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Research Paper

Histone Deacetylase Class IIb Inhibition Improves Amyloid-β-induced Learning and Memory Deficits in Male Rats

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a neurodegenerative disease associated with progressive impairment of cognitive function. The primary pathological features of AD include aggregation of amyloid-β (Aβ) and hyperphosphorylation of the tau protein. Histone deacetylases (HDACs) play a crucial role in the pathophysiology of neurodegenerative diseases. This study aimed to investigate the potential neuroprotective effects of HDAC6 and HDAC10 inhibition in a rodent model of AD.

Methods: Learning and memory deficits were induced by bilateral intra-hippocampal Aβ injections in male Wistar rats. Tubacin (HDAC6 inhibitor) and bufexamac (HDAC6 and 10 inhibitors) were microinjected 30 minutes after Aβ injection. The possible molecular changes in the hippocampus following Aβ injection were also assessed by western blotting analysis of pCREB/CREB and Pp70/P70 ratios.

Results: Our results revealed that bufexamac significantly recovered learning and memory impairments induced by Aβ in the Morris water maze (MWM) task. Tubacin improved memory decline without affecting learning. Bilateral intra-hippocampal injection of each of the HDAC inhibitors significantly increased the pCREB/CREB and Pp70/p70 ratios compared to the Aβ group, which was concurrent with behavioral alterations.

Conclusion: HDAC IIb treatment may be a promising strategy for improving learning and memory impairments in an animal model of AD, suggesting that HDAC targeting is a valuable strategy for further investigation.

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Highlights

- Bufexamac recovered the Aβ-induced learning and memory impairments in male rats with AD.
- Tubacin improved memory, but had no effect on learning.
- The HDAC inhibitors increased the pCREB/CREB and Pp70/p70 ratios.

Plain Language Summary

Alzheimer's disease (AD) is a chronic and progressive disease that is associated with memory impairment. There is still no definitive cure for AD. The number of patients is increasing daily. Histone deacetylases may be involved in this disease due to their role in memory function. In this study, we assessed the effect of Tubacin and bufexamac on learning and memory in male rats with AD. It was found that Bufexamac recovered the Aβ-induced learning and memory impairments. Tubacin also improved memory, but had no effect on learning.

1. Introduction

Alzheimer's disease (AD) is characterized by a slow decline in hippocampal-related functions, including cognitive impairment, memory loss, and behavioral and functional disorders (Cooper & Ma, 2017). Epigenetic modifications play a role in AD pathogenesis. Epigenetics is the relationship between genetics and the environment. Histone acetylation by histone acetyltransferases and histone deacetylation by histone deacetylases (HDACs) are the most extensively studied histone post-translational modifications relevant to neurocognitive disorders (Peixoto & Abel, 2013).

Histone acetylation activates gene transcription, while histone deacetylation is closely associated with gene transcriptional repression (Lu et al., 2015). It has been reported that acetylation and deacetylation hemostasis are disturbed in neurodegenerative states (d'Ydewalle et al., 2011; Gibson & Murphy, 2010; Gräff & Tsai, 2013). Numerous studies have demonstrated that histone acetylation plays a crucial role in mitigating learning and memory impairment (Liu et al., 2009).

Furthermore, treatment with the HDAC inhibitor, sodium butyrate, stimulated hippocampal axonal regeneration and improved learning and memory in the CK-p25 mouse model of AD (Fischer et al., 2007). In addition, the HADC inhibitor, phenylbutyrate, increased axonal density and reduced tau hyperphosphorylation (Ricobaraza et al., 2009). Finally, decreased histone acetylation levels have been observed in the hippocampus and cerebral cortex of aged rats (Peleg et al., 2010; Walker et al., 2013).

In the HDAC family proteins, class IIb includes HDACs 6 and 10 (Xu et al., 2007; Sartor et al., 2015). The role of HDAC6 in AD has been previously described (Zhang et al., 2013; Simões-Pires et al., 2013). It is found in both the cytoplasm and nucleus and significantly increases during AD progression. Studies have shown that the acetylation activity and expression of HDAC6 increase in the cortex and hippocampus of patients with AD (Gräff et al., 2012; Ding et al., 2008). Although the function of HDAC6 in the cytoplasm has been verified in several studies, the role of another cytoplasmic deacetylase, HDAC10, a class IIb histone deacetylase (Tong et al., 2002), has not been clarified (Fischer et al., 2002; Kao et al., 2002). HDAC10 is closely related to HDAC6 (Guardiola & Yao, 2002), and can be shuttled between the nucleus and cytoplasm. HDAC10 can also recruit many other HDACs, indicating that it may act as a recruiter rather than a deacetylase. However, when HDAC10 is expressed through recombination, it exhibits deacetylation activity (Guardiola & Yao, 2002; Fischer et al., 2002; Kao et al., 2002; Tong et al., 2002). HDAC10 regulates reactive oxygen species (ROS) in gastric cancer cells. Notably, HDAC10 expression is substantial in various regions of the hippocampus, including CA1, CA3, and the dentate gyrus (Broide et al., 2007). However, its function in the hippocampus has not been extensively studied. The current study aimed to investigate the outcome of inhibiting class IIb HDACs on learning and memory deficits induced by amyloid-β (Aβ) injection. It is reported that the cyclic adenosine monophosphate response element binding protein (CREB) and ribosomal protein S6 kinase phosphorylation are crucial in spatial learning and memory formation (Mizuno, 2002). To evaluate the possible molecular changes in the hip-

pocampus due to Aβ injection, the phosphorylated cyclic adenosine monophosphate response element binding protein (pCREB)/CREB and 70 kD ribosomal protein S6 kinase (Pp70/P70) ratio were assessed.

2. Materials and Methods

Animals

In this study, adult male Wistar rats, weighing 250-300 g, were housed in groups of 2-3 per Plexiglas cage. The room temperature was maintained at 22±2 ˚C, and a 12-h light–dark cycle (lights on at 07:00) was implemented, with free access to water and food. A total of 64 male rats (n=8 per group) were divided randomly into eight groups (intact, saline, dimethyl sulfoxide [DMSO], Aβ, bufexamac, tubacin, bufexamac+Aβ, tubacin+Aβ).

