BIOGRAPHICAL SKETCH

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NAME: Lee, Lu-Yuan

eRA COMMONS USER NAME (credential, e.g., agency login): LU-YUAN.LEE

POSITION TITLE: Fred Zechman Professor of Physiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
National Taiwan University, Taipei	BS	1969	Mechanical Engineering
University of Mississippi, Jackson, MS	MS	1972	Mechanical Engineering
University of Mississippi, Jackson, MS	PhD	1975	Physiology & Biophysics
University of California San Francisco, San Francisco, CA	Postdoctoral Fellow	1978	Pulmonary Physiology

A. Personal Statement

Bronchial hyperreactivity is a characteristic feature of airway inflammatory diseases such as asthma. When bronchial hyperreactivity develops during airway mucosal inflammation, the excitability of chemosensitive nerve endings innervating the airways is drastically elevated.

In healthy lungs, these tachykinin-containing sensory terminals located superficially in the airway mucosa play an important role in protecting the airways against inhaled irritants. Stimulation of these sensory endings elicits extensive cardiopulmonary reflex responses such as cough, bronchospasm, hypersecretion of mucus, etc. However, when these nerve endings become hypersensitive as a result of inflammation or injury of airway mucosa, a given level of stimulus will then evoke more sustained and intense stimulation. Thus, greater intensities of the reflex reactions as well as the neurogenic inflammation mediated through local release of tachykinins can lead to the development of bronchial hyperreactivity.

My research team has been investigating the pathophysiological mechanisms underlying the airway hypersensitivity during acute and chronic airway inflammatory diseases in the last 35 years supported by NIH funding. Some of our most recent publications are listed below, and a complete list is presented in: http://www.ncbi.nlm.nih.gov/myncbi/lu-yuan.lee.1/bibliography/47994128/public/?sort=date&direction=ascending

(Google Scholar: h-index: 43; i10-index: 112)

a. Lee LY, Lin RL, Khosravi M, and Xu F. Reflex bronchoconstriction evoked by inhaled nicotine aerosol in guinea pigs: role of the nicotinic acetylcholine receptor. J. Appl. Physiol. 125(1):117-123, 2018. PubMed PMID: 29369741
b. Khosravi M, R.L. Lin, and L.-Y. Lee. Inhalation of Electronic Cigarette Aerosol Induces Reflex Bronchoconstriction by Activation of Vagal Bronchopulmonary C-fibers. Am J Physiol Lung Cell Mol Physiol. 315(4):L467-L475, 2018. PubMed PMID: 29847989
c. Hsu C.C., Y.S. Lin, R.L. Lin, and L.-Y. Lee. Immediate and delayed potentiating effects of tumor necrosis factor-alpha on TRPV1 sensitivity of rat vagal pulmonary sensory neurons. Am. J. Physiol. Lung Cell Mol. Physiol. 313: L293-304, 2017. PubMed PMID: 28522561
d. Zhang C., R.L. Lin, J. Hong, M. Khosravi, and L.-Y. Lee. Cough and expiration reflexes elicited by inhaled irritant gases are intensified in ovalbumin-sensitized mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 312: R718-26, 2017. PubMed PMID: 28228416

B. Positions and Honors

Positions and Employment

1975-1978	Postdoctoral Fellow, Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA
1978-1984	Assistant Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY
1984-1992	Associate Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY
1985-1985	Visiting Scholar, Department Physiology & Biophysics, UTMB, Galveston, TX
1992-present	Professor, Department of Physiology and Biophysics, University of Kentucky, Lexington, KY
1992-1992	Visiting Scholar, Department Pharmacol, Karolinska Inst, Stockholm
1994-1997	Director of Research, Department of Physiology, University of Kentucky, Lexington, KY
1997-1997	Visiting Scientist, Novartis Institute for Medical Sciences, London, UK
1997-2000	Co-director of Graduate Studies, Department of Physiology, University of Kentucky, Lexington, KY
2004-2012	Coordinator, University of Kentucky Lung Biology Research Group, Lexington, KY

Other Experience and Professional Memberships

1991-present	Ad Hoc Member, NIH/NHLBI Special Emphasis Panel and various other Study Sections
1992-1995	Fogarty Senior International Fellowship, NIH
1995-1999	Regular Member, NIH Respiratory and Applied Physiology Study Section
2005-present	Editorial Board, Journal of Applied Physiology
2007-present	Editorial Board, Respiration Physiology and Neurobiology
2010-present	Editorial Board, Frontiers in Autonomic Neuroscience
2010-	Fellow, Biomedical Engineering Society
2011-present	Editorial Board, Frontiers in Respiratory Physiology
2016-	Fellow, American Physiological Society

