Effects of Magnetic Nanomaterials on Biological Neural signals

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By sending electrical, optical, chemical, auditory, or magnetic stimuli to specific neural tissue, a process known as neuromodulation may be used to alter neuronal activity. Through active research efforts, the development of nanotechnology has recently revolutionized neuromodulation techniques. On the one hand, the adaptable nano-science toolbox promoted neuromodulation techniques that were previously associated with huge devices toward shrunk devices with soft mechanics, closely packed components, and long-lasting performance. The neurological issue may be seamlessly integrated with these nanoscale instruments due to their enhanced spatial resolution and precise targeting capabilities. In addition, magnetic nanoparticles represent a significant aspect of magnetic neuromodulation development. Deep brain stimulation is possible with the use of superparamagnetic nanoparticles, which can be delivered to the brain and controlled remotely. Additionally, by regulating certain ion channels, force-generating or heat-dissipating super-paramagnetic nanoparticles can be employed for wireless neuromodulation. Specific cells' ion channels are targeted by taking advantage of their inherent functionality or via genetic modification. Magnetic nanoparticles' magnetic forces activate mechanosensitive channels, such as TREK1 and Piezo1, and magnetic nanoparticles that produce heat in response to an external alternating magnetic field can activate heat-sensitive ion channels, such as TRPV1.

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1. Introduction

The earliest known examples of iron-based nanomedicine date back to 1957, when iron-based microparticles were reported to be used in the thermal ablation of lymphoma in vivo[1]. Due to the improvements in its surface modification, biocompatibility, stability, and functionality, iron-based nanomedicine is employed for the diagnosis or treatment of clinical disorders [2]. The FDA has approved the use of magnetic iron oxide nanomaterials Resovist® (Berlin, Germany) and Feridex® (Berlin, Germany) for the magnetic resonance imaging of liver tumors. Feraheme® (Delaware, Waltham, MA, USA) is approved as an intravenous iron supplement for the treatment of iron-deficient anemia, among other conditions [3]. Due to their excellent in vivo compatibility, the steady controllability of batch preparation, and their affordable manufacture, iron-based nanomedicines have been employed extensively in clinical settings.

2. Tumor Microenvironment

The tumor immunological microenvironment plays a key role in controlling an organism's immune response to a tumor [4]. Despite new evidence suggesting active immunity, agents such as tumor vaccines can promote the infiltration and activation of T cells, natural killer (NK) cells, and dendritic cells (DCs), and increase the intensity of the immune response. During the development of tumors, the body can create a tumor immunological microenvironment that negatively affects the strength of the immune response to the tumor and impedes the immune system's lethal impact on the tumor, via several methods. For instance, immune suppression can lead to a significant infiltration of immunosuppressive cells into the tumor site, including myeloid-derived suppressor cells (MDSCs), M2 macrophages, tumor-associated macrophages, regulatory T cells, and so on [5].

Extensive use has been made of magnetic nanoparticles in magnetic resonance imaging (MRI), magnetic targeting, and magnet-responsive drug delivery due to their outstanding controllability and magnetic driving force. Additionally, magnetic nanoparticles have been shown to control the activation of anti-tumor immunity. By manipulating magnetic fields, Schneck et al. created a platform for reductionist T cell activation [6]. Paramagnetic nanoparticles decorated with diverse signaling molecules form the basis of this platform. Each of these signaling molecules serves a unique purpose in the activation of the associated signaling pathway. However, T cell activation often necessitates the synchronization of some signaling molecules, such as costimulatory and T cell-receptor-specific signals. To increase T cell activation for immunotherapy, these single-signal nanoparticles might bind to the appropriate receptors and then use a magnetic field to stimulate the aggregation of these surface-bonded antigens or stimuli.

The adoptive transfer of NK cells is a component of NK cell immunotherapy, which is gaining more attention as a possible immunotherapy for the treatment of a variety of diseases. Importantly, in contrast to many competing cytotoxic T lymphocyte therapies, NK cells may specifically destroy tumor cells without prior exposure to tumor-specific antigens. However, the success of the therapy is frequently only moderate in solid tumors that have already developed. To generate significant numbers of functional NK cells for cancer treatment, the ex vivo activation of NK cells with exogenous cytokines is commonly required but ineffective. Another option for treatment is the local delivery of NK cells under image guidance. There are not enough non-invasive methods to keep track of NK cells. To improve the therapeutic effectiveness of NK cells for solid tumors, Sim et al. created nanocomplexes (HAPF) made of therapeutically relevant materials (hyaluronic acid, protamine, and ferumoxytol) to enable the magneto-activation and MRI visibility of NK cells [7]. In NK cells, an enhanced self-assembled HAPF nanocomplex was successfully bound and tagged. An exogenic AC magnetic field application could activate HAPF-labeled NK cells to improve their innate cytolytic capability. Actin filaments and NKG2D receptors, which are unique to NK cells, were activated. Then, as a result of the elevation of the NK cell activation markers Perf/Gzmb and NKG2D activation receptors, the cytolytic potential was enhanced. Additionally, MRI-visible HAPF-NK cells allowed for NK cells to be monitored after transcatheter hepatic intra-arterial local NK cell administration. In an HCC rat model, it was demonstrated that locally injected HAPF-NK cells, activated by a magnetic field, have potential therapeutic effects by slowing the development of solid tumors.