Surgery

Rats (n=8 per group) were deeply anaesthetized by i.p. injection of a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg). During stereotaxic surgery, stainless steel guide cannulas were fixed bilaterally into the dorsal hippocampus (AP: -3.8, ML: ±2.2, DV: -2.7) according to the rat atlas (Paxinos & Watson, 2009) and were fixed using acrylic cement. The guide cannula was one mm above the injection site, and the injection needle was one mm longer than the guide cannula.

Drugs preparation and administration

The Aβ 25-35 peptide (Sigma, USA) was dissolved and stored at -20 ˚C. Aggregation of Aβ 25–35 was performed by incubating in vitro at 37 ˚C for 4 days. Bufexamac and tubacin (Selleckchem, USA) were dissolved in DMSO.

For intra-hippocampal injection of Aβ (5 µg/2.5 µL each side), a five µL Hamilton syringe was used. The same intra-hippocampal injection volume was previously used (Ghorbandaiepour et al., 2024). The injection needle was 30 gauge. The animals were allowed to move freely in their standard boxes during all injections. Tubacin (20 µg/rat) and bufexamac (20 µg/rat) or DMSO (2.5%) as their vehicle were microinjected 30 minutes after Aβ injection.

All microinjections were performed at a speed of 0.5 µL/min, and the injection needle was left in place for an additional 2 minutes to allow the solution to completely diffuse from the cannula tip and minimize drug backflow. The Morris water maze (MWM) test was performed ten days after surgery. Figure 1 shows the experimental procedure.

Behavioral testing

The water maze was a black circular pool (150×60 cm). The water temperature was (20±1 ˚C), and filled to a depth of 25 cm. Previously, ambient temperatures (19-22 ˚C) have been used for rats. The behavior outcome reported no fatigue or hypothermia (Lindner & Ribkoff, 1991). Four distinct quadrants were considered in the tank, and the release points were designated as zones 1, 2, 3 and 4. A circular platform (11 cm in diameter) was positioned at the center of the first quadrant, 1.5 cm below the water surface. Extra-maze visual cues, including computers, bookshelves, and posters on the wall, were identified and maintained in fixed positions throughout all experiments. The animals' behavior was recorded using a digital camera positioned above the center of the maze. The swimming path, latency to find the platform, travelled distance, and time spent in the target quadrant were recorded.

The animals underwent three days of training sessions. Over the first three days, a hidden platform was placed in a fixed location. In learning sessions, four trials with various starting locations were considered. In each trial, animals were released from one of the four different starting zones. The allowed time to swim and find the hidden platform was 90 seconds.

Upon finding the platform, the animals were allowed to remain there for 20 s until the start of the subsequent trial. The probe trial was performed without a platform, and the released point was in the opposite zone (Naderi et al., 2023). Finally, to assess animal visual ability and sensory-motor coordination, the visible platform test was performed. To assess whether the surgical procedure or drug treatments over time had no adverse impact on vision, the visible platform test was conducted on day 4 after the probe trial in all animals to avoid habituation (Paul et al., 2009).

Tissue preparation

After completing the behavioral tests, the rats were immediately sacrificed by carbon dioxide (CO_2) inhalation, decapitated, and their hippocampi were isolated on ice and stored in liquid nitrogen for 24 h. They were then stored at -80 ˚C until molecular analysis.

Molecular assessment: Western blot analysis

The hippocampi were homogenized on ice. The RIPA lysis buffer consisted of Tris-hydrochloride (HCl) (50 mM, pH 8.0); sodium chloride (NaCl) (150 mM); Tri-

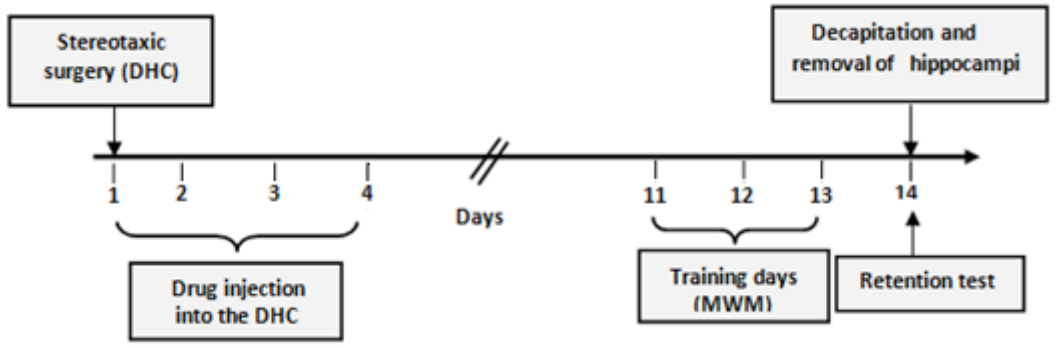

Figure 1. The time line and design of experimental procedures of the study

Abbreviations: DHC: Dorsal hippocampus; MWM: Morris water maze.

Note: The animals underwent a one-week handling period before the start of the study.

ton X-100 (1%); Na-deoxycholate (0.5%); and sodium dodecyl sulfate (SDS) (0.1%). The cocktail was supplemented with protease and phosphatase inhibitors. The lysates were centrifuged (14000 rpm, 30 minutes, 4 ˚C) to remove debris. The protein content of the samples was quantified using the Lowry method, and equal amounts of protein (50 µg) were separated by 12% polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride (PVDF) membranes. The membranes were then incubated with blocking buffer (5% BSA) and probed overnight at 4 ˚C with primary antibodies. Then, they were washed in Tris-buffered saline with Tween 20 (TBS-T) and incubated for 1:5 h with horseradish peroxidase antibody. Immunoreactivity was visualized using an enhanced chemiluminescence (ECL) kit (Amersham, UK). Ultimately, the radiographic films were scanned, and the protein band density of the blots was calculated using ImageJ software, version (RRID: SCR_003070) (Mohammadi et al., 2023).

