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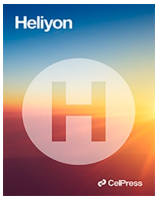

Research article

Effects of treadmill exercise on endoplasmic reticulum protein folding and endoplasmic reticulum-associated protein degradation pathways in APP/PS1 mice

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ABSTRACT

A hallmark of Alzheimer's disease (AD) is the disruption of protein homeostasis (proteostasis), manifested by the misfolding and aggregation of proteins. Molecular chaperones and the endoplasmic reticulum (ER)-associated protein degradation (ERAD) pathway in the ER are essential for correct protein folding and degradation of misfolded proteins respectively, thus contributing to the maintenance of proteostasis. The present study aimed to investigate whether the beneficial effects of exercise in an AD mice model is associated with changes in ER protein folding and ERAD. APP/PS1 transgenic and wild-type mice were subjected to treadmill exercise for three months. The levels of molecular chaperones, specifically protein disulfide isomerases (PDIs) and heat shock proteins (HSPs), as well as ERAD-associated molecules were analyzed in the hippocampus. The result revealed a decrease in mRNA levels of *PDIA2*, *PDIA3*, *PDIA4*, *PDIA5*, *PDIA6*, *HSPA1B*, *HSPA8*, *HSP90B1*, *DNAJB2*, *CRYAB*, and *CNX*, an increase in mRNA levels of *HSPA5* and *HSPH1*, an increase in protein levels of HERPUD1, and a decrease in protein levels of VCP in APP/PS1 mice. However, following a 3-month treadmill exercise regimen, an increase in mRNA levels of *PDIA2*, *PDIA4*, *PDIA6*, *HSPA1A*, *HSPA8*, *HSP90AB1*, and *DNAJB2*, as well as an increase in protein levels of VCP and DERL2, and a decrease in protein levels of HERPUD1 were noted. Overall, our findings indicate that disruptions in hippocampal ER protein folding and ERAD pathways may be implicated in AD, with exercise serving as a regulator of these pathways.

1. Introduction

Alzheimer's disease (AD) is characterized by a progressive neurodegenerative process that leads to cognitive decline and memory impairment, ultimately causing significant disability and necessitating dependence on caregivers for those afflicted. Although pharmacological interventions are available for symptomatic relief, a definitive cure for AD remains elusive. As a result, there is an increasing focus on non-pharmacological approaches, specifically physical activity, as potential means to alleviate cognitive decline

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and enhance the quality of life for individuals with AD [1,2]. However, further research is needed to elucidate the precise mechanisms by which exercise impacts the progression of AD and to improve exercise interventions designed for this population.

Recent research indicates that AD is marked by a disturbance in protein homeostasis, characterized by increased accumulation of β-amyloid (Aβ) and phosphorylated Tau protein (p-Tau), diminished synthesis of synaptic proteins, and compromised pathways for removing abnormal proteins [3,4]. The endoplasmic reticulum (ER) plays a vital role in regulating proteostasis, a process that monitors protein biogenesis, folding, trafficking, and degradation [5]. Protein folding within the ER is aided by a variety of resident chaperones, in which protein disulfide isomerases (PDIs) plays a critical role to ensure the efficiency of the protein folding process. Peptide-binding proteins, particularly heat shock proteins (HSPs), prevent aggregation and actually reduce the rate of protein folding. The calnexin (CNX)-calreticulin (CRT) cycle is responsible for protein quality control, and the ER-associated protein degradation (ERAD) system facilitates the degradation of misfolded proteins [6]. Disruptions in these critical processes can induce ER stress, which, if prolonged, may result in cellular damage and apoptosis, and has been increasingly recognized as a significant factor in the progression of AD [7]. Consequently, investigating ER protein folding and ERAD pathways may offer a promising approach for alleviating excessive ER stress and could potentially contribute to the mitigation of AD pathology. Supporting this, previous findings have indicated that abnormal expression of ER protein folding chaperones [8–10] and compromised ERAD pathway [11,12] exist in the brains of both AD patients and animal models. Moreover, mutations in the APP and PS1 genes, which are critical to AD, further exacerbate these disruptions. Specifically, mutations in APP can increase protein misfolding during synthesis, while PS1 mutations disrupt ER protein homeostasis, intensifying ER stress and contributing to the accumulation of toxic proteins such as Aβ and p-Tau [13–15].

