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Research Article

Effect of Vortioxetine on Cognitive Functions in an Amyloid β1–42 induced Rat Model of Alzheimer's Disease

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ABSTRACT

Aim: This study aimed to examine whether vortioxetine can improve cognitive performance in a rat model of Alzheimer's disease induced through intrahippocampal administration of Amyloid-β1–42.

Material and Methods: An experimental Alzheimer's disease model was generated via stereotaxic bilateral injections of Amyloid-β1–42 into the hippocampus. Twenty-eight rats were randomly assigned to four groups (n=7 each): Group 1 (control) received only saline; Group 2 was administered beta-amyloid to establish the Alzheimer model; Group 3 received beta-amyloid plus donepezil (reference treatment); and Group 4 received beta-amyloid in combination with vortioxetine for 14 days. Cognitive function was assessed using the passive avoidance paradigm. Upon completion of behavioral evaluations, animals were euthanized, and their brains were collected for histopathological examination.

Results: Median latency times in the passive avoidance task were: Group 1, 300 seconds (19.5–300); Group 2, 10.3 seconds (1–300); Group 3, 300 seconds (33.1–300); and Group 4, 300 seconds (8.9–300). Statistical testing revealed a significant difference among groups ($p < 0.05$). Group 4 exhibited the longest median latency. Groups 1, 3, and 4 showed significantly higher latency scores compared with Group 2. Histopathological findings demonstrated that vortioxetine reduced degenerative changes in hippocampal pyramidal neurons.

Conclusion: This work represents the first experimental study to evaluate vortioxetine's effects on cognition in an Amyloid-β1–42-induced Alzheimer model. The results suggest that vortioxetine may improve cognitive outcomes and may attenuate neuronal injury.

Keywords: Alzheimer's disease, avoidance behavior, beta-amyloid protein, donepezil, hippocampus, rats, vortioxetine.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by a gradual deterioration of memory, spatial orientation, and higher-order cognitive processes. It remains the primary cause of dementia in Western societies (1). A hallmark pathological feature of AD is the accumulation of amyloid-β peptides, which is believed to play a pivotal role in disease onset and progression. Numerous experimental studies have demonstrated that administering Aβ peptides to laboratory animals can successfully replicate many of the clinical and neuropathological characteristics observed in human Alzheimer's pathology (2).

In the early phases of AD, impairments across several neurotransmitter pathways become apparent (3). Depression is also highly prevalent among individuals with AD, and growing evidence suggests that depressive symptoms may accelerate the transition from mild cognitive impairment to established Alzheimer's disease (4,5). Given the overlap in serotonergic dysfunction between AD and major depressive disorder, selective serotonin reuptake inhibitors (SSRIs) have frequently been evaluated as therapeutic candidates. However, despite their widespread use, SSRIs have not consistently shown benefits in improving depressive symptoms or mitigating the cognitive decline associated with AD (6).

Vortioxetine is distinct from classical antidepressants because it exerts multimodal activity on multiple neurotransmitter systems simultaneously (7). Although limited, both preclinical and clinical findings indicate that vortioxetine may ameliorate not only depressive symptoms but also cognitive deficits in AD patients (8,9). Considering these potential advantages, the present study was designed to investigate the influence of vortioxetine on learning and memory performance in an amyloid-beta injection–based rat model of Alzheimer's disease.

MATERIAL AND METHODS

Ethical approval

All experimental procedures were conducted in accordance with institutional guidelines following approval by the Local Animal Research Ethics Committee of Bolu Abant İzzet Baysal University (approval date: 18.07.2018; approval number: 2018/24).

Study design

Selection and Description of Participants

A total of 28 healthy adult male Wistar rats, weighing 250–300 g and obtained from the Experimental Animal Center of Bolu Abant İzzet Baysal University, were enrolled in the

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study. The animals were randomly assigned, via a computer-generated randomization sequence, into four groups of seven animals each:

- Group 1 (Gr1, n=7): control group receiving saline,
- Group 2 (Gr2, n=7): Alzheimer's disease model induced by beta-amyloid,
- Group 3 (Gr3, n=7): beta-amyloid plus donepezil (reference treatment),
- Group 4 (Gr4, n=7): beta-amyloid plus vortioxetine (experimental treatment).

