



Cite this: DOI: 10.1039/d5cp03734d

Terahertz-induced conformational dynamics of synaptotagmin III

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Synaptotagmin regulates neurotransmitter release by sensing changes in Ca^{2+} concentration, playing a crucial regulatory role in nerves, muscles, and various other systems. Terahertz (THz) waves, a safe and efficient new tool, have been widely used in biomedicine in recent years, but the regulation of synaptotagmin by THz waves remains an unclear issue. In this research, we use density functional theory and molecular dynamics simulations to calculate the THz spectra of the Ca^{2+} binding site and to identify the microscopic vibrational modes corresponding to the characteristic spectral peaks. Through molecular dynamics simulations, we find that 54.65 THz electromagnetic wave stimulation can influence the binding strength of Ca^{2+} to the synaptotagmin pocket and significantly alter the conformation of synaptotagmin. These findings suggest a possible mechanism for THz-mediated modulation of Ca^{2+} -dependent protein dynamics at the molecular level.

Received 27th September 2025,
Accepted 15th April 2026

DOI: 10.1039/d5cp03734d

rsc.li/pccp

1 Introduction

The intricate release of neurotransmitters was regulated by a sophisticated protein synergy network, wherein the core structure comprises the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) synaptobrevin, syntaxin-1, and synaptosomal-associated protein 25 (SNAP-25), forming a tightly woven four-helix bundle.^{1–3} This structure plays a key role in coordinating the fusion of synaptic vesicles with the plasma membrane and the base step in membrane fusion.⁴ Ca^{2+} could bind to functional proteins, playing a vital role in the developmental and memory processes of organisms.^{5–8}

Synaptotagmin (Syt), a pivotal protein in neuronal synapses, is primarily present on the synaptic vesicle membrane of neurons, playing a crucial role in the intricate process of synaptic vesicle fusion and neurotransmitter release. It can sense changes in Ca^{2+} concentration and facilitate the fusion of synaptic vesicles and cell membranes through interactions with other fusion proteins, releasing neurotransmitters into the synaptic cleft.^{9,10} Synaptotagmin III (Syt3) belongs to the synaptic vesicle protein family and acts as a Ca^{2+} sensor. It flows into nerve terminals under action potential stimulation, triggering synaptic vesicle

fusion and releasing neurotransmitters.^{11,12} The relevant process is shown in Fig. 1. Featuring a unique C2 domain with multiple Ca^{2+} binding sites, the Syt3 C2A and C2B subdomains (C2AB) can sense and capture Ca^{2+} , inducing conformational changes that mediate the functions of synapse-binding proteins.^{13,14} Syt3 affects the change of membrane curvature in the form of Ca^{2+} -dependent binding and participates in Ca^{2+} dependent exocytosis

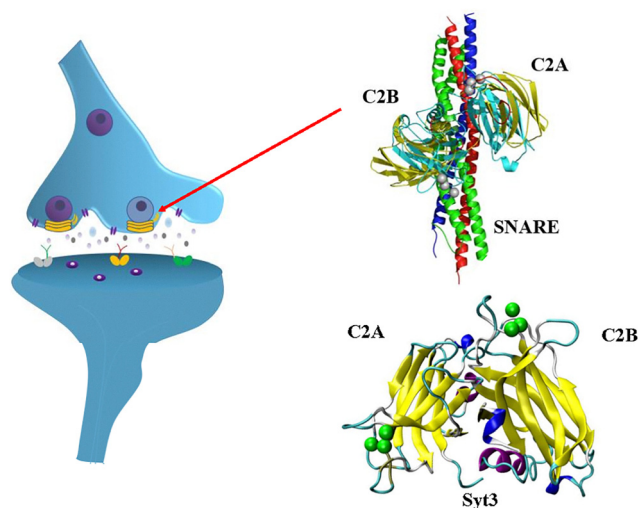


Fig. 1 Schematic diagram of synaptic information transmission. The SNARE complex senses changes in Ca^{2+} concentration, stimulates the fusion of the vesicle membrane and the presynaptic membrane, and completes the release of neurotransmitters. Neurotransmitters carry chemical information to the prominent posterior membrane receptors to complete information transmission.

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in the nervous system.^{15,16} Aberrations associated with it have been implicated in various neurological diseases, including Alzheimer's disease and schizophrenia.¹⁷ Previous studies have shown that impairments in hippocampal synaptic function and neuronal degeneration contribute to the development of Alzheimer's disease.¹⁸ At present, the sensitivity of Ca^{2+} binding within the C2AB domains to external physical perturbations has not been fully elucidated at the molecular level. Therefore, a deeper understanding of THz modulation of Ca^{2+} binding will provide important complementary insights into the functional regulation of synaptotagmin during neurotransmitter release.

The wavelengths of molecular vibrations range from micro-waves to infrared, with the low-frequency modes and high-frequency modes occurring in different ranges. Their photon energies are low, allowing them to influence molecular interactions without disrupting chemical bonds.^{19–22} Because THz frequencies overlap with the vibrational modes of many biomolecules and functional groups, they can be selectively targeted based on their chemical properties and can offer new approaches to disease treatment.^{23,24} THz waves have great potential in regulating the molecular structure, cell activity and ion channels.^{25,26} Chen *et al.* used molecular dynamics (MD) simulations to show that THz waves at specific frequencies can disrupt hydrogen bonds between proteins and nicotine, promoting its release from acetylcholine receptors.²⁷ Voltage-gated Ca^{2+} channels, such as $\text{Ca}_v1.2$ and $\text{Ca}_v2.1$, are widespread in the nervous system. Sun *et al.* demonstrated through MD simulations and experiments that 42.5 THz waves can enhance Ca^{2+} signaling.^{28,29} Li *et al.* reported that a 42.55 THz wave, resonating with $-\text{COO}^-$ groups, significantly increases Ca^{2+} permeability through voltage-gated channels.³⁰ Liu *et al.* showed that

mid-infrared light at specific wavelengths can modulate ion channels and neural signals.³¹

In this research, we focused on Syt3 and studied the effect of THz waves on the stability of Syt3 binding to Ca^{2+} by MD simulation. By constructing a simulation environment that is like the physiological environment, we could approximately examine the protein dynamics under set external conditions.³² We found that 54.65 THz waves changed the binding strength of Ca^{2+} to the pocket and made the conformation of Syt3 more flexible, which provides a possible new perspective on the regulation of neurotransmitter release processes by THz waves, as well as their potential relevance to neurodegenerative diseases.

