A Computational Model of Interactions Between Neuronal and Astrocytic Networks: The Role of Astrocytes in the Stability of the Neuronal Firing Rate

Recent research in neuroscience indicates the importance of tripartite synapses and gliotransmission mediated by astrocytes in neuronal system modulation. Although the astrocyte and neuronal network functions are interrelated, they are fundamentally different in their signaling patterns and, possibly, the time scales at which they operate. However, the exact nature of gliotransmission and the effect of the tripartite synapse function at the network level are currently elusive. In this paper, we propose a computational model of interactions between an astrocyte network and a neuron network, starting from tripartite synapses and spanning to a joint network level. Our model focuses on a two-dimensional setup emulating a mixed in vitro neuron-astrocyte cell culture. The model depicts astrocyte-released gliotransmitters exerting opposing effects on the neurons: increasing the release probability of the presynaptic neuron while hyperpolarizing the post-synaptic one at a longer time scale. We simulated the joint networks with various levels of astrocyte contributions and neuronal activity levels. Our results indicate that astrocytes prolong the burst duration of neurons, while restricting hyperactivity. Thus, in our model, the effect of astrocytes is homeostatic; the firing rate of the network stabilizes to an intermediate level independently of neuronal base activity. Our computational model highlights the plausible roles of astrocytes in interconnected astrocytic and neuronal networks. Our simulations support recent findings in neurons and astrocytes in vivo and in vitro suggesting that astrocytic networks provide a modulatory role in the bursting of the neuronal network.

General information

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Contributors: Lenk, K., Satuvuori, E., Lallouette, J., Ladrón-de-Guevara, A., Berry, H., Hyttinen, J. A. K.
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INT=bmte,"Satuvuori, Eero"
INT=bmte,"Ladrón-de-Guevara, Antonio"
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Research output: Contribution to journal › Article › Scientific › peer-review

Unique Features of Network Bursts Emerge From the Complex Interplay of Excitatory and Inhibitory Receptors in Rat Neocortical Networks

Spontaneous network activity plays a fundamental role in the formation of functional networks during early development. The landmark of this activity is the recurrent emergence of intensive time-limited network bursts (NBs) rapidly spreading across the entire dissociated culture in vitro. The main excitatory mediators of NBs are glutamatergic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-Methyl-D-aspartic-acid receptors (NMDARs) that express fast and slow ion channel kinetics, respectively. The fast inhibition of the activity is mediated through gamma-aminobutyric acid type A receptors ($GABA_A$Rs). Although the AMPAR, NMDAR and $GABA_A$R kinetics have been biophysically characterized in detail at the monosynaptic level in a variety of brain areas, the unique features of NBs emerging from the kinetics and the complex interplay of these receptors are not well understood. The goal of this study is to analyze the contribution of fast $GABA_A$Rs on AMPAR- and NMDAR- mediated spontaneous NB activity in dissociated neonatal rat cortical cultures at 3 weeks in vitro. The networks were probed by both acute and gradual application of each excitatory receptor antagonist and combinations of acute excitatory and inhibitory receptor antagonists. At the same time, the extracellular network-wide activity was recorded with microelectrode arrays (MEAs). We analyzed the characteristic NB measures extracted from NB rate profiles and the distributions of interspike intervals, interburst intervals, and electrode recruitment time as well as the similarity of spatio-temporal patterns of network activity under different receptor antagonists. We show that NBs were rapidly initiated and recruited as well as diversely propagated by AMPARs and temporally and spatially maintained by NMDARs. $GABA_A$Rs reduced the spiking frequency in AMPAR-mediated networks and dampened the termination of NBs in NMDAR-mediated networks as well as slowed down the recruitment of activity in all networks. Finally, we show characteristic super bursts composed of slow NBs with highly repetitive spatio-temporal

patterns in gradually AMPAR blocked networks. To the best of our knowledge, this study is the first to unravel in detail how the three main mediators of synaptic transmission uniquely shape the NB characteristics, such as the initiation, maintenance, recruitment and termination of NBs in cortical cell cultures in vitro.

General information

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Contributors: Teppola, H., Aćimović, J., Linne, M. L.
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Research output: Contribution to journal › Article › Scientific › peer-review

Reduced level of docosahexaenoic acid shifts GPCR neuroreceptors to less ordered membrane regions

G protein-coupled receptors (GPCRs) control cellular signaling and responses. Many of these GPCRs are modulated by cholesterol and polyunsaturated fatty acids (PUFAs) which have been shown to co-exist with saturated lipids in ordered membrane domains. However, the lipid compositions of such domains extracted from the brain cortex tissue of individuals suffering from GPCR-associated neurological disorders show drastically lowered levels of PUFAs. Here, using free energy techniques and multiscale simulations of numerous membrane proteins, we show that the presence of the PUFA DHA helps helical multi-pass proteins such as GPCRs partition into ordered membrane domains. The mechanism is based on hybrid lipids, whose PUFA chains coat the rough protein surface, while the saturated chains face the raft environment, thus minimizing perturbations therein. Our findings suggest that the reduction of GPCR partitioning to their native ordered environments due to PUFA depletion might affect the function of these receptors in numerous neurodegenerative diseases, where the membrane PUFA levels in the brain are decreased. We hope that this work inspires experimental studies on the connection between membrane PUFA levels and GPCR signaling.