Throughout the study, rats were maintained under standard laboratory conditions with free access to food and water. Environmental parameters included controlled temperature (20–25°C), approximately 50% humidity, and a 12:12-hour light/dark cycle. Amyloid-β (1–42) was purchased from Abcam (Cambridge, UK; Cat. no. ab120301), while all remaining reagents were sourced from Sigma-Aldrich (St. Louis, MO, USA). Animals were housed identically to minimize confounding influences and were monitored daily for signs of distress. No unanticipated adverse events occurred. Humane endpoints were predefined as >20% weight loss, severe lethargy, or self-injury.

The experimental workflow is summarized in Figure 1. In Gr1, bilateral intrahippocampal injections of saline (4 µL total) were administered following anesthesia. Gr2, Gr3, and Gr4 received bilateral injections of Amyloid-β1–42 (4 µg/µL; 1 µL per hippocampus, 8 µg total). After the surgical procedure, rats in Gr1 and Gr2 were given oral saline for 14 days, whereas Gr3 received donepezil (5 mg/kg) and Gr4 received vortioxetine (10 mg/kg) orally for the same duration. The vortioxetine dose was selected based on previously published studies (8). No animals or data points were excluded, and all subjects were free of prior experimental manipulation.

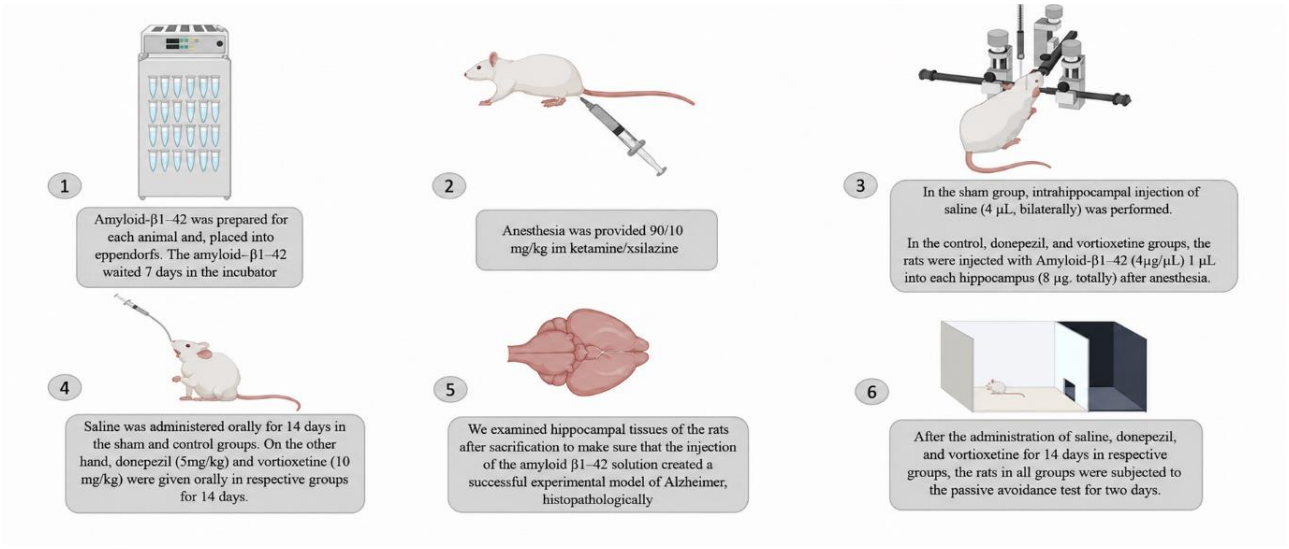

Figure 1. The design of the experiment.

