Original Research Article

Lipid mediator Leukotriene D4-induces airway epithelial cells proliferation through EGFR/ERK1/2 pathway

Neeraj Dholia, Umesh C.S. Yadav

School of Life Sciences, Central University of Gujarat, Gandhinagar, 382030, Gujarat, India

ABSTRACT

Background: Cysteinyl leukotrienes (CysLTs), the potent lipid inflammatory mediators, are elevated in many pathological conditions and implicated in various inflammatory diseases including asthma, however their role in airway epithelial cells modulation is not clearly understood. We have investigated the effects of a CysLT, Leukotriene D_4 (LTD_4) on human airway epithelial cells, and assessed its role and mode of action in these cells.
Methodology: Human small airway epithelial cells (SAECs) and A549 cells were incubated with different concentrations of LTD_4 for different time intervals. Subsequently trypan blue dye exclusion assay, MTT assay, Western blotting, RT-PCR and immunofluorescence experiments were performed to examine the effects of LTD_4 on proliferation and related molecular changes in the airway epithelial cells.
Results: The treatment of human airway epithelial cells with LTD_4 resulted in a significant increase in cell proliferation and modulation in the expression of receptors, $CysLT_1R$ and $CysLT_2R$ in SAECs as well as A549 cells. In both types of cells, LTD_4 increased the expression levels of PCNA and c-myc, and trans-activated EGF receptor and increased the activation of ERK1/2. When treated along with epidermal growth factor (EGF), LTD_4 showed a marginal additive effect in ERK1/2 and EGFR phosphorylation compared to LTD_4 alone in both types of airway epithelial cells.
Conclusion: In conclusion, these results suggest that sustained presence of lipid inflammatory mediator LTD_4 could induce human airway epithelial cell proliferation through ERK1/2 phosphorylation, either directly via $CysLT_1$ receptor or by transactivating EGFR.

1. Introduction

Cysteinyl leukotrienes (CysLTs) are important lipid mediators in a number of inflammatory pathologies [1,2]. The levels of CysLTs have been reported to be elevated in several pathological conditions including asthma, COPD, cancers, cardiovascular diseases and obesity-induced chronic inflammation [1,3–6]. In these conditions, CysLTs have been shown to activate the molecular pathways that lead to onset and progression of pathogenesis. For example, CysLTs have been shown to induce endothelial cells that contribute to atherosclerosis; in colon, CysLTs are implicated in loss of barrier function, and in asthma CysLTs are known to induce bronchial spasm by modulating airway smooth muscles [2,7,8]. In a study by Ravasi et al. CysLT was found to activate proliferation in airway smooth muscle cells [9], However, very little is known regarding the effects of CysLTs on the lung epithelial cells. Indeed, there is hardly any study showing the status of CysLT receptors and their actions in the small airway epithelial cells. It has been reported that CysLTs synergize with epidermal growth factor (EGF) and

induce signals by trans-activating epidermal growth factor receptor (EGFR) [9,10]. However, it is not known whether this interaction also occurs in the airway epithelial cells. We, therefore, strived to investigate the effect of CysLTs and EGF on the airway epithelial cells using primary human small airway epithelial cells (SAECs) as well as airway epithelial cell line A549.

Two types of structural airway cells are critical in asthma pathogenesis, airway epithelial cells and airway smooth muscle cells. The role of CysLTs in pathophysiology of asthma by constricting airway smooth muscle is well known and is an important target in the current asthma treatment regimen [11,12]. The role of CysLTs in airway epithelial cells is not clearly understood. Airway epithelial cells are first line of defence against inhaled particles, pathogens and allergens and thus critical for the overall health of lungs. Therefore, we hypothesised that the lipid inflammatory mediator such as Leukotriene D_4 (LTD_4) could induce airway epithelial cell proliferation and hyperplasia, and its sustained presence during chronic inflammatory conditions may lead to aberrant airway epithelial cell physiology leading to breathing

* Corresponding author at: Metabolic Disorder & Inflammatory Pathologies Laboratory, School of Life Sciences, Central University of Gujarat, Sector 30, Gandhinagar, 382030, Gujarat, India.
E-mail address: umeshyadav@cug.ac.in (U.C.S. Yadav).

