Differential mobility spectrometry imaging for pathological applications

Pathologic examination of clinical tissue samples is time consuming and often does not involve the comprehensive analysis of the whole specimen. Automated tissue analysis systems have potential to make the workflow of a pathologist more efficient and to support in clinical decision-making. So far, these systems have been based on application of mass spectrometry imaging (MSI). MSI provides high fidelity and the results in tissue identification are promising. However, the high cost and need for maintenance limit the adoption of MSI in the clinical setting. Thus, there is a need for new innovations in the field of pathological tissue imaging. In this study, we show that differential ion mobility spectrometry (DMS) is a viable option in tissue imaging. We demonstrate that a DMS-driven solution performs with up to 92% accuracy in differentiating between two grossly distinct animal tissues. In addition, our model is able to classify the correct tissue with 81% accuracy in an eight-class setting. The DMS-based system is a significant innovation in a field dominated by mass-spectrometry-based solutions. By developing the presented platform further, DMS technology could be a cost-effective and helpful tool for automated pathological analysis.

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Contributors: Kontunen, A., Tuominen, J., Karjalainen, M., Anttalainen, O., Tolonen, T., Kumpulainen, P., Lepomäki, M., Vehkaoja, A., Oksala, N., Roine, A.
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Effects of aerobic and strength training on aerobic capacity, muscle strength, and gene expression of lymphomonocytes in patients with stable CAD

This study examined the effectiveness, suitability, and safety of a mixed interval-type aerobic and strength training program (MIAST) on physical fitness in patients with stable coronary artery disease (CAD) without history of myocardial infarction (MI). Twenty-three patients with stable CAD were randomly assigned to a MIAST (n = 12; mean age 58.6 years) or control (n = 11; 63.3 years) group. The MIAST group participated in the progressive training program twice a week for 21 weeks. Peak oxygen uptake (VO_{2peak}), workload, and exercise time were measured as were maximal muscle strength, serum lipids, glucose concentration, and the cross-sectional area (CSA) of knee extensors. The safety and suitability of the program were assessed by wireless electrocardiogram (ECG) monitoring and exercise diaries. VO_{2peak} (6.9%; $P < 0.05$) and exercise time (11.2%; $P < 0.05$) improved significantly after 12 weeks of training in the MIAST group compared to the control group. Muscle strength (19.9%; $P < 0.05$) and CSA (2.2%; $P < 0.05$) increased, and serum lipids and blood glucose tended to decrease after the training. The successful training program (increase in maximal oxygen uptake) increased the gene expression of oxygen metabolism and decreased the gene expression of inflammation pathways in lymphomonocytes. The MIAST program, including interval-type aerobic and strength training, was safe, did not cause any adverse effects, and led to significant improvements in physical fitness in patients with stable CAD.

General information

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Organisations: BioMediTech, Research group: Sensor Technology and Biomeasurements (STB), Jyväskylän yliopisto, LIKES Research Centre for Physical Activity and Health, Finnish Institute for Health and Welfare, Suomen Terveystalo Oyj , Central Finland Health Care District, Lapland University of Applied Sciences, Central Finland Hospital
Contributors: Lehti, M., Valkeinen, H., Sipilä, S., Perhonen, M., Rottensteiner, M., Pullinen, T., Pietiläinen, R., Nyman, K., Vehkaoja, A., Kainulainen, H., Kujala, U. M.
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Source ID: 85090358912
Research output: Contribution to journal › Article › Scientific › peer-review

Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism
Context: Some previous studies have suggested increased cancer risk in hyperthyroid patients treated with radioactive iodine (RAI). It is unclear whether the excess cancer risk is attributable to hyperthyroidism, its treatment, or the shared risk factors of the two diseases. Objective: The objective was to assess cancer morbidity and mortality in hyperthyroid patients treated with either RAI or surgery. Patients: We identified 4334 patients treated surgically for hyperthyroidism in Finland during 1986-2007 from the Hospital Discharge Registry and 1814 patients treated with RAI for hyperthyroidism at Tampere University Hospital. For each patient, three age-and gender-matched controls were chosen. Informationoncancer diagnoses was obtained from the Cancer Registry. The follow-up began 3 months after the treatment and ended at cancer diagnosis, death, emigration, or the common closing date (December 31, 2009). Results: The overall cancer incidence was not increased among the hyperthyroid patients compared to their controls (rate ratio [RR], 1.05;95%confidence interval [CI], 0.96-1.15). However, the risk of cancers of the respiratory tract (RR, 1.46; 95% CI, 1.05-2.02) and the stomach (RR, 1.64; 95% CI, 1.01-2.68) was increased among the patients. The overall cancer mortality did not differ between the patients and the controls (RR, 1.08; 95% CI, 0.94-1.25). The type of treatment did not affect the overall risk of cancer (hazard ratio for RAI vs thyroidectomy, 1.03; 95% CI, 0.86-1.23) or cancer mortality (hazard ratio, 1.04; 95% CI, 0.91-1.21). Conclusions: In this cohort of Finnish patients with hyperthyroidism treated with thyroidectomy or RAI, the overall risk of cancer was not increased, although an increased risk of gastric and respiratory tract cancers was seen in hyperthyroid patients. Based on this large-scale, long-term follow-up study, the increased cancer risk in hyperthyroid patients is attributable to hyperthyroidismandshared risk factors, not the treatment modality.

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Contributors: Ryödi, E., Metso, S., Jaatinen, P., Huhtala, H., Saaristo, R., Välimäki, M., Auvinen, A.
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Original language: English
ASJC Scopus subject areas: Endocrinology, Diabetes and Metabolism, Biochemistry, Endocrinology, Clinical Biochemistry , Biochemistry, medical
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Research output: Contribution to journal › Article › Scientific › peer-review

I microRNA nella placca aterosclerotica

MicroRNA (miRNA) are noncoding RNA that regulate gene expression by hindering translation. miRNA expression profiles have been shown to differ in vivo and in vitro in many cellular processes associated with cardiovascular disease (CVD). The progression of CVD has also been shown to alter the blood miRNA profile in humans. Content: We summarize the results of animal and cell experiments concerning the miRNA profile in the atherosclerotic process and the changes which occur in the blood miRNA profile of individuals with CVD. We also survey the relationship of these CVD-related miRNA and their expression in the human advanced atherosclerotic plaque, thereby providing more insight into miRNA function in human atherosclerotic lesions. The miRNA miR-126, -134, -145, -146a, -198, - 210, -340*, and -92a were found to be expressed differently in the blood of individuals affected and unaffected by CVD. These differences paralleled those seen in tissue comparisons of miRNA expression in advanced atherosclerotic plaques and healthy arteries. Furthermore, several miRNA associated with atherosclerosis in in vitro studies (such as miR-10a, -126, -145, -146a/b, -185, -210, and -326) were expressed in plaques in a similar pattern as was predicted by the in vitro experiments. The clinical implications of miRNA in atherosclerosis as biomarkers and as possible drug targets are also reviewed. miRNA profiles in in vitro and in vivo studies as well as in human peripheral blood are quite representative of the miRNA expression in human atherosclerotic plaques. miRNA appear promising in terms of future clinical applications.

General information

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Contributors: Raitoharju, E., Oksala, N., Lehtimäki, T.
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Original language: Italian
ASJC Scopus subject areas: Clinical Biochemistry, Biochemistry, medical, Medical Laboratory Technology
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Electrophoretic mobilities of neutral analytes and electroosmotic flow markers in aqueous solutions of Hofmeister salts

Small neutral organic compounds have traditionally the role of EOF markers in electrophoresis, as they are expected to have zero electrophoretic mobility in external electric fields. The BGE contains, however, ions that have unequal affinities to the neutral molecules, which in turn results in their mobilization. In this study we focused on two EOF markers-thiourea and DMSO, as well as on N-methyl acetamide (NMA) as a model of the peptide bond. By means of CE and all atom molecular dynamics simulations we explored mobilization of these neutral compounds in large set of Hofmeister salts. Employing a statistical mechanics approach, we were able to reproduce by simulations the experimental electrophoretic mobility coefficients. We also established the role of the chemical composition of marker and the BGE on the measured electrophoretic mobility coefficient. For NMA, we interpreted the results in terms of the relative affinities of cations versus anions to the peptide bond.