Given the critical role of ER stress in AD, previous research has shown that treadmill exercise can reduce neuronal cell death and inflammation in aged presenilin 2 mutant mice and improve cerebrovascular dysfunction in APP/PS1 transgenic mice, primarily through the regulation of ER stress [16,17]. Our own investigations have previously shown that treadmill exercise can decrease Aβ accumulation in the brains of APP/PS1 transgenic mice, potentially through the modulation of ER stress [18]. Despite these insights, the precise mechanisms by which exercise alleviates ER stress remain unclear. Notably, exercise has been observed to modulate the expression of protein folding chaperones, including PDIs and HSPs, in the brains of AD mice [19]. This observation prompted us to hypothesize that exercise may facilitate protein folding and improve quality control within the ER, thereby mitigating the ER stress. This previously unexplored mechanism forms the central focus of the present research.

Therefore, the current research aims to determine if AD pathology is associated with abnormalities in ER protein folding and ERAD pathways, as well as to explore the potential link between the beneficial effects of exercise on AD pathology and the modulation of ER protein folding and ERAD. To this end, we utilized an APP/PS1 transgenic mouse model to assess the effects of treadmill exercise on the expression of protein folding chaperones, including PDIs, HSPs, and CNX, as well as ERAD-related molecules.

2. Materials and methods

2.1. Animals and groups

All animal procedures were approved by the Institutional Animal Care and Use Committee of East China Normal University (m20190405). Male APP/PS1 transgenic mice and wild-type C57BL/6 mice were purchased from the Model Animal Research Center of Nanjing University, China. All mice were housed under controlled conditions of temperature (22 ± 2 °C), humidity (50 ± 10 %), and a 12-h light-dark cycle, with ad libitum access to food and water. At the age of 3 months, the APP/PS1 mice and WT mice were randomly divided into four groups: WT sedentary group (WT-Sed, n = 11), WT exercise group (WT-Exe, n = 11), APP/PS1 sedentary group (APP/PS1-Sed, n = 11), and APP/PS1 exercise group (APP/PS1-Exe, n = 11).

2.2. Exercise protocols

As previously described [18], mice in the exercise group were subjected to a moderate-intensity exercise programme. In the exercise paradigm, the mice were running on a treadmill apparatus for 45 min per day, 5 days per week for 3 months. The regular treadmill exercise was performed daily at 18:00–20:00.

2.3. Tissue preparation

After three months of exercise, the mice were euthanized via CO_2 inhalation in compliance with established ethical guidelines. The brain was isolated and the hippocampus was dissected on ice-plate, snap-frozen in liquid nitrogen, and stored at −80 °C for analysis.

2.4. Real-Time PCR

Total RNA was isolated from the frozen hippocampal tissues utilizing TRIzol reagent (Sangon Biotech, Shanghai, B610409-0025) and purified according to the manufacturer's instructions. Subsequently, cDNA was extracted using a reverse transcription kit (Yeasen Biotech, Shanghai, 11141ES60). For quantitative PCR (qPCR), the SYBR Green (Yeasen Biotech, Shanghai, 11202ES03) was utilized. The detection was conducted on the QuantStudio3 and 5 Real-Time PCR Systems. Relative expression levels of target gene mRNA were calculated using the $2^{-\Delta\Delta Ct}$ method with *GAPDH* as the reference gene. The primer sequences are listed in Supplementary Table 1.

2.5. Simple Western (WES)

Total protein from the frozen hippocampal tissue were extracted using a radio immuno precipitation assay buffer. The protein samples were analyzed with a Simple Western assay using the WES™ system (ProteinSimple, Bio-Techne) and the WES™ kit (SM-W004 and DM-001, ProteinSimple, Bio-Techne). The primary antibodies were used for the Simple Western assays are listed in Supplementary Table 2. We used 0.5ug/ul total protein loaded into the assay. The results were presented as electrophoregrams representative of the chemiluminescence peak and as a lane view of the chemiluminescence signal detected in the capillary. The relative amount of each protein was quantified by the Compass for SW software (ProteinSimple, San Jose, CA), following the default settings. The relative expression levels of the target protein were determined by utilizing GAPDH or β-Tubulin as an internal reference protein, and the data were subsequently normalized.

2.6. Statistical analysis

All mean values were reported as mean ± SEM. Statistical analysis was performed using GraphPad Prism V8. Statistical significance of differences was determined by two-way ANOVA followed by Bonferroni post hoc comparisons. Statistical significance was considered if $P < 0.05$ or 0.01.