Statistical analysis

Data were analyzed using GraphPad Prism software, version 7.01. Data obtained from the MWM training days were analyzed using a two-way analysis of variance (ANOVA). Tukey's post hoc test was used for multiple comparisons. For the probe test and molecular data analysis, the one-way ANOVA analysis was used. The results are presented as Mean±SEM and P<0.05 is considered statistically significant.

Results

Intrahippocampal injection of bufexamac improved spatial learning and memory impairments induced by Aβ injection

As shown in (Figure 2A), a main effect of days ($F_{2, 14}$=63.56, P<0.0001) and groups ($F_{3, 21}$=5.952, P<0.01) was observed on the travelled distance to find the hidden platform during all training days. However, the interaction between days and groups was not significant ($F_{6, 42}$=0.8386, P=0.5472). Multiple comparisons using Tukey's post-hoc test showed that bufexamac significantly reversed the effects of Aβ learning impairment on the second and third training days (P<0.01 and P<0.001, respectively).

As illustrated in Figure 2B, bufexamac significantly reduced the escape latency to the platform during the second and third days of training compared to Aβ treatment. Two-way ANOVA with repeated measures revealed a main effect of days ($F_{2, 14}$=55.90, P<0.0001) and groups ($F_{3, 21}$=5.012, P<0.001) on the escape latency to the hidden platform during the second and third days of training. However, the interaction between days and groups was insignificant ($F_{6, 42}$=0.8205, P=0.2461). Multiple comparisons using Tukey's test revealed a significant difference in this parameter between the Aβ and Aβ + bufexamac groups on the second and third training days (P<0.01 and P<0.001, respectively) (Figure 2B).

Data analysis by one-way ANOVA in the probe test showed a statistically significant difference in the time spent in the target quadrant between the Aβ group and the Saline, DMSO and Aβ + bufexamac groups (P<0.0001, P<0.01, and P<0.001, respectively) (Figure 2C).

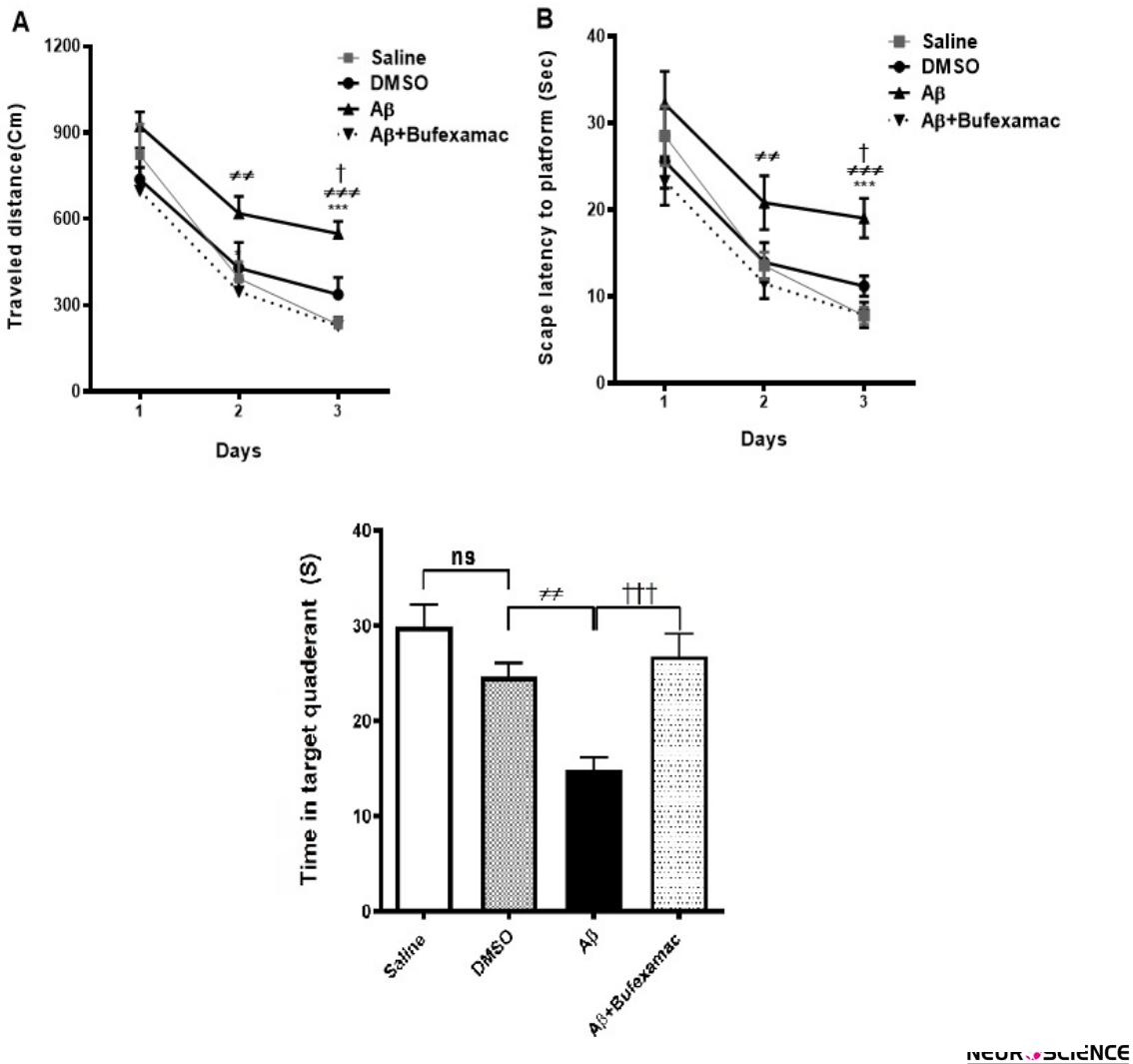

Figure 2. Effect of intra-hippocampal injection of bufexamac on spatial learning and memory impairments induced by Aβ

Note: Injection of bufexamac significantly improved the performance of the impaired animals during the training days in the MWM task. Rats receiving bufexamac (A) travelled shorter distances, and (B) spent less time (escape latency) finding the hidden platform compared to the Aβ group during the second and third days of training (C). Following bufexamac intra-hippocampal injection, the time spent in the target quadrant on the probe day significantly increased compared to the Aβ group. Data are presented as the Mean±SEM. ***P<0.001 compared to the saline group and ##P<0.01 and ###P<0.001 compared to the DMSO group on the training days, and ***P<0.001 compared to the saline group. ##P<0.01 compared to the DMSO group and †††P<0.001 compared to the Aβ group on the probe day (n=8 per each group).