General information

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Organisations: Computational Science X (CompX), Charles University in Prague, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Soft Matter and Functional Materials, Helmholtz-Zentrum Berlin
Contributors: Křížek, T., Kubíčková, A., Hladílková, J., Coufal, P., Heyda, J., Jungwirth, P.
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Original language: English
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Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

Recurrent thyroid cancers have more peritumoural lymphatic vasculature than nonrecurrent thyroid cancers
Background: The goal of the study was to evaluate angiogenesis and lymphangiogenesis in differentiated thyroid cancer and recurrences. Methods: Twenty-seven patients with recurrent differentiated thyroid cancer (20 papillary and seven follicular thyroid carcinomas) and 24 nonrecurrent thyroid cancers were included in this study. Additionally, 24 thyroid adenomas were included as benign controls. All thyroid cancer recurrences were operatively managed, and local recurrences in cervical lymph nodes or cervical soft tissue were histologically confirmed. Altogether, a total of 108 samples were evaluated using CD31 and D2-40 immunohistochemical staining and microscopy. Results: As measured in primary tumours, the median density of CD31-positive vascular structures was 327 vessels (v)/mm^2 for recurrent cancers, 362 v/mm^2 for nonrecurrent cancers and 484 v/mm^2 for thyroid adenomas (P = 0·017). Among the subgroups, the lowest median vascular density of 316 v/mm^2 was found in recurrent papillary cancers and the highest vascular density of 604 v/mm^2 was observed in nonrecurrent follicular cancers (P = 0·018). The median density of D2-40-positive peritumoural lymphatic vessels was 101/mm^2 in recurrent cancers, 56·1/mm^2 in nonrecurrent cancers and 53·9/mm^2 for adenomas (P = 0·015). In the subgroups, peritumoural lymphatic vascular density was 102 v/mm^2 in recurrent papillary cancers and 56·0 v/mm^2 in nonrecurrent papillary cancers (P = 0·044). Conclusions: Recurrent thyroid cancers expressed less intratumoural microvessels than thyroid adenomas. A high density of peritumoural lymphatic vessels was found in recurrent papillary cancers. High blood vessel density may be a marker for less aggressive tumours, while high peritumoural lymphatic vasculature is a marker for more aggressive and recurrence-prone tumours.

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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital
Contributors: Hakala, T., Sand, J., Kellokumpu-Lehtinen, P. L., Huhtala, H., Leinonen, R., Kholová, I.
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Peer-reviewed: Yes

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Original language: English
ASJC Scopus subject areas: Medicine(all), Clinical Biochemistry, Biochemistry
Keywords: Angiogenesis, Head and neck cancer, Histopathology, Lymphangiogenesis, Thyroid, Thyroid cancer
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Analysis of free, mono- and diacetylated polyamines from human urine by LC-MS/MS

Polyamines are promising biochemical markers of cancer and many other pathophysiological conditions, and thus their concentrations in biological fluids are a matter of interest. However, since the concentrations of these compounds are low, their quantitation is typically based on methods requiring laborious sample preparation. Here we developed and validated an LC-MS/MS method to analyze simultaneously free (DAP, PUT, CAD, SPD, SPM) monoacetylated (AcPUT, AcCAD, N^1AcSPD, N^8AcSPD, N^1AcSPM) and diacetylated (DiAcPUT, DiAcCAD, DiAcSPD, DiAcSPM) polyamines from human urine without the need for derivatization. Deuterium labeled polyamines were the internal standards for each analyte. Diluted urine samples spiked with internal standards were filtered through a strong anion exchange resin prior to LC-MS/MS analysis. The chromatographic separation of 14 polyamines was achieved in 12min on C18 column with 0.1% HFBA (v/v) as the ion-pairing agent and a water-acetonitrile gradient. Ionization was performed with positive electrospray ionization (ESI) and detection was with a triple quadrupole mass spectrometer with selected reaction monitoring. Calibration curves ranged from up to 5 to 10,000nM. The accuracy and precision of the method were determined using urine based quality control samples, and matrix effects were examined by using standard addition methods. This novel method is suitable for elucidating differences in urinary polyamine excretion in cancer patients and healthy humans.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Ita-Suomen yliopisto, Tampere University Hospital, Karolinska University Hospital, School of Management (JKK)
Contributors: Häkkinen, M. R., Roine, A., Auriola, S., Tuokko, A., Veskimäe, E., Keinänen, T. A., Lehtimäki, T., Oksala, N. , Vepsäläinen, J.
Number of pages: 9
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Publication information