Preparation of the Amyloid β1–42-Induced Alzheimer Model

Rats were anesthetized with intramuscular ketamine (90 mg/kg) and xylazine (10 mg/kg). After shaving and disinfecting the scalp with 2% chlorhexidine, each animal was secured in a stereotaxic frame (Ambala, India). A midline incision exposed the skull, and the bregma was identified. A 0.8 mm burr hole was drilled using stereotaxic coordinates: 3.6 mm posterior, 2.4 mm lateral, and 2.8 mm ventral from the bregma.

A total of 1 µL of pre-incubated (7 days at 37°C) Amyloid β1–42 solution (4 µg/µL) was injected bilaterally into the hippocampus using a Hamilton microsyringe at a controlled rate of 0.5 µL/min. Upon completion, the scalp was sutured, and animals were recovered. The preparation protocol for oligomeric Aβ1–42 followed the methodology originally described by Brouillette et al. (10).

Evaluation of Memory and Cognitive Function

Passive Avoidance Test

The passive avoidance task, the primary behavioral measure, was used to assess learning and memory in rodents with central nervous system impairments. This paradigm, also known as the inhibitory avoidance test, evaluates the ability of the animal to refrain from entering a dark compartment associated with an aversive stimulus. Longer latency times reflect better memory retention (11). All behavioral assessments were conducted by investigators blind to group assignments.

After 14 days of treatment with saline, donepezil, or vortioxetine, each rat underwent a two-day passive avoidance protocol.

- Day 1 (Acquisition): The rat was placed in an illuminated compartment connected to a dark chamber by a guillotine door. Upon entering the dark compartment, the rat received a 0.5 mA foot shock for 3 seconds.
- Day 2 (Retention): The latency to enter the dark compartment was recorded, with a cutoff time of 300 seconds. Animals that avoided entering for 300 seconds were considered to have successfully learned the task.

Brain Tissue Preparation and Histopathological Evaluation

After completion of behavioral testing, animals were euthanized under anesthesia via cervical dislocation. Brains were removed, and one hemisphere was fixed in 10% formaldehyde. Tissues were processed routinely, embedded in paraffin, and sectioned at 4–5 µm thickness.

After deparaffinization and rehydration, sections were stained with hematoxylin and eosin (H&E). A single experienced pathologist, blinded to group identity, evaluated samples under light microscopy for degenerative changes in pyramidal neurons, including nuclear shrinkage, nucleolar loss, and cytoplasmic eosinophilia (Figure 2A–D).

Statistical Analysis

Data were summarized as median (minimum–maximum). The Shapiro–Wilk test indicated non-normal distribution; therefore, non-parametric methods were used. Group comparisons were performed using the Kruskal–Wallis test, followed by Mann–Whitney U tests for pairwise analyses. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using IBM® SPSS® Statistics 22.0.

Power Analysis

Power analysis was performed using G*Power software. Based on pilot observations, a large effect size was estimated for the expected difference in passive avoidance latency between the vortioxetine-treated group and the Aβ-only group. Using $\alpha = 0.05$ and power = 0.80, the minimum required sample size was calculated as seven animals per group. This sample size was therefore used for each experimental group.

RESULTS

Results from the passive avoidance test demonstrated significant differences in memory performance among the experimental groups. Median latency values were as follows: Gr1, 300 seconds (19.5–300); Gr2, 10.3 seconds (1–300); Gr3, 300 seconds (33.1–300); and Gr4, 300 seconds (8.9–300). Analysis using the Kruskal–Wallis test revealed a statistically significant overall difference among the groups ($p < 0.05$). Pairwise comparisons performed using the Mann–Whitney U test demonstrated that the latency times of Gr1, Gr3, and Gr4 were significantly higher than those of Gr2, whereas no statistically significant differences were observed among Gr1, Gr3, and Gr4 (Table 1, Table 2, Figure 2).

