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English Version[1]

Research progress of biological effects of cell membrane under infrared and terahertz irradiation

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Abstract

Irradiation of terahertz electromagnetic wave including its short-wave band in infrared wave shows broad and important application prospects in biological science due to its noninvasive and nonionizing nature. Cell membrane is an important biological barrier for keeping cell integrity and homeostasis, and it is also the cellular structure that electromagnetic fields act first on in the case of terahertz irradiation. The responses of cell membrane to the electromagnetic fields are the mechanisms for most of the biological effects of terahertz irradiation. First, in this paper expatiated are the application safety of terahertz irradiation and its new application prospects in life medicine, neural regulation, and artificial intelligence. Then, systematically described are the researches and developments in the biological effects of cell membrane under

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terahertz electromagnetic irradiation from the following four aspects: the dielectric characteristics of response of phospholipid membrane to terahertz electromagnetic irradiation, the transmembrane transport of ions through membrane ion channel proteins under the irradiation, the transmembrane transport of macromolecules and ions through phospholipid membrane under the irradiation, and the potential applications and role of biological effects of cell membrane under the irradiation. Meanwhile, introduced in this paper are the scientific discoveries that terahertz electromagnetic irradiation is able to activate voltage-gated calcium channels, voltage-gated potassium channels and active transport calcium channels in cell membrane and to create hydrophilic pores on the phospholipid membrane of cell membrane. Finally, the directions of future efforts to study the biological effects of cell membrane under terahertz irradiation are presented.

Keywords: biological effects of infrared and terahertz irradiation, membrane ion channel protein, electromagnetic field interaction, substance transmembrane transport

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1. Introduction

Terahertz (THz) science and technology has important applications in many fields such as communication, environmental monitoring, biological imaging, next-generation information technology (IT) industry, and national defense, and is known as "one of the ten technologies that will change the future world" [1-7]. The wide application of terahertz science and technology has led people to think about the safety of terahertz electromagnetic irradiation [5, 8], and the research came into being on the biological effects of terahertz irradiation [9, 10]. In recent years, the in-depth research on the biological effects of terahertz irradiation has revealed that the terahertz irradiation can regulate biological activities and functions in a non-contact manner [11-20], and thus showing new important scientific and application values in key fields such as life medicine [11-13,15,21], neural regulation [14,19,20,22,23], and artificial intelligence [24, 25].

The electromagnetic wave band of terahertz irradiation ranges from the microwave to infrared wave: the long-wave band of terahertz wave coincides with the millimeter wave band, and the short-wave band overlaps with the infrared wave band [1, 2]. Terahertz waves conventionally refer to the waves in a range of 0.1－10 THz [1, 2, 26], and also the waves in a range of 0.3－10 THz [27]. The most probable band of the physical field of vertebrate neural signals ranges from 0.5 to 100 THz. Therefore, in the study of the physical mechanism of biological nervous system, 0.5－100 THz band is called the generalized terahertz band [24, 28], and the relevant research field is termed terahertz biology [28]. According to the studies by the vibrational models based on the quantum theory, the stretching vibrational frequency of the chemical bond in certain atomic groups in biomolecules like proteins is ina range of $10^{12}-10^{14}$ Hz [29], which is in the generalized terahertz band. In addition, in the terahertz irradiation and detection, there are some studies in which the electromagnetic waves ranging from sub-THz to 100 THz are regarded as ultra-broadband terahertz electromagnetic waves [30]. Therefore, in this paper, the conventional terahertz band (0.1－10 THz) and the generalized terahertz band (0.5－100 THz) are both considered as the band of terahertz electromagnetic waves (0.1－100 THz).

The safety of terahertz irradiation applications can be reflected by its non-ionizing radiation nature. Because the photon energy of terahertz wave is far lower than the energy of various chemical bonds, terahertz irradiation does not cause any harmful ionization damage to organisms, tissues, cells, or biomolecules [2]. The researchers have conducted experimental studies of terahertz irradiation on the eyes and skins of living organisms, and found that the terahertz electromagnetic fields of the power level of nW/cm^2, $\mu W/cm^2$ or even mW/cm^2 with a relatively long irradiation time (a few minutes to tens of minutes) cause no harmful biological damage to eye corneal tissue, crystalline lens cells, retinal ganglion cells or skin fibroblasts. When the ruptured corneas of live rabbits are exposed to 0.1－1.8 THz electromagnetic field with the power of 2.5－68.8 nW/cm^2 for 5 min, the normal biological functions of the rabbits' eyes are not affected, and the epithelial cell regeneration and epithelization are both improved in corneal tissue [31]. After 24 h of the irradiation of 0.12 THz electromagnetic field with the power of 5 mW/cm^2 on the human corneal epithelial cell lines and crystalline lens cell lines, it is found by measuring the genotoxicity, morphological changes and heat stress protein expression in these cells, that the terahertz electromagnetic field itself causes no harmful damage to human eye cells [32]. Retinal ganglion cells are exposed to 0.1－2.0 THz electromagnetic field with the power level of μW/cm^2 for 5－40 min, and it is found that the apoptosis rate of the cells significantly decreases 0－12 h after the irradiation compared with the non-irradiated, indicating that terahertz irradiation causes no harmful damage to the retinal ganglion cells, and that contrarily it inhibits the apoptosis of the ganglion cells in unfavorable environments [10]. When adult skin fibroblasts are exposed to 2.52 THz electromagnetic field with the power of 84.8 mW/cm^2 for 5－80 min, more than 95% of the exposed cells are still alive 24 h after the exposure in all the irradiation groups, and the transcriptional level of deoxyribonucleic acid (DNA) repair genes is not up-regulated in the measurement of the transcriptional activation of the genes related to DNA damage pathway, indicating that DNA and skin cells are not damaged by terahertz electromagnetic irradiation [33, 34]. In addition, the non-invasive characteristics of terahertz irradiation is also shown in the study of the irradiation of 53.53 THz electromagnetic wave (5.6 μm mid-infrared wave) on zebrafish and mouse cerebral cortex [19, 20]. Because the eyes, skins and heads of organisms are organs in direct exposure to the external environment, it evidences the safety of application of terahertz irradiation, on the one hand, that terahertz irradiation causes no harmful biological damage to the eyes, skins and cerebral cortex.

It is worth mentioning that certain damage may also occur when the terahertz electromagnetic irradiation intensity or dose is increased to a large enough extent. In the experimental studies about the adult skin fibroblasts and human Jurkat cell line, it is found that when the power of the terahertz irradiation increases up to a value as large as 227 mW/cm^2, the expression of a few specific genes in skin cells is up-regulated. At the same time, the Jurkat suspension cells show the signs of cell death after 12-s irradiation, and the cell death rate is close to 80% in the case of 40-min irradiation. The researchers have pointed out that the cause of the Jurkat cells death may be related to the high-temperature dehydration and drying, or the inflammatory cytokine necrosis and apoptosis induced by the high-intensity terahertz irradiation [35]. In the experimental study of the rat glial cell line under the electromagnetic irradiation of 0.12－0.18 THz continuous wave with the average power of 3.2 mW/cm^2, the number of apoptotic cells increases 1.5 times for 1-min irradiation, and it doubles again for 3-min irradiation [36]. At the biological-tissue level, researchers have exposed the wet chamois cloth to 0.1 － 1 THz electromagnetic field for 2 s, and using the conventional damage score determination and probit analysis techniques they found find that the minimum irradiation power that can cause biological tissue to damage needs to be as large as 7.16 W/cm^2. This attests to the safety of application of terahertz irradiation, on the other hand [8].

