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Research Article

Combination of Cholecalciferol and Rivastigmine Improves Cognitive Dysfunction and Reduces Inflammation in STZ Induced Alzheimer's Model Experimentally in Rats

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Abstract. *Background.* Alzheimer's disease (AD) is a multifactorial disease, and the mechanisms underlying its pathogenesis are complex. Several studies have implicated amyloid β (Aβ) accumulation, hyperphosphorylated tau, oxidative stress, metal dysregulation, mitochondrial dysfunction, and inflammatory response as major interconnecting networks leading to neuronal and synaptic degeneration. *Aim.* The present study was designed to evaluate the neuroprotective effects of cholecalciferol (vitamin D3) and rivastigmine, alone and in combination, on the progression of Alzheimer's disease induced by intracerebroventricular administration of streptozotocin and possible anti-inflammatory mechanisms of action. *Materials and Methods.* Adult male albino rats were divided randomly into five groups: group I acts as control. In group II (Alzheimer's group), Alzheimer's was induced by single bilateral intracerebroventricular injection of STZ (3mg/kg). Group III (cholecalciferol treated group) rats received cholecalciferol (42 IU/kg, s.c.) for 21 days immediately after ICV-STZ injection. Group IV (rivastigmine-treated group) Alzheimer's rats received rivastigmine (1.5 mg/kg, s.c.) for a period of 21 days immediately after ICV-STZ injection. Group V (rivastigmine + cholecalciferol) rats received rivastigmine plus cholecalciferol for 21 days immediately after ICV-STZ injection. Cognitive impairment was evaluated by Morris Water Maze test. Serum and brain pro-inflammatory mediators (TNF-α and IL-1β) were measured. Also, brain level of acetylcholine was measured. Moreover, serum and brain levels of amyloid beta peptide were evaluated. *Results.* After 21 days of induction of Alzheimer's, the ICV-STZ induced significant impairment of memory and declined cognition as manifested by the increased latency period in Morris Water Maze test. Serum and brain levels of TNF-α, IL-1β, and amyloid peptide were significantly increased. On the other hand, brain acetylcholine level was significantly decreased compared with the control group. All these parameters were significantly improved by rivastigmine alone and in combination with vitamin D3. These results clearly pointed to the pivotal role of rivastigmine and vitamin D3 in STZ induced Alzheimer's in rats by improving inflammatory status. *Conclusion.* The present study concludes the neuroprotective effect of rivastigmine and vitamin D3 in Alzheimer's disease rats by reducing inflammatory mediators (TNF-α and IL-1β) and amyloid β peptide and improving acetylcholine levels in brain.

Keywords: Alzheimer's, ICV-STZ, vitamin D3, rivastigmine, TNF-α.

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1. Introduction

AD is a common neurodegenerative disease that is characterized by progressive impairment of memory and other cognitive functions leading to complete incapacity and death. It is the leading cause of dementia, accounting for about 50% of all cases worldwide [46].

AD is a multifactorial disease, and the mechanisms underlying its pathogenesis are complex. Several studies have implicated amyloid β (Aβ) accumulation, hyperphosphorylated tau, oxidative stress, metal dysregulation, mitochondrial dysfunction, and inflammatory response as major interconnecting networks leading to neuronal and synaptic degeneration [47].

The presence of inflammatory process seems to be playing important role in the progression of the disease. It has been observed that increased levels of proinflammatory cytokines, including tumor necrosis factor alpha, interleukin 1B (IL-1B), interleukin 6 (IL-6), and interferon γ (IFN-γ), may suspend phagocytosis of amyloid Aβ in brains of patients with AD [41].

Recent studies have identified that low serum concentrations of vitamin D can substantially increase the risk of AD [20]. In addition to modulating neurite growth, proliferation, differentiation, and calcium signaling, vitamin D has also been implicated in neuroprotection and may alter neurotransmission and synaptic plasticity [15].

Also, vitamin D regulates the amyloid beta metabolic aspects. The promising role of 1, 25$(OH)_2$D in recovering the ability of the macrophages to phagocytose soluble amyloid β protein came to surface in a very recent work in macrophages from patients with Alzheimer's disease [23]. Another study has shown its ability to attenuate amyloid β (Aβ) accumulation by stimulating phagocytosis of the Aβ peptide [1] and enhancing brain-to-blood Aβ efflux across BBB [36], resulting in a decreased number of amyloid plaques [19].

Rivastigmine is a cholinesterase inhibitor (ChEI) with a structural formula different from that of currently available ChEIs. Rivastigmine is classified as an intermediate-acting or pseudo-irreversible agent due to its long inhibition on AChE of up to 10 hours. Preclinical biochemical studies indicated that rivastigmine has central nervous system selectivity over peripheral inhibition. It ameliorated memory impairment in rats with forebrain lesions.

The present study was designed to evaluate the neuroprotective effects of cholecalciferol (vitamin D3) and rivastigmine, alone and in combination, on the progression of Alzheimer's disease induced by intracerebroventricular administration of streptozotocin and possible mechanisms of action.

2. Materials and Methods

2.1. Drugs and chemicals

- Cholecalciferol (vitamin D), white powder, was purchased from Sigma, St. Louis, MO, USA, dissolved in ethanol. Each .025mcg is equal to 1 I.U. of vitamin D3.
- Rivastigmine, white powder, was purchased from Novartis Co., Cairo, Egypt.
- Streptozotocin (STZ), powder creamy white, was purchased from Sigma Chemicals co., USA, dissolved in citrate buffer (pH 4.5) according to the method of Burwell (2001).
- Thiopental sodium (vial) was purchased from E.I.P.I. CO., Egypt.