Table 1. Median latency times in the passive avoidance test across experimental groups.

Groups	Gr1	Gr2	Gr3	Gr4
Time (seconds)	300 (19.5-300)[b]	10.3 (1-300)[a]	300 (33.1-300)[b]	300 (8.9-300)[b]

Data are presented as median (minimum–maximum). Group comparisons were performed using the Kruskal–Wallis test followed by Mann–Whitney U test for pairwise comparisons. Groups not sharing the same letter are significantly different from each other ($p < 0.05$).

Table 2. Pairwise comparisons of latency times among experimental groups in the passive avoidance test.

Groups (I)	Groups (J)	Significance (p-value)
Gr1	Gr2	**0.018**
	Gr3	0.740
	Gr4	0.630
Gr2	Gr3	**0.015**
	Gr4	**0.022**
Gr3	Gr4	0.810

Pairwise comparisons were performed using the Mann–Whitney U test following Kruskal–Wallis analysis. A p-value < 0.05 was considered statistically significant.

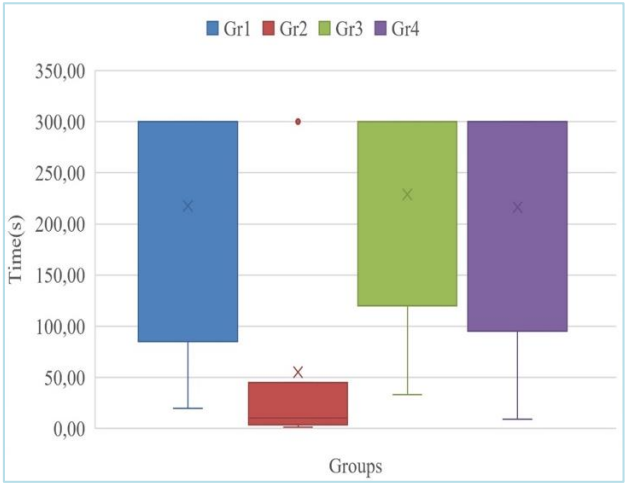

Figure 2. Median values of latency times of the groups.

Histopathological assessments focused on degenerative changes in hippocampal pyramidal neurons, including alterations in the cytoplasm, nucleus, and nucleolus. In Gr2, neuronal damage was prominent, with moderate-to-severe degeneration evident throughout the tissue. Typical findings included nuclear shrinkage, poorly visible nucleoli, and eosinophilic, contracted cytoplasms consistent with chromatolysis.

A significant histopathological difference was identified between Gr1 and Gr2 ($p < 0.05$). No statistically meaningful differences were observed among Gr1, Gr3, and Gr4. However, comparisons between Gr2 and both Gr3 and Gr4 showed significant reductions in neuronal degeneration ($p < 0.05$). Overall, these findings indicate that vortioxetine treatment mitigated cytoplasmic and nuclear deterioration in hippocampal pyramidal neurons (Table 3, Figure 3).

Table 3. Comparison of histopathological scores between groups.

Groups	Median (Min-Max)
Gr1	1 (1-2)[b]
Gr2	2 (1-4)[a]
Gr3	2 (1-3)[b]
Gr4	2 (1-2)[b]

Group comparisons were performed using the Kruskal–Wallis test followed by Mann–Whitney U test for pairwise comparisons. Groups not sharing the same letter are significantly different from each other ($p < 0.05$).