In addition, recent researches have shown that terahertz irradiation can modulate biological activities and functions, enabling terahertz irradiation to possess the functions and effects as a kind of life medicine, such as promoting the recovery of damaged biological tissues and life functions, and also benefiting the treatment of angina pectoris. In 2005, Ostrovskiy et al. [11] used 0.15 THz electromagnetic field to irradiate a burned part of patients, and found that terahertz irradiation can promote the recovery of the patients' local burned skin tissues. In 2015, Chen et al. [13] exposed the sciatic nerve tissue of rats after surgery to 0.3－100 THz electromagnetic field and found that terahertz irradiation accelerates the rehabilitation of the injured sciatic nerve tissue of rats. In 2018, Wei et al. [15] exposed the spermatozoa from the patients with asthenospermia to 0.1－3 THz electromagnetic field, and found that terahertz irradiation for 5 min and more can significantly improve the sperm motility. In 2008, Kirichuk et al. [12] sampled the whole blood from the patients with unstable angina pectoris treated with isoket and exposed it to 0.24 THz electromagnetic field with the power of 1 mW/cm^2. It is found that the blood viscosity decreases after the irradiation. When the terahertz-irradiated isoket is added to the blood, the blood viscosity decreases more and the deformability of the erythrocytes in the blood increases with no changes in the aggregation of the erythrocytes. That is undoubtedly conducive to the treatment of unstable angina pectoris. In the same year, Kirichuk et al. [21] also employed the immobilization stress to make female and male rats have abnormal platelet aggregation. They exposed those rats to 0.15 THz electromagnetic field, and found that the platelet aggregations of the rats are completely recovered after the irradiation, and the recovery of the platelet function is more significant in female rats.

Terahertz irradiation is also able to produce non-contact and non-invasive neural regulation. In 2021, Liu et al. [19] employed the electromagnetic waves in 52－85 THz band (3.5－5.8 μm mid-infrared waves) to irradiate the nerve cells in mouse prefrontal cortex slices and the head of larval zebrafish from a distance of 70－300 μm. It is found that terahertz electromagnetic wave can produce gain control over spiking activities, regulate the waveform of action potential and regulate the neuronal activities in larval zebrafish producing sensorimotor reflexive behavior. There is no biological damage caused in the neural regulation, and the regulation effect is reversible and independent of the increase of temperature. It shows that terahertz irradiation in this frequency band can modulate the neural signals in a non-thermal, non-contact, reversible and non-invasive manner. In the same year, Zhang et al. [20] exposed the brain neurons in mice to 53.53 THz electromagnetic wave (5.6 μm mid-infrared wave) through the opened skull or non-invasively through a thinned intact skull, and showed that the 53.53 THz irradiation can cause the firing activities in brain neurons at a targeted cortical area in vivo. During the terahertz irradiation targeting the auditory cortex of the brain, the learning speed of the mice in auditory associative learning tasks is 50% faster. Those show the regulation effect of terahertz electromagnetic irradiation on neural activities and functions.

Terahertz irradiation also shows important scientific and application values in the field of brain-machine interfaces and artificial intelligence. Currently, brain-machine interface has become the frontier development direction in future research of artificial intelligence [37]. In 2019, Liu et al. [24] found that terahertz electromagnetic waves can transmit in the myelin sheath on the nerve axon membrane, and the electromagnetic energy can be supplemented and amplified at the nodes of Ranvier between two adjacent myelin sheaths. This enables the neurotransmission of terahertz electromagnetic waves to pass through myelinated nerves, showing important scientific and application values in non-invasive brain-machine interfaces. In 2021, Wang et al. [25] studied the electromagnetic characteristics caused by the different vibration modes of neural microtubulins. It is shown that microtubule vibration can produce a stronger electromagnetic field between adjacent microtubules than thermal noise, and there are multiple vibrational modes in the terahertz band. Those are conducive to the application of terahertz wave in the brain-machine interface. In addition, the regulation effect of the terahertz irradiation on the brain neural activities and functions [14, 19, 20] makes the research on the biological effects of terahertz irradiation possess important scientific values and practical application significance in the exploration of brain cognitive science and the study of cognitive mechanism, as well as the development of brain-like artificial intelligence.

The new application values of terahertz electromagnetic irradiation in key fields such as life medicine, neural regulation and artificial intelligence, and the safety of application of terahertz irradiation mentioned above are all due to the scientific research on the biological effects of terahertz irradiation. The essence of the scientific research on the biological effects of terahertz irradiation is to study the changes in the biological performance indexes of biological samples (including biological systems, biological tissues, cells or molecules) after terahertz electromagnetic waves have passed through them, that is, to study the electromagnetic interaction between terahertz electromagnetic waves and the biological samples and to reveal its internal mechanisms [3]. Biological cells are the basic life units, which make up the biological tissues, biological systems and organisms, and they are also the basic functional units for producing biological activities and performing biological functions [38]. The basic life units that can sense the action of electromagnetic field under the terahertz irradiation are the biological cells. According to the biophysical structure of the biological cell, the terahertz electromagnetic field firstly acts on the cell membrane in the cell under the irradiation. Cell membrane is the biological barrier to protect cells, which separates the cellular internal environment from the external environment, and the substance transmembrane transport function of cell membrane maintains the basic cellular metabolism, homeostasis and various biological activities and functions [38]. Most of the biological effects of terahertz irradiation are directly or indirectly (secondarily) attributed to the interaction between terahertz electromagnetic fields and cell membranes [39-41]. Therefore, the studies of the electromagnetic interaction between terahertz electromagnetic field and cell membrane and its internal mechanisms are of great significance for the application based on the biological effects of terahertz irradiation.

In recent years, the research findings on the biological effects of cell membrane under terahertz irradiation have sprung up constantly and fruitfully. Also, the scientific research work has been constantly deepened from the cellular level to an even more microscopic level, reaching the molecular and atomic-group level. However, there is a lack of papers reviewing the research outputs in this field. In this paper, the research advancements and scientific discoveries of the biological effects of cell membrane under terahertz electromagnetic irradiation are reviewed from the following four aspects: the dielectric characteristics of response of cell membrane to terahertz electromagnetic irradiation, the ion transmembrane transport through ion channel proteins in cell membrane under the irradiation, the transmembrane transport of macromolecules and ions through phospholipid membrane part of cell membrane under the irradiation, and the potential applications and roles of biological effects of cell membrane under the irradiation in key fields such as life medicine, neural regulation, and artificial intelligence. And based on the current research progress, the future research development and direction of the biological effects of cell membrane under terahertz electromagnetic irradiation are prospected for the applications of terahertz wave.

2. Dielectric characteristics of cell membrane response to terahertz irradiation

The frequencies of the intrinsic vibration modes on the neuronal surface lie in a range from terahertz to far-infrared frequency [42]. Besides, the vibrational and rotational frequencies of biological macromolecules and the vibrational frequencies of the weak interactions such as intermolecular hydrogen bonds and van der Waals forces, are also in the terahertz range [1, 4]. When terahertz electromagnetic waves of different frequencies pass through the cell membrane, the molecules on the membrane cause various time delays and vibrational absorption, leading to the dielectric characteristics of response of the cell membrane to the terahertz irradiation, which is also commonly referred to as the terahertz time domain spectral properties of the cell membrane. Because the main components of the cell membrane are phospholipid molecules and the basic architecture of the membrane is a phospholipid bilayer structure, researchers commonly study the dielectric characteristics of response of the cell membranes to the terahertz irradiation with phospholipid molecules such as DOPC, DPPC, DMPC, and DMPG.