2 Methods

2.1 System construction and MD simulation parameter setting

The structure of Syt3 and Ca^{2+} was obtained from the RCSB database (PDBID: 3HN8).³³ The PDB structure contains three identical chains. We selected one of the chains as the initial structure and marked the Ca^{2+} in the binding site, as shown in Fig. 2. The C2A domain spans residues 255 to 421, and the C2B domain covers residues 429 to 573. All MD simulations were performed using the GROMACS software package (version 5.1.0).³⁴ We employed AMBER14SB to describe the protein force field because among the AMBER protein force fields, ff14SB has been extensively validated and widely used in protein simulations. Compared with earlier versions, it offers improved accuracy in backbone and side-chain conformational distributions.³⁵

Firstly, the Ca^{2+} -binding protein was immersed in a 10.34 Å cube, and the cube was filled with a water model of TIP3P

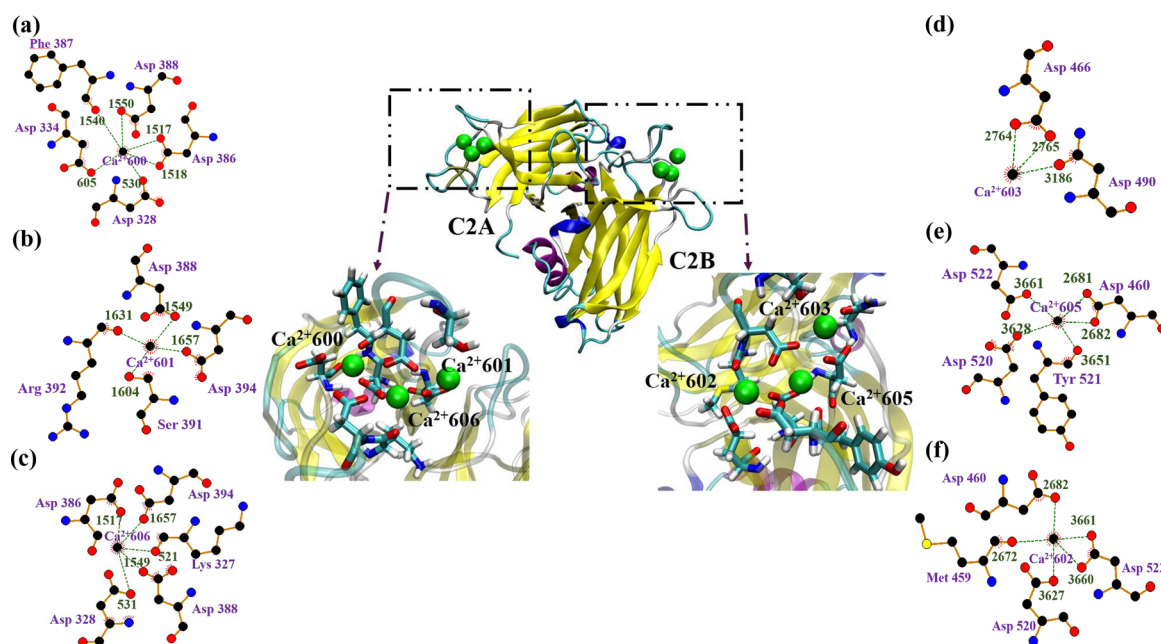


Fig. 2 Structural representation of the Syt3 C2AB domain with bound Ca^{2+} . The protein is shown in cartoon mode, and all Ca^{2+} are presented as vdW spheres. The (a–c) and (d–f) figures are correspond to the C2A and C2B domains respectively. Insets detail Ca^{2+} coordination in the binding pockets: black, red, and dark blue spheres represent C, O, and N atoms, and green dashed lines indicate Ca^{2+} coordination bonds.

charge.³⁶ The minimum distance between the protein surface and the box wall was set to be greater than 8 Å, and after the addition of counterions, the conjugate gradient method was used to minimize the energy. The convergence criterion was 100 kJ mol⁻¹ nm⁻¹, and the step size was 0.01 nm. Then the restricted MD simulation was carried out with a time step of 1 fs and a total time of 100 ps, using the resonance model to constrain the cartesian coordinates of the protein–ligand, the protein–ligand was limited to the initial position, and the solvent was freely balanced. After the protein released, the ligand restriction condition remained, and the constraint simulation of 400 ps was carried out to achieve a better interaction between the protein and ligands. Finally, the product phase was obtained by simulating the whole system for a long time without any restraint using an integral time step of 2 fs. To keep the temperature of the system at 300 K, the velocity-rescale hot bath with a time constant of 0.2 ps was used,³⁷ and the temperature of the solute–solvent was controlled separately. The pressure was controlled using a Berendsen bath with a time constant of 0.5 ps for the equilibrium phase and Parrinello–Rahman bath with a time constant of 2 ps for the product phase.^{38,39} The electrostatic interaction was calculated by the PME method with a short-range electrostatic interaction distance of 1 nm in real space,⁴⁰ and the van der Waals (vdW) interaction was calculated by the cut-off method with a cutoff distance of 1 nm.