ORIGINAL ARTICLE

Efficient microwave synthesis, functionalisation and biocompatibility studies of SPION based potential nano-drug carriers

Namita Saxena[1] · Neeraj Dholia[2] · Satyaprasad Akkireddy[3] · Anupinder Singh[4] · Umesh C. S. Yadav[2] · Charu Lata Dube[1]

Abstract

Superparamagnetic iron oxide nanoparticles are much desired for various biomedical applications due to their biocompatible, biodegradable and superparamagnetic nature. In contrast to high-temperature synthesis methods, present study investigates the facile low-temperature co-precipitation process without inert atmosphere. For its efficient, homogenous, in core heating and environment friendly nature microwave energy at two powers of 180 and 450 W was used for synthesis and functionalisation of nanoparticles. It was found in the study, that microwave power plays a decisive role in controlling the size, coating and drug loading percentage of the particles. The synthesis process has been made more economic and simpler by the use of domestic oven, and serine coated particles with mean sizes around 6.8 and 10 nm, narrow size distribution (standard deviations of 1.4 and 1.6 nm), almost rectangular shape and magnetization values of approx. 48 and 42 emu/g were obtained at 180 and 450 W power, respectively. Particles were found to have properties such as near to zero remanence and coercivity, good crystallization and colloidal stability. The biocompatibility of the uncoated and serine coated particles was confirmed by the MTT assay on A 549 epithelial cells. Synthesized particles were found to have all the suitable properties for potential application in biomedical fields. Doxorubicin hydrochloride was loaded efficiently on both the synthesized particles, with loading efficiency obtained up to 6.8% wt/wt, for assessing their suitability as potential drug delivery agents.

Keywords Superparamagnetic iron oxide nanoparticles · Microwave synthesis · Drug delivery · Doxorubicin

Introduction

Superparamagnetic iron oxide nanoparticles (SPIONs) are a class of nanoparticles which find various applications in different areas of biomedical interest such as drug delivery, MRI, hyperthermia, cell sorting, gene delivery, biosensor, etc. (Ali et al. 2016; Kudr et al. 2017; Wu et al. 2015). For

✉ Namita Saxena
saxenanamita29@gmail.com

✉ Charu Lata Dube
dubecharu@gmail.com

1 School of Nano Sciences, Central University of Gujarat, Sector 30, Gandhinagar, Gujarat, India

2 School of Life Sciences, Central University of Gujarat, Sector 30, Gandhinagar, Gujarat, India

3 FCIPT, Institute for Plasma Research, GIDC, Sector 25, Gandhinagar, Gujarat, India

4 Department of Physics, Guru Nanak Dev University, Amritsar, Punjab, India

all these biomedical applications they should have optimum physicochemical properties like size (10–100 nm), narrow size distribution, good magnetic parameters, stable aqueous dispersions and suitable surface characteristics for in vivo applications (Issa et al. 2013; Unsoy et al. 2012).

High-temperature methods using organic solvents can attain good control over the crystal structure, shape, size, size distribution and magnetic properties (Wu et al. 2015; Issa et al. 2013; Laurent et al. 2008), but they use toxic chemicals, harsh reaction conditions and produce hydrophobic particles, whose post-synthesis surface treatment is necessary. Co-precipitation process of synthesis is an easy, scalable, environment friendly, non-cumbersome and low-temperature process. But keeping control over the size and size distribution of the particles is a daunting task in this process. During the kinetic process of synthesis, separation of the nucleation and growth is very difficult thus leading to wider size distribution (Laurent et al. 2008). Heat transfer by convection currents leads to non-uniform heating, temperature variations in the medium and hence wider size

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Elastic properties and zone centre frequencies of Cu$_2$O by LCAO method

K L Galav[a], S S Paliwal[b], V Maurya[b*], G Sharma[a] & K B Joshi[b]

