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Effect of 3.1-THz radiation on pathological progression in *Caenorhabditis elegans* Alzheimer's disease model

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Terahertz (THz) radiation, an emerging frequency band of the electromagnetic spectrum, has been widely applied across various fields. However, its ability to resonate with the energy levels of biomolecules has raised significant concerns regarding its biosafety. A growing body of research indicates that THz radiation can markedly influence the structure and function of proteins. Alzheimer's disease (AD), a neurodegenerative disorder characterized by the abnormal aggregation of amyloid proteins, has been shown in prior studies to be modulated by THz radiation in terms of amyloid aggregation. Building on this, the present study utilized the CL4176 strain of *Caenorhabditis elegans* as an animal model for AD. Using a self-designed and constructed radiation system based on quantum cascade lasers, the study investigated changes in the pathological progression of AD under 3.1-THz electromagnetic radiation exposure. By evaluating lifespan, motility, feeding behavior, reactive oxygen species (ROS) levels, and aging markers in the *Caenorhabditis elegans* model, the study highlights the potential biological risks of 3.1-THz radiation for individuals with AD. These findings provide crucial experimental evidence to support the promotion and standardization of THz technology applications.

Keywords: terahertz biological effects, Alzheimer's disease, vibrational analysis, biosafety

PACS: 87.50.–a, 87.19.xr, 33.20.Tp, 28.52.Nh

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder resulting from impaired brain function, primarily characterized by a significant decline in key cognitive abilities such as memory, movement, and cognition. According to statistics from the World Health Organization (2017–2020), over 55 million people worldwide suffer from dementia, with nearly 10 million new cases diagnosed each year, of which more than 60% are attributed to AD. The number of patients is projected to reach a staggering 139 million by 2050.[1] Given this alarming trend, "preventive treatment" in traditional Chinese medicine should not remain merely a theoretical concept but serve as an urgent call to action. *The Lancet* medical journal identified 12 high-risk factors for dementia in its report, *Dementia Prevention, Intervention*, and *Care: Lancet Commission* 2020,[2] providing a scientific framework for AD prevention. However, it is noteworthy that this authoritative report does not include electromagnetic radiation as a major risk factor, possibly due to ongoing debates regarding its safety.

One of the key pathological features of AD is the abnormal aggregation of amyloid β-protein (Aβ). Aβ aggregates exhibit significant neurotoxicity, making the Aβ cascade hypothesis the predominant theory explaining the pathogenesis of AD.[3] Currently, the known external factors that promote Aβ aggregation are primarily chemical in nature, such as metal ions[4] or pH variations.[5] However, with the widespread application of electromagnetic waves, studies have indicated that individuals in occupations with prolonged exposure to high-intensity electromagnetic fields face a significantly increased risk of developing AD.[6–8] Consequently, an increasing number of studies are now focusing on the effects of electromagnetic waves on Aβ aggregation.[9]

The terahertz (THz) wave is regarded as the most promising electromagnetic band in the field of biology. Traditionally, electromagnetics defines the THz spectrum as ranging from 0.1 THz–10 THz, which coincides with the weak interaction energy levels necessary for maintaining the stability of biological macromolecules. However, in 2018, Liu[10] expanded this range to 0.5 THz–100 THz based on the energy spectrum corresponding to biological signal processing. Due to this biological relevance, concerns have been raised regarding the potential biological effects of THz radiation. Due to the unique characteristics of photon energy levels, the terahertz band has emerged as one of the most

