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Study of Cognitive Function Enhancing Effect of Nimodipine by using Morris Water Maze Test

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ABSTRACT

Objective: To study effect of nimodipine on the cognitive function by using morris water maze test.
Materials and Method: The effect of nimodipine on the cognitive function was studied using morris water maze test in albino mice. Albino mice of both sex were divided into three groups *viz.* young control group (n=10), old control group (n=10) and nimodipine treated old mice group (n=10). The first two groups were treated with normal saline whereas last group was treated with nimodipine (2mg/kg I.P. [Intraperitoneal]) for 10 days. The animals were tested on 1st, 5th, 9th and 10th day of the trial. vehicle and nimodipine were given half an hour before the test.
Results: In Morris water maze test the mice has to search the hidden platform. Young mice were competent from the beginning in learning and memory and their performance further increased with the training, as evident by significant decrease in latency to find the platform and increasing number of crossing over the platform area. On the contrary aged mice did not show significant performance in any parameter. However treatment with nimodipine in another group of aged mice showed significant improvement in all the parameters of the water maze test but did not reach the performance of young mice.
Conclusion: The study suggestions that nimodopine enhances cognitive function in mice.

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Calcium regulates variety of signaling pathways (Carafoli, 2002; Clampham, 1995 and Grrenberg, 1995). Acute uncontrolled calcium influx can cause neuronal death by overstimulation of N- methyl D asparate (NMDA) type glutamate receptors (Lee *et al.,* 1999; Rothman and Olnay, 1987). These observations indicate that elevation of L-type channel activity causes neuronal dysfunction during aging .Influx of calcium through L- type calcium channel is robustly increased in old rodents (Disterhoft *et al.,* 1994). Elevated L-type channel activity during aging responsible for up regulation of afterhyperpolarization in hippocampal CA1 neurons which may contribute to age related deficit in learning and memory (Norris *et al.,* 1998; Thibault *et al.,* 2001).

Calcium channel blockers apart from having action on cardiovascular system are also known to have effect on central nervous system. Nimodipine is highly lipophilic dihydropyridine (DHP) calcium channel blocker. It has selective DHP binding sites in the limbic system *i.e.* hippocampus, olfactory bulb, amygdala and frontal cortex (Cortex *et al.,* 1984; Schoemaker and Langer *et al.,* 1985). Hippocampus is crucial for learning and memory. Nimodipine may prevent in part of the damage of neuronal cell resulting from disrupted regulation of calcium homeostasis.

In the present study, the effect of nimodipine on cognitive function by using water maze test in young and old mice was examined. Old mice like humans exhibit accelerated forgetting under appropriate testing conditions (Zometzer *et al.,* 1982) and show deficits in spatial learning (Gallagher and Pelleymounter *et al.,* 1988).

MATERIALS AND METHODS

Animals:

Albino mice with average weight (15-25 gm) of either sex were used throughout the study. They were kept under standard 12 hour light dark cycle and fed with food ad libitum. Approval of institutional animal ethics committee was obtained. The experiments were performed between 9 A.M. to 12 noon in an experimental room. Animals were divided into three groups.

Group I – Young mice (12-14 weeks of age) treated with normal saline

Group II- Old mice (> 50 weeks of age) treated with normal saline

Group III - Old mice (> 50 weeks of age) treated with nimodipine (2mg/kg).

All the drugs were administered intraperitoneally

Apparatus and test procedure: (Reddy, 1997)

For the evaluation of nimodipine, water maze test was used. The apparatus consisted of a large rectangular tank of 90 cm x 60 cm diameter and 50 cm in height. The pool was filled with water (22^0C) to a depth of 22 cm and rendered opaque by addition of milk. The floor of the tank was marked into 4 quadrants (north-east, north-west, south-east, south-west). The escape platform was located in the middle of North West quadrant. The platform was hidden by arranging its top surface just beneath the water surface. This platform had a coarse surface for good grip for the mice.

Procedure:

– Base line trials- Mice were submitted to 2 baseline trials. During these trials platform was kept visible so that animal could escape. Mice were individually put in the maze. Mice were allowed to swim freely until they found the platform or until 160 seconds elapsed. If the mouse found the platform it was allowed to remain there for 10 seconds and then returned to its home cage. If mouse was unable to find the platform within 160 seconds it was then placed on the platform for 10 second and maximum score of 160 assigned. Trials were performed with an intertrial interval of 4 hours. Mice did not receive either test drug or vehicle during these trials.

– Acquisition trial - During this trial platform was kept 2 cm below the surface of water. Nimodipine was given to test group and normal saline was given to control groups. Mice were allowed to swim freely until they found hidden platform or 180 seconds elapsed. Mice were tested on day 1, day 5 and day 9 of acquisition trial. Results were expressed as latency to find the hidden platform (Plate 1).