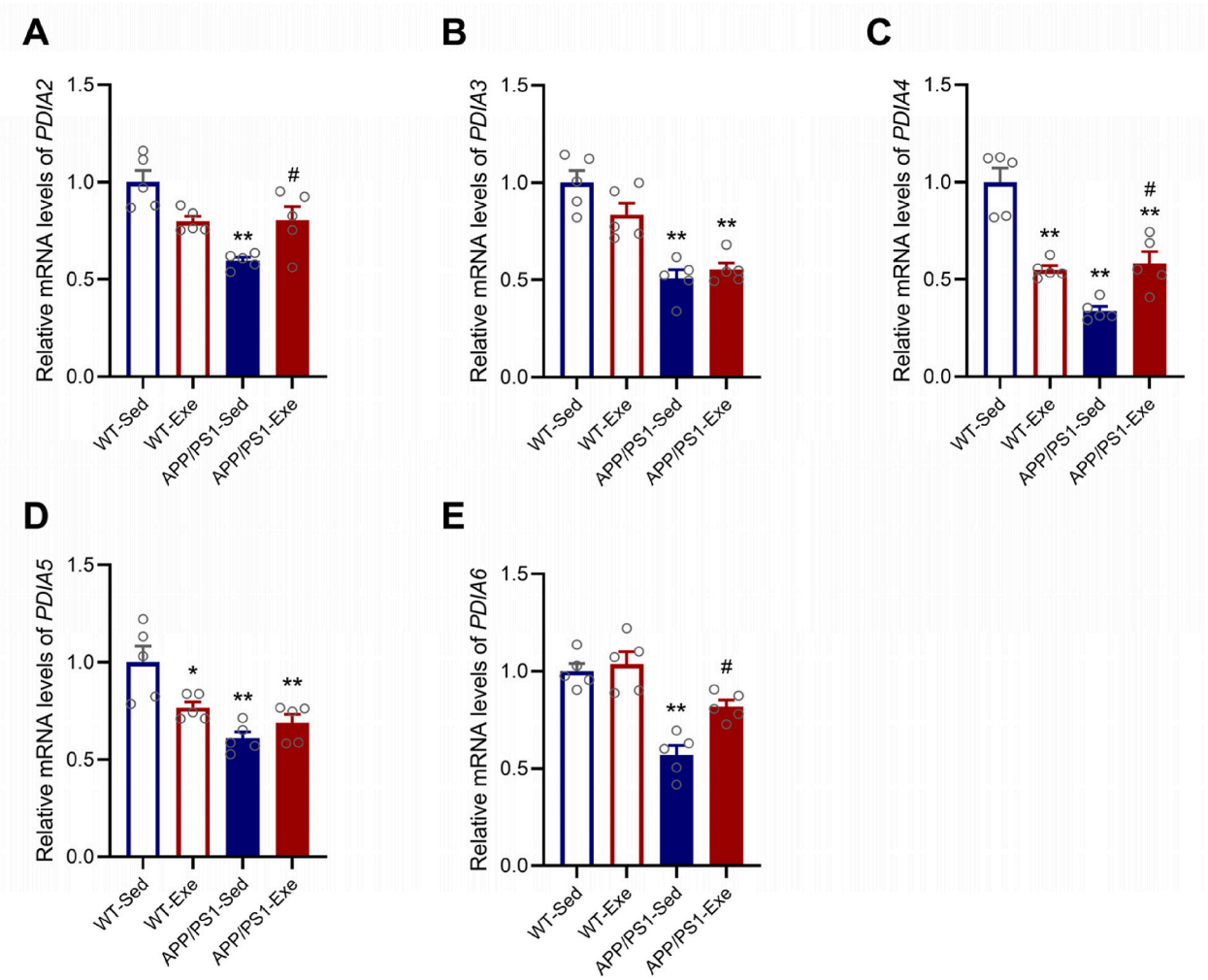

Fig. 1. Effects of exercise on hippocampal PDIs mRNA levels. The relative mRNA levels of *PDIA2* (A), *PDIA3* (B), *PDIA4* (C), *PDIA5* (D), and *PDIA6* (E) in hippocampus. Data are presented as means ± SEM (n = 5 per group). $^{**}p < 0.01$ versus WT-Sed, $\#p < 0.05$, $\#\#p < 0.01$ versus APP/PS1-Sed.

3. Results

3.1. Effects of exercise on hippocampal PDIs mRNA levels

Fig. 1 shows the mRNA levels of PDIs in mouse hippocampus. Compared to the WT-Sed group, the mRNA levels of *PDIA4* ($P < 0.01$,