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promising regions of the electromagnetic spectrum in biological research.[11] The biological effects of terahertz radiation have been extensively investigated in various areas, including ion channels,[12–14] DNA,[15–17] drug interactions,[18] neuronal activity,[19,20] pain perception,[21] cancer treatment,[22] mental disorders,[23] learning and memory.[24] Moreover, numerous studies have demonstrated that THz radiation can influence the aggregation behavior of Aβ. As early as 2019, Kawasaki *et al.*[25] in Japan found that THz radiation in the range of 3.75 THz–4.29 THz could degrade Aβ fibrils. Similarly, Peng *et al.*[26] discovered that electromagnetic radiation at 34.88 THz could induce the depolymerization of Aβ oligomers through resonance. These findings suggest that THz radiation at specific frequencies may be safe. However, a study conducted by our research group in 2022 revealed that 3.1-THz radiation significantly promoted Aβ oligomerization while inhibiting further fibril formation, without exhibiting cytotoxicity to healthy cells.[27] Furthermore, Chen *et al.*[28] found that 42.55 THz enhanced the aggregation propensity of Aβ monomers through molecular dynamics simulations. These studies provide significant insights into the molecular-level effects of THz waves on Aβ interactions. However, two critical limitations remain: first, these findings have not been validated in living organisms at the macroscopic level; second, the precise energy-matching relationship between frequency and molecular structure has yet to be explained from the perspective of quantum mechanics.

To address the challenge of characterizing the effects of THz wave intervention on Aβ at the level of living organisms, this study focuses on the model organism *Caenorhabditis elegans* (*C. elegans*), which is small, easy to cultivate, and highly observable. Additionally, due to its transparent body, THz radiation can easily penetrate the *C. elegans*, enabling a comprehensive intervention effect. As the first organism to have its entire genome sequenced, *C. elegans* can be genetically engineered to model various diseases. For instance, the transgenic strain CL4176 expresses Aβ1-42, developing normally at 16 °C but expressing Aβ upon exposure to 25 °C, thereby mimicking neurodegenerative characteristics similar to those observed in AD patients.[29] Based on these advantages, this study applied 3.1-THz electromagnetic radiation to CL4176 *C. elegans* to investigate its biological effects. Furthermore, building upon previous research, all-atom force field molecular dynamics simulations were employed to model the behavior of Aβ1-42 under a THz electric field. Quantum chemical calculations were also performed to analyze the energy matching between frequency and molecular structure, providing a microscopic perspective to verify and explain the observed experimental phenomena. This study explores the potential impact of THz radiation on AD and assesses the potential safety risks associated with 3.1-THz radiation.

2. Materials and methods

2.1. Experimental method

As shown in Fig. 1, the schematic diagram illustrates a self-designed THz radiation system. Radiation treatment was administered every 48 hours, with each session lasting 2 hours. Following irradiation, assessments were conducted on the nematode's lifespan, locomotor activity, feeding behavior, reactive oxygen species (ROS) levels, and lipofuscin accumulation. Further methodological details can be found in the supplementary materials.

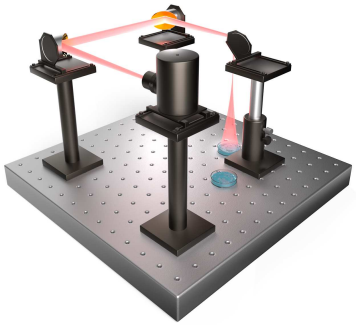


Fig. 1. Schematic diagram of the THz wave irradiation system.

2.2. Computer simulation method

Molecular dynamics simulations were performed using GROMACS software,[30–35] with the all-atom Amber14SB force field[36] and the TIP3P water model[37] applied to simulate the protein and solvent, respectively. Quantum chemical calculations were performed using the ORCA software package.[38] The B3LYP (Becke three-parameter hybrid functional with Lee–Yang–Parr correlation) functional[39] and the def2-TZVP(-f) basis set[40] were selected. The D3 dispersion correction[41,42] was applied to accurately model the dispersion effect in the system. The CPCM implicit water model was used to account for solvent effects. The calculated vibrational spectrum was visualized using Multiwfn software.[43,44] Further details of the computer simulation can be found in supplementary materials S5.

3. Results and analysis

3.1. Effect of THz radiation on the lifespan of nematodes

As shown in Fig. 2 and Table 1, treatment with 3.1-THz radiation significantly shortened the lifespan of nematodes, with an overall reduction of approximately 21.4%. This result is consistent with our previous findings. Our earlier studies demonstrated that electromagnetic radiation at a 3.1-THz frequency promotes the aggregation of Aβ monomers while

inhibiting the process of oligomeric fibrillation.[27] This suggests that, under the influence of 3.1-THz radiation, a significant proportion of Aβ in the aggregation system remains in the form of highly toxic oligomers. This effect is amplified in the nematode body, leading to increased mortality.