Journal: JOURNAL OF CHROMATOGRAPHY B: ANALYTICAL TECHNOLOGIES IN THE BIOMEDICAL AND LIFE SCIENCES
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ASJC Scopus subject areas: Analytical Chemistry, Biochemistry, Clinical Biochemistry, Cell Biology
Keywords: Cancer diagnostic markers, Liquid chromatography-tandem mass spectrometry, N-acetylated, Polyamines, Prostate cancer, Urine
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MicroRNAs in the atherosclerotic plaque

BACKGROUND: MicroRNAs (miRNA, miR) are noncoding translation. miRNA expression profiles have been shown to differ in vivo and in vitro in many cellular processes associated with cardiovascular diseases (CVDs). The progression of CVDs has also been shown to alter the blood miRNA profile in humans. CONTENT: We summarize the results of animal and cell experiments concerning the miRNA profile in the atherosclerotic process and the changes which occur in the blood miRNA profile of individuals with CVD. We also survey the relationship of these CVD-related miRNAs and their expression in the human advanced atherosclerotic plaque, thereby providing more insight into miRNA function in human atherosclerotic lesions. The miRNAs miR-126, -134, -145, -146a, -198, -210, -340*, and -92a were found to be expressed differently in the blood of individuals affected and unaffected by CVD. These differences paralleled those seen in tissue comparisons of miRNA expression in advanced atherosclerotic plaques and healthy arteries. Furthermore, several miRNAs associated with atherosclerosis in in vitro studies (such as miR-10a, -126, -145, -146a/b, -185, -210, and -326) were expressed in plaques in a similar pattern as was predicted by the in vitro experiments. The clinical implications of miRNAs in atherosclerosis as biomarkers and as possible drug targets are also reviewed. SUMMARY: miRNA profiles in in vitro and in vivo studies as well as in human peripheral blood are quite representative of the miRNA expression in human atherosclerotic plaques. miRNAs appear promising in terms of future clinical applications.

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MoE publication type: A2 Review article in a scientific journal
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), School of Management (JKK), Tampere University Hospital
Contributors: Raitoharju, E., Oksala, N., Lehtimäki, T.
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Original language: English
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Source: Scopus
Source ID: 84889770418
Research output: Contribution to journal › Review Article › Scientific › peer-review

Exogenously added BMP-6, BMP-7 and VEGF may not enhance the osteogenic differentiation of human adipose stem cells

In the present study bone morphogenetic protein (BMP)-6 alone or in synergy with BMP-7 and vascular endothelial growth factor (VEGF) were tested with human adipose stem cells (hASCs) seeded on cell culture plastic or 3D bioactive glass. Osteogenic medium (OM) was used as a positive control for osteogenic differentiation. The same growth factor groups were also tested combined with OM. None of the growth factor treatments could enhance the osteogenic differentiation of hASCs in 3D-or 2D-culture compared to control or OM. In 3D-culture OM promoted significantly total collagen production, whereas in 2D-culture OM induced high total ALP activity and mineralization compared to control and growth factors groups, but also high cell proliferation. In this study, hASCs did not respond to exogenously added growth although various parameters of the study set-up may have affected these findings contradictory to the previous literature.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, University of Twente, BioMediTech, Univ of Oulu
Contributors: Kyllönen, L., Haimi, S., Säkkinen, J., Kuokkanen, H., Mannerström, B., Sándor, G. K. B., Miettinen, S.
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ASJC Scopus subject areas: Clinical Biochemistry, Endocrinology, Cell Biology
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Source ID: 84885098878
Research output: Contribution to journal › Article › Scientific › peer-review

Epithelium percentage estimation facilitates epithelial quantitative protein measurement in tissue specimens