In 2008—2009, Paparo et al. [43, 44] measured the dielectric response characteristics of the DOPC phospholipid bilayer membranes with different hydration levels and of the pure water in a frequency range of 0.2—1.8 THz by terahertz time-domain spectroscopy, fit the characteristic curves of dielectric response by second-order Debye relaxation model, and analyzed the values of the first- and second-order relaxation time in the dielectric response. It is found that the first-order relaxation time in the dielectric response is significantly lower in the case of water molecules bound to the phospholipid membrane than in the case of bulk water. Owing to the fact that the measurements by terahertz time-domain spectroscopy are significantly sensitive to the highly collective vibrational modes of the hydrogen bond networks in water molecules, and that the first-order relaxation time is closely related to the number of water molecules in the hydrogen bond network, they suggested that the confinement of water molecules between the bilayers restricts the extent to which the highly collective vibrations can occur in the hydrogen bond networks. That speeds up the first-order relaxation response and ends up in a ‘blue’ shift of the collective vibrational mode that corresponds to an apparent reduction in the first-order relaxation time when seen in the time domain. The results also indicate the existence of sparsely distributed water ‘pools’ in the phospholipid membranes in the case of the aqueous environments where water molecules can be bound to the membrane.

In 2011, Hishida and Tanaka [45] measured the dielectric response characteristics of DMPC multilamellar phospholipid membrane vesicles with different hydration degrees in a frequency range of 0.4－2.7 THz by terahertz time-domain spectroscopy, and combined the x-ray observation of the phospholipid lamellar structure. It is shown that there exists a long-range hydration effect on up to 4－5 water molecular layers on the phospholipid membrane, and that most of the water molecules are hydration water in the lamellae. And the condensation of those water molecules is also suggested to take place in the hydration layer.

In 2017, Pan and Lü [46] used three types of phospholipid molecules, i.e. DOPG, DOPC and DOPE, to form phospholipid membrane vesicles (water droplet surrounded by phospholipid membrane) in water, and then measured the dielectric response characteristics of those types of phospholipid emulsions in a frequency range of 0.4－0.8 THz by terahertz time-domain spectroscopy. It is revealed that the hydration state and the hydration water dynamics on the membrane-water interface rely on the phospholipid headgroup components.

A further study of the characteristics of the hydration water on the membrane-water interface finds that the hydration water can be classified as three classes, i.e. free water, whose dynamical behavior is distinct from that of bulk water to a much small extent; loosely bound water, whose dynamical behavior is slower than that of the free water by one order of magnitude; tightly bound water, whose dynamical behavior is comparable to that of the phospholipid molecules [47]. Guo et al. [48] studied the influence of the hydration degree of DOPC phospholipid membrane on the reflected terahertz electromagnetic wave from the phospholipid membrane during 30 — 100 THz electromagnetic wave irradiation by the finite-difference-time-domain method. Figure 1 shows the electric field distribution normal to the phospholipid membrane during 30 THz Gaussian pulse irradiation. Zhu et al. [49] conducted the molecular dynamics simulations to reveal that a relatively weak stimulus of terahertz electromagnetic wave can enhance the permeation of the water channel on the membrane to the confined water by approximately one order of magnitude, showing superpermeation, and meanwhile efficiently restrict the thermal effect of bulk water. In addition, Zhu et al. [50] also disclosed that the 31.5 THz ± 1.0 THz electromagnetic stimulus can induce the resonance on the vibration mode of the confined water, resulting in a structural phase transition of the confined water molecules from quasi-two-dimensional (2D) "ice" to 2D liquids at room temperature.

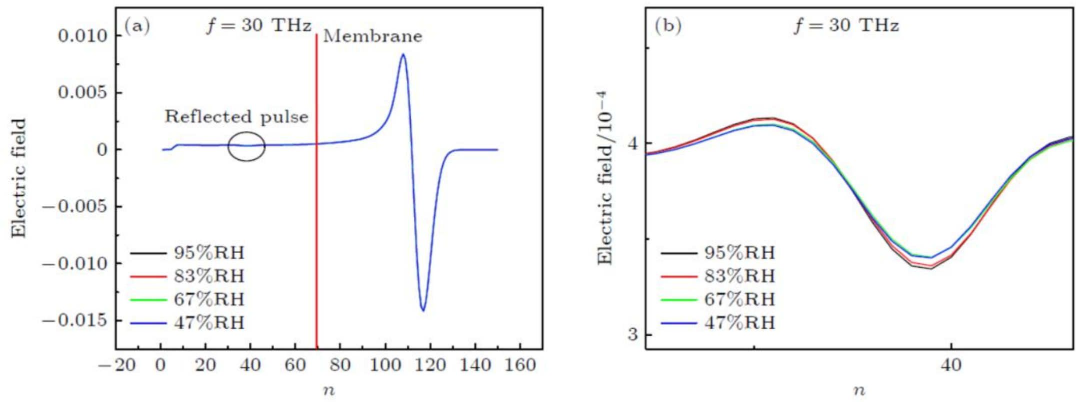

Fig. 1. (a) Distributions of electric field versus n (where n denotes the number of spatial grids in the direction perpendicular to the cell membrane in the numerical simulation, and n =70 refers to the location of the cell membrane.) in the case of DOPC phospholipid membrane irradiated perpendicularly by Gaussian pulse at center frequency of 30 THz for four hydration levels of the DOPC phospholipid membrane: 95%, 83%, 67% and 47%, and (b) enlarged reflected pulse electric field waveforms in panel (a) due to phospholipid membrane under terahertz irradiation [48] .

3. Substance transmembrane transport in cell membrane under terahertz irradiation

The transmembrane transport of molecules and ions on the cell membrane maintain the basic metabolism, homeostasis and various biological activities and functions, and it is also the exclusive pathway for cells to exchange substances and energy with the extracellular environment [38]. For the small molecules such as glucose, amino acids, water, oxygen, and carbon dioxide, some of them can directly achieve transmembrane transport through diffusion, and some need the help of the transport proteins on the membrane, which can even make the molecules transport from the high concentration side to the low concentration side. These transport proteins are basically open all the time and belong to non-gated channels. For the inorganic ions essential for the life activities, their transmembrane transport ordinarily requires the help of ion channel proteins on the cell membrane, and the ion channel proteins are normally closed, that is, the transmembrane current due to ion transport is almost zero (≪fA). Those ion channel proteins are only open / activated in some specific situations, resulting in ion current (fA－pA) for the transmembrane transport, and belong to gated channels. The channel proteins whose open / activation is dependent on binding to specific molecular groups are referred to as ligand-gated channels, and the channel proteins whose open / activation is dependent on the change in membrane potential are named voltage-gated channels [38].

Terahertz irradiation induces the biological electric field in the cell area to change, thereby affecting the switches of the open / activation and closed states of the voltage-gated ion channels on the cell membrane, and causing the life ions to realize the transmembrane transport. The ion transmembrane transport would result in the change in the ion concentration in the cell, which has a chance to lead the other types of ion channels to work, such as active transport channels in the cell membrane. In addition, for some hydrophilic, membrane-impermeable macromolecules, they could also transport through cell membrane along with various ions when terahertz electromagnetic irradiation can form hydrophilic transport pathways in the cell membrane .

3.1. Ion transmembrane transport through ion channel proteins in cell membrane under terahertz irradiation

3.1.1. Ion transmembrane transport through cell membrane voltage-gated calcium channels under terahertz irradiation

Calcium ions play an important role in life activities. The voltage-gated calcium channel (VGCC), also named voltage-activated calcium channel (VACC) [51], embedded in the cell membrane, is the main type of channel protein in cell membrane responsible for the transmembrane transport of calcium ions in cells like nerve cells and muscle cells. This type of channel protein provides a key link between electrical signals and nonelectrical life activities, and plays a crucial role in significant biological activities and functions, such as neurotransmitter release, hormone secretion, heart beat regulation, muscle contraction, and gene transcription [52].

