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Magnetomechanical regeneration of bone tissue using of superparamagnetic nanoparticles

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Abstract. Here we evaluated the ability of superparamagnetic ferroarabinogalactan nanoparticles functionalized with RGD peptide (an integrin receptor ligand) to accelerate the repair of a cranial vault defect under the influence of a low-frequency alternating magnetic field. A defect of the cranial vault was used as a model of a bone injury, which is usually used on rodents, since the structure of the cranial vault allows creating a standardized burr hole that can be analyzed using histological and radiographic analysis. Functionalization of ferroarabinogalactans with the RGD peptide was performed by incubation of ferroarabinogalactans with the peptide. The study of the effectiveness of magnetomechanical transduction in vivo was carried out on 8-week-old male ICR mice. Magnetomechanical stimulation of bone tissue caused regeneration in the group of animals treated with FeAG functionalized with the RGD peptide (the cranial defect was practically restored after 7 days). At the same time, in the groups of control animals, the restoration of the bone defect did not occur during this time. After 2 weeks of magnetomechanical therapy, cranial vault defects in the animals of the experimental group were completely restored. Mice in the control groups did not recover. Ferroarabinogalactans effectively restore bone defects in a low-frequency magnetic field.

Key words: regeneration, bone, ferroarabinogalactan, integrin, mechanotransduction.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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Introduction

The ability to control bone tissue regeneration by the alternating magnetic field acting remotely on cell receptors has recently become one of the most promising areas in regenerative medicine. Stimulation of membrane mechanosensitive receptors, depending on the type of receptor and the magnitude of the field, can stimulate or suppress cellular functions such as apoptosis, contraction, differentiation, migration, proliferation, and secretion [1]. Magnetic nanoparticles have become a unique tool for controlling cell functions through mechanotransduction. Remote control is one of the main advantages of the method. Here we evaluated the ability of superparamagnetic ferroarabinogalactan nanoparticles functionalized with RGD peptide (an integrin receptor ligand) to accelerate the repair of a cranial vault defect under the influence of a low-frequency alternating magnetic field.

Material and methods

A defect of the cranial vault was used as a model of a bone injury, which is usually used on rodents, since the structure of the cranial vault allows creating a standardized burr hole that can be analyzed using histological and radiographic analysis [2].

Ferroarabinogalactans used for magnetomechanical transduction were obtained at the Irkutsk Institute of Chemistry. A.E. Favorsky SB RAS according to the method described in the patent [3]. Functionalization of ferroarabinogalactans with the RGD peptide was performed by incubation of ferroarabinogalactans with the peptide [4].

The study of the effectiveness of magnetomechanical transduction in vivo was carried out on 8-week-old male ICR mice. Animal experiments were performed in the accordance with the ethical standards of working with animals with the permission of the local ethical committee of the Krasnoyarsk State Medical University. prof. V.F. Voyno-Yasenetsky. Before the surgery, mice were anesthetized with inhalation anesthesia.

To prove the stimulation of bone tissue regeneration by mechanotransduction, 5 experimental groups of animals were used. The control group of mice No. 1 were injected with physiological solution at the site of the skull defect. Control group No. 2 were injected only with a sterile nanoparticles (FeAG). Control group No. 3 were injected with RGD peptide-functionalized feroarabinogalactan nanoparticles (FeAG-RGD) but not placed in a magnetic field. Mice from the control mice of group No. 4 were placed at intervals of one day in an alternating magnetic field (50 Hz, 100 Oe) for 15 minutes. Animals of the experimental group were injected with FeAG-RGD and after 10 min were placed in an alternating magnetic field (50 Hz, 100 Oe) for 15 minutes. The therapy was repeated every 48 hours for 7-14 days. Manipulations on animals were accompanied by observation of their behavior, body temperature, coat and body weight. Observations indicated that mice of all groups remained active throughout the therapy, had normal coat and stable body weight and body temperature.

Results and discussion

Magnetomechanical stimulation of bone tissue caused regeneration in the group of animals treated with FeAG functionalized with the RGD peptide (the cranial defect was practically restored after 7 days). At the same time, in

the groups of control animals, the restoration of the bone defect did not occur during this time. After 2 weeks of magnetomechanical therapy, cranial vault defects in the animals of the experimental group were completely restored. Mice in the control groups did not recover.

Histological studies have shown the overgrowth of fibrinoreticular tissue with a small amount of collagen fibers in mice of the control group in the area of the defect 7 days after the surgery. Bone fibers were located discretely. On the periphery there were bone beams with a dystrophic defect and signs of impaired cell mineralization. On the periphery, an admixture of inflammatory cells, including segmented leukocytes, was observed, and osteoclastic destruction of bone elements was detected in the form of the appearance of huge osteoclasts.

In the defect area of mice after FeAG-RGD mediated magnetomechanical stimulation, an immature osteoid is seen in the form of mesh masses with a large number of osteoclasts on the periphery and a large number of inflammatory cells - granulocytes, neutrophils and eosinophils, located both at the edges of the defect and in the regeneration zone. In the area of the defect, repair took place and a callus was formed. The first inner lamina was already formed, and a pronounced layer of osteoblasts and adjacent fibrous tissue were visible. The second bone plate was formed (fig.).

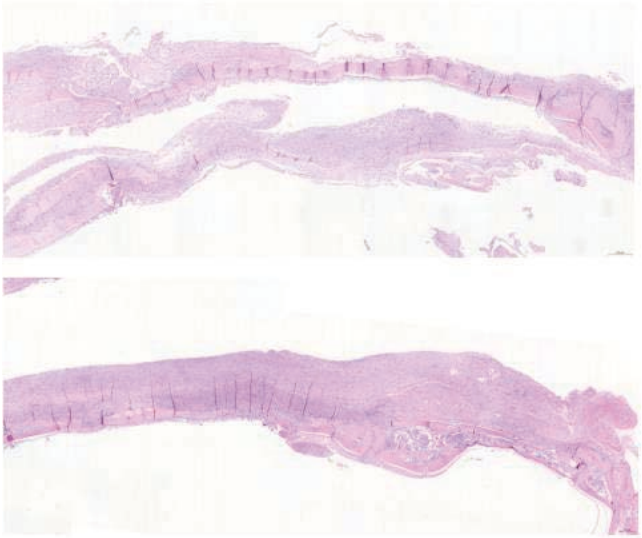

Figure. Histological studies of defect zones in control mice (top) and mice after 7 days of FeAG-RGD mediated magnetomechanical stimulation of bone tissue regeneration (bottom).

Conclusion

Thus, the studies have shown the high efficiency of superparamagnetic ferroarabinogalactan nanoparticles functionalized with the RGD peptide (integrin ligand) to accelerate the repair of a defect in the bones of the calvarium under the influence of a low-frequency alternating magnetic field.

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