General information

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Organisations: Physics, University of Helsinki, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Universitat Autònoma de Barcelona, University of Texas Health Science Center at Houston, MEMPHYS
Contributors: Javanainen, M., Enkavi, G., Guixà-Gonzaléz, R., Kulig, W., Martinez-Seara, H., Levental, I., Vattulainen, I.
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Viability of Mouse Retinal Explant Cultures Assessed by Preservation of Functionality and Morphology
Purpose: Retinal explant cultures provide simplified systems where the functions of the retina and the effects of ocular therapies can be studied in an isolated environment. The purpose of this study was to provide insight into long-term preservation of retinal tissue in culture conditions, enable a deeper understanding of the interdependence of retinal morphology and function, and ensure the reliability of the explant technique for prolonged experiments. Methods: Retinal explants from adult mice were cultured as organotypic culture at the air-medium interface for 14 days in vitro (DIV). Retinal functionality was assessed by multielectrode array technique and morphology by immunohistochemical methods at several time points during culture. Results: Retinal explants retained viability for 14 DIV, although with diminishing neuronal activity, progressing neuronal loss, and increasing reactive gliosis. We recorded spontaneous retinal ganglion cell (RGC) activity up to 14 DIV with temporally changing distribution of RGC firing rates. Light responsiveness was measurable from RGCs for 7 DIV and from photoreceptors for 2 DIV. Apoptotic cells were detected beginning at 3 DIV with their density peaking at 7 DIV. The number of RGCs gradually decreased by 70% during 14 DIV. The change was accompanied by the loss of RGC functionality, resulting in 84% loss of electrically active RGCs. Conclusions: Retinal explants provide a valuable tool for studies of retinal functions and development of ocular therapies. However, critical for long-term use, retinal functionality was lost before structural loss, emphasizing a need for both functional and morphologic readouts to determine the overall state of the cultured retina.

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Contributors: Alarautalahti, V., Ragauskas, S., Hakkarainen, J. J., Uusitalo-Järvinen, H., Uusitalo, H., Hyttinen, J., Kalesnykas, G., Nymark, S.
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DUPL=47898722
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Source ID: 85065551723
Research output: Contribution to journal › Article › Scientific › peer-review

Advances in Human Stem Cell-Derived Neuronal Cell Culturing and Analysis

This chapter provides an overview of the current stage of human in vitro functional neuronal cultures, their biological application areas, and modalities to analyze their behavior. During the last 10 years, this research area has changed from being practically non-existent to one that is facing high expectations. Here, we present a case study as a comprehensive short history of this process based on extensive studies conducted at NeuroGroup (University of Tampere) and Computational Biophysics and Imaging Group (Tampere University of Technology), ranging from the differentiation and culturing of human pluripotent stem cell (hPSC)-derived neuronal networks to their electrophysiological analysis. After an introduction to neuronal differentiation in hPSCs, we review our work on their functionality and approaches for extending cultures from 2D to 3D systems. Thereafter, we discuss our target applications in neuronal developmental modeling, toxicology, drug screening, and disease modeling. The development of signal analysis methods was required due to the unique functional and developmental properties of hPSC-derived neuronal cells and networks, which separate them from their much-used rodent counterparts. Accordingly, a line of microelectrode array (MEA) signal analysis methods was developed. This work included the development of action potential spike detection methods, entropy-based methods and additional methods for burst detection and quantification, joint analysis of spikes and bursts to analyze the spike waveform compositions of bursts, assessment methods for network synchronization, and computational simulations of synapses and neuronal networks.

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Organisations: Research group: Computational Biophysics and Imaging Group, BioMediTech, NeuroGroup, Danish Research Institute of Translational Neuroscience - DANDRITE, Aarhus Universitet, Department of Biomedicine, Tampere University
Contributors: Ylä-Outinen, L., Tanskanen, J. M., Kapucu, F. E., Hyysalo, A., Hyttinen, J. A., Narkilahti, S.
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Astrocyte lineage cells are essential for functional neuronal differentiation and synapse maturation in human iPSC-derived neural networks

Human astrocytes differ dramatically in cell morphology and gene expression from murine astrocytes. The latter are well known to be of major importance in the formation of neuronal networks by promoting synapse maturation. However, whether human astrocyte lineage cells have a similar role in network formation has not been firmly established. Here, we investigated the impact of human astrocyte lineage cells on the functional maturation of neural networks that were derived from human induced pluripotent stem cells (hiPSCs). Initial in vitro differentiation of hiPSC-derived neural progenitor cells and immature neurons (glia+ cultures) resulted in spontaneously active neural networks as indicated by synchronous neuronal Ca^{2+} transients. Depleting proliferating neural progenitors from these cultures by short-term antimitotic treatment

resulted in strongly astrocyte lineage cell-depleted neuronal networks (glia− cultures). Strikingly, in contrast to glia+ cultures, glia− cultures did not exhibit spontaneous network activity. Detailed analysis of the morphological and electrophysiological properties of neurons by patch clamp recordings revealed reduced dendritic arborization in glia− cultures. In addition, a reduced action potential frequency upon current injection in pyramidal-like neurons was observed, whereas the electrical excitability of multipolar neurons was unaltered. Furthermore, we found a reduced dendritic density of PSD95-positive excitatory synapses, and more immature properties of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) miniature excitatory postsynaptic currents (mEPSCs) in glia− cultures, suggesting that the maturation of glutamatergic synapses depends on the presence of hiPSC-derived astrocyte lineage cells. Intriguingly, addition of the astrocyte-derived synapse maturation inducer cholesterol increased the dendritic density of PSD95-positive excitatory synapses in glia− cultures.

