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RESEARCH

Fasted-State Aerobic Exercise Enhances Cognition and Hippocampal BDNF Signaling in an Alzheimer's Disease Rat Model

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Abstract

Alzheimer's disease (AD) is a multifactorial disorder that demands a comprehensive management strategy. Both aerobic exercise training and intermittent fasting (IF) have been shown to ameliorate AD symptoms, yet the impact of exercise in the fasted state remains understudied. This study compared the effects of four weeks of moderate-intensity treadmill running in either a fasted or a normal fed state on cognitive function and hippocampal BDNF signaling in an amyloid-β $(Aβ)_{1–42}$-injected rat model of AD. Twenty-month-old male Wistar rats were allocated into five groups ($n=12$ each): AD, AD plus IF (ADIF), AD plus exercise training (ADET), AD plus IF plus exercise training (ADIFET), and control. AD was induced by bilateral intra-hippocampal $Aβ_{1–42}$ injection. Exercise interventions (fasted or fed) were conducted 5 days/week for 4 weeks. Aβ injection significantly impaired learning and memory and reduced hippocampal levels of PKA, CREB, and BDNF ($p<0.001$). Both fasting and exercise independently elevated plasma and hippocampal β-hydroxybutyrate (βHB) ($p<0.001$), with the highest βHB increase observed in the fasted-exercise group ($p<0.01$). All intervention groups (ADIF, ADET, and ADIFET) demonstrated significant improvements in cognitive performance and hippocampal levels of PKA, CREB, and BDNF ($p<0.001$). The combined fasting plus exercise group produced greater benefits than either IF or exercise alone ($p<0.05$), and exercise alone outperformed fasting alone ($p<0.05$). These findings indicate that aerobic exercise in the fasted state offers superior neuroprotective and cognitive benefits, likely via upregulation of βHB/PKA/CREB/BDNF signaling, highlighting fasted-state exercise as a promising therapeutic approach for AD.

Keywords Alzheimer's disease · Aerobic exercise · Intermittent fasting · Cognitive function · B-hydroxybutyrate · BDNF

Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 50 million individuals worldwide and imposing substantial burdens on healthcare systems and families [1]. It is characterized by progressive neurodegeneration, cognitive decline, and accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles [2]. These complex pathologies make AD a multifactorial disorder that demands comprehensive therapeutic approaches. The progressive nature of the disease, combined with limited pharmaceutical interventions, has increased research efforts toward identifying effective non-pharmacological strategies that can attenuate cognitive decline and potentially modify disease progression.

The hippocampus, a brain structure critical for learning and memory formation, is particularly vulnerable in AD pathophysiology. Hippocampal atrophy and dysfunction

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are early hallmarks of the disease and correlate strongly with cognitive impairment severity [3]. Brain-derived neurotrophic factor (BDNF) emerges as a pivotal molecular mediator of hippocampal neuroplasticity and cognitive function. This neurotrophin promotes synaptic plasticity, supports neuronal survival, and facilitates memory consolidation [4]. Importantly, BDNF levels are markedly reduced in AD patients, even before plaque and tangle formation [5], suggesting its potential as both a biomarker and therapeutic target.

Intermittent fasting (IF), a kind of caloric restriction, has emerged as a strategy with neuroprotective potential in AD models. Preclinical evidence demonstrates that IF enhances hippocampal neurogenesis and synaptic plasticity through pathways involving BDNF and cyclic adenosine monophosphate response element-binding protein (CREB) [6]. Fasting-induced metabolic stress appears to trigger adaptive neuroplasticity, as evidenced by synaptic changes and improved cognition in fasting animals [7, 8]. The metabolic shift during fasting promotes ketone body production, particularly β-hydroxybutyrate (βHB), which serves as an alternative brain fuel source and exhibits neuroprotective properties [9].

Aerobic exercise training has attracted substantial scientific attention as another promising non-pharmacological intervention for AD management. Accumulating evidence demonstrates that moderate-intensity aerobic exercise positively correlates with cognitive function and memory in both healthy individuals and those with cognitive impairment [10–12]. Greater aerobic fitness and physical activity have also been associated with larger hippocampal volume and preserved cognition in aging [13]. Exercise-induced neuroprotection likely involves multiple mechanisms, including increased BDNF expression, improved cerebral blood flow, reduced neuroinflammation, and enhanced neurogenesis [5, 12]. Exercise also elevates βHB levels, which have been reported to promote hippocampal BDNF expression [14], potentially linking exercise-driven metabolic changes to brain plasticity.

Although many studies have examined exercise or fasting alone in mitigating Aβ-related damage, to our knowledge, no study has investigated their combined effect in an AD model. Limited research in other contexts (e.g., obesity) has yielded mixed results when combining exercise with IF/caloric restriction [15–19]. It remains unclear what types of strategies using exercise and fasting are most effective in targeting AD symptoms. Here, we hypothesized that exercise in a fasted state would provide additional neuroprotection benefits by augmenting βHB production. Therefore, the aim of this study was to investigate the effect of a 4-week moderate-intensity aerobic running, either in the fasted state (when βHB concentration was already elevated) or in the normal fed state, on cognitive function and hippocampal protein kinase A (PKA)/CREB/BDNF signaling in a rat model of AD.

Methods

Animals

Sixty male Wistar rats (20 months old, 630 ± 20 g) were obtained from the Animals Center of Pasture Institute, Iran. All animals were housed in groups (3 rats per cage) under controlled conditions (22 ± 1 °C, 50–60% humidity, 12/12 h light/dark cycle). Animal care and experimental procedures followed the guidelines of the National Institutes of Health and were approved by the Research Ethics Committee of Islamic Azad University, Central Tehran Branch (Approval No. IR.IAU.CTB.REC.1400.015).

Experimental Design

After a one-week familiarization with the new environment, animals underwent an acclimatization phase for a week. The animals were subjected to fasting (~14 h) and treadmill running in a fasting state (10 min, speed 5 m/min, incline 0%) three times over one week. Rats were then randomly assigned to five groups (n = 12 each): AD, AD plus IF (ADIF), AD plus exercise training (ADET), AD plus IF plus exercise training (ADIFET), or control. The group sizes (n = 12/group) were selected based on prior similar studies [15, 19]. A schematic of the study design is shown in Fig. 1.

Aβ Injection Procedure

To induce an AD-like pathology, $A\beta_{1-42}$ (Abcam, Germany) was prepared in 3% DMSO at 5 µg/µL, aliquoted, and stored at − 80 °C. Aliquots were incubated at 37 °C for 7 days before use to promote fibrillization. One week post-acclimatization, rats were anesthetized (ketamine 80 mg/kg + xylazine 10 mg/kg, i.p.) and placed in a stereotaxic frame. After a midline scalp incision, bilateral hippocampal burr holes were drilled using Paxinos and Watson coordinates: AP −3.8 mm, ML ± 2.2 mm, DV −2.7 mm. A Hamilton syringe infused 1 µL of fibrillar $A\beta_{1-42}$ into each hippocampus at 0.2 µL/min; the needle was left in place for 5 min to prevent backflow [20].