Background: The rapid advancement of high-throughput tools for quantitative measurement of proteins has demonstrated the potential for the identification of proteins associated with cancer. However, the quantitative results on cancer tissue specimens are usually confounded by tissue heterogeneity, e.g. regions with cancer usually have significantly higher epithelium content yet lower stromal content. Objective: It is therefore necessary to develop a tool to facilitate the interpretation of the results of protein measurements in tissue specimens. Methods: Epithelial cell adhesion molecule (EpCAM) and cathepsin L (CTSL) are two epithelial proteins whose expressions in normal and tumorous prostate tissues were confirmed by measuring staining intensity with immunohistochemical staining (IHC). The expressions of these proteins were measured by ELISA in protein extracts from OCT embedded frozen prostate tissues. To eliminate the influence of tissue heterogeneity on epithelial protein quantification measured by ELISA, a color-based segmentation method was developed in-house for estimation of epithelium content using H&E histology slides from the same prostate tissues and the estimated epithelium percentage was used to normalize the ELISA results. The epithelium contents of the same slides were also estimated by a pathologist and used to normalize the ELISA results. The computer based results were compared with the pathologist's reading. Results: We found that both EpCAM and CTSL levels, measured by ELISA assays itself, were greatly affected by epithelium content in the tissue specimens. Without adjusting for epithelium percentage, both EpCAM and CTSL levels appeared significantly higher in tumor tissues than normal tissues with a p value less than 0.001. However, after normalization by the epithelium percentage, ELISA measurements of both EpCAM and CTSL were in agreement with IHC staining results, showing a significant increase only in EpCAM with no difference in CTSL expression in cancer tissues. These results were obtained with normalization by both the computer estimated and pathologist estimated epithelium percentage. Conclusions: Our results show that estimation of tissue epithelium percentage using our color-based segmentation method correlates well with pathologists' estimation of tissue epithelium percentages. The epithelium contents estimated by color-based segmentation may be useful in immuno-based analysis or clinical proteomic analysis of tumor proteins. The codes used for epithelium estimation as well as the micrographs with estimated epithelium content are available online.

General information

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Organisations: Prostate cancer research center (PCRC), Johns Hopkins University
Contributors: Chen, J., Eshghi, S. T., Bova, G. S., Li, Q. K., Li, X., Zhang, H.
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Article number: 18
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ASJC Scopus subject areas: Molecular Biology, Molecular Medicine, Clinical Biochemistry
Keywords: Cancer, Computer-aided classification, Epithelium, Stroma
DOIs:

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Source ID: 84903713636
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.

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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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ASJC Scopus subject areas: Clinical Biochemistry, Cell Biology, Physiology
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Source: Scopus
Source ID: 84863147021
Research output: Contribution to journal › Article › Scientific › peer-review

Neuroprotective effect of RO-20-1724-a phosphodiesterase4 inhibitor against intracerebroventricular streptozotocin induced cognitive deficit and oxidative stress in rats
Cyclic nucleotides viz cGMP and cAMP are known to play an important role in learning and memory processes. Enhancement of cyclic nucleotide signalling through inhibition of phosphodiesterases (PDEs) has been reported to be beneficial in several neurodegenerative disorders associated with cognitive decline. The present study was undertaken to investigate the effect of RO-20-1724-a PDE4 inhibitor on streptozotocin (STZ) induced experimental sporadic dementia of Alzheimer's type. The STZ was injected twice intracerebroventrically (3 mg/kg i.c.v.) on alternate days (day 1 and day 3) in rats. The STZ injected rats were treated with RO-20-1724 (125, 250 and 500 μg/kg i.p.) for 21 days following first i.c.v. STZ administration. Learning and memory in rats were assessed by passive avoidance [PA (days 14 and 15)] and Morris water maze [MWM (days 17, 18, 19, 20 and 21)] following first i.c.v. STZ administration. On day 22 rat cerebral homogenate was used for all the biochemical estimations. The pharmacological inhibition of PDE4 by RO-20-1724 significantly attenuated STZ induced cognitive deficit and oxidative stress. RO-20-1724 was found to not only improve learning and memory in MWM and PA paradigms but also restore STZ induced elevation in cholinesterase activity. Further, RO-20-1724 significantly reduced malondialdehyde and nitrite levels, and restored the glutathione levels indicating attenuation of oxidative stress. Current data complement previous studies by providing evidence for a subset of cognition enhancing effects after PDE4 inhibition. The observed beneficial effects of RO-20-1724 in spatial memory may be due to its ability to restore cholinergic functions and possibly through its antioxidant mechanisms.