Honors

1980-1983	Young Investigator Research Award, NIH/NHLBI
1983	Silver Pointer Award (best instructor elected by first year medical students)
1994-96	Master Teacher Award, University of Kentucky College of Medicine
2000	Abraham Flexner Master Educator Award, University of Kentucky College of Medicine
2002-present	Fred W. Zechman Endowed Professor of Physiology, University of Kentucky
2004-present	Wethington Award for Research, University of Kentucky College of Medicine
2008	Clinical and Translational Science Mentor Recognition Award, University of Kentucky
2009	Holsinger Teaching Award, University of Kentucky, Department of Physiology
2014	Outstanding Achievement Award, 10th Joint Meeting of International Symposium on Respiratory Diseases and ATS
2018	Golden Podium Award (course co-director, outstanding second year medical course)

C. Contribution to Science

1. Role of vagal bronchopulmonary C-fibers in regulating respiratory functions: My longstanding research interest focuses on the functions and properties of airway sensory nerves. The research conducted in my lab during the last 30+ years has contributed to the existing knowledge about the role of vagal bronchopulmonary C-fibers in regulating various cardiopulmonary functions under both healthy and disease conditions. In particular, our recent investigations have uncovered some of the important mechanisms underlying the heightened activities of these afferents that developed during airway inflammation. These studies ranged from ion channels to human subjects; some representative invited reviews are listed below:

a. Lee LY, Yu J. Sensory nerves in lung and airways. Compr Physiol. 2014 Jan;4(1):287-324. PubMed PMID: 24692141.

b. Gu Q, Lee LY. Airway irritation and cough evoked by acid: from human to ion channel. Curr Opin Pharmacol. 2011 Jun;11(3):238-47. PubMed PMID: 21543258; PubMed Central PMCID: PMC3133870.
c. Burki NK, Lee LY. Mechanisms of dyspnea. Chest. 2010 Nov;138(5):1196-201. PubMed PMID: 21051395; PubMed Central PMCID: PMC2972628.
d. Lee LY, Pisarri TE. Afferent properties and reflex functions of bronchopulmonary C-fibers. Respir Physiol. 2001 Mar;125(1-2):47-65. PubMed PMID: 11240152.

2. Role of nicotine in airway irritation evoked by cigarette smoke inhalation: Inhaled cigarette smoke causes airway irritation, cough and reflex bronchoconstriction. Our research team has conducted several seminal studies in both human subjects and electrophysiological recording of vagal bronchopulmonary sensory neurons. Our studies have established the first evidence that nicotine is primarily responsible for the airway irritation and coughing caused by cigarette smoke inhalation, and the action is mediated through an activation of nicotinic acetylcholine receptors expressed on the sensory terminals innervating the airway mucosa. This finding has completely changed the previously existing concept in the literature that the irritant effects of cigarette smoke was caused mainly by the particulate matter contained in the smoke.

a. Lee LY, Gu Q. Cough sensors. IV. Nicotinic membrane receptors on cough sensors. Handb Exp Pharmacol. 2009;PubMed PMID: 18825337.
b. Lee LY, Gerhardstein DC, Wang AL, Burki NK. Nicotine is responsible for airway irritation evoked by cigarette smoke inhalation in men. J Appl Physiol. 1993 Nov;75(5):1955-61. PubMed PMID: 8307845.
c. Lee LY, Kou YR, Frazier DT, Beck ER, Pisarri TE, Coleridge HM, Coleridge JC. Stimulation of vagal pulmonary C-fibers by a single breath of cigarette smoke in dogs. J Appl Physiol. 1989 May;66(5):2032-8. PubMed PMID: 2568354.
d. Lee LY, Burki NK, Gerhardstein DC, Gu Q, Kou YR, Xu J. Airway irritation and cough evoked by inhaled cigarette smoke: role of neuronal nicotinic acetylcholine receptors. Pulm Pharmacol Ther. 2007;20(4):355-64. PubMed PMID: 17137814.

3. Airway hypersensitivity induced by eosinophil granule-derived cationic proteins: Eosinophils and other inflammatory cells infiltrate into the airways during anaphylactic reaction and mucosal inflammation. A number of low molecular weight, highly cationic, cysteinine/arginine-rich proteins are synthesized and secreted by eosinophils, and play a key role in the mucosal injury and asthma pathogenesis. In a series of studies in collaboration with Dr. Gerald Gleich (Mayo Clinic), we have demonstrated that human eosinophil granule-derived cationic proteins can stimulate vagal bronchopulmonary C-fiber endings, and enhance the excitability of isolated rat vagal pulmonary neurons to capsaicin, proton and ATP by inhibiting the sustained delayed-rectifier voltage-gated K+ current and the A-type, fast-inactivating K+ current in these sensory neurons. These novel findings have provided new insights into the mechanisms and involvement of vagal bronchopulmonary sensory nerves in the airway hypersensitivity induced by eosinophil infiltration and inflammation.