Animals Feeding and Intermittent Fasting

One week after surgery, animals in the ADIF and ADIFET groups underwent IF intervention for 4 weeks. IF was applied from 06:00 to 20:00 (~14 h) daily. This regimen

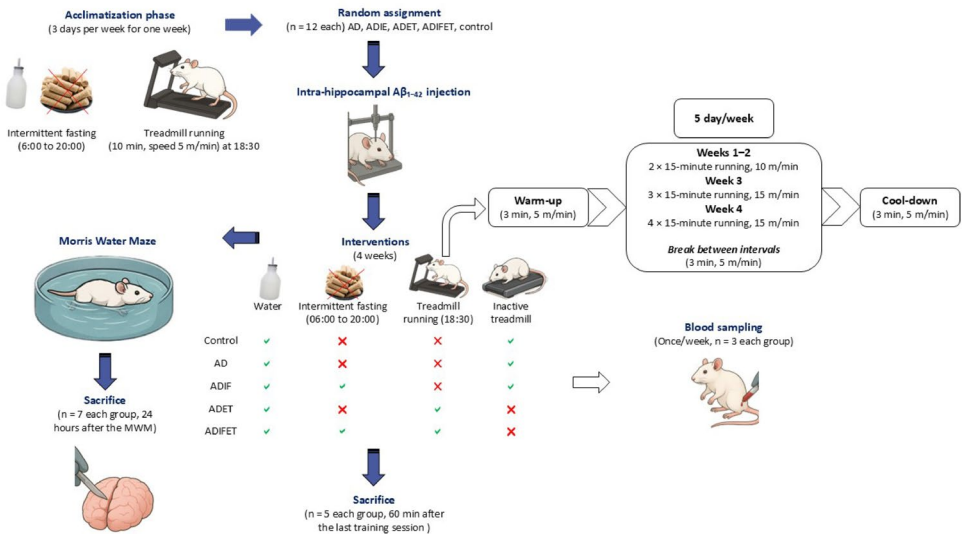

Fig. 1 Schematic representation of study design

was chosen because it is known to confer neuroprotective effects [19] and to significantly increase βHB concentration in rodents [21, 22]. Food was available during the 10-hour active phase (zeitgeber time (ZT)12– ZT22, where ZT0 = lights on, ZT12 = lights off) [8]. Water was available *ad libitum* at all times. Rats in the AD, ADET, and control groups had continuous access to food, except during the exercise training time.

Body Weight Monitoring

Body weight was measured once weekly during the 4-week intervention using a calibrated digital scale (ASC6, Taiwan). Measurements were taken at the same time of day (ZT0, onset of the light phase) and at least 24 h after the last exercise session to minimize diurnal variation and acute post-exercise effects.

Exercise Training Protocol

Seven days after surgery, rats in the exercise groups began running on a motorized treadmill (BioMed Easy Technologies, China) 5 days/week for 4 weeks. The progressive training protocol was as follows:

Weeks 1–2: Two 15-min runs at 10 m/min (with 3-min walks at 5 m/min between runs). Week 3: Three 15-min runs at 15 m/min (with 3-min walks at 5 m/min between runs). Week 4: Four 15-min runs at 15 m/min (with 3-min walks at 5 m/min between runs).

Each exercise session started at 18:30 (after a 12.5-h fast) and included a 3-min warm-up and a 3-min cool-down at 5 m/min. The treadmill incline was 0%. A mild 0.5 mA electric stimulus (non-stressful) was used to maintain consistent running. To control for handling and environmental factors, rats in the AD, ADIF, and control groups were placed on an identical, inactive treadmill equipped with the same shock parameters, but without enforced exercise.

Cognitive Function Assessment

To evaluate spatial learning and memory, the Morris Water Maze (MWM) was administered 48 h after the final exercise session. The apparatus consisted of a circular metal pool with matte-black walls, filled to a depth of 30 cm with water maintained at 21 ± 2 °C. Animal movements were captured by an overhead camera and analyzed using EthoVision 7 software. Twenty-four hours before training, each rat swam freely for 2 min without a platform to acclimate to the environment (habituation). Over 4 consecutive days, each animal completed 4 trials per day to locate a hidden platform positioned at the center of the southeast quadrant. At the start of each trial, rats were gently placed on the platform for 15–20 s before being released randomly from one of the 4 cardinal points. They then swam to the submerged platform, upon which they remained for 20 s. Escape latency (time to reach the platform) was recorded for every trial (acquisition/learning phase). Twenty-four hours after the final acquisition session, spatial memory retention was assessed in a single, 60-s probe trial during which the platform was removed. The cumulative time spent in the target quadrant was measured (Probe Trial). Immediately following the probe trial, a white platform was raised to the water surface to confirm sensorimotor integrity and motivation. Each rat was randomly released into the water from the 4 cardinal directions in 4 trials. Rats needed to swim to and climb onto this visible platform, and escape latency was recorded. Any animal failing to locate the platform within 60 s in any of the four visible-platform trials was excluded from further analysis (visible-platform control) [23].

Sampling and Sacrificing

For hippocampal βHB measurements, 5 animals per group were randomly anesthetized by injection of a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) 60 min after the last training session. The remaining rats were sacrificed 24 h after behavioral testing. Brains were rapidly removed; hippocampi were dissected on ice, frozen in liquid nitrogen, and stored at −80 °C until analyses.

Glucose and βHB Measurement

The glucose and βHB levels in blood were measured 4 times (once a week) before and 60 min after exercise. At each time, 3 animals were randomly selected from each group, and blood samples were collected from the tip of their tails. After treatment, these animals were moved to their cages and given free access to food and water. Blood samples were centrifuged at 3000×g for 10 min at 4 °C, and the plasma was stored at −80 °C until glucose and βHB analysis. Hippocampal tissues were homogenized in 1 mL PBS, treated by two freeze–thaw cycles to break cell membranes, and centrifuged at 5000×g for 5 min at 4 °C. Plasma and hippocampal supernatants were applied to measure βHB by the ELISA method (ab83390, Abcam), according to the manufacturer's instructions. The glucose oxidase method (Beckman Instruments, Palo Alto, CA) was used to measure plasma glucose levels.

Western Blotting

Hippocampal tissues were homogenized in ice-cold RIPA buffer (Cell Signaling Technology, Danvers, MA) containing protease and phosphatase inhibitor cocktails. Lysates were centrifuged at 12,000 × g for 15 min at 4 °C, and the supernatant was collected for protein quantification by the bicinchoninic acid (BCA) assay. Equal amounts of protein (20–30 µg per lane) were denatured in Laemmli sample buffer at 95 °C for 5 min, separated on 10–12% SDS–PAGE gels, and transferred onto PVDF membranes using a semi-dry blotting system. Membranes were blocked for 1 h at room temperature in 5% non-fat dry milk in Tris-buffered saline with 0.1% Tween-20 (TBST). Blots were then incubated overnight at 4 °C with primary antibodies against PKA catalytic subunit (1:1,000; ab227848, Abcam), total CREB (1:1,000; ab32515, Abcam), and BDNF (1:500; ab108319, Abcam) diluted in blocking buffer. After three 10-min washes in TBST, membranes were incubated with an appropriate HRP-conjugated secondary antibody (1:5,000) for 2 h at room temperature. Following further washes, immunoreactive bands were visualized via enhanced chemiluminescence and imaged on a digital detection system. Band intensities were quantified by densitometry using ImageJ, with PKA, CREB, and BDNF signals normalized to β-actin (1:1,000; loading control; ab227387, Abcam). All experiments were performed in duplicate.

Statistical Analysis

Normality was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated by Levene's test. The two-way (week/day × group) and three-way (time × week × group) repeated measures analysis of variance (ANOVA) were used to evaluate body weight and daily learning during the acquisition phase, as well as plasma parameters (glucose and βHB), respectively. For the primary analysis of treatment effects, a 2 × 2 factorial ANOVA was conducted with IF (present vs. absent) and exercise (present vs. absent) as between-subjects factors. This analysis included the four AD groups to specifically examine the main effects and interaction effects of the interventions. To analyze these effects relative to healthy controls, a one-way ANOVA comparing all five groups (including the control) was used. When significant effects were detected, Fisher's Least Significant Difference (LSD) post hoc tests were applied. Effect size was calculated using partial eta squared (ηp^2) (<0.01, 0.01–0.059, 0.06–0.139, and ≥0.14 for trivial, small, moderate, and large effects, respectively). Analyses were performed in SPSS version 27, and significance was set at $p < 0.05$.