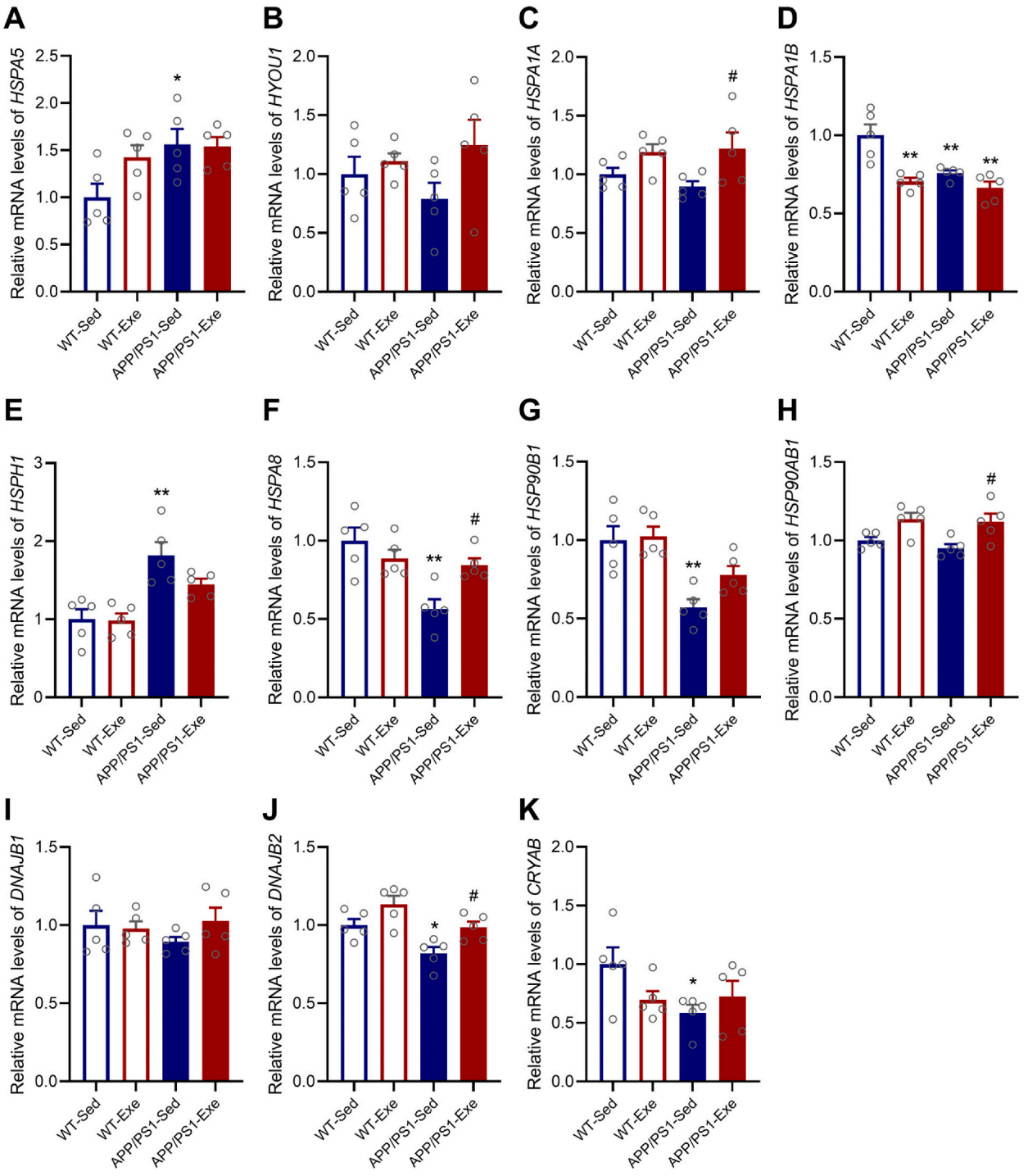

Fig. 2. Effects of exercise on hippocampal HSPs mRNA levels. The relative mRNA levels of *HSPA5* (A), *HYOU1* (B), *HSPA1A* (C), *HSPA1B* (D), *HSPH1* (E), *HSPA5* (F), *HSP90B1* (G), *HSP90AB1* (H), *DNAJB1* (I), *DNAJB2* (J), and *CRYAB* (K) in hippocampus. Data are presented as means ± SEM (n = 5 per group). *$p < 0.05$, **$p < 0.01$ versus WT-Sed, #$p < 0.05$, ##$p < 0.01$ versus APP/PS1-Sed.

Fig. 1C) and *PDIA5* ($P < 0.05$, Fig. 1D) were significantly decreased in the WT-Exe group; the mRNA levels of *PDIA2* ($P < 0.01$, Fig. 1A), *PDIA3* ($P < 0.01$, Fig. 1B), *PDIA4* ($P < 0.01$, Fig. 1C), *PDIA5* ($P < 0.01$, Fig. 1D), and *PDIA6* ($P < 0.01$, Fig. 1E) were significantly decreased in the APP/PS1-Sed group; and the mRNA levels of *PDIA3* ($P < 0.01$, Fig. 1B), *PDIA4* ($P < 0.05$, Fig. 1C), and *PDIA5* ($P < 0.01$, Fig. 1D) were significantly decreased in the APP/PS1-Exe group. These results suggest that the expression of PDIs is altered in both exercise-treated and transgenic mice, indicating changes in the efficiency of protein folding within the endoplasmic reticulum. Interestingly, when compared to the APP/PS1-Sed group, the APP/PS1-Exe group demonstrated significant increases in the mRNA levels of *PDIA2* ($P < 0.05$, Fig. 1A), *PDIA4* ($P < 0.05$, Fig. 1C), and *PDIA6* ($P < 0.05$, Fig. 1E). These findings indicate that exercise may reverse the dysregulation of PDIs expression, thereby enhancing the efficiency of the protein folding process in the hippocampus of APP/PS1 transgenic mice.