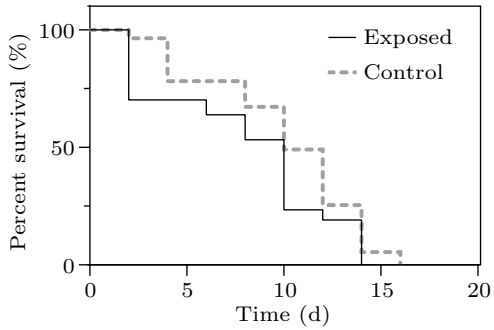


Fig. 2. Effect of 3.1-THz radiation on the lifespan of nematodes.

Table 1. Statistical analysis of the lifespan in nematodes.

Groups	Lifespan	Number
Radiation	8.32±0.54	120
Control	10.59±0.63	120
p value	< 0.05	

3.2. Effect of THz radiation on the motility of AD nematodes

The 3.1-THz electromagnetic radiation also impacts the motility of nematodes. Due to the neurotoxic effects of Aβ, its deposition in the nervous system leads to a decline in the motility of nematodes, eventually resulting in paralysis. In this study, nematode motility was assessed by measuring the frequency of head swings, with the results shown in Fig. 3(a). Following the initial irradiation, there was no significant difference between the radiation and control groups. However, by the fourth day, the head swing frequency in the radiation group significantly decreased, indicating that the enhanced induction of radiation toxicity on Aβ began to manifest pathologically, accelerating the development of AD in nematodes. On day six, the difference in head swing frequency between the radiation and control groups increased further, suggesting a cumulative enhancement of Aβ-induced nervous system damage. Notably, previous studies from our research group showed that the effect of THz radiation on Aβ aggregation does not follow a nonlinear relationship with radiation duration. However, in the animal model, prolonged radiation exposure results in a linear increase in toxicity. This discrepancy is likely due to the fact that the toxicity of Aβ does not increase linearly with the degree of aggregation. Moreover, this accumulation underscores the irreversible nature of Aβ oligomer-induced nerve damage. These findings provide strong support for the energy accumulation theory of THz radiation effects, as proposed by Zhao *et al.* in 2019.[45]

3.3. Effect of THz radiation on the feeding ability of AD nematodes

Similar to its effect on motility, Aβ deposition also impairs the feeding ability of nematodes. Feeding ability can be assessed by observing the swallowing behavior of the nematodes. The swallowing process is accompanied by the reciprocating motion of the pharyngeal pump. Thus, feeding ability can be evaluated by counting the number of pharyngeal pump vibrations per unit of time. The statistical results are shown in Fig. 3(b). The frequency of pharyngeal pump vibrations in the radiation group also followed a similar trend, with increasing radiation exposure. These results corroborate the findings from the analysis in Subsection 3.2.

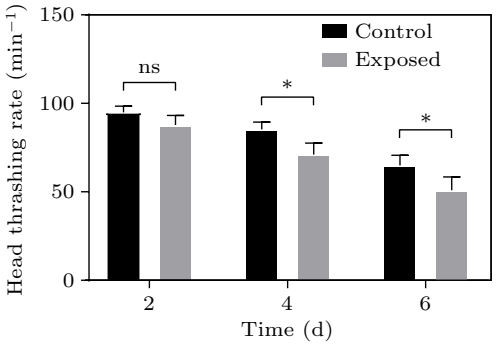


Fig. 3. Statistics of nematodes head swing frequency. $*$: $p < 0.05$.

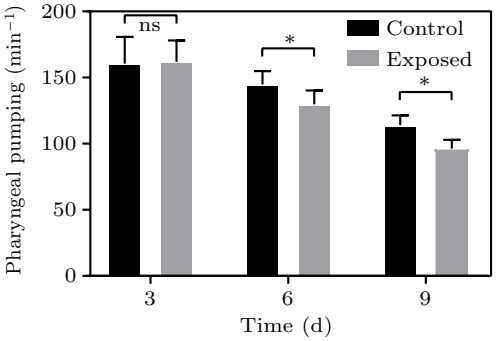


Fig. 4. Statistical analysis of nematodes pharyngeal pump vibration frequency. $*$: $p < 0.05$.