Results

Previous studies and our pilot data confirm that intra-hippocampal $A\beta_{1-42}$ injections impair cognitive function [20, 24]. One week post-injection, $A\beta_{1-42}$-infused rats (n = 7) exhibited significant deficits in spatial learning and memory, evidenced by increased escape latency, as well as reduced time spent in the target quadrant, compared with healthy controls. These deficits persisted for at least 6 weeks (data not shown).

The analysis of body weight revealed significant main effects for both week ($F = 7.747$, $p < 0.001$, $\eta p^2 = 0.15$) and group ($F = 7.944$, $p < 0.001$, $\eta p^2 = 0.41$), as well as a significant interaction between week and group ($F = 8.736$, $p < 0.001$, $\eta p^2 = 0.44$). Body weight did not differ significantly from baseline in control, AD, and ADET animals ($p > 0.05$). The ADIF groups showed significant reductions in body weight from baseline during weeks 1–4 and relative to controls ($p < 0.01$). The ADET group also had lower body weight than the control group during weeks 2–4 ($p < 0.001$). Additionally, animals in the ADIF groups lost significantly

more weight than those in the ADET group ($p<0.05$; Fig. 2).

A 2×2 ANOVA indicated main effects of IF (F=7.568, $p<0.05$, $\eta p^2=0.24$) and exercise (F=14.249, $p<0.001$, $\eta p^2=0.37$), but no interaction effect of IF × exercise (F=0.015, $p>0.05$, $\eta p^2=0.001$) on the 4-day mean escape latency. The two-way repeated measures ANOVA revealed significant main effects of day (F=125.361, $p<0.001$, $\eta p^2=0.81$) and group (F=6.462, $p<0.001$, $\eta p^2=0.46$), but no significant day × group interaction (F=0.54, $p>0.05$, $\eta p^2=0.1$) for escape latency. One-way ANOVA conducted for each day showed no significant difference among groups on day 1 ($p>0.05$), but significant differences on day 2 (F=4.558, $p<0.01$, $\eta p^2 = 0.52$), day 3 (F=5.379, $p<0.01$, $\eta p^2 = 0.56$), and day 4 (F=4.909, $p<0.01$, $\eta p^2 = 0.54$). The AD group had longer escape latencies than the control group on days 2–4 ($p<0.001$). The ADIFET group (days 2–4, $p<0.001$), the ADET group (days 2 and 4, $p<0.05$), and the ADIF group (day 4, $p<0.01$) all showed significantly shorter escape latencies compared with the AD group. Moreover, the ADIFET group demonstrated a greater reduction in latency than the ADIF group ($p<0.05$) but did not differ significantly from the ADET group ($p=0.085$) on day 2 (Fig. 3A).

Both IF (F=8.190, $p<0.01$, $\eta p^2=0.25$) and exercise (F=20.755, $p<0.001$, $\eta p^2=0.46$) significantly improved memory performance, but there was not a significant IF × exercise interaction (F=0.064, $p>0.05$, $\eta p^2=0.003$). One-way ANOVA indicated a significant between-group difference for memory (F=10.568, $p<0.001$, $\eta p^2=0.58$). The time spent in the targeted quadrant was reduced after $A\beta_{1-42}$ injection ($p<0.001$), while the impairment was ameliorated by IF ($p<0.05$), exercise ($p<0.01$), and IF plus exercise ($p<0.001$). Moreover, the ADIFET group spent more time in the targeted quadrant than the ADIF animals ($p<0.01$; Fig. 3B).

In the visible platform test, a 2×2 ANOVA revealed no significant effects from IF (F=0.029, $p>0.05$, $\eta p^2=0.001$), exercise (F=0.056, $p>0.05$, $\eta p^2=0.002$), or their interaction (F=0.007, $p>0.05$, $\eta p^2=0.000$), and a one-way ANOVA showed no group differences (F=0.039, $p=0.997$, $\eta p^2=0.005$), indicating similar sensorimotor function and motivation (Fig. 3C).

Plasma βHB levels showed significant main effects of time (F=81.164, $p<0.001$, $\eta p^2=0.89$) and group (F=69.676, $p<0.001$, $\eta p^2=0.96$), and a significant time × group interaction (F=28.019, $p<0.001$, $\eta p^2=0.92$). In all weeks, pre-exercise plasma βHB was higher in the IF animals than in controls ($p<0.01$). Treadmill running increased plasma βHB compared to pre-exercise ($p<0.001$). Post-exercise plasma βHB was significantly higher in ADIFET rats than in ADIF or ADET rats at each weekly timepoint ($p<0.001$; Table 1).

Significant main effects of time (F=66.748, $p<0.001$, $\eta p^2=0.87$) and group (F=114.986, $p<0.001$, $\eta p^2=0.98$), as well as time × group interaction (F=12.958, $p<0.001$, $\eta p^2=0.84$), were observed for plasma glucose levels. Treadmill running significantly reduced plasma glucose in the ADET group in the second and fourth weeks, as well as in the ADIFET group in the first week, compared to pre-exercise levels ($p<0.05$). The post- to pre-exercise reduction in plasma glucose at the other timepoints did not reach statistical significance ($p>0.05$). Post-exercise plasma glucose was significantly lower in ADIFET rats than in the ADET group at each weekly timepoint ($p<0.001$). Pre- and post-exercise plasma glucose levels were lower in the IF animals than in the control, AD, and ADET groups throughout all measurements ($p<0.001$). There were no significant differences in pre-exercise glucose levels between the ADET, AD, and control groups at any time ($p>0.05$; Table 1), indicating that neither Aβ treatment nor exercise training alters baseline glucose metabolism. Taken together, these results

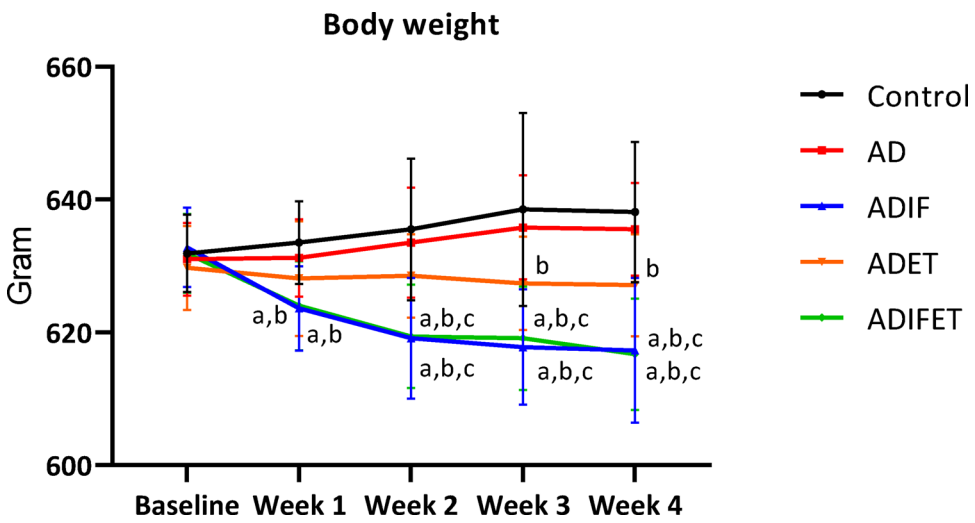

Fig. 2 Effect of intermittent fasting, exercise in the normal fed state, and exercise in the fasted state on the animals' body weight ($n=12$/group). Main effects of time ($p<0.001$, $\eta p_2 = 0.15$) and group ($p<0.001$, $\eta p^2 = 0.41$), and interaction effects ($p<0.001$, $\eta p^2 = 0.44$) were detected for body weight analysis. a $p<0.001$ significant difference from baseline. b $p<0.01$ significant difference from control. c $p<0.05$ significant difference from ADET group