3.2. Effects of exercise on hippocampal HSPs mRNA levels

The HSPs are integral in preventing protein aggregation and modulating the rate of protein folding. To investigate the impact of exercise on these processes, we assessed the mRNA levels of various HSPs in the hippocampus of mice, as shown in Fig. 2. Compared to the WT-Sed group, the mRNA levels of *HSPA1B* were significantly decreased in the WT-Exe group ($P < 0.05$, Fig. 2D); the mRNA levels of *HSPA5* ($P < 0.05$, Fig. 2A) and *HSPH1* ($P < 0.01$, Fig. 2E) were significantly increased, while the mRNA levels of *HSPA1B* ($P < 0.01$, Fig. 2D), *HSPA8* ($P < 0.01$, Fig. 2F), *HSP90B1* ($P < 0.01$, Fig. 2G), *DNAJB2* ($P < 0.05$, Fig. 2J), and *CRYAB* ($P < 0.05$, Fig. 2K) were significantly decreased in the APP/PS1-Sed group; and the mRNA levels of *HSPA1B* were significantly decreased ($P < 0.01$, Fig. 2D) in the APP/PS1-Exe group. Compared to the APP/PS1-Sed group, the mRNA levels of *HSPA1A* ($P < 0.05$, Fig. 2C), *HSPA8* ($P < 0.05$, Fig. 2F), *HSP90AB1* ($P < 0.05$, Fig. 2H), and *DNAJB2* ($P < 0.05$, Fig. 2J) were significantly increased in the APP/PS1-Exe group. These findings suggest that exercise may mitigate the aggregation of misfolded proteins, thereby potentially enhancing protein homeostasis in the hippocampus of APP/PS1 transgenic mice.

3.3. Effects of exercise on hippocampal CNX mRNA and protein levels

Fig. 3 shows the mRNA and protein levels of CNX in mouse hippocampus. Compared to the WT-Sed group, the mRNA levels of *CNX* was significantly decreased in the APP/PS1-Sed group ($P < 0.01$, Fig. 3A). However, we did not observe any significant changes on the protein levels of CNX in hippocampus among the four groups (Fig. 3B).

3.4. Effects of exercise on hippocampal ERAD-related protein levels

Given the observed changes in molecular chaperones expression in APP/PS1 mice, which may indicate disruptions in ER protein folding and increased misfolded protein aggregation, we next examined potential alterations in the ERAD pathway. Fig. 4 shows the protein levels of ERAD-related molecules in mouse hippocampus. Compared to the WT-Sed group, the protein levels of VCP were significantly reduced ($P < 0.01$, Fig. 4A and D), while the protein levels of HERPUD1 were significantly increased ($P < 0.01$, Fig. 4A and F) in the APP/PS1-Sed group. Additionally, the levels of DERL2 protein were significantly elevated ($P < 0.01$, Fig. 4A and E) in the APP/PS1-Exe group when compared to the WT-Sed group. Furthermore, compared to the APP/PS1-Sed group, the levels of VCP ($P < 0.01$, Fig. 4A and D) and DERL2 ($P < 0.01$, Fig. 4A and E) proteins were significantly increased in the APP/PS1-Exe group, while the level of HERPUD1 protein was significantly decreased ($P < 0.01$, Fig. 4A and F).