a. Lee LY, Gu Q, Gleich GJ. Effects of human eosinophil granule-derived cationic proteins on C-fiber afferents in the rat lung. J Appl Physiol. 2001 Sep;91(3):1318-26. PubMed PMID: 11509531.
b. Lee LY, Gu Q. Mechanisms of bronchopulmonary C-fiber hypersensitivity induced by cationic proteins. Pulm Pharmacol Ther. 2003;16(1):15-22. PubMed PMID: 12657496.
c. Gu Q, Wiggers ME, Gleich GJ, Lee LY. Sensitization of isolated rat vagal pulmonary sensory neurons by eosinophil-derived cationic proteins. Am J Physiol Lung Cell Mol Physiol. 2008 Mar;294(3):L544-52. PubMed PMID: 18178677.
d. Gu Q, Lim ME, Gleich GJ, Lee LY. Mechanisms of eosinophil major basic protein-induced hyperexcitability of vagal pulmonary chemosensitive neurons. Am J Physiol Lung Cell Mol Physiol. 2009 Mar;296(3):L453-61. PubMed PMID: 19136577; PubMed Central PMCID: PMC2660213.

4. Involvement of TRPV1 thermal sensitivity in airway inflammation-induced hypersensitivity: In the last ten years, our research team has carried out a series of studies demonstrating that a slight increase in temperature within the normal physiological range can activate and sensitize bronchopulmonary sensory neurons, and this action is mediated primarily through the thermal-sensitive properties of the transient receptor potential vanilloid type 1 (TRPV1) channels. In addition, we have demonstrated that both the expression and sensitivity of TRPV1 in pulmonary sensory nerves are up-regulated in an animal model of allergic asthma. These novel findings, supported by our more recent studies in patients with asthma and allergic rhinitis, begin to unveil the important role of the TRPV1 thermal sensitivity in the manifestation of various symptoms in airway

inflammatory diseases. The current proposal aims to further investigate the possible involvement of TRPV1 as a potential trigger of the pathophysiology during asthma exacerbation.

a. Ni D, Lee LY. Effect of increasing temperature on TRPV1-mediated responses in isolated rat pulmonary sensory neurons. Am J Physiol Lung Cell Mol Physiol. 2008 Mar;294(3):L563-71. PubMed PMID: 18178674.
b. Zhang G, Lin RL, Wiggers M, Snow DM, Lee LY. Altered expression of TRPV1 and sensitivity to capsaicin in pulmonary myelinated afferents following chronic airway inflammation in the rat. J Physiol. 2008 Dec 1;586(Pt 23):5771-86. PubMed PMID: 18832423; PubMed Central PMCID: PMC2655410.
c. Lee LY, Gu Q. Role of TRPV1 in inflammation-induced airway hypersensitivity. Curr Opin Pharmacol. 2009 Jun;9(3):243-9. PubMed PMID: 19269247; PubMed Central PMCID: PMC2704095.
d. Hayes D Jr, Collins PB, Khosravi M, Lin RL, Lee LY. Bronchoconstriction triggered by breathing hot humid air in patients with asthma: role of cholinergic reflex. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1190-6. PubMed PMID: 22505744; PubMed Central PMCID: PMC3373066.

5. Interaction between TRPV1 and transient receptor potential ankyrin type 1 (TRPA1) in Pulmonary Sensory Neurons: TRPA1 and TRPV1 receptors are co-expressed in vagal pulmonary C-fiber sensory nerves. Because both these channels are sensitive to a number of endogenous inflammatory mediators, they are likely activated simultaneously during airway inflammation. In an ongoing series of studies, our research team has reported a distinct potentiating effect induced abruptly by simultaneous activations of TRPA1 and TRPV1 by their respective selective agonists at near-threshold concentrations. This synergistic effect was dependent upon the extracellular Ca2+, and totally absent when either the TRPA1 or the TRPV1 agonist was replaced by a non-TRPA1 and non-TRPV1 chemical activator of these neurons, demonstrating the selectivity of the interaction between these two TRP channels. These findings suggest that the TRPA1-TRPV1 interaction may play an important role in regulating the function and excitability of pulmonary sensory neurons during airway inflammation.