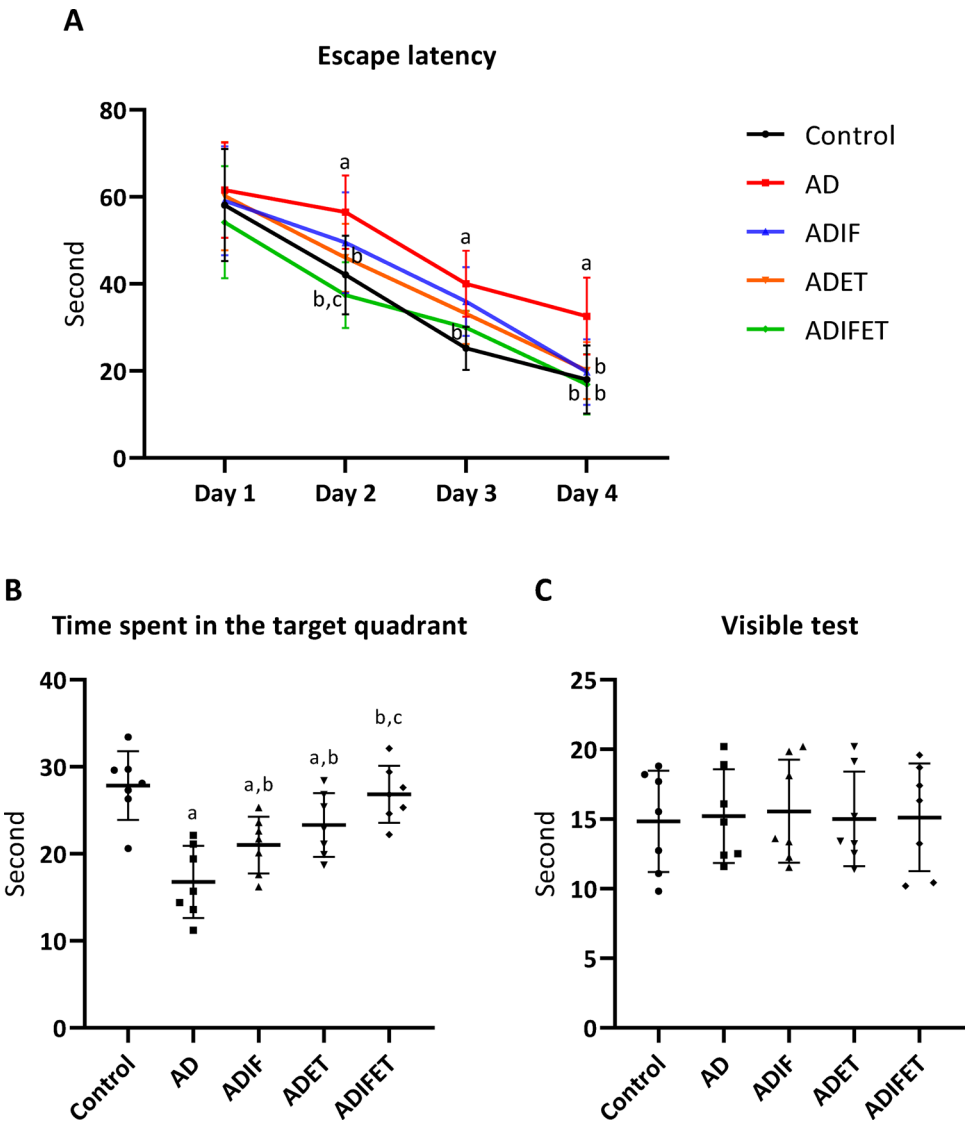

Fig. 3 Effect of intermittent fasting, exercise in the normal fed state, and exercise in the fasted state on spatial learning and memory in $A\beta_{1-42}$-injected rat model of AD ($n=7$/group). The escape latency in the acquisition phase (**A**). The time spent in the target quadrant in the probe trial (**B**). Time to find the platform in the visible test (**C**). Main effects of day ($p<0.001$, $\eta p^2 = 0.81$) and group ($p<0.001$, $\eta p^2 = 0.46$), but no significant day × group interaction ($p>0.05$, $\eta p^2 = 0.1$) were detected for escape latency. There was also a between-group difference in performance in the probe trial ($p<0.001$, $\eta p^2 = 0.58$). a $p<0.05$ significant difference from control. b $p<0.05$ significant difference from AD. c $p<0.05$ significant difference from ADIF

confirm that the IF successfully induced a metabolic state of ketosis (high βHB, low glucose) in both exercised and non-exercised animals, whereas the standard diet (with or without exercise) kept animals in a carbohydrate-dependent metabolic state.

A 2×2 ANOVA showed main effects of IF ($F=65.318$, $p<0.001$, $\eta p^2=0.8$) and exercise ($F=125.457$, $p<0.001$, $\eta p^2=0.89$), but no interaction effect of IF × exercise ($F=0.163$, $p>0.05$, $\eta p^2=0.01$) for βHB concentration in the hippocampus. Hippocampal βHB also revealed significant differences between the groups ($F=66.921$, $p<0.001$, $\eta p^2=0.93$). Both IF and exercise increased hippocampal βHB ($p<0.001$). The ADIFET animals had higher hippocampal βHB than either ADIF or ADET ($p<0.001$), and ADET had higher βHB than ADIF ($p<0.05$; Fig. 4).

A 2×2 factorial ANOVA revealed significant main effects of IF and exercise on hippocampal PKA ($F=24.421$, $p<0.001$, $\eta p^2=0.5$; and $F=29.410$, $p<0.001$, $\eta p^2=0.55$, respectively), CREB ($F=61.291$, $p<0.001$, $\eta p^2=0.72$; and $F=142.690$, $p<0.001$, $\eta p^2=0.86$, respectively), and BDNF ($F=70.523$, $p<0.001$, $\eta p^2=0.75$; and $F=169.016$, $p<0.001$, $\eta p^2=0.88$, respectively) levels, indicating that each intervention independently increased these protein expressions. The IF × exercise interaction on PKA ($F=0.153$, $p>0.05$, $\eta p^2=0.006$), CREB ($F=4.062$, $p>0.05$, $\eta p^2=0.145$), and BDNF ($F=3.366$, $p>0.05$, $\eta p^2=0.123$) did not reach statistical significance, suggesting that the combined effect of IF and exercise was not significantly greater than the sum of their individual effects within the factorial model. Hippocampal PKA ($F=26.945$, $p<0.001$, $\eta p^2=0.84$), CREB ($F=65.170$, $p<0.001$, $\eta p^2=0.92$), and BDNF ($F=79.468$, $p<0.001$, $\eta p^2=0.94$) protein levels exhibited significant between-group differences, as analyzed by one-way ANOVA. $A\beta_{1-42}$ injection significantly reduced PKA, CREB, and BDNF ($p<0.001$). However, IF, exercise, and the combination of IF and exercise compensated for the

Table 1 Plasma glucose and βHB levels during the four-week intervention period ($n=3$/group)