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Data-driven study of synchronous popula on ac vity in generic spiking neuronal networks: How much do we capture using the minimal model for the considered phenomena?

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Organisations: Faculty of Biomedical Sciences and Engineering, Research group: Computational Neuro Science-CNS, Research group: Computational Neuro Science-CNS
Contributors: Acimovic, J., Teppola, H., Mäki-Marttunen, T. M., Linne, M.
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Assessment of mutation probabilities of KRAS G12 missense mutants and their long-timescale dynamics by atomistic molecular simulations and Markov state modeling

A mutated KRAS protein is frequently observed in human cancers. Traditionally, the oncogenic properties of KRAS missense mutants at position 12 (G12X) have been considered as equal. Here, by assessing the probabilities of occurrence of all KRAS G12X mutations and KRAS dynamics we show that this assumption does not hold true. Instead, our findings revealed an outstanding mutational bias. We conducted a thorough mutational analysis of KRAS G12X mutations and assessed to what extent the observed mutation frequencies follow a random distribution. Unique tissue-specific frequencies are displayed with specific mutations, especially with G12R, which cannot be explained by random probabilities. To clarify the underlying causes for the nonrandom probabilities, we conducted extensive atomistic molecular dynamics simulations (170 μs) to study the differences of G12X mutations on a molecular level. The simulations revealed an allosteric hydrophobic signaling network in KRAS, and that protein dynamics is altered among the G12X mutants and

as such differs from the wild-type and is mutation-specific. The shift in long-timescale conformational dynamics was confirmed with Markov state modeling. A G12X mutation was found to modify KRAS dynamics in an allosteric way, which is especially manifested in the switch regions that are responsible for the effector protein binding. The findings provide a basis to understand better the oncogenic properties of KRAS G12X mutants and the consequences of the observed nonrandom frequencies of specific G12X mutations.

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Organisations: Physics, Research group: Biological Physics and Soft Matter, University of Eastern Finland, University Hospital Tuebingen, Eberhard-Karls University Tuebingen, University of Helsinki, MEMPHYS-Center for Biomembrane Physics
Contributors: Pantsar, T., Rissanen, S., Dauch, D., Laitinen, T., Vattulainen, I., Poso, A.
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Concerted regulation of npc2 binding to endosomal/lysosomal membranes by bis(monoacylglycero)phosphate and sphingomyelin
Niemann-Pick Protein C2 (npc2) is a small soluble protein critical for cholesterol transport within and from the lysosome and the late endosome. Intriguingly, npc2-mediated cholesterol transport has been shown to be modulated by lipids, yet the molecular mechanism of npc2-membrane interactions has remained elusive. Here, based on an extensive set of atomistic simulations and free energy calculations, we clarify the mechanism and energetics of npc2-membrane binding and characterize the roles of physiologically relevant key lipids associated with the binding process. Our results capture in atomistic detail two competitively favorable membrane binding orientations of npc2 with a low interconversion barrier. The first binding mode (Prone) places the cholesterol binding pocket in direct contact with the membrane and is characterized by membrane insertion of a loop (V59-M60-G61-I62-P63-V64-P65). This mode is associated with cholesterol uptake and release. On the other hand, the second mode (Supine) places the cholesterol binding pocket away from the membrane surface, but has overall higher membrane binding affinity. We determined that bis(monoacylglycero)phosphate (bmp) is specifically required for strong membrane binding in Prone mode, and that it cannot be substituted by other anionic lipids. Meanwhile, sphingomyelin counteracts bmp by hindering Prone mode without affecting Supine mode. Our results provide concrete evidence that lipids modulate npc2-mediated cholesterol transport either by favoring or disfavoring Prone mode and that they impose this by modulating the accessibility of bmp for interacting with npc2. Overall, we provide a mechanism by which npc2-mediated cholesterol transport is controlled by the membrane composition and how npc2-lipid interactions can regulate the transport rate.

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Organisations: Physics, Research group: Biological Physics and Soft Matter, University of Helsinki, FIN-00014 University of Helsinki, Minerva Foundation Institute for Medical Research Helsinki, Memphys—Center for Biomembrane Physics, Laboratory of Physics
Contributors: Enkavi, G., Mikkolainen, H., Güngör, B., Ikonen, E., Vattulainen, I.
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Atomistic fingerprint of hyaluronan–CD44 binding

Hyaluronan is a polyanionic, megadalton-scale polysaccharide, which initiates cell signaling by interacting with several receptor proteins including CD44 involved in cell-cell interactions and cell adhesion. Previous studies of the CD44 hyaluronan binding domain have identified multiple widespread residues to be responsible for its recognition capacity. In contrast, the X-ray structural characterization of CD44 has revealed a single binding mode associated with interactions that involve just a fraction of these residues. In this study, we show through atomistic molecular dynamics simulations that hyaluronan can bind CD44 with three topographically different binding modes that in unison define an interaction fingerprint, thus providing a plausible explanation for the disagreement between the earlier studies. Our results confirm that the known crystallographic mode is the strongest of the three binding modes. The other two modes represent metastable configurations that are readily available in the initial stages of the binding, and they are also the most frequently observed modes in our unbiased simulations. We further discuss how CD44, fostered by the weaker binding modes, diffuses along HA when attached. This 1D diffusion combined with the constrained relative orientation of the diffusing proteins is likely to influence the aggregation kinetics of CD44. Importantly, CD44 aggregation has been suggested to be a possible mechanism in CD44-mediated signaling.