2.2. Animals

Fifty adult albino rats weighing (120-150gm) were used. They were brought from experimental animal breeding farm, Helwan, Cairo. All animals were housed in controlled laboratory conditions at 20-25C in a 12h light/dark cycle and had free access to standard laboratory chow (El-Nasr Company, Abou-Zaabal, Cairo, Egypt) and water. They were acclimatized for one week and caged (10/cage) in fully ventilated room (at room temperature) in Pharmacology Department, Benha Faculty of Medicine. All experimental protocols were approved by the ethics committee of Benha University.

2.3. Study design

After acclimatization for 1 week, rats were randomly divided into five experimental groups, with 10 rats each, and treated for 3 weeks as follows:

Group I: normal control rats: rats did not undergo any surgical operation.

Group II: Alzheimer's untreated group: streptozotocin (STZ) was administrated by single injection (intracerebroventricular) bilaterally (3mg/kg) (1.5mg/kg per each ventricle) [29].

Group III: rivastigmine treated group: rivastigmine (1.5 mg/kg/day, s.c.) was administered once daily for 21 days after injection of STZ [44].

Group IV: cholecalciferol treated group: vitamin D3 (42I.U/kg, s.c.) was administered for 21 days after injection of STZ [48].

Group V: rivastigmine (1.5mg/kg/day) and cholecalciferol (42 I.U/kg, s.c.) treated group for 21 days after injection of STZ [44, 48].

2.4. Experimental design

Rats were anaesthetized by thiopental sodium (40mg/kg intraperitoneal) and scalp washed by using iodine solution, incision was made on midline, and a hole was made through the skull (0.8 mm post bregma). The STZ groups received bilateral ICV injection of STZ (3mg/kg) (1.5mg/kg, in each ventricle). The rats were observed daily for behavior and health conditions. Each group was subjected to the following evaluations.

2.4.1. Behavioral parameters

- *Morris Water Maze test*

  All the behavioral data were recorded before surgery and on day 21 in all groups. Spatial learning was estimated as a measure of cognitive function of mice three weeks after injection of STZ by the Morris water maze test as described previously by Tsukuda et al. (2009). The maze was a round black pool with 150 cm diameter, 60 cm height. The maze was filled with water to a depth of 40 cm with temperature of about 23˚C. An escape platform of 10 cm diameter was located 2 cm beneath the surface of the water at a fixed position in the center. Each mouse was trained 5 times a day at 20-minute intervals for 5 consecutive days. The test was performed blindly. In each trial, mice were given

120 seconds to find the platform. The time spent to find the platform (escape latency) was recorded. Mean swim latency for all of the trials on each day in each group was calculated.

2.4.2. Biochemical parameters

At the end of the experiment, blood samples were collected from the retrobulbar sinus of rat's eye by using heparinized capillary tubes. Two ml of blood were delivered in clean, dry test tubes and allowed to clot at room temperature. The serum was separated by centrifugation at 2000 rounds/minute for 10 minutes. Sera were kept in tightly closed vials at -20ºC until used to measure the biochemical parameters. Then, rats were sacrificed and brain dissected out, washed with saline solution, dried, and weighed. Then they were homogenized immediately in solution containing Tris-Hcl (50 mM, pH 7.4) and sucrose (300 mM). The tissue homogenate was centrifuged at 10000 RPM for 10 min at 4˚C, and the supernatant was separated for measuring brain total protein concentrations to express the concentration of different brain parameters per mg protein according to the method of Lowry et al. (1951).

- *Serum and brain level of tumor necrosis factor-alpha*

  Estimation of serum and brain TNF-α was determined using a commercially available kit (Medgenix TNF-α ELISA Kit) according to the manufacturer's instructions.

- *Serum and brain level of IL-1β*

  Estimation by ELISA technique using (Ray Bio ® Mouse IL-1β) by following the manufacturer's instruction according to the protocol of Howord and O'Gara (1992).

- *Acetylcholine (ACh) levels in brain tissue*

  Brain Ach levels were measured by the colorimetric method, a choline/acetylcholine assay kit (BioVision Inc., California, USA), and expressed as µmol/mg protein according to the method of Ellman et al. (1961).

- *Estimation of serum and brain levels amyloid B (Aβ)*

  Aβ were measured in serum and brain tissue homogenates using ELISA Kit [4] according to the manufacturer's instructions.

3. Statistical Analysis [13]

Data are represented as mean ± SEM. Multiple comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's test as a post-hoc test. The 0.05 level of probability was used as the criterion for significance. All statistical analyses were performed using GraphPad InStat version software package.