		Control	AD	ADIF	ADET	ADIFET
Glucose levels (mg/dL)						
Week 1	Pre-exercise	125 ± 11	131 ± 17	75 ± 8[a, b]	123 ± 19[c]	78 ± 7[a, b, d]
	Post- exercise	122 ± 5	126 ± 10	71 ± 6[a, b]	106 ± 9[c]	73 ± 7[a, b, d, e]
Week 2	Pre-exercise	125 ± 12	128 ± 12	73 ± 9[a, b]	120 ± 8[c]	77 ± 12[a, b, d]
	Post- exercise	122 ± 3	125 ± 6	72 ± 8[a, b]	107 ± 6[c, e]	74 ± 10[a, b, d]
Week 3	Pre-exercise	131 ± 14	124 ± 14	79 ± 14[a, b]	129 ± 22[c]	79 ± 6[a, b, d]
	Post- exercise	126 ± 8	119 ± 6	75 ± 11[a, b]	107 ± 10[c]	74 ± 5[a, b, d]
Week 4	Pre-exercise	124 ± 12	122 ± 9	77 ± 12[a, b]	123 ± 9[c]	69 ± 8[a, b, d]
	Post- exercise	120 ± 5	121 ± 4	75 ± 9[a, b]	107 ± 6[c, e]	66 ± 6[a, b, d]
βHB levels (µmol/L)						
Week 1	Pre-exercise	135 ± 143	151 ± 38	471 ± 91[a, b, d]	170 ± 85	443 ± 118[a, b, d]
	Post- exercise	156 ± 69	199 ± 59	499 ± 101[a, b]	496 ± 159[a, b, e]	1002 ± 270[a, b,c, d, e]
Week 2	Pre-exercise	153 ± 75	167 ± 38	546 ± 194[a, b, d]	158 ± 96	524 ± 125[a, b, d]
	Post- exercise	188 ± 63	173 ± 91	583 ± 199[a, b]	523 ± 161[a, b, e]	1060 ± 197[a, b,c, d, e]
Week 3	Pre-exercise	163 ± 119	143 ± 86	617 ± 184[a, b, d]	181 ± 102	640 ± 196[a, b, d]
	Post- exercise	178 ± 110	173 ± 100	635 ± 101[a, b]	540 ± 146[a, b, e]	1360 ± 454[a, b,c, d, e]
Week 4	Pre-exercise	146 ± 61	156 ± 70	633 ± 113[a, b, d]	147 ± 62	679 ± 143[a, b, d]
	Post- exercise	205 ± 36	156 ± 32	630 ± 104[a, b]	593 ± 159[a, b, e]	1600 ± 555[a, b,c, d, e]

Data are presented as mean ± standard deviation. βHB, β-hydroxybutyrate; AD, Alzheimer's disease; ADIF, Alzheimer's disease plus intermittent fasting; ADET, Alzheimer's disease plus exercise training; ADIFET, Alzheimer's disease plus intermittent fasting plus exercise training. There were main effects of time ($p < 0.001$, $\eta p^2 = 0.89$) and group ($p < 0.001$, $\eta p^2 = 0.96$), and a time × group interaction effect ($p < 0.001$, $\eta p^2 = 0.92$) on plasma βHB levels. Main effects of time ($p < 0.001$, $\eta p^2 = 0.87$) and group ($p < 0.001$, $\eta p^2 = 0.98$), as well as time × group interaction ($p < 0.001$, $\eta p^2 = 0.84$), were also observed for plasma glucose levels. a $p < 0.05$ significant difference from control; b $p < 0.05$ significant difference from AD; c $p < 0.05$ significant difference from ADIF; d $p < 0.05$ significant difference from ADET; e $p < 0.05$ significant difference from pre-exercise.

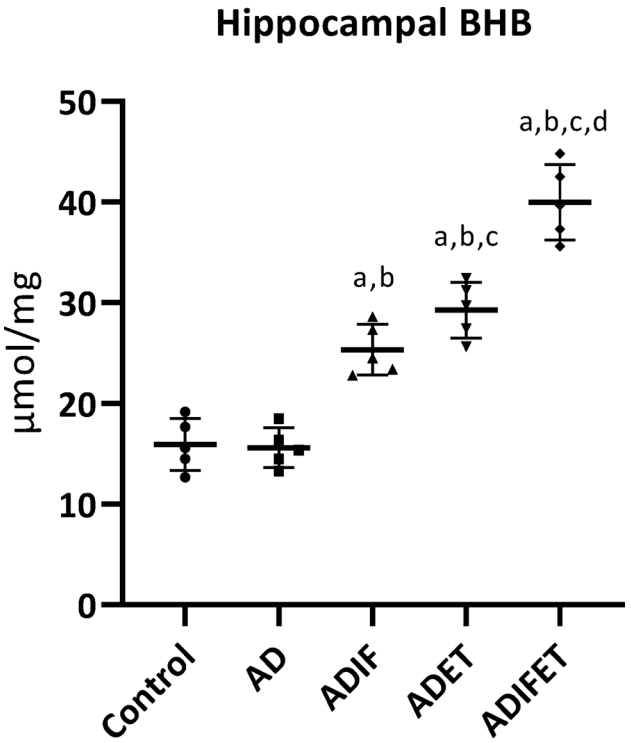

Fig. 4 The hippocampal βHB concentration 60 min after the last training session ($n=5$/group). Hippocampal βHB analysis revealed differences between the groups ($p<0.001$, $\eta p^2 = 0.93$). a $p<0.01$ significant difference from control; b $p<0.05$ significant difference from AD; c $p<0.05$ significant difference from ADIF; d $p<0.05$ significant difference from ADET

reduction to some extent ($p<0.01$). The ADIFET group showed greater increases in PKA, CREB, and BDNF than ADIF or ADET ($p<0.01$). Moreover, exercise alone produced larger increases in CREB ($p<0.05$) and BDNF ($p<0.01$) than fasting alone (Fig. 5).

Discussion

In the present study, we investigated whether four weeks of aerobic running in the fasted state could further enhance cognitive function and hippocampal PKA/CREB/BDNF signaling compared with normal fed-state exercise in an $A\beta_{1-42}$ injected rat model of AD. Our results demonstrated that $A\beta_{1-42}$ injection impaired learning and memory and reduced hippocampal expression of PKA, CREB, and BDNF. Notably, both fasting and exercise alone elevated plasma and hippocampal βHB levels, while the combination of fasting and exercise produced the highest increase in βHB. Consequently, ADIF, ADET, and ADIFET groups all showed improvements in cognitive performance and restoration of hippocampal neurotrophic signaling, with the combined IF and exercise intervention providing superior benefits, and exercise outperforming fasting alone. These findings confirm our initial hypothesis that fasted-state exercise offers additive neuroprotection, likely via βHB-mediated mechanisms (Fig. 6).

