AIMS AND OBJECTIVES
The main aims and objectives of the present study were to (i) develop an animal model(s) for the study of cognition, learning and memory related behaviours, (ii) elucidate the neurotransmitter and their receptor mechanisms in learning and memory with special emphasis to cholinergic, GABAergic (influence of positive and negative ligands to GABA/BZ receptor complex) and excitatory amino acid receptor modulators and (iii) evaluate newer agents speculated to improve learning and memory including angiotensin converting enzyme inhibitors.

The approach, to achieve the above objectives, has been broadly discussed under the following heads, namely (i) Evidence for GABA/BZ receptor modulation in short-term memory passive avoidance task paradigm in mice : GABA_A and GABA_B receptor modulation, (ii) 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, (iii) 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, (iv) Effect of NMDA receptor ligands on neocortical and hippocampal EEG activity of rat brain : possible implication in learning and memory, (v) Evaluation of learning and memory mechanisms employing
EVIDENCE FOR GABA/BZ RECEPTOR MODULATION IN SHORT-TERM MEMORY PASSIVE AVOIDANCE TASK PARADIGM IN MICE: GABA_A AND GABA_B RECEPTOR MODULATION

Progressive decline of learning and memory has been attributed to deficient cholinergic neurotransmission in several neuropsychiatric disorders including AD, PD, KD and HC (Bowen and Davison, 1986; Defeudis, 1988; Smith, 1988). Several studies with cholinergic muscarinic blockers and cholinotoxins suggest a predominant role for the cholinergic system in learning and memory in humans as well as in animals (Fisher and Hanin, 1986; Moroni et al., 1984; Schwartz et al., 1984; Walsh et al., 1984; Fisher et al., 1991). Scopolamine-induced deficits in acquisition, immediate retention and working (short-term) memory resembled AD and this model has been used as a pharmacological tool in various clinical and experimental paradigms (Bartus, 1978; Drachman and Leavitt, 1974; Flood and Cherkin, 1986; Preston et al., 1989a, b). A variety of pharmacologically diverse groups of agents reverse these deficits suggesting the possible participation of multiple neurotransmitter systems in scopolamine-induced deficits (Flood and Cherkin, 1986; Sarter and Stephens, 1988; Smith, 1988; Vogelsang and Piercy, 1986).

Recently, benzodiazepine-induced amnesic deficits, quite similar to scopolamine, have gained considerable attention
as both produce transient impairment in acquisition and retention. BZ antagonists and β-carbolines, a new class of drugs, have been demonstrated to improve scopolamine-induced dementia disorders (Jensen et al., 1987; Lal et al., 1988; Sarter and Stephens, 1988). However, Preston and Coworkers (1989b) were unable to demonstrate the cross-reversal of scopolamine- and BZ- induced deficits by flumazenil and physostigmine, respectively. In another clinical study, pantoyl-GABA, an analogue of GABA, has been reported to facilitate cholinergic functions in the CNS (Nakahiro et al., 1985). Moreover, various noncompetitive cholinergic blockers have been reported to inhibit GABA receptor gated chloride ion channels (Schwartz and Mindlin, 1988). These evidences tend speculations to the possible influence of GABA/BZ receptor modulation in learning and memory deficits associated with scopolamine treatment.

In the present study, therefore, an attempt has been made to investigate the behavioural expression of amnesia induced by cholinergic receptor antagonists on passive avoidance step-down task paradigm in mice which has been reported to be a better model for studying the effects of drugs having sedative property (Ichihara et al., 1988). Furthermore, the role of GABA/BZ receptor complex was investigated using various specific and nonspecific agonists, antagonists and inverse agonists acting on GABA/BZ receptors.
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

