilitated retention irrespective of the treatment administered after training, while animals treated with the vehicle before training only show improved retention if they were treated with amlodipine immediately after training.

3.2. Effect of amlodipine administered chronically after active avoidance training

These results are shown in Fig. 3. A 2 × 2 ANOVA calculated for these data reveal a significant effect for drug group ($F[1,42] = 25.82$; $p = < 0.001$) and a significant effect for test day ($F[1,42] = 8.89$; $p = < 0.005$). The significant interaction between these two variables ($F[1,42] = 19.04$; $p = < 0.001$) shows that the forgetting, which occurred in the vehicle-treated group was completely alleviated in the group treated with amlodipine during the 14-day retention interval. The effect of a single amlodipine treatment at different times after training is shown in Fig. 4. A one-way ANOVA computed for these data indicates a significant difference among the four groups. Newman–Keuls post hoc tests revealed that the group treated with amlodipine 1 day post-training had

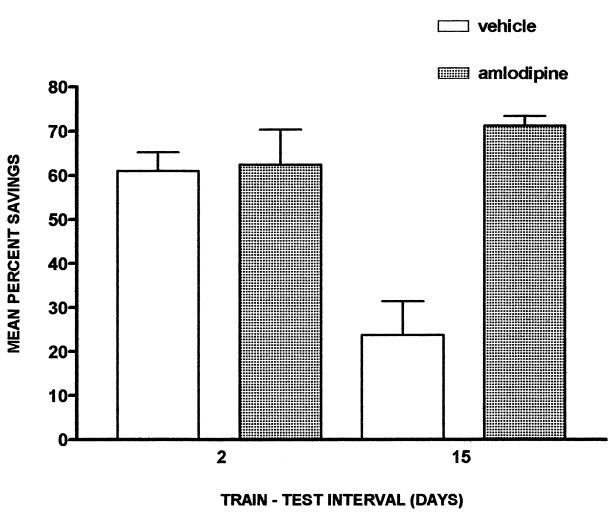

Fig. 4. Mean (+S.E.M) percent savings for mice tested either 2 or 15 days after active avoidance training. One day after training, half of the mice ($N = 24$) were treated with amlodipine and the other half with the vehicle. Half of the animals in each group ($N = 12$) were tested 1 day after treatment (2 days post training) and the other half, 14 days after treatment (15 days post training).

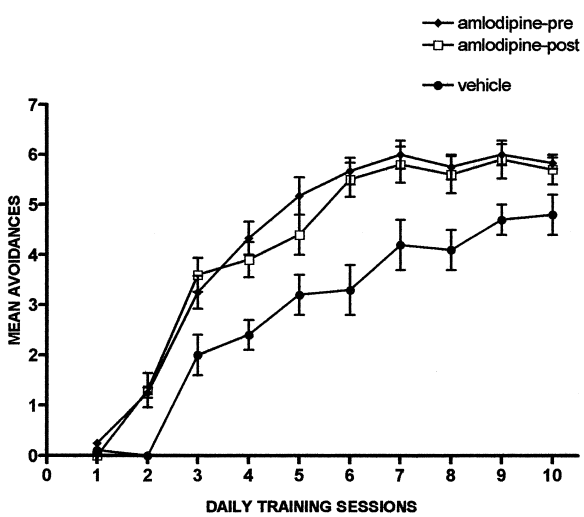

Fig. 5. Effect of chronic amlodipine treatment on acquisition of active avoidance. Mice were given seven trials a day for 10 days. Amlodipine was injected either 1 h before or immediately after the daily training session. The vehicle group was treated 1 h prior to training. Values are mean (+S.E.M) avoidances.

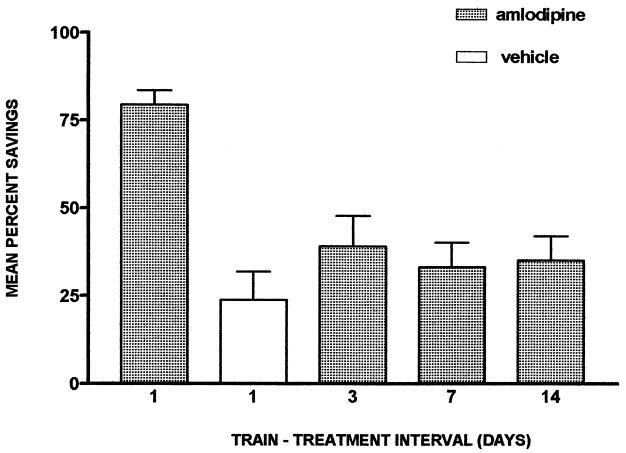

Fig. 6. Effect of acute injections of amlodipine (5 mg/kg) administered either 1, 3, 7 or 14 days following active avoidance training. A control group was injected with the vehicle 1 day post training. All mice were tested 14 days after the training session. Retention scores are expressed as mean (+S.E.M) percent savings.

significantly higher ($p = < 0.001$) percentage savings scores than the other three interval groups. Savings scores of the groups treated with amlodipine 3, 7 or 14 days after training were not different from the group treated with the vehicle on day 1 and tested on day 14.

3.3. Effect of daily amlodipine treatments on acquisition of one-way active avoidance

These results are shown in Fig. 5. A 3 (groups) × 10 (daily training sessions) ANOVA indicated a significant difference in the rate of learning among the three treatment groups ($F[2,31] = 29.06$; $p = < 0.001$) and a significant increase in mean avoidances across training days ($F[9,279] = 123.05$; $p = < 0.0001$; Fig. 6). Planned comparisons revealed that the two amlodipine-treated groups had significantly faster rates of acquisition than the vehicle group (vehicle vs. amlodipine 5 mg/kg $F = 39.89$, $p = < 0.001$; vs. amlodipine 10 mg/kg $F = 19.58$, $p = < 0.001$, and vs. amlodipine 5 mg/kg post $F = 27.96$, $p = < 0.001$).