In 2017, Bo et al. [14] established a cell model of neuroblastoma (rodent neuroblastoma × glioma hybrid cell, NG108-15 cell) based on electrodynamics and thermodynamics, on whose cell membrane the voltage-gated calcium channels and active transport calcium channels are taken into account at a whole cell level. The numerical study of calcium ion flux via voltage-gated calcium channels in response to 2.5 THz electric pulse irradiation shows that terahertz irradiation can activate cell membrane voltage-gated calcium channels and facilitate the transmembrane calcium influx as shown in Fig. 2. In 2020, Bo et al. [53] proposed the electromagnetic interaction theory between terahertz fields and physiological ions at the cellular level, pointing out that the quasi-magnetostatic problems exist in the cell ion transmembrane transport under terahertz electromagnetic irradiation and also the terahertz frequency range in which the effects of magnetic fields can be neglected. For the case of low-frequency terahertz sine wave irradiation that conforms to the quasi-magnetostatic conditions, the effects of the frequency, duration and electric field intensity of electromagnetic irradiation on the calcium flux via voltage-gated calcium channel and the corresponding increment of intracellular calcium concentration are studied. And the numerical simulation of the temperature change in the cell system shows that the activation of voltage-gated calcium channel and hence the increase in intracellular calcium concentration by terahertz radiation are non-thermal effects. Meanwhile, it is also pointed out that with the continuous increase in the irradiation time, the temperature change in the cell system would increase to a non-negligible level, and then the concurrent thermal effect would gradually become significant. In the same year, Bo et al. [18] carried out further research on the problem that the calcium flux caused by the activation of the voltage-gated calcium channel under the low-frequency terahertz sine wave irradiation would decrease sharply with the increase in the irradiated amplitude of electric field, that is, the inhibition effect of terahertz irradiation on voltage-gated calcium channel, causing the intracellular calcium concentration to first increase and then decrease sharply with the irradiated amplitude of electric field increasing. Bo et al. proposed a way to reduce the inhibition effect by modulation by using low-frequency terahertz Gaussian pulse on the calcium flux via voltage-gated calcium channel, and carried out the numerical simulations for verification. The results show that the curve of the increase of intracellular calcium concentration versus the amplitude of electric field becomes more flat by modulation by using the low-frequency terahertz Gaussian pulse on the calcium flux as shown in Fig.3(a), which greatly reduces the inhibition effect on voltage-gated calcium channel compared with the case of the sine wave irradiation. Furthermore, for causing the same increment of the calcium concentration, as shown in Fig.3(b), the temperature increase during terahertz Gaussian pulse irradiation is much smaller, and therefore it is less likely to cause the concurrent thermal effect in the modulation of the calcium flux by using the terahertz Gaussian pulse.

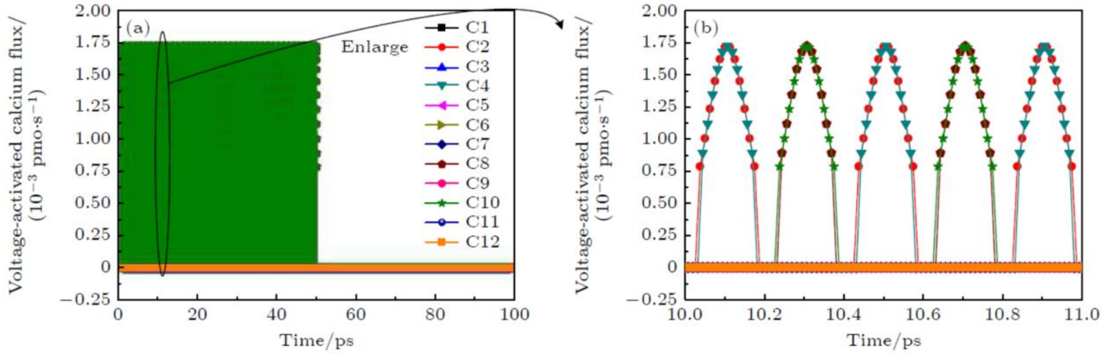

Fig. 2. Terahertz irradiation activated cell membrane voltage-gated calcium channels, inducing transmembrane transport calcium influx: (a) Calcium fluxes at voltage-gated calcium channel models C1, C2, …, C12 in cell membrane under the terahertz irradiation with pulse duration of 50 ps and frequency of 2.5 THz; (b) enlarged view of 1-ps time during terahertz irradiation in panel (a) [14] .

In 2018, Wei et al. [15] used the terahertz electromagnetic fields to irradiate the semens from mild asthenospermia patients. The experimental details are listed in Table 1. It is observed that the calcium concentration in sperm cells increases and the sperm motility is significantly enhanced under terahertz irradiation. After the addition of nifedipine to the extracellular solution in order to block the cell membrane VGCC, or the addition of the calcium chelator ethylene glycol tetraacetic acid (EGTA) in order to reduce the extracellular calcium concentration, the sperm motility enhancement is weakened as shown in Fig. 4. Although the intracellular calcium concentration under terahertz irradiation in the case when the VGCC is blocked is not measured nor compared with that in the case when the VGCC is unblocked, the influence of VGCC on the sperm motility under terahertz irradiation testifies on the other side that terahertz irradiation can activate the VGCC in cell membrane and thus increase the intracellular calcium concentration.

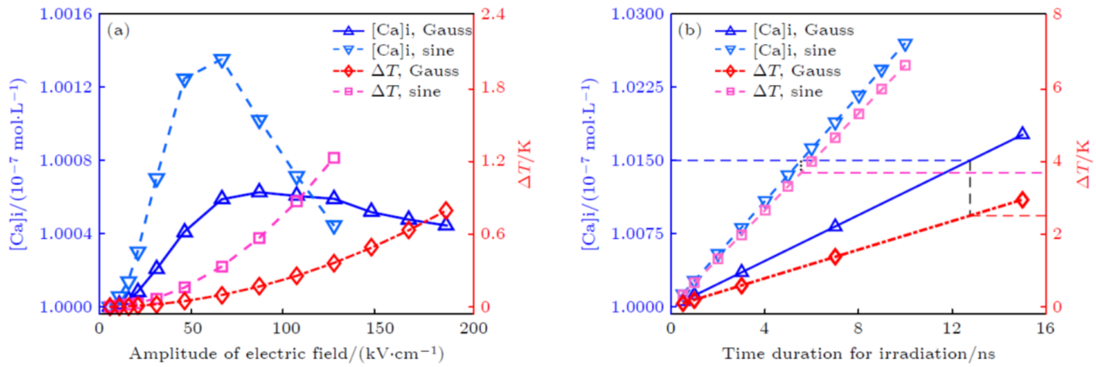

Fig. 3. Reduced inhibition effect on voltage-gated calcium channel and increased concurrent system temperature in the case of low-frequency terahertz Gauss pulse irradiation (marked by 'Gauss' in the figure) compared with those in the case of low-frequency terahertz sine wave irradiation (marked by 'sine' in the figure). [Ca]i denotes the intracellular calcium concentration after increase induced by the transmembrane transport calcium flux due to the activation of voltage-gated calcium channel in cell membrane under terahertz electromagnetic irradiation, ΔT is the maximum temperature rise in the cell system under terahertz irradiation. (a) THz Gauss pulse flattens more the relation curve of [Ca]i with terahertz-irradiated electric field amplitude than THz sine wave irradiation, indicating the decrease of inhibitory effect on voltage-gated calcium channel. (b) To raise the [Ca]i to an identical amount, terahertz Gauss pulse irradiation induces much less concurrent ΔT than terahertz sine wave irradiation [18] .

