Assessment of PIV performance in validating CFD models from nasal cavity CBCT scans

Objective: The aim of our study was to investigate how well Particle Image Velocimetry (PIV) measurements could serve Computational Fluid Dynamics (CFD) model validation for nasal airflow.
Material and methods: For the PIV measurements, a silicone model of the nose based on cone beam computed tomography (CBCT) scans of a patient was made. Corresponding CFD calculations were conducted with laminar and two turbulent models (k-ω and k-ω SST).
Results: CFD and PIV results corresponded well in our study. Especially, the correspondence of CFD calculations between the laminar and turbulent models was found to be even stronger. When comparing CFD with PIV, we found that the results were most convergent in the wider parts of the nasal cavities.
Conclusion: PIV measurements in realistically modelled nasal cavities succeed acceptably and CFD calculations produce corresponding results with PIV measurements. Greater model scaling is, however, necessary for better validations with PIV and comparisons of competing CFD models.

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Contributors: Ormiskangas, J., Valtonen, O., Kivekäs, I., Dean, M., Poe, D., Järnstedt, J., Lekkala, J., Harju, T., Saarenrinne, P., Rautiainen, M.
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Simulation of the Effects of Extracellular Calcium Changes Leads to a Novel Computational Model of Human Ventricular Action Potential With a Revised Calcium Handling

The importance of electrolyte concentrations for cardiac function is well established. Electrolyte variations can lead to arrhythmias onset, due to their important role in the action potential (AP) genesis and in maintaining cell homeostasis. However, most of the human AP computer models available in literature were developed with constant electrolyte concentrations, and fail to simulate physiological changes induced by electrolyte variations. This is especially true for Ca^{2+}, even in the O'Hara-Rudy model (ORd), one of the most widely used models in cardiac electrophysiology. Therefore, the present work develops a new human ventricular model (BPS2020), based on ORd, able to simulate the inverse dependence of AP duration (APD) on extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$), and APD rate dependence at 4 mM extracellular K^+. The main changes needed with respect to ORd are: (i) an increased sensitivity of L-type Ca^{2+} current inactivation to $[Ca^{2+}]_o$; (ii) a single compartment description of the sarcoplasmic reticulum; iii) the replacement of Ca^{2+} release. BPS2020 is able to simulate the physiological APD-$[Ca^{2+}]_o$ relationship, while also retaining the well-reproduced properties of ORd (APD rate dependence, restitution, accommodation and current block effects). We also used BPS2020 to generate an experimentally-calibrated population of models to investigate: (i) the occurrence of repolarization abnormalities in response to hERG current block; (ii) the rate adaptation variability; (iii) the occurrence of alternans and delayed after-depolarizations at fast pacing. Our results indicate that we successfully developed an improved version of ORd, which can be used to investigate electrophysiological changes and pro-arrhythmic abnormalities induced by electrolyte variations and current block at multiple rates and at the population level.

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Contributors: Bartolucci, C., Passini, E., Hyttinen, J., Paci, M., Severi, S.
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Tidal breathing flow profiles during sleep in wheezing children measured by impedance pneumography
For the first time, impedance pneumography (IP) enables a continuous analysis of the tidal breathing flow volume (TBFV), overnight. We studied how corticosteroid inhalation treatments, sleep stage, and time from sleep onset modify the nocturnal TBFV profiles of children. Seventy children, 1–5 years old and with recurrent wheezing, underwent three, full-night TBFVs recordings at home, using IP. The first recorded one week before ending a 3-months inhaled corticosteroids treatment, and remaining two, 2 and 4 weeks after treatment. TBFV profiles were grouped by hour from sleep onset and estimated sleep stage. Compared with on-medication, the off-medication profiles showed lower volume at exhalation peak flow, earlier interruption of expiration, and less convex middle expiration. The differences in the first two features were significant during non-rapid eye movement (NREM), and the differences in the third were more prominent during REM after 4 h of sleep. These combinations of TBFV features, sleep phase, and sleep time potentially indicate airflow limitation in young children.

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Contributors: Gracia-Tabuenca, J., Seppä, V., Jauhiainen, M., Paassilta, M., Viik, J., Karjalainen, J.
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Source: Scopus
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Membrane-Dependent Binding and Entry Mechanism of Dopamine into Its Receptor

Synaptic neurotransmission has recently been proposed to function via either a membrane-independent or a membrane-dependent mechanism, depending on the neurotransmitter type. In the membrane-dependent mechanism, amphipathic neurotransmitters first partition to the lipid headgroup region and then diffuse along the membrane plane to their membrane-buried receptors. However, to date, this mechanism has not been demonstrated for any neurotransmitter-receptor complex. Here, we combined isothermal calorimetry measurements with a diverse set of molecular dynamics simulation methods to investigate the partitioning of an amphipathic neurotransmitter (dopamine) and the mechanism of its entry into the ligand-binding site. Our results show that the binding of dopamine to its receptor is consistent with the membrane-dependent binding and entry mechanism. Both experimental and simulation results showed that dopamine favors binding to lipid membranes especially in the headgroup region. Moreover, our simulations revealed a ligand-entry pathway from the membrane to the binding site. This pathway passes through a lateral gate between transmembrane alpha-helices 5 and 6 on the membrane-facing side of the protein. All in all, our results demonstrate that dopamine binds to its receptor by a membrane-dependent mechanism, and this is complemented by the more traditional binding mechanism directly through the aqueous phase. The results suggest that the membrane-dependent mechanism is common in other synaptic receptors, too.

General information

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Organisations: Research group: Biological Physics and Soft Matter, Physics, University of Helsinki, Universitat Heidelberg , Uniwersytet Jagiellonski w Krakowie, University of Eastern Finland, Turku University Hospital, MEMPHYS, University of Turku
Contributors: Lolicato, F., Juhola, H., Zak, A., Postila, P. A., Saukko, A., Rissanen, S., Enkavi, G., Vattulainen, I., Kepczynski, M., Róg, T.
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EXT="Postila, Pekka A."
EXT="Enkavi, Giray"
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Sodium channels enable fast electrical signaling and regulate phagocytosis in the retinal pigment epithelium

Background: Voltage-gated sodium (Na_V) channels have traditionally been considered a trademark of excitable cells. However, recent studies have shown the presence of Na_V channels in several non-excitable cells, such as astrocytes and macrophages, demonstrating that the roles of these channels are more diverse than was previously thought. Despite the earlier discoveries, the presence of Na_V channel-mediated currents in the cells of retinal pigment epithelium (RPE) has been dismissed as a cell culture artifact. We challenge this notion by investigating the presence and possible role of Na_V channels in RPE both ex vivo and in vitro. Results: Our work demonstrates that several subtypes of Na_V channels are found in human embryonic stem cell (hESC)-derived and mouse RPE, most prominently subtypes $Na_V1.4$, $Na_V1.6$, and $Na_V1.8$. Whole cell patch clamp recordings from the hESC-derived RPE monolayers showed that the current was inhibited by TTX and QX-314 and was sensitive to the selective blockers of the main Na_V subtypes. Importantly, we show that the Na_V channels are involved in photoreceptor outer segment phagocytosis since blocking their activity significantly reduces the efficiency of particle internalization. Consistent with this role, our electron microscopy results and immunocytochemical analysis show that $Na_V1.4$ and $Na_V1.8$ accumulate on phagosomes and that pharmacological inhibition of Na_V channels as well as silencing the expression of $Na_V1.4$ with shRNA impairs the phagocytosis process. Conclusions: Taken together, our study shows that Na_V channels are present in RPE, giving this tissue the capacity of fast electrical signaling. The channels are critical for the physiology of RPE with an important role in photoreceptor outer segment phagocytosis.

