磁性纳米颗粒介导的电磁神经治疗的最新进展

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摘要：目的 介绍磁性纳米颗粒的性质和生物医学应用，以及通过磁性纳米颗粒介导的电磁神经刺激治疗的最新进展。为今后优化刺激参数、提高磁神经刺激效率提供参考。**方法** 总结近年来国内外对磁性纳米颗粒的研究进展，并重点分析基于磁性纳米颗粒的神经磁刺激方法及效果。**结果** 磁性纳米颗粒具有成像、靶向给药、磁热疗等生物医学应用，以磁性纳米颗粒为基础进行神经磁刺激的类型可分为磁热刺激、磁电刺激及磁机械力刺激三种。这种刺激方式安全、高效且精准性高，能够改善传统磁刺激方式的缺陷。**结论** 磁性纳米颗粒性质独特，是近年来研究最多、发展速度最快的纳米材料之一。利用磁性纳米颗粒介导的神经磁刺激具有广阔的应用前景。

关键词： 磁性纳米颗粒；经颅磁刺激；神经系统疾病；神经调节
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Recent Progress on Electromagnetic Nerve Therapy Mediated by Magnetic Nanoparticles

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ABSTRACT: The work aims to introduce the properties and biomedical applications of magnetic nanoparticles, and the latest progress of electromagnetic nerve stimulation therapy mediated by magnetic nanoparticles, so as to provide reference for optimizing stimulation parameters and improving the efficiency of magnetic nerve stimulation in the future. The research progress of magnetic nanoparticles at home and abroad in recent years was summarized, and the methods and effects of neuromagnetic stimulation based on magnetic nanoparticles were emphatically analyzed. Magnetic nanoparticles had biomedical applications such as imaging, targeted administration and magnetic hyperthermia. The types of neuromagnetic stimulation based on magnetic nanoparticles can be divided into three types: magnetic-thermal stimulation, magneto-electrical stimulation and magnetic-mechanical stimulation. This stimulation method was safe, efficient and accurate, which can improve the defects of traditional magnetic stimulation. Magnetic nanoparticles have unique properties. It is one of the nanometer materials and one of the most studied and fastest developing nanomaterials in recent years. Neuromagnetic stimulation mediated by magnetic nanoparticles has broad prospects of application.

KEY WORDS: magnetic nanoparticle; transcranial magnetic stimulation; nervous system disease; neuromodulation

Neurological diseases seriously endanger human health. According to the World Health Organization (WHO), hundreds of millions of people worldwide are affected by neurological diseases[1]. Nervous system diseases include central nervous system and peripheral nervous system diseases, most of which are mental diseases and neurodegenerative diseases. Patients with neurological diseases are often accompanied by disorders of consciousness, cognitive disorders, movement disorders, sensory disorders and balance disorders. Taking Alzheimer's

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disease (AD) as an example, the clinical manifestations of patients are memory impairment, aphasia, agnosia, executive dysfunction and even changes in personality and behavior[2-4]. In order to control these diseases, researchers are working hard to develop effective treatments. However, due to the existence of the blood-brain barrier (BBB), drug-based treatment methods still have the problem of how to efficiently deliver drugs to the brain[5].

Regulating nerves through physical fields is a rapidly developing field, which can be achieved through electricity, magnetism, sound, light[6-10], etc. The clinical applications of deep brain stimulation (DBS) and vagus nerve stimulation (VNS) are increasing. DBS technology embeds microelectrodes in specific nuclei deep in the brain, and performs high-frequency electrical stimulation through a pulse generator buried under the skin of the chest, thereby changing the excitability of the corresponding nucleus to achieve the purpose of treatment. DBS has been widely used clinically to treat movement disorders caused by diseases such as Parkinson's disease[11-12]. Vagus nerve stimulation (VNS) has been approved by the FDA as a treatment for epilepsy and depression[13]. However, surgical complications such as infection, pain and rare cerebral parenchymal hemorrhage may often occur during electrode implantation. Sometimes there may be disconnected leads and the battery needs to be replaced[14]. As a result, researchers are turning their attention to non-implantable devices to avoid the adverse effects of the device itself on the body.