3.4. Effect of THz radiation on oxidative stress in AD nematodes

ROS are by-products of cellular respiration and are typically eliminated by cellular metabolism. However, in AD, the accumulation of Aβ oligomers often disrupts mitochondrial function and autophagy, significantly reducing the body's antioxidant capacity.[46] Additionally, Aβ oligomers can interact with ions to catalyze ROS production.[47] The combination of these two mechanisms results in ROS accumulation, making ROS a key marker of Aβ toxicity in nematodes. As shown in Fig. 5, the fluorescence intensity of ROS in the AD model nematodes, after three rounds of irradiation, was significantly higher than that in the control group. Figure 5(c) demonstrates the substantial increase in ROS content in the irradiated nematodes. These results further confirm the enhancing effect of 3.1-THz electromagnetic radiation on Aβ toxicity.

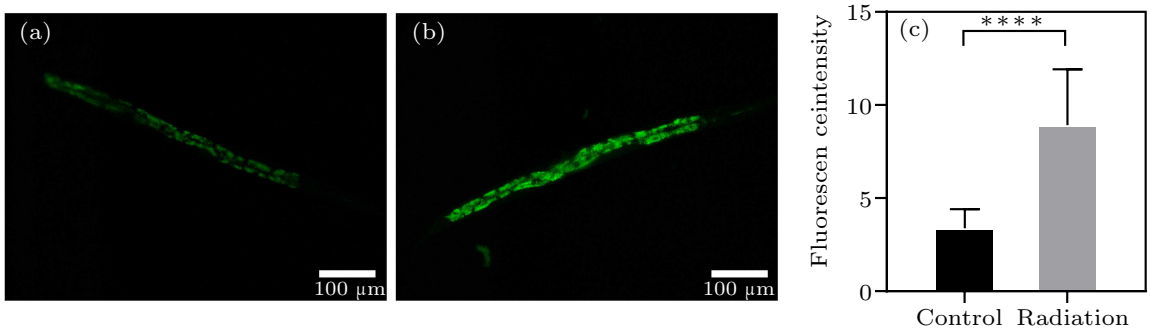


Fig. 5. Effect of 3.1-THz radiation on ROS content in nematodes. (a) Fluorescence image of ROS in the control group; (b) fluorescence image of ROS in nematodes after irradiation; (c) bar chart displaying the mean and standard deviation of ROS fluorescence intensity in the irradiation and control groups. $****$: $p < 0.0001$.

3.5. Effect of THz radiation on aging in AD nematodes

Lipofuscin is a polymer composed of incompletely degraded lipids and proteins, primarily produced in lysosomes, and is a by-product of oxidative damage. Numerous studies have shown that lipofuscin content is positively correlated with aging,[48,49] making its accumulation a key indicator of nematode aging. As shown in Fig. 6, the fluorescence intensity of lipofuscin in AD model nematodes, after three rounds of irradiation, was significantly higher than that in the control group. In aging studies, the excessive accumulation of lipofuscin in the experimental group was not directly caused by the increased toxicity of Aβ, but was more likely a downstream product of oxidative stress. That is, the heightened toxicity of Aβ triggered an intensified oxidative stress response in nematodes, leading to further generation and accumulation of lipofuscin. The strong correlation between ROS and lipofuscin further supports the role of 3.1-THz radiation in promoting the pathological progression of AD *in vivo*.