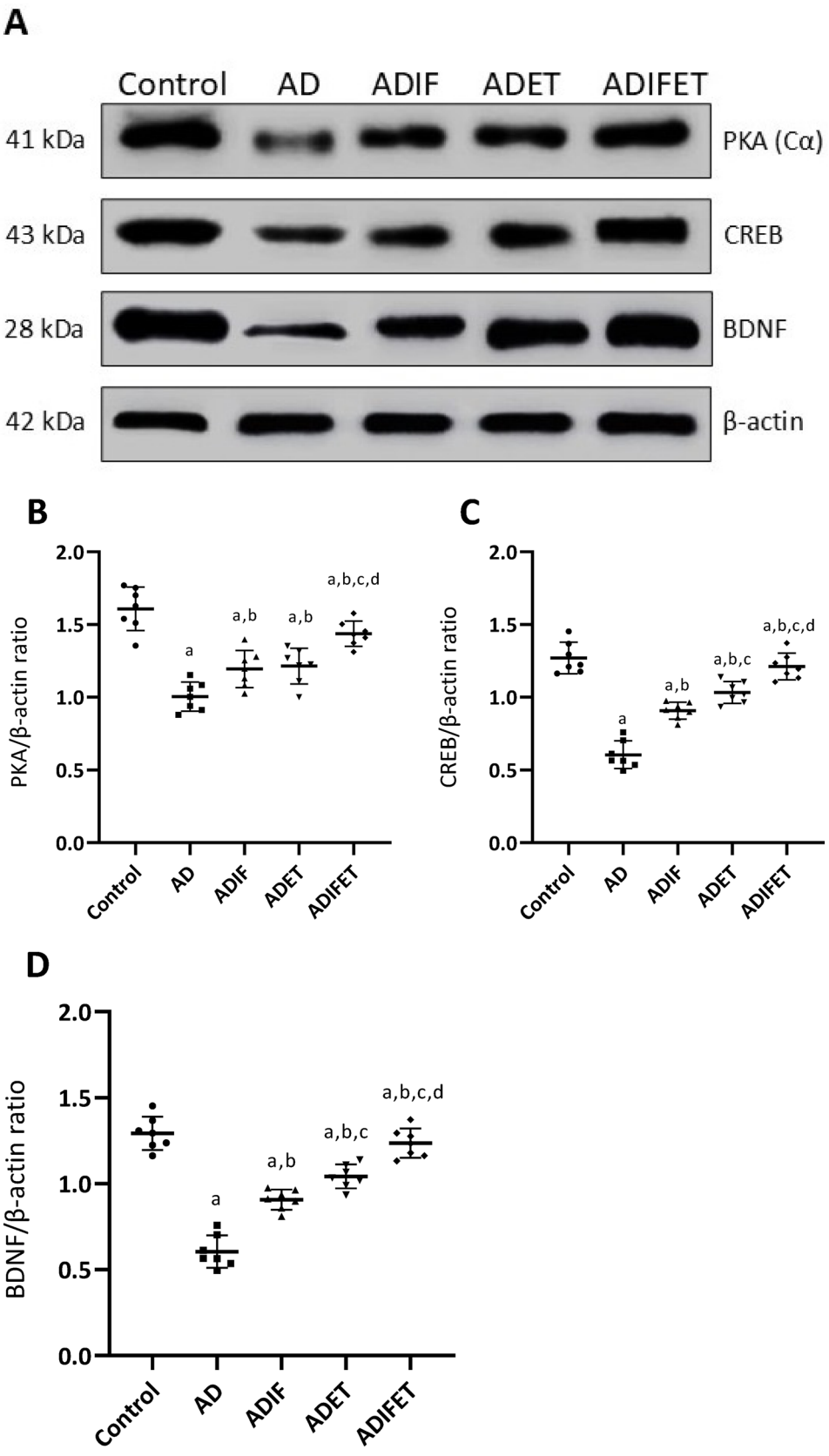

Fig. 5 Effect of intermittent fasting, exercise in the normal fed state, and exercise in the fasted state on PKA, CREB, and BDNF in $A\beta_{1-42}$-injected rat model of AD ($n=7$/group). Between-group differences were detected on hippocampal PKA ($p<0.001$, $\eta_p^2=0.84$), CREB ($p<0.001$, $\eta p^2 = 0.92$), and BDNF ($p<0.001$, $\eta p^2 = 0.94$) protein levels. Expression of PKA, CREB, and BDNF as analyzed using Western blot (**A**). The normalized amounts of PKA (**B**), CREB (**C**), and BDNF (**D**) to β-actin. a $p<0.01$ significant difference from control; b $p<0.01$ significant difference from AD; c $p<0.05$ significant difference from ADIF; d $p<0.01$ significant difference from ADET

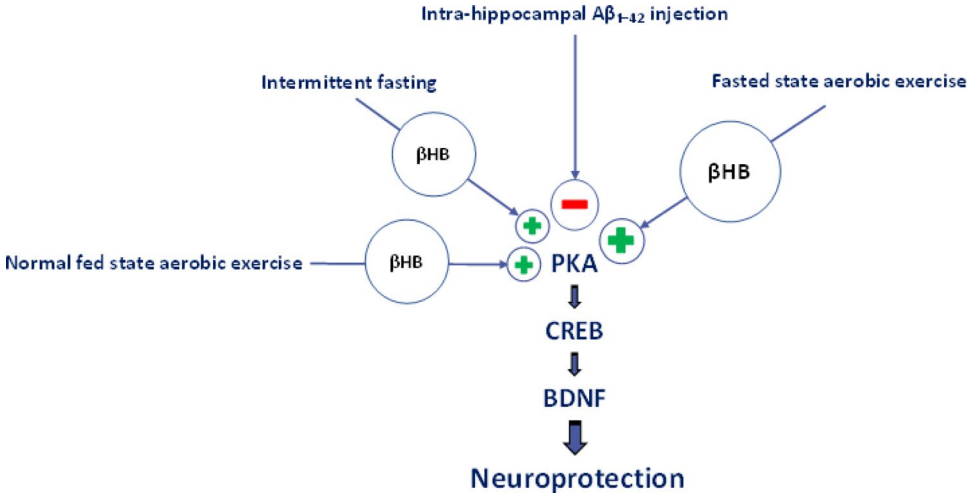

Fig. 6 Schematic abstract. Both intermittent fasting and aerobic exercise exert neuroprotective effects, in part through activation of the βHB/PKA/CREB/BDNF pathway in the hippocampus of AD rats. The combined intervention—fasted-state exercise—produces greater neuroprotective benefits than either intermittent fasting or aerobic exercise alone

Bilateral hippocampal $A\beta_{1–42}$ injection is a well-established AD model that triggers neuroinflammation, neuronal loss, brain atrophy, and cognitive deficits [20, 25, 26]. As expected, Aβ-injected rats showed longer escape latencies and reduced target-quadrant time, indicating spatial learning and memory impairments.

BDNF is critical for neuronal survival and synaptic plasticity, both of which are compromised in AD [27]. Low BDNF levels are linked to AD progression [28, 29], making it a potential therapeutic target. We observed that $A\beta_{1–42}$ injection reduced PKA–CREB–BDNF levels, consistent with the role of Aβ pathology in impairing hippocampal plasticity [30].

Aerobic exercise is known to improve cognitive function via multiple pathways. It stimulates the release of growth factors like BDNF, which promotes neuroplasticity and neurogenesis [31]. The PKA/CREB/BDNF cascade represents a critical signaling pathway whereby exercise-induced neuronal activity leads to CREB phosphorylation and subsequent BDNF transcription [32]. Our study demonstrated that aerobic training improved learning and memory performance and elevated PKA, CREB, and BDNF. Consistent with these findings, Luo et al. [33] reported that chronic aerobic training reversed hypoxia-induced memory impairment and deficits in hippocampal PKA–CREB–BDNF signaling. Similarly, Azimi et al. [24] found that moderate treadmill exercise rescued spatial memory and activated the hippocampal AMPK–PGC-1α–FNDC5–BDNF pathway in an $A\beta_{1–42}$ rat model.

Our IF intervention also yielded cognitive and molecular benefits, consistent with previous reports. Baik et al. [34] showed that 3 months of IF in healthy mice significantly increased hippocampal BDNF, phosphorylated CREB, and synaptic/neurogenesis markers. Long-term IF has been shown to enhance hippocampal neurogenesis and long-term potentiation, improving motor coordination, learning, and memory compared to *ad libitum* feeding [35, 36]. It has been suggested that these beneficial effects arise from metabolic reprogramming. During fasting, the brain shifts from glucose to ketone body utilization [37], and βHB serves not only as a fuel but also as a signaling molecule that upregulates neurotrophic factors, autophagy, and stress resilience [38, 39]. Fasting also reduces inflammatory markers and oxidative stress while promoting mitochondrial biogenesis in AD models [40].

Although we observed considerable main effects of both IF and exercise interventions across neurotrophic signaling and cognitive function, the IF × exercise interaction did not reach conventional significance (i.e., no strong statistical evidence of supra-additive synergy). However, one-way ANOVA post hoc comparisons showed that the combined IF plus exercise interventions produced the greatest improvement in cognitive function, which was accompanied by a greater increase in neurotrophic signaling. Taken together, these results mostly indicate convergent, cumulative effects; the two interventions additively increase the βHB/PKA/CREB/BDNF axis and thereby produce the largest behavioral benefit, while not ruling out the possibility of biological synergy that the present sample, timing, or measures were underpowered to detect.