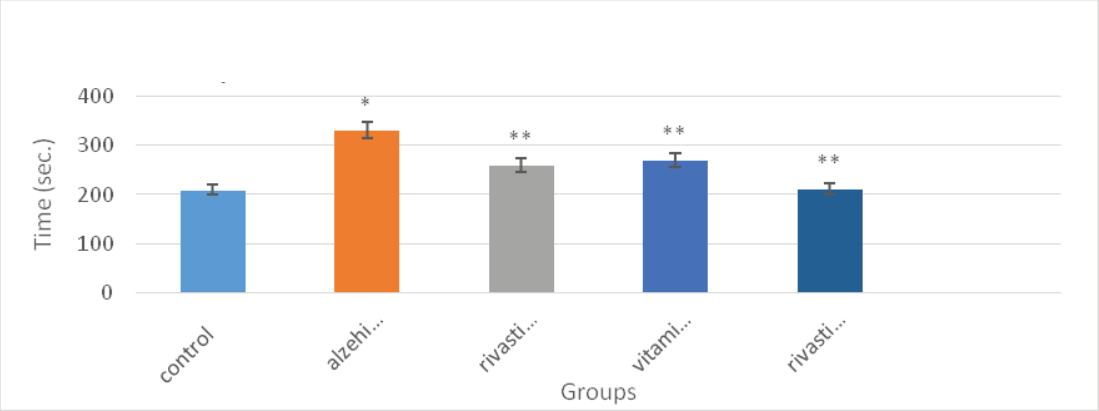

Figure 1: Effects of rivastigmine (1.5mg/kg) and vitamine D3 (42 IU/kg) on latency time in Morris water Maze in rats with STZ-induced alzheimer. *: significant difference from control group. **: significant difference from Alzheimer's group.

4. Results

4.1. Effect of rivastigmine and vitamin D3 on behavior changes

In the present study, ICV injection of STZ induced Alzheimer's model as evidenced by impairment of cognition function in the form of significant increase ($p < 0.05$) in latency time of Morris water maze test (Figure 1).

Pretreatment with cholecalciferol at a dose of 42 IU/kg at the same time of induction of Alzheimer's model is manifested by the significant decrease ($p < 0.05$) in latency time in cholecalciferol pretreated group when compared with Alzheimer's group (Figure 1).

Pretreatment with rivastigmine at a dose of 1.5mg/kg produced significant ($p < 0.05$) decrease in latency time in rivastigmine pretreated group when compared with Alzheimer's group (Figure 1).

Pretreatment with cholecalciferol plus rivastigmine produced marked improvement in learning and cognition manifested by the significant decreases ($p < 0.05$) in latency time compared with Alzheimer's group (Figure 1).

4.2. Biochemical parameters

After 21 days of induction of Alzheimer's, estimation of TNF-α and IL-1β serum and brain levels show that ICV injection with STZ resulted in significant increase ($p < 0.05$) in both parameters compared to the control group (Figures 2, 3, 4, and 5).

Pretreatment with rivastigmine at a dose of 1.5mg/kg at the same time of induction of Alzheimer's produced marked decrease ($p < 0.05$) in serum TNF-α andIL-1β in rivastigmine pretreated group when compared with the control group (Figures 2, 3, 4, and 5).

At the same time, pretreatment with cholecalciferol at a dose of 42 IU/kg produced significant decrease ($p < 0.05$) in TNF-α and IL-1β serum levels ($p < 0.05$) as compared to Alzheimer's group (Figures 2, 3, 4, and 5).

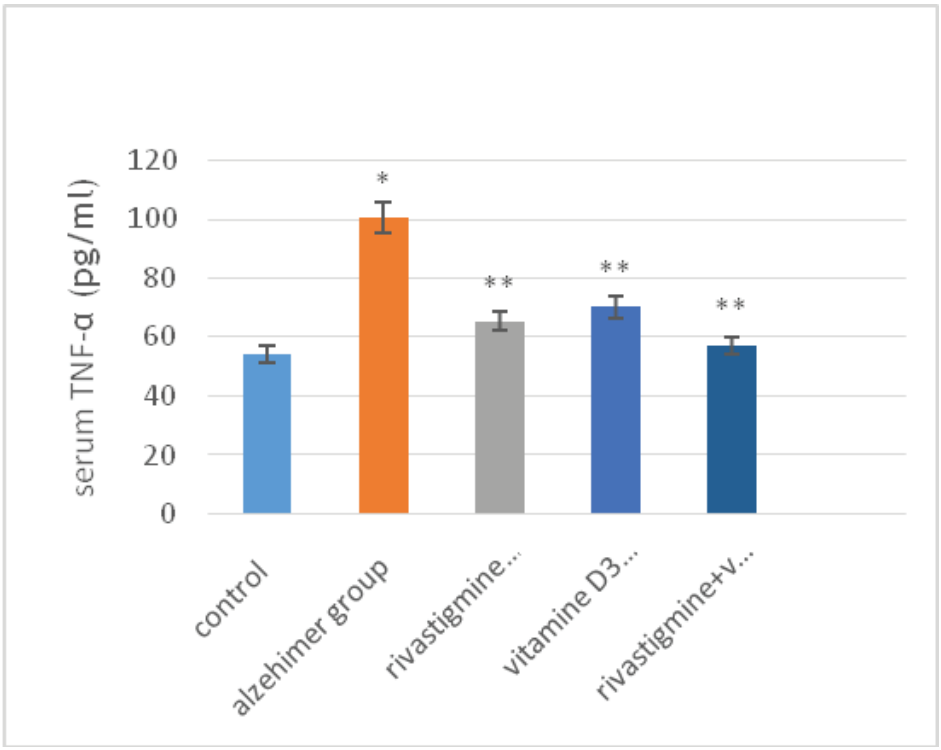

Figure 2: Effect of rivatigmine and vitamin D3 on serum TNF-α level in ICV-STZ induced alzheimer model in rats.