Intra hippocampal injection of tubacin not affecting learning but improved memory impairment due to Aβ treatment

As shown in (Figure 3A), tubacin did not affect the learning impairment due to Aβ treatment in both travelled distances and escape latency to the hidden platform. Two-way ANOVA with repeated measures revealed a main effect of days ($F_{2, 14}$=36.08, P<0.0001) and groups ($F_{3, 21}$=3.012, P<0.05) on the escape latency to the hidden platform during the first, second and third days of training. However, the interaction between days and groups was not statistically significant ($F_{6, 42}$=1.551, P=0.1854). However, multiple comparisons using Tukey's post-hoc test showed no difference in this parameter between the Aβ and Aβ + tubacin groups on any of the training days (Figure 3B).

The results of the one-way ANOVA in the retrieval test revealed a statistically significant difference in the time spent in the target quadrant between the Aβ group and the Saline, DMSO, and Aβ + tubacin groups (P<0.0001, P<0.01, and P<0.001, respectively) (Figure 3C).

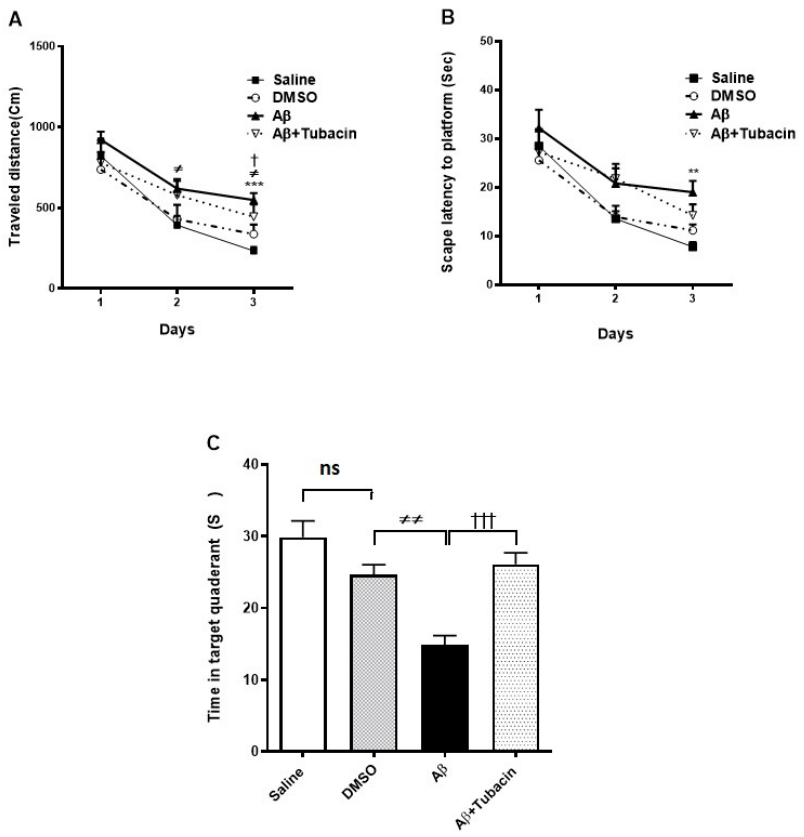

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Figure 3. Effect of intra-hippocampal injection of Tubacin on spatial learning and memory impairments induced by Aβ

Note: Tubacin injection significantly improved the performance of Aβ-treated animals during training days in the MWM task. This treatment significantly decreased (A) travelled distance and (B) latency to find the hidden platform (escape latency) compared to the Aβ (25-35) group during the second and third days of training (C). Tubacin intra-hippocampal injection significantly increased the time spent in the target quadrant compared to the Aβ group on the probe day. Data are shown as Mean±SEM. **P<0.01, ***P<0.001 compared to the saline group and $^{\#}$P<0.05 compared to the DMSO group on the training days. ***P<0.001 compared to the saline group, $^{\#\#}$P<0.01 compared to the DMSO group and †††P<0.001 compared to the Aβ group (n=8 per each group).

Visuomotor activity did not change during the experiments

A visible platform test was performed on day 4, following the probe trial, in all experimental groups to assess the animals' vision. The results of one-way ANOVA followed by Tukey's test did not show any significant differences among groups ($F_{7, 56}$=0.8300, P=0.5669, Figure 4).

Molecular assessment

Aβ treatment decreased Pp70/p70 ratio in the hippocampal area recovered by bufexamac and tubacin treatment

The phosphorylation of P70 (S6K1), a kinase involved in enhancing protein synthesis processes, was measured after MWM. The ratio of the phosphorylated to total Pp70/P70 density bands showed that Aβ injection caused a significant decrease in Pp70/p70 compared to the saline group ($F_{7, 32}$=0.3300, P<0.05). Bilateral intra-hippocampal injection of the HDAC inhibitor bufexamac significantly increased the Pp70/p70 ratio compared to the Aβ group ($F_{7, 32}$=0.3300, P<0.05). Tubacin significantly increased the Pp70/p70 ratio compared to the Aβ group ($F_{7, 32}$=0.0.3300, P<0.05, Figure 5).

Aβ treatment decreased pCREB/CREB ratio in the hippocampal area recovered by bufexamac and tubacin treatment

CREB, a transcription factor related to learning and memory processes, was measured after MWM. The ratio of the phosphorylated to the total form of pCREB/CREB density bands showed that intra CA1 bilateral injection (5 μg) of Aβ caused a significant decrease in pCREB/CREB compared to the saline group ($F_{7, 32}$=0.5049, P<0.05).