In this study, we considered only the influence of electromagnetic waves polarized along the z-direction, as previous studies have consistently shown that the effect of the polarization direction is negligible.⁴¹ Due to the intrinsic timescale limitations of classical MD simulations, studies investigating THz wave modulatory effects universally employ V nm⁻¹ scale electric field amplitudes; this elevated field strength is necessary to accelerate molecular relaxation and response processes, allowing statistically significant effects to be observed within computationally feasible simulation windows, and represents a well-established standard for proof-of-principle MD studies aimed at uncovering fundamental molecular mechanisms. Experimentally, Jang and Kim reported that state-of-the-art femtosecond laser based optical rectification can generate THz pulses with peak electric field strengths reaching 0.04 V nm⁻¹.⁴² While the experimentally achievable field strength is lower than the 0.7 V nm⁻¹ amplitude applied in our simulations, this difference is fully justified for the present proof of principle investigation.

Accordingly, the 0.7 V nm⁻¹ electric field used in this study should be regarded as an enhanced, non-physiological field strength intended to facilitate the observation of field-induced effects within the limited simulation timescale, rather than to quantitatively reproduce experimental conditions, such simulations can provide valuable qualitative insights into the possible mechanisms by which THz fields may influence ligand–receptor interactions, and rapid advances in THz source technology are continuously pushing the limits of peak field strength, bringing higher-amplitude THz pulses closer to experimental realization, and enabling future validation of the mechanistic findings reported here.

When calculating the spectrum, the trajectory was saved every 1 fs, and the simulation time was 80 ps. The dipole

moment at each moment was substituted into formulas (1) and (2) for spectral analysis. In the product phase of the simulation, the simulation step was 2 fs, and the system coordinates were saved every 4 ps for subsequent analysis. The whole trajectory was fitted to the first frame using CR atoms by the least-squares method to remove the overall translational and rotational motion and avoid the impact of periodicity. The root-mean-square fluctuation (RMSF) value of the residue was averaged on the atoms within the residue. The RMSF value of the crystal was determined by experiment and transformed using the formula $\langle \Delta r_i^2 \rangle = 3B_i/(8\pi^2)$. The values of the corresponding parameters in the formula are obtained from the downloaded PDB file.

2.2 The calculation of vibration spectra

The vibrational spectra calculated from MD simulations are based on the Fourier transform of some autocorrelation functions, and the infrared spectra depends on the molecular dipole moment. Compared with the dipole moment, the derivative of the dipole moment is more accurate. The infrared intensity is given by the following equation:⁴³

$$A(\omega) \propto \int \langle \dot{\mu}(\tau) \dot{\mu}(t + \tau) \rangle_{\tau} e^{-i\omega t} dt \quad (1)$$

$$\langle \dot{\mu}(\tau) \dot{\mu}(t + \tau) \rangle_{\tau} = \frac{1}{2\pi} \left| \int f(t) e^{-i\omega t} dt \right|^2 e^{i\omega t} d\omega \quad (2)$$

where $A(\omega)$ represents the spectral intensity on the vertical axis and μ denotes the dipole moment vector.

Based on the structure of the restricted MD simulation, the conventional MD simulation with a time step of 1 fs and a total time of 80 ps was carried out, and one frame per 1 fs was saved for dipole moment analysis. The software VMD can be used to obtain the dipole moment of the region of interest at any time, so the vibration spectrum can be calculated and the molecular structure and visual analysis can be performed.⁴⁴

The quantum chemical calculation software ORCA was used in this paper to calculate the vibration spectrum of specific amino acids that interact with Ca²⁺ and to compare it with the vibration spectrum calculated by MD simulation.⁴⁵ The structure was extracted from the product phase of MD simulation, and the vibration spectrum was calculated using the B3LYP density functional theory method and the def2-TZVP basis set with the auxiliary basis set def2/J and D3BJ for dispersion correction.^{46–49}

3 Results and discussion

3.1 Electrostatic interaction mechanisms in Ca²⁺ binding stability

We performed three independent MD simulations without THz (w/o THz) and plot the temperature profile over the course of the simulation to confirm the thermal stability of the system. Additionally, RMSD curves of the protein backbone and Ca²⁺ relative to the protein backbone were plotted to assess the structural stability of the protein and the binding stability of the Ca²⁺. All figures are shown in Fig. S1. The RMSD curve of

the protein backbone reaches a stable value at around 80 ns and remains at around 0.25 nm. The Ca^{2+} relative to the protein backbone binding reaches a stable value after 80 ns and remains near 0.20 nm.

Fig. 2 shows the molecular interactions of Ca^{2+} with the binding pocket based on LigPlot.⁵⁰ The acid groups that interact with Ca^{2+} are mainly $-\text{COO}^-$ and $-\text{C}=\text{O}$, which are charged polar groups. In general, THz waves can affect the interaction between functional groups and ligands, affecting the binding of ligands to sites. This provides a way to find the factors that affect the binding sites in the future.

Electrostatic potential (ESP) on the vdW surface is often investigated because it is very closely related to intermolecular electrostatic interactions.⁵¹ It can be used to study the interaction strength between proteins and ligands and predict the binding ability. We performed the ESP analysis using Multiwfn and VMD to evaluate the interaction of Ca^{2+} surrounding

sites^{52–54} and calculate the extreme potential energy points on the vdW surface. As shown in Fig. 3, the blue area corresponds to lower energy and the red area corresponds to higher energy. The blue area is almost all in a cage-like structure, surrounding the Ca^{2+} , so the pocket can capture the Ca^{2+} more firmly, the pocket where Ca^{2+} 601 is located is close to the positive potential area, and the positive potential area reduces the attraction of the pocket to the Ca^{2+} . From the perspective of interaction energy, the interaction energy between Ca^{2+} 601 and the pocket is the weakest. The Ca^{2+} 603 shows weaker binding due to fewer interacting amino acid residues, while other pockets hold Ca^{2+} more tightly by forming a more complete low-potential pocket with more residues involved.