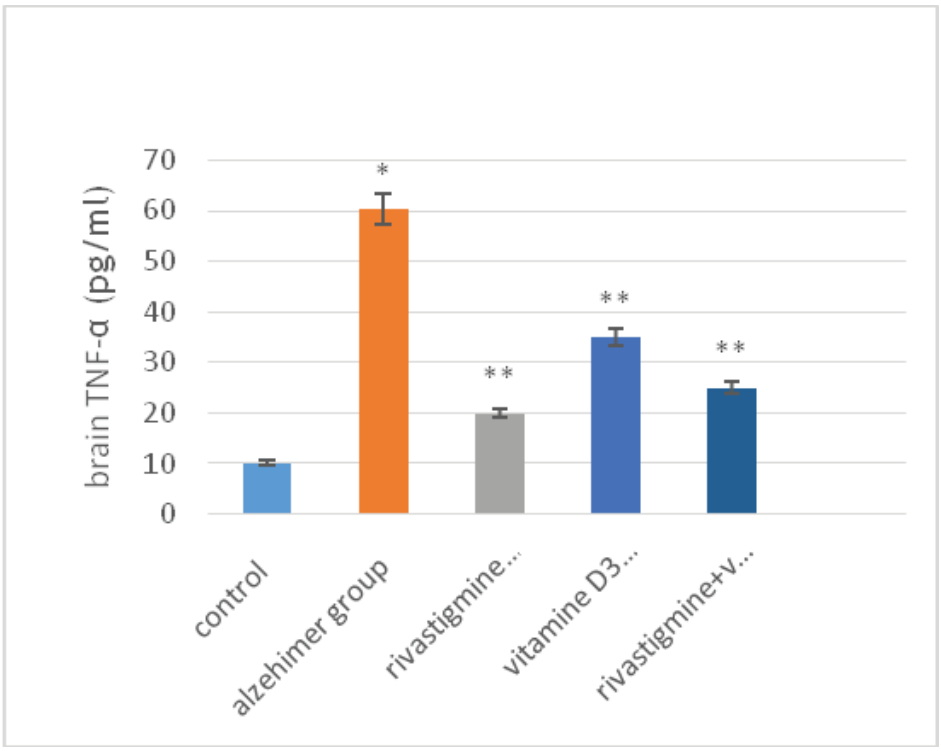

Figure 3: Effect of rivatigmine and vitamin D3 on brain TNF-α level in ICV-STZ induced alzheimer model in rats.

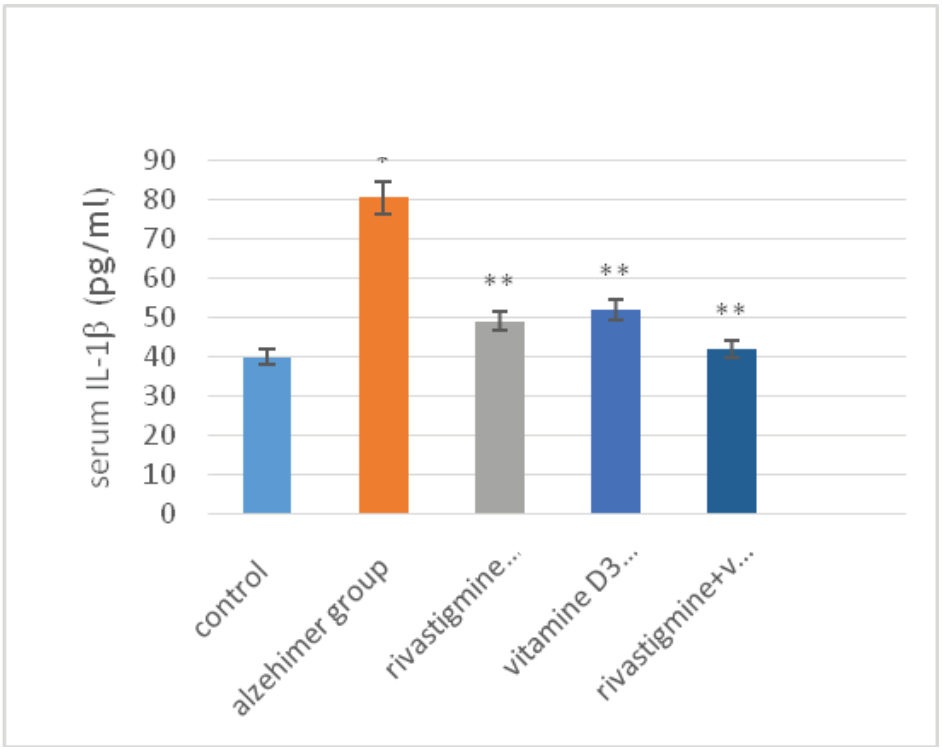

Figure 4: Effect of rivatigmine and vitamin D3 on serum level IL-1β in ICV-STZ induced alzheimer model in rats.

Table 1: Effects of rivastigmine and vitamin D3 on brain Ach levels with ±SEM in all studied groups.

Parameters Groups	Acetylcholine (Ach) (umol/mg protein)
Control	5.52 ± 0.23
Alzheimer's group	0.31 ± 0.01*
Rivastigmine group	5.16 ± 0.22**
Cholecalciferol group	4.8 ± 0.31**
Rivastigmine + cholecalciferol group	5.44 ± 0.42**

*significant difference from control group.

**significant difference from Alzheimer's group.

Furthermore, pretreatment with rivastigmine plus vitamin D3 produced marked improvement in TNF-α and IL-1β serum levels ($p < 0.05$) compared with Alzheimer's group (Figures 2, 3, 4, and 5).