The effects of fasted-state exercise in AD have not been directly studied before, and related studies in other models reported mixed results. For example, Pratchayasakul et al. [15] found that combining caloric restriction with exercise produced greater metabolic and neurocognitive benefits than either intervention alone in obese ovariectomized rats. In contrast, Albrahim et al. [19] reported that, although exercise and IF each protected against neuronal damage in ovariectomized rats, their combination yielded no additional benefit. The explanation for this discrepancy could be attributed to the fasting and the exercise protocols. In our study, all rats (including fasting groups) had water *ad libitum* and

underwent 5 sessions/week, with exercise time and intensity gradually increasing from 2 × 15 min at 10 m/min (week 1) to 4 × 15 min at 15 m/min (week 4). In comparison, Albrahim et al. [19] deprived rats of food and water for ~13 h and used 8 treadmill sessions over the first 2 weeks (the speed and duration were not reported), followed by a 15-min session at 18–25 m/min, 4 sessions/week for the next 2 weeks. The ketone bodies were not reported in the aforementioned study, and it is possible that their shorter exercise regimen did not increase βHB.

In addition, our observation that normal fed-state exercise outperformed fasting alone may reflect the inherent neuromodulatory effects of exercise. Exercise increases cerebral blood flow, releases peripheral myokines, and promotes an overall anabolic environment conducive to synaptic remodeling [5, 12]. When exercise is combined with fasting, these benefits appear augmented, resulting in greater cognitive improvements. The superiority of exercise in the fasting state over either fasting or exercise alone may be attributed to the cumulative enhancement of βHB availability. Fasting increases βHB production via enhanced fatty acid oxidation [38], while aerobic exercise in this state can further stimulate ketogenesis [41]; therefore, the resultant higher βHB levels likely provide an additive neuroprotective stimulus. This dual activation not only provides alternative energy under impaired glucose metabolism (a hallmark of AD pathology [42]) but also may exert epigenetic modifications that favor synaptic plasticity and neuronal repair [14]. βHB is an endogenous inhibitor of class I histone deacetylases (HDACs), and HDAC inhibition by βHB has been linked to de-repression of Bdnf promoters and enhanced BDNF transcription [14, 43]. A recent study also shows βHB can alter specific histone marks (e.g., increasing H3K4me3) at Bdnf promoters, providing a direct epigenetic route to trophic signaling [44]. In addition, βHB supports mitochondrial function and antioxidant defenses, improving mitochondrial biogenesis and redox homeostasis via effects on PGC-1α and chromatin remodeling, mechanisms that can protect synapses from amyloid-related stress and sustain neuronal energy for plasticity [45]. Together, these βHB complementary mechanisms link metabolic interventions (such as fasting) with exercise and suggest that combining interventions (such as fasting state exercise) can additively enhance neural plasticity and resilience to AD pathology.

Although our findings in aged AD-model rats are promising, their translation to older adults will require carefully supervised, individualized approaches. Frailty, sarcopenia, glycemic instability, polypharmacy, and tolerability, adherence, and safety issues may limit strict regimens. Future studies should explore optimal fasting durations, exercise intensities, and long-term feasibility combined with monitoring for glycemic control, nutritional status, and medication interactions. Investigating dose–response effects and potential sex differences would also strengthen clinical relevance.

Several limitations should be considered when interpreting these results. Although 20-month-old $A\beta_{1-42}$-injected rats model age-related vulnerability to amyloid toxicity, animal models cannot fully recapitulate the complexity of human AD (e.g., chronic tau pathology, decades-long progression, genetic heterogeneity, sex differences, and common comorbidities such as diabetes), which limits direct clinical extrapolation. This study exclusively used male rats. Since sex hormones may influence both metabolic and neurotrophic responses to exercise and fasting in AD pathology, female rats may present different results. Hippocampal βHB was only measured 60 min after the final exercise session, and this single time point may not capture dynamic changes during the intervention or the temporal relationship with cognitive improvement. Moreover, hippocampal βHB was assayed in a randomly selected subset of animals (n = 5 per group), while the remaining animals (n = 7 per group) underwent behavioral testing; because hippocampal βHB and behavioral outcomes were obtained from different animals, subject-level correlation analysis between βHB and cognition or protein expressions was not possible. To partially address temporal dynamics, we measured blood βHB at four time points (once a week) during the intervention. Because blood βHB readily crosses the blood-brain barrier [46], these data provide an indirect measure of metabolic change. However, correlation analysis between body weight changes and βHB levels, as well as between βHB levels and behavioral/molecular outcomes in future studies, could strengthen the mechanistic interpretation. In factorial ANOVA, the IF × exercise interaction for CREB ($F = 4.062$, $p = 0.055$, $\eta_p^2 = 0.145$) and BDNF ($F = 3.366$, $p = 0.075$, $\eta_p^2 = 0.123$) did not reach conventional statistical significance despite moderate to high effect sizes. Interaction tests typically require larger samples to detect modest effects, so the study's relatively small sample size may have limited power to detect true interactions. Finally, the relatively short intervention period and potential ceiling effects in molecular or behavioral measures may have constrained the emergence or detection of synergistic effects.

Conclusion

In summary, our findings demonstrate that aerobic exercise in the fasted state provides additional benefits over fed-state exercise, largely mediated by enhanced βHB production. Elevated βHB appears to activate the PKA/CREB/BDNF pathway, promoting synaptic plasticity and cognitive function in the Aβ-injected rat model of AD. Future

studies should further elucidate the molecular mechanisms underlying this additive effect and evaluate the translational potential of combined fasting and exercise interventions to develop effective interventions against AD.

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Author Contributions D.K., F.K., and H.S. designed the study; F.K., D.K., and M.B. performed the experiments; D.K., T.A., and O.K. analyzed and interpreted the data; F.K., T.A., H.S., and O.K. prepared the initial draft. D.K. H.S., and M.B. reviewed and edited the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability All data sets are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declared no potential conflicts of interest.

Ethical Approval The animal experiment was approved by the Ethics Committee of Islamic Azad University, Central Tehran Branch (Approval No. IR.IAU.CTB.REC.1400.015).

Declaration of AI Tools Used in the Writing Process Once the authors prepared the manuscript, https://chatgpt.com/ was used to improve the readability and language of the work. The authors then carefully reviewed and modified the text as necessary, assuming full responsibility for the content of the publication.