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Contributors: Johansson, J. K., Karema-Jokinen, V. I., Hakanen, S., Jylhä, A., Uusitalo, H., Vihinen-Ranta, M., Skottman, H., Ihalainen, T. O., Nymark, S.
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Metabolic syndrome is associated with decreased heart rate variability in a sex-dependent manner: a comparison between 252 men and 249 women

Impaired heart rate variability (HRV) is associated with increased risk of cardiovascular disease, but evidence regarding alterations of HRV in metabolic syndrome (MetS) remains elusive. In order to examine HRV in MetS, we subjected 501 volunteers without atherosclerosis, diabetes or antihypertensive medication, mean age 48 years, to passive head-up tilt. The subjects were divided to control men (n = 131), men with MetS (n = 121), control women (n = 191) and women with MetS (n = 58) according to the criteria by Alberti et al. (Circulation, 2009, 120, 1640). In unadjusted analyses (i) men and women with MetS had lower total power and high-frequency (HF) power of HRV than controls whether supine or upright (P<0·05 for all). (ii) Supine low-frequency (LF) power of HRV was lower in men (P = 0·012) but not in women (P = 0·064) with MetS than in controls, while men and women with MetS had lower upright LF power of HRV than controls (P <0·01 for both). (iii) The LF:HF ratio did not differ between subjects with and without MetS. After adjustment for age, smoking habits, alcohol intake, height, heart rate and breathing frequency, only the differences in upright total power and HF power of HRV between women with MetS and control women remained significant (P<0·05). In conclusion, reduced total and HF power of HRV in the upright position may partially explain why the relative increase in cardiovascular risk associated with MetS is greater in women than in men. Additionally, the present results emphasize that the confounding factors must be carefully taken into consideration when evaluating HRV.

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Organisations: Faculty of Biomedical Sciences and Engineering, Research group: Physiological Measurement Systems and Methods Group, Tampere University Hospital, Central Hospital of Seinäjoki
Contributors: Kangas, P., Tikkakoski, A., Uitto, M., Viik, J., Bouquin, H., Niemelä, O., Mustonen, J., Pörsti, I.
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Normalization of force to muscle cross-sectional area: A helpful attempt to reduce data scattering in contractility studies?

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Organisations: Faculty of Biomedical Sciences and Engineering, Hamburg-Eppendorf, University of Murcia, University of Freiburg
Contributors: Pecha, S., Koivumäki, J., Geelhoed, B., Kempe, R., Berk, E., Engel, A., Reichenspurner, H., Eschenhagen, T., Ravens, U., Kaumann, A., Christ, T.
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Source ID: 85056564696
Research output: Contribution to journal › Editorial › Scientific › peer-review

Quantifying branch architecture of tropical trees using terrestrial LiDAR and 3D modelling

Key message: A method using terrestrial laser scanning and 3D quantitative structure models opens up new possibilities to reconstruct tree architecture from tropical rainforest trees. Abstract: Tree architecture is the three-dimensional arrangement of above ground parts of a tree. Ecologists hypothesize that the topology of tree branches represents optimized adaptations to tree's environment. Thus, an accurate description of tree architecture leads to a better understanding of how form is driven by function. Terrestrial laser scanning (TLS) has demonstrated its potential to characterize woody tree structure. However, most current TLS methods do not describe tree architecture. Here, we examined nine trees from a Guyanese tropical rainforest to evaluate the utility of TLS for measuring tree architecture. First, we scanned the trees and extracted individual tree point clouds. TreeQSM was used to reconstruct woody structure through 3D quantitative structure models (QSMs). From these QSMs, we calculated: (1) length and diameter of branches > 10 cm diameter, (2) branching order and (3) tree volume. To validate our method, we destructively harvested the trees and manually measured all branches over 10 cm (279). TreeQSM found and reconstructed 95% of the branches thicker than 30 cm. Comparing field and QSM data, QSM overestimated branch lengths thicker than 50 cm by 1% and underestimated diameter of branches between 20 and 60 cm by 8%. TreeQSM assigned the correct branching order in 99% of all cases and reconstructed 87% of branch lengths and 97% of tree volume. Although these results are based on nine trees, they validate a method that is an important step forward towards using tree architectural traits based on TLS and open up new possibilities to use QSMs for tree architecture.

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Contributors: Lau, A., Bentley, L. P., Martius, C., Shenkin, A., Bartholomeus, H., Raumonen, P., Malhi, Y., Jackson, T., Herold, M.
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Automatic optimization of an in silico model of human iPSC derived cardiomyocytes recapitulating calcium handling abnormalities
The growing importance of human induced pluripotent stem cell-derived cardiomyoyctes (hiPSC-CMs), as patient-specific and disease-specific models for studying cellular cardiac electrophysiology or for preliminary cardiotoxicity tests, generated better understanding of hiPSC-CM biophysical mechanisms and great amount of action potential and calcium transient data. In this paper, we propose a new hiPSC-CM in silico model, with particular attention to Ca^{2+} handling. We used (i) the hiPSC-CM Paci2013 model as starting point, (ii) a new dataset of Ca^{2+} transient measurements to tune the parameters of the inward and outward Ca^{2+} fluxes of sarcoplasmic reticulum, and (iii) an automatic parameter optimization to fit action potentials and Ca^{2+} transients. The Paci2018 model simulates, together with the typical hiPSC-CM spontaneous action potentials, more refined Ca^{2+} transients and delayed afterdepolarizations-like abnormalities, which the old Paci2013 was not able to predict due to its mathematical formulation. The Paci2018 model was validated against (i) the same current blocking experiments used to validate the Paci2013 model, and (ii) recently published data about effects of different extracellular ionic concentrations. In conclusion, we present a new and more versatile in silico model, which will provide a platform for modeling the effects of drugs or mutations that affect Ca^{2+} handling in hiPSC-CMs.