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Organisations: Physics, Research group: Biological Physics and Soft Matter, University of Helsinki, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic
Contributors: Vuorio, J., Vattulainen, I., Martinez-Seara, H.
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Network-wide adaptive burst detection depicts neuronal activity with improved accuracy

Neuronal networks are often characterized by their spiking and bursting statistics. Previously, we introducedan adaptive burst analysis methodwhich enhances the analysis power for neuronal networks with highly varying firing dynamics. The adaptation is based on single channels analyzing each element of a network separately. Such kind of analysis was adequate for the assessment of local behavior, where the analysis focuses on the neuronal activity in the vicinity of a single electrode. However, the assessment of the whole network may be hampered, if parts of the network are analyzed using different rules. Here, we test how using multiple channels and measurement time points affect adaptive burst detection. The main emphasis is, if network-wide adaptive burst detection can provide new insights into the assessment of network activity. Therefore, we propose a modification to the previously introduced inter-spike interval (ISI) histogram based cumulative moving average (CMA) algorithm to analyze multiple spike trains simultaneously. The network size can be freely defined, e.g., to include all the electrodes in a microelectrode array (MEA) recording. Additionally, the method can be applied on a series of measurements on the same network to pool the data for statistical analysis. Firstly, we apply both the original CMA-algorithm and our proposed network-wide CMA-algorithm on artificial spike trains to investigate how the modification changes the burst detection. Thereafter, we use the algorithms on MEA data of spontaneously active chemically manipulated in vitro rat cortical networks. Moreover, we compare the synchrony of the detected bursts introducing a new burst synchrony measure. Finally, we demonstrate howthe bursting statistics can be used to classify networks by applying k-means clustering to the bursting statistics. The results showthat the proposed network wide adaptive burst detection provides a method to unify the burst definition in the whole network and thus improves the assessment and classification of the neuronal activity, e.g., the effects of different pharmaceuticals. The results indicate that the novel method is adaptive enough to be usable on networks with different dynamics, and it is especially feasible when comparing the behavior of differently spiking networks, for example in developing networks.

General information

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Morphological Differentiation Towards Neuronal Phenotype of SH-SY5Y Neuroblastoma Cells by Estradiol, Retinoic Acid and Cholesterol

Human SH-SY5Y neuroblastoma cells maintain their potential for differentiation and regression in culture conditions. The induction of differentiation could serve as a strategy to inhibit cell proliferation and tumor growth. Previous studies have shown that differentiation of SH-SY5Y cells can be induced by all-trans-retinoic-acid (RA) and cholesterol (CHOL).

However, signaling pathways that lead to terminal differentiation of SH-SY5Y cells are still largely unknown. The goal of this study was to examine in the RA and CHOL treated SH-SY5Y cells the additive impacts of estradiol (E_2) and brain-derived neurotrophic factor (BDNF) on cell morphology, cell population growth, synaptic vesicle recycling and presence of neurofilaments. The above features indicate a higher level of neuronal differentiation. Our data show that treatment for 10 days in vitro (DIV) with RA alone or when combined with E_2 (RE) or CHOL (RC), but not when combined with BDNF (RB), significantly ($p < 0.01$) inhibited the cell population growth. Synaptic vesicle recycling, induced by high-K^+ depolarization, was significantly increased in all treatments where RA was included (RE, RC, RB, RCB), and when all agents were added together (RCBE). Specifically, our results show for the first time that E_2 treatment can alone increase synaptic vesicle recycling in SH-SY5Y cells. This work contributes to the understanding of the ways to improve suppression of neuroblastoma cells' population growth by inducing maturation and differentiation.

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Contributors: Teppola, H., Sarkanen, J. R., Jalonen, T. O., Linne, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

The effects of neuron morphology on graph theoretic measures of network connectivity: The analysis of a two-level statistical model

We developed a two-level statistical model that addresses the question of how properties of neurite morphology shape the large-scale network connectivity. We adopted a low-dimensional statistical description of neurites. From the neurite model description we derived the expected number of synapses, node degree, and the effective radius, the maximal distance between two neurons expected to form at least one synapse. We related these quantities to the network connectivity described using standard measures from graph theory, such as motif counts, clustering coefficient, minimal path length, and small-world coefficient. These measures are used in a neuroscience context to study phenomena from synaptic connectivity in the small neuronal networks to large scale functional connectivity in the cortex. For these measures we provide analytical solutions that clearly relate different model properties. Neurites that sparsely cover space lead to a small effective radius. If the effective radius is small compared to the overall neuron size the obtained networks share similarities with the uniform random networks as each neuron connects to a small number of distant neurons. Large neurites with densely packed branches lead to a large effective radius. If this effective radius is large compared to the neuron size, the obtained networks have many local connections. In between these extremes, the networks maximize the variability of connection repertoires. The presented approach connects the properties of neuron morphology with large scale network properties without requiring heavy simulations with many model parameters. The two-steps procedure provides an easier interpretation of the role of each modeled parameter. The model is flexible and each of its components can be further expanded. We identified a range of model parameters that maximizes variability in network connectivity, the property that might affect network capacity to exhibit different dynamical regimes.