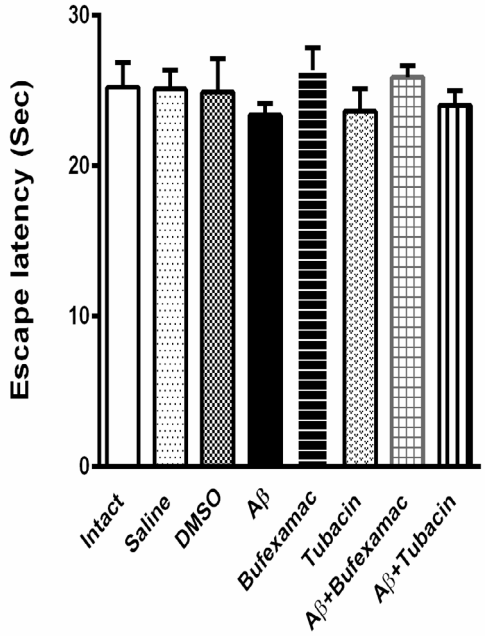

Figure 4. Comparison of visuomotor activity between different experimental groups

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Note: No significant difference was observed in the ability of animals from different experimental groups to find the visible platform in the visible test.

Bilateral intra-hippocampal injection of HDAC 6 and 10 inhibitor bufexamac (20 µg) significantly increased the pCREB/CREB ratio compared to the Aβ group ($F_{7, 32}$=0.5049, P<0.001). Also, HDAC 6 inhibitor Tubacin (20 µg) significantly increased the pCREB/CREB ratio compared to the Aβ group ($F_{7, 32}$=0.5049, P<0.001, Figure 6).

4. Discussion

In the present study, Aβ administration induced neurotoxicity, as demonstrated by spatial memory impairment and a significant decrease in the pCREB/CREB and Pp70/p70 ratios. Our data were consistent with previously published studies that reported memory decline in rodent Aβ models (Aminyavari, 2019; Karimi-Zandi, 2022). CREB is responsible for various neurophysiological phenomena, such as plasticity, and has been implicated in cognitive decline (Tanis, 2008). In the present study, a decrease in the pCREB/CREB and Pp70/p70 ratios was used as a molecular confirmation criterion for cognitive alteration. Tubacin, a specific HDAC6 inhibitor, significantly reversed memory impairments induced by Aβ in the MWM task. The upregulation of HDAC6 in AD and its correlation with tau hyperphosphorylation have been reported. Therefore, the beneficial effect of tubacin may be related to the modification of the aforementioned effects (Ding et al., 2008). Evidence shows that cytosolic HDAC6 regulates the acetylation of non-histone proteins, such as p53, FOXP3, heat shock protein 90, tubulin, Tau, cortactin, and peroxiredoxin (Li et al., 2013; Hubbert et al., 2002; Zhang et al., 2007). Since these proteins play a role in learning and memory processes, their acetylation by HDAC6 inhibitors can be effective in improving memory impairments resulting from AD (Selenica et al., 2014). Reduction or inhibition of HDAC6 decreased Aβ plaques in Aβ protein precursor (AβPP)swe/PS1ΔE9 mice, ameliorated tau pathologies in rTg4510 mice and primary cultured neurons, and ultimately improved cognitive deficits. In addition, tau acetylation has been reported to compete with tau phosphorylation at several HDAC6-regulated sites, thereby inhibiting tau aggregation (Carlomagno et al., 2017; Cook et al., 2014; Guardiola & Yao, 2002).

Among all parameters that play a role in the occurrence and development of AD, epigenetic factors should be considered carefully because they result from the interaction of multiple factors. It has even been proposed that an imbalance in histone acetylation occurs at a very early stage of AD, before the decline in cognition (Marinho et al., 2023).

No reports have compared the selective inhibitors of class IIb members in this context. Although various labs have studied the effect of HDAC6 inhibition on AD de-

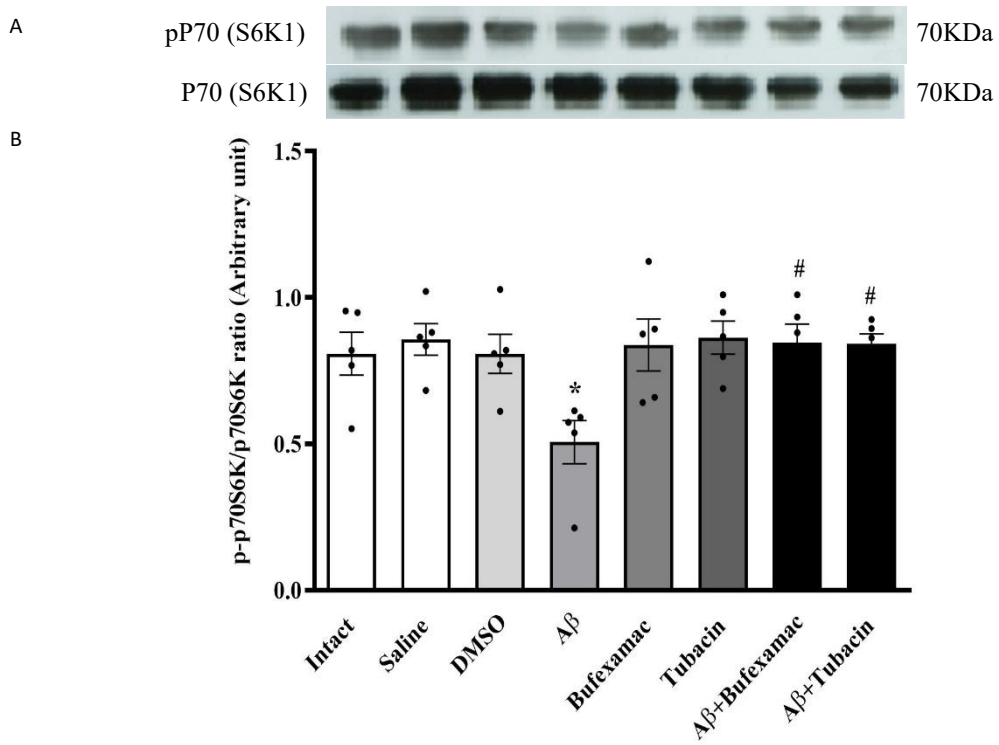

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Figure 5. The densities of Pp70 and their ratios to p70 (Pp70/p70 ratio) measured in all experimental groups

Note: One-way ANOVA revealed a significant decrease in the Pp70/p70 ratio in the Aβ group compared to the control group. A significant increase in this ratio was detected in the Aβ-treated group receiving bufexamac (Aβ + bufexamac) or tubacin (Aβ + tubacin) compared to the Aβ group. B: Densities of Pp70 and p70 bands and their ratios in all experimental groups were evaluated. Data are shown as Mean±SEM. *P<0.05 compared to the control group in the Aβ group and #P<0.05 compared to the Aβ group in the Aβ + bufexamac and Aβ + tubacin groups (n=5 per group). The phosphorylation levels of proteins and their ratios were calculated about the total amount; therefore, the effect of β-actin was neutralized.

velopment, research on HDAC10 inhibition has been largely neglected.