[a]Department of Pure and Applied Physics, University of Kota, Kota 324 005, India
[b]Department of Physics, M L Sukhadia University, Udaipur 313 001, India

The elastic properties and the phonon frequencies at the Brillouin zone centre have been investigated for the cubic cuprous oxide. The calculations under the framework of density functional theory have been carried out by deploying the periodic linear combination of atomic orbitals method. After settling the crystal structure the elastic constants have been determined. The absolute values of elastic constants are well in agreement with the experimental reports. The vibrational frequencies at the centre of the Brillouin zone are classified as the Raman and Infrared active modes and compared with the available experimental data. The contribution of vibrational modes to the Gibbs free energy, entropy and heat capacity has also been found.

Keywords: LCAO method, Elastic properties, Vibration frequencies, Cuprous oxide

1 Introduction

The quantum mechanical studies using state of art first-principles methods enable to design and tune properties of materials. Especially the consistency and order of accuracy in calculations have evolved immensely in last few years which are mandatory for the elastic and vibrational properties. Cuprous oxide has received considerable attention because copper is very important in technological applications and readily available[1]. This is one of the oldest and very important semiconductor but its elastic, thermal and vibration properties are less well understood[2,3]. Elastic properties can give information in terms of acoustic behavior and a detailed picture of the chemical bonding. Earlier experimental studies of elastic properties revealed unusual temperature dependence[4]. A discrepancy in the compressibility is found and crystal instability, impending phase transformation at higher pressure are suggested[5,6]. The lattice dynamics of Cu$_2$O has been studied experimentally by infrared (IR) and Raman spectroscopy, excitation luminescence, and inelastic neutron scattering[7-10]. On the theoretical side, first-principles calculations are reported[11]. Some discrepancies in the phonon bands are also pointed out by Linnera and Karttunen[12]. These studies helped to gain understanding of the nature of the electron-phonon interaction. Moreover, information about the spin–phonon interaction is also discussed[13,14]. The vibrational properties of solids are

directly associated with the phonon dispersion which is very insightful in understanding the phase transition. In this work, we study elastic constants and give the phonon dispersion within the framework of density functional theory (DFT). For this, we have applied the periodic linear combination of atomic orbitals (LCAO) method embodied in the CRYSTAL14 package[15].

2 Crystal Structure and Computational Method

The space group of cubic cuprous oxide is Pn3m. The unit cell of cuprous oxide consists of two formula units. The BCC sublattice is formed by two oxygen atoms and each oxygen atom is surrounded by a tetrahedron of copper atoms whereas an FCC sublattice is formed by copper atoms which are linearly coordinated with two oxygen atoms. In the pressure range 10-12 GPa, the experimental and theoretical studies show that, the cubic cuprite phase transforms into the hexagonal CdI$_2$-like phase[16-19].

The first-principles periodic LCAO method is applied. The salient features can be found in our earlier work[15,20]. The Gaussian basis sets proposed for Cu and O are directly taken[21,22]. The Perdew-Burke-Ernzerhof (PBE) ansatz based on the generalized gradient approximation (GGA) is applied to treat the exchange and correlation (XC) part of the Kohn-Sham Hamiltonian [23]. The Monkhorst and Pack[24] net of 16×16×16 is taken for the self-consistent calculations. The structure is optimized with an iterative method based on the total energy gradients

Inflammation Research

ORIGINAL RESEARCH PAPER

Cysteinyl leukotriene D_4 (LTD$_4$) promotes airway epithelial cell inflammation and remodelling

Neeraj Dholia[1] · Gurupreet S. Sethi[2] · Amarjit S. Naura[3] · Umesh C. S. Yadav[4]

Abstract

Objective Cysteinyl leukotrienes (CysLTs), a group of inflammatory lipid mediators, are found elevated in obese-asthmatic patients. Leukotriene D_4 (LTD$_4$), a representative CysLT, is implicated in promoting lung inflammation and remodelling in allergic asthma, but its role in non-allergic asthma, especially in obese-asthmatic patients, is not known. Here, using primary human small airway epithelial cells (SAECs) we have investigated the mechanism of LTD$_4$-induced inflammation and remodelling and assessed high proneness of obese mice to develop asthma upon challenge with allergen ovalbumin (OVA).