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Organisations: Research group: Computational Neuro Science-CNS, Department of Signal Processing, University of Oslo
Contributors: Acimovic, J., Mäki-Marttunen, T., Linne, M.
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Keywords: Graph theory, Motifs, Network connectivity, Neurite density field, Neuron morphology, Theoretical model
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Podocyte apoptosis is prevented by blocking the Toll-like receptor pathway
High serum lipopolysaccharide (LPS) activity in normoalbuminuric patients with type 1 diabetes (T1D) predicts the progression of diabetic nephropathy (DN), but the mechanisms behind this remain unclear. We observed that treatment of cultured human podocytes with sera from normoalbuminuric T1D patients with high LPS activity downregulated 3-phosphoinositide-dependent kinase-1 (PDK1), an activator of the Akt cell survival pathway, and induced apoptosis. Knockdown of PDK1 in cultured human podocytes inhibited antiapoptotic Akt pathway, stimulated proapoptotic p38 MAPK pathway, and increased apoptosis demonstrating an antiapoptotic role for PDK1 in podocytes. Interestingly, PDK1 was downregulated in the glomeruli of diabetic rats and patients with type 2 diabetes before the onset of proteinuria, further suggesting that reduced expression of PDK1 associates with podocyte injury and development of DN. Treatment of podocytes in vitro and mice in vivo with LPS reduced PDK1 expression and induced apoptosis, which were prevented by inhibiting the Toll-like receptor (TLR) signaling pathway with the immunomodulatory agent GIT27. Our data show that LPS downregulates the cell survival factor PDK1 and induces podocyte apoptosis, and that blocking the TLR pathway with GIT27 may provide a non-nephrotoxic means to prevent the progression of DN.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Helsinki, Department of Pathology, Laboratory Animal Centre, Helsinki University Central Hospital, Folkhälsan Institute of Genetics, Division of Nephrology, Diabetes and Obesity Research Program, University of Bristol, Baker IDI Heart and Diabetes Institute
Contributors: Saurus, P., Kuusela, S., Lehtonen, E., Hyvönen, M. E., Ristola, M., Fogarty, C. L., Tienari, J., Lassenius, M. I., Forsblom, C., Lehto, M., Saleem, M. A., Groop, P. H., Holthöfer, H., Lehtonen, S.
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Source: Scopus
Source ID: 84940860220
Research output: Contribution to journal › Article › Scientific › peer-review

Effects of cytokine activation and oxidative stress on the function of the human embryonic stem cell–derived retinal pigment epithelial cells
PURPOSE. In several retinal complications, such as age-dependent macular degeneration (AMD), oxidative stress is increased and cytokine level is elevated. These are shown to alter the activation and expression of matrix metalloproteinase (MMP) both in human primary and immortalized retinal pigment epithelial (RPE) cells. However, the effects on human embryonic stem cell (hESC)–derived RPE cells remain to be elucidated. METHODS. The mature hESC-RPE cells were exposed to inflammatory cytokines (IFN-γ or TNF-α) for 24 hours or oxidative stress (H_2O_2) for 1 hour. Effects on barrier properties were analyzed with transepithelial electrical resistance (TEER), the expression of MMP-1,

MMP-2, MMP-3, MMP-9, collagen I, and collagen IV genes with quantitative RT-PCR, and the expression of MMP- 1 and MMP-3 proteins with Western blot or ELISA, respectively. Also, activation and secretion of MMP-2 and -9 proteins were analyzed with zymography. RESULTS. In normal state, mature hESC-RPE cells expressed MMP-1, -2, -3, and -9 genes in low levels, respectively. Tumor necrosis factor-α increased MMP-1 and -2 gene expression, and H_2O_2 increased MMP-3 and -9 gene expression. Zymography revealed IFN-γ– and TNF-α– induced secretion of MMP-2 and high-molecular-weight species of MMP (HMW MMP), but H_2O_2 decreased their secretion. Furthermore, TNF-α and H_2O_2 significantly decreased barrier properties. CONCLUSIONS. Here, cytokines induced the MMP-1 and -2 gene and protein expression. Also, H_2O_2 induced MMP-3 and -9 gene expression, but not their protein secretion. These data propose that under oxidative stress and cytokine stimuli, mature hESC-RPE cells resemble their native counterpart in the human eye in regard to MMP secretion and expression and could be used to model retinal disorders involving alterations in MMP activity such as AMD, diabetic retinopathy, or proliferative vitreoretinopathy in vitro.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Computer Science Institute, Fimlab Laboratories Ltd
Contributors: Juuti-Uusitalo, K., Nieminen, M., Treumer, F., Ampuja, M., Kallioniemi, A., Klettner, A., Skottman, H.
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Research output: Contribution to journal › Article › Scientific › peer-review

Patient-specific induced pluripotent stem cell—derived RPE cells: Understanding the pathogenesis of retinopathy in long-chain 3-hydroxyacyl-CoA dehydrogenase deiciency