Fig. 4 illustrates the variation of the total interaction energy, comprising electrostatic and vdW interactions, as a function of simulation time. The simulations are performed three times independently, and the curves shown in the figure represent

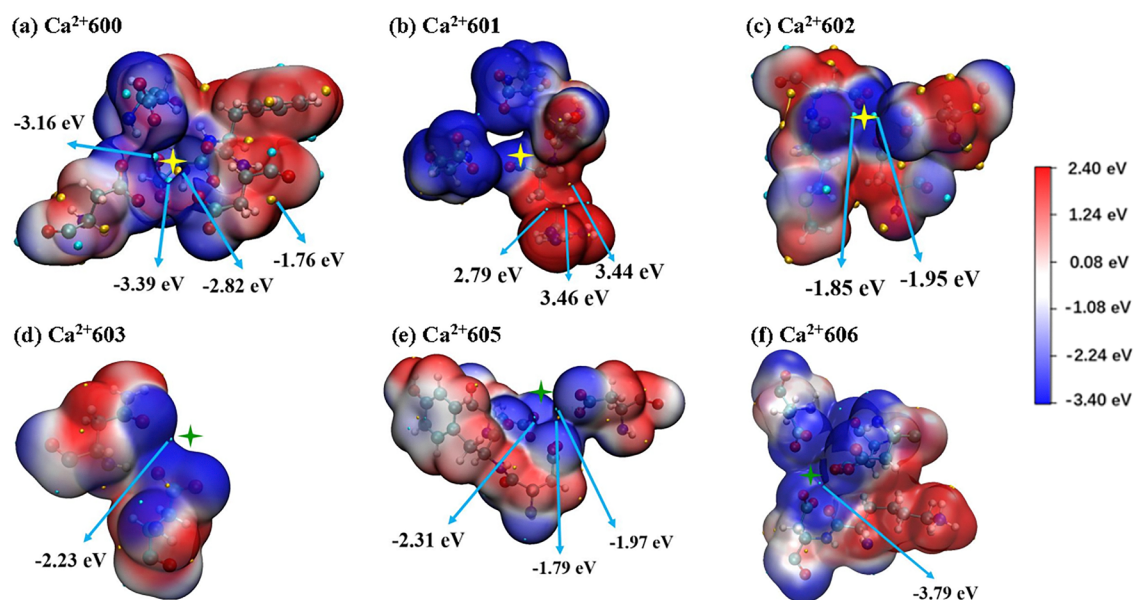


Fig. 3 (a)–(f) The ESP energy map of the six binding pockets is illustrated based on the vdW surface, with the green asterisk indicating the position of the Ca^{2+} within the pocket. Regions with a more negative potential energy are depicted in deeper blue. The yellow and cyan spheres denote the maximum and minimum values of the local electrostatic potential on the surface, respectively. Key extremum points are highlighted with arrows.

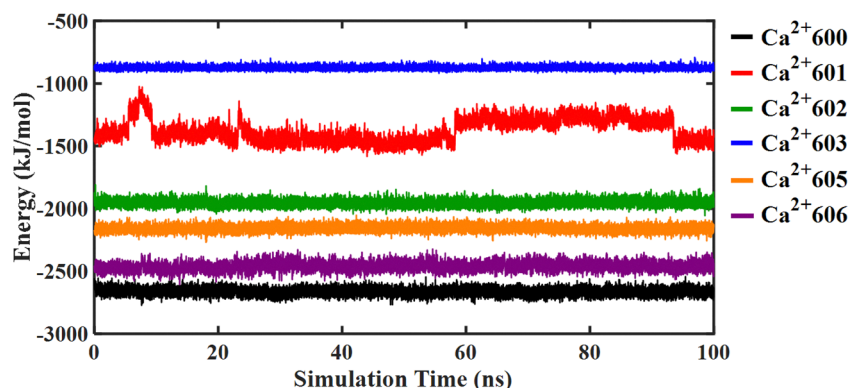


Fig. 4 The average interaction energy curves of three independent simulations of each Ca^{2+} and its respective pocket amino acid in a 100 ns MD simulation. The total interaction energy is the sum of electrostatic energy and vdW interaction energy.

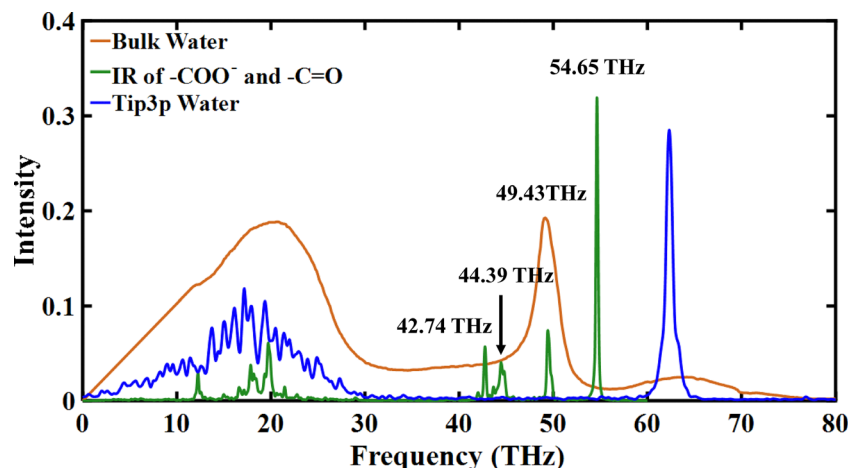


Fig. 5 The vibrational spectra of aspartic acid Asp residues are systematically calculated, with three distinct spectral profiles presented in the figure: the characteristic liquid water (red curve), Asp functional groups (green curve), and MD simulated water model (blue curve).

the average interaction energy. The interaction energy curves with error bars for each Ca^{2+} are presented in Fig. S2. The results show that the Ca^{2+} 603 exhibits the weakest interaction with the binding site, making it the most prone to dissociation and transition into a free state. This observation is reflected in its comparatively higher interaction energy. Notably, this finding aligns well with previous structural studies of Syt3.³³ The C2B region binds two Ca^{2+} , and we will not retain Ca^{2+} 603 in subsequent MD simulations to correspond to the natural situation.