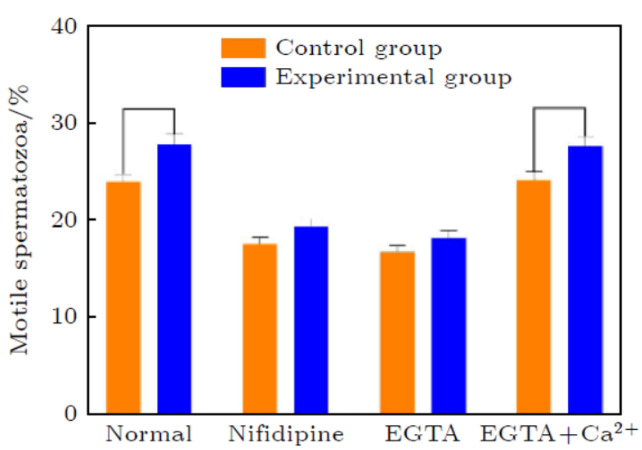

Fig. 4. Effect of terahertz electromagnetic irradiation on sperm motility in the case of blocking

voltage-gated calcium channels with nifedipine or reducing the extracellular calcium concentration with EGTA. 100-μL washed sperm cells were incubated with phosphate-buffered saline with nothing (Normal), 30 mmol/L nifedipine (Nifidipine), 1 mmol/L EGTA (EGTA), or 1 mmol/L EGTA supplemented with calcium ions (EGTA+Ca^{2+}), respectively. Then ten minutes later, experimental groups were irradiated for 60 min. Sperm motility was measured using computer-assisted semen analysis after the terahertz irradiation. Sperm samples were taken from 10 mild asthenospermia patients and each sample was assigned to each group. *$p<0.05$ [15] .

In 2020, Bo [54] developed the electromagnetic interaction theory between terahertz fields and physiological ions at the molecular level of channel proteins. Then, under the low-frequency terahertz irradiation that conforms to the quasi-magnetostatic problem, the electric polarization response to the low-frequency terahertz irradiation is deduced at the interface between the inner side of the channel protein and the interior solution environment from the electric field boundary conditions of Maxwell's equations with the assistance of a physical model of voltage-gated ion channel protein with simplified structures. After that, the calcium transport dynamics along the channel axis under low-frequency terahertz irradiation is numerically studied by Brownian dynamics simulation method. It is revealed that terahertz irradiation can promote calcium ions to cross the energy barrier existing in the channel, causing the calcium ions to implement the transmembrane transport. At the molecular level, this also verifies that terahertz irradiation can activate the voltage-gated calcium channel. In 2021, Guo et al. [55] numerically studied the motion and trajectories of single calcium ion and multiple calcium ions in the channel under low-frequency terahertz irradiation by Brownian dynamics simulation method with the help of a physical model of more sophisticated and complex spatial structure illustrated in Fig. 5(a) for mimicking the protein of voltage-gated calcium channel. As shown in Fig. 5(b), the results indicate that the rate of calcium ion transport increases significantly with the increase in the amplitude and frequency of the irradiated electric field. In addition, the results also show that the time scale of calcium transmembrane transport process is in the magnitude of picosecond, corresponding to the frequency spectrum concentrated in the terahertz range.

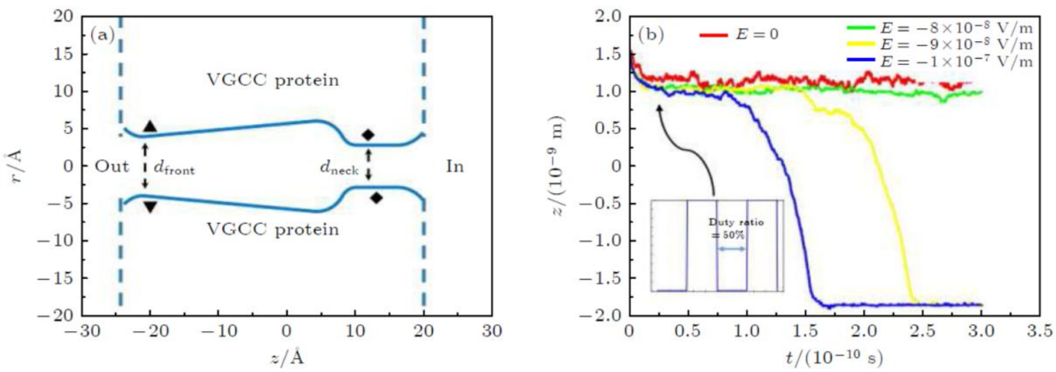

Fig. 5. Brownian dynamics simulation of calcium ion transmembrane transport in voltage-gated calcium channel under low-frequency terahertz irradiation: (a) Brownian dynamics two-dimensional structure model of a voltage-gated calcium channel protein, with ▲ denoting dipole and ◆ representing negative charge residues; (b) motion trajectories of calcium ion transmembrane transport in the direction of the channel irradiated by 1 THz pulse train with different electric field amplitudes [55] .

In 2021, Li et al. [56] constructed a molecular dynamics model of voltage-gated calcium channel. And by molecular dynamics simulation methods, Li et al. simulated the protein of voltage-gated calcium channel under the electromagnetic irradiation at 42.55 and 52.61 THz, which are the resonant frequencies of the carboxyl group (-COO^-) and the carbonyl group (-C=O) respectively in the channel. It is found that the terahertz irradiation can change the free energy profile of calcium ion in the channel, reducing the free energy required for calcium transmembrane transport, and thereby enhancing the permeability of voltage-gated calcium channel to calcium ions. This modeling and simulation research shows at the level of atomic group within the protein molecule that the terahertz irradiation of the mid-infrared wave at the frequencies resonant with the carboxyl and carbonyl in the channel can also enhance the permeability of voltage-gated calcium channels to calcium ions, and hence increasing the conductance of the calcium channel and promoting the transmembrane transport of calcium ions.

3.1.2. Ion transmembrane transport through cell membrane voltage-gated potassium channels under terahertz irradiation

Cell membrane voltage-gated potassium channel (VGKC) is a key type of ion channel responsible for potassium transmembrane transport in cells such as nerve cells and muscle cells. And VGKC plays an important role in the generating and propagating of action potentials [57]. In 2021, Liu et al. [19] recorded the action potential waveforms with patch clamp in pyramidal cells in mouse prefrontal cortex slices. The experimental details are listed in Table 1. As shown in Fig. 6, it is found that the potassium ion flux via the voltage-gated potassium channel is increased and the action potential waveform is shortened in the pyramidal cells during the electromagnetic irradiation of 53.53 THz (5.6 μm mid-infrared wave) that is at the frequency resonant with the carbonyl group in VGKC. That produces the modulatory effects on neuronal signaling. The modulatory effect disappears after the withdrawal of the 53.53 THz electromagnetic irradiation and appears again when the pyramidal cell is exposed to the irradiation again, and thus showing the nature of reversibility and repeatability.

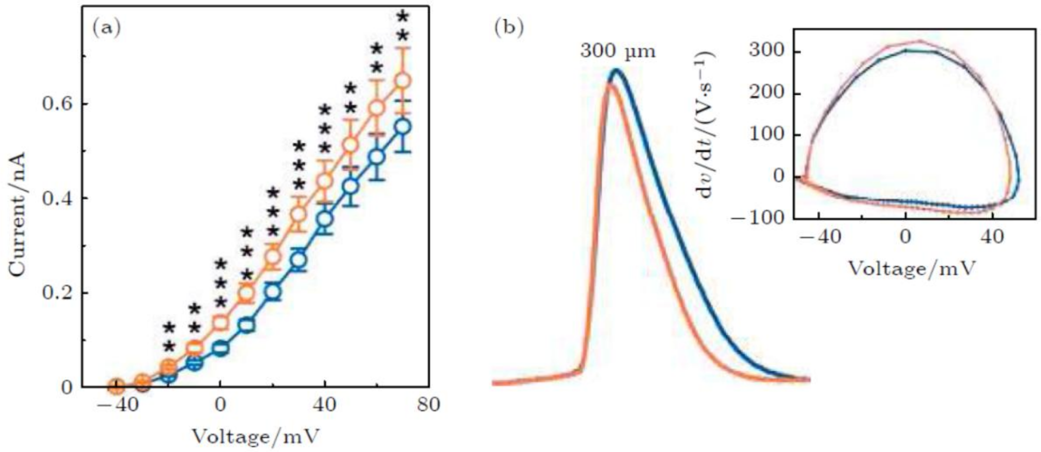

Fig. 6. (a) Current-voltage curves of potassium ion transmembrane transport in voltage-gated potassium channel and (b) action potential waveforms and their phase plots in pyramidal cells before (blue) and during (orange) high-frequency terahertz electromagnetic irradiation in midinfrared frequency range at a position 300 μm away. [19] .