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Contributors: Paci, M., Pölönen, R., Cori, D., Penttinen, K., Aalto-Setälä, K., Severi, S., Hyttinen, J.
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EXT="Penttinen, Kirsi"
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Monitoring of heart rate and inter-beat intervals with wrist plethysmography in patients with atrial fibrillation
Objective: Atrial fibrillation (AF) causes marked risk for patients, while silent fibrillation may remain unnoticed if not suspected and screened. Development of comfortable yet accurate beat-to-beat heart rate (HR) monitoring with good AF detection sensitivity would facilitate screening and improve treatment. The purpose of this study was to evaluate whether a wrist-worn photoplethysmography (PPG) device can be used to monitor beat-to-beat HR accurately during post-operative treatment in patients suffering from AF and whether wrist-PPG can be used to distinguish AF from sinus rhythm (SR). Approach: Twenty-nine patients (14 with AF, 15 with SR, mean age 71.5 years) with multiple comorbidities were monitored during routine post-operative treatment. The monitoring included standard ECG, finger PPG monitoring and a wrist-worn PPG monitor with green and infrared light sources. The HR from PPG sensors was compared against ECG-derived HR. Main results: The wrist PPG technology had very good HR and beat detection accuracy when using green light. For the SR group, the mean absolute error (MAE) for HR was 1.50 bpm, and for the inter-beat intervals (IBI), the MAE was 7.64 ms. For the AF group, the MAE for HR was 4.28 bpm and for IBI, the MAE was 14.67 ms. Accuracy for the infrared (IR) channel was worse. Finger PPG provided similar accuracy for HR and better accuracy for the IBI. AF detection sensitivity using green light was 99.0% and the specificity was 93.0%. Performance can be improved by discarding unreliable IBI periods. Significance: Results suggest that wrist PPG measurement allows accurate HR and beat-to-beat HR monitoring also in AF patients, and could be used for differentiating between SR and AF with very good sensitivity.

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Organisations: Faculty of Biomedical Sciences and Engineering, Tampere University Hospital, PulseOn SA, Pulseon Oy, University of Tampere, Medical School
Contributors: Harju, J., Tarniceriu, A., Parak, J., Vehkaoja, A., Yli-Hankala, A., Korhonen, I.
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Cholesterol Protects the Oxidized Lipid Bilayer from Water Injury: An All-Atom Molecular Dynamics Study

In an effort to delineate how cholesterol protects membrane structure under oxidative stress conditions, we monitored the changes to the structure of lipid bilayers comprising 30 mol% cholesterol and an increasing concentration of Class B oxidized 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) glycerophospholipids, namely, 1-palmitoyl-2-(9′-oxo-nonanoyl)-sn-glycero-3-phosphocholine (PoxnoPC), and 1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine (PazePC), using atomistic molecular dynamics simulations. Increasing the content of oxidized phospholipids (oxPLs) from 0 to 60 mol% oxPL resulted in a characteristic reduction in bilayer thickness and increase in area per lipid, thereby increasing the exposure of the membrane hydrophobic region to water. However, cholesterol was observed to help reduce water injury by moving into the bilayer core and forming more hydrogen bonds with the oxPLs. Cholesterol also resists altering its tilt angle, helping to maintain membrane integrity. Water that enters the 1-nm-thick core region remains part of the bulk water on either side of the bilayer, with relatively few water molecules able to traverse through the bilayer. In cholesterol-rich membranes, the bilayer does not form pores at concentrations of 60 mol% oxPL as was shown in previous simulations in the absence of cholesterol.

General information

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Organisations: Physics, Forschungszentrum Jülich (FZJ), Masaryk University, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark, Heinrich Heine University Düsseldorf
Contributors: Owen, M. C., Kulig, W., Rog, T., Vattulainen, I., Strodel, B.
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Differential processing in modality-specific Mauthner cell dendrites

Key points: The present study examines dendritic integrative processes that occur in many central neurons but have been challenging to study in vivo in the vertebrate brain. The Mauthner cell of goldfish receives auditory and visual information via two separate dendrites, providing a privileged scenario for in vivo examination of dendritic integration. The results show differential attenuation properties in the Mauthner cell dendrites arising at least partly from differences in cable properties and the nonlinear behaviour of the respective dendritic membranes. In addition to distinct modality-dependent membrane specialization in neighbouring dendrites of the Mauthner cell, we report cross-modal dendritic interactions via backpropagating postsynaptic potentials. Broadly, the results of the present study provide an exceptional example for the processing power of single neurons. Animals process multimodal information for adaptive behavioural decisions. In fish, evasion of a diving bird that breaks the water surface depends on integrating visual and auditory stimuli with very different characteristics. How do neurons process such differential sensory inputs at the dendritic level? For that, we studied the Mauthner cells (M-cells) in the goldfish startle circuit, which receive visual and auditory inputs via two separate dendrites, both accessible for in vivo recordings. We investigated whether electrophysiological membrane properties and dendrite morphology, studied in vivo, play a role in selective sensory processing in the M-cell. The results obtained show that anatomical and electrophysiological differences between the dendrites combine to produce stronger attenuation of visually evoked postsynaptic potentials (PSPs) than to auditory evoked PSPs. Interestingly, our recordings showed also cross-modal dendritic interaction because auditory evoked PSPs invade the ventral dendrite (VD), as well as the opposite where visual PSPs invade the lateral dendrite (LD). However, these interactions were asymmetrical, with auditory PSPs being more prominent in the VD than visual PSPs in the LD. Modelling experiments imply that this asymmetry is caused by

active conductances expressed in the proximal segments of the VD. The results obtained in the present study suggest modality-dependent membrane specialization in M-cell dendrites suited for processing stimuli of different time domains and, more broadly, provide a compelling example of information processing in single neurons.