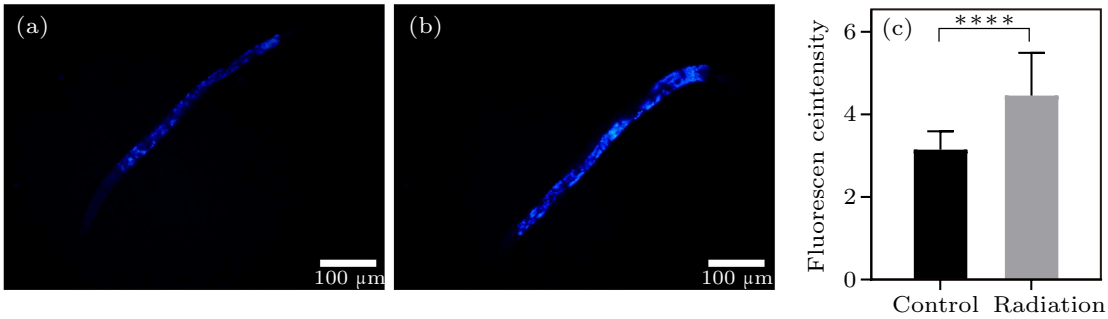


Fig. 6. Effect of 3.1-THz radiation on lipofuscin content in nematodes. (a) Fluorescence image of lipofuscin in the control group; (b) fluorescence image of lipofuscin in nematodes after irradiation; (c) bar chart displaying the mean and standard deviation of lipofuscin fluorescence intensity in the irradiation and control groups. $****$: $p < 0.0001$.

3.6. Molecular dynamics simulation of THz radiation on Aβ1-42

To elucidate the molecular mechanism of THz wave effects on AD nematodes, all-atom molecular dynamics simulations were employed to investigate the behavior and conformational changes of Aβ1-42 molecules in both the electric field and natural states. This approach allowed us to analyze the toxic effects of Aβ1-42 expressed in nematodes under an electric field. Figure 7 presents the molecular dynamics trajectory of Aβ1-42 under the influence of a 3.1-THz electric field. The simulation clearly shows that under the THz electric field, Aβ1-42 molecules rapidly unfold from their α-helix structure, transitioning into a disordered conformation that exposes hydrophobic groups more extensively. In contrast, in the natural state without an electric field, Aβ1-42 maintains partial α-helix and random coil structures, preserving its structural stability during the simulation time. This observation aligns with previously reported structural characteristics of amyloid proteins in water. These findings demonstrate the interference of THz waves with the secondary structure of Aβ1-42 and are consistent with the results from earlier atomic force field simulations. To further investigate this phenomenon, quantitatively analyzed was performed on the changes in the secondary structure of Aβ1-42 under the influence of the THz electric field, as shown in Fig. 8(a). In the presence of THz radiation, the number of secondary structures decreases rapidly, notably with an increase in β-sheet formation, which is associated with aggregation.

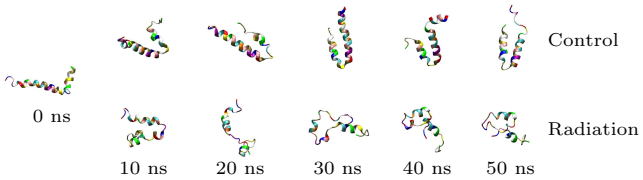


Fig. 7. Molecular dynamics trajectory of Aβ1-42.

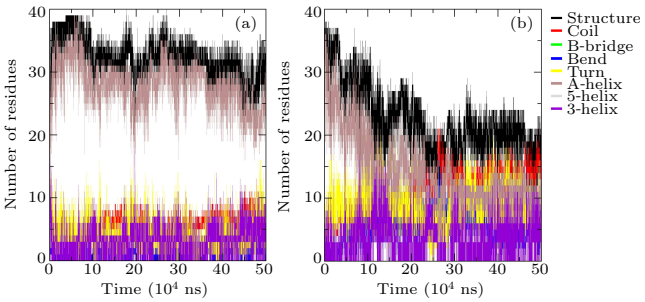


Fig. 8. Secondary structure analysis: (a) changes in the secondary structure of Aβ 1-42 in the absence of a THz electric field; (b) changes in the secondary structure of Aβ 1-42 under a 3.1-THz electric field.