Methods Primary human small airway epithelial cells (SAECs) were stimulated with different concentrations of LTD$_4$ for different time intervals and various inflammatory markers were measured through cytokine array, membrane-based ELISA and Western blotting. An air–liquid interface (ALI) model of SAECs was used to study the effects of LTD$_4$-induced remodelling in SAECs using Western blotting, H&E staining and PAS staining. Further, OVA-based murine model was used to examine the propensity of high-fat diet (HFD)-fed obese mice to develop asthma symptoms by studying the infiltration of inflammatory cells (assessed by bronchioalveolar lavage (BAL) cytology) and airway remodelling (assessed by histopathology) upon allergen exposure.

Results The human primary small airway epithelial cells (SAECs) treated with LTD$_4$ showed significant alterations in the levels of inflammatory markers such as GM-CSF, TNF-α, IL-1β, EGF and eotaxin in dose- and time-dependent manner. Further, LTD$_4$ enhanced the activation of inflammasomes as evidenced by increased levels of NALP3, cleaved caspase-1 and IL-1β. LTD$_4$ also enhanced inflammation by increasing the expression of COX-2 in SAECs. The airway remodelling markers Vimentin and Muc5AC were found elevated in ALI culture of SAECs when stimulated with LTD$_4$, as it also increased TGF-β levels and activation of Smad2/3 phosphorylation in SAECs. Last, sensitization and challenge of HFD-fed obese mice with OVA showed increased infiltration of inflammatory cells in BAL and enhanced levels of remodeling phenotypes like loss of cilia, mucus cell metaplasia and collagen deposition in mice lung tissues.

Conclusion The results suggest that LTD$_4$ could induce inflammatory response in human airway epithelial cell by activating NALP3 inflammasome. LTD$_4$ could further promote airway epithelial cells' remodelling through TGF-β/smad2/3-mediated pathway. Our in vivo results suggested that obesity predisposed the OVA challenged mice to develop lung inflammation and remodelling akin to asthma-like phenotypes during obesity.

Keywords Cysteinyl leukotrienes · Leukotriene D_4 · Airway epithelial cells · Inflammasome · Airway inflammation · Airway remodelling

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Principal
Maa Bharti P.G. College
Mahaveer Nagar-III, Kota

RESEARCH ARTICLE

Montelukast Induces Mesenchymal Properties in A549 Lung Epithelial Cells

Neeraj Dholia

Faculty of Agriculture and Veterinary Science, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India.
School of Life Sciences, Central University of Gujarat, Gandhinagar, Gujarat, India.

*Address for Correspondence
Neeraj Dholia
Faculty of Agriculture and Veterinary Science,
Jayoti Vidyapeeth Women's University,
Jaipur, Rajasthan, India.
Email: neerdholia@gmail.com

ABSTRACT

Background: Epithelial to mesenchymal transition (EMT) is an important event in the progression and metastasis of cancer. Montelukast is a cysteinyl leukotriene receptor antagonist, is used in asthma management, has been implicated in modifying cell behaviour, but its role in EMT is not clear. **Objective:** Our objective was to know the role of Montelukast in inducing mesenchymal properties and migration of A549 cells and what are the probable molecular alterations occurs due to this. **Methodology:** A549 cell line was used as an *In vitro* model for present studies, where wound healing assay, migration assay, invasion assay, gelatin zymography and western blotting experiments were performed subsequent to Montelukast treatment of cells. **Results:** The results show that a complete healing of wounds created by scraping the cells in monolayer by 5 and 10 µM Montelukast groups. Impact on migration and invasion measured by boyden chamber assay showed a significant increase in migration and invasion potential of cells in Montelukast treated A549 cells. Further with the help of zymography increased MMP-2 and MMP-9 activity was observed which were confirmed by western blotting where increased level of MMP-2, MMP-9 and decreased level of E-cadherin was observed. **Conclusion:** These results suggest that Montelukast increases EMT in A549 human lung epithelial cells.