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Evaluation of optogenetic electrophysiology tools in human stem cell-derived cardiomyocytes
Current cardiac drug safety assessments focus on hERG channel block and QT prolongation for evaluating arrhythmic risks, whereas the optogenetic approach focuses on the action potential (AP) waveform generated by a monolayer of human cardiomyocytes beating synchronously, thus assessing the contribution of several ion channels on the overall drug effect. This novel tool provides arrhythmogenic sensitizing by light-induced pacing in combination with non-invasive, all-optical measurements of cardiomyocyte APs and will improve assessment of drug-induced electrophysiological aberrancies. With the help of patch clamp electrophysiology measurements, we aimed to investigate whether the optogenetic modifications alter human cardiomyocytes' electrophysiology and how well the optogenetic analyses perform against this gold standard. Patch clamp electrophysiology measurements of non-transduced stem cell-derived cardiomyocytes compared to cells expressing the commercially available optogenetic constructs Optopatch and CaViar revealed no significant changes in action potential duration (APD) parameters. Thus, inserting the optogenetic constructs into cardiomyocytes does not significantly affect the cardiomyocyte's electrophysiological properties. When comparing the two methods against each other (patch clamp vs. optogenetic imaging) we found no significant differences in APD parameters for the Optopatch transduced cells, whereas the CaViar transduced cells exhibited modest increases in APD-values measured with optogenetic imaging. Thus, to broaden the screen, we combined optogenetic measurements of membrane potential and calcium transients with contractile motion measured by video motion tracking. Furthermore, to assess how optogenetic measurements can predict changes in membrane potential, or early afterdepolarizations (EADs), cells were exposed to cumulating doses of E-4031, a hERG potassium channel blocker, and drug effects were measured at both spontaneous and paced beating rates (1, 2 Hz). Cumulating doses of E-4031 produced prolonged APDs, followed by EADs and drug-induced quiescence. These observations were corroborated by patch clamp and contractility measurements. Similar responses, although more modest were seen with the I_{Ks} potassium channel blocker JNJ-303. In conclusion, optogenetic measurements of AP waveforms combined with optical pacing compare well with the patch clamp gold standard. Combined with video motion contractile measurements, optogenetic imaging provides an appealing alternative for electrophysiological screening of human cardiomyocyte responses in pharmacological efficacy and safety testings.

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Organisations: Faculty of Biomedical Sciences and Engineering, Research group: Computational Biophysics and Imaging Group, BioMediTech, FIN-00014 University of Helsinki, BioMediTech Institute and Faculty of Biomedical Sciences and Engineering
Contributors: Björk, S., Ojala, E. A., Nordström, T., Ahola, A., Liljeström, M., Hyttinen, J., Kankuri, E., Mervaala, E.
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Inhibition of Aβ Amyloid Growth and Toxicity by Silybins: The Crucial Role of Stereochemistry
The self-assembling of the amyloid β (Aβ) peptide into neurotoxic aggregates is considered a central event in the pathogenesis of Alzheimer's disease (AD). Based on the "amyloid hypothesis", many efforts have been devoted to designing molecules able to halt disease progression by inhibiting Aβ self-assembly. Here, we combine biophysical (ThT assays, TEM and AFM imaging), biochemical (WB and ESI-MS), and computational (all-atom molecular dynamics) techniques to investigate the capacity of four optically pure components of the natural product silymarin (silybin A, silybin B, 2,3-dehydrosilybin A, 2,3-dehydrosilybin B) to inhibit Aβ aggregation. Despite TEM analysis demonstrated that all the four investigated flavonoids prevent the formation of mature fibrils, ThT assays, WB and AFM investigations showed that only silybin B was able to halt the growth of small-sized protofibrils thus promoting the formation of large, amorphous aggregates. Molecular dynamics (MD) simulations indicated that silybin B interacts mainly with the C-terminal hydrophobic segment ^{35}MVGGVV^{40} of Aβ40. Consequently to silybin B binding, the peptide conformation remains predominantly unstructured along all the simulations. By contrast, silybin A interacts preferentially with the segments ^{17}LVFF^{20} and ^{27}NKGAII^{32} of Aβ40 which shows a high tendency to form bend, turn, and β-sheet conformation in and around these two domains. Both 2,3-dehydrosilybin enantiomers bind preferentially the segment ^{17}LVFF^{20} but lead to the formation of different small-sized, ThT-positive Aβ aggregates. Finally, in vivo studies in a transgenic Caenorhabditis elegans strain expressing human Aβ indicated that silybin B is the most effective of the four compounds in counteracting Aβ proteotoxicity. This study underscores the pivotal role of stereochemistry in determining the neuroprotective potential of silybins and points to silybin B as a promising lead compound for further development in anti-AD therapeutics.

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Organisations: Physics, Centro S3, ENEA/CREATE/Università Degli Studi Napoli Federico II, STMicroelectronics, Università degli Studi di Catania, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri
Contributors: Sciacca, M. F., Romanucci, V., Zarrelli, A., Monaco, I., Lolicato, F., Spinella, N., Galati, C., Grasso, G., D'Urso, L., Romeo, M., Diomede, L., Salmona, M., Bongiorno, C., Di Fabio, G., La Rosa, C., Milardi, D.
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How management intensity and neighborhood composition affect the structure of beech (Fagus sylvatica L.) trees

Key message: The intensity of silvicultural interventions and the neighborhood composition determine branching patterns, crown shape, and trunk attributes of beech (Fagus sylvaticaL.) trees.Abstract: The intensity of silvicultural interventions and the composition of tree species are important forest management decisions. Both determine tree shape and thus influence the value of a tree, be it in terms of economy (trunk form, branchiness), or in terms of ecology (microhabitats). However, our knowledge on the distinct changes in tree architecture due to silvicultural management intensity or different neighborhood diversities is still limited, especially if the focus is on single tree attributes, e.g., branching patterns or crown shapes. We used terrestrial laser scanner data to calculate 25 structural measures for 55 European beech (Fagus sylvatica L.) trees that grew either in pure stands along a gradient of management intensity or in intra or interspecific neighborhoods in unmanaged stands. We found a lower height of maximal horizontal crown extension, a higher crown surface area, and straighter trunks with increasing management intensity. Moreover, our study revealed that beech trees surrounded by valuable hardwoods showed a lower height of maximal horizontal crown extension, a lower height–diameter ratio, and longer branches with flatter branch angles than beech trees surrounded by conspecific neighbors. Our findings provide evidence of phenotypic plasticity of European beech to diverse environmental conditions. The differences in tree structure indicate an increasing crown competition with decreasing management intensity and stronger competitive pressure for beech surrounded by conspecific neighbors in comparison to alien neighbors.

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Organisations: Mathematics, Research group: Inverse Problems, University of Goettingen, Department of Applied Health Research
Contributors: Juchheim, J., Annighöfer, P., Ammer, C., Calders, K., Raumonen, P., Seidel, D.
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Calcium Assists Dopamine Release by Preventing Aggregation on the Inner Leaflet of Presynaptic Vesicles

In this study, the dopamine-lipid bilayer interactions were probed with three physiologically relevant ion compositions using atomistic molecular dynamics simulations and free energy calculations. The in silico results indicate that calcium is able to decrease significantly the binding of dopamine to a neutral (zwitterionic) phosphatidylcholine lipid bilayer model mimicking the inner leaflet of a presynaptic vesicle. We argue that the observed calcium-induced effect is likely in crucial role in the neurotransmitter release from the presynaptic vesicles docked in the active zone of nerve terminals. The inner leaflets of presynaptic vesicles, which are responsible for releasing neurotransmitters into the synaptic cleft, are mainly composed of neutral lipids such as phosphatidylcholine and phosphatidylethanolamine. The neutrality of the lipid head group region, enhanced by a low pH level, should limit membrane aggregation of transmitters. In addition, the simulations suggest that the high calcium levels inside presynaptic vesicles prevent even the most lipophilic transmitters such as dopamine from adhering to the inner leaflet surface, thus rendering unhindered neurotransmitter release feasible.