Purpose. Retinopathy is an important manifestation of trifunctional protein (TFP) deficiencies but not of other defects of fatty acid oxidation. The common homozygous mutation in the TFP a-subunit gene HADHA (hydroxyacyl-CoA dehydrogenase), c.1528G>C, affects the long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) activity of TFP and blindness in infancy. The pathogenesis of the retinopathy is unknown. This study aimed to utilize human induced pluripotent stem cell (hiPSC) technology to create a disease model for the disorder, and to derive clues for retinopathy pathogenesis. Methods. We implemented hiPSC technology to generate LCHAD deficiency (LCHADD) patient-specific retinal pigment epithelial (RPE) monolayers. These patient and control RPEs were extensively characterized for function and structure, as well as for lipid composition by mass spectrometry. Results. The hiPSC-derived RPE monolayers of patients and controls were functional, as they both were able to phagocytose the photoreceptor outer segments in vitro. Interestingly, the patient RPEs had intense cytoplasmic neutral lipid accumulation, and lipidomic analysis revealed an increased triglyceride accumulation. Further, patient RPEs were small and irregular in shape, and their tight junctions were disorganized. Their ultratructure showed decreased pigmentation, few melanosomes, and more melanolysosomes. Conclusions. We demonstrate that the RPE cell model reveals novel early pathogenic changes in LCHADD retinopathy, with robust lipid accumulation, inefficient pigmentation that is evident soon after differentiation, and a defect in forming tight junctions inducing apoptosis. We propose that LCHADD-RPEs are an important model for mitochondrial TFP retinopathy, and that their early pathogenic changes contribute to infantile blindness of LCHADD.

General information

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Organisations: BioMediTech, Integrated Technologies for Tissue Engineering Research (ITTE), University of Helsinki, BioMediTech, VTT Technical Research Centre of Finland, Children’s Hospital, Helsinki University Central Hospital

Contributors: Polinati, P. P., Ilmarinen, T., Trokovic, R., Hyotylainen, T., Otonkoski, T., Suomalainen, A., Skottman, H., Tynitiina, T.
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In silico study on structure and dynamics in bursting neuronal networks
In vitro cell cultures have been widely used as a model system for studying neuronal development and electroresponsiveness in the absence of in vivo regulation. These networks are characterized by population bursts that vary largely in both frequency and shape (Wagenaar et al., BMC Neurosci. 2000). In this work we study the interplay of structure and activity in simulated spontaneously bursting networks. The computational approach is useful due to the difficulty of gaining enough control on the structure in in vitro experiments, although promising attempts are being made in cultured neuronal networks (Wheeler, Proc. IEEE 2010). Recently, the effect of network structure on activity has been analyzed through, e.g., the degree distribution width (Roxin, Front. Comp. Neurosci. 2011) and occurrence of second-order connections (Zhao et al. 2011, Front. Comp. Neurosci. 2011). In the present work we apply a set of graph measures to a wide set of different networks in order to determine which of the structural measures are relevant in the prediction of the bursting network activity. The network activity is quantified using standard measures such as number of bursts and burst duration.
We use two neuron models that are applicable to small (N=100) spontaneously bursting networks, namely, an integrate-and-fire model with short-term plasticity (Tsodyks et al., J. Neurosci. 2000) and a more detailed point-neuron model with four ionic and three synaptic currents (Golomb et al., J. Neurophysiol. 2006). We show that when the in-degree is sharp (binomial), the network activity is best predicted by using the clustering coefficient of the underlying graph. By contrast, when a broad in-degree is used (power-law), the maximum eigenvalue of the connectivity matrix becomes dominant in predicting the network activity. The results are consistent across the two neuron models. In our work the neurons are identical by their features, and no input is applied to the network, and hence all statistical difference between the compared networks is caused by the network structure and the network structure only.
The obtained results shed light on the relevance of different aspects of structure. In in vivo applications the full connectome is rarely accessible, but estimates of certain structural measures may be assessed indirectly (Vlachos et al., PLoS Comp. Biol. 2012). Extracting the structure-function relationship in neuronal networks may have implication on both the way experiments are conducted and on how biologically inspired artificial intelligence will be designed in the future.

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Contributors: Mäki-Marttunen, T. M., Acimovic, J., Ruohonen, K. P., Linne, M.
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Publisher: Society for Neuroscience (SfN)
Article number: 300.26/DDD70
ASJC Scopus subject areas: Cellular and Molecular Neuroscience, Neuroscience (miscellaneous), Applied Mathematics
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http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=11797e11-d125-4e7e-b77e-b19fd7d32528&cKey=34320433-3c96-47d0-97cc-fa64305a073f&mKey=%7b70007181-01C9-4DE9-A0A2-EEBFA14CD9F1%7d

Research output: Chapter in Book/Report/Conference proceeding › Conference contribution › Scientific › peer-review