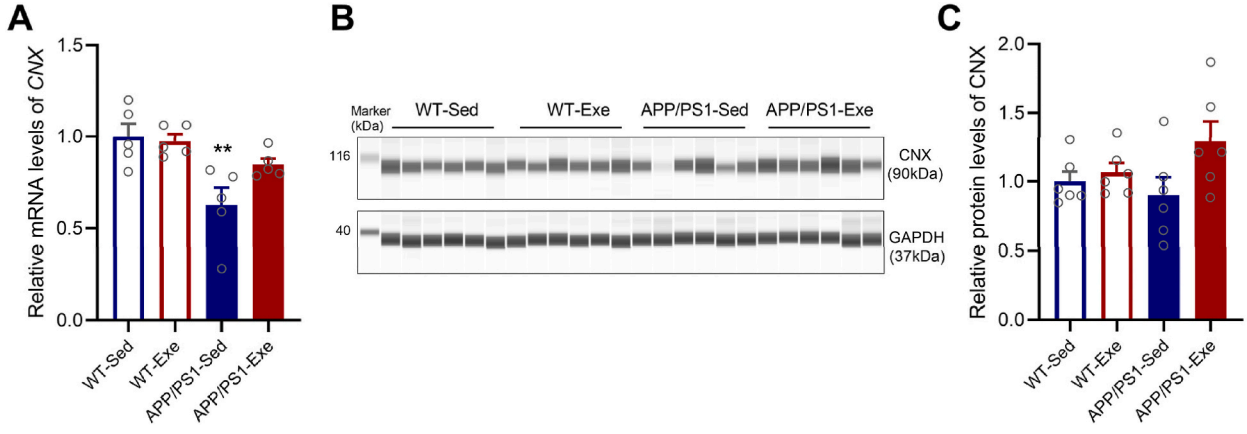

Fig. 3. Effects of exercise on hippocampal CNX mRNA and protein levels. (A) The relative mRNA levels of *CNX* in hippocampus. (B) Protein bands and the relative protein levels of CNX. Data are presented as means ± SEM (n = 5 per group). $^{**}p < 0.01$ versus WT-Sed.

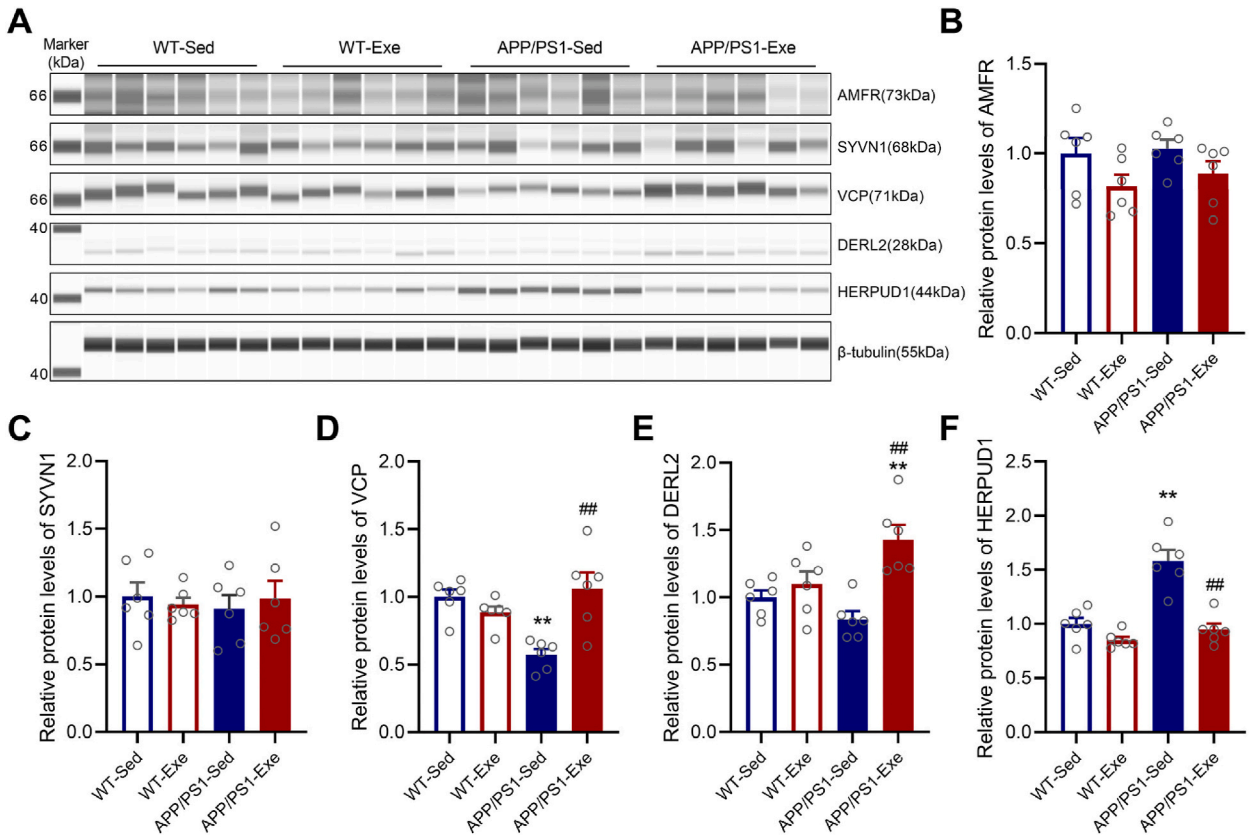

Fig. 4. Effects of exercise on hippocampal ERAD-related protein levels. Protein bands (A) and the relative protein levels of AMFR (B), SYVN1 (C), VCP (D), DERL2(E) and HERPUD1 (F). Data are presented as means ± SEM (n = 6 per group). $^{**}p < 0.01$ versus WT-Sed, $\#\#p < 0.01$ versus APP/PS1-Sed.