Keywords: EMT, Montelukast, zymography, E-cadherin, MMP, A549

INTRODUCTION

Montelukast (ML) is a leukotriene receptor antagonist, acts as anti-inflammatory by blocking the leukotriene receptor (Tintiger *et al.*, 2010). Like ML, pranlukast and zafirlukast are also approved leukotriene receptor antagonist drugs. It

30058

Application of linear programming in small mechanical based industry for profit maximization

Amit Kumar Jain [a], Sarla Chouhan [b], Rajesh Kumar Mishra [c], P.R.S. Choudhry [d], Hemlata Saxena [a], Ramakant Bhardwaj [e,*]

[a] Department of Mathematics, Career Point University, Kota 324005, India
[b] Department of Mathematics and Computational Science, SGSITS, Indore 453441, India
[c] Department of Mathematics, Atal Bihari Bajpeyee Hindi V V, Bhopal 462042, India
[d] Department of Mathematics, Govt. Model Science College, Jabalpur 482001, India
[e] Department of Mathematics, AMITY University, Kolkata 700157, India

ABSTRACT

The main object of this paper is to find application of linear programming in small ayurvedic items production industry and for this to determine optimal production planning for manufacturing ayurvedic mixture or paste which improve the immunity power of human body and fulfil the requirement of vitamins in human body to get maximum profit.
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Selection and peer-review under responsibility of the scientific committee of the International Conference on Advances in Design, Materials and Manufacturing.

1. Introduction

The main factors for success of any small industries are planning of production, demand, capacity, workforce and manpower. In industries production planning is most important factor to satisfy customers. It is very difficult tasks for production manager to decide number of daily or monthly production subject to demand of market, capacity and available resources of industry. The three main objective of any industry are minimization of production cost, maximization of production quantity and maximum utilization of available resources and for this linear programming technique is an effective tool. This technique help to production manager to take better decision and to use limited available resources in better way for improvement of profit. Linear programming can be applied in various fields of business, economic situation, engineering problems, transportation, telecommunication, production or manufacturing industries. Linear programming technique are generally use to determine optimal solutions and decisions related to manufacturing industries problems.

Many Researchers worked in small manufacturing industries for maximum profit by using linear programming technique in different fields as:

Balogun et al. [9] in (2012) worked with linear programming technique for maximum production in Coca-Cola bottling company to get maximum profit. Igbinehi et al. [5] in (2015) worked with linear programming technique for maximum profit in production of local soap. Akpan, N.P. et al. [8] in (2016) worked with linear programming technique for maximum profit in bakery industry.

M. Patidar et al. [6] in (2018) worked with linear programming technique for preparation of Mathri and Namkeen in a small scale industry for maximum profit. D. Naveena Jyothi et al. [4] in (2019) worked with linear programming technique for production planning in an engineering industry. O. Solaja et al [10] in (2019) worked with linear programming technique in production planning. Further our works can also be seen for profit maximization in [1–3]. Further work was done in [7] for different models.

The main intension of this paper is to find optimal production planning for a small ayurvedic items production industry to get maximum profit.

The general form of linear programming problem is
Optimize

* Corresponding author.
E-mail addresses: drrkbhardwaj100@gmail.com, rbhardwaj@kol.amity.edu (R. Bhardwaj).

Theoretical insight into electronic and optical behaviour of H-adsorbed Zn-terminated Zn_3N_2-(100)-non-polar surface

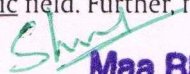M. Kaur [a] 👤 ✉, K. Kabra [a], M. Rérat [b], G. Sharma [a]

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Highlights

- Present study deals with the electronic and optical details of a controversial compound Zn_3N_2 and the alterations that are realised after adsorbing atomic Hydrogen on its (100) non polar surface.

