KOSOMBE 2008년도

제37회 대한의용생체공학회 춘계학술대회

"Biomedical Optics in Korea"

포스터 I ~II

학생논문경연

구연 I ~IV

일시 : 2008년 5월 9일(금)-10일(토)

장소 : 충북대학교 개신문화관

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전기자극에 의한 Neuronal cell migration에 대한 연구

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A study of neuronal cell migration induced by electrical stimulation on microelectrode arrays

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Abstract

A variety of methods have been employed to control neuronal migration in neural networks. Recently, we found that electrical stimulation can induce neuronal cell migration in neural networks cultured for more than three weeks on microelectrode arrays (MEAs). Immunocytochemistry data showed that the aggregation of neurons was related to the emergence of glia in culture. In this study, when co-cultured with glia, we could induce neuronal migration at one week in culture by electrical stimulation while the same condition of stimulation caused neural necrosis in neuron-only cultures. In addition, the stimulation-induced migration was inhibited by blocking action potential in neural networks using voltage-gated sodium channel blocker, tetrodotoxin (TTX). These results indicate that neuronal cell migration is dependent on neuronal activity evoked by electrical stimulation. Thus, electrical stimulation may provide a useful means for modifying neural networks and improving the interface between electrodes and neurons.

Keywords: Electrical stimulation, Neuronal migration, Microelectrode array, Glia, Neuronal activity

Introduction

Cell migration plays a critical role in the nervous systems. Developing neurons constantly search for cues which help to target positions of neurons and form neuronal networks. Recently, we reported that neuronal cell migration was induced by electrical stimulation at specific conditions on Microelectrode arrays (MEAs). According to the previous results, however, even same electrical stimulation can induce either cellular migration or necrosis depending on the culture ages. In the present study, however, it is possible that even young hippocampal neurons can migrate by electrical stimulation because culturing with glia has an effect on the viability of neuronal cells to electrical stimulation. Moreover, to find out why neuron cells migrate to electrical stimulating electrode, we investigated whetherneuronal migration induced by electrical stimulation was activity-dependent

Materials & Methods

Microelectrode arrays (MEAs) were fabricated using a semiconductor process. MEAs were formed with 32 electrodes (48 array) and 200 um site spacing. The exposed area of each electrode site was 100um^2.

In cell culturing, hippocampal neurons were cultured from embryonic day 18 rat pups (SD rats). One group was to be cultured with glia in the plating medium for 5 days, the other group was cultured with serum-free Neurobasal media. At 5 DIV, the media of both groups were replaced with fresh serum-free Neurobasal media. All animal procedures were approved by Institute of Laboratory Animal Resources in Seoul National University.

In electrical stimulation, biphasic-current pulses with the 50 us pulse-width, 20 Hz pulses at 30 uA were applied to cultures at DIV 7 for all experiments. All electrical stimulating experiments were performed for 72 h unless cell death occurred.

Results

In neuron only case, cell debris and cell necrosis were observed around stimulating electrodes after electrical stimulation like the previous results. However, in the case of neuron cultured with glia, neuronal cell migration to stimulating electrodes was observed without cell death.
Above all things, on the assumption that neuronal migration is related to neuronal activity, neurons cultured with glia were stimulated with 500nM tetrodotoxin (TTX) to reduce increase of neuronal activity by electrical stimulation As a result, in the case of neurons stimulated with TTX, neuronal migration to stimulating electrode was not observed during electrical stimulation. Contrastively, it appeared that the case of ES without TTX showed the remarkable degree of cell migration before and after electrical stimulation.

Conclusion

These results described that neuronal cell migration induced by electrical stimulation is not caused by electrical force but dependent on increase in neuronal activity by electrical stimulation through blocking Na^+ channel. And in advance of previous research, even young hippocampal neurons cell migration was induced by electrical stimulation using co-culturing with glia.