Among them, magnetic neuromodulation does not require implantation of invasive electrodes or optical devices, which is an ideal neuromodulation method. Transcranial magnetic stimulation (TMS) has been widely used in the treatment of depression and neuropathic pain, and has shown good application prospects in other diseases such as Parkinson's disease and motor dysfunction in the chronic phase of stroke[15-16]. TMS uses the magnetic field generated by an external coil to penetrate the skull to stimulate the cranial nerves, and has developed repetitive transcranial magnetic stimulation (rTMS), deep transcranial magnetic stimulation (dTMS) and intermittent theta burst stimulation (iTBS) based on clinical needs. Even so, TMS still has some technical limitations, including poor penetration, insufficient focus accuracy of magnetic stimulation, and limited stimulation depth. Since the biological effects produced by the magnetic field depend on the sensitivity of the tissue, magneto-neuromodulation therapy mediated by magnetic nanoparticles (MNPs) may be an interesting solution. Targeted delivery of MNPs to specific tissues can significantly enhance the local sensitivity of the tissue. When a weak magnetic field covers multiple cortical areas, the area containing MNPs will be activated, while other areas will only have little impact. In the previous work of our research group, we accurately delivered superparamagnetic nanoparticles (SPIO) to the left prefrontal cortex (PrL) and used a 0.1T magnetic field for magnetic stimulation. It was found that after 5 days of 10Hz magnetic stimulation, the depression-like symptoms of chronic unpredictable mild stress (CUMS) mice can be quickly improved[17]. This work may give researchers some hints that using MNPs to enhance magnetic stimulation is an effective method.

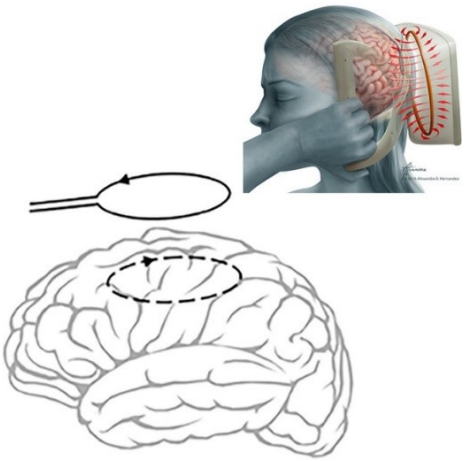

Fig.1　The basic principle of TMS

However, MNPs are facing more daunting challenges while making good progress. Due to the advantages of non-invasive nano-scale magnetic stimulation, efficient, fast and safe nano-scale magnetic stimulation technology has become an important tool for future scientific research. In recent years, more and more researches have focused on how to stimulate the signal pathways or neurons of the human body under the action of external magnetic fields[18-19]. Here, MNPs act as a transducer for generating or converting stimuli. The stimulation effect can be roughly divided into three types: magneto-thermal stimulation of superparamagnetic nanoparticles, magneto-electrical stimulation of magnetoelectric nanoparticles, and magneto-mechanical stimulation.

Herein, we introduce the application of MNPs in the field of biomedicine in recent years, and summarize the latest research on MNPs in nerve stimulation and signal transduction. In addition, we summarize the research progress of magneto-thermal, magneto-electrical and magneto-mechanical stimulation, and analyze the future development direction of magnetic stimulation.

1　Transcranial Magnetic Stimulation (TMS)

When the magnetic field acts on the human body, it will produce biological effects related to human life phenomena. With the continuous development of brain science research, the biological effects of magnetic fields have been paid more and more attention to the regulation of brain nerve activity. TMS applies the magnetic field generated by the coil through the skull to the brain area under the coil. Subsequently, this magnetic field induces an electric field in the brain tissue, which changes the action potential of cortical nerve cells, thereby affecting the metabolism and neuroelectric activity in the brain (Fig.1, adapted with permission from Ref [20]). This technique originated in a study by Barker et al[21]. in 1985. They placed a planar coil on the scalp of a normal person's movement area, and a clear motor evoked potential was recorded on the opposite hand of the subject. So far, TMS has achieved rapid development. According to the different pulse frequency, TMS is divided into three stimulation modes: single pulse TMS (sTMS), double pulse TMS (pTMS) and repetitive TMS (rTMS). Among them, rTMS

achieves the purpose of exciting or inhibiting the function of the local cerebral cortex through continuous and adjustable repeated stimulation, which greatly expands the application range of magnetic stimulation[22-26].

The use of pulsed magnetic fields to stimulate the cerebral cortex has been regarded as a new generation of disease detection and treatment method. TMS has been widely used in clinical neurophysiology, nerve repair, surgical process monitoring and other fields. rTMS has been approved by the FDA for the treatment of major depression. In addition, rTMS also shows good effects in the treatment of dyskinesias, addiction, and neurological rehabilitation[24,27-28]. Liu et al[29]. appliedrTMS to the left dorsolateral prefrontal cortex (DLPFC). The desire of heroin use disorder patients was significantly reduced, and this treatment effect can last up to 60 days after stopping the treatment. Guan and colleagues showed that high-frequency rTMS stimulation of the ipsilateral primary motor cortex (M1) can promote the recovery of exercise in patients with acute stroke, and the effect can last for 1 month, a single course of rTMS in the acute phase can induce improvement in upper limb function that lasts for 1 year[30].