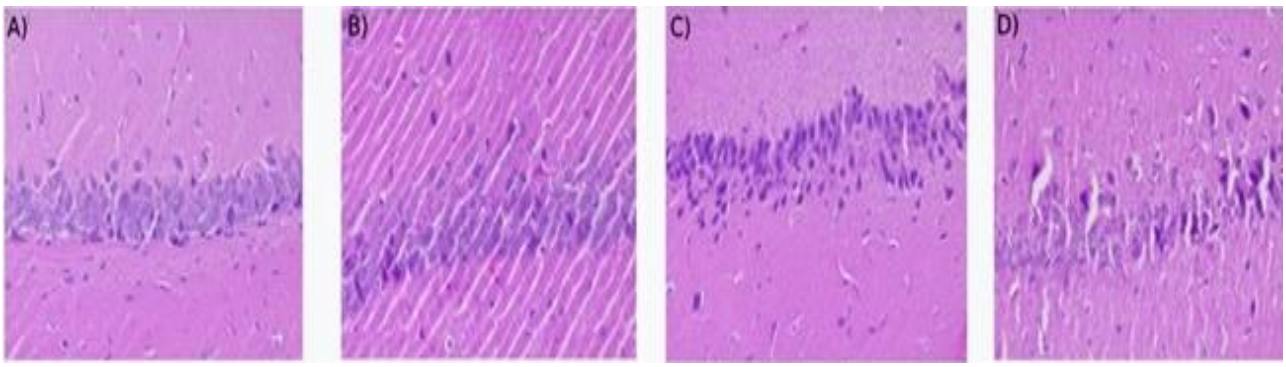

Figure 3. Histopathologic evaluation of hippocampal area (H&E, x40); A) Grade 1: No change in hippocampal area. B) Dispersed neuronal damage in hippocampal area. C) Mild neuronal damage in hippocampal area. D) Wide neuronal damage in all hippocampal areas.

DISCUSSION

The present study evaluated whether vortioxetine could counteract cognitive deficits in a rat model of Alzheimer's disease (AD) induced by Amyloid-β1–42 administration. The principal outcome of the experiment was that vortioxetine was associated with improved memory performance, showing a pattern of effects similar to that observed with donepezil, a well-established therapeutic agent for AD.

In the early phases of Alzheimer's disease, profound synaptic alterations—including reductions in synaptic density, mitochondrial dysfunction, and structural disruption—emerge in several vulnerable brain regions such as the temporal cortex, parietal areas, hippocampus, and subcortical nuclei. Although extracellular amyloid plaque accumulation and intracellular neurofibrillary tangle formation are key pathological signatures of AD, the extent of synaptic impairment has been shown to correlate most strongly with the degree of cognitive decline (12). Neurotransmitter systems, which are central to synaptic communication, thus play a crucial role in sustaining cognitive processes (13). Multiple neurotransmitter pathways—including cholinergic, dopaminergic, GABAergic, serotonergic, histaminergic, and glutamatergic systems—are disrupted as the disease progresses (14). Donepezil, an acetylcholinesterase inhibitor, was among the first agents developed to address cholinergic deficits and has demonstrated clinical efficacy across the spectrum of AD severity (15,16).

Dysregulation of the serotonergic system is a hallmark of depressive disorders (17), and depression affects nearly half of individuals with Alzheimer's disease (18). Moreover, some researchers propose that depressive symptoms may accelerate the trajectory from mild cognitive impairment to clinically manifest AD (19). AD pathology also includes reductions in serotonergic neurons and diminished expression of several serotonin receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, and 5-HT6), further implicating serotonergic dysfunction in disease progression (20).

Previous preclinical work has suggested that selective serotonin reuptake inhibitors (SSRIs) may attenuate amyloid accumulation and enhance cognitive performance (21,22). Additionally, a clinical study involving citalopram demonstrated decreased amyloid production in humans (23). However, findings from randomized controlled trials investigating sertraline in AD patients have been disappointing, showing little to no benefit in affective or cognitive outcomes (24,25). Two meta-analyses further support these conclusions, indicating that SSRIs and SNRIs exert minimal therapeutic impact on depressive symptoms in AD populations (26,27).