a. Hsu CC, Lin RL, Lee LY, Lin YS. Hydrogen sulfide induces hypersensitivity of rat capsaicin-sensitive lung vagal neurons: role of TRPA1 receptors. Am J Physiol Regul Integr Comp Physiol. 2013 Oct 1;305(7):R769-79. PubMed PMID: 23842678; PubMed Central PMCID: PMC3798805.
b. Lin YJ, Lin RL, Ruan T, Khosravi M, Lee LY. A synergistic effect of simultaneous TRPA1 and TRPV1 activations on vagal pulmonary C-fiber afferents. J Appl Physiol. 2015 Feb 1;118(3):273-81. PubMed PMID: 25414245; PubMed Central PMCID: PMC4312849.
c. Hsu CC, Lee LY. Role of calcium ions in the positive interaction between TRPA1 and TRPV1 channels in bronchopulmonary sensory neurons. J Appl Physiol. 2015 Jun 15;118(12):1533-43. PubMed PMID: 25858491; PubMed Central PMCID: PMC4469923.
d. Lee LY, Hsu CC, Lin YJ, Lin RL, Khosravi M. Interaction between TRPA1 and TRPV1: Synergy on pulmonary sensory nerves. Pulm Pharmacol Ther. 2015 Aug 14;PubMed PMID: 26283426.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/lu-yuan.lee.1/bibliography/47994128/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 AI123832-01 Lee, Lu-Yuan (PI) 01/15/16-01/14/20
National Institute of Allergy and Infectious Diseases
Role of TRPV1 in asthma exacerbation.
This study aims to investigate: if both the thermal sensitivity and the TRPV1 expression are enhanced in pulmonary sensory neurons by chronic airway allergic inflammation; and if the airway temperature is elevated in asthmatics during the allergic inflammatory reaction.
Role: PI

UL1TR001998 Lee & Khosravi (Co-PI) 12/01/16-11/30/18
NIH/NCATS / Kentucky Center for Clinical and Translational Science (CCTS)
CTSA Pilot Project: Assessing effects of electronic cigarettes on airway function in asthma.

This seed grant was awarded by the University of Kentucky CCTS funded by the NIH National Center for Advancing Translational Sciences to support a pilot study of the pulmonary effects of inhaling e-cigarettes on the airway functions in patients with asthma.
Role: Co-PI

R25 GM125680-01 Frazier (PI) 09/01/18-08/31/23
National Institute of General Medical Sciences
Interactive Mentoring to Enhance Research Skills (IMERS)
This IMERS Project aims to organize workshops and provide innovative trainings for the minority college faculty members in the preparation of competitive grant applications and research proposals.
Role: Co-I

T32 GM118292-01A1 Smith Bret (PI) 07/01/2017-06-30/22
National Institute of General Medical Sciences
Graduate Training in Integrative Physiology
To fund training for PhD students studying integrative aspects of physiology at the behavioral, systems, cellular, and molecular levels.
Role: Training Faculty

Completed Research Support

R01 AI123832-Administrative Supplement Lee, Lu-Yuan (PI) 08/05/16-12/31/16
National Institute of Allergy and Infectious Diseases
Role of TRPV1 in asthma exacerbation.
This administrative supplement provides additional funds to support the clinical trial study on role of TRPV1 in asthma exacerbation using the technique of the segmental bronchoprovocation with allergen in asthmatics.
Role: PI

DM090277 Lee, Lu-Yuan (PI) 10/01/10-10/31/15
Department of Defense
Pulmonary Stress Induced by Hyperthermia: Role of Airway Sensory Nerves
We hypothesize that thermal stress evokes reflex bronchoconstriction and other respiratory dysfunctions in patients with airway inflammatory diseases, including asthma, allergic rhinitis, post viral infection and laryngopharyngeal reflux. (There is no overlap with this proposal.)
Role: PI

UL1TR000117 Lee, Lu-Yuan (PI) 12/19/14-12/19/15
University of Kentucky Center for Clinical and Translational Science (CCTS)
Exploring the Role of TRPV1 in Asthma Exacerbation
This seeding grant was awarded by the University of Kentucky CCTS funded by the NIH National Center to study the involvement of TRPV1 activation by an increase in airway mucosa in asthma exacerbation.
Role: PI

R01 HL96914 Lee, Lu-Yuan (PI) 09/01/09-12/31/15
National Heart, Lung and Blood Institute
Role of TRPV1 in Airway Hypersensitivity Induced by Allergic Inflammation
This project aimed to determine whether the airway hypersensitivity caused by allergic inflammation results from increased excitability of the bronchopulmonary C-fiber sensory nerves in an animal model of asthma.
Role: PI

R01 HL107462 Fadi Xu (PI) 04/01/11-03/31/16
National Heart, Lung and Blood Institute
Prenatal Nicotinic Exposure and Depressed Hypoxic Ventilatory Response in SIDS Model
The major objective is to elucidate how prenatal nicotinic exposure inhibits the hypoxic ventilatory response and contributes to the cardiorespiratory failure (death) in rat pups during severe hypoxia.
Role: Co-Investigator