4.3. Effect of rivastigmine and vitamin D3 on acetylcholine levels in brain tissue

As regards acetylcholine, estimation of Ach levels shows that ICV-STZ administration resulted in significant decrease ($p < 0.05$) compared to the control group (Table 1, Figure 4).

Pretreatment with rivastigmine at a dose of 1.5mg/kg at the same time of induction of Alzheimer's produced marked increase in Ach brain levels ($p < 0.05$) compared with Alzheimer's group (Table 1, Figure 6).

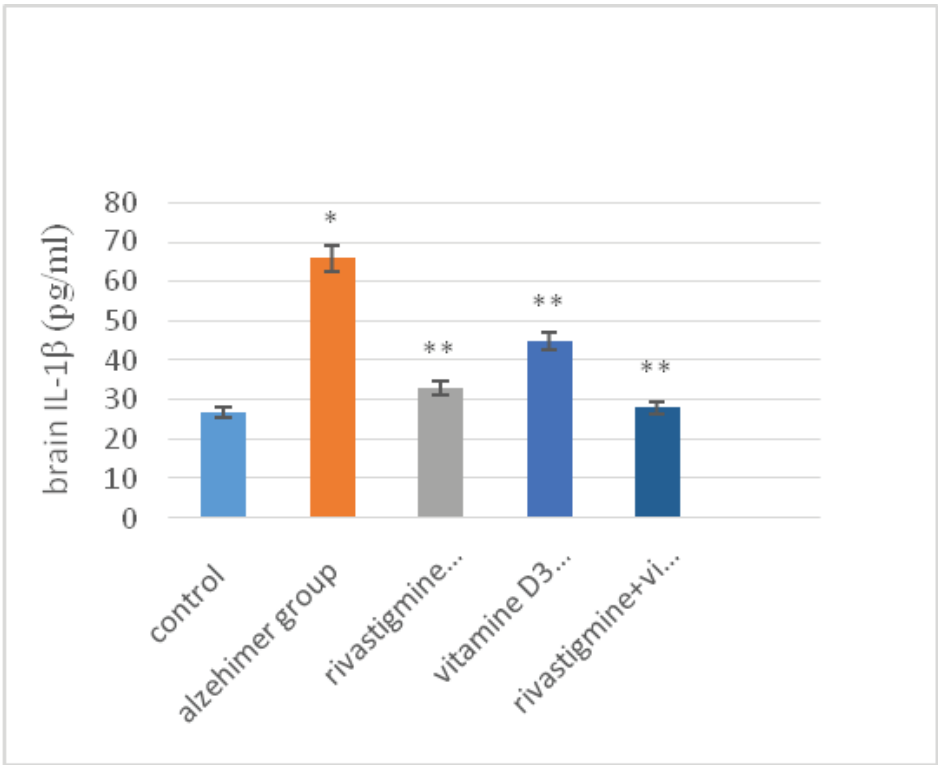

Figure 5: Effect of rivastigmine and vitamin D3 on brain IL-1β level in ICV-STZ induced alzheimer model in rats. *: significant difference from control group. **: significant difference from Alzheimer's group

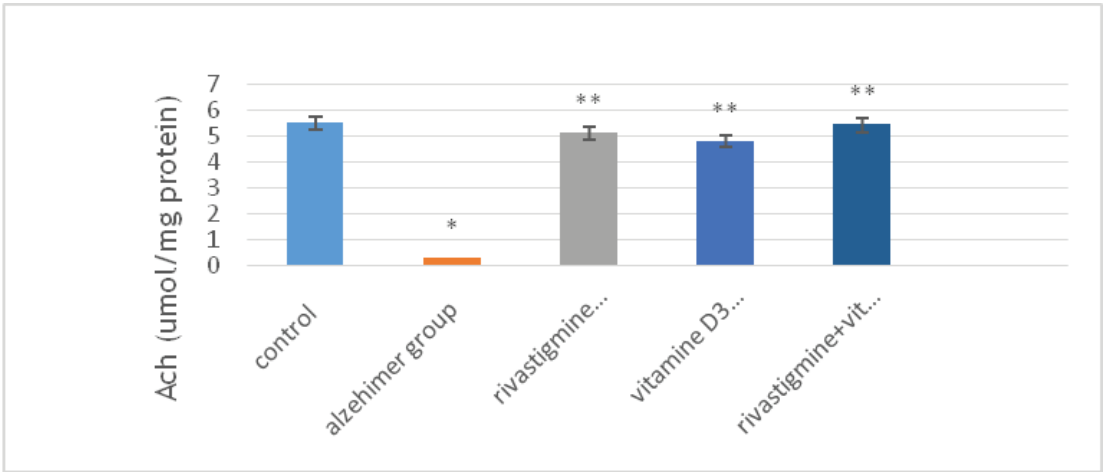

Figure 6: Effect of rivatigmine and vitamin D3 on brain Acetylcholine level in ICV-STZ induced alzheimer model in rats.

At the same time, pretreatment with vitamin D3 at a dose of 42 IU/kg produced significant increase ($p < 0.05$) in Ach brain levels compared to Alzheimer's group (Table 1, Figure 6).

Meanwhile, pretreatment with rivastigmine and vitamin D3 produced marked increase in Ach ($p < 0.05$) compared with Alzheimer's group (Table 1, Figure 6).