Radioligand binding studies have demonstrated severe cell loss in cortical and hippocampal glutamatergic nerve terminals (Cowburn et al., 1988; Hardy et al., 1987; Schwacz and Meldrum, 1985) and reduced levels of glutamate in neocortical and pyramidal hippocampal neurons in AD brains (Greenamyre et al., 1985b, 1987). Out of various receptor subtypes through which EAAs mediate their action, NMDA receptors have been amply described in synaptic plasticity, cognitive performance and memory functions (Defeudis, 1989; Lodge, 1989; Maragos et al., 1987). One of the recent observations that NMDA-receptor complex is an essential component for the induction of LTP, is speculated to be an attractive mechanism in learning and memory (Fagg, 1985; Collingridge and Singer, 1990). Involvement of NMDA-receptor in early learning and synaptic specificity in ocular and olfactory learning has been suggested (Monaghan et al., 1989). Several studies with competitive and noncompetitive antagonists, such as ketamine and MK 801 of NMDA receptors have been shown to impair early learning and acquisition in various behavioural paradigms. The noncompetitive NMDA receptor antagonist showed impairment of acquisition for longer duration and does not affect retention of memory (Butelman, 1989a,b; Whinshaw and Auer, 1989; Morris et al., 1986).

Though the growing number of evidences suggest the role of EAA in learning and memory, the interaction with other neurotransmitter systems cannot be ruled out. Recently several group of workers indicated that ACh by interacting
with muscarinic receptors can decrease the threshold of EAA-induced neurotoxicity (Mattson, 1989; Mattson and Kater, 1988b; Defeudis, 1990). Further, McGeer and coworkers (1984) showed that application of NMDA in cortical neurons produced retrograde degeneration of cholinergic neurons in rats which involved the presynaptic glutamatergic dysfunction. In the light of these observations the present study was undertaken to explore the role of MK 801 and ketamine in step-down passive avoidance task paradigm in mice. Further, the effects were compared with scopolamine-induced short-term memory deficit which has long been used as a pharmacological tool to study nootropic effects of drugs.

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

MK 801 is the most potent and selective noncompetitive NMDA receptor antagonist, which appears to act within the ion channel coupled to NMDA receptors now known as phencyclidine (PCP) receptors (Wong et al., 1986; Lodge and Johnson, 1990). MK 801 and related drugs are reported to possess useful effects in progressive neurodegenerative disorders including epilepsy (Woodruff et al., 1988; Forster et al., 1987; Dingledine et al., 1990; Loo et al., 1987). It also produces amnesic locomotor and anticonflict activities (de Belleroche and Rose, 1987; Clineschmidt et al., 1982; Whinshaw and Auer, 1989). The limbic area which is involved in behavioural tolerance to stress and anxiety is densely innervated with glutamatergic receptor system (Robinson and Coyle, 1987) and may play an important role in emotions and cognitive functions (Kulkarni and Verma, 1991).
Besides potent excitatory neurotoxicity, glutamate also acts as a precursor to major inhibitory neurotransmitter, GABA (Fonnum, 1984; Shank and Campbell, 1982). GABA acting through GABA/BZ chloride ionophore complex, plays a predominant role in the neurochemistry of anxiety and stress (Biggio et al., 1984; Concas et al., 1985). Recently it has been suggested that behavioural anxiety is associated with decreased number of GABA and BZ receptors in cerebral cortex (Rago et al., 1988). Several studies have suggested for an interaction of NMDA receptor and GABA/BZ receptor complex (Cheetam et al., 1988; Loscher et al., 1988; Kulkarni and Ticku, 1989; Kulkarni et al., 1990) in the manifestation of behavioural patterns and drug action. This study was designed to investigate the role of BZ receptor ligands namely, diazepam (agonist), FG-7142 (partial inverse agonist) and flumazenil (Ro 15-1788, antagonist) in elevated plus-maze behavioural paradigm, a model of anxiety in rodents (Pellow et al., 1985; Lister, 1987; Harro et al., 1988). Further, the interaction of NMDA receptor antagonist MK 801 with these ligands was investigated to study the interrelationship between GABAergic and glutamatergic systems in anxiety related behavioural expression in rodents.

