doi 10.18699/bgrs2024-7.3-13

Wireless magnetoelectric interface for deep brain stimulation

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Key words: core-shell nanoparticles, magnetoelectric effect, nose-to-brain transport, deep brain stimulation

Motivation and Aim: Magnetoelectric (ME) nanoparticles (NPs) can transform magnetic-field energy to electric-field energy and vice versa, which makes them attractive for the development of novel approaches to wireless control of biological systems. ME NPs have a range of potential applications, such as drug delivery, cancer treatment, control over cell differentiation and stimulation of neurons.[1-7] The wireless brain–machine interface is one of the most intriguing and promising issues that can be addressed using ME NPs. Nonetheless, to provide an effective particle–neuron coupling for in vivo deep brain stimulation, ME NPs must meet several requirements: low toxicity, high efficiency of ME coupling at weak magnetic fields, controlled delivery.

Methods and Algorithms: A new approach for ultrafast *in situ* fabrication of stabilised colloidal highly efficient magnetoelectric (ME) core–shell nanoparticles (NPs) was developed on the basis of biocompatible magnetic $MnFe_2O_4$ (MFO) and ferroelectric $Ba_{0.85}Ca_{0.15}Zr_{0.1}Ti_{0.9}O_3$ (BCZT) using a microwave-assisted hydrothermal method. MFO NPs were used as a control for all our experiments to evaluate the role of mechanical stimulation in observed biological effects of MFO@BCZT NPs due to possible magnetic particle rotation in AC magnetic field. The toxicity of the synthesised NPs with and without AMF (7 mT, 10 Hz) exposure was evaluated by the MTT assay. We performed T_2*-weighted MRI and TEM to assess the ability of MFO@BCZT NPs to be taken up by the mouse olfactory epithelium and transported throughout the olfactory system. The ability of MFO@BCZT NPs to alter olfactory neuronal activity *in vivo* during AMF stimulation was studied by Mn-enhanced MRI. Manganese ions act as agonists to potential-dependent calcium channels, and hence their accumulation is proportional to the neuronal functioning. The mice were then exposed to clean air or odour (0.01% acetophenone) with or without AMF stimulation (7 mT, 10 Hz). Throughout all the experiments, the animals were kept in their respective home cages.

Results: Opposite effects on growth of cancer and normal cells were revealed *in vitro* by electrostimulation via ME MFO@BCZT NPs using a low-intensity AC magnetic field (7 mT, 10 Hz). Enhanced uptake and trans-synaptic axonal transport of MFO@BCZT NPs to the brain and were detected *in vivo*. Using T2*-weighted MRI and specific inhibitors of axonal transport we showed the prevalence of transneuronal movement of MFO@BCZT NPs from mouse nasal cavity to the brain.

The application of the AC magnetic field did not influence the MOB T_1-weighted MRI signal during clean air or odor presentation in control and MFO NP–treated animals but enhanced this signal in MFO@BCZT NP–treated mice.

The behavioural experiments indicated that mice were able to detect and recognise odour stimuli with equal proficiency in the presence or absence of NPs or AC magnetic field. This ability is determined by the number of olfactory neurons and the activity of MOB

interneurons.[8] There was statistical significance only for the effect of the AC magnetic field on the total time of sniffing of the odorant in MFO@BCZT NP–treated, but not MFO NP–treated mice. This parameter directly depends on the activity or number of olfactory receptor neurons.[8]

Conclusion: Thus, in this study, a novel advanced strategy is established based on non-invasive intracellular ME nanosized electrodes for neurological theranostics and targeted drug delivery to the central nervous system

by means of ME MFO@BCZT NPs as a non-invasive platform for wireless electrical stimulation.

Funding: The study is supported by RSF grant № 23-14-00179.

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