Chronic administration of the L-type calcium channel blocker nimodipine can facilitate the acquisition of sequence learning in a radial-arm maze

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Nimodipine, a dihydropyridine L-type voltage-gated calcium-channel blocker, was examined for its potential effect on the acquisition of a complex-arm sequence task in an automated radial maze. Young (60-day-old) male Wistar rats were injected with saline or nimodipine (5 mg/kg) 15 min prior to radial maze training, or immediately following the radial maze testing. The results of the learning task (over 7 days of testing) showed that rats injected with nimodipine each training session acquired the task more quickly and more efficiently compared to saline-treated animals. There were no significant differences for rats that were pre-/post-treated with nimodipine during the maze-learning task. The number of incorrect arm entries and number of additional lever presses in the same arm were found to be significantly lower in rats treated with nimodipine compared to saline-injected controls. The beneficial effect of nimodipine treatment occurred only in rats that were acquiring the task, and not in rats that had already learned the arm sequence paradigm. There were no potential non-specific influences on locomotor activity or appetite caused by chronic nimodipine treatments. These results strongly suggest that nimodipine can facilitate the acquisition of a complex learning task. *Behavioural Pharmacology* 15:133–139 © 2004 Lippincott Williams & Wilkins.

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Introduction

The dihydropyridine, nimodipine, is a potent L-type voltage-gated calcium-channel blocker that can exhibit strong effects in the central nervous system (LeVere *et al.*, 1989). There has been much controversy regarding the potential nootropic effect of nimodipine on memory enhancement. Numerous studies have shown that nimodipine can improve various aspects of learning and memory (Levy *et al.*, 1991; Kane and Robinson, 1999). Oral administration of nimodipine in older rats for 1 week can decrease the time required to acquire a spatial water-maze task and increase time spent in the ('goal') quadrant where the escape platform was previously located on probe trials (Schuurman *et al.*, 1987). The memory-enhancing effects of both acute and chronic administration of nimodipine have also been well documented in younger rats (Levy *et al.*, 1991; McMonagle-Strucko and Fanelli, 1993), as well as in brain-damaged animals (Scriabine *et al.*, 1989; Nyakas *et al.*, 1991; Schuurman, 1993; Sze *et al.*, 1998).

In contrast, many studies have also reported that following acute administration, nimodipine can impair learning performance in mice (Maurice *et al.*, 1995). Maurice and colleagues (1995) showed that at relatively low doses nimodipine can decrease spontaneous alterations in the Y-maze, impair step-down latency in a passive avoidance task, and diminish place learning in a water-maze paradigm. These results support the concept that long-term potentiation (LTP), a cellular correlate of learning and memory, requires a transient rise in postsynaptic levels of Ca^{2+} in order to activate the necessary cascade of multiple calcium-dependent intracellular events that may be important for causing the long-lasting changes in synaptic responsiveness underlying the long-term retention of memory (Collingridge *et al.*, 1988; Nicoll *et al.*, 1988; Bliss and Collingridge, 1992; Geinisman, 2000).

Furthermore, a well-documented correlation exists between impaired induction and maintenance of LTP and diminished retention of newly acquired information. It has been argued that by inhibiting the activity-dependent changes in synaptic efficacy associated with calcium signaling and LTP induction, significant degrees of learning and memory deficits can be observed when animals are later tested for memory retention (Butelman, 1990; Richter-Levin *et al.*, 1998; Sacchetti *et al.*, 2001; Cain *et al.*, 2002; Freir and Herron 2003; Lisman, 2003; Weisskopf *et al.*, 1999). However, the paradoxical

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observation of improved learning or enhanced memory in rats treated with calcium-channel blockers challenges these interpretations and suggests that further studies are needed to characterize the pharmacological and behavioral effects of these classes of drugs (Levy *et al.*, 1991; Zupan *et al.*, 1996; Vetulani *et al.*, 1997).

In the present study we investigated the effects of systemically administered nimodipine on the learning of a sequence pattern, using a four-arm automated radial-maze paradigm in male rats. The effects of nimodipine on baseline motor activity were also quantified, to ensure that nimodipine did not produce any conspicuous effects on locomotor behavior during radial-maze testing that could result in either an increase or decrease in sequence completions. Finally, the effects of nimodipine on feeding behavior were also investigated. To conduct the radial-maze testing, subjects are required to be placed on a food deprivation schedule during the duration of behavioral testing (Persinger *et al.*, 1994). It was our concern that nimodipine may influence the appetite of the nimodipine-treated rats and that this could serve as a motivational factor in their performance of the radial-maze paradigm.

