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MEMORY RECUPERATIVE POTENTIAL OF RIFAMPICIN IN ALUMINUM CHLORIDE-INDUCED DEMENTIA: ROLE OF PREGNANE X RECEPTORS

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Abstract—The present study has been designed to investigate the potential of rifampicin [Pregnane X receptors (PXR) agonist] in experimental dementia. Aluminum chloride ($AlCl_3$) [100 mg/kg, *p.o.* for 42 days] was administered to Wistar rats ($n = 6$) to induce dementia. Morris water maze (MWM) test was used to assess learning and memory and rota rod test was used to assess locomotor activity of the animals. A battery of biochemical tests and histopathological evaluation using hematoxylin and eosin (H&E) and Congo Red stains were performed at the end of the study. $AlCl_3$-treated rats demonstrated impaired cognition and locomotor activity on MWM apparatus and rota rod test, respectively. These animals exhibited a significant rise in acetylcholinesterase (AChE) activity (138 ± 3.6), thiobarbituric acid reactive species (TBARS) level (15 ± 1.6), nitrite (56 ± 2.4) level and myeloperoxidase (MPO) activity (4.1 ± 0.9) along with decline in reduced glutathione (GSH) level (22 ± 1.3) in comparison to the control group ($p < 0.05$). Further the H&E and Congo Red-stained cerebral cortex sections of $AlCl_3$-treated rats indicated severe neutrophilic infiltration and amyloid deposition. Rifampicin-treated $AlCl_3$-rats exhibited significant attenuation in memory deficits, biochemical parameters like AChE activity (33 ± 1.4), TBARS level (4.1 ± 1.0), nitrite level (64 ± 2.6), MPO activity (3.6 ± 1.0) and GSH level (53 ± 2.4) along with improved histopathological alterations and locomotor activity when compared with $AlCl_3$-treated rats ($p < 0.05$). Combined administration of ketoconazole (a PXR antagonist) and rifampicin to $AlCl_3$-treated animals reversed the rifampicin-induced protective effects. Therefore the results obtained from the study indicate a defensive role of rifampicin in memory dysfunction which may probably be due to its anti-cholinesterase, anti-oxidative, anti-inflammatory and amyloid lowering effects. Moreover the study speculates the potential of PXR in the pathophysiology of dementia which is subject to further evaluation.
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Abbreviations: Aβ, amyloid beta; AChE, acetylcholinesterase; $AlCl_3$, aluminum chloride; BBB, blood–brain barrier; DMSO, dimethyl sulfoxide; ELT, escape latency time; GSH, glutathione; H&E, hematoxylin and eosin; MPO, myeloperoxidase; MWM, Morris water maze; P-gp, P-glycoprotein; PXR, Pregnane x receptors; TBARS, thiobarbituric acid reactive species; TSTQ, time spent in target quadrant.

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Key words: dementia, aluminum chloride, rifampicin, pregnane X receptors, amyloid beta, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder signified by age related impairment in cognition and memory and is the most familiar cause of dementia (Budimir, 2011; Ohyagi and Miyoshi, 2013). Pathologically AD is characterized by senile plaques which are extracellular proteinaceous deposits of amyloid beta (Aβ) peptide and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein (Ivan et al., 2013; Meraz Rios et al., 2010). Synaptic loss, degeneration, oxidative stress and neuroinflammation are also the important hallmarks of AD pathology which ultimately induce neuronal dysfunction and cell body loss (Jennifer and Chris, 2013). The plaques and tangles get accumulated in brain regions associated with learning, memory and emotional behavior such as the entorhinal cortex, hippocampus, basal forebrain and amygdala (Budimir, 2011). Disturbance between clearance and production of Aβ results in its accumulation within the brain. Studies have indicated that majority of AD patients, including late onset cases (sporadic AD) and some familial AD cases, do not exhibit augmented Aβ production (Deane and Zlokovic, 2007). Perhaps increasing evidence reveal that increased Aβ level is a consequence of its defective clearance across the blood–brain barrier (BBB). Reports have signified that the brain contains high concentration of transition metals like zinc, iron, copper and aluminum which contribute toward the neuronal activity within the synapse and help in the functioning of metalloproteins (Budimir, 2011). Several reports have revealed that disturbed metal ion homeostasis due to excessive absorption of metals, genetic defects, aging and drug interactions may culminate into severe neurotoxic states such as AD (Myhre et al., 2013; Ohyagi and Miyoshi, 2013). Various experiments have established aluminum neurotoxicity in different animal models of AD, amyotrophic lateral sclerosis and Guam Parkinson's dementia (Kurland, 1988; Sumathi et al., 2011). The exposure of aluminum to humans occurs since it is extensively employed in industries, in manufacturing clays, glasses and alum and in pharmacological agents including antacids and antiperspirants. Aluminum easily penetrates the BBB via specific high-affinity receptors for transferrin (TfR)