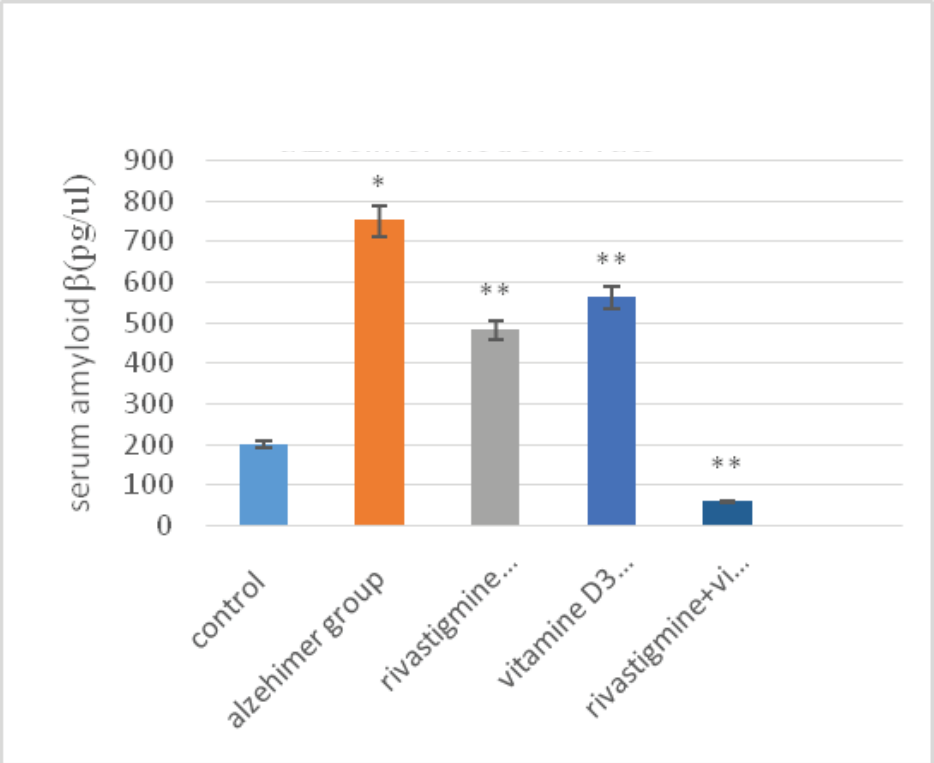

Figure 7: Effect of rivatigmine and vitamin D3 on serum amyloid β level in ICV-STZ induced alzheimer model in rats.

4.4. Effect of rivastigmine and vitamin D3 on serum and brain levels of amyloid β

As regards serum and brain amyloid β, estimation of amyloid β levels shows that ICV-STZ administration resulted in significant increase ($p < 0.05$) in both serum and brain levels compared to the control group (Figures 7, 8).

Pretreatment with rivastigmine at a dose of 1.5mg/kg at the same time of induction of Alzheimer's produced marked decrease in brain and serum levels ($p < 0.05$) compared with Alzheimer's group (Figures 7, 8).

At the same time, pretreatment with vitamin D3 at a dose of 42 IU/kg produced significant decrease ($p < 0.05$) in brain and serum levels of amyloid β levels compared to Alzheimer's group (Figures 7, 8).

5. Discussion

Alzheimer's disorder (AD) is a neurodegenerative disorder characterized by progressive degeneration of hippocampal and cortical neurons that lead to impairment of memory and cognitive ability. It is the most common cause of dementia [46]. Impairment of the short term memory is the first clinical feature, and when the condition progresses, more cognitive abilities are impaired, such as the ability to calculate and use common objects and tools [14].

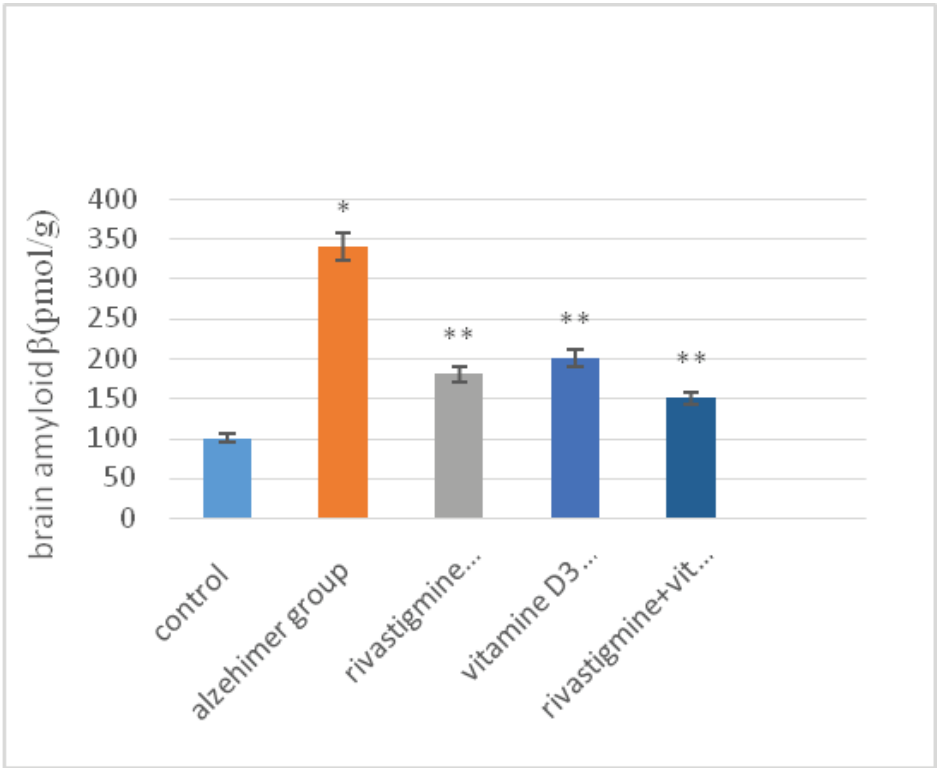

Figure 8: Effect of rivatigmine and vitamin D3 on brain amyloid β level in ICV-STZ induced alzheimer model in rats.