Methods

Subjects

Male Wistar rats, approximately 60 days of age, were used in the present study. They were obtained from Charles River (Quebec). All animals were treated in accordance with the Canadian Council on Animal Care (CACC) guidelines. Rats were housed (3–4 per cage) in standard metal colony cages, with food and water freely available, until 3 days prior to the onset of radial-maze training. Three days before four-arm radial-maze training, the food supply was restricted to the hours of 15.00–17.00 h, with water still freely available. Light onset in the colony was 07.30 h, with a 12:12 light:dark cycle. Ambient temperature was maintained at 20 ± 1°C.

Automated radial-maze procedure and error tabulation

The apparatus used was a custom-constructed, automated four-arm radial maze, which has been described in detail elsewhere (Persinger *et al.*, 1994). Briefly, the maze consisted of a 20-cm wide central arena with four 36-cm long by 20-cm wide arms, constructed of Plexiglas, radiating outwards from each side of the central arena at 90°. At the distal end of each arm a standard operant lever and pellet dispenser were located. The rat was required to enter the arm and press the lever at the end of the arm in order to obtain a 50 mg Noyes food pellet reward. A piece of corkboard was placed on the top of the maze to prevent escape. Because all of the arm sections were transparent, it is quite possible that subjects could have utilized different stimuli found in the room as extramaze cues, in order to orient themselves successfully and navigate the four-arm automated radial maze. Operant training lasted for 3 days and subjects were allowed a maximum of 90 min in the apparatus, or until a maximum of 50 rewards (criterion response) was acquired.

The complex maze task required the subject to learn a specific sequence of arm entries within the radial maze. The rat was required to navigate the maze by first entering arm 4 and pressing the lever in order to obtain a food reward, then arm 2, followed by arm 1, and finally arm 3. During a sequence only one reward was associated with a single lever press in each arm. If multiple lever presses in the same arm had occurred, no extra rewards were given. *Lever-pressing errors* were recorded if the rat pressed the lever multiple times in the same arm after the single reward had been collected, or as the number of lever presses in an incorrect arm within the sequence. *Entry errors* were recorded if the rat deviated from the set sequence mentioned above (i.e. went from arm 4 to arm 1 instead of arm 2). For clarity, the two types of pressing errors will be presented separately as either multiple same-arm presses or multiple incorrect-arm presses. Finally, if the rat deviated from the prescribed sequence (i.e. an entry error had occurred) the pattern did not have to be re-started. The rat simply had to visit the next appropriate arm that was required for the sequence to be completed.

Upon removal, the radial maze was cleaned using a diluted 0.4% acetic acid solution in an attempt to mask any olfactory cues. All subjects were tested for 30 min/day between 08.00 h and 14.00 h, for 7 consecutive days.

Experiment 1: Radial maze learning

A total of 12 rats ($n = 4$/group) were randomly assigned to one of three treatment groups prior to the 7 days of testing. Each subject received either subcutaneous (s.c.) injections of physiological saline (0.9%; 1 ml/kg), nimodipine (5 mg/kg) 15 min prior to each daily testing session in the radial maze, or nimodipine (5 mg/kg) administered immediately after the daily training session had ended. The rat was placed in the central arena of the radial maze and the number of pattern completions, the speed of pattern completions and the relative activity in each arm of the maze were recorded on an IBM 486 personal computer. Our rationale for administering nimodipine at this dosage came from previous pilot work (unpublished data) and observations made by others (Nyakas *et al.*, 1991; Saade *et al.*, 2003) that suggested a maximum effect for nimodipine at this dose.

Experiment 2: Post-acquired sequence learning

To determine the effect of nimodipine on rats that had already learned successfully the arm sequence task, subjects ($n = 8$) were trained on the paradigm for 7 days,

to ensure that all subjects were at a point where stable acquisition of the sequence task would have reached its maximum (arm-sequence learning typically asymptotes by day 6 or day 7 during testing: Martin and Fournier, unpublished observations). During this initial acquisition period, rats received a daily injection of saline 15 min before entry into the maze. None of these rats was administered nimodipine during the initial acquisition period.