Furthermore, Saeid et al. showed that ferumoxytol nanoparticles limit tumor growth through indirect effects on the TME: monocytes are attracted to malignant tumors by chemotactic cytokines and are normally polarized to anti-

inflammatory M2 phenotypes [8]. Superparamagnetic iron oxide nanoparticles (SIONPs) have been demonstrated to shift the phenotype of M2 macrophages toward the high CD86+, tumor necrosis factor (TNF)-positive M1 macrophage subtype, according to earlier in vitro studies. A subsequent autocrine feedback loop that maintains the generation of TNF and nitric oxide (NO) can be created by the cancer cells' continued M1 polarization, as a result of apoptosis. Therefore, the regulation of the tumor-immune microenvironment, mediated by magnetic nanoparticles, can achieve accurate and effective immune cell activation in development.

3. Biological Neural Signal

By sending electrical, optical, chemical, auditory, or magnetic stimuli to specific neural tissue, a process known as neuromodulation may be used to alter neuronal activity [9]. This technique has given scientists important tools to both study how the brain works and to control the activity of damaged neural circuits to slow down the course of illnesses. The application of neuromodulation in neuroscience research has resulted in a plethora of findings regarding functional connectivity in brain networks. Furthermore, neuromodulation technologies, capable of enhancing, restoring, and replacing motor, sensory, and cognitive skills, have been used to develop therapeutic routes and devices for the treatment of neuropsychiatric disorders.

Through active research efforts, the development of nanotechnology has recently revolutionized neuromodulation techniques [10]. On the one hand, the adaptable nano-science toolbox promoted neuromodulation techniques that were previously associated with huge devices toward shrunk devices with soft mechanics, closely packed components, and long-lasting performance. The neurological issue may be seamlessly integrated with these nanoscale instruments due to their enhanced spatial resolution and precise targeting capabilities [11]. However, some of the drawbacks of conventional macroscale neuromodulation techniques may be overcome using nanomaterials with advantageous physical and chemical characteristics. For example, nanomaterials and nanoscale devices can add the advantage of a high spatial and temporal resolution to modulated models with a high penetration depth, thus enabling new grafted forms of neuromodulated models.

In addition, magnetic nanoparticles represent a significant aspect of magnetic neuromodulation development [12]. Deep brain stimulation is possible with the use of superparamagnetic nanoparticles, which can be delivered to the brain and controlled remotely. Additionally, by regulating certain ion channels, force-generating or heat-dissipating super-paramagnetic nanoparticles can be employed for wireless neuromodulation. Specific cells' ion channels are targeted by taking advantage of their inherent functionality or via genetic modification. Magnetic nanoparticles' magnetic forces activate mechanosensitive channels, such as TREK1 and Piezo1, and magnetic nanoparticles that produce heat in response to an external alternating magnetic field can activate heat-sensitive ion channels, such as TRPV1. The fact that there is no discernible change in the neuronal density or glial response between the stimulated and unstimulated patients is significant because it shows that little to no tissue damage is caused by the magnetic nanoparticles' briefly dispersed heat. For example, Huang et al. were the first to use superparamagnetic nanoparticles with a changing magnetic field to generate heat and activate the temperature-sensitive TRPV1 channel, leading to the activity of some anesthetized worms.

It should be noted that magnetic-nanomaterial-based neuromodulation methods only require the implementation of a low magnetic field intensity, compared to repetitive transcranial magnetic stimulation (rTMS), but both modulation methods mainly work in the 0–20 Hz region [13]. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) suggested that the exposure limit is frequency-dependent [14]. The upper limit for continuous public exposure in the 1–8 Hz frequency band is around 400 Oe. In addition, tissue heating and other negative side effects may result from strong AC magnetic fields. Therefore, in comparison to high-strength rTMS, the use of low-strength magnetic fields in nanoparticle-mediated treatments is advantageous.

For instance, by stimulating the signaling pathway for the mitogen-activated protein kinase, Fe_3O_4 nanoparticles can also promote neurite development. The ability to use nanoparticles to improve the mechanical characteristics of the nerve guiding conduit (NGC) has also been demonstrated in earlier research, which is even more significant. Chen et al. created a multilayered composite NGC (ML-NGC), loaded with melatonin (MLT) and Fe_3O_4 by electrospinning it [15]. With MLT minimizing oxidative damage and Fe_3O_4 promoting neurite renewal, this three-layer scaffold is thought to offer enough mechanical strength for neurite sprouting; it will, therefore, establish the ideal milieu for nerve regeneration.

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