Significance of graph theoretic measures in predicting neuronal network activity

One of the most prominent patterns of activity observed in developing cortical neuronal networks in vitro is network-wide spontaneous bursting (Wagenaar et al. 2005). In this work, we study computationally the spontaneous emergence of bursts and the effect of network structure on burst shape and frequency. Recent computational structure-function approaches show the effect of, e.g., second-order connections (Zhao et al. 2011) and degree distribution widths (Roxin 2011) on activity patterns. We aim to study a wider set of graph-theoretical measures using networks with identical in-degree distributions. We apply a biophysically plausible point-neuron model of a cortical cell (Golomb et al. 2006). The model network consists of a small (N=100) number of neurons, both excitatory pyramidal neurons and inhibitory interneurons. A model of short-term depression (Golomb and Amitai 1997) is used for glutamatergic synapses. The activity simulation is run over a wide set of classes of network structure. To quantify the structure of the network, we consider graph theoretical measures such as clustering coefficient, geodesic path length, node-betweenness and occurrence of different motifs. We restrict to unweighted bidirectional graph representation, hence the synaptic weights between the neurons are uniform. We study the significance of different graph theoretic measures using a prediction framework: How well can a bursting property, such as burst duration or frequency, be estimated using various measures of structure as attributes? We show that the prediction of bursting properties is improved by taking one or more of the aforementioned measures as prediction attributes. It is best improved when the prediction is based on the clustering coefficient or occurrence of the most highly connected motifs. We confirm the results using a noise-driven LIF model with short-term depression (Tsodyks et al. 2000). We conclude that the significance of measures of clustering is prominent compared to other measures of structure.

General information

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Organisations: Department of Signal Processing, Faculty of Biomedical Sciences and Engineering, Research group: Computational Neuro Science-CNS, Research group: Computational Neuro Science-CNS
Contributors: Mäki-Marttunen, T. M., Acimovic, J., Ruohonen, K. P., Linne, M.
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ASJC Scopus subject areas: Cellular and Molecular Neuroscience, Neuroscience (miscellaneous), Applied Mathematics
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http://cosyne.org/cosyne12/Cosyne2012_program_book.pdf

Research output: Chapter in Book/Report/Conference proceeding › Conference contribution › Scientific › peer-review

Inhibition of Casein kinase-2 induces p53-dependent cell cycle arrest and sensitizes glioblastoma cells to tumor necrosis factor (TNFα)-induced apoptosis through SIRT1 inhibition

Glioblastoma multiforme (GBM) are resistant to TNFα-induced apoptosis and blockade of TNFα-induced NF-κB activation sensitizes glioma cells to apoptosis. As Casein kinase-2 (CK2) induces aberrant NF-κB activation and as we observed elevated CK2 levels in GBM tumors, we investigated the potential of CK2 inhibitors (CK2-Is)-DRB and Apigenin in sensitizing glioma cells to TNFα-induced apoptosis. CK2-Is and CK2 small interfering RNA (siRNA) reduced glioma cell viability, inhibited TNFα-mediated NF-κB activation, and sensitized cell to TNFα-induced apoptosis. Importantly, CK2-Is activated p53 function in wild-type but not in p53 mutant cells. Activation of p53 function involved its increased transcriptional activation, DNA-binding ability, increased expression of p53 target genes associated with cell cycle progression and apoptosis. Moreover, CK2-Is decreased telomerase activity and increased senescence in a p53-dependent manner. Apoptotic gene profiling indicated that CK2-Is differentially affect p53 and TNFα targets in p53 wild-type and mutant glioma cells. CK2-I decreased MDM2-p53 association and p53 ubiquitination to enhance p53 levels. Interestingly, CK2-Is downregulated SIRT1 activity and over-expression of SIRT1 decreased p53 transcriptional activity and rescued cells from CK2-I-induced apoptosis. This ability of CK2-Is to sensitize glioma to TNFα-induced death via multiple mechanisms involving abrogation of NF-κB activation, reactivation of wild-type p53 function and SIRT1 inhibition warrants investigation.

General information

Publication status: Published

MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), National Brain Research Centre, Paras Hospitals
Contributors: Dixit, D., Sharma, V., Ghosh, S., Mehta, V. S., Sen, E.
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Research output: Contribution to journal › Article › Scientific › peer-review

Cortical spreading depression in alpha-synuclein knockout mice

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Ita-Suomen yliopisto
Contributors: Pelkonen, A., Yavich, L.
Number of pages: 4
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COX-2 regulates the proliferation of glioma stem like cells
Cancer stem-like cells (CSCs) possessing features of neural precursor cells (NPC) influence initiation, recurrence and chemoresistance of glioblastoma multiforme (GBM). As inflammation is crucial for glioblastoma progression we investigated the effect of chronic IL-1β treatment on CSCs derived from glioblastoma cell line U87MG. Exposure to IL-1β for 10 days increased (i) accumulation of 8-OHdG - a key biomarker of oxidative DNA damage; (ii) DNA damage response (DDR) indicators γH2AX, ATM and DNA-PK; (iii) nuclear and cytoplasmic p53 and COX-2 levels and (iv) interaction between COX-2 and p53. Despite upregulating p53 expression IL-1β had no effect on cell cycle progression, apoptosis or self renewal capacity of CSCs. COX-2 inhibitor Celecoxib reduced self renewal capacity and increased apoptosis of both control and IL-1β treated CSCs. Therefore the ability of COX-2 to regulate proliferation of CSCs irrespective of exposure to IL-1β, warrants further investigation of COX-2 as a potential anti-glioma target.