Following 7 days of testing, subjects were then randomly assigned (4/group) into one of two possible treatment conditions. For each of the seven additional days of testing, rats was given either nimodipine before entry (5 mg/kg, s.c.) or saline 15 min before being tested on the arm-sequence task. The total duration of testing (including the 7 days during the acquisition period of the task) was 14 days.

Experiment 3: Free feeding and open-field testing

In order to control for any non-specific effects that nimodipine could have on either locomotor or feeding behavior, subjects ($n = 12$, 6/group) were randomly assigned and received either physiological saline (0.9%; 1 ml/kg; s.c.) or nimodipine (5 mg/kg; s.c.); they were tested both for free feeding and open-field activity. The total duration of testing was 8 days and each subject was tested 1 day on free feeding and the next day for locomotor activity in the open field, for a total of 4 days of testing for each measure. Subjects that received nimodipine or saline for free-feeding testing were administered the same drug for days when open-field testing was conducted. Since the testing days alternated, it was our main concern to determine the chronic effects of nimodipine on the final days of testing (i.e. days 7 and 8). In other words, chronic injections of nimodipine were administered for the radial-maze testing and it was our goal to establish the effects of chronic nimodipine administration on feeding and locomotor behavior by keeping the injection schedule constant. Subjects were injected 15 min prior to either free feeding or open-field testing.

For the free-feeding test, Purina Rat chow was ground up and placed in a heavy, sturdy container which was located at the end of an empty plastic shoebox cage. The subjects were then allowed to free feed for 30 min and the amount of food consumption (in grams) was recorded. We allocated one rat per shoebox cage and any excess rat chow that had been extruded from the container was carefully collected and returned to the container when the 30 min had elapsed, for measurement.

For open-field testing, each subject was placed in a custom-constructed square box (60 cm × 60 cm × 30 cm deep) that was subdivided into 25 equal squares by black lines. The rat was then placed in the center of the open-field arena and allowed to roam freely for 2 min. A crossing between squares was scored as soon as the rat crossed a line with both hind legs. The frequency of rearing or grooming behavior was recorded. The rats were also quantified on defecation and micturition. Upon removal from the open-field arena, this area was then cleaned with a 0.4% acetic acid solution in order to mask any possible olfactory confounds.

Statistical analyses

All analyses were performed using SPSSX software loaded on a VAX 4000 computer. Major statistical tools included repeated-measures multivariate analysis of variance (MANOVA) with one level repeated (sessions) and one level not repeated (drug treatment), to analyze the number of pattern completions, entry errors, lever-pressing errors (two types: same arm or different arm), and the speed of the pattern completions over the days of testing. Both the free-feeding and open-field tests were analyzed using a MANOVA with one level repeated (4 days of testing) and one level not repeated (drug treatment). *Post-hoc* analyses included Tukey's (0.05), paired *t*-tests (with familywise error rate controlled using Bonferroni alpha-adjustment), and independent *t*-tests where appropriate.

Results

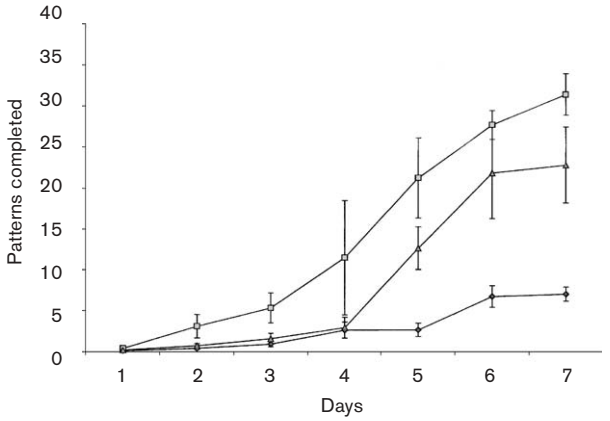
Effect of nimodipine on radial-maze learning

Figure 1 shows the means and standard errors of the mean (SEM) for the number of successful sequence completions (trials) per session for each training day. Nimodipine injections given either before or after daily testing sessions facilitated the acquisition of the maze task [$F(2,9) = 9.01$, $P < 0.01$, $\eta^2 = 67\%$], with all three groups acquiring the task over time [$F(6,54) = 80.56$, $P < 0.001$]. *Post-hoc* analysis showed that the source of the treatment effect was an increase in the number of pattern completions by animals injected with nimodipine (irrespective of the time of injection) on sessions 5, 6 and 7, compared to saline-treated animals.