(Kumar et al., 2011). Evidences indicate that excessive intake of aluminum causes the deposition of Aβ in the central nerve cells, enhances amyloid precursor protein expression, induces protein misfolding and self aggregation of highly phosphorylated cytoskeletal proteins (Kumar et al., 2011), generates oxidative stress conditions and increases acetylcholinesterase (AChE) activity (Castorina et al., 2010; Kawahara and Kato-Negishi, 2011; Naidu et al., 2013). Current therapeutic strategies used for symptomatic relief from AD include AChE inhibitors (donepezil, rivastigmine, galantamine), glutamate regulator memantine, antioxidants, calcium antagonists, metal chelators, non-steroidal anti-inflammatory drugs and Muscarinic receptor antagonists (Birks et al., 2009; Konstantina et al., 2013). However newer agents need to be developed that delay the onset and limit the progression of disease. An additional approach may be to investigate the drugs that are accepted for other indications but which may also interact with AD-related pathophysiological pathways. Pregnane X receptors (PXR), a nuclear receptor, is involved in identifying foreign toxic substances and up-regulating the expression of proteins involved in the detoxification and clearance of these substances from the body (Kliewer et al., 2002) and have been isolated in rat brain capillaries (Bauer et al., 2004; Julia et al., 2013). They have been designated as the master regulators of xenobiotic defense since they control the metabolism and efflux transport of xenobiotics (Banerjee et al., 2013). It has been suggested that ligand activation of PXR, up-regulates the expression of P-glycoprotein (P-gp, Abcb1) the best known (ATP binding cassette protein) ABC transporters that can stimulate the efflux of Aβ from the brain (Scheer, 2010). P-gp is located at the luminal side of brain endothelial cells and plays a vital role in the extrusion of drugs and toxins from the brain (Gary et al., 2013). Studies employing P-gp null mice and isolated brain capillaries have suggested that clearance of Aβ across BBB is governed by P-gp (Kuhnke et al., 2007). Rifampicin which is clinically utilized as an anti-tubercular drug, also acts as an agonist of PXR (Haslam, 2008; Scheer, 2010). Protective effects of rifampicin against AD have been previously reported (Tomiyama et al., 1996; Abuznait et al., 2011). A recent study has demonstrated that wild-type mice treated with rifampicin potentially up-regulates the expression of P-gp at the BBB (Abuznait et al., 2011). However the mechanism underlying the up-regulation of P-gp by rifampicin and its protective effect in AD is not yet clearly understood. Clinical studies have also evaluated the therapeutic potential of rifampicin in patients suffering from AD. Loeb et al. have reported the results of a study examining the outcome of rifampicin (300 mg) and doxycycline (200 mg) in mild-to-moderate AD. The primary outcome was alterations in Standardized Alzheimer's Disease Assessment Scale cognitive subscale (SADAScog) at 6 months and 12 months along with significant changes in tests of dysfunctional behavior, depression, and functional status at 12 months (Loeb et al., 2004). This study suggested that therapy with doxycycline and rifampin may have a therapeutic role in patients with mild-to-moderate AD. The outcome of another multicenter, blinded, factorial, randomized, controlled trial enrolling over 406 patients with mild-to-moderate AD, was recently reported (Molloy et al., 2013). However, 12 months of treatment with doxycycline (100 mg) or rifampicin (300 mg), alone or in combination, showed no beneficial effects on cognition or function in AD in this study (Molloy et al., 2013). In the present investigation we have made efforts to evaluate the effects of rifampicin in experimental dementia and to possibly suggest the role of PXR in dementia.

EXPERIMENTAL PROCEDURES

Experimental animals

Wistar rats of either sex (180–200 g) were employed for the study and sustained in the departmental animal house. Rats were maintained at standard laboratory pellet chow diet and water *ad libitum*. The rats were exposed to 12-h-light and 12-h-dark cycle. Animals were acclimatized to laboratory conditions prior to experimental study. The experiments were performed between 09:30 and 17:30 h in semi sound proof laboratory conditions. The experimental protocol was duly approved and the experiments were performed in accordance with guidelines of institutional animal ethics committee (IAEC) (Reg. No. 1201/a/08/CPCSEA). Adequate measures were taken to minimize pain and discomfort with animal experimental procedures. Animals were taken care as per the guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Ministry of environment and forest, Government of India.

Drugs and reagents

All reagents and chemicals used in this study were of analytical grade and were freshly prepared before use. Rifampicin (Unichem laboratories Ltd., Maharashtra, India) and ketoconazole (Surya life sciences Ltd., Gujarat, India) were procured as gift samples and were dissolved in dimethyl sulfoxide (DMSO, 1% v/v) for administration to the animals. Donepezil was purchased from Sigma Aldrich (Mumbai, India).

Laboratory models

Interoceptive behavioral model. Aluminum chloride ($AlCl_3$)-induced dementia. $AlCl_3$ was dissolved in distilled water and administered orally at a dose of 100 mg/kg/day for a period of 42 days (6 weeks) (Kumar et al., 2011). Dose volume of 5 ml/100 g body weight was considered for administration to the animals.

Exteroceptive behavioral model. Morris water maze (MWM) test. MWM test was employed to assess learning and memory of the animals (Morris, 1984). MWM is a swimming based-model where the animal learns to escape on to a hidden platform. It consisted of large circular pool (150 cm in diameter, 45 cm in height, filled to a depth of 30 cm with water at 28 ± 1 °C). The

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