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Organisations: Computational Science X (CompX), Neuropharmacology Div., ISF College of Pharmacy
Contributors: Sharma, V., Bala, A., Deshmukh, R., Bedi, K. L., Sharma, P. L.
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Original language: English
ASJC Scopus subject areas: Biochemistry, Clinical Biochemistry, Pharmacology, Toxicology, Behavioral Neuroscience, Biological Psychiatry
Keywords: Alzheimer's disease, Cognitive dysfunction, Oxidative stress, Phosphodiesterase4, RO-20-1724, Streptozotocin
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Source ID: 84857569798
Research output: Contribution to journal › Article › Scientific › peer-review

Counterion condensation in short cationic peptides: Limiting mobilities beyond the Onsager-Fuoss theory

We investigated the effect of the background electrolyte (BGE) anions on the electrophoretic mobilities of the cationic amino acids arginine and lysine and the polycationic peptides tetraarginine, tetralysine, nonaarginine, and nonalysine. BGEs composed of sodium chloride, sodium propane-1,3-disulfonate, and sodium sulfate were used. For the amino acids, determination of the limiting mobility by extrapolation, using the Onsager-Fuoss (OF) theory expression, yielded consistent estimates. For the peptides, however, the estimates of the limiting mobilities were found to spuriously depend on the BGE salt. This paradox was resolved using molecular modeling. Simulations, on all-atom as well as coarse-grained levels, show that significant counterion condensation, an effect not accounted for in OF theory, occurs for the tetra- and nonapeptides, even for low BGE concentrations. Including this effect in the quantitative estimation of the BGE effect on mobility removed the discrepancy between the estimated limiting mobilities in different salts. The counterion condensation was found to be mainly due to electrostatic interactions, with specific ion effects playing a secondary role. Therefore, the conclusions are likely to be generalizable to other analytes with a similar density of charged groups and OF theory is expected to fail in a predictable way for such analytes.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Charles University in Prague
Contributors: Wernersson, E., Heyda, J., Kubíčková, A., Křížek, T., Coufal, P., Jungwirth, P.
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Publication date: Mar 2012
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ASJC Scopus subject areas: Biochemistry, Clinical Biochemistry
Keywords: Background electrolyte effects, Counterion condensation, Ion-pairing, Limiting mobility, Molecular modeling
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Modification of olivomycin A at the side chain of the aglycon yields the derivative with perspective antitumor characteristics

A novel way of chemical modification of the antibiotic olivomycin A (1) at the side chain of the aglycon moiety was developed. Interaction of olivomycin A with the sodium periodate produced the key acid derivative olivomycin SA (2) in

86% yield. This acid was used in the reactions with different amines in the presence of benzotriazol-1-yl-oxy-trispyrrolidino-phosphonium hexafluorophosphate (PyBOP) or diphenylphosphoryl azide (DPPA) to give corresponding amides. Whereas olivomycin SA was two orders of magnitude less cytotoxic than the parent antibiotic, the amides of 2 demonstrated a higher cytotoxicity. In particular, N,N-dimethylaminoethylamide of olivomycin SA showed a pronounced antitumor effect against transplanted experimental lymphoma and melanoma and a remarkably high binding constant to double stranded DNA. The therapeutic effects of this derivative were achievable at tolerable concentrations, suggesting that modifications of the aglycon's side chain, namely, its shortening to methoxyacetic residue and blocking of free carboxyl group, are straightforward for the design of therapeutically applicable derivatives of olivomycin A.

General information

Publication status: Published
MoE publication type: A2 Review article in a scientific journal
Organisations: Frontier Photonics, Russian Academy of Medical Sciences, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences
Contributors: Tevyashova, A. N., Shtil, A. A., Olsufyeva, E. N., Luzikov, Y. N., Reznikova, M. I., Dezhenkova, L. G., Isakova, E. B., Bukhman, V. M., Durandin, N. A., Vinogradov, A. M., Kuzmin, V. A., Preobrazhenskaya, M. N.
Number of pages: 7
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Journal: BIOORGANIC AND MEDICINAL CHEMISTRY
Volume: 19
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Medicine, Molecular Biology, Pharmaceutical Science, Drug Discovery, Clinical Biochemistry, Organic Chemistry
Keywords: Antibiotics, Antitumor activity, Aureolic acid, Chemical modifications, Drug-DNA complexes, Olivomycin A, Olivomycin SA
DOIs:

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Research output: Contribution to journal › Review Article › Scientific › peer-review

Treatments with sodium selenate or doxycycline offset diabetes-induced perturbations of thioredoxin-1 levels and antioxidant capacity