As expected, there was a significant main effect for the average speed to complete a pattern [$F(6,54) = 69.10$, $P < 0.01$], indicating that, on average, the subjects tended to complete patterns faster as training progressed. However, those rats that were treated with nimodipine either before or after the daily testing session showed faster average pattern completions compared to saline-treated controls [$F(2,9) = 6.99$, $P < 0.05$, $\eta^2 = 61\%$]. *Post-hoc* analysis revealed that rats treated with nimodipine demonstrated a faster completion of the pattern on days 5, 6 and 7, compared to controls.

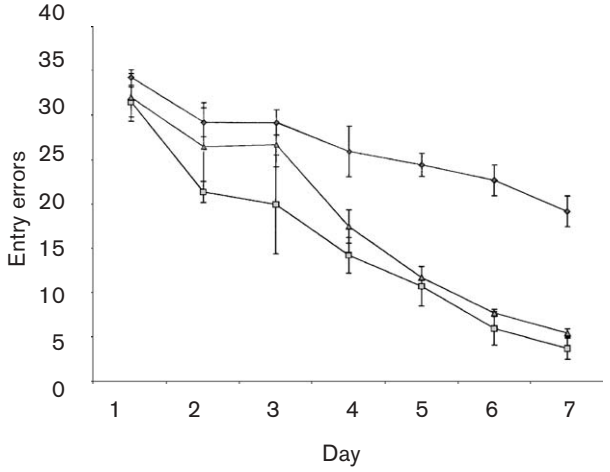
The means and SEM for the number of entry errors for each daily session are presented in Fig. 2. As expected,

Fig. 1



The total number of patterns completed over the 30 min testing session is shown for the 7 testing days. Rats injected with nimodipine prior to testing (■) or after testing (▲) had more pattern completions overall, compared to saline-injected rats (♦). Error bars denote the standard error of the mean.

Fig. 2



The number of entry errors for rats treated with either nimodipine (5 mg/kg) prior to testing (■) or nimodipine (5 mg/kg) after testing (▲), compared to saline-injected controls (♦). Error bars denote standard error of the mean.

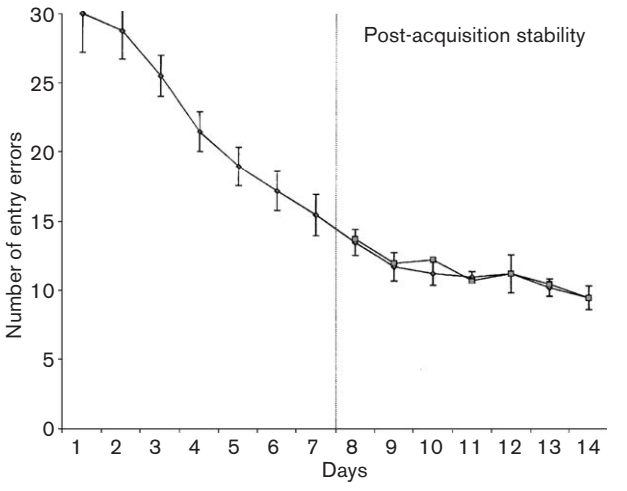
there was a significant effect for entry errors over the multiple testing days [$F(6.54) = 53.04$, $P < 0.001$, $\eta^2 = 87\%$], with a significant reduction in entry errors as testing progressed. The rats injected with nimodipine prior to or after maze testing made significantly fewer entry errors, compared to saline-treated controls [$F(2,9) = 15.70$, $P < 0.01$, $\eta^2 = 77\%$]. There were no differences in entry errors between rats treated with nimodipine before or after maze testing. The interaction between the treatment and day of testing was not significant [$F(12,54) = 0.94$, NS]. The significant differences between the nimodipine and saline-treated rats did not become apparent until the fourth day of testing, after which these differences remained until the end of the testing sessions. The number of additional bar presses in the same arm also differed significantly between groups [$F(2,9) = 6.73$, $P < 0.05$, $\eta^2 = 54\%$, results not shown]. *Post-hoc* analysis revealed that nimodipine-treated rats made significantly fewer additional bar presses compared to saline-treated controls. There were no significant differences between groups for the number of bar presses in an incorrect arm [$F(2,9) = 2.13$, NS].