In the present study, bufexamac, a class IIb-specific HDAC inhibitor, significantly increased the Pp70/p70 and pCREB/CREB ratios compared to the Aβ group. These alterations were parallel to improvements in memory. Besides, its usage resulted in learning recovery, a characteristic that did not ensue upon tubacin injection. An explanation for this extra positive effect could be its broader inhibitory effects, including those on HDAC6 and 10. Tubacin selectively inhibits HDAC6, while bufexamac has a selective inhibitory effect on HDAC6 and 10 (Bantscheff et al., 2011). Using Tubastatin as another inhibitor of class IIb HDAC, which can inhibit HDAC10 with higher affinity than HDAC6, may be one possible approach to validate this assumption. Thus, the point of interference can be limited (Oehme et al., 2013).

The second hypothesis for this outcome may be related to its anti-inflammatory properties, which are a primary feature of bufexamac and cannot be ruled out. In a study by Oehme et al. (2013) the possibility of a compensatory effect of HDAC6 for HDAC10 has been rejected (Bantscheff et al., 2011). Therefore, members of class IIb have individual and perhaps distinct roles in the context of neurodegenerative diseases.

Despite these possibilities, the efficacy of HDACs may vary based on the context (tissue and pathological condition), as well as the concentration of these components. The unknown mechanism of their action, as well as the main target and pathway, are the major issues with HDACs that need to be solved. It should be considered that these inhibitors can affect multiple pathways due to their inherent characteristics. Answering these questions may lead to a broader, safer, and more practical solution.

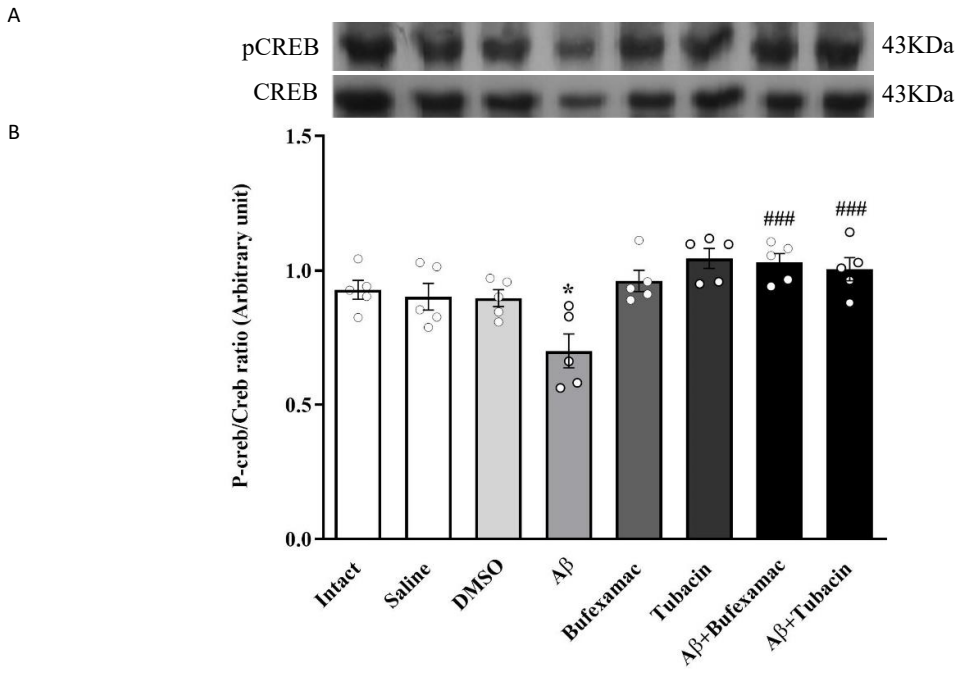

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Figure 6. pCREB)/CREB ratio and pCREB and CREB Levels in the control, Aβ and treatment groups

A) The densities of pCREB and their ratios to CREB (pCREB/CREB ratio) were measured in all experimental groups

Note: The data analysis, conducted using one-way ANOVA, showed a significant decrease in the pCREB/CREB ratio in the Aβ group compared to the control groups, as well as a significant increase in this ratio in the Aβ + bufexamac and Aβ + tubacin groups compared to the Aβ group.

B) Densities of pCREB and CREB bands and their ratios in all experimental groups were evaluated

Note: Data are presented as the Mean±SEM. $^{*}P<0.05$ compared to the control in Aβ group and $^{###}P<0.001$ compared to the Aβ group in the Aβ + bufexamac and Aβ + tubacin groups (n=5 per group).

5. Conclusion

In conclusion, the present study showed that HDAC IIb inhibition may present a promising opportunity for developing new therapeutic strategies for learning and memory impairments in rodent models of Alzheimer's-like diseases.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Committee of Tehran University of Medical Sciences, Tehran, Iran (Code: 96-03-87-36403). All experiments were performed by the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80-23, revised 1996).

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Authors' contributions

Conceptualization: Fereshteh Motamedi, Zahra Mansouri and Maryam Zahmatkesh; Methodology: All authors; Investigation, data curation, software, formal analysis, and writing the original draft: Zahra Mansouri; Validation, formal molecular analysis: Fariba Khodagholi; Supervision, project administration, resources, and funding acquisition: Maryam Zahmatkesh; Review and editing: Fereshteh Motamedi, Maryam Zahmatkesh and Fariba Khodagholi.

Conflict of interest

The authors declared no conflict of interest.