- Major Vacillations in reported data are supposed to get settled down to some extent on the basis of these absolute theoretical outcomes.

- Relative stability of the H-adsorbed systems represents the adsorption to be energetically favourable and in turn, indicating the potential applications in H-storage devices.

- Tuning of the band gap is an important outcome that may emerge new possibilities in optoelectronic field.

- Optical response of the material is also modified significantly, allowing more absorption possibilities in the optimum range of solar radiations. Consequently, efficiencies are supposed to get enhanced efficiently.

Abstract

Present paper deals with the study of electronic and optical behaviour of a II_3-V_2 group semiconductor compound Zn_3N_2 and corresponding significant alterations, that are realised after H-adsorption on its (100) non-polar surface. Calculations are performed applying the linear combination of atomic orbitals method. The relative stability of H-adsorbed systems represents the adsorption to be energetically favourable, indicating possible applications in H-storage devices. A direct electronic band gap of 1.59eV at gamma point is reported, which is further converted into conducting and again semiconducting for slab and adsorbed configurations, respectively. This tuning of the band gap is very important outcome that may emerge new possibilities in optoelectronic field. Further, favourable alterations are

DFT investigation of mechanical and vibrational properties of CuTe

K. Kabra [a] 👤 ✉, S. Arora [a], K.B. Joshi [b], G. Sharma [a]

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Abstract

The electronic, mechanical, vibrational and thermal properties of CuTe have been investigated using the PBEsol functional within the scope of the density functional theory. The electronic properties are investigated after optimizing the crystal structure and it is found that CuTe is a metal in ambient conditions. The elastic constants satisfy Born's stability criterion. Mechanical properties suggest that CuTe is highly anisotropic. In particular, the bulk modulus is found quite large along the b-axis. Anisotropy of elastic moduli and wave velocities suggest anisotropy in thermal conductivity. The minimum thermal conductivity is observed along [001] direction. The supercell method is applied to get phonon dispersion curves and the Raman and Infrared active modes are analyzed. The frequencies and the symmetry of the most of optic modes are in agreement with earlier results.

Introduction

In the pursuit of materials with desired physical and chemical properties, materials physics has witnessed tremendous progress on the modeling and investigations of the properties of materials in the last two decades. Recent investigations have highlighted the transition metal chalcogenides (TMC) to owe specific mechanical, thermoelectric and superconducting properties [[1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14]]. Investigations of thermoelectric properties of copper chalcogenides favor Phonon-Liquid-Electron-Crystal model which is an extension to Phonon-Glass-Electron-Crystal (PGEC) [3,5,15] model. Among copper chalcogenides major attention is paid to copper telluride, $Cu_{2-x}Te$, due to its excellent transport coefficients as compared to the other thermoelectric materials [6,16]. Besides this, good conducting nature of $Cu_{2-x}Te$ system enables usage as effective back contact conductive material for gaining high-efficiency of CdTe solar cells [[17], [18], [19]]. Thus, from the applications viewpoint copper telluride might be useful in the utilization of clean and green energy sources.

$Cu_{2-x}Te$ exists in wide range of compositions such as CuTe, $Cu_{1.25}Te$, $Cu_{1.4}Te$, $Cu_{1.5}Te$, $Cu_{1.75}Te$, and Cu_2Te [[17], [18], [19], [20]]. Although investigations on $Cu_{2-x}Te$ (for $2 \geq x > 1$) compounds have appeared in recent years, the studies on CuTe, the vulcanite, are limited. There have been reports on CuTe thin films [18,[21], [22], [23]], nanowires [24] and bulk samples, but its comprehensive study is yet missing. Electronic properties of CuTe thin films reported energy band gap of 1.5eV whereas optical properties show strong birefringent and pleochroic nature of bulk CuTe [21,25]. Electrical resistivity measurements reported metallic behavior of CuTe down to 4K [26]. Recent studies on $Cu_{2-x}Te$ have revealed that compounds with a high Cu deficiency are beneficial for development of green energy devices [27].