Effect of nimodipine on post-acquired sequence learning

The numbers of patterns completed increased significantly over the 14 days of testing [$F(13,78) = 27.18$, $P < 0.001$, $\eta^2 = 82\%$], with both groups showing more complete patterns as testing sessions continued. There was no significant interaction between treatment and day of testing [$F(13,78) = 0.46$, NS]. *Post-hoc* analysis revealed that pattern completion became stable by day 7 for all subjects and remained relatively stable throughout the entire duration of testing.

Figure 3 shows the mean number of entry errors and SEM for the 14 days of testing. There was a significant reduction in the number of entry errors, additional bar presses in the same arm, and additional bar presses in a wrong arm as testing progressed [all Fs ≥ 28.74, $P < 0.001$]. There was no significant interaction between treatment and day of testing [all Fs < 0.85]. *Post-hoc* analysis revealed that all errors asymptote by day 8 and remained stable for the entire duration of testing.

Fig. 3



The number of entry errors for rats that were treated with saline for 7 days and then treated with either saline (♦) or nimodipine (■) for an additional 7 days (post-acquisition period). Error bars denote standard error of the mean.

Effect of nimodipine on free-feeding and open-field behavior

A significant main effect of days of open-field testing was found for the number of squares crossed [$F(3,18) = 9.60$, $P < 0.01$, $\eta^2 = 62\%$]. The interaction between drug and days of open-field testing was not significant [$F(3,18) = 0.88$, NS]. *Post-hoc* analysis revealed that significantly more squares were crossed for all animals on the first day of testing, compared to all other days. All other behavioral measures recorded during open-field testing were not significant [all Fs < 1.58].

The free-feeding data revealed that there were no significant difference between the groups in food consumption, over all days of testing [$F(3,18) = 0.66$, NS]. The interaction between treatment and days tested for free feeding was also not significant [$F(3,18) = 1.72$, NS]. Taken together, these results suggest that when administered chronically, nimodipine did not aversely affect locomotor or appetitive behavior during testing.

Discussion

Many studies have cited increasing evidence that supports a role for calcium-channel blockers in enhancing various aspects of memory and learning, in both animal and human subjects (Levy *et al.*, 1991; McMonagle-Strucko and Fanelli, 1993; Batuecas *et al.*, 1998; Quevedo *et al.*, 1998; Sze *et al.*, 1998). Conversely, L-type calcium-channel blockers have also been shown to disrupt both normal learning and memory retention (Lee and Lin, 1991; Maurice *et al.*, 1995). These paradoxical findings are troublesome when attempting to determine the precise contribution and role that L-type voltage-gated calcium channels may play during the initial steps involved in the long-term retention of newly acquired information. The present study demonstrated that *chronic* injections of nimodipine significantly enhanced the acquisition for learning a sequence task in a young (60-day-old) rat population.

Nimodipine-treated rats were shown to acquire the learning task more quickly when compared to saline-treated controls. These rats also completed the task faster and more proficiently (i.e. fewer errors) than rats not treated with nimodipine. Furthermore, nimodipine treatments caused a significant reduction in the numbers of entry errors. We found that the major difference between nimodipine groups and controls, for maze-learning performance and maze proficiency (as inferred by the number of errors made during testing), became apparent by about day 5 of training, and that this significant difference remained until testing had ended. There were also no differences for time of nimodipine injection (before or after maze learning) on any of the learning measures assessed in the automated radial maze. Taken together, these results imply that nimodipine improved learning of a complex series of arm-sequence entries in a radial maze.

Nimodipine had no effect on the stability of arm-sequence recall when administered to subjects that had already acquired this learning task. These results suggest that nimodipine is effective when administered during the initial period of acquisition and not when learning is established. In other words, nimodipine can only exert an influence for improving the acquisitional and performance measures in subjects when administered during the initial period of learning, and not when acquisition and learning has stabilized (i.e. post-acquisition).

Interestingly, nimodipine has been shown previously to decrease locomotor activity when administered alone or in combination with phenytoin in rats (Schuurman *et al.*, 1987; Balakrishnan *et al.*, 1998). We were concerned that the chronic injections of nimodipine may have caused a non-specific change in the overall locomotor activity in these animals. Differences in locomotor activity (as inferred by the number of squares crossed in the open field) were found not to be significant between nimodipine-treated groups and saline controls, although a typical pattern of habituation of locomotor activity was observed. Moreover, chronic administration of nimodipine was found not to alter appetite in these animals. Taken together, these results strongly argue against any non-specific changes in either motoric activity or appetite behavior in rats chronically treated with nimodipine during maze learning.