3.2 Vibrational spectra analysis of functional groups

The characteristic vibration of molecules is manifested in the chemical bond vibration of characteristic functional groups, and different functional groups produce bond absorption at different positions in the vibration spectrum. In general, identical functional groups from different amino acids exhibit vibrational modes at similar positions in the spectrum. Based on the autocorrelation function of the dipole moment obtained by the trajectory, we calculate the vibration spectra of $-\text{COO}^-$ and $-\text{C}=\text{O}$, as shown by the green curve in Fig. 5. There are obvious absorption peaks at 42.74 THz, 44.39 THz, 49.43 THz, and 54.65 THz. Notably, the band at 54.65 THz corresponds to the $-\text{C}=\text{O}$ stretching vibration of the deprotonated $-\text{COOH}$ group, and as the $-\text{C}=\text{O}$ bond is not localized in this case, it is still assigned to the stretching mode of the $-\text{COO}^-$ group. Combined with the existing experimental spectra, we identify and classify the vibration modes in Table 1.⁵⁵ In addition, another weak vibration peak at 44.39 THz appears near 42.74 THz. Since there was no corresponding functional group vibration mode near

this frequency, we believe that it was caused by the accuracy of MD simulation. We see that the error between the simulation and the experiment in the high frequency band was over 80 cm^{-1} , which was a normal error caused by the molecular force field. In addition, we need to explain that if the frequency of the external field is consistent with the MD simulation results, the same physical phenomena are still present.

THz frequencies within water's intense absorption bands were generally avoided. We calculate the vibrational spectrum of the TIP3P water model (blue curve) and compare it with experimental data (red curve) in Fig. 5. The simulated 54.65 THz lies well outside the intense absorption regions in both curves, making it a suitable frequency for MD simulation.⁵⁶ Meanwhile, we recognize that the TIP3P water model has limitations in accurately reproducing the vibrational spectra of water in the THz frequency range. However, the primary focus of this study is the resonance between the applied THz field and the vibrational modes of Ca^{2+} -coordinating functional groups ($-\text{C}=\text{O}$ and $-\text{COO}^-$) within the protein binding pocket. Therefore, the selection of the characteristic frequencies associated with these functional groups is reasonable.

3.3 THz wave effects on Syt3 stability and Ca^{2+} binding

The MD simulation process is set under w/o THz and 54.65 THz conditions, and the field is 0.7 V nm^{-1} . The simulation time is $3\text{ }\mu\text{s}$, and each environment is repeated 3 times. Fig. S3 presents the absorption spectra of Tip3p water under different MD conditions. The absorption at 54.65 THz is weaker, indicating that water has a weak absorption of THz waves at 54.65 THz. Monitoring the system temperature during the simulation reveals that the temperature rise at 54.65 THz was only 0.34 K, which means that we can ignore the thermal effect. The system temperature is shown in Fig. S3(a) and (b).

To evaluate the stability of the system during the later stage of the simulation, we plotted the RMSD profiles of the protein and Ca^{2+} (relative to the protein) in Fig. S4. Due to THz stimulation and thermal fluctuations, Syt3 may undergo pronounced conformational motions. The observed variations in

Table 1 The comparison of the center peak positions of the vibration modes of $-\text{COO}^-$ and $-\text{C}=\text{O}$ groups based on MD simulation and experimental measurements (cm^{-1})

Method	Symmetrical stretching of $-\text{COO}^-$ (cm^{-1})	Asymmetric stretching of $-\text{COO}^-$ (cm^{-1})	Stretching vibrations of the $-\text{COO}^-$ (cm^{-1})
MD simulation	1424.52	1647.50	1821.48
Experiment	1401	1605	1702–1750

the protein RMSD profiles reflect its conformational heterogeneity. Given the flexible linker between the two domains, multiple metastable states are expected, and THz irradiation may facilitate more evident conformational transitions. In contrast, the RMSD of Ca^{2+} relative to the protein exhibits pronounced fluctuations and increases rapidly at early times, indicating that Ca^{2+} has dissociated from the binding site and diffused freely within the water box and the large fluctuations in the curve were due to the periodicity of the water box.

The interaction between Ca^{2+} and the pocket atom O is central to assessing the stability of Ca^{2+} binding to Syt3 (Fig. 6(a–e)). The blue and orange curves correspond to simulations w/o THz irradiation and under 54.65 THz irradiation, respectively. The peak observed before 2 μs arises from periodic boundary conditions and does not affect the structure. The results showed that THz waves had a relatively minor effect on Ca^{2+} in the bound state. The distances between Ca^{2+} 600, Ca^{2+} 602, Ca^{2+} 605 and pocket residues remain stable, while the distance between Ca^{2+} 606 and the functional group increases under THz irradiation. In addition, we show the curve of the coordination number of Ca^{2+}

in Fig. 6(f). According to the crystallographic study of the coordination length of Ca^{2+} with $-\text{COO}^-$, we choose the cut-off distance of 2.6 Å.⁵⁷ Fig. 6(f) shows that THz waves decrease Ca^{2+} occupancy in the pocket, indicating that THz waves decrease the interaction between Ca^{2+} and pockets.

