Induction of plasticity phenomena in human induced pluripotent stem cell-derived cortical neurons

Aoi Odawara¹, Naoki Matsuda¹, Gong Cheng², Ryan Arant² and Ikuro Suzuki³
¹Tohoku Institute of Technology, sendai, Japan, ²Alpha med scientific, Osaka, Japan

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 (hiCCNs; Axol Bioscience Inc., UK) were cultured (density, 1.0 × 10⁶ cells/cm²) on MEA chips (MED-PS15A; Alpha Med Scientific). The cultures were grown at 37°C in a 5% CO₂/95% air atmosphere. Half of the media was exchanged between 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.

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

(A) Poststimulus time histogram (PSTH) (n = 120 experiments, at 64 electrodes) within 450 ms in evoked responses before (blue), after 1 h (red), and 24 h (green). Test stimuli were applied to 52 ch at 115 days in vitro. It was a different sample from that shown in Fig. 3 (B, E) Grids showing the 64 electrodes where colored electrodes changed the number of spikes per one stimulus before and after 1 h (a) and before and after 24 h (B-b). After 24 h, 43 electrodes were increased and 4 electrodes were decreased. (E-b) After 1 h, 47 electrodes decreased. On the other hand, 23 electrodes increased and ten electrodes maintained a spike decrease. (C, F) Histogram of electrodes represent rate of changed number of spikes in an electrode. Bin size is 10%. (a) Change rate before and after 1 h. (b) Change rate before and after 24 h. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) (D) PSTH at test stimulus site 30 ms.

We also detected the phenomenon for late-phase LTP (L-LTP) like plasticity.

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

Reference