Diabetes is associated with increased oxidative stress and impaired antioxidant defenses. Thioredoxin-1 (TRX-1) is a cytosolic thiol antioxidant and redox-active protein which plays a vital role in the maintenance of reduced intracellular redox state. In this study, the authors examined whether 4-week treatments with sodium selenate and doxycycline-a metalloproteinase-2 inhibitor which also has antioxidant-like effects-offset perturbations in oxidative stress and antioxidant protection in rat liver and skeletal muscle in streptozotocin-induced diabetes (SID) model. Experimental diabetes decreased TRX-1 levels in skeletal muscle and liver. On the other hand, SID increased oxidative stress marker protein carbonyl levels and decreased oxygen radical absorbance capacity (ORAC), an indicator of antioxidant capacity, in liver. A 4-week treatment of sodium selenate to diabetic rats decreased blood glucose levels moderately, while doxycycline treatment caused a reduction in weight loss of diabetic rats. Both doxycycline and sodium selenate prevented diabetes-induced decrease of TRX-1 levels in skeletal muscle, whereas only doxyxycline was effectively preventing diabetes-induced decrease of TRX-1 in liver. Furthermore, both treatments prevented diabetes-induced altered levels of protein carbonyls and ORAC in liver, and restored free and total protein thiol levels in both skeletal muscle and liver. In conclusion, the data of this study provides further evidence that sodium selenate and doxycycline treatments may control oxidative stress and improve antioxidant defense in diabetes.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Ita-Suomen yliopisto, Ankara University, Tampere University Hospital
Contributors: Atalay, M., Bilginoglu, A., Kokkola, T., Oksala, N., Turan, B.
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Journal: MOLECULAR AND CELLULAR BIOCHEMISTRY
Volume: 351
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Original language: English
ASJC Scopus subject areas: Clinical Biochemistry, Molecular Biology, Cell Biology
Keywords: Liver, Oxidative stress, Oxygen radical absorbance capacity, Protein carbonyls, Protein thiols, Skeletal muscle , Thioredoxin-1
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Ultrasound-assisted extraction in the determination of arsenic, cadmium, copper, lead, and silver in contaminated soil samples by inductively coupled plasma atomic emission spectrometry
An extraction method was developed for the determination of toxic elements in contaminated soil samples by inductively coupled plasma atomic emission spectrometry (ICP-AES). The determination of arsenic, cadmium, lead, and silver in ultrasound-assisted extracts of SRM 2710 and SRM 2711 by ICP-AES was carried out with high accuracy and precision (RSD<3.7%). The certified concentrations of the SRMs were obtained for arsenic, cadmium, lead, and silver by using an ultrasound-assisted extraction method with a digestion solution of (1+1)-diluted aqua regia. The determination of copper in SRMs by the ultrasound-assisted extraction method and analysis by ICP-AES failed to obtain the certified concentrations at the 95% level of confidence using (±2 s) as confidence limits of the mean. However, the same results were observed with the use of the microwave digestion method and reflux, which is the ISO 11466 standard method. The analysis of the SRMs showed that the ultrasound-assisted extraction method is highly comparable with the other methods used for such purposes. The major advantages of the ultrasound-assisted extraction method compared to the microwave and reflux methods are the high treatment rate (50 samples simultaneously in nine minutes) and low reagent usage, the main benefit of which are the low chloride and nitrate concentrations in the extracts.

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Contributors: Väisänen, A., Suontamo, R., Silvonen, J., Rintala, J.
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Scopus rating (2002): SJR 0.72 SNIP 0.771
Original language: English
ASJC Scopus subject areas: Clinical Biochemistry, Analytical Chemistry
Keywords: Contaminated soil, Elemental analyses, ICP-AES, Toxic metals, Ultrasound-assisted extraction
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URLs:

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Solid-phase bromination and Suzuki coupling of 2-carboxyindoles

As part of an ongoing lead discovery project we have developed a convenient method for the modification and substitution of indole moieties at the 3-position. Selective bromination of three different 2-carboxyindoles was followed by Suzuki cross-coupling with aryl and heteroaryl boronic acids on a Merrifield resin solid-phase. After column chromatography, yields of the 3- substituted indoles ranged from 42-98%.

General information

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Contributors: Tois, J., Franzén, R., Aitio, O., Laakso, I., Huuskonen, J., Taskinen, J.
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ASJC Scopus subject areas: Clinical Biochemistry, Chemistry (miscellaneous), Pharmacology
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