In response to clinical application problems, some new TMS technologies have also been developed. Generally speaking, the TMS treatment process will last 30~45 minutes. The intermittent theta burst stimulation (iTBS) only takes 1~3 minutes, which greatly relieves the pressure of patients. iTBS consists of 3 pulses of 50 Hz and repeats at a frequency of 5 Hz, 2 s on and 8 s off, and 600 pulses are generated in about 3 minutes. What's important is that iTBS of about 3 minutes and high frequency rTMS of 37.5 minutes produced similar effects[31]. Another crucial technique is deep transcranial magnetic stimulation (dTMS), which uses an H-shaped coil. Compared with TMS, the magnetic field dTMS generates can stimulate deeper brain areas. But this also leads to a larger magnetic field spread and a decrease in signal specificity. A possible effective solution is to combine with MNPs, which will be described in detail later.

TMS has achieved very significant effects in the treatment of patients with neurological diseases, Parkinson's disease, mental illness and depression. Compared with traditional drug treatments and electrical stimulation treatments, TMS has the advantages of non-invasiveness, significant effects, and less damage, and provides new ideas for people to study the pathogenesis of clinical diseases. However, the specific treatment mechanism of TMS is not yet clear. Due to the specificity of brain tissue, different stimulation parameters and stimulation locations must be designed for different diseases. In addition, the structure of the TMS coil seriously affects the focus accuracy of the stimulation. The magnetic field may stimulate multiple brain regions at the same time, resulting in insignificant therapeutic effects or even canceling each other out. Therefore, there is an urgent need to innovate and improve magnetic stimulation technology to meet the needs of rapidly developing scientific research.

2 Magnetic Nanoparticles (MNPs)

MNPs have broad application prospects in the fields of mechanics, electronics, optics, magnetism, chemistry and biology. Among them, MNPs represented by iron oxide nanoparticles are attracting more and more attention in the field of medical health. In addition to its own ferromagnetism, MNPs are characterized by their superparamagnetism, which makes MNPs widely applied in the fields of MRI image enhancement[32], magnetic biological separation[33-34] and drug targeted conduction[35-37]. At the same time, nano-iron oxide is currently one of the few inorganic nanomaterials approved by the US Food and Drug Administration (FDA) for clinical use.

2.1 Magnetic Properties of MNPs

As a widely researched material, MNPs have the characteristics of surface effect, small molecule effect, quantum size effect and easy surface function. In addition, its two most prominent features are ferromagnetism and paramagnetism. MNPs with larger size exhibit ferromagnetism, and ferromagnetic MNPs become paramagnetic when they reach the Curie temperature. When the size of MNPs is reduced to a critical size, ferromagnetism will be converted to superparamagnetism, that is, MNPs have a strong magnetic response under the action of an external magnetic field. MNPs can be restored to a dispersed state when the external magnetic field is removed. Using this property, researchers can control the properties and behavior of MNPs in the body through an external magnetic field, and after removing the external magnetic field, the particles can return to the initial state, which can trigger in vivo diagnosis and treatment[38-39].

By precisely adjusting the composition and crystal structure of nanoparticles, the magnetic properties of MNPs can be further improved without changing the particle size and morphology. Lee et al[40]. used soft magnetic materials to modify the surface of hard magnetic ferrite nanoparticles based on exchange coupling, which greatly improved the magnetocaloric effect of MNPs. Additionally, another strategy to enhance the magnetic properties of MNPs is to regulate the internal spin order structure, so as to obtain a stronger magnetic response. A common method is to dope manganese, zinc, cobalt and other metal elements in the iron oxide component to obtain different new ferrite nanoparticles. For example, the manganese-zinc ferrite nanostructure is a high-performance soft magnetic composite ferrite with a spinel structure. These doped MNPs have the characteristics of high magnetic properties, low coercivity, biological activity, and chemical stability. It is worth mentioning that due to the extremely small size and large specific surface area of nanoparticles, the atomic properties on the surface of MNPs have a significant impact on magnetic properties. Therefore, magnetic properties of MNPs can be enhanced by adjusting the distribution of surface atomic magnetic moments, affecting the interaction between particle magnetic moments and the environment, and adjusting the magnetic coupling between particles, etc[38,41]. These tunable magnetic properties help clinically design new detection and treatment strategies that can respond to specific pathological events and generate highly specific signals.