General information
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Organisations: Computational Science X (CompX), National Brain Research Centre
Contributors: Sharma, V., Dixit, D., Ghosh, S., Sen, E.
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Original language: English
ASJC Scopus subject areas: Cellular and Molecular Neuroscience, Cell Biology
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Source: Scopus
Source ID: 80052927442
Research output: Contribution to journal › Article › Scientific › peer-review

Effects of local structure of neuronal networks on spiking activity in silico
The structure of the neuronal network, including synaptic connectivity, is the basis for information transfer in the network. Various graph-theoretic measures such as degree distribution, mean geodesic path length, clustering coefficient and motif distribution exist for analysing the structure of networks [1], and each of them captures only one perspective of the properties that are crucial regarding the activity in the network. In this work, we vary the local structure of neuronal networks and observe changes in their activity in silico, i.e. in simulations where the activity of single neurons and their interaction is modeled. The local structure is analysed through the occurrence of different motifs, i.e. different patterns of connectivity. The effect of motifs on network dynamics has been widely studied in different types of networks: from the stability point of view in networks with unspecified dynamics [2], in artificial neural networks [3], and from synchronization point of view in spiking neuronal networks [4]. Our work focuses on noise-driven neuronal networks, where the activity can be characterised by spike trains of neurons in the network, and particularly by the bursting behaviour of the network.

To study the local structure of networks we consider the occurrences of three separate connectivity patterns: (1) the bidirectional edges, (2) the loops of three nodes, and (3) the feed-forward motifs of triples of nodes. Networks with one of these three local connectivity patterns promoted are generated – we abbreviate these networks (L1), (L2) and (L3). In addition, different distance-dependent networks are generated, including networks with ring topology (RT) and biologically plausible topology, obtained by the NETMORPH [5] simulator (NM). All networks except for NM have binomially distributed in-degree, as is the case with the random networks (RN) that are widely used in neuronal activity simulations. Small illustrations of these network structures are shown in Figure Figure1.1. Neuronal activity in these types of networks of size N=100 is simulated using the model presented in [6]. The simulations show a difference in the activity of these networks. Preliminary results indicate, that network bursts occur more frequently in distance dependent networks RT and NM, especially in RT. Accordingly, the overall spiking frequency is high in these networks, but also in L3 networks.

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MoE publication type: Not Eligible
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Contributors: Mäki-Marttunen, T. M., Acimovic, J., Ruohonen, K. P., Linne, M.
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ASJC Scopus subject areas: Neuroscience (miscellaneous), Cellular and Molecular Neuroscience, Signal Processing
Keywords: spiking neuronal network, structure, complex networks
URLs:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3240304/
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Emergence of global and local structural features during development of neuronal networks

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MoE publication type: A4 Article in a conference publication
Organisations: Faculty of Biomedical Sciences and Engineering
Contributors: Acimovic, J.
Publication date: 6 Jun 2011

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ASJC Scopus subject areas: Signal Processing, Cellular and Molecular Neuroscience, Neuroscience (miscellaneous)
Keywords: morphology, connectivity, complex networks, neurite, dendritic structure
URLs:

https://iris.unimore.it/retrieve/handle/11380/699320/40887/WCSB_villanibarbieriserra_final_TICSP.pdf
Research output: Chapter in Book/Report/Conference proceeding › Conference contribution › Scientific › peer-review

Pathway analysis of expression data: Deciphering functional building blocks of complex diseases

General information
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MoE publication type: A1 Journal article-refereed
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Contributors: Emmert-Streib, F., Glazko, G. V.
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Effects of structure on spontaneous activity in simulated neuronal networks

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Organisations: Department of Signal Processing, BioMediTech, Research group: Computational Neuro Science-CNS, Faculty of Biomedical Sciences and Engineering, Department of Mathematics, Research group: Computational Neuro Science-CNS
Contributors: Mäki-Marttunen, T., Acimovic, J., Ruohonen, K., Linne, M.
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ASJC Scopus subject areas: Cellular and Molecular Neuroscience, Neuroscience (miscellaneous), Applied Mathematics, Signal Processing
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Neural networks, cell cultures and some older work on data analysis.

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ASJC Scopus subject areas: Cellular and Molecular Neuroscience, Neuroscience (miscellaneous), Modelling and Simulation, Signal Processing, Human-Computer Interaction
Keywords: computational neuroscience, spiking networks, complex networks, cortical networks, brain-machine interfaces
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Influence of the neural network topology on the learning dynamics
We study the influence of the topology of a neural network on its learning dynamics. The network topology can be controlled by one parameter p_{rw} to convert the topology from regular to random in a continuous way [D.J. Watts and S.H. Strogatz, Collective dynamics of small-world networks, Nature 393 (1998) 440-442]. As test problem, which requires a recurrent network, we choose the problem of timing to be learned by the network, that means to connect a predefined input neuron with a output neuron in exactly T_f time steps. We analyze the learning dynamics for different parameters numerically by counting the number of paths within the network which are available for solving the problem. Our results show, that there are parameter values for which either a regular, small-world or random network gives the best performance depending strongly on the choice for the predefined input and output neurons.

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Contributors: Emmert-Streib, F.
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A constrained HMM-based approach to the estimation of perceptual switching dynamics in pigeons

We describe a method for the analysis of behavioural data from experiments on perception of bistable stimuli in pigeons. The approach is based on a Hidden Markov Model (HMM) with additional linear factorial constraints for which a modified Baum-Welch algorithm is derived. It allows the estimation of the perceptual switching events, which might directly relate to transitions between states of activation of corresponding neural populations. From the resulting time series, characteristics of the underlying perceptual dynamics can be estimated. We also demonstrate that-inspite of the Markov assumption-the method can reveal certain non-Markovian contributions to the dynamics. (C) 2001 Elsevier Science B.V. All rights reserved.

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