In order to navigate the arm-sequence task successfully and obtain maximum food reinforcement, we would expect that subjects may have used a complex interplay of extrinsic (i.e. extramaze) and intrinsic (i.e. kinesthetic or vestibular) cues during testing (Olton and Collison *et al.*, 1979; Suzuki *et al.*, 1980; Brown, 1992; Brown *et al.*, 1993; Babb and Crystal, 2003). We cannot exclude the possibility that nimodipine-treated rats may have utilized a navigational strategy for learning the arm-sequence paradigm that differed from the strategy employed by saline-treated controls. However, since all animals had access to the same extramaze cues throughout the entire duration of testing, and since there has been no reported evidence that nimodipine-treatments could alter sensory processing (i.e. visual, kinesthetic, or vestibular) that would be important for this type of maze learning, we feel that this alternative explanation is unlikely.

Although the exact mechanism that is responsible for producing the facilitation in learning often observed in nimodipine-treated animals is currently unknown, it may be of interest to note that previous studies have shown that nimodipine can increase hippocampal CA1 excitability (Thompson *et al.*, 1990; Moyer *et al.*, 1992) and

decrease the threshold for long-term potentiation induction (Kullmann *et al.*, 1992; Christie *et al.*, 1995). There is also the possibility that the blockade of L-type voltage-gated calcium channels could have caused non-specific ('compensatory') changes in the regulation of receptors and/or enzymes, protein synthesis, or activation of different kinds of calcium-mediated phosphorylation signaling and gene transcription (Bading *et al.*, 1993; Baudry *et al.*, 1993; Cavus and Teyler, 1996; Quevedo *et al.*, 1998; Morgan and Teyler, 1999; Borroni *et al.*, 2000; Purcell *et al.*, 2003). These differences may explain why nimodipine exerts a beneficial effect on learning and memory in one context, and a deleterious effect in another (Raymond and Redman, 2002). Another possibility is that the action of nimodipine may be through a vasodilatory effect that can alter local cerebral blood flow and thus local neuronal activity (Quevedo *et al.*, 1998; Disterhoft, 1980). Any, or even all, of these kinds of changes that could accompany the administration of nimodipine would strongly influence the degree of synaptic changes that are necessary for the successful learning and retention of the information important for this task.

Previous studies of dihydropyridine effects on learning and memory have been contradictory. Calcium-channel antagonists can improve or enhance learning acquisition and performance (Levy *et al.*, 1991; McMonagle-Strucko and Fanelli, 1993; Kane and Robinson, 1999; Saade *et al.*, 2003; Shinnick-Gallagher *et al.*, 2003; Veng *et al.*, 2003), disrupt or impair learning and memory (Lee and Lin, 1991; Maurice *et al.*, 1995), or cause no change (Isaacson *et al.*, 1989; Vetulani *et al.*, 1997; Cardenas *et al.*, 1998). These seemingly divergent findings may be attributed to differences in both the behavioral and inferences of learning that are being tested and measured, differences in the dose of nimodipine being used, age differences of the subjects, or strain differences.

One possibility is that the nootropic and beneficial effects of dihydropyridines on learning may resemble a typical inverted U-shaped dose–response curve (Deyo *et al.*, 1989; Quevedo *et al.*, 1998). As often reported (Deyo *et al.*, 1989; Lee and Lin, 1991; Levy *et al.*, 1991; McMonagle-Strucko and Fanelli, 1993; Maurice *et al.*, 1995; Kane and Robinson, 1999), the positive effects of nimodipine found on learning acquisition disappear at low doses (0.3–1 mg/kg) or high doses (> 10 mg/kg). As a result we would speculate that nimodipine, at the dose employed in this study, may not have acted as full blocker of the L-type calcium channel, but instead may have acted as a modulator. Thus at our dose (5 mg/kg) nimodipine may have acted to hold the channels open rather than close or block them. This kind of dual pharmacological action for dihydropyridines has been suggested by others (Fulga and Stroescu, 1997) and has also been shown to take place involving other types of pharmacological antagonists that act at entirely different receptor systems than nimodipine (Powell *et al.*, 2002).

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