2.2 Biological Effects of MNPs

In addition to magnetic properties, MNPs also have

many vital biological effects due to the chemical composition, particle size, morphology and surface modification. MNPs can be injected intravenously into the body like a drug. Due to the enhanced permeability and retention effect (EPR), it is easier to penetrate into tumor tissues and stay for a long time[42]. MNPs can bind to specific tissues through surface modification. Targeting molecules that can bind to specific tissue receptors through surface modification can also achieve active targeting *in vivo*. The interaction between nanoparticles and cells after entering the body is very complicated. According to our previous simulation study, the size, hydrophilicity and surface modification of the nanoparticles could affect their entry into the cells after MNPs were injected into the human body[43-44]. Nanoparticles can also activate specific signal pathways after entering the cell, causing unexpected changes in the fate of the cell[45]. Therefore, in clinical use, it is vital to design suitable surface modification molecules to meet the requirements of good biocompatibility.

Moreover, the overall properties of MNPs can also be adjusted through the assembly and interaction between particles. The realization and regulation of the self-assembled structure of MNPs has become a key point to understand the internal structural composition relationship and improve the performance of related magnetic materials. Through van der Waals interaction, electrostatic interaction, entropy drive, hydrogen bonding, polymer template, external field control, surface ligand molecular bonding and other assembly methods, nanoparticle assembly structures with various morphologies can be prepared on multiple scales. Due to the different interactions between particles in the assembled structure, the nanoparticle assembled structure can exhibit a variety of new collective properties and effects[46-47].

Iron oxide nanoparticles still have new biological effects discovered, which can be used as nanozymes. Yan Xiyun's research group[48] discovered in experiments that iron oxide nanoparticles could also catalyze the color reaction between hydrogen peroxide and the substrate, which had an effect similar to horseradish peroxidase. Xiao and colleagues[49] found that Fe_3O_4MNPs exhibit an intrinsic lytic activity in disruption of yeast cells, which the biocatalytic reaction kinetics was similar to that of natural zymolyase. Compared with natural enzymes, nanozymes have many advantages. Fe_3O_4 nanozymes show higher stability under extreme conditions, such as temperature (4 ℃~90 ℃) and pH (2~12)[50]. Fe_3O_4 nanoparticles can be stored for a long time and reused many times[51]. In addition, the activity of Fe_3O_4 nanozymes can be adjusted by adding dopants and adjusting the size, structure or morphology[52]. By surface modification or hybridization with other nanomaterials[53], nanozymes with the best activity can be designed for specific purposes need.

2.3　Biomedical Applications of MNPs

MNPs have many beneficial properties, which can be used in a variety of biomedical applications (Fig.2, adapted with permission from Ref 54.). MNPs have paramagnetic properties, so they can be used as imaging contrast agents. Traditional iron oxide nanoparticle magnetic resonance contrast agents are usually used as single-modal

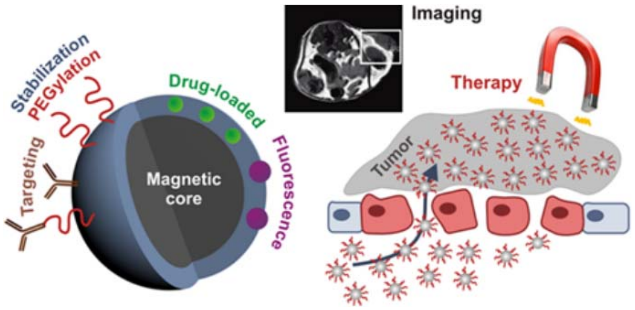

Fig.2　Biomedical applications of magnetic nanoparticles

contrast agents, which are prone to false positive signals. Using T1/T2 dual-modality magnetic resonance imaging can better enhance the accuracy and sensitivity of its imaging diagnosis. By optimizing the size and surface of iron oxide nanoparticles, doped paramagnetic elements can be used to construct T1/T2 dual-mode iron oxide nanoprobes[55-56].In addition, due to the limitations of magnetic resonance, the construction of multi-mode imaging probes based on iron oxide is an important research direction[57-59]. Li et al[59]. prepared Fe_3O_4/Au nanoparticles and used them for magnetic resonance-electron computed tomography (MR-CT) dual-modality imaging. The nanoparticles had high T2 relaxation efficiency, good X-ray attenuation characteristics and a high Fe_3O_4/Au molar ratio, which significantly improved the accuracy of imaging.