Experimental models of Alzheimer's disease resembling the human situation are an integral tool for increasing the understanding of complex mechanisms as well as for developing therapeutic strategies for this disease.

The present study aimed at exploring the neuroprotective effects of rivastigmine and vitamin D3 through their anti-inflammatory properties by the analysis of their effects on behavior changes and measurement of serum and brain TNF-α, IL-1β, in addition to the estimation of brain acetylcholine, serum, and brain amyloid β levels.

In this work, intracerebroventricular (ICV) injection of streptozotocin (STZ) causes inflammation, impairment of brain metabolism, cholinergic deficits, neuronal loss, and other Alzheimer-like alterations resulting in cognitive dysfunction, as a good model of sporadic-AD [21].

ICV-injection of STZ was chosen in this study, and animals were sacrificed after 21 days of STZ injection as by time, AD would be established as proven by previous experimental works [7].

In the present study, induction of Alzheimer's significantly increased the duration of latency time in Morris water maze test after 21 days of ICV-STZ injection. These observations are in consistence with those of previous results, which revealed that ICV-STZ treated rats showed long term cognitive deficits as early as 2 weeks after single ICV-STZ (3mg/kg) injections and maintained for at least 12-14 weeks [37].

In the present work, plasma and brain levels of pro-inflammatory cytokines (TNF-α and IL-1β) were significantly increased. Furthermore, serum and brain amyloid β had a remarkable increase after induction of AD.

It is known that inflammation plays an important role in the pathogenesis of AD. Tumor necrosis factor-alpha is the major cytokine synthesized by activated microglia and neurons, initiating the inflammatory cascade. Postmortem AD brains have revealed that increased TNF-α is accompanied with Aβ plaques, and TNF-α is upregulated in both CSF and serum and correlates with the disease severity [28]. Similarly, the current study confirms and extends previous findings of Salkovic-Petrisic et al. (2013). Consistent with our reports, Birch et al. (2014) found a direct link between proinflammatory cytokines and Aβ generation by showing that TNF-α and IFN-γ can transcriptionally upregulate β-secretase beta site amyloid precursor protein cleaving enzyme 1 [38].

In the present work, besides the elevation of plasma and brain levels of proinflammatory mediators (TNF-α and IL-1β), serum and brain amyloid β protein were significantly increased, while brain acetylcholine level decreased after induction of AD in rats. In accordance with this work, Stamouli and Politis (2016) found that increased levels of proinflammatory cytokines including TNF-α, IL-1β, IL-6, and IFN-γ may suspend phagocytosis of amyloid Aβ in brains of patient's astrogliosis and neural death. These changes in the brain parenchyma are often accompanied by changes in the level of these inflammatory proteins in peripheral blood [39].

The present study focuses on the effect of rivastigmine and vitamin D3 on experimental Alzheimer's model and possible anti-inflammatory effects. Rivastigmine, alone and in combination with vitamin D3, efficiently improved cognition function and brain level of acetylcholine. These results are in agreement with those of Wang et al. (2000) who found that rivastigmine was effective in antagonizing the scopolamine-induced spatial memory impairment in female rats. Dintino et al. (2005) found that chronic administration of selective acetylcholinesterase inhibitors (rivastigmine and donepezil) restores cognitive performance, choline acetyltransferase activity, and nerve growth factor mRNA expression and correlates with a decline in choline acetyltransferase activity and nerve growth factor mRNA level in cerebral cortex, hippocampus, and basal forebrain in experimental allergic encephalomyelitis in rats. A study by Zugno et al. (2013) revealed that rivastigmine was effective to improve the cognitive deficit in different tasks (immediate memory, long term memory, and short term memory) and decrease the acetylcholinesterase activity in the cerebral cortex, hippocampus, and striatum induced by ketamine in rats.

Furthermore, vitamin D alone and in combination with rivastigmine significantly improved cognition impairment and elevated brain acetylcholine level. These results are in line with those of Hajiluian et al. (2017) who observed that vitamin D reversed HFD-induced cognitive impairments by reduction of the NF-κB and elevation of BDNF concentrations and modulation of the BBB permeability in rats' hippocampus in high fat diet induced obese rat. Alrefaie and Alhayani (2015) demonstrate the potential effect of vitamin D3 supplementation on cognitive function in diabetic animals. It is possible that this effect is mediated through enhancing the prefrontal cortex cholinergic transmission in streptozotocin induced diabetic rats.

The present study focuses on the effect of rivastigmine alone and vitamin D3 on experimental AD and possible anti-inflammatory effects. Rivastigmine alone and in combination with vitamin D3 efficiently reduced serum and brain TNF-α, IL-1β levels. In the present work, besides the cognitive impairment, serum and brain levels of proinflammatory cytokines (TNF-α, IL-1β) were significantly increased. The anti-inflammatory response in the AD is reflected in reduced serum and brain levels of TNF-α and IL-1β. Our data indicate that rivastigmine and vitamin D3

exhibit an anti-inflammatory effect as evidenced by the significantly decreased serum and brain levels of TNF-α and IL-1β. This id confirmed by amyloid β improvement compared to the AD group.