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References

Bantscheff, M., Hopf, C., Savitski, M. M., Dittmann, A., Grandi, P., & Michon, A. M., et al. (2011). Chemoproteomics profiling of HDAC inhibitors reveals selective targeting of HDAC complexes. *Nature Biotechnology, 29*(3), 255–265. [DOI:10.1038/nbt.1759] [PMID]

Broide, R. S., Redwine, J. M., Aftahi, N., Young, W., Bloom, F. E., & Winrow, C. J. (2007). Distribution of histone deacetylases 1-11 in the rat brain. *Journal of Molecular Neuroscience, 31*(1), 47–58. [DOI:10.1007/BF02686117] [PMID]

Carlomagno, Y., Chung, D. C., Yue, M., Castanedes-Casey, M., Madden, B. J., & Dunmore, J., et al. (2017). An acetylation-phosphorylation switch that regulates tau aggregation propensity and function. *The Journal of Biological Chemistry, 292*(37), 15277–15286. [DOI:10.1074/jbc.M117.794602] [PMID]

Cook, C., Carlomagno, Y., Gendron, T. F., Dunmore, J., Scheffel, K., & Stetler, C., et al. (2014). Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. *Human Molecular genetics, 23*(1), 104–116. [DOI:10.1093/hmg/ddt402] [PMID]

Cooper EL, Ma MJ. Alzheimer disease: Clues from traditional and complementary medicine. Journal of Traditional and Complementary Medicine. 2017; 7(4):380-385. [DOI:10.1016/j.jtcme.2016.12.003] [PMID]

d'Ydewalle, C., Krishnan, J., Chiheb, D. M., Van Damme, P., Irobi, J., & Kozikowski, A. P., et al. (2011). HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. *Nature Medicine, 17*(8), 968–974. [DOI:10.1038/nm.2396] [PMID]

Ding, H., Dolan, P. J., & Johnson, G. V. (2008). Histone deacetylase 6 interacts with the microtubule-associated protein tau. *Journal of Neurochemistry, 106*(5), 2119–2130. [DOI:10.1111/j.1471-4159.2008.05564.x] [PMID]

Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M., & Tsai, L. H. (2007). Recovery of learning and memory is associated with chromatin remodelling. *Nature, 447*(7141), 178–182. [DOI:10.1038/nature05772] [PMID]

Fischer, D. D., Cai, R., Bhatia, U., Asselbergs, F. A., Song, C., & Terry, R., et al. (2002). Isolation and characterization of a novel class II histone deacetylase, HDAC10. *The Journal of Biological Chemistry, 277*(8), 6656–6666. [DOI:10.1074/jbc.M108055200] [PMID]

Ghorbandaiepour, T., Sadroddiny, E., Zahmatkesh, M., & Hassanzadeh, G. (2024). Inhibition of hippocampal melatonin synthesis by siRNA induced learning and memory deficits in male rats. *Hormones and Behavior, 164*, 105599. [DOI:10.1016/j.yhbeh.2024.105599] [PMID]

Gibson, C. L., & Murphy, S. P. (2010). Benefits of histone deacetylase inhibitors for acute brain injury: A systematic review of animal studies. *Journal of Neurochemistry, 115*(4), 806–813. [DOI:10.1111/j.1471-4159.2010.06993.x] [PMID]

Gräff, J., Rei, D., Guan, J. S., Wang, W. Y., Seo, J., & Hennig, K. M., et al. (2012). An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature, 483*(7388), 222–226. [DOI:10.1038/nature10849] [PMID]

Gräff, J., & Tsai, L. H. (2013). The potential of HDAC inhibitors as cognitive enhancers. *Annual Review of Pharmacology and Toxicology, 53*, 311–330. [DOI:10.1146/annurev-pharmtox-011112-140216] [PMID]

Guardiola, A. R., & Yao, T. P. (2002). Molecular cloning and characterization of a novel histone deacetylase HDAC10. *The Journal of Biological Chemistry, 277*(5), 3350–3356. [DOI:10.1074/jbc.M109861200] [PMID]

Hubbert, C., Guardiola, A., Shao, R., Kawaguchi, Y., Ito, A., & Nixon, A., et al. (2002). HDAC6 is a microtubule-associated deacetylase. *Nature, 417*(6887), 455–458. [DOI:10.1038/417455a] [PMID]

Kao, H. Y., Lee, C. H., Komarov, A., Han, C. C., & Evans, R. M. (2002). Isolation and characterization of mammalian HDAC10, a novel histone deacetylase. *The Journal of Biological Chemistry, 277*(1), 187–193. [DOI:10.1074/jbc.M108931200] [PMID]

Karimi-Zandi, L., Zahmatkesh, M., Hassanzadeh, G., & Hosseinzadeh, S. (2022). Increment of CSF fractalkine-positive microvesicles preceded the spatial memory impairment in amyloid beta neurotoxicity. *Cytokine, 160*, 156050. [DOI:10.1016/j.cyto.2022.156050] [PMID]

Li, Y., Shin, D., & Kwon, S. H. (2013). Histone deacetylase 6 plays a role as a distinct regulator of diverse cellular processes. *The FEBS Journal, 280*(3), 775–793. [DOI:10.1111/febs.12079] [PMID]

Lindner, M. D., & Gribkoff, V. K. (1991). Relationship between performance in the Morris water task, visual acuity, and thermoregulatory function in aged F-344 rats. *Behavioural Brain Research, 45*(1), 45–55. [DOI:10.1016/S0166-4328(05)80179-2] [PMID]

Liu, R. T., Zou, L. B., & Lü, Q. J. (2009). Liquiritigenin inhibits Abeta(25-35)-induced neurotoxicity and secretion of Abeta(1-40) in rat hippocampal neurons. *Acta Pharmacologica Sinica, 30*(7), 899–906. [DOI:10.1038/aps.2009.74] [PMID]

Lu, X., Wang, L., Yu, C., Yu, D. & Yu, G. 2015. Histone acetylation modifiers in the pathogenesis of Alzheimer's disease. *Frontiers in Cellular Neuroscience, 9*, 226. [DOI:10.3389/fncel.2015.00226]