3.1.3. Ion transmembrane transport through cell membrane active transport channel under terahertz irradiation

Active transport ion channels on the cell membrane actively transport the ions through the membrane by consuming the energy from cell metabolism, maintaining the equilibrium concentrations of the various types of life ions on both sides of the cell membrane [58, 59]. Bo et al. [18, 53] found that low-frequency terahertz irradiation can activate the cell membrane active transport calcium channel, which is also named cell membrane calcium pump, to transport calcium ions through the membrane. In addition, during the low-frequency terahertz irradiation, the calcium flux via the active transport calcium channels is much less than that via the voltage-gated calcium channels and therefore this part of the calcium transmembrane flux and its effect on the change in intracellular calcium concentration can be ignored during the irradiation [18, 53].

3.2. Transmembrane transport of macromolecules and ions through phospholipid membrane part of cell membrane under terahertz irradiation

In recent years, Cherkasova et al. [41] and Zapara et al. [60] have observed that terahertz irradiation can cause the transmembrane transport of membrane-impermeable macromolecules such as dye molecules and hemoglobin. And hence they assumed that it is due to the appearance of electroporation in cell membrane under terahertz irradiation. Because these macromolecules are soluble in water, it is believed that the hydrophilic pores formed by the membrane electroporation, that is to say, the pores formed in the cell membrane are permeable to aqueous solution. The resulting hydrophilic pores can close after a period of time, making the cell membrane restore to a state that is impermeable to the macromolecules, without significant concurrent temperature changes. The related experimental details are listed in Table 1. For the applications of the biological effects of terahertz irradiation, it is essential to make clear the mechanisms underlying these processes.

In 2018, Tang et al. [61] established a model system of a cell membrane patch, composed of phospholipid bilayer membrane, and simulated the membrane under the irradiation of the picosecond electric field pulse train of terahertz repetition frequency and the sinusoidal electric field of terahertz frequency by molecular dynamics simulation. The appearing of the electroporation in the membrane is determined by observing whether the water bridge forms across the membrane in the simulation. And the changes in the dipole moments of interfacial water and bulk water molecules and the total potential energy of the system are simulated. The results show that the electric field pulse train of terahertz repetition frequency causes the membrane electroporation, while the terahertz sinusoidal electric field causes no electroporation in the case of the low-frequency terahertz irradiation of 0.1－0.9 THz whose electric field amplitudes are not large enough. The difference between those two types of the terahertz irradiations is as follows. The electric field direction in the sinusoidal electric field irradiation reverses periodically with the period of the sinusoidal function, while the direction in the electric field pulse train irradiation never reverses. Therefore, the sinusoidal electric field irradiation contains exclusively the terahertz frequency components, while the electric field pulse train irradiation contains not only the terahertz frequency components but also the direct current component. In addition, in 2015, Vernier et al. [62] also carried out the molecular dynamics simulations of the electroporation process of phospholipid bilayer membrane under terahertz irradiation with a type of picosecond electric pulse. Nevertheless, the electromagnetic frequency of this type of picosecond pulse employed, which is a single 320 ps-duration electric pulse having both positive and negative polarities, is mainly concentrated in the frequency range of megahertz (MHz) and the lower frequency range, and its gigahertz (GHz) and THz frequency components are relatively small.

In 2020, Tang et al. [16] further studied the electroporation of phospholipid bilayer membrane under the irradiation of the picosecond pulse train containing both positive polarity and negative polarity with a terahertz repetition frequency by molecular dynamics simulation. The simulation results show that the reason why the membrane electroporation does not occur under the irradiation of the bipolar picosecond pulse train of terahertz repetition frequency is that the membrane interfacial water molecules is constantly flipped and is redirected as the electric field of the bipolar picosecond pulse train reverses, making the water molecules fail to keep moving into one direction or leave the phospholipid-water interface. Therefore, the bipolar picosecond pulse train is less likely to implement the membrane electroporation than the unipolar picosecond pulse train. That reveals a bipolar cancellation of the membrane electroporation of the picosecond pulse train irradiation by the irradiation of bipolar picosecond pulse train of terahertz repetition frequency. In the same year, Tang et al. [63] used the molecular dynamics simulation to further study the influence of a KcsA potassium channel protein embedded in the phospholipid bilayer membrane (see Fig. 7(a)) on the membrane electroporation under the irradiation of picosecond pulse train with terahertz repetition frequency. The simulation results show that the electroporation still occurs on the phospholipid bilayer membrane rather than on the channel protein molecule itself as shown in Fig. 7(b). In addition, the existence of the channel protein can affect the average pore formation time of the phospholipid bilayer membrane, and the effect is related to the system size of the phospholipid membrane embedded with the potassium channel. The simulation results also show that the protein fluctuation under picosecond pulse train irradiation or no filed irradiation is stronger than under constant electric field irradiation, and that the protein fluctuation increases with the augment of the repetition frequency of the pulse train.

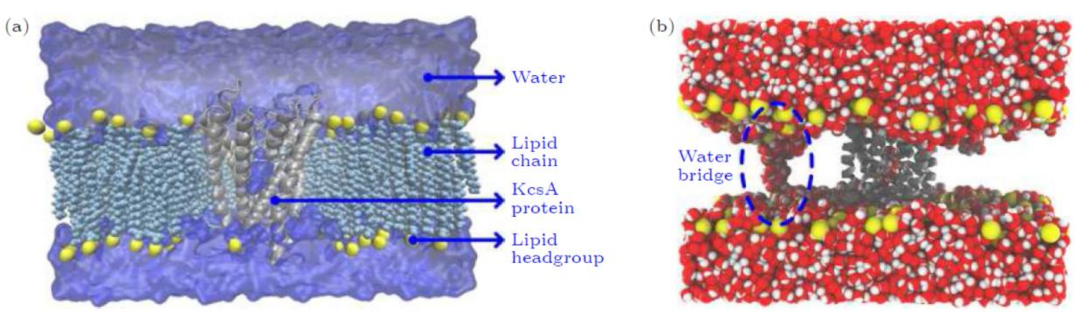

Fig. 7. (a) Molecular dynamics simulation model of phospholipid bilayer membrane inserted with a

KcsA potassium channel protein, with phospholipid headgroups represented by yellow balls, lipid chains denoted by light blue beaded chains, KcsA channel marked by gray helical structure, and water being transparent, and (b) water bridge formed at 4.24 ns under irradiation of picosecond pulse trains (psPT) with 0.9 THz, meaning that the membrane electroporation takes place[63] .