General information

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Organisations: Physics, Research group: Biological Physics and Soft Matter, Structural Bioinformatics Laboratory, Abo Akad Univ, Abo Akademi University, Dept Phys, University of Helsinki, MEMPHYS, University of Southern Denmark
Contributors: Mokkila, S., Postila, P. A., Rissanen, S., Juhola, H., Vattulainen, I., Róg, T.
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Phase partitioning of GM1 and its bodipy-labeled analog determine their different binding to Cholera Toxin
Driven by interactions between lipids and proteins, biological membranes display lateral heterogeneity that manifests itself in a mosaic of liquid-ordered (Lo) or raft, and liquid-disordered (Ld) or non-raft domains with a wide range of different properties and compositions. In giant plasma membrane vesicles and giant unilamellar vesicles, specific binding of Cholera Toxin (CTxB) to GM1 glycolipids is a commonly used strategy to label raft domains or Lo membrane environments. However, these studies often use acyl-chain labeled bodipy-GM1 (bdGM1), whose headgroup accessibility and membrane order or phase partitioning may differ from those of GM1, rendering the interpretation of CTxB binding data quite problematic. To unravel the molecular basis of CTxB binding to GM1 and bdGM1, we explored the partitioning and the headgroup presentation of these gangliosides in the Lo and Ld phases using atomistic molecular dynamics simulations complemented by CTxB binding experiments. The conformation of both GM1 and bdGM1 was shown to be largely similar in the Lo and Ld phases. However, bdGM1 showed reduction in receptor availability when reconstituted into synthetic bilayer mixtures, highlighting that membrane phase partitioning of the gangliosides plays a considerable role in CTxB binding. Our results suggest that the CTxB binding is predominately modulated by the partitioning of the receptor to an appropriate membrane phase. Further, given that the Lo and Ld partitioning of bdGM1 differs from those of GM1, usage of bdGM1 for studying GM1 behavior in cells can lead to invalid interpretation of experimental data.

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Organisations: Physics, Research group: Biological Physics and Soft Matter, German Center for Diabetes Research, University of Helsinki, University of Texas Health Science Center at Houston, Weatherall Institute of Molecular Medicine, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark
Contributors: Rissanen, S., Grzybek, M., Orlowski, A., Róg, T., Cramariuc, O., Levental, I., Eggeling, C., Sezgin, E., Vattulainen, I.
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The Integrin Receptor in Biologically Relevant Bilayers: Insights from Molecular Dynamics Simulations

Integrins are heterodimeric (αβ) cell surface receptors that are potential therapeutic targets for a number of diseases. Despite the existence of structural data for all parts of integrins, the structure of the complete integrin receptor is still not available. We have used available structural data to construct a model of the complete integrin receptor in complex with talin F2–F3 domain. It has been shown that the interactions of integrins with their lipid environment are crucial for their function but details of the integrin/lipid interactions remain elusive. In this study an integrin/talin complex was inserted in biologically relevant bilayers that resemble the cell plasma membrane containing zwitterionic and charged phospholipids, cholesterol and sphingolipids to study the dynamics of the integrin receptor and its effect on bilayer structure and dynamics. The results of this study demonstrate the dynamic nature of the integrin receptor and suggest that the presence of the integrin receptor alters the lipid organization between the two leaflets of the bilayer. In particular, our results suggest elevated density of cholesterol and of phosphatidylserine lipids around the integrin/talin complex and a slowing down of lipids in an annulus of ~30 Å around the protein due to interactions between the lipids and the integrin/talin F2–F3 complex. This may in part regulate the interactions of integrins with other related proteins or integrin clustering thus facilitating signal transduction across cell membranes.

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Organisations: Department of Physics, University of Oxford, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark
Contributors: Kalli, A. C., Rog, T., Vattulainen, I., Campbell, I. D., Sansom, M. S. P.
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Source ID: 84980023830
Research output: Contribution to journal › Article › Scientific › peer-review

Oxysterols Versus Cholesterol in Model Neuronal Membrane. I. The Case of 7-Ketocholesterol. The Langmuir Monolayer Study

Oxysterols are products of cholesterol oxidation. They can be formed endogenously (in both enzymatic and non-enzymatic reactions) as well as exogenously (delivered with food). Recent studies clearly demonstrate cytotoxic properties of these

compounds, being mainly due to their incorporation into natural lipid bilayers. This process can influence mechanical and physicochemical properties of biomembrane—mainly by modifying the interactions between its components, which may result in the disruption of proper functioning of cell membrane and could lead to its degradation. Therefore, it can be assumed that oxysterols may affect the initiation of neurodegenerative diseases, including Alzheimer's disease. However, the mode of action of these molecules at the molecular level is not fully known. To get a better understanding of the role of oxysterols in neurodegeneration, it is of great importance to examine mutual interactions between oxysterols and neuronal membrane components. One of the most promising techniques that can be used to analyze such interactions is the Langmuir monolayer technique. In this work, we have prepared an artificial neuronal membrane modeled as multicomponent Langmuir monolayer built up with cholesterol, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), and sphingomyelin (SM). To examine whether there are any changes in the membrane properties under oxidative stress, in this paper we have investigated the impact of the representative ring-oxidized oxysterol: 7-ketocholesterol (7-KC). Our results show that replacing cholesterol with 7-KC increases the interaction between molecules in the model membrane.

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Contributors: Wnętrzak, A., Makyła-Juzak, K., Filiczkowska, A., Kulig, W., Dynarowicz-Łątka, P.
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Current densities and total contact currents during forest clearing tasks under 400kV power lines
The aim of the study was to analyze all values of electric currents from measured periods while performing tasks in forest clearing. The objective was also to choose and analyze measurement cases, where current measurements successfully lasted the entire work period (about 30min). Two forestry workers volunteered to perform four forest clearing tasks under 400kV power lines. The sampling frequency of the current measurements was 1sample/s. The maximum values of the current densities were 1.0-1.2mA/m^2 (calculated internal EFs 5.0-12.0mV/m), and the average values were 0.2-0.4mA/m^2. The highest contact current was 167.4μA. All measured values during forest clearing tasks were lower than basic restrictions (0.1V/m and 0.8V/m) of the International Commission on Non-Ionizing Radiation Protection. Bioelectromagnetics.