References

1. Better MA (2023) Alzheimer's disease facts and figures. Alzheimers Dement 19:1598–1695
2. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J (2018) NIA-AA research framework: toward a biological definition of alzheimer's disease. Alzheimer's Dement 14:535–562
3. Mu Y, Gage FH (2011) Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener 6:1–9
4. Bekinschtein P, Cammarota M, Medina JH (2014) BDNF and memory processing. Neuropharmacology 76:677–683
5. Jaberi S, Fahnestock M (2023) Mechanisms of the beneficial effects of exercise on brain-derived neurotrophic factor expression in Alzheimer's disease. Biomolecules 13:1577
6. Mattson MP, Longo VD, Harvie M (2017) Impact of intermittent fasting on health and disease processes. Ageing Res Rev 39:46–58
7. Boccardi V, Pigliautile M, Guazzarini AG, Mecocci P (2023) The potential of fasting-mimicking diet as a preventive and curative strategy for Alzheimer's disease. Biomolecules 13:1133
8. Whittaker DS, Akhmetova L, Carlin D, Romero H, Welsh DK, Colwell CS, Desplats P (2023) Circadian modulation by time-restricted feeding rescues brain pathology and improves memory in mouse models of alzheimer's disease. Cell Metabol 35:1704–1721 e1706
9. Newman JC, Verdin E (2017) β-Hydroxybutyrate: a signaling metabolite. Annu Rev Nutr 37:51–76
10. Alghadir AH, Gabr SA, Al-Eisa ES (2016) Effects of moderate aerobic exercise on cognitive abilities and redox state biomarkers in older adults. Oxid Med Cell Longev 2016:2545168
11. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, Szabo AN, Mailey EL, Wójcicki TR, White SM (2013) The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp 34:2972–2985
12. Yang L, Yuan Z, Peng C (2025) Effects of aerobic exercise on cognitive function and quality of life in patients with Alzheimer's disease: a systematic review and meta-analysis. BMJ Open 15:e090623
13. Wang R, Holsinger RD (2018) Exercise-induced brain-derived neurotrophic factor expression: therapeutic implications for Alzheimer's dementia. Ageing Res Rev 48:109–121
14. Sleiman SF, Henry J, Al-Haddad R, El Hayek L, Haidar EA, Stringer T, Ulja D, Karuppagounder SS, Holson EB, Ratan RR (2016) Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. Elife. https://doi.org/10.7554/eLife.15092
15. Pratchayasakul W, Arunsak B, Suparan K, Sriwichaiin S, Chunchai T, Chattipakorn N, Chattipakorn SC (2022) Combined caloric restriction and exercise provides greater metabolic and neurocognitive benefits than either as a monotherapy in obesity with or without estrogen deprivation. J Nutr Biochem 110:109125
16. Hugenschmidt CE, Leng X, Lyles M, Michael L, Dougherty A, Babcock P, Baker LD, Brinkley TE, Nicklas BJ (2019) Cognitive effects of adding caloric restriction to aerobic exercise training in older adults with obesity. Obesity 27:1266–1274
17. Keawtep P, Sungkarat S, Boripuntakul S, Sa-Nguanmoo P, Wichayanrat W, Chattipakorn SC, Worakul P (2024) Effects of combined dietary intervention and physical-cognitive exercise on cognitive function and cardiometabolic health of postmenopausal women with obesity: a randomized controlled trial. Int J Behav Nutr Phys Act 21:28
18. Žlibinaitė L, Solianik R, Vizbaraitė D, Mickevičienė D, Skurvydas A (2020) The effect of combined aerobic exercise and calorie restriction on mood, cognition, and motor behavior in overweight and obese women. J Phys Act Health 17:204–210
19. Albrahim T, Alangry R, Alotaibi R, Almandil L, Alburikan S (2023) Effects of regular exercise and intermittent fasting on neurotransmitters, inflammation, oxidative stress, and brain-derived neurotrophic factor in cortex of ovariectomized rats. Nutrients 15:4270
20. Khodadadi D, Gharakhanlou R, Naghdi N, Salimi M, Azimi M, Shahed A, Heysieattalab S (2018) Treadmill exercise ameliorates spatial learning and memory deficits through improving the clearance of peripheral and central amyloid-beta levels. Neurochem Res. https://doi.org/10.1007/s11064-018-2571-2
21. Fu J, Liu S, Li M, Guo F, Wu X, Hu J, Wen L, Wang J, Li X (2024) Optimal fasting duration for mice as assessed by metabolic status. Sci Rep 14:21509
22. Jensen TL, Kiersgaard M, Sørensen DB, Mikkelsen L (2013) Fasting of mice: a review. Lab Anim 47:225–240
23. Khodadadi D, Gharakhanlou R, Naghdi N, Salimi M, Azimi SM, Shahed A (2018) The effect of 4 weeks of exercise preconditioning on soluble amyloid beta level and memory impairment in rats with alzheimer's disease induced by Aβ1–42 injection. Razi J Med Sci 24:74–84
24. Azimi M, Gharakhanlou R, Naghdi N, Khodadadi D, Heysieattalab S (2018) Moderate treadmill exercise ameliorates amyloid-β-induced learning and memory impairment, possibly via increasing AMPK activity and up-regulation of the PGC-1α/FNDC5/BDNF

pathway. Peptides. https://doi.org/10.1016/j.peptides.2017.12.027
25. Baleriola J, Walker CA, Jean YY, Crary JF, Troy CM, Nagy PL, Hengst U (2014) Axonally synthesized ATF4 transmits a neurodegenerative signal across brain regions. Cell 158:1159–1172
26. Sotthibundhu A, Sykes AM, Fox B, Underwood CK, Thangnipon W, Coulson EJ (2008) β-amyloid1–42 induces neuronal death through the p75 neurotrophin receptor. J Neurosci 28:3941–3946
27. Alqahtani SM, Al-Kuraishy HM, Al Gareeb AI, Albuhadily AK, Alexiou A, Papadakis M, Hemeda LR, Faheem SA, El-Saber Batiha G (2025) Unlocking alzheimer's disease: the role of BDNF signaling in neuropathology and treatment. Neuromol Med 27:36
28. Ventriglia M, Zanardini R, Bonomini C, Zanetti O, Volpe D, Pasqualetti P, Gennarelli M, Bocchio-Chiavetto L (2013) Serum brain-derived neurotrophic factor levels in different neurological diseases. Biomed Res Int 2013:901082
29. Kim K, Byun MS, Yi D, Jung JH, Sohn BK, Jung G, Ahn H, Lee JY, Lee YS, Kim YK (2025) Serum brain-derived neurotrophic factor and progression to MCI in cognitively normal older adults. Alzheimer's & Dementia 20:e088177
30. Wang L-S, Tao X, Liu X-M, Zhou Y-F, Zhang M-D, Liao Y-H, Pan R-L, Chang Q (2019) Cajaninstilbene acid ameliorates cognitive impairment induced by intrahippocampal injection of amyloid-β1–42 oligomers. Front Pharmacol 10:1084
31. Cotman CW, Berchtold NC (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 25:295–301
32. Vaynman S, Ying Z, Gomez-Pinilla F (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590
33. Luo S, Shi L, Liu T, Jin Q (2025) Aerobic exercise training improves learning and memory performance in hypoxic-exposed rats by activating the hippocampal PKA–CREB–BDNF signaling pathway. BMC Neurosci 26:13
34. Baik S, Rajeev V, Fann D, Jo D, Arumugam T (2020) Intermittent fasting increases adult hippocampal neurogenesis. Brain Behav 10:e01444
35. Fontán-Lozano Á, Sáez-Cassanelli JL, Inda MC, de los Santos-Arteaga M, Sierra-Domínguez SA, López-Lluch G, Delgado-García JM, Carrión ÁM (2007) Caloric restriction increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor. J Neurosci 27:10185–10195
36. Singh R, Lakhanpal D, Kumar S, Sharma S, Kataria H, Kaur M, Kaur G (2012) Late-onset intermittent fasting dietary restriction as a potential intervention to retard age-associated brain function impairments in male rats. Age 34:917–933
37. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A (2018) Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 19:81–94
38. Brocchi A, Rebelos E, Dardano A, Mantuano M, Daniele G (2022) Effects of intermittent fasting on brain metabolism. Nutrients 14(6):1–23
39. Longo VD, Mattson MP (2014) Fasting: molecular mechanisms and clinical applications. Cell Metab 19:181–192
40. Li L, Wang Z, Zuo Z (2013) Chronic intermittent fasting improves cognitive functions and brain structures in mice. PLoS One 8:e66069
41. Kwak SE, Bae JH, Lee JH, Shin HE, Zhang D, Cho SC, Song W (2021) Effects of exercise-induced beta-hydroxybutyrate on muscle function and cognitive function. Physiol Rep 9:e14497
42. Kumar V, Kim S-H, Bishayee K (2022) Dysfunctional glucose metabolism in Alzheimer's disease onset and potential pharmacological interventions. Int J Mol Sci 23:9540
43. Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, Grueter CA, Lim H, Saunders LR, Stevens RD (2013) Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 339:211–214
44. Hu E, Du H, Shang S, Zhang Y, Lu X (2020) Beta-hydroxybutyrate enhances BDNF expression by increasing H3K4me3 and decreasing H2AK119ub in hippocampal neurons. Front Neurosci 14:591177
45. Gambardella J, Jankauskas SS, Kansakar U, Varzideh F, Avvisato R, Prevete N, Sidoli S, Mone P, Wang X, Lombardi A (2023) Ketone bodies rescue mitochondrial dysfunction via epigenetic remodeling. Basic Translational Sci 8:1123–1137
46. White H, Venkatesh B, Jones M, Worrall S, Chuah T, Ordonez J (2013) Effect of a hypertonic balanced ketone solution on plasma, CSF and brain beta-hydroxybutyrate levels and acid–base status. Intensive Care Med 39:727–733