Long-term potentiation and depression phenomena in human induced pluripotent stem cell-derived cortical neurons

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Background
Plasticity such as long-term potentiation (LTP) and long-term potentiation depression (LTD) in neuronal networks has been analyzed using in vitro and in vivo techniques in simple animals to understand learning, memory, and development in brain function. Human induced pluripotent stem cell (hiPSC)-derived neurons may be effectively used for understanding the plasticity mechanism in human neuronal networks, thereby elucidating disease mechanisms and drug discoveries. In this study, we attempted the induction of LTP and LTD phenomena in a cultured hiPSC-derived cerebral cortical neuronal network using multi-electrode array (MEA) systems.

Material & Methods

-Cell Culture
  hiPSC-derived cerebral cortical neurons (hyCCNs; Axol Bioscience Inc., UK) were cultured (density, 1.0 × 10^5 cells/cm^2) on MEA chips (Med Scientific). The cultures were grown at 37°C in a 5% CO2/95% air atmosphere. Half of the media was exchanged from 5 to 7 days.

-Extracellular recording
  The extracellular signals in evoked responses and spontaneous firings were obtained by the MEA system (Med64-Basic; Alpha Med Scientific) and stored on a personal computer. A sampling rate of 20 kHz/channel and low cut filter of 100 Hz was used. The cultures were maintained at 37°C in a 5% CO2 incubator during the recordings and stimulation. Firing analyses were performed using Mobius software (Alpha Med-Scientific) and MATLAB.

Results

Result 1 Induction of LTP and LTD by HFS

We also detected LTP and LTD phenomena in a hiPSC-derived neuronal network as the change of spike pattern.

Result 2 Cross-correlation histogram (CCH)

The cross-correlation of responses revealed that spike patterns with specific timing were generated during LTP induction and disappeared during LTD induction and that the hiPSC-derived cortical neuronal network has the potential to repeatedly express the spike pattern with a precise timing change within 0.5 ms.

Result 3 Induction of late-phase long-term potentiation (L-LTP)-like plasticity

Induction of LTP-LTD by high frequency stimulation (HFS)

We detected LTP and LTD phenomena by high frequency stimulation (HFS). (A) Induction of LTP (a) The waveforms represent the typical evoked responses before and after HFS. The number of spikes was increased after stimulation. (b) Time course of the number of spikes in evoked responses at 45 ch before and after HFS for 60 min, respectively. Test stimuli were applied to 35 ch every 30 s. The average before HFS for 60 min presented 100%. (c) grids showing the 64 electrodes where colored electrodes changed the number of spikes per one stimulus. Electrodes that detected a higher increase of the number of spikes are shown in red (maximum: 14 spikes). (d) Histogram represents the number of electrodes in the change rate of the number of spikes. Bin size is 10%. (e) Psth stimulus time histogram (PSTH) (n = 120 experiments, at 64 electrodes) within 450 ms in evoked responses. Blue and red show before and after HFS, respectively. (B) Induction of LTD. (a) Typical evoked responses before and after HFS. (b) Time course of the number of spikes in evoked responses at 45 ch before and after HFS for 60 min, respectively. (c) grids showing the 64 electrodes where colored electrodes changed the number of spikes. (d) The number of electrodes in the changed rate of the number of spikes. (e) PSTH before and after HFS.

Conclusion

- HFS induced LTP and LTD phenomena in hiPSC-derived cortical neurons.
- Spike patterns were generated or disappeared in induction of plasticity.
- hiPSC-derived neurons express the spike pattern with a precise timing change.
- HFS induced LTP-LIKE plasticity and the change of synchronized burst firing.
- MEA system is beneficial for clarifying the function of hiPSC-derived neurons.

Reference


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