In 2021, Bo et al. [64] investigated the effect of the membrane electroporation on the conductance of the membrane permeability for ion transmembrane transport at the whole cell level (see Fig. 8(a)) on the basis of the electromagnetic interaction theory between terahertz fields and physiological ions at a cellular level [53]. The whole transmembrane ion currents are fully taken into consideration including cell membrane capacitive ion current, the net ion current of the ion channel proteins and the ion current due to the ion transmembrane transport via the hydrophilic pores formed by the membrane electroporation. As shown in Fig. 8(b), the numerical results show that the conductance increases first at the cell membrane of the cell perpendicular to the terahertz electric field under the irradiation of the picosecond Gauss pulse train with terahertz repetition frequency. And then the phenomenon of the increase in the conductance occurs and extends gradually towards the cell membrane parallel to the terahertz electric field from the cell membrane perpendicular to the field, indicating that the formation of the membrane electroporation is easier at the cell membrane perpendicular to the terahertz electric field than at the membrane parallel to the field. In addition, the numerical results also show that as for the cell membrane perpendicular to the terahertz electric field, the membrane is easier to electroporate, where the direction of the terahertz electric field is identical to that of the biological electric field from the membrane potential. And as the intensity of the terahertz electric field increases, the pore formation time decreases and the membrane conductance increases accordingly.

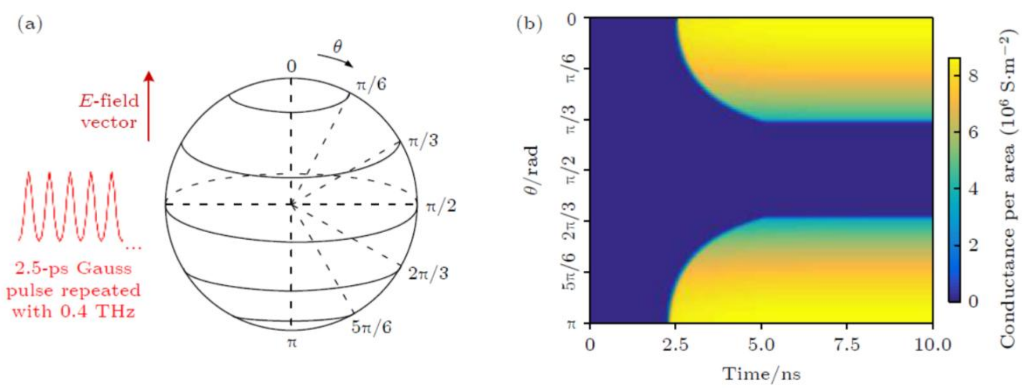

Fig. 8. (a) Schematic illustration of the model of a cell irradiated by 2.5 ps Gauss pulse train with repetition frequency of 0.4 THz, with θ denoting polar angle in spherical coordinate system, red arrow referring to electric field *E*-field vector of irradiation, and (b) time-dependent membrane conductance per unit area due to the transmembrane transport ions at different θ values of cell caused by the formation of cell membrane hydrophilic pores, with color bar on the right side denoting conductance per unit area in S/m^2 [64].

Table 1. Experimental details about biological effects of terahertz irradiation on cell membrane.

Type of terahertz source	Terahertz band of source	Terahertz source power and mode (pulse/ continuous)	Terahertz source polarization	Experimental objective	Experimental materials	Experimental results	Reference
Photoconductive antenna	0.1-3 mm (0.1-3 THz）	Average power density is about 60 μW/cm^2, / (irradiation time 60 min）	/	To study the effects of terahertz irradiation on sperm	sperm cells	Terahertz irradiation enhances sperm motility (21% higher than the control group) and increases intracellular calcium concentration (fluorescence intensity of the calcium ion indicators is 21% higher than the control group); When extracellular calcium ions are removed or cell membrane voltage-gated calcium channels are blocked, the results of this effect are not statistically significant compared with the control group.	[15]
Quantum cascade laser	5-11 μm (27-60 THz）	Power density is 0.003 μW/μm^2 at a distance of 300 μm from the laser source pulse (pulse width is 100-500 ns, repetition frequency is 10-100 kHz, irradiation time is 10-200 s)	/	To study whether mid-infrared waves with specific wavelengths have nonthermal modulatory effects on ion channel activities, neural signaling, and sensorimotor behavior	Pyramidal cells in mouse prefrontal cortex slices, zebrafish larvae	During the period of electromagnetic wave irradiation with a wavelength of 5.6μm (53.53THz), the irradiation can nonthermally increase the potassium current via the voltage-gated potassium channel (the slope of the current-voltage curve increases by 9% compared with the control group), and shorten the action potential waveform in pyramidal cells (decrease by 21% compared with the control group). When the irradiation is off, the modulatory effect disappears, and the modulatory effects reappear when the irradiation is on again. For the startle response of zebrafish C-bend caused by ultraviolet (UV) stimulation, 5.6 μM-wavelength irradiation inhibits the startle response in weak UV stimulation and enhances the startle response in strong UV stimulation (in the startle response, the slope of fish tail angle-UV intensity curve increases by 109% compared with the control group, and the slope of fish tail angular velocity-UV intensity curve increases by 116% compared with the control group).	[19]
Free electron laser	130 and 150 μm (2.3 and 2.0 THz)	Average power density is 0.5-20 mW/cm^2 , pulse (pulse width is 30-100 ps, repetition frequency is 4.6-11.2 MHz, irradiation time is 0.6 min at 2.3	/	To study whether terahertz irradiation can cause cell membrane integrity and barrier properties to change	Cultured neurons of molluscan shellfish Lymnaea stagnalis in vitro	2.3-THz irradiation can cause reversible electroporation of cell membrane to increase by 87% compared with the control group, the extracellular dye molecules to enter into cells, and the cell membrane barrier properties and integrity to change; 2.0-THz irradiation causes no electroporation of cell membrane.	[41, 60]

		THz and 60 min at 2.0 THz）					
Backward wave tube	0.9-1.7 mm (0.18-0.33 THz）	3-mW/cm^2, / (irradiation time is 180 min)	/	To study the effects of terahertz irradiation on blood cells	Erythrocyte suspension	Terahertz irradiation causes the osmotic resistance of erythrocytes to decrease, and hemoglobin to release from the erythrocytes into the extracellular environment.	[41]
Free electron laser	130 μm (2.3 THz）	Average power density is 0.5-20 mW/cm^2, pulse (pulse width is 30-100 ps, repetition frequency is 4.6-11.2 MHz, irradiation time is 30 s)	/	To examine whether membrane electroporation under 2.3 THz irradiation can be caused by the activated oxygen metabolites on the cell membrane	Cultured neurons of molluscan shellfish lymnaea stagnalis in vitro	After the addition of antioxidants, the cell membrane electroporation is weakened (by 93% less than that in the control group). Antioxidants can serve as a modulator of the change in cell membrane permeability to protect cells from being affected adversely in this process.	[60]

4. Potential applications and role of biological effects of cell membrane under terahertz irradiation

4.1. Potential applications of terahertz irradiation as a life medicine

Ion transmembrane transport in the cell membrane plays an important role in biological activities and functions. For example, the transmembrane transport of calcium ions causes the intracellular calcium concentration to increase, and thus promoting the cell division or enhancing the sperm motility [65,66]. Terahertz irradiation, which is non-invasive and non-ionizing, can cause the calcium ions to implement the transmembrane transport thereby increasing the intracellular calcium concentration [14, 15, 18, 53], so as to facilitate the division of cells and the formation of new cells in injured biological tissues, producing an effect similar to a kind of life medicine, and assisting in speeding up the rehabilitation of the injured biological tissues. In addition, the increase in the calcium concentration in sperm cells by terahertz irradiation also contributes to the rehabilitation of asthenospermia [15]. Therefore, it is effective to realize the application of terahertz irradiation as a life medicine by modulating the ion transmembrane transport in cell membrane with terahertz electromagnetic fields.