4. Discussion

In this study, we identified aberrant expression of PDIs, HSPs, CNX, and ERAD-related molecules in the hippocampus of APP/PS1 mice, indicating potential disruptions in ER protein folding and ERAD processes in AD pathology. Additionally, our findings suggest that a three-month of treadmill exercise may partially reverse the abnormal expression of PDIs, HSPs, and ERAD-related molecules in APP/PS1 animals, implicating the beneficial effects of exercise in the regulation of hippocampal ER protein folding and ERAD.

PDIs in the ER mediate the formation and rearrangement of disulfide bonds, ensuring proper folding of newly synthesized proteins [20]. Previous research has shown that PDIs can interact with Aβ [21]. Pharmacologically stimulating PDIs reduced amyloid plaques and neurofibrillary tangles in the brains of 5 × FAD mice, indicating a potential role in regulating the progression of AD pathology [22]. The current study shows that the mRNA levels of *PDIA2*, *PDIA3*, *PDIA4*, *PDIA5*, and *PDIA6* were reduced in APP/PS1 mice, suggesting that the downregulation of these PDIs may be associated with the accumulation of misfolded proteins in the AD brain. Notably, Hüttenrauch et al. reported that exercise upregulated *PDIA3*, *PDIA4* and *PDIA6* in a Tg4-42 AD mouse model [19]. Similarly, our findings demonstrate that exercise increased *PDIA2*, *PDIA4*, and *PDIA6* in the hippocampus of APP/PS1 mice. Previous studies have identified ER chaperones, including PDIs and HSPs, as key targets of the unfolded protein response (UPR), a crucial mechanism that mitigates ER stress by regulating their transcription to support protein folding and quality control [23]. Thus, the exercise-induced upregulation of PDIs observed at the mRNA level in our study may facilitate proper protein folding in the ER, suggesting a potential link between the transcriptional regulation of PDIs and the neuroprotective effects associated with physical exercise.

The HSPs serve as molecular chaperones, playing key roles in protein folding, transport, and assembly processes. Research has identified increased expression of several HSPs, particularly those belonging to the HSP70, HSP90, and HSP40 families, in the brains of AD patients or animal models [8,24]. Notably, recent studies have demonstrated that HSP90 can promote the formation of small oligomeric layers of Tau protein, thereby inhibiting the development of longer neurofibrillary tangles [10]. Interestingly, voluntary wheel running has been shown to mitigate neuronal loss and memory deficits in AD mice, potentially through the upregulation of various HSPs including *CRYAB*, *HSPA1B*, *HSP90AB1*, *DNAJB1*, *DNAJB2*, and *HSPH1* [19]. In the current study, increased mRNA levels of *HSPA5* and *HSPH1* were detected in APP/PS1 mice and concomitant with decreased mRNA levels of *HSPA8*, *HSPA1B*, *HSP90B1*, *DNAJB2*, and *CRYAB*. Consistent with these results, He et al. [25] reported an increase in hippocampal *HSPA5* mRNA levels in APP/PS1 mice. Our previous study has demonstrated that the protein expression of GRP78, encoded by the *HSPA5* gene, is elevated in

the hippocampus of APP/PS1 mice, and was reversed by treadmill exercise [18]. Interestingly, treadmill exercise did upregulate the mRNA of *HSPA1A* and *HSP90AB1* in APP/PS1 mice. These findings are supported by previous studies showing that wheel running can also increase the expression of *HSPA1A* and *HSP90AB1* in AD mice [19]. These findings imply that exercise could have a preventive effect against AD by modulating HSPs expression. However, we only measured mRNA changes and did not assess protein levels of these chaperones. Future research should include protein-level analyses to confirm these findings and elucidate the mechanisms involved.