Due to the easy functionalization of the surface of MNPs and the characteristics of targeted drug delivery and controlled drug release, it has gradually become one of the promising materials in the field of drug delivery and new diagnosis and treatment. Magnetic drug delivery systems should be characterized by non-toxic or low toxicity and high drug delivery efficiency. In order to construct a suitable magnetic drug delivery system, researchers combined MNPs with other materials or ligands based on the magnetic hyperthermia of MNPs to achieve remote control-triggered drug release behavior[60-62]. Moghadam et al[63]. coated SiO_2 on the surface of prepared magnetic iron oxide nanoparticles (MIONPs), functionalized with chitosan (CT) in trimethylamine solution after chlorine functionalization, and loaded nevirapine (Nev) drug onto the above CT-SiL-MIONPs system. The value of Nev loading efficiency and the controlled delivery effect of Nev@CT-SiL-MIONPs were determined by ultraviolet and visible spectrophotometry (UV-Vis). The results demonstrated that the above nanomaterials showed superparamagnetism, and MNPs loaded with Nev were more effective against Hela cancer cell line than the nevirapine itself. Jing et al[64]. prepared a multifunctional nanomaterial by loading chitosan and metformin on Mn-doped Fe_3O_4@MoS_2 nanoflowers. The Mn-doped Fe_3O_4 core was also used as a T1/T2 magnetic resonance imaging (MRI) reagent for sensitive and accurate cancer diagnosis, while the MoS_2 nanosheet was used as an effective near-infrared photothermal converter for potential photothermal therapy.

Another important application of MNPs is hyperthermia, in which MNPs are positioned on tumor tissues. MNPs generate hysteresis loss under the action of an external alternating magnetic field, thereby generating heat, thereby achieving local fixed-point heating and rapidly increasing the temperature at the tumor site. By 42 ℃ to

45 ℃, tumor cells are selectively killed by using the characteristics that the tumor cells are less tolerant to heat than normal cells. Tumor hyperthermia has the advantages of no tissue penetration depth limitation, physical treatment without drug resistance, and low toxicity side effects of iron oxide preparation[65-66]. Although magnetic hyperthermia based on iron oxide nanoparticles has been clinically applied, the problem of low magnetothermal efficiency remains to be solved. Hassan et al[67]. encapsulated cobalt and manganese-doped hexagonal iron oxide nanoparticles (CoMn-IONP) in biocompatible polyethylene glycol-b-polycaprolactone (PEG-PCL)-based nanocarriers. Compared with single IONP, CoMn-IONP has a faster heating rate and a better tumor killing effect. In addition, the use of vortex MNPs for magnetic hyperthermia is a potentially effective solution. MNPs with vortex magnetic domains have both weak magnetic interactions between particles and better magnetic properties, due to the unique closed magnetization distribution, larger particle size, and magnetization reversal characteristics in an external magnetic field. The unique magnetic vortex structure makes the ferrimagnetic vortex domain iron oxide nanorings have negligible remanence and large hysteresis loss. The specific absorption rate is an order of magnitude higher than that of superparamagnetic nanoparticles, and only a low dose can effectively inhibit tumor growth[68]. Magnetic hyperthermia can also be combined with radiotherapy, chemotherapy and immunotherapy to improve curative effect and reduce side effects[69-71]. Espinosa et al[71]. used low-concentration iron oxide nanoparticles (0.25 mol/L) and low-intensity 808 nm laser radiation (0.3 W/cm^2) for dual-mode hyperthermia. Compared with single magnetic hyperthermia or photothermal therapy, the thermal efficiency was significantly improved, which can effectively treat tumors.

3 Progress in MNPs-mediated Nerve Magnetic Stimulation

In conventional electrical stimulation therapy, electrodes are placed near nerve tissue and directly generate electric fields by electrical stimulation. With the deepening of research, nerve stimulation technology began to use light, magnetic energy or ultrasound as the energy source[36,72]. Since magnetic neuromodulation does not require the implantation of invasive electrodes or optical devices, this technique is considered to have good prospects for clinical neuronal activation. Studies by Young et al[73]. showed that magnetic fields in the millitesla(mT) range could penetrate the brain without attenuating signals or causing side effects because the biological tissue had low conductivity and negligible magnetic susceptibility. Magnetic neural stimulation mediated by MNPs is roughly classified into three forms: magneto-thermal stimulation by superparamagnetic nanoparticles, magneto-electrical stimulation by magnetoelectric nanoparticles, and magneto-mechanical stimulation.

3.1 Magneto-thermal Stimulation

Magneto-thermal stimulation is the process by which alternating magnetic fields (AFM) induce the heating of MNPs to produce stimulation. This process triggers a thermosensitive cation channel of the transient receptor potential vanillic acid (TRPV) family, which leads to depolarization and cell membrane action. The realization of magneto-thermal stimulation relies on the transient receptor potential vanilloid subtype 1 (TRPV1) channel in the TRPV family[74]. The TRPV1 channel is a protein expressed by the TRPV1 gene in the human body. When the temperature of MNPs exceeds 43 ℃, the TRPV1 channel opens, causing a large number of cations to flow into the cells, thereby activating neural activity[75]. Chen et al.[76] showed that magneto-thermal stimulation can regulate the excitatory state of mouse neurons. Under the alternating magnetic field, the magneto-thermal stimulation of the ventral tegmental area of the mouse could induce the brain-targeted area to be excited, and this regulation achieved effective stimulation for up to one month.

