Abstract

Neuronal activity can be recorded non-invasively and with a high degree of temporal resolution using multielectrode arrays (MEAs). However, the signals recorded with MEAs are small, usually 0.01%–0.1% of intracellular recordings. We recently showed that the amplitude of action potential recordings can be amplified ~6-fold by covering neuronal networks with an electrically resistive sheet, consisting of glial cells. However, further amplification is required to record smaller signals, such as the postsynaptic potentials. Here, we used equivalent circuit models to investigate theoretically the effect of resistive sheet impedance on the signal amplification. We show that by using a cell sheet with a resistance of over 1 MΩ, the signal amplification effect of the coverage reaches 100-times. This finding provides a quantitative guideline for future experiments aiming toward further increase of the signal.

1. Introduction

Multielectrode array (MEA) technology is widely used to record neuronal activity in from cultured neurons and brain slice preparations to study intrinsic neuronal dynamics [1,2] and the effect of electrical or pharmaceutical stimulations [3]. However, the amplitude of extracellularly recorded signals is usually small, in the order of ten to a hundred microvolts. This is 3–4 orders of magnitude lower than the intracellular change of membrane potential in an action potential (~100 mV).

We recently proposed a method to increase the signal amplitude taking advantage of the electrical resistivity of the cell’s plasma membrane [4]. By covering cultured neurons with a sheet of glial cells, impedance is inserted serially to the neuron-electrode seal. This amplifies the signal recorded with the extracellular electrode. Here, we used equivalent circuit simulation to quantitatively investigate the dependence of the signal amplification effect on the resistivity and the capacitance of the glial sheet.

2. Simulation methods

Circuit simulations were performed using TINA-TI (Texas Instrument). The passive analog circuit model and its correspondence with the neuronal cell-electrode interface are illustrated in Fig. 1. The circuit model was prepared based on a previous report [1], and the resistive glial sheet was inserted serially next to the non-junctional impedance, the voltage source and seal resistance. The equivalent circuit of measurement device was simplified only I-V converter and low-pass filter. Values for the junctional and non-junctional membrane impedances were obtained from the literature with appropriate modifications [1]. The parameters obtained from electrochemical impedance (EIS) measurements were used for the electrode and the glial sheet impedance. A depolarizing pulse mimicking a neuronal action potential (100 mV and 1 ms) was applied to the voltage source, and the amplitude of the output passed through filter was measured.

Fig. 1 (a) Schematic illustration depicting the relationship between an equivalent circuit model using analogue passive elements and actual experiment [4]. (b) Equivalent circuit model of TINA-TI composed impedance of cell membrane and electrode, and simplified circuit of measurement device.
3. Results and discussion

Previously, we studied experimentally the effect of covering cultured neurons with a glial sheet and observed that the signal amplitude increased nearly 6 times [4]. This effect was also confirmed in an equivalent circuit simulation. Insertion of a glial cell impedance ($R_g = 41 \, k\Omega$, $C_g = 114 \, pF$), which was measured experimentally through EIS measurements, to the circuit model (Fig. 1) increased the amplitude of output by 4.7 times [4].

Next we investigated the effect of impedance values on the signal amplitude. Although $R_g$ measured for the glial cell sheet was relatively small ($41 \, k\Omega$), the resistance of plasma membrane in the order of $\sim G\Omega$ [5]. Hence there remains a room for further improvement in its impedance.

Figure 2 shows the calculated amplitude for different values of the glial cell-sheet resistance. The amplitude are normalized relative to that calculated without the cell sheet. It indicates that when the resistance is over 1 M$\Omega$, the output signal increases more than nearly 20-times.

The effect of capacitance on the signal amplitude is summarized in Figure 3. Within the rage of the capacitance we simulated, it was found that the effect was minor compared to the resistance.

From these results, we can expect to have larger effect of glial cell sheet coverage by increasing its resistivity. This can be achieved, for example by culturing glial cells in multilayers [6] and pining in the interspace between glial cells or by using other types of cells that form tight-junctions, such as epithelial cells [7].

4. Conclusions

We used equivalent circuit models of neuron-electrode junction to study the effect of covering neurons with a resistive film. We found that the signal amplitude increases nearly 22-fold when the resistance of the resistive film is higher than 1 M$\Omega$. Combination of the method with other approaches of signal amplification, such as three-dimensionally structuring the chip electrodes [8], we can expect to have even larger signals. These technologies have the potential to expand the applications of MEA devices in fundamental studies and in biomedical applications.

Acknowledgements

The work was supported by the Research Fellowships for Young Scientists (No. 15J03545) and the Grant-in-Aid for Young Scientists (B) (No. 15K17449) from the Japan Society for the Promotion of Science, by the CREST Program from the Japan Science and Technology Agency, and by a research grant from the Asahi Glass Foundation. The authors wish to thank Professor Shutaro Katsurabayashi (Fukuoka University) for providing reagents and Mr. Hidesato Takaoki (Tohoku University) for technical support.

References