Together we can fight diabetes

SCIENTIFIC ABSTRACTS

The Ramanbhai Foundation 3rd International Symposium on

Current Trends in Pharmaceutical Sciences

"ADVANCES IN DIABETES THERAPY - BASIC SCIENCE AND CLINICAL ASPECTS"

February 1-4, 2007

www.rbfsymposium.net

ZRC MISSION

ZRC aims to be

the most admired

pharmaceutical research center

for innovation in life science

dedicated to alleviating

human sufferings.


Our Mission
We are dedicated to life...
in all its dimensions.
Our world is shaped by a passion
for innovation, commitment
to partners and concern for people
in an effort to create healthier
communities, globally.
Zydus
dedicated to life

Conference Venue :

Zydus Research Centre

Sarkhej - Bavla N.H. 8A, Moraiya, Ahmedabad - 382 210, Gujarat, India. Phone: +91-2717-250801,
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Message from Chairman and Managing Director

Mr. Pankaj R. Patel
Chairman and Managing Director
Zydus Cadila Healthcare Ltd.
Ahmedabad, India.

Dear Delegates,

It is my immense pleasure to invite you to the Ramanbhai Foundation 3rd International Symposium.

This symposium has been conceptualised as a platform for exchanging scientific thoughts amongst the scientists engaged in pharmaceutical research at academic institutions and industries. The theme of the present symposium is "Advances in Diabetes Therapy – Basic Science and Clinical Aspects".

India, as you are aware, is battling with a host of traditional health problems. Compounding this, is the increasing incidence of non-communicable diseases or lifestyle diseases, which are posing a big challenge to all healthcare professionals. India is fast emerging as the diabetes capital of the world, accounting for 35 million of the estimated 150 million diabetic patients worldwide. As per WHO estimates, the number of diabetics worldwide is expected to touch 300 million by 2025, with India being the worst affected.

Studies indicate that diabetes can turn fatal and lead to complications such as coronary artery disease, peripheral vascular disease, neuropathy, retinopathy, nephropathy, etc. People with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30-40 times more likely to undergo amputation, two to four times more likely to develop myocardial infarction and twice as likely to suffer a stroke than non-diabetics.

This symposium aims to bring together experts from both the academia and industry to deliberate on the ways and means of fighting the diabetes epidemic through research and identifying new therapies and clinical interventions.

Zydus Research Centre had first organised the international research symposium in 2003 on the theme: 'Recent Trends in Pharmaceutical Sciences'. The objective was to create a platform for research scientists and professionals to exchange views and insights on current developments. Since then it has been held every two years. Scientists, academicians and experts from across the world converged once again in 2005 at ZRC to share their thoughts on the 'Role of Genomics and Proteomics.'

We welcome you to the symposium so that, "Together we can fight Diabetes".

With warm regards,

Pankaj R. Patel

Chief Patron

About Ramanbhai Foundation

The Ramanbhai Foundation is dedicated to encourage learning and knowledge-sharing in the field of pharmaceutical research, education and healthcare. This mission is based on the philosophy of our late Founder Chairman, Mr. Ramanbhai B. Patel, who believed in the importance of research and enriching oneself through an ongoing quest for learning.

Under the aegis of the Foundation, the group organises The Ramanbhai Foundation International Symposium on the latest trends in Pharmaceutical Sciences, once every two years. The current Ramanbhai Foundation International Symposium is the third in the series of events devoