SUMMARY AND CONCLUSION
The possible involvement of GABA/BZ receptor modulation in scopolamine-induced short-term memory deficits was investigated in mice. Passive avoidance step-down task behaviour was observed. Latency of mice to reach shock-free zone (SFZ) and number of mistakes the animal made in 15 min were used as separate parameters for acquisition and memory retention, respectively. Atropine, scopolamine caused a delay in reaching SFZ and increased number of mistakes. However, pirenzepine showed a partial influence, as it delayed the latency only. Physostigmine reversed the scopolamine-induced increase in number of mistakes although it caused a delay in the time to reach SFZ. GABA (50, 75 and 100 mg/kg) and almost all GABA agonists including fengabine (10 mg/kg); sodium valproate (30 and 60 mg/kg), picrotoxin (0.5, 1 and 2 mg/kg) showed retention enhancing effects in scopolamine -treated and -untreated animals. Though, GABA (100 mg/kg), sodium valproate (60 mg/kg), fengabine (5 mg/kg) also delayed the animals in reaching SFZ. GABA\textsubscript{A} agonist, muscimol (0.05 and 0.1 mg/kg) and GABA\textsubscript{B} agonist, (±)baclofen (0.25, 0.5 and 1 mg/kg) and (-)baclofen (0.25
and 0.5 mg/kg) also displayed memory enhancing action. Whereas, GABA<sub>A</sub> antagonist produced hind limb rigidity, GABA<sub>B</sub> antagonist, CGP 35348 did not show any effect per se, but reversed the (±)baclofen-induced delay in latency, without affecting retention enhancing action of (±)baclofen. Combined administration of subeffective dose of GABA (50 mg/kg) with picrotoxin (2 mg/kg) and (±)baclofen (0.25 mg/kg), showed significant improvement in acquisition and retention. However, the effect of GABA (100 mg/kg) on acquisition was reversed by bicuculline (2 mg/kg) and by CGP 35348 (100 mg/kg) while improving retention. The retention enhancing effect of GABA was potentiated by physostigmine, but the latency in reaching SFZ was further delayed.

The specific benzodiazepine antagonist Ro 15-1788 (10 mg/kg) and inverse agonist FG-7142 (10 mg/kg) very significantly reversed the scopolamine-induced deficits. Ro 15-1788 (5 mg/kg) did not show any effect, per se, and in scopolamine-treated animals, as well. These results suggest that GABA/BZ receptor modulation, particularly GABA<sub>B</sub> receptors, influences the cholinergic neurotransmission in scopolamine-induced short-term memory deficits in passive avoidance paradigm. Further, the observations support the potentials of BZ antagonists and inverse agonists as possible therapeutic agents in dementia.

EFFECTS OF DIZOCILPINE (MK 801) AND KETAMINE, NONCOMPETITIVE NMDA RECEPTOR ANTAGONISTS ON SHORT-TERM MEMORY DEFICITS IN PASSIVE AVOIDANCE STEP-DOWN TASK PARADIGM IN MICE

The phenomenon of long-term potentiation (LTP) formation in hippocampal and neocortical brain areas has been suggested as a mechanism for learning and memory, where
NMDA receptors play a significant role. Various agonists have been proposed to facilitate LTP and thereby learning and memory. Competitive and noncompetitive antagonists of NMDA receptors block LTP formation and produce attentional or acquisition deficit in animals. A series of experiments were carried out using noncompetitive NMDA antagonist, MK 801 (0.01-0.1 mg/kg) and ketamine (1-10 mg/kg), in passive avoidance step-down task paradigm in mice. MK 801 showed complete disruption of acquisition at higher dose, while very low doses showed improvement in retention. MK 801 further, showed additive or potentiating influence on scopolamine-induced deficits as physostigmine failed to reverse completely the memory deficits.

The results of the interaction of NMDA antagonist with scopolamine provide a basis for the speculation that cholinergic- and NMDA-antagonism may play a hand in hand role in short-term memory disturbances in passive avoidance step-down paradigm in mice.

MK 801 PRODUCES ANTIANXIETY EFFECT IN ELEVATED PLUS-MAZE AND EVIDENCE FOR GABA/BZ RECEPTOR INTERACTION WITH MK 801 IN ANXIETY RELATED BEHAVIOUR IN RATS AND MICE

The antianxiety effect of noncompetitive NMDA receptor antagonist MK 801 was investigated on elevated plus-maze paradigm in rats and mice. During a five minute session of the test the number of entries the animal made in open or/and enclosed arm, preference of the animal for the first entry and average time each animal spent in open and enclosed arm were noted as parameters for anxiety (fear like)-related movements. The effect of MK 801 was further
explored by studying its interaction with the specific anxiolytic agent, diazepam; the anxiogenic β-carboline agent, FG-7142 and the central BZ receptor antagonist Ro 15-1788. MK 801 (0.05-0.1 mg/kg) produced anxiolytic profile at all the doses in rats and mice. It increased the preference of the animal for open arm in a dose dependent manner in mice and the effect was potentiated by diazepam in either of the species. Both, FG-7142 and Ro 15-1788 reversed the effects of MK 801 and diazepam, when these agents were concomitantly administered.

The study revealed the anxiolytic profile of MK 801 and further tends to speculate that NMDA receptor antagonism simultaneously modulate the GABA/BZ receptor ionophore complex and thereby affect anxiety related behaviours in rodents in elevated plus-maze apparatus.

EFFECT OF NMDA RECEPTOR LIGANDS ON NEOCORTICAL AND HIPPOCAMPAL EEG ACTIVITY OF RAT BRAIN: POSSIBLE IMPLICATION IN LEARNING AND MEMORY

Neocortex and hippocampus play an important role in motor activity, neuronal plasticity and learning and memory mechanisms. Electroencephalographic (EEG) activity of neocortex and hippocampus of rat brain following NMDA receptor agonist, N-methyl-D-aspartate (NMDA), (0.25-2 nmol in 10 μl, icv and noncompetitive NMDA receptor antagonists, MK 801 (0.025-0.1 mg/kg, ip) and ketamine (10-50 mg/kg) at 0, 0.5, 4, 8 and 24 hours was recorded. The electrodes were implanted stereotaxically in hippocampus and neocortex, respectively. NMDA (0.25 and 1 nmol) showed longer lasting
decrease in amplitude and in frequency in cortical region, while 2 nmol produced epileptogenic neurotoxicity. Opposite effect, i.e., increase in amplitude in both, hippocampus and neocortex was observed with MK 801 and ketamine. These agents showed a longer lasting influence. Administration of MK 801 (0.05 mg/kg) and ketamine (50 mg/kg) prior to NMDA (2 nmol) protected 40 percent animals from NMDA-induced neurotoxicity and blockade of NMDA-induced long-term effects.

The EEG effects of NMDA agonist and NMDA-induced neurotoxicity at higher dose and its modification by NMDA antagonists, MK 801 and ketamine, suggested that beside NMDA agonist (NMDA), its antagonists may also affect longer lasting changes in hippocampus and cortex. These antagonists reverse NMDA-mediated long term influence in these brain areas and thus play a significant role in learning and memory mechanisms.

EVALUATION OF LEARNING AND MEMORY MECHANISMS EMPLOYING ELEVATED PLUS-MAZE IN RATS AND MICE

The utility of elevated plus-maze in the evaluation of learning and memory mechanisms was investigated. Both, adult rats and mice, displayed significantly reduced transfer latency (TL) from open arm to enclosed arm on the 2nd day trial, when compared to 1st day trial group. However, young rats (2-3 months old) failed to show such an effect. Scopolamine (0.1-0.5 mg/kg) and MK 801 (0.05-0.1 mg/kg) did not affect the shortened TL on elevated plus-maze paradigm in rats, while nootropics, like piracetam (150 mg/kg) reduced the shortened TL. This memory enhancing effect was reversed by scopolamine (0.3 mg/kg) and MK 801 (0.1 mg/kg).
Lower doses of MK 801 (0.03 and 0.05 mg/kg) treated animals displayed the shortened TL in mice. Both these agents produced significant acquisition deficits in mice, as they delayed the 1st day and 2nd TL, when administered 30 min prior to the 1st day trial. However, physostigmine also showed similar effect at higher doses, which might be attributed to its effect on skeletal muscles. Moreover, physostigmine reversed the scopolamine- and MK 801- induced deficits.

The results extend the validity of elevated plus-maze for evaluation of possible nootropic action of drugs in rodents. Further, the participation of cholinergic and NMDA receptors in information processes has been suggested.

REVERSAL OF SCOPOLAMINE- AND MK 801- INDUCED MEMORY DEFICITS BY ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN RATS AND MICE

The mood elevating action of angiotensin converting enzyme inhibitors, including captopril and enalapril, had been suggested in recent years. In the present study, the effect of captopril and enalapril was investigated on step-down task and elevated plus-maze paradigm in rats and mice. The parameters used under the study were essentially the same as described in earlier sections. Captopril (5, 15 and 30 mg/kg) did not affect either the acquisition or retention per se, while enalapril (30 and 60 mg/kg) delayed the mice in reaching SFZ. In scopolamine-treated animals captopril (15 and 30 mg/kg) reversed the acquisition and retention deficits. Enalapril, though improved retention but further delayed the latency in scopolamine-treated mice. The nootropic, aniracetam (100 mg/kg) produced retention
enhancing action. Captopril (15 mg/kg) accentuated the retention enhancing action of aniracetam (60 mg/kg). (±)Baclofen-induced delayed latency of mice in reaching SFZ was reversed by captopril, without affecting retention improving action. On elevated plus-maze apparatus, captopril-treated animals displayed the shortened TL, while the enalapril-treated animals did not show such an effect. These effects were reversed by prior administration of scopolamine (0.3 mg/kg) and MK 801 (0.1 mg/kg), both in rats and mice. These effects were found comparable to that of nootropics, i.e. piracetam (dealt in earlier section).

These results provide a basis for retention enhancing action of ACEIs. Further, captopril was found superior over enalapril in improving retention or consolidation phase of memory, and proposed to involve cholinergic and NMDA receptor modulation.