Göteborg, 2022

Human iPSC-derived neuronal networks
Development and application for compound evaluation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 25 februari 2022, klockan 09.00

av Julia Izsak

Fakultetsopponent:

Professor Bastian Hengerer

Boehringer Ingelheim Pharma GmbH & Co-KG, Biberach, Germany

Avhandlingen baseras på följande delarbeten

I. Robust Generation of Person-Specific, Synchronously Active Neuronal Networks Using Purely Isogenic Human iPSC-3D Neural Aggregate Cultures. Izsak, J., Seth, H., Andersson, M., Vizlin-Hodzic, Dz., Theiss, S., Hanse, E., Ågren, H., Funa, K., Illes, S. *Front Neurosci.* 2019; 13:35

II. Human Cerebrospinal Fluid Promotes Neuronal Circuit Maturation of Human Induced Pluripotent Stem Cell-Derived 3D Neural Aggregates. Izsak, J., Seth, H., Theiss, S., Hanse, E., Illes, S. *Stem Cell Reports.* 2020; 14(6):1044-1059

III. TGF-β1 Suppresses Proliferation and Induces Differentiation in Human iPSC Neural in vitro Models. Izsak, J., Vizlin-Hodzic, Dz., Iljin, M., Strandberg, J., Jadasz, J., Olsson Bontell, T., Theiss, S., Hanse, E., Ågren, H., Funa, K., Illes, S. *Front Cell Dev Biol.* 2020; 8:571332

IV. Differential acute impact of therapeutically effective and overdose concentrations of lithium on human neuronal single cell and network function. Izsak, J., Seth, H., Iljin, M, Theiss, S., Ågren, H., Funa, K., Aigner, L., Hanse, E., Illes, S. *Transl Psychiatry.* 2021; 11(1):281

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Development and application for compound evaluation

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Abstract

Research on human brain development and function in health and disease has been hampered by limited access to primary human tissue and limited translatability of animal studies. This knowledge gap is encouraging the use of human induced pluripotent stem cell (hiPSC)-derived neural *in vitro* models. The current hope is that person-specific hiPSC-based *in vitro* models for human brain development and neuronal network function will increase the success in translating research results from bench to bedside. The aim of this thesis was to characterize and validate a person-specific human iPSC-based neural *in vitro* model to study the development, properties, and pharmacological modulation of human neuronal networks. In the first article we presented a procedure to generate 3D neural aggregates comprising astrocytes, oligodendrocytes and highly functional neurons that generated synchronous neuronal networks in less than three weeks. Further, by culturing hiPSC-derived 3D neural aggregates in human cerebrospinal fluid (hCSF), we demonstrated in article II that this adult brain-like milieu promotes morphological and functional maturation. Although hCSF is superior to currently used cell culture media, it has very limited availability for routine cell culturing purposes. This motivated the search for soluble factors that can mimic the observed maturational effects. In article III, we identified TGF-β1 as a physiologically relevant factor that can suppress proliferation and enhance neuronal and glial differentiation in a human 3D neural *in vitro* model. In article IV, we utilized this optimized model to provide insights in how therapeutically effective and overdose concentrations of lithium influence human single neuronal and network function. We showed that epileptiform discharges caused by overdose concentrations of lithium were suppressed by the antiepileptic drug Perampanel. The demonstrated functional impact of clinically relevant pharmacological compounds on human neuronal network function represents a proof-of-concept for the enhanced translational value of the human 3D neural aggregate *in vitro* model. The work presented in this thesis advances the field with a fast functional isogenic *in vitro* hiPSC-derived neuronal network model with improved physiological relevance and applicability for drug evaluation. Hopefully, our findings will bring the field of neuroscience closer to more translatable modeling and more successful clinical trials in the future.

Keywords: human induced pluripotent stem cell, neuronal network, microelectrode array, *in vitro*

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