4.2. Potential applications of terahertz irradiation in regulating neurobiological activities and functions

The transmembrane transport of calcium, sodium and potassium ions is also the basis for neural activities and functions. The transmembrane transport of calcium ions increases the calcium concentration in cells, and thus causes the release of neurotransmitters and triggers off the communication between nerve cells. The transmembrane transport of sodium and potassium ions can generate and propagate the action potentials on the cell membrane and realize the communication of electrical signals within a nerve cell [57]. Terahertz irradiation regulates the switches of the open / activation and closed states of the ion channel proteins in cell membrane [14, 18, 19, 53, 55, 56], which can regulate the transmembrane transport of ions to have a modulatory effect on neural electrical activities, for instance, regulating the voltage-gated potassium channel in the cell membrane to cause the action potential waveforms to change, so as to realize the applications of terahertz irradiation in brain function and neural regulation [19].

In addition, terahertz irradiation can also induce the hydrophilic pores to form in the phospholipid membrane part of the cell membrane [16, 41, 60, 61, 63, 64], which does not only facilitate the transmembrane transport of the substances such as pharmaceutical molecules, but also contribute to the modulation of the transmembrane transport of life ions [64]. Therefore, the regulation of the formation of reversible hydrophilic pores in the phospholipid membrane with terahertz irradiation can have an auxiliary modulatory effect on the neurobiological activities, etc.

4.3. Potential applications of terahertz irradiation in artificial intelligence

The short-wave band (mid-infrared wave band) of the terahertz wave can transmit in the myelin sheath of nerve axon membrane and the nodes of Ranvier between the myelin sheaths. Owing to the good penetration of mid-infrared wave to biological tissues, there is no need to implant electrodes or other equipment in human-machine / brain-machine communication [24]. Terahertz wave band is the potential electromagnetic band for the sixth-generation (6G) communication, and possesses the characteristics of ultra-wideband communication, whose bandwidth is theoretically three orders of magnitude larger than the millimeter wave bandwidth [26, 67]. Therefore, terahertz electromagnetic wave provides an ultra-wideband communication channel for the information transmission at the interface between human and machine / brain and machine non-invasively.

In addition, the intracellular concentrations of life ions such as calcium, sodium, and potassium are also important storage units and parameters for the information in brain cognitive functions such as brain memory, brain information processing and computation [68-70]. The transmembrane transport of ions under terahertz irradiation can cause the concentrations of those types of key life ions in nerve cells to change [14, 18, 19, 53], so as to realize the applications of terahertz electromagnetic waves in the study of brain cognitive mechanism in a non-invasive and non-ionizing way, and further to play a critical role in developing the frontier of artificial intelligence inspired by biological brain.

5. Summary and prospect

The in-depth development of the interdiscipline of terahertz science and technology and biological science has constantly shown and demonstrated the extensive and important application values of terahertz electromagnetic waves. The researches of the biological effects under terahertz irradiation do not only reveal the application safety of terahertz irradiation, but also showthe new important scientific and application values of terahertz electromagnetic waves in key fields such as life medicine, neural regulation, and artificial intelligence. Most of biological effects under terahertz irradiation are due to the biological effects of cell membrane under terahertz irradiation, and the cell membrane is also the cellular structure that terahertz electromagnetic fields first act on during the terahertz irradiation.

In recent years, researchers have conducted extensive and in-depth researches of the biological effects of cell membranes under terahertz irradiation. Revealed are the effects of the hydration water at the interface between the cell membrane and the bulk aqueous solution on the dielectric properties of response of the phospholipid membranes under the terahertz irradiation, and on the physical characteristics of the hydration water as well. Additionally, the scientific phenomena are discovered that terahertz electromagnetic irradiation can activate the voltage-gated calcium channels, voltage-gated potassium channels, and active transport calcium channels in the cell membrane for the transmembrane transport of life ions. And the scientific phenomenon is also discovered that terahertz electromagnetic irradiation can form hydrophilic pores in the phospholipid membrane part of the cell membrane for the transmembrane transport of macromolecules and life ions. The induced transmembrane transport of the ions and macromolecules can regulate the biological activities and functions like neural activities, etc, and lays critical foundations for the applications of terahertz irradiation in the key fields such as life medicine, neural regulation, and artificial intelligence.

Although researchers have carried out a number of researches of the biological effects of cell membrane under terahertz irradiation, the relevant experimental researches are rare and it is needed to carry out plentiful researches. The existing experimental researches indicate that 2.3 THz electromagnetic irradiation can produce reversible membrane electroporation in nerve cells [41, 60], 0.1—3 THz electromagnetic irradiation can activate the cell membrane voltage-gated calcium channels, resulting in the enhancement of sperm motility [15], and 53.53 THz electromagnetic wave can resonate with the carbonyl groups in the voltage-gated potassium channel, thereby activating the cell membrane voltage-gated potassium channel in the nerve cells [19]. Nevertheless, there is no significant resonant peak in a frequency range of 0.1—3 THz for the atomic groups responsible for the gating in the voltage-gated calcium channel [56], hence the activation of the voltage-gated calcium channel by terahertz irradiation in this frequency range is unlikely to be caused by the frequency resonance with the terahertz wave. Therefore, it is essential to study the activation mechanism of voltage-gated calcium channel under the terahertz irradiation at the non-resonant frequencies. For example, are the voltage-gated calcium channels activated directly by the terahertz irradiation? or is the activation of the voltage-gated calcium channels a secondary effect after the activation of voltage-gated sodium channels or after the formation of cell membrane electroporation by terahertz irradiation? etc. It is further essential to study the modulation of non-resonant terahertz electromagnetic waves, especially the terahertz waves in a range of 0.1—10 THz, on the cell membrane voltage-gated sodium channels, voltage-gated potassium channels, voltage-gated calcium channels and membrane electroporation, as well as the terahertz electromagnetic parameters for the activation of those types of voltage-gated ion channels and the formation of membrane electroporation. In the short-wave band (mid-infrared wave band) of the generalized terahertz wave, it is also essential to study the modulation of the electromagnetic frequencies of terahertz irradiation on the cell membrane voltage-gated ion channels, and to explore the physical processes and mechanisms of the electromagnetic interactions between the terahertz waves at the short-wave band and the proteins of voltage-gated ion channels and the phospholipid membranes when the electromagnetic frequencies of the terahertz irradiation are not at the resonant frequencies of the atomic groups responsible for the gating of the voltage-gated ion channels.

In the experimental study of the dielectric characteristics of response of cell membrane under terahertz irradiation, the phospholipid membranes made from phospholipid molecules in water for mimicking the biological membranes are used to study the dielectric response characteristics of cell membrane [43-46]. In the future studies, it is essential to design experiments to extract and purify the cell membrane in biological cells, and to measure the dielectric response characteristics of the cell membrane, whose two sides are in the standard physiological solution. And the dielectric response characteristics of the cell membrane in different types of biological cells are needed to be measured and compared in the studies.

Since cell membrane plays a very important role in biological activities and functions, the current research progress and scientific discoveries of the biological effects of cell membrane under terahertz irradiation are just a tip of the iceberg. In order for the wide applications of terahertz irradiation, a large number of the unknown biological effects of cell membrane and the related mechanisms need to be further studied and uncovered, including the theoretical and experimental researches to uncover the microphysical mechanisms of brain cognitive process, such as the microphysical mechanisms of brain cognitive formation and information processing at a cellular level and molecular level by developing quantum biology under terahertz irradiation at an atomic level, the basic researches of the construction and development of the cell models for the applications of terahertz irradiation in the exploration of brain cognitive mechanisms and human-machine / brain-machine information transmission, and the application researches of the construction of body domain communication network and human-machine / brain-machine interfaces based on the terahertz waves. Although there are still so many problems on the road to the applications of terahertz irradiation, there are sufficient reasons to believe that they can be solved one day through the scientists' efforts. **References**

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