The renin–angiotensin system (RAS) mediates several classic physiologies including body water and electrolyte homeostasis, blood pressure, sexual behaviors, and the regulation of pituitary gland hormones. These functions appear to be mediated by the angiotensin II (Ang II)/AT1 receptor subtype system (Wright et al., 2008). A second subtype, AT2, has also been implicated in the regulation of blood pressure, renal function, and vascular growth (de Gasparo et al., 1999). Beside peripheral RAS which control blood pressure, a separate RAS exist in central nervous system (Wright et al. 1997) where it regulates numerous physiological and behavioral processes including cognitive functions (Gard, 2002). However, the exact role played by central RAS in learning and memory is not yet clear.

In the recent years, it has been found that drugs affecting RAS i.e. angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor (ATR) blockers showed memory improvement in animals and human being (Fogari et al., 2004; Jenkins et al., 2007). Further, it has been found that Ang II is associated with disturbed cholinergic function (Barnes et al., 1990) and oxidative stress (Griendling et al., 1994), the important factors implicated in pathophysiology of dementia (Pratico, 2002). Clinical studies showed that benefits of ACE inhibitors (ACEIs) and ATR blockers are not just confined to decreasing blood pressure in hypertensive patients but they also improve overall quality of life by affecting some other aspects of physiology (Tedesco et al., 1999).

In healthy male subjects, single doses of captopril have been shown to improve short-term memory (Currie et al., 1990). Use of antihypertensive drugs, particularly ACEIs and ATR blockers, is associated with a lower rate of cognitive decline in older adults, including those with Alzheimer Disease (AD).
(Gard P.R. 2002; Braszko et al., 2003). Further, chronic AT1 receptor blockade by losartan improved cognitive function in elderly hypertensive patients. In animal models of memory deficit also ACEIs and ATR blockers showed improvement. The scopolamine induced impairment in passive avoidance and Morris water maze task was reversed by captopril or ceranapril. Perindopril, an ACEI, have a positive influence on memory in swim maze task in rats (Jenkins et al., 2007). In another study, rats made hypertensive by Goldblatt method, had a poor acquisition, retrieval of the learned behavior due to possible disturbance in memory consolidation process and this state was reversed with ACEI enalapril and AT1 receptor antagonist losartan (Srinivasan et al., 2005). It has been reported that decrease in endogenous Ang II activity in the brain by ACEIs and ATR blockers result in improved cognitive performance by enhancing cGMP pathways. Very recently, Kumaran et al., (2008) have shown the involvement of ACE in cerebral hypoperfusion induced anterograde memory impairment and cholinergic dysfunction in rats. Moreover, in our recent publication, we have reported that treatment with candesartan ameliorates oxidative stress, cholinergic dysfunction and memory impairment in intracerebral streptozotocin induced model of dementia (Tota et al., 2009). Further treatment with perindopril has been reported to reduce beta amyloid induced impairment in memory in rats (Hou et al., 2008). From above discussion, it can be deduced that suppression of RAS by ACEIs and ATR blockers exerts a favorable effect on memory.

It is well known that the central cholinergic system plays an important role in learning and memory. A substantial body of literature suggests that learning and memory deficits in AD are attributed to decline in the cholinergic systems of the basal forebrain. The degree of cholinergic neurodegeneration in patients with
AD correlates well with functional loss (Carli et al., 2000). Based on the cholinergic hypothesis, many attempts have been made to reverse cognitive deficits by increasing brain cholinergic activity through the use of acetylcholinesterase inhibitors, acetylcholine precursors and cholinergic agonists. In fact, a selective acetylcholinesterase inhibitor, donepezil, has been used for the treatment of mild AD (Doody, 1999). RAS is closely intertwined with cholinergic system and this is accentuated with the fact that elevated brain AngII levels interfere with acetylcholine (ACh) release that in turn interferes with cognitive processing (Barnes et al., 1990). But, to the best of our knowledge, no study has explored the role of ACEIs and AT1 receptors antagonists on the learning & memory in ethylcholine aziridinium (AF64A), a selective cholinergic neurotoxin, induced model of dementia. In animals, cholinergic deficits can be induced by administration of selective cholinotoxin AF64A. It has been reported that intracerebroventricular (ICV) administration of AF64A in rodents induces memory deficit along with selective decline in ACh, acetylcholinesterase (AChE) and cholineacetyltransferase (ChAT) content in the brain (Murai et al., 1994; Hanin, 1996).

Free radicals and oxidative stress have been implicated as the prime candidates mediating the behavioral impairments and memory deficits in AD (Cantuti-Castelvetri et al., 2000). Though it is not clear precisely how oxidative stress exerts its deleterious effects, but some of this damage may include lipid and protein peroxidation, increase in DNA oxidation products, and deficits in calcium regulatory mechanisms that may eventually lead to cell death (Pratico, 2002). Thus, antioxidants have been proposed as having putative positive benefits in altering, reversing or forestalling the neurobehavioral decrements (Nakajima et al., 2009).
Recent preclinical research has demonstrated a link between RAS and oxidative stress both in periphery and brain. Ang II has been shown to stimulate production of excessive amounts of reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and peroxynitrite. Binding of Ang II to AT1 receptor activates NADPH oxidase which plays a pivotal role in the development of oxidative stress (Griendling et al., 1994). This overproduction of ROS has been implicated in neurodegenerative diseases and aging (Pratico, 2002). Moreover ACEIs and ATR blockers have been reported to reduce oxidative stress in aged rats. Recently, AT1 receptor blocker, candesartan, exhibited antioxidative action as evidenced by reduced lipid peroxidation and elevated antioxidant enzyme levels in brain (Tota et al., 2009). Antioxidant action of ATR blockers is further strengthened by a study which showed oral administration of valsartan for 4 weeks significantly attenuated the increased expression of NADPH oxidase together with inhibition of oxidative stress (Nakayama et al., 2005). But so far no study has explored beneficial effects of ACEIs and ATR blockers on memory impairment and brain oxidative damage induced by central injection of colchicine in rodents. ICV administration of colchicine in rats has been shown to induce persistent memory deficit coupled with increased oxidative stress and cholinergic dysfunction demonstrating its usefulness as an experimental tool to study pathophysiological aspects of dementia (Yu et al., 1997; Kumar et al., 2007a, b, c).

Therefore, the present study utilized AF64A and colchicine induced memory impairment models to elucidate the mechanism of modulation of memory function by central RAS especially in context of oxidative stress and cholinergic dysfunction. These factors reported to play an important role in pathophysiology of clinical dementia. The outcome of this work will have a greater translational
relevance in the treatment of cognitive impairment associated with cardiovascular disease and metabolic syndrome. Therefore, the precise information of involvement of central RAS in learning and memory will help in focusing those medications which apart from acting as antihypertensive can also impart neuroprotection as has been observed in PROGRESS clinical trial with perindopril, an ACE inhibitor.
1.2. References:


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