3.4 THz wave effects on C2A–C2B domain interactions

We further investigated the effect of THz waves on the interaction between the C2AB domains and computed the interaction energy curve between the C2A and C2B domains, as presented in Fig. 7(a). Compared with the w/o THz condition, THz stimulation reduces the energy between the C2A and C2B domains. The absolute value of the interaction energy decreases by 100 kJ mol^{-1} . Fig. 7(b) shows that THz waves lead to an overall rightward shift in the vdW energy distribution within the C2AB region. The vdW interaction is closely related to the interdomain distance between C2A and C2B, and this observation suggests that their relative positions have been altered.

We analyse the torsion angle and bending angle of the C2AB region, with their detailed definitions illustrated in Fig. 8(a).

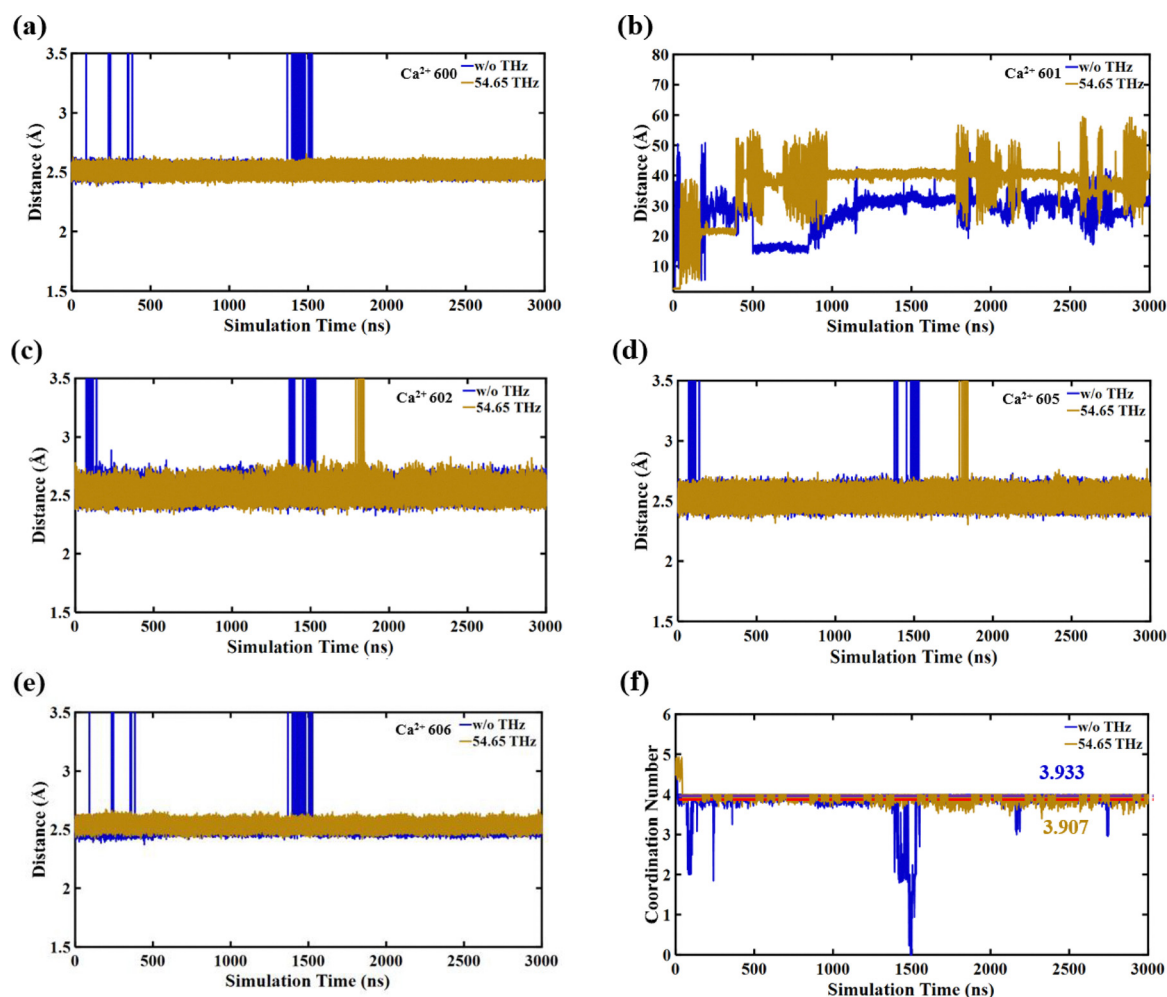


Fig. 6 (a)–(e) Average distances between each Ca^{2+} and its pocket functional groups from three independent simulations vary with the simulation time. (f) Number of Ca^{2+} ions in the pocket over 3 μs simulation (w/o THz, blue; 54.65 THz, orange), with trajectories stabilizing after 2 μs . Ca^{2+} is considered pocket-bound when its distance to functional groups is < 2.6 Å.

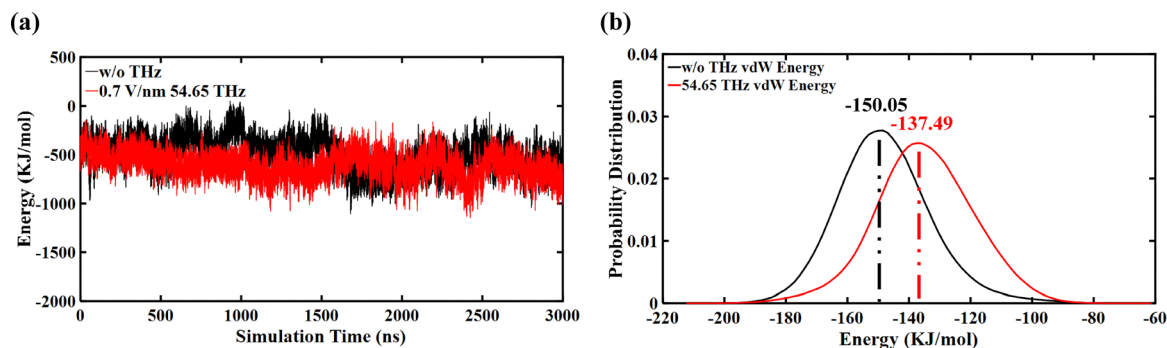


Fig. 7 (a) and (b) The average interaction energy in the C2AB region from three independent simulations varying with the simulation time and the vdW energy distribution. It is divided into w/o THz (black curve) and 54.65 THz (red curve). In (b), the vertical axis represents the relative probability distribution value, which is meaningless.