For MNPs entering the human body, they tend to combine with each other through dipole interaction, which may change the magnetic response strength. Therefore, proper surface modification is necessary. Huang et al.[19]coupled a streptavidin and a light-sensitive fluorescent probe to the surface of MNPs. Through the interaction of biotin and streptavidin, the nanoparticles were specifically targeted to the surface of the cell membrane, and the local temperature was raised by radio frequency (RF) magnetic field heating to open the TRPV1 channel, and the Ca^{2+} concentration was increased from 100 nmol/L to 1.6 mmol/L. Using voltage-sensitive materials, they observed changes in membrane potential of hippocampal neurons. This work demonstrates that opening the TRPV1 pathway by heating MNPs can induce action potentials without causing cell damage. Romero et al.[77] immobilized allyl isothiocyanate (AITC, a stimulant for TRPV1 channels) on the surface of MNPs. After exposure to a magnetic field, the heat released by the MNP causedAITC to release and bind to the TRPV1 channel, which in turn triggers Ca^{2+} influx. The amount of nanoparticle required for this work was greater than the amount of magnetization that was achieved by magnetotherapeutic neuron adjustment by three orders of magnitude lower.

Besides, the researchers designed a magnetic response genetic circuit based on gene regulation methods using TRPV1 channels and ferrocene-containing proteins. Ferritin is a globular protein about 12 nm in diameter surrounded by iron clusters about 5 nm in diameter. The Jeffery Friedman team has made some progress in ferritin-based neuromodulation. They coupled a green fluorescent protein (GFP)-tagged fusion ferritin to an anti-GFP-TRPV1 channel protein. In an alternating magnetic field, a synthetic DNA fragment was initiated by the magneto-thermal effect of the iron core in the fusion ferritin, which activated the downstream gene to express insulin, thereby reducing blood glucose in the mouse[78]. In another study, they mutated the TRPV1 channel, which allowed chloride ions to flow into cells in the presence of a magnetic field, which increased insulin levels and inhibits mice from eating, thereby lowering blood sugar[79].

How to apply magnetic thermal stimulation to specific neurons is a key issue in research. Munshi et al.[80] reported that the magnetocaloric genetic stimulation provided infinite deep brain activation, enough to evoke the

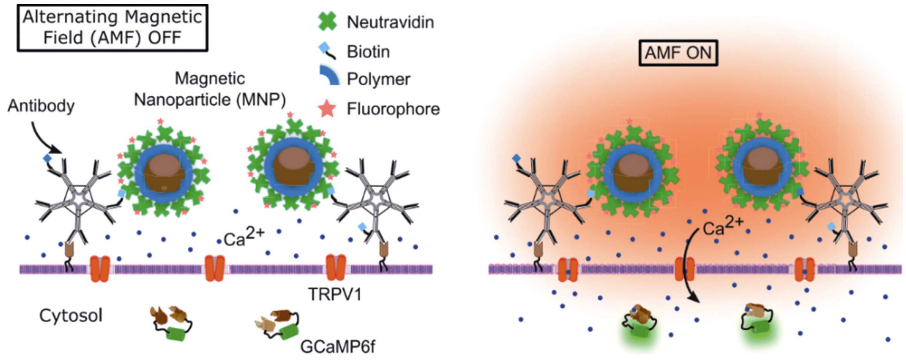

Fig.3　MNPs-mediated magnetic thermal nerve stimulation

motor behavior of awake mice. The magnetocaloric genetic stimulation in the motor cortex caused motion, and deep brain stimulation in the striatum caused rotation about the body axis, and stimulation near the ridge between the ventral and dorsal striatum caused gait freezing. By combining MNPs with neuronal membranes, they achieved neural stimulation in vivo without increasing overall tissue temperature successfully (Fig.3, adapted with permission from Ref 80.). Moreover, they also demonstrated how to apply magnetic nanoparticle heating to silence target neurons[81]. Rat hippocampal neuronal cultures were transfected to express the temperature-gated chloride channel octaamine 1 (TMEM16A). Spontaneous discharge was suppressed within a few seconds after alternating application of magnetic fields to magnetic nanoparticle-modified neurons expressing the octaamine 1 (TMEM16A) channel. Their work showed that applying a magnetic field for 5 s will result in 12 s of silence. After the silent period, spontaneous activities resumed immediately.

The use of magnetocaloric temperature to release nerve agents to inhibit nerves is also a promising therapeutic approach. Yu et al. [82]prepared a superparamagnetic nanoparticle made of Fe_3O_4 (nuclear), thermally responsive polymer hydrogel (shell) and nerve agent (N-isopropylacrylamide monomer, NIPA-M). The temperature generated by the external magnetic field during direct injection into the cardiac ganglion plexus (GP) released NIPA-M in the hydrogel, thereby inhibiting GP activity.