– Probe test - It was carried out on 10th day of acquisition trial. Nimodipine was given to test group and normal saline was given to control groups. In which the platform was removed from the water tank and the mouse was allowed to swim for 60 seconds. Number of times the mouse crossed the area where the platform had been placed during the trial was recorded (Plate 2).

Plate 1: Shows acquisition trial on Morris water maze

Plate 2: Shows probe test on Morris water maze

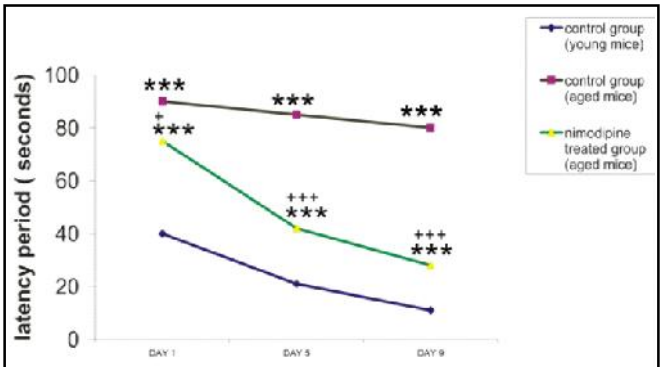
Statistical analysis:

Numerical variables were reported in terms of mean and standard deviation. Statistical analysis of results was done by unpaired student t test. In this analysis, variables showing p value less than 0.05 and 0.001 were considered to be statistically significant and highly significant, respectively.

RESULTS AND DISCUSSION

Fig. 1 shows mean latency to escape on hidden platform. On day one aged control mice required more time ($p < 0.001$ versus young control) to find the platform whereas nimodipine treated aged mice showed less time than aged controlled mice ($p = 0.05$), but more time than young control mice ($p < 0.001$).

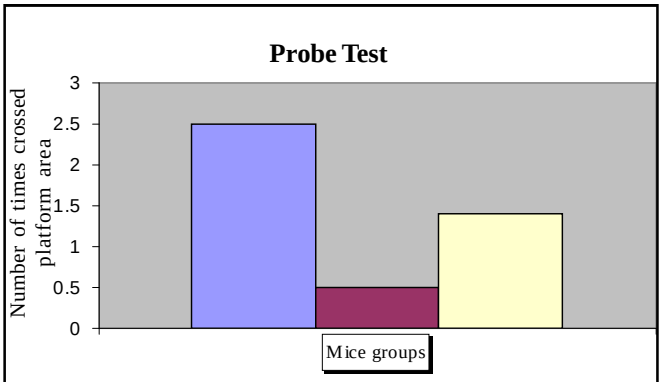
On day 5 and 9 aged control mice required significantly more time ($p < 0.001$ versus young control) to find the platform whereas nimodipine treated aged mice required less time than aged control mice ($p < 0.001$) ,but more time than young control mice ($p < 0.001$).



*** p<0.001 vs control group (young mice)
+ p=0.05 vs control group (aged mice)
+++ p<0.001 vs control group (aged mice)

Fig. 1: Effect of nimodipine (2mg/kg,IP) on latency to find the hidden platform in the acquisition trial of the Morris water maze. Values are mean ± SEM of latency to find the hidden platform

Fig. 2 shows mean number of crossings of the area where the platform had been located during training. Aged control mice showed significantly ($p < 0.001$ versus young control) less number of crossings whereas nimodipine treated aged mice showed ($p=0.02$) more number of crossings of the platform area than aged control mice but the number of crossings were less ($p<0.001$) than young control mice.



*** p<0.001 vs control group (young mice)
++ p=0.02 vs control group (aged mice)
+++ p<0.001 vs control group (aged mice)

Fig. 2: Effect of nimodipine (2mg/kg,IP) on number of crossing of the area where the platform had been located during trial of the Morris water maze. Values are mean ± SEM of number of crossing over the platform area

Nimodipine is a central nervous system selective DHP calcium channel blocker. The aim of the present study was to examine the effect of nimodipine on cognitive function in albino mice. Among the dosage of nimodipine which were tested *i.e.* 2 ,4 and 8 mg /kg intraperitoneally, except 2 mg/kg , rest of the doses *i.e.* 4 and 8 mg/kg showed marked sedative effect**,** as evidenced by significant reduction in mice performance on rota rod (80-100 % fall and less time spent on the rod). The later two dosages significantly potentiates phenobarbitone sleeping time and markedly delayed recovery. Therefore, in present study, nimodipine 2 mg/kg,; intraperitoneally was the dose used throughout the testing.

Young mice were competent in learning and memory right from the beginning and their performance further increased with training. In contrast, aged mice did not show significant performance in all the parameters of the test. However, daily treatment by nimodipine in another group of aged mice lead to significant improvement in all the parameters of the test on day 1 and after training on day 9, but it did not reach the performance of young mice.