These results are in agreement with those of Erbaş et al. (2014) who reported that cholecalciferol (vitamin D3) improves cognitive dysfunction and reduces inflammation in a rat fatty liver model of metabolic syndrome. Several studies have demonstrated that the use of vitamin D inhibits the intensity of the inflammatory response in different processes including renal and testicular injury [3] and non-osteopenic and osteoporotic postmenopausal females [31].

Many studies describe beneficial effects of vitamin D on inhibition of inflammation. The literature available, including studies in animal models, demonstrates decreased expression of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. According to some other experimental studies, vitamin D, through selective blockage of NF-kB signaling pathway, leads to a significant decrease in inflammatory IL-1β and TNF-α expression [49].

A cross-talk between proinflammatory cytokines and oxidative stress occurs in development of the inflammatory response in AD; particularly, TNF-α amplifies the inflammatory cascade through different mechanisms, such as activated microglial cells that kill adjacent neurons by the release of toxic products such as reactive oxygen species and proteolytic enzymes, enhances βAPP production, and speeds up the processing of βAPP into the insoluble Aβ peptide [50]. This insoluble peptide binds to microglial cell surface receptors and stimulates nuclear factor κB (NF-κB), further enhancing the production of cytokines [32] leading to a downward spiral of chronic inflammation.

In addition to the microglial cells, another cell type implicated in the pathogenesis of AD is the astrocyte. When astrocytes are stimulated by proinflammatory cytokines such as IL-1 and IL-6, they become activated and promote inflammation through the secretion of cytokines such as tumor necrosis factor α (TNF-α) and IL-6 [9].

Modulation of the TNF-α pathway led to the improvement in the cognitive ability of animal models. In addition, the biochemical parameters of AD pathology such as extracellular plaque load, intracellular tau phosphorylation, and microglial and astrocyte activation were all shown to be decreased through the inhibition of the TNF-α pathway. Inhibition of this signaling pathway prevents the strong activation of microglial cells, keeping them in a state of moderate activation where they play a neuroprotective role by enhancing the clearance of βAPP [10].

Results of the present work demonstrated that rivastigmine alone and in combination with vitamin D significantly improved inflammatory response through significant decrease of serum and brain level of TNF-α and IL-1β in AD rats. These results are in agreement with those of Richardson et al. (2013) who found statistically significantly decreased activity of inflammatory blood markers (blood interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha) and enhancement of neuronal transmission by using rivastigmine in Alzheimer's patients. Also, Gubandruet al. (2013) reported that rivastigmine manifests powerful anti-inflammatory effects by inhibiting TNF-α and IL-6 in Alzheimer's patients. Another recent study by Matsuda and Hisatsune (2017) revealed that rivastigmine significantly enhanced neurogenesis and suppression of gliosis, which together ameliorated the memory decline through inhibition of the hippocampus proinflammatory cytokines IL-1β and TNF-α and gliosis, in type II diabetic-AD model mice.

AD can be viewed as a vicious cycle, in which excess production and deposition of amyloid beta peptides promote microglial activation, and the resultant production of inflammatory mediators further increases amyloid beta production while inducing death and dysfunction of neurons [25].

The present study focuses on the effect of rivastigmine and vitamin D on serum and brain levels of amyloid B peptide. Rivastigmine alone and in combination with vitamin D significantly decreases both serum and brain level of amyloid B compared with AD group. A previous study by Sobów et al. (2009) found that a change in plasma amyloid beta peptide (1-42) level might constitute a novel biochemical predictor of long term rivastigmine treatment efficacy in AD. In addition, Mohamedet al. (2016) reported that rivastigmine had significantly decreased brain amyloid peptide and had neuroprotective and anti-inflammatory effects on the AD mouse models.

These results are consistent with those of Mizwicki et al. (2013) who found that, in vitro, 1, 25 vitamin D3 rebalances inflammation to promote Aβ phagocytosis and suggest that low vitamin D3 and docosahexaenoic acid intake or poor anabolic production of 1,25 vitamin D3 could contribute to AD onset/pathology. Epidemiological and experimental studies suggest that 1,25-dihydroxyvitamin D3 (1,25D) plays a neuroprotective role in neurodegenerative diseases including Alzheimer's disease. Analyses of the transcriptomic response of human brain pericytes to 1,25D demonstrate that human brain pericytes in culture respond to 1,25D by regulating genes involved in the control of neuroinflammation [20].

Also, Raha et al. (2016) found that Vitamin D2 suppresses amyloid β 25-35 induced microglial activation in microglial cells by blocking the NF-κB inflammatory signaling pathway.

6. Conclusion

The present study concludes that vitamin D3, alone and in combination with rivastigmine, had neuroprotective effect in STZ induced AD rats. The study also postulates the mechanism of their action as treatment with AD reduces inflammatory markers (TNF-α and IL-1β), which decreases the concentration of serum and brain levels of amyloid beta peptide in the AD rat. This decreased concentration of βA peptide in the AD rat increases the concentration of acetylcholine in the brain tissue, and thereby it protects the neurodegeneration in STZ induced AD rats.

Competing Interests

The authors declare no competing interests.

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