3.2　Magneto–electrical Stimulation

The magneto-electric effect is the phenomenon that the material is polarized under the action of an external magnetic field or the material is induced to magnetize under the action of an applied electric field. Due to the magnetoelectric effect, the magnetoelectric nanoparticles have a strong magneto-electric coupling effect and can convert the magnetic field into an electric field, which has a certain influence on the biochemical processes and histology of normal cells and cancer tissues. Balbaa et al. [83] examined the effect of micro electric fields generated by magnetoelectric nanoparticles on precancerous liver tissue. The results showed that HepG-2 cells increased cytochrome C (Cyt C, mitochondrial markers) and alpha-fetoprotein (tumor markers). The authors believed that the possible mechanism was that the micro-electric field may trigger ion channels on the organelle membrane through membrane nano electroporation to control Ca^{2+} conduction

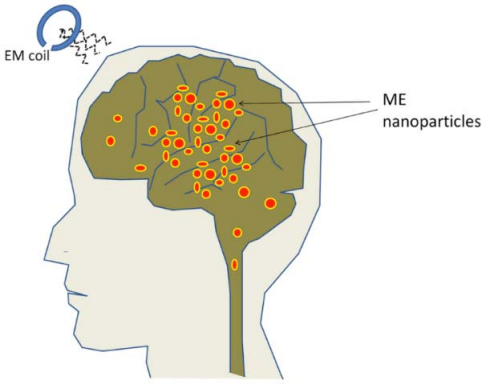

Fig.4　Deep brain stimulation using magnetoelectric (ME) nanoparticles

to guide gene expression.

MNPs are emerging as neural stimulation transducers to control neural activity through locally generated magnetic and/or electric fields. In 2012, Yue et al. [84]firstly described the application of magnetoelectric nanoparticles in the field of brain stimulation. In this study, they calculated the matching frequency and concentration of magnetoelectric nanoparticles necessary for the standardization of electrical pulse sequences in four regions of the brain by Parkinson's model patients and the effect of magnetoelectric nanoparticles on non-invasive stimulation of the patient's brain was simulated (Fig.4, adapted with permission from Ref 84.). Guduru et al. [85]injected about 10 μg of $CoFe_2O_4$-$BaTiO_3$ nanoparticles intravenously in the tail vein and directed them through BBB by direct current. The surgically connected EEG headset showed that MNPs could be used to apply 100 Oe of alternating current to modulate the electrical waveform deep in the brain. Moreever, in order to enhance the efficacy of TMS, Li et al. [86] injected superparamagnetic iron oxide nanoparticles (SPION) coated with chitosan and polyethylene glycol intravenously, and the particles were delivered to the brain by permanent magnets attached to the forehead of the mouse. Nanoparticles overcame the BBB and the maximum MEP amplitude recorded by the single rat in the SPIONs + magnet group was significantly higher than that in the saline group (5.78 ± 2.54 vs 1.80 ± 1.55 mV, $P = 0.015$). In the M1 region, the number density of c-fos-positive cells in the SPIONs + magnet group was 3.44 times that in the saline group.This suggested that intravenous injection of SPIONs may enhance the effect of TMS, which enhances the accuracy of TMS.

In addition to its effect on the brain, Wu et al[87]. designed a self-powered composite nanofiber (CNF) composed of modified multi-walled carbon nanotubes (m-MWNT) coated Fe_3O_4 / PCL fibers. During the application of an external magnetic field, the output current of the nanocomposite increased due to the presence of MNPs. These CNFs were used to replace the sciatic nerve of bullfrogs and achieved effective functional electrical stimulation. For magneto-electrical stimulation, an important question is how to ensure the efficiency of stimulation after delivering the magnetoelectric nanoparticles to the target location. Direct injection of MNPs into the neural position may be a valuable solution, but more research is needed to enhance efficiency.

3.3 Magneto–mechanical Stimulation

Mechanics plays an important role in many physiological processes and pathological processes. Metastatic cancer accounts for more than 90% of the total number of cancers, and the force acting on the cells plays a role in regulating the metastasis process[88-89]. In addition, some studies have reported the role of mechanics in neuronal growth, and external mechanical stretching has been shown to enhance axonal elongation under controlled conditions, which can complement existing spinal cord injury treatments[90-92]. The magnetic field is mediated by MNPs to produce mechanical effects. For MNPs placed in a magnetic field, if the magnetic field has a gradient▽H, they are subjected to a force F=(m▽) B, and the direction is directed to a region with a higher field density.