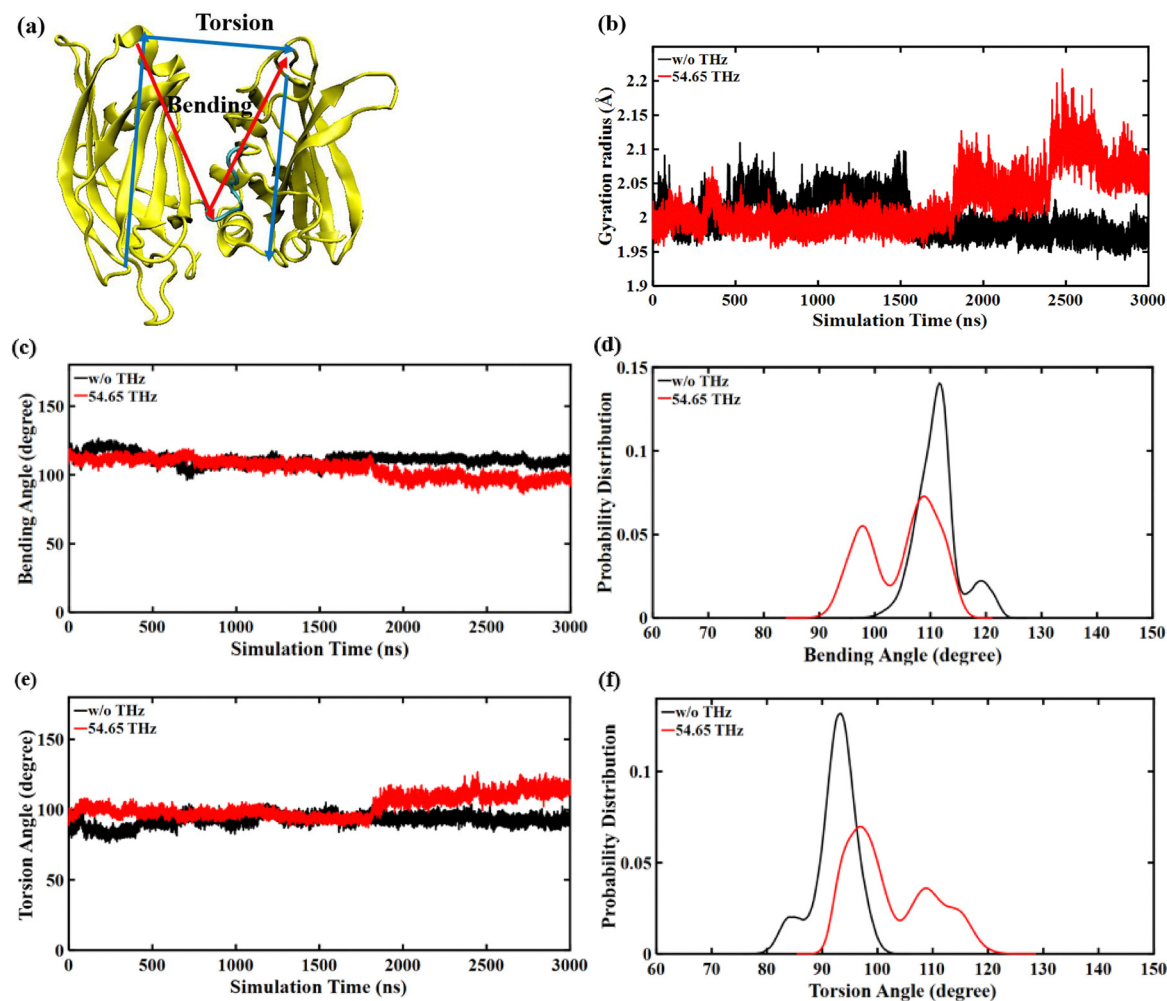


Fig. 8 (a) and (b) The definition of the relative torsion and bending angles in the C2AB region and the curve of the radius of gyration changes with the simulation time. (c) and (d) The curves and distributions of the average bending angle from three independent simulations vary with the simulation time. (e) and (f) The curves and distributions of the average torsion angle from three independent simulations vary with the simulation time. The curve was divided into w/o THz (black curve) and 54.65 THz (red curve). In (d) and (f), the vertical axis represents the relative probability distribution value, which was meaningless.

Our 3 μ s simulations reveal that bending and interdomain rotation occur in the C2AB domain during the middle and late simulation stages. The results are shown in Fig. 8(c–f) and Fig. S5. Notably, the bending and torsion angles exhibit more

obvious changes under THz irradiation relative to w/o THz. The bending angle shifts toward lower values, and the torsion angle increases, with a pronounced conformational change emerging at approximately 1.8 μ s.