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Contributors: Korpinen, L., Kuisti, H., Elovaara, J.
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A new algorithm to improve assessment of cortical bone geometry in pQCT

High-resolution peripheral quantitative computed tomography (HR-pQCT) is now considered the leading imaging modality in bone research. However, access to HR-pQCT is limited and image acquisition is mainly constrained only for the distal third of appendicular bones. Hence, the conventional pQCT is still commonly used despite inaccurate threshold-based segmentation of cortical bone that can compromise the assessment of whole bone strength. Therefore, this study addressed whether the use of an advanced image processing algorithm, called OBS, can enhance the cortical bone analysis in pQCT images and provide similar information to HR-pQCT when the same volumes of interest are analyzed. Using pQCT images of European Forearm Phantom (EFP), and pQCT and HR-pQCT images of the distal tibia from 15 cadavers, we compared the results from the OBS algorithm with those obtained from common pQCT analyses, HR-pQCT manual analysis (considered as a gold standard) and common HR-pQCT analysis dual threshold technique.We found that the use of OBS segmentation method for pQCT image analysis of EFP data did not result in any improvement but reached similar performance in cortical bone delineation as did HR-pQCT image analyses. The assessments of cortical cross-sectional bone area and thickness by OBS algorithm were overestimated by less than 4% while area moments of inertia were overestimated by ~5-10%, depending on reference HR-pQCT analysis method. In conclusion, this study showed that the OBS algorithm performed reasonably well and it offers a promising practical tool to enhance the assessment of cortical bone geometry in pQCT.

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Contributors: Cervinka, T., Sievänen, H., Lala, D., Cheung, A. M., Giangregorio, L., Hyttinen, J.
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μCT based assessment of mechanical deformation of designed PTMC scaffolds

BACKGROUND: Advances in rapid-prototyping and 3D printing technologies have enhanced the possibilities in preparing designed architectures for tissue engineering applications.Amajor advantage in custom designing is the ability to create structures with desired mechanical properties. While the behaviour of a designed scaffold can be simulated using bulk material properties, it is important to verify the behaviour of a printed scaffold at the microstructure level. OBJECTIVE: In this study we present an effective method in validating the mechanical behaviour of designed scaffolds using a CT with an in-situ mechanical deformation device. METHODS: The scaffolds were prepared from biodegradable poly(trimethylene carbonate) (PTMC) by stereolithography and images obtained using a high-resolution CT with 12.25 m isometric voxels. The data was processed (filtering, segmentation) and analysed (surface generation, registration) to extract relevant deformation features. RESULTS: The computed local deformation fields, calculated at sub-pore resolutions, displayed expected linear behaviour within the scaffold along the compressions axis. On planes perpendicular to this axis, the deformations varied by 150-200 m. CONCLUSIONS: μ CT based imaging with in-situ deformation provides a vital tool in validating the design parameters of printed scaffolds. Deformation fields obtained from micro-tomographic image volumes can serve to corroborate the simulated ideal design with the realized product.

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Organisations: Department of Electronics and Communications Engineering, Research group: Computational Biophysics and Imaging Group, BioMediTech, Integrated Technologies for Tissue Engineering Research (ITTE), Department of Biomaterials Science and Technology, University of Twente
Contributors: Narra, N., Blanquer, S. B. G., Haimi, S. P., Grijpma, D. W., Hyttinen, J.
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A motion artifact generation and assessment system for the rapid testing of surface biopotential electrodes

Dry electrodes can reduce cost while increasing the usability and comfort of wearable monitoring systems. They are, however, susceptible to motion artifacts. The present electrode testing methods lack reliability and do not separate the factors that affect the motion artifact. In this paper, we introduce a first generation motion artifact generation and assessment system that generates the speed, amplitude, and pattern-wise programmable movement of the electrode. The system simultaneously measures electrode-skin impedance, the motion artifact, and one channel of an electrocardiogram that contains the motion artifact and monitors the mounting force applied to the electrode. We demonstrate the system by comparing the applied movement and the measured signals for electrode movements up to 6 mm and movement frequencies from 0.4 Hz to 4 Hz. Results show that the impedance change and surface potential are visually clearly related to the applied motion, with average correlations of 0.89 and 0.64, respectively. The applied force, electrode location, and electrode structure all affect the motion artifact. The setup enables the motion of the electrode to be accurately controlled. The system can be used as a precursor to the testing of integrated systems because it enables thorough, repeatable, and robust motion artifact studies. The system allows a deeper insight into motion artifacts and the interplay of the various factors that affect them.

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Contributors: Cömert, A., Hyttinen, J.
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Effect of Omeprazole Dose, Nonsteroidal Anti-inflammatory Agents, and Smoking on Repair Mechanisms in Acute Peptic Ulcer Bleeding
Background: Peptic ulcer bleeding (PUB) is a major cause of upper gastrointestinal bleeding. The effect of omeprazole on mucosal repair is unknown. Aims: We studied the effect of omeprazole, nonsteroidal anti-inflammatory agents, and smoking on PUB. Methods: There were 43 PUB patients who received regular or high dose of omeprazole for 72 h. Biopsies from antrum and corpus were taken before and after treatment. Biopsy samples from 20 celiac disease patients worked as controls. The expression of Ki-67, Bcl-2, COX-2, Hsp27, and Hsp70 was analyzed from patients and controls. Results: Bcl-2 expression in PUB patients was lower than in controls. However, Bcl-2 increased significantly from 5.0 (SD 4.5) to 9.1 % (SD 6.7), p = 0.0004, in the antrum after omeprazole. In univariate analysis, a high omeprazole dose caused a more profound increase in Ki-67 expression in the corpus: 35.3 % (SD 54.8) than a regular dose: −10.1 % (SD 40.6), p = 0.022. In multivariate analysis, Ki-67 decreased significantly in the corpus between the pre- and posttreatment period (p = 0.011), while a high omeprazole dose (p = 0.0265), the use of NSAIDs (p = 0.0208), and smoking (p = 0.0296) significantly increased Ki-67 expression. Bcl-2 in the corpus increased significantly (p = 0.0003) after treatment. Conclusions: Our findings suggest that Bcl-2 may be an important factor in the pathogenesis of a peptic ulcer and PUB. In addition, high-dose omeprazole increased the expression of Ki-67, which may enhance the healing process of a peptic ulcer.