Magneto-mechanical stimulation is the process of converting a non-invasive physical input into a receptor-specific biological output. The mechanical force between MNPs caused by the magnetic field enhances calcium influx in the cortical neural network. Tay et al.[92] found that nanomagnetic stimulation of ferromagnetic nanoparticles can induce calcium influx in the cortical neural network, with substantially no observable cytotoxicity. The stimulated neural network showed an average increase of 20% in calcium fluorescence signal. Subsequently, in order to verify whether the magnetic stimulation activated a specific type of calcium channel, the ω-conotoxin GVIA (omega-conotoxin GVIA, a mechanically sensitive one) was utilized. The N-type calcium channel inhibitor blocked the calcium channel, and it was found that the stimulation of the nano-magnetic force was inhibited, indicating that the mechanically sensitive ion channel plays an important role in regulating calcium influx (Fig.5, adapted with permission from Ref 92.). Previously, it was reported that a ferritin-based magnetoprotein assembly was designed and fused to the TRP family ion channel[78,93]. For example, “Magneto 2.0” designed by Wheeler and colleagues[93], by fusion of paramagnetic ferritin with a temperature-sensitive ion channel TRPV4, can be activated when exposed to a magnetic field. Moreover, “Magneto 2.0” can control the deep brain activity of free mice. This work may also suggest the effect of magnetic mechanical forces between MNPs. However, there is still some controversy. Meister believes that the mechanical force between nanoparticles is at least eight orders of magnitude weaker than the force required to activate

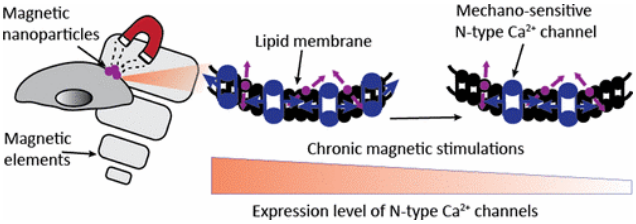

Fig.5 Mechanical stimulation based on MNPs to restore the balance of mechanically sensitive ion channels in neural networks[92]

mechanoreceptors[94]. Therefore, the idea of magneto-mechanical force-activated ion channels still needs more institutional support.

Guidance in the growth and development of axons is a complex mechanochemical process, and recent studies have shown that the mechanical properties of the environment and the mechanical forces generated within the growth cone can affect the guidance of axons. Mechanical regulation of neurons is important in addition to the nervous system and is also critical for the repair of trauma such as spinal cord injury. Hemphill et al. suggested that pathological mechanical transduction may play an important role in traumatic brain injury[95]. Riggio et al. applied tension to neuronal cells to stimulate neurite initiation or axonal elongation in the desired direction, based on the synergistic use of MNPs and magnetic fields. In neuron-like cell lines, they confirmed that MNPs preferentially directed neurite outgrowth by inducing a net angular displacement (about 30°) in the direction of the neurite, preferentially along the direction of the external magnetic field[90]. Liu et al. developed a nano-hydroxyapatite-coated magnetic nanoparticle by ultrasonic assisted coprecipitation. Adding the particles to primary cultured dorsal root ganglion (DRG) neurons can effectively promote axon growth, and the axon guidance signal Netrin-1 significantly increased[96].

4 Conclusion and Future Directions

Activating neural stimulation through nanoparticles is an exciting breakthrough in the past years. As a powerful tool, MNPs can be used alone or in combination with other methods, including synthetic biology, to promote innovative neurostimulation protocols. These new technologies not only enable high spatial resolution and cell-specific non-invasive or minimally invasive nerve stimulation, but also improve safety by significantly reducing the power required for primary stimulation. In this article, we have introduced the properties of MNPs and the three magnetic stimulation methods. How to use MNPs as a mediated, precise magnetic and magnetic-other effect on the signal path is the main concern of researchers. The development of nanomaterials such as those related to magneto-mechanical, magneto-electric, magneto-thermal and other transduction mechanisms in neurostimulation schemes has received great concern. Magnetic field transformation of MNPs can convert a magnetic field into a local mechanical force to activate a mechanically sensitive ion channel, such as a TREK-1. The temperature generated by magneto-thermal stimulation can open the TRPV1

channel, allowing Ca^{2+} to flow into the cell and activate neurons.

At present, cranial nerve is still the main target of magnetic stimulation, and perhaps other nerves in the body need some attention. For example, many cardiovascular diseases are associated with cardiac ganglion plexus (GP), and some works have shown that electrical stimulation of GP can play a therapeutic role. Moreover, quite a few nerve stimulation studies are still in the verification phase in vitro. How to deliver MNPs to the nerve parts accurately, safely and efficiently is an urgent problem to be solved. In summary, the application of MNPs for precise nerve stimulation is highly promising and challenging, which requires researchers to work harder to solve the problems of biocompatibility, efficiency and stability.

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