Functional characterization of iPS-derived neurons grown on micro electrode arrays (MEA) and their application to phenotypic modeling of disease models and neurotoxicity assessment in comparison to primary mouse cultures.

Introduction

Primary cultures are widely used for testing drug candidates in phenotypic in vitro models. Moreover, they serve as the gold standard and are used to evaluate human induced pluripotent stem cell-derived (hiPSC) neuronal cultures to transfer current models into the human background. The goal is to increase predictability, sensitivity and specificity.

We cultured different hiPSC-derived CNS neurons including TH dopaminergic hiPSC neurons on MEAs and recorded the spontaneous electrical network activity over weeks in culture using micro electrode arrays (MEAs).

Methods

Spinal train data sets from hiPSC neurons were compared with hundreds of data sets from primary mouse neuron/glial cultures from 4 different brain tissue cultures. grown on multi-electrode arrays (MEAs).

Primary culture: primary mouse tissue cultured from embryos (NMRI) were cultured on MEAs for 4 weeks.

hiPSC culture: we cultured Dopa.4U Neurons (AstroGenesis AG, Germany) on 12-well MEAs (Axion Biosystems) for 3-4 weeks.

Data analysis: multi-parametric data analysis of more than 200 spike train parameters and classification analysis were performed using NeuroProof software tools mNEuVEx and PatternExpert.

Results

Human iPS-derived Neurons: Dopa.4U

Acute functional response to receptor modulators is comparable between Dopa.4U and primary mouse cortex.

Conclusions

Primary cell cultures show brain region-specific activity pattern which can be clearly distinguished by pattern recognition methods. We show that the pattern complexity from hiPSC dopa neuron cultures is most similar to primary mouse ventral midbrain/cortex co-cultures and that this phenotype can be induced and restored thereby providing a means for in vitro disease modeling. In conclusion, well-characterized functional human iPS-derived neuronal in vitro systems and comparison to known primary models increase the predictive value for disease modeling, neurotoxicity assessment and compound screening.

Brain Region-Specific Cell Cultures with Unique Network Activity Patterns

MPP+ affects functional activity development of Dopa.4U neurons

Functional phenotype can be shifted and used as a readout for disease modeling

NeuroProof Technology

Phenotypic Screening with MEA-Neurochips

MAESTRO Recording System

Multimodal Characterization of Neuronal Network Activity

Feedback:

- Extracellular action potential on a single-neuron and network activity level
- Spatial neuronal activity changes as well as synchronization and oscillation in time scales of spikes and bursts
- Each specific spike train is described by 200 parameters in 6 categories:
  1. General Activity
  2. Burst Structure
  3. Oscillation
  4. Synchronization

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