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Contributors: Rantanen, T., Udd, M., Honkanen, T., Miettinen, P., Kärjä, V., Rantanen, L., Julkunen, R., Mustonen, H., Paavonen, T., Oksala, N.
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Original language: English
ASJC Scopus subject areas: Physiology, Medicine(all), Gastroenterology
Keywords: High and regular dose, Nonsteroidal anti-inflammatory agents, Omeprazole, Peptic ulcer bleeding, Repair mechanisms, Smoking
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Source ID: 84922393478
Research output: Contribution to journal › Article › Scientific › peer-review

Movement of NH_3 through the human urea transporter B: A new gas channel

Aqua-porins and Rh proteins can function as gas (CO_2 and NH_3) channels. The present study explores the urea, H_2O, CO_2, and NH_3 permeability of the human urea transporter B (UT-B) (SLC14A1), expressed in Xenopus oocytes. We monitored urea uptake using [^{14}C]urea and measured osmotic water permeability (P_f) using video microscopy. To obtain a semiquantitative measure of gas permeability, we used microelectrodes to record the maximum transient change in surface pH (ApHS) caused by exposing oocytes to 5% CO_2/33 mM HCO_3 (pH_S increase) or 0.5 mM NH3/NH^ (pH_S decrease). UT-B expression increased oocyte permeability to urea by > 20-fold, and Pf by 8-fold vs. H_2O-injected control oocytes. UT-B expression had no effect on the CO_2-induced ApH_S but doubled the NH_3-induced ApH_S. Phloretin reduced UT-B-dependent urea uptake (J_{urea}) by 45%, Pf by 50%, and (- ApH_S)NH_3 by 70%. p-Chloromercuribenzene sulfonate reduced J_{urea} by 25%, Pf by 30%, and (ApH_S)NH_3 by 100%. Molecular dynamics (MD) simulations of membrane-embedded models of UT-B identified the monomeric UT-B pores as the main conduction pathway for both H_2O and NH_3 and characterized the energetics associated with permeation of these species through the channel. Mutating each of two conserved threonines lining the monomeric urea pores reduced H2O and NH3 permeability. Our data confirm that UT-B has significant H_2O permeability and for the first time demonstrate significant NH_3 permeability. Thus the UTs become the third family of gas channels. Inhibitor and mutagenesis studies and results of MD simulations suggest that NH_3 and H_2O pass through the three monomeric urea channels in UT-B.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Case Western Reserve University, Department of Applied Physics, Department of Biochemistry, Univ Illinois, University of Illinois System, University of Illinois Urbana-Champaign, Frederick Seitz Mat Res Lab, Dept Mat Sci & Engn
Contributors: Ryan Geyer, R., Musa-Aziz, R., Enkavi, G., Mahinthichaichan, P., Tajkhorshid, E., Boron, W. F.
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Publication information

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Volume: 304
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Scopus rating (2013): CiteScore 6.9 SJR 2.073 SNIP 1.212
Original language: English
ASJC Scopus subject areas: Physiology, Urology
Keywords: Ammonia transport, Carbon dioxide transport, Membrane protein, Urea transport, Water transport
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10.1152/ajprenal.00609.2012
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Effect of exercise on bone structural traits, physical performance and body composition in breast cancer patients - A 12-month RCT

In this 12-month RCT, we examined whether aerobic impact exercise training (3x/week) could facilitate breast cancer survivors' recovery by enhancing their bone structural strength, physical performance and body composition. After the adjuvant chemoand/or radiotherapy, 86 patients were randomly assigned into the training or control group. Structural bone traits were assessed with pQCT at the tibia and with DXA at the femoral neck. Agility (figure-8 running), jump force and power (force platform), grip strength and cardiovascular fitness (2-km walk test) were also assessed. Training effects on outcome variables were estimated by two-way factorial ANCOVA using the study group and menopausal status as fixed factors. Bone structural strength was better maintained among the trainees. At the femoral neck, there was a small but significant 2% training effect in the bone mass distribution (p=0.05). At the tibial diaphysis, slight 1% to 2% training effects (p=0.03) in total cross-sectional area and bone structural strength were observed (p=0.03) among the postmenopausal

trainees. Also, 3% to 4% training effects were observed in the figure-8 running time (p=0.03) and grip strength (p=0.01). In conclusion, vigorous aerobic impact exercise training has potential to maintain bone structural strength and improve physical performance among breast cancer survivors.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), UKK Institute Finland, Tampere University Hospital, Pirkanmaa Cancer Society, Helsinki University Central Hospital
Contributors: Nikander, R., Sievänen, H., Ojala, K., Kellokumpu-Lehtinen, P. L., Palva, T., Blomqvist, C., Luoto, R., Saarto, T.
Number of pages: 9
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Peer-reviewed: Yes

Publication information

Journal: Journal of Musculoskeletal and Neuronal Interactions
Volume: 12
Issue number: 3
ISSN (Print): 1108-7161
Ratings:

Scopus rating (2012): CiteScore 3.8 SJR 0.872 SNIP 0.932
Original language: English
ASJC Scopus subject areas: Endocrinology, Diabetes and Metabolism, Orthopedics and Sports Medicine, Physiology
Keywords: Bone, Breast cancer, Exercise, Muscle, Rehabilitation
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Research output: Contribution to journal › Article › Scientific › peer-review

Cysteine-rich protein 1 is regulated by transforming growth factor-β1 and expressed in lung fibrosis

Transforming growth factor-β (TGF-β) is a diverse cytokine regulating growth, apoptosis, differentiation, adhesion, invasion, and extracellular matrix production. Dysregulation of TGF-β is associated with fibrotic disorders and epithelial-mesenchymal transition, and has been linked with idiopathic pulmonary fibrosis (IPF). Cysteine-rich protein 1 (CRP1) is a small LIM-domain containing protein involved in smooth muscle differentiation. Here, we show that TGF-β1 increases the expression of CRP1 protein and that CRP1 levels increase in a biphasic fashion. A rapid transient (15-45min) increase in CRP1 is followed by a subsequent, sustained increase in CRP1 a few hours afterwards that lasts several days. We find that TGF-β1 regulates the expression of CRP1 through Smad and non-conventional p38 MAPK signaling pathways in a transcription-independent manner and that the induction occurs concomitant with an increase in myofibroblast differentiation. Using CRP1 silencing by shRNA, we identify CRP1 as a novel factor mediating cell contractility. Furthermore, we localize CRP1 to fibroblastic foci in IPF lungs and find that CRP1 is significantly more expressed in IPF as compared to control lung tissue. The results show that CRP1 is a novel TGF-β1 regulated protein that is expressed in fibrotic lesions and may be relevant in the IPF disease.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Haartman Institute, University of Helsinki, Johns Hopkins School of Medicine, School of Management (JKK)
Contributors: Järvinen, P. M., Myllärniemi, M., Liu, H., Moore, H. M., Leppäranta, O., Salmenkivi, K., Koli, K., Latonen, L., Band, A. M., Laiho, M.
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Publication information

Journal: Journal of Cellular Physiology
Volume: 227
Issue number: 6
ISSN (Print): 0021-9541
Ratings:

Scopus rating (2012): CiteScore 6.6 SJR 1.978 SNIP 1.121

Original language: English
ASJC Scopus subject areas: Clinical Biochemistry, Cell Biology, Physiology
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Research output: Contribution to journal › Article › Scientific › peer-review

Mesopic background lights enhance dark-adapted cone ERG flash responses in the intact mouse retina: A possible role for gap junctional decoupling