Dementia in Alzheimer's disease has been related to disrupted calcium homeostasis. Alzheimer's β amyliod protein also interferes with calcium homeostasis (De Jorge *et al.* 1993). Hippocampus is known to store new information during learning in mammals and showed enhanced firing rate during learning. Increasing calcium mediated afterhyperpolarization is likely mechanism for this firing. Aging brain exhibited learning deficits because ageing hippocampal neurons shows afterhyperpolarization. Nimodipine may improve learning by increasing firing rate of hippocampal neurons and slowing hyperpolarization. The age related learning impairments in rabbits is reversed by the selective L- type calcium channel blocker-nimodipine (Deyo *et al.*, 1989). There are clinical studies supporting memory and learning enhancing potential of nimodipine in elderly dementia patients (Ban *et al.*, 1990), in Alzheimers disease (Grobe-Einsler and Traber, 1992), in electroconvulsive therapy induced amnesia (Cohen and Swartz, 1990) and in brain lesion induced amnesia (De Jorge and Traber, 1993)**.**

Conclusion:

Learning and memory in aged mice were significantly enhanced after nimodipine treatment. Nimodipine may prevent in part the damage of neuronal cells resulting from disrupted regulation of calcium homeostasis. Nimodipine may be acting on hippocampus through calcium related mechanism. Further studies on animals and humans are needed to elucidate the exact mechanism of action of nimodipine in learning and memory.

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REFERENCES

Ban, T.A., Morey, L. and Agugila, E. (1990). Nimodipine in the treatment of old age dementia. Prog *Neuropsychopharmacol Boil. Psychiatry.*, **14**(4):525-551.

Carafoli, E. (2002). Calcium signaling. A tale for all seasons. *Proc. Natl. Acad. Sci., USA* , **99**:1115-1122.

Clampham, D.E. (1995). Calcium signaling. Cell : 80259- 80268.

Cohen, M.R. and Swartz, C.M. (1990). Absence of nimodipine premedication effect on memory after electroconvulsive therapy. *Neuropsychobiology*, **24**(4):165-168.

Cortex, R., Supravila, P., Karobath, M. and Palacios, J.M. (1984). Calcium antagonist binding sites in the rat brain . Quantitative autoadiographic mapping using 1-4 dihydropyridine (3h) DN 200-100 and (3H) PY 108-68. *J. Neurol. Transm.*, **60**:169-197.

De Jorge, M.C. and Traber, J. (1993). Nimodipine: Cognition ageing and degeneration. *Clin. Neurophamacol*, **16** (1):525-530.

Deyo, R.A., Straube, K.T. and Disterhoft, J.F. (1989). Nimodipine facilitates associative learning in aging rabbits. *Science*, **243**(4892):809-811.

Disterhoft, J.P., Gispen, N.H., Traber, J. and Khachaturian, Z.S. (1994). eds Calcium hypothesis of Alzheimers disease and brain aging. *Ann. NY Acad. Sci.*, **747**: 1-11.

Gallagher, M. and Pelleymounter, M.A. (1988). Spatial learning deficits in old rats : A model for memory decline in the aged. *Necrobiol. Ageing*, **9**:549-556.

Ghosh, A. and Grrenberg, M.E. (1995). Calcium signaling in neurons : Molecular mechanisms and cellular consequence. *Sciences,* **268**: 239- 247.

Grobe-Einsler-R, Traber J. (1992). Clinical results with nimodipine in Alzheimers disease. *Clin. Neuropharmacol*, **15**(1):416A-417A.

Lee, J.M., Zipfel, G.J. and Choi, D.W. (1999). The changing landscape of ischemic brain injury mechanisms. *Nature*, **399**: A7- A14.

Norris, C.M., Halpain, S. and Foster, T.C. (1998). Reversal of age related alternations seen in synaptic plasticity by blockade of L- type Calcium channels. *J. Neurosci.*, **18**(9): 3171- 3179.

Rothman, S.M. and Olney, J.W. (1987). Excitotoxicity and the NMDA receptor. *Trends Neuro. Sci.*, **10**: 299-302.

Reddy, R.S. (1997). Assessment of nootropic and amnesic activity of centrally acting agents. *Indian J. Pharmacol.*, **29**:208-217.

Schoemaker, H. and Langer, S.Z. (1985) (3H). Diltazem binding to calcium channel antagonist recognition sites in rat cerebral cortex. *European . J. Pharmacol.*, **111**:273-237.

Thibault, O., Hadley, R. and Land field, P.W. (2001). Elevated post synaptic calcium and L type calcium channel activity in aged hippocampal neurons : Relationship to impaired synaptic plasticity. *J. Neurosci.*, **21**(24) :9744-9756.

Zometzer, S.F., Thompson, R. and Rogers, J. (1982). Rapid forgetting in aged rats. *Behar. Nectrol. Biol.*, **36**:49-60.

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