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Development of Three-Dimensional Bio-Reactor Using Magnetic Field Stimulation to Enhance PC12 Cell Axonal Extension

Authors : Eiji Nakamachi, Ryota Sakiyama, Koji Yamamoto, Yusuke Morita, Hidetoshi Sakamoto

Abstract : The regeneration of injured central nerve network caused by the cerebrovascular accidents is difficult, because of poor regeneration capability of central nerve system composed of the brain and the spinal cord. Recently, new regeneration methods such as transplant of nerve cells and supply of nerve nutritional factor were proposed and examined. However, there still remain many problems with the canceration of engrafted cells and so on and it is strongly required to establish an efficacious treating method of a central nerve system. Blackman proposed the electromagnetic stimulation method to enhance the axonal nerve extension. In this study, we try to design and fabricate a new three-dimensional (3D) bio-reactor, which can load a uniform AC magnetic field stimulation on PC12 cells in the extracellular environment for enhancement of an axonal nerve extension and 3D nerve network generation. Simultaneously, we measure the morphology of PC12 cell bodies, axons, and dendrites by the multiphoton excitation fluorescence microscope (MPM) and evaluate the effectiveness of the uniform AC magnetic stimulation to enhance the axonal nerve extension. Firstly, we designed and fabricated the uniform AC magnetic field stimulation bio-reactor. For the AC magnetic stimulation system, we used the laminated silicon steel sheets for a yoke structure of 3D chamber, which had a high magnetic permeability. Next, we adopted the pole piece structure and installed similar specification coils on both sides of the yoke. We searched an optimum pole piece structure using the magnetic field finite element (FE) analyses and the response surface methodology. We confirmed that the optimum 3D chamber structure showed a uniform magnetic flux density in the PC12 cell culture area by using FE analysis. Then, we fabricated the uniform AC magnetic field stimulation bio-reactor by adopting analytically determined specifications, such as the size of chamber and electromagnetic conditions. We confirmed that measurement results of magnetic field in the chamber showed a good agreement with FE results. Secondly, we fabricated a dish, which set inside the uniform AC magnetic field stimulation of bio-reactor. PC12 cells were disseminated with collagen gel and could be 3D cultured in the dish. The collagen gel were poured in the dish. The collagen gel, which had a disk shape of 6 mm diameter and 3mm height, was set on the membrane filter, which was located at 4 mm height from the bottom of dish. The disk was full filled with the culture medium inside the dish. Finally, we evaluated the effectiveness of the uniform AC magnetic field stimulation to enhance the nurve axonal extension. We confirmed that a 6.8□ increase in the average axonal extension length of PC12 under the uniform AC magnetic field stimulation at 7 days culture in our bio-reactor, and a 24.7□ increase in the maximum axonal extension length. Further, we confirmed that a 60□ increase in the number of dendrites of PC12 under the uniform AC magnetic field stimulation. Finally, we confirm the availability of our uniform AC magnetic stimulation bio-reactor for the nerve axonal extension and the nerve network generation.

Keywords : nerve regeneration, axonal extension , PC12 cell, magnetic field, three-dimensional bio-reactor
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