The cone-driven flash responses of mouse electroretinogram (ERG) increase as much as twofold over the course of several minutes during adaptation to a rod-compressing background light. The origins of this phenomenon were investigated in the present work by recording preflash-isolated (M-)cone flash responses ex vivo in darkness and during application of various steady background lights. In this protocol, the cone stimulating flash was preceded by a preflash that maintains rods under saturation (hyperpolarized) to allow selective stimulation of the cones at varying background light levels. The light-induced growth was found to represent true enhancement of cone flash responses with respect to their darkadapted state. It developed within minutes, and its overall magnitude was a graded function of the background light intensity. The threshold intensity of cone response growth was observed with lights in the low mesopic luminance region, at which rod responses are partly compressed. Maximal effect was reached at intensities sufficient to suppress ~90% of the rod responses. Light-induced enhancement of the cone photoresponses was not sensitive to antagonists and agonists of glutamatergic transmission. However, applying gap junction blockers to the dark-adapted retina produced qualitatively similar changes in the cone flash responses as did background light and prevented further growth during subsequent light-adaptation. These results are consistent with the idea that cone ERG photoresponses are suppressed in the dark-adapted mouse retina by gap junctional coupling between rods and cones. This coupling would then be gradually and reversibly removed by mesopic background lights, allowing larger functional range for the cone light responses.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Aalto University, Department of Biomedical Engineering and Computational Science
Contributors: Heikkinen, H., Vinberg, F., Nymark, S., Koskelainen, A.
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ISSN (Print): 0022-3077
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Original language: English
ASJC Scopus subject areas: Physiology, Neuroscience(all)
Keywords: Electroretinogram, Light adaptation, Photoreceptor, Retina, Rod-cone coupling
DOIs:
10.1152/jn.00536.2010
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http://www.scopus.com/inward/record.url?scp=79956275463&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 79956275463
Research output: Contribution to journal › Article › Scientific › peer-review

Computational modeling of electrophysiology and pharmacotherapy of atrial fibrillation: Recent advances and future challenges

The pathophysiology of atrial fibrillation (AF) is broad, with components related to the unique and diverse cellular electrophysiology of atrial myocytes, structural complexity, and heterogeneity of atrial tissue, and pronounced disease-associated remodeling of both cells and tissue. A major challenge for rational design of AF therapy, particularly pharmacotherapy, is integrating these multiscale characteristics to identify approaches that are both efficacious and independent of ventricular contraindications. Computational modeling has long been touted as a basis for achieving such integration in a rapid, economical, and scalable manner. However, computational pipelines for AF-specific drug screening

are in their infancy, and while the field is progressing quite rapidly, major challenges remain before computational approaches can fill the role of workhorse in rational design of AF pharmacotherapies. In this review, we briefly detail the unique aspects of AF pathophysiology that determine requirements for compounds targeting AF rhythm control, with emphasis on delimiting mechanisms that promote AF triggers from those providing substrate or supporting reentry. We then describe modeling approaches that have been used to assess the outcomes of drugs acting on established AF targets, as well as on novel promising targets including the ultra-rapidly activating delayed rectifier potassium current, the acetylcholine-activated potassium current and the small conductance calcium-activated potassium channel. Finally, we describe how heterogeneity and variability are being incorporated into AF-specific models, and how these approaches are yielding novel insights into the basic physiology of disease, as well as aiding identification of the important molecular players in the complex AF etiology.

General information
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MoE publication type: A2 Review article in a scientific journal
Organisations: Faculty of Biomedical Sciences and Engineering, Simula Research Laboratory, Centre for Molecular Medicine Norway, Nordic European Molecular Biology Laboratory Partnership, University of Oslo, Center for Cardiological Innovation, University of Eastern Finland
Contributors: Vagos, M. R., van Herck, I. G., Sundnes, J., Arevalo, H. J., Edwards, A. G., Koivumäki, J. T.
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Source: Scopus
Source ID: 85053074392
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MicroRNAs in atherosclerosis

Micro-ribonucleic acids (miRNAs) are a class of endogenous non-coding ribonucleic acids that regulate gene expression. MiRNAs have been shown to act as key regulators in the vascular system, with wide-ranging physio-pathological effects. Atherosclerotic disease is a leading cause of morbidity and mortality worldwide. This review presents current knowledge on miRNAs implicated in atherosclerosis susceptibility, development and progression. They are involved in cell phenotype switching, response to shear stress, cell senescence, adhesion molecule expression, macrophage response to oxidised low-density lipoprotein, Toll-like receptor 4 expression, neointimal lesion formation, plaque angiogenesis and cellular cholesterol homeostasis. Clinically, early work has demonstrated the utility of miRNAs for differentiating patients with arterial disease from controls and predicting future cardiac events; this highlights potential diagnostic and prognostic roles. MiRNA involvement in the crucial stages of atherosclerosis promises new hope in treating arterial disease. However, issues regarding multiple miRNA targets, stability and delivery continue to present challenges.

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Contributors: Hosin, A. A., Prasad, A., Viiri, L. E., Davies, A. H., Shalhoub, J.
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ASJC Scopus subject areas: Physiology, Cardiology and Cardiovascular Medicine, Medicine(all)
Keywords: Atherosclerosis, Cardiovascular disease, Metabolism, MicroRNA, Vascular smooth muscle cells
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10.1159/000368193
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Source ID: 84917705795
Research output: Contribution to journal › Review Article › Scientific › peer-review

Systematic review of wireless phone use and brain cancer and other head tumors
We conducted a systematic review of scientific studies to evaluate whether the use of wireless phones is linked to an increased incidence of the brain cancer glioma or other tumors of the head (meningioma, acoustic neuroma, and parotid gland), originating in the areas of the head that most absorb radiofrequency (RF) energy from wireless phones. Epidemiology and in vivo studies were evaluated according to an agreed protocol; quality criteria were used to evaluate the studies for narrative synthesis but not for meta-analyses or pooling of results. The epidemiology study results were heterogeneous, with sparse data on long-term use (≥10 years). Meta-analyses of the epidemiology studies showed no statistically significant increase in risk (defined as P

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Contributors: Repacholi, M. H., Lerchl, A., Röösli, M., Sienkiewicz, Z., Auvinen, A., Breckenkamp, J., D'Inzeo, G., Elliott, P. , Frei, P., Heinrich, S., Lagroye, I., Lahkola, A., Mccormick, D. L., Thomas, S., Vecchia, P.
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Issue number: 3
ISSN (Print): 0197-8462
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ASJC Scopus subject areas: Biophysics, Radiology Nuclear Medicine and imaging, Physiology
Keywords: Brain cancer, Head tumors, Radiofrequency fields, Systematic review, Wireless phones
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Source ID: 84857800702
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