3.7. Quantum chemical calculation of Aβ1-42 structure

As presented in Subsection 3.6, all-atom molecular dynamics simulations were unilized to investigate the structural changes of Aβ1-42 under THz radiation. The results are consistent with findings from previous studies conducted by both the our research group and other researchers. However, the frequency-specific mechanism underlying these structural changes remains unclear, particularly the energy matching relationship between the 3.1-THz frequency and the Aβ1-42 structure. This section presents a more in-depth analysis of the Aβ1-42 structure at the quantum level. Figure 9 presents the optimized hydrophobic core structure, which retains a well-defined α-helix conformation. The illustration shows the vibration analysis results of the optimized hydrophobic core. The analysis indicates a distinct vibrational mode at 3.12 THz, suggesting that the structure can specifically interact with electromagnetic waves at the 3.1-THz frequency (and other characteristic frequencies observed). This interaction facilitates resonance. Further visualization reveals that this vibrational mode reflects the collective motion of hydrophobic groups within the hydrophobic core, and the characteristics of this collective vibration align well with the vibrational features of the THz band. This resonance absorption may be a key mechanism by which the 3.1-THz electromagnetic wave specifically disrupts the α-helix structure in the hydrophobic region of Aβ1-42.

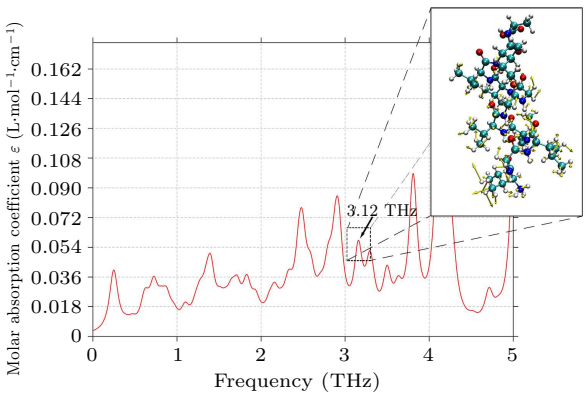


Fig. 9. Vibration analysis of the Aβ1-42 hydrophobic core.

4. Conclusion

This study investigated the effects of long-term exposure to 3.1-THz radiation (0.27 MW) on the AD model CL4176 *C. elegans*, simulating the chronic exposure of AD patients to a THz electromagnetic field. Comprehensive analyses of lifespan, motility, feeding behavior, oxidative stress levels, and aging status revealed that prolonged 3.1-THz radiation significantly impacted the physiological and pathological characteristics of the nematodes.

The results demonstrated that long-term radiation notably shortened the lifespan of CL4176 nematodes and reduced their motility and feeding ability. Further investigation showed that 3.1-THz radiation induced elevated oxidative stress levels, which significantly accelerated the aging process in the nematodes. This accelerated aging mechanism was closely linked to the aggregation of Aβ protein in the nematodes. The parallel investigation using wild-type (N2) nematodes, which do not express Aβ, further reinforces this conclusion (see supplementary materials). In conjunction with all-atom molecular dynamics simulations, it was observed that 3.1-THz radiation interfered with the secondary structure of Aβ protein, promoting rapid aggregation of Aβ monomers into oligomers, while inhibiting further transformation into fibrils (a phenomenon previously verified in our studies). This effect led to the deposition of the most toxic oligomeric form of Aβ in the nematodes, thereby enhancing the pathogenicity of Aβ, worsening neuronal damage, and accelerating the pathological progression of AD. Additionally, the irreversible nature of Aβ's damage to the nervous system contributed to cumulative neuronal damage, which partially supports the energy accumulation theory proposed by our research group in 2019.

This study underscores the potential exacerbating effects of 3.1-THz electromagnetic radiation on Aβ toxicity and the pathological features of AD at the animal model level. These findings suggest that long-term exposure to 3.1-THz radiation may pose potential biological risks for AD patients, including exacerbating neurotoxicity and accelerating disease progression. Accordingly, while exploring the potential applications of THz technology, it is crucial to consider its biological safety. Further investigations are warranted to define its safety thresholds and assess its generalizability across diverse animal models. This work offers a valuable reference for the development of AD intervention strategies and the future safety assessments of THz technology.

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