The CNX-CRT cycle is essential for ER protein quality control, ensuring properly folded proteins are transported to the Golgi apparatus while misfolded proteins are refolded or degraded through the ERAD pathway [26]. CNX and CRT are identified as pivotal components of the CNX-CRT cycle. Research has indicated a reduction in both mRNA and protein levels of CRT in the brains of individuals with AD [27]. Animal studies have demonstrated a decrease in the expression of CNX and CRT in the white matter of aging mice, indicating an age-dependent trait [28]. Our study showed decreased CNX mRNA levels in APP/PS1 mice, while CNX protein levels did not change significantly. This discrepancy between mRNA and protein levels may be due to the fact that the 6-month-old APP/PS1 mice used in our study represent an early stage of AD pathology, where only mRNA differences are observable. Future research should further investigate whether CNX expression has an age-dependent characteristic, which could clarify its role in AD pathology. Additionally, our study found that exercise did not significantly impact CNX expression, either at the mRNA or protein level, in APP/PS1 mice. In contrast, our previous research showed that exercise could normalize the protein level of CRT in the hippocampus of APP/PS1 mice [29]. These results suggest that exercise may primarily modulate the CRT-CNX cycle by regulating CRT function.

The ERAD pathway comprises three sequential processes: the identification and ubiquitination of improperly folded proteins, their retrotranslocation to the cytoplasm, and subsequent degradation by the ubiquitin-dependent proteasome system [30]. Autocrine motility factor receptor (AMFR) and synovial apoptosis inhibitor 1 (SYVN1) AMFR and SYVN1, E3 ubiquitin ligases involved in ERAD function, showed no differences among groups, indicating they are not involved in AD pathology. Valosin-containing protein (VCP) is predominantly localized in the ER and facilitates the retrotranslocation of misfolded proteins to the cytoplasm through its interaction with ubiquitinated proteins [31]. Recent research shows that VCP mutations in AD brains promote Tau aggregation, while treatment with recombinant VCP reduces Tau aggregation in AD animal models [32]. Our current found that APP/PS1 transgenesis reduced VCP protein levels in the mouse hippocampus, which was subsequently restored by treadmill exercise. Furthermore, our study revealed that exercise resulted in an increase in hippocampal Derlin-2 (DERL2) protein levels in APP/PS1 mice. DERL2, a protein known for its role in the retrotranslocation of misfolded proteins in the ERAD pathway [33], facilitates interactions between VCP and misfolded proteins [34]. The simultaneous upregulation of DERL2 and VCP in exercised APP/PS1 mice implies that exercise may potentially augment the retrotranslocation capabilities of ERAD.

Homocysteine-responsive ER-resident ubiquitin-like domain member 1 protein (HERPUD1) is an ER transmembrane protein with an N-terminal ubiquitin-like (UBL) domain [35]. In the process of ERAD, HERPUD1 interacts with the 26S proteasome, modulating its interactions with ubiquitinated substrates to facilitate their degradation [36]. Elevated levels of HERPUD1 have been detected in the frontal and temporal cortex of patients with AD [24] and in the brains of 3 × Tg AD model mice [37]. Our study identified increased levels of HERPUD1 protein in APP/PS1 mice. The upregulation of HERPUD1 has been shown to enhance the production of Aβ [38], whereas the deletion of HERPUD1 has been found to decrease Aβ levels [39]. Additionally, George et al. [40] demonstrated that exercise can ameliorate cognitive impairments and neuronal injury in mice with chronic alcohol consumption by suppressing the expression of HERPUD1. Our current study revealed that a three-month of treadmill exercise could reduce the protein levels of HERPUD1 in APP/PS1 mice, suggesting potential involvement of the ERAD proteasomal pathway in the mechanism underlying exercise intervention in AD.

5. Conclusion

This study revealed that APP/PS1 mice exhibited abnormal expression of PDIs, HSPs, CNX, and ERAD-related molecules in the hippocampus, which was partially reversed by exercise. The findings indicate that disruptions in hippocampal ER protein folding, quality control, and ERAD mechanisms may be implicated in AD. Furthermore, the beneficial effects of exercise in AD may be linked to the regulation of these pathways. Overall, these findings highlight the therapeutic potential of targeting ER protein folding and ERAD pathways in AD, as well as the promising role of exercise as an intervention. Although this study supports our hypotheses, several limitations must be acknowledged. First, we did not directly assess Aβ aggregation in relation to exercise, leaving unresolved whether exercise mitigates Aβ toxicity or enhances neuronal resilience, and this aspect warrants further investigation. Second, while our focus was on ER protein folding and ERAD, broader mechanisms of exercise, including epigenetic factors such as HDAC inhibition [41,42], remain underexplored and should be addressed in future research. Finally, we did not evaluate the protein expression of specific ERAD substrates linked to AD, which limits our understanding of the physiological relevance of our findings. Future studies should include these substrates to clarify their role in ER protein folding and AD pathology.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Jie Xia: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Jing Wang:** Writing – review &

editing, Validation, Methodology, Investigation. **Na Zhao:** Writing – review & editing, Investigation. **Qiang Zhang:** Writing – review & editing, Methodology, Investigation. **Bo Xu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38458.

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