Marinho, D., Ferreira, I. L., Lorenzoni, R., Cardoso, S. M., Santana, I., & Rego, A. C. (2023). Reduction of class I histone deacetylases ameliorates ER-mitochondria cross-talk in Alzheimer's disease. *Aging Cell, 22*(8), e13895. [DOI:10.1111/acel.13895] [PMID]

Mizuno, M., Yamada, K., Maekawa, N., Saito, K., Seishima, M., & Nabeshima, T. (2002). CREB phosphorylation as a molecular marker of memory processing in the hippocampus for spatial learning. *Behavioural Brain Research, 133*(2), 135–141. [DOI:10.1016/s0166-4328(01)00470-3] [PMID]

Mohammadi, S., Zahmatkesh, M., Asgari, Y., Aminyavari, S., & Hassanzadeh, G. (2023). Evaluation of hippocampal arylalkylamine N-acetyltransferase activity in amyloid-β neurotoxicity. *Journal of Molecular Endocrinology, 71*(2), e220161. [DOI:10.1530/JME-22-0161] [PMID]

Oehme, I., Linke, J. P., Böck, B. C., Milde, T., Lodrini, M., & Hartenstein, B., et al. (2013). Histone deacetylase 10 promotes autophagy-mediated cell survival. *Proceedings of the National Academy of Sciences of the United States of America, 110*(28), E2592–E2601. [DOI:10.1073/pnas.1300113110] [PMID]

Paul, C. M., Magda, G., & Abel, S. (2009). Spatial memory: Theoretical basis and comparative review on experimental methods in rodents. *Behavioural Brain Research, 203*(2), 151–164. [DOI:10.1016/j.bbr.2009.05.022] [PMID]

Paxinos, G. & Watson, C. (2009). *The rat brain in stereotaxic coordinates*. New York: Academic Press. [Link]

Peixoto, L., & Abel, T. (2013). The role of histone acetylation in memory formation and cognitive impairments. *Neuropsychopharmacology, 38*(1), 62–76. [DOI:10.1038/npp.2012.86] [PMID]

Peleg, S., Sananbenesi, F., Zovoilis, A., Burkhardt, S., Bahari-Javan, S., & Agis-Balboa, R. C., et al. (2010). Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science, 328*(5979), 753–756. [DOI:10.1126/science.1186088] [PMID]

Ricobaraza, A., Cuadrado-Tejedor, M., Pérez-Mediavilla, A., Frechilla, D., Del Río, J., & García-Osta, A. (2009). Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer's disease mouse model. *Neuropsychopharmacology, 34*(7), 1721–1732. [DOI:10.1038/npp.2008.229] [PMID]

Aminyavari, S., Zahmatkesh, M., Khodagholi, F., & Sanati, M. (2019). Anxiolytic impact of Apelin-13 in a rat model of Alzheimer's disease: Involvement of glucocorticoid receptor and FKBP5. *Peptides, 118,* 170102. [DOI:10.1016/j.peptides.2019.170102] [PMID]

Sartor, G. C., Powell, S. K., Brothers, S. P., & Wahlestedt, C. (2015). Epigenetic readers of lysine acetylation regulate cocaine-induced plasticity. *The Journal of Neuroscience, 35*(45), 15062–15072. [DOI:10.1523/JNEUROSCI.0826-15.2015] [PMID]

Selenica, M. L., Benner, L., Housley, S. B., Manchec, B., Lee, D. C., & Nash, K. R., et al. (2014). Histone deacetylase 6 inhibition improves memory and reduces total tau levels in a mouse model of tau deposition. *Alzheimer's Research & Therapy, 6*(1), 12. [DOI:10.1186/alzrt241] [PMID]

Simões-Pires, C., Zwick, V., Nurisso, A., Schenker, E., Carrupt, P. A., & Cuendet, M. (2013). HDAC6 as a target for neurodegenerative diseases: What makes it different from the other HDACs?. *Molecular Neurodegeneration, 8*, 7. [DOI:10.1186/1750-1326-8-7] [PMID]

Naderi, S., Khodagholi, F., Pourbadie, H. G., Naderi, N., Rafiei, S., & Janahmadi, M., et al. (2023). Role of amyloid beta (25-35) neurotoxicity in the ferroptosis and necroptosis as modalities of regulated cell death in Alzheimer's disease. *Neurotoxicology, 94*, 71–86. [DOI:10.1016/j.neuro.2022.11.003] [PMID]

Tanis, K. Q., Duman, R. S., & Newton, S. S. (2008). CREB binding and activity in brain: Regional specificity and induction by electroconvulsive seizure. *Biological Psychiatry, 63*(7), 710–720. [DOI:10.1016/j.biopsych.2007.08.003] [PMID]

Tong, J. J., Liu, J., Bertos, N. R., & Yang, X. J. (2002). Identification of HDAC10, a novel class II human histone deacetylase containing a leucine-rich domain. *Nucleic Acids Research, 30*(5), 1114–1123. [DOI:10.1093/nar/30.5.1114] [PMID]

Walker, M. P., LaFerla, F. M., Oddo, S. S., & Brewer, G. J. (2013). Reversible epigenetic histone modifications and Bdnf expression in neurons with aging and from a mouse model of Alzheimer's disease. *Age, 35*(3), 519–531. [DOI:10.1007/s11357-011-9375-5] [PMID]

Xu, W. S., Parmigiani, R. B., & Marks, P. A. (2007). Histone deacetylase inhibitors: Molecular mechanisms of action. *Oncogene, 26*(37), 5541–5552. [DOI:10.1038/sj.onc.1210620] [PMID]

Zhang, L., Sheng, S., & Qin, C. (2013). The role of HDAC6 in Alzheimer's disease. *Journal of Alzheimer's Disease, 33*(2), 283–295. [DOI:10.3233/JAD-2012-120727] [PMID]

Zhang, X., Yuan, Z., Zhang, Y., Yong, S., Salas-Burgos, A., & Koomen, J., et al. (2007). HDAC6 modulates cell motility by altering the acetylation level of cortactin. *Molecular Cell, 27*(2), 197–213. [DOI:10.1016/j.molcel.2007.05.033] [PMID]

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