In contrast, vortioxetine has shown promise. Katona et al. reported that vortioxetine produced significant improvements in mood, processing speed, verbal learning, and memory in a clinical trial (28). Unlike conventional SSRIs, vortioxetine is classified as a multimodal antidepressant, combining serotonin transporter inhibition with direct receptor modulation (29). It functions as a 5-HT1A agonist, a partial 5-HT1B agonist, and an antagonist at 5-HT1D, 5-HT3, and 5-HT7 receptors. Through this diverse pharmacodynamic profile, vortioxetine enhances serotonergic, noradrenergic, dopaminergic, cholinergic, histaminergic, and glutamatergic transmission while concurrently suppressing GABAergic signaling (30,31). Given that AD disrupts several of these neurotransmitter systems simultaneously, vortioxetine's broad mechanism of action may explain its capacity to improve cognitive function.

Multiple randomized controlled trials involving patients with major depressive disorder have demonstrated cognitive benefits of vortioxetine that appear independent of its antidepressant effects (28,32,33). In two of these studies, vortioxetine outperformed duloxetine in enhancing cognitive performance.

Evidence regarding vortioxetine in Alzheimer's disease remains limited. Only one clinical investigation has assessed its effects in AD: a 12-month open-label study by Cumbo et al., which found that vortioxetine led to greater improvements in Mini-Mental State Examination scores compared with other antidepressants in AD patients with comorbid depression (9). Preclinical data are similarly scarce; Torrisi et al. reported that vortioxetine prevented memory impairment and depressive-like behavior in an Aβ1–42 mouse model, with the passive avoidance test used as the primary cognitive measure (8). Another study by Sharp et al. demonstrated that vortioxetine reversed cognitive deficits in a rat model of androgen deprivation therapy, further supporting its procognitive potential (34).

The present findings expand this body of evidence by demonstrating that vortioxetine may improve learning and memory impairments induced by amyloid β1–42. Given that AD-related neurodegeneration simultaneously affects

numerous neurotransmitter systems, vortioxetine's multimodal activity may offer therapeutic advantages over SSRIs, whose narrower pharmacological profile may be insufficient to address the disease's complex neurochemistry.

Despite these promising results, the study has several limitations. The Aβ1–42 injection model, while widely used, does not fully recapitulate the multifaceted pathology of human AD, particularly the development of tau pathology, extensive neuronal loss, and chronic inflammatory changes (2). Additionally, the study relied on behavioral and histological analyses without accompanying molecular assessments, such as quantification of amyloid deposition, tau phosphorylation, or pro-inflammatory markers. The relatively small sample size (n=7 per group), although supported by power calculations, limits the generalizability of the conclusions. Furthermore, the study evaluated only a single dose of vortioxetine and a 14-day treatment period; prolonged administration or dose-response evaluations may yield additional insights. Another limitation is that only male rats were used, precluding the evaluation of sex-specific differences. Finally, the passive avoidance test measures a specific aspect of learning and memory; incorporating additional cognitive tests could provide a more comprehensive behavioral profile.

CONCLUSION

In conclusion, this study provides one of the earliest experimental investigations exploring the effects of vortioxetine on cognitive dysfunction in an amyloid β1–42-induced rat model of Alzheimer's disease. Despite the limitations of the study, the findings suggest that vortioxetine may improve learning and memory performance and may attenuate histopathological signs of neuronal degeneration. In addition, its effects appeared to be comparable to those observed with donepezil, a well-established therapeutic agent for Alzheimer's disease.

Given vortioxetine's known benefits in addressing cognitive deficits in major depressive disorder, these findings suggest that the drug may have potential relevance for individuals with Alzheimer's disease, particularly those exhibiting depressive symptoms unresponsive to conventional treatments. Nevertheless, further preclinical and clinical studies are needed to clarify vortioxetine's mechanisms of action, long-term effects, and possible role in the management of cognitive impairment associated with Alzheimer's disease.

DECLARATIONS

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Ethical Approval: The study was conducted in accordance with the approval of Bolu Abant İzzet Baysal University Animal Research Local Ethics Committee (HAYEK), dated February 20, 2020, and numbered 14.

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