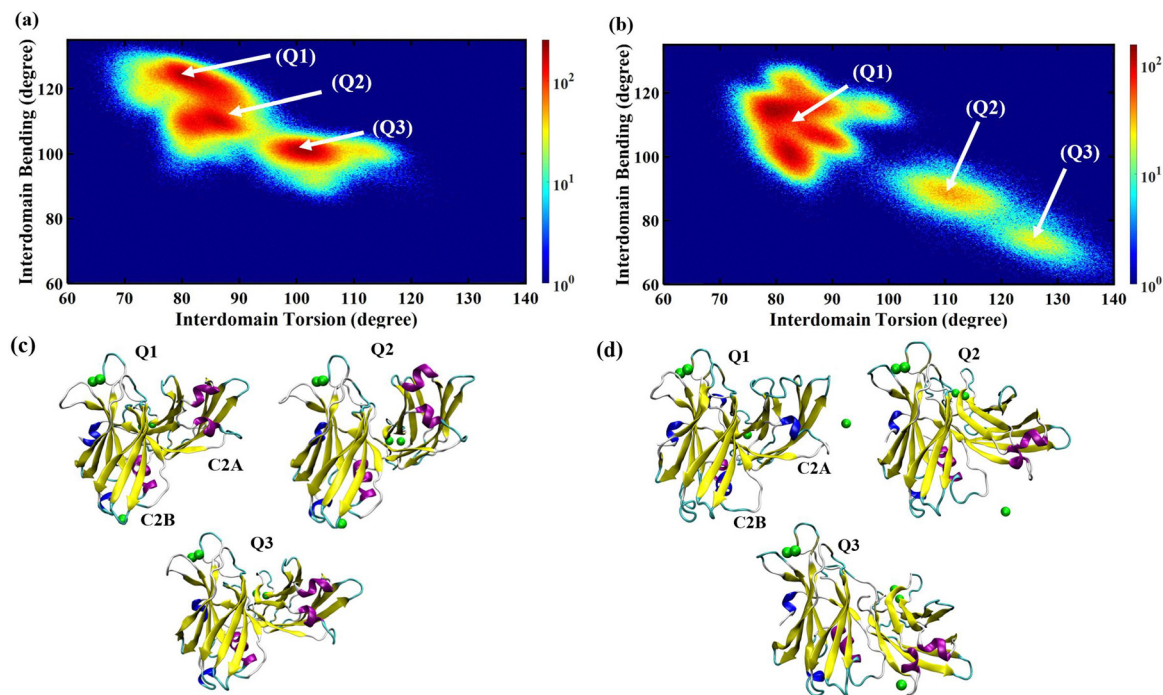


Fig. 9 (a) and (b) The FES diagram calculated with the torsion and bending angles of the C2AB region as the reaction coordinates is divided into w/o THz and 54.65 THz. The larger the scale, the more conformations are present in the region. (c) and (d) Several feature regions and the corresponding high-density conformational states are marked in the figure.

Free energy surface (FES) is a powerful tool for studying the conformational changes and reaction pathways of molecular systems. In the research of MD simulation and thermodynamics, the FES diagram quantitatively describes the free energy distribution of the system under different reaction coordinates by visualization, which provides a key physical insight for understanding the molecular conformational transition and reaction mechanism.⁵⁸ We use the torsion angle and bending angle of the C2AB as the reaction coordinates to obtain a two-dimensional FES map, as shown in Fig. 9(a and b). All data points in the figure are superimposed from three independent simulations. The darker the colour, the higher the conformational distribution density in this region. The characteristic conformations under w/o THz and 54.65 THz irradiation conditions in Fig. 9(c and d) are calculated based on the cluster analysis of GROMACS. THz wave induced perturbation shifts the system conformational landscape from a relatively compact state to a more distributed configuration across three distinct regions, thereby enhancing the conformational flexibility of the C2AB. As neurotransmitter release from presynaptic vesicles depends critically on the structural dynamics of synaptic binding proteins involved in vesicle-membrane association, we hypothesize that THz irradiation may modulate the efficiency of neurotransmitter exocytosis.

4 Conclusions

In this work, based on the reported crystal structure of the Syt3 C2AB domain, we perform the microsecond-scale MD simulations using GROMACS to investigate whether the THz waves at specific frequencies affect Ca^{2+} binding with Syt3.

In the analysis of the C2AB domain binding with six Ca^{2+} ions, we find Ca^{2+} is primarily bound with $-\text{COO}^-$ and $-\text{C}=\text{O}$ of Asp residues. To further characterize the Ca^{2+} binding micro-environment, we employed ESP analysis to examine the local electrostatic properties of the Ca^{2+} binding pockets. The results revealed that the binding pockets of Ca^{2+} 601 and Ca^{2+} 603 present unfavorable electrostatic environments for ion retention. Specifically, the Ca^{2+} 601 pocket features a large region of positive electrostatic potential, whereas the Ca^{2+} 603 pocket is enclosed in a relatively small spatial region surrounded by positive potential zones. These findings are further supported by interaction energy profile analysis between the Ca^{2+} ions and their corresponding binding pockets.

The vibrational spectrum of $-\text{COO}^-$ and $-\text{C}=\text{O}$ shows the strongest absorption peak at 54.65 THz, which avoids the strong absorption peak of water. By comparing simulations of 54.65 THz waves with w/o THz, we find that THz waves can change the binding strength of Ca^{2+} by affecting the distance between Ca^{2+} and amino acids. Further analysis shows that THz waves can weaken vdW interactions in the C2AB region and significantly affect the conformational changes of Syt3. This study provides conceptual insights and computational evidence for the potential modulation of neurotransmitter release by THz waves.

Author contributions

Hui Ning: conceptualization, methodology, writing – original draft, and formal analysis. Xinqiao Zhou: visualization and formal analysis. Yun Shi: visualization and formal analysis. Qin Zhang: visualization and formal analysis. Lixia Yang:

visualization and funding acquisition. Yuankun Sun: visualization and writing – review and editing. Shaomeng Wang: writing – review and editing and resources. Yubin Gong: funding acquisition and supervision.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). The Supporting Information primarily includes data used to assess the stability of the molecular dynamics simulations, interaction energy profiles between the six Ca^{2+} and their binding pockets, as well as the torsional and bending angle curves of C2AB. See DOI: <https://doi.org/10.1039/d5cp03734d>.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (under grants 62527804, T2241002, 62427806, 62588201, and 62501129) and the Sichuan Province Innovative Talent Funding Project for Postdoctoral Fellows.

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