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

Electrophysiological and radioligand binding studies employing fairly selective agonist (glutamate) and antagonists (2APV, AP5) suggested widespread distribution of NMDA receptor system(s) in neocortical and hippocampal brain
areas which are associated with motor and cognitive functions (Davies et al., 1982; Foster and Fagg, 1987; Fagg, 1985; Cowburn et al., 1988; Young and Fagg, 1990). MK 801 produced cortical desynchronisation and typical cortical complexes (Sagretella et al., 1989). Presence of atropine sensitive and resistant hippocampal EEG activity with low doses of MK 801 have also been reported by Whinshaw and Auer (1989). The present study was designed to investigate EEG changes in rat neocortex and hippocampal brain areas due to NMDA and its modification by noncompetitive NMDA receptor antagonists, MK 801 and ketamine to understand long lasting effect of these agents, if any.

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

The phenomenon of approach-avoidance conflict in rodents on exposure to an elevated (open) maze alley was demonstrated by Montgomery (1958) almost three decades ago. Montgomery 1958 showed that animals clearly preferred the enclosed arm and that the elevated maze alley evoked greater strength of fear than enclosed alley. Based on these observations Pellow and coworkers (1985) and Lister (1987) developed elevated plus-maze apparatus to measure anxiety-related behaviour in rats and mice, respectively.

Based on the natural aversion of mice and rats to high and open spaces, Itoh and coworkers (1990, 1991) reported that transfer latency (TL), the time in which mouse moves from the open arms to the enclosed arms, on the 2nd day onwards was shorter than on the 1st day and suggested that
this can be utilised as a parameter for studying learning and memory processes. They further demonstrated that shortened transfer latency was observed when mice spent even 10 sec in enclosed arm after entering it. However, in anxiety-related study, Pellow and coworkers (1985) showed that aversion to open arms did not habituate over time even on three days exposure of animals on elevated plus-maze. The impairment of learning and memory induced by administration of scopolamine or electroconvulsive shock was reflected by prolonged TL (Itoh et al., 1990) and other amnesic compounds including MK 801 and diazepam (Itoh et al., 1991). But whether the acquisition or consolidation/retention was reflected by this parameter i.e., TL, remains unanswered. Similarly, whether rats can also exhibit the similar behaviour on elevated plus-maze is not known. The present study was attempted to investigate the utility of elevated plus-maze to evaluate learning and memory effect of drugs in rats and mice. Further, the effect of scopolamine and various nootropic agents was studied in the present study.

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

Besides antihypertensive action, the angiotensin converting enzyme inhibitors (ACEIs), captopril and enalapril, have been shown to possess mood elevating properties, which runs parallel to antihypertensive response in patients (Etienne and Zubenko, 1987; Zubensko and Nixon, 1984). The competitive inhibition of ACE activity in the periphery, resulting in decreased rate of conversion of angiotensin I to angiotensin II which result in a
secondary increase in plasma renin activity by suspending negative feedback of renin activity and directly reducing aldosterone secretion. Several workers proposed that an indirect effect of angiotensin II on the hypothalamic-pituitary-adrenal axis by stimulation of adrenocorticotropic hormone (Maran and Yates, 1977; Ramsay et al., 1978) or an indirect effect on median eminence and paraventricular nuclei with influence on the release of other neuropeptides like corticotropin releasing factor with behavioural effects resulting from glucocorticoid action as responsible for memory enhancing effect of captopril and related drugs (Deicken, 1986). Interestingly, piracetam and its derivatives have been shown to have these peripheral mechanisms in memory enhancing effect, which depends on the presence of adrenal steroids (Mondadori and Petschke, 1987; Mondadori et al., 1989). Further, Mondadori and Etienne (1990) demonstrated that though aldosterone-receptor blockade was able to reverse memory enhancing effect of piracetam, it was not the case with ACEIs. Several reports recently suggested that captopril has unique feature as it facilitates the memory retrieval and the effect was more pronounced than other piracetam-like agents. However, enalapril lacks the memory enhancing effect (Mondadori and Etienne, 1990).

In the present study attempts were made to demonstrate the nootropic effect of ACEIs, captopril and enalapril using step-down passive avoidance task paradigm and elevated plus-maze apparatus. Further, the effect of these agents on scopolamine- and MK 801-induced acquisition and retention deficits was studied and the two paradigms were compared to understand retention facilitatory influence of nootropics.