4. Discussion

These findings indicate that chronic administration of the calcium channel blocker amlodipine can facilitate memory storage, alleviate spontaneous forgetting and accelerate learning rate. These results provide no evidence that the effectiveness of post-training treatment in enhancing memory storage is diminished by repeated dosing as is apparently the case with D-cycloserine. Post-training treatment with amlodipine enhances memory consolidation in both amlodipine and vehicle pretreated animals. The results depicted in Fig. 2 indicate that chronic pretreatment can facilitate storage in the absence of a post-training treatment, since the group pretreated for 14 days and given the vehicle immediately after training showed test scores comparable to the group treated with amlodipine after training. This presumably resulted from elevated blood levels of amlodipine, following the chronic regimen which persisted into the post-training period. Amlodipine has an elimination half life of about 11 h in the mouse after acute administration (Personal communication, Dr. M. Dodd, Pfizer) so that with the addition of metabolic accumulation resulting from the chronic treatment, it is likely that enough active drug was still present at the time of training to strengthen memory storage.

Chronic amlodipine administration after training can also alleviate forgetting. Results depicted in Fig. 3 show that spontaneous forgetting of active avoidance learning apparent in vehicle-treated animals was completely eliminated in the group, in which amlodipine was administered daily throughout the retention interval. However, the results of acute dosing at intervals throughout the 14-day interval indicate that the abolition of forgetting is not dependent on repeated daily treatments. Results shown in Fig. 4 indicate that animals who received a single treatment, 24 h post training and thereafter, remained undisturbed for the remainder of the retention interval, exhibited a level of retention indistinguishable from those animals treated daily for 14 days. Acute treatments at any other time, including 30 min before the test, failed to improve retention. This finding suggests that the opportunity for pharmacological alleviation of forgetting is restricted to a temporally limited period after encoding. Chronic treatments administered outside this time window are likely to be unprofitable. It is of interest that forgetting could not be alleviated by pre-testing administration of amlodipine. A previous study has reported that pre-testing amlodipine administration can facilitate retrieval of a 24-h memory of passive avoidance weakened by under training (Quartermain et al., 1993). The present study fails to confirm this finding under conditions, where a moderately strong memory of active avoidance training has been weakened by the imposition of a long training to testing interval.

The third experiment in this series showed that daily amlodipine treatments accelerated the acquisition of a one-way active avoidance response. The group treated with amlodipine, prior to the training sessions, exhibited a sharply increased rate of learning, relative to vehicle controls beginning on the third session and by session seven were avoiding on six of the seven trials; a level of acquisition which vehicle-treated animals did not attain on the final session. It is of interest to note that the group treated with amlodipine immediately after each session has comparable training scores to the pretreated group. This suggests that the acceleration in rate of learning was probably not the result of non-specific effects, such as altered activity levels or increased sensitivity to foot shock.

The mechanisms through which amlodipine (and other calcium channel antagonists) facilitate memory in neuro-

logically normal young adult animals is unknown. Enhancement of learning and memory in aged animals by nimodipine (e.g. Deyo et al., 1989) has been attributed to the reversal of age-associated disturbances in neuronal calcium homeostasis, but this explanation is not readily applicable to young adults who presumably have normal neuronal calcium regulation. It has been suggested that nimodipine-induced memory enhancement in young adult animals may be due to increased cerebral perfusion, resulting from dilation of the cerebral vasculature (Deyo and Hittner, 1995). Several studies have shown that nimodipine increases cerebral blood flow (Haws et al., 1983; Mohamed et al., 1984; McCalden et al., 1984), but other studies have failed to demonstrate an increase (Harris et al., 1982; Edvinsson et al., 1983). Although the effects of amlodipine on cerebral blood flow have not been extensively investigated, two recent studies failed to show significant increases (Pandita-Gunawardena and Clarke, 1999; Cai et al., 1996). On balance, it does not appear that increased cerebral blood flow is a robust enough phenomenon to serve as an explanation for the enhancement of retention, which accompanies treatment with amlodipine and other dihydropyridines.

Since amlodipine is known to bind to the α_1-subunit of the Ca^{2+}-channel complex (Nayler, 1994), it has been assumed that the memory enhancing effects are mediated by the direct blockade of neuronal calcium channels (Quartermain et al., 1993). However, recent unpublished data from this laboratory has suggested that memory enhancement may be independent of amlodipine's calcium channel blocking action. Amlodipine has a highly stereospecific effect on calcium channels; its levorotary (−) enantiomer having 1000 times greater affinity for the Ca^{2+} channel than the dextrorotatory (+) enantiomer (Arrowsmith et al., 1986). We administered different concentrations of the (−) the (+) enantiomer and the racemate to mice, immediately after training in two different learning tasks. Retention tests carried out 24 h later indicated that both the (−) and the (+) enantiomers produced strong enhancement of memory statistically indistinguishable from that produced by the racemate (MS submitted). These data suggest that the effect of amlodipine on memory probably cannot be explained by either enhanced blood flow or by alterations in neural excitability dependent on reduced calcium influx through voltage-gated calcium channels. We are currently examining other potential explanations for the memory-facilitating effect of amlodipine. It is possible that neurotransmitters may be mediating the effect, since it is known that some Ca^{2+} antagonists interact with transmitter binding sites (DeFeudis, 1987). Amlodipine has also been shown to inhibit free radical-induced damage to membrane lipids independent of channel blockade (Mason et al., 1999), suggesting as another possibility that drug-induced modulation of the biophysical properties of the membrane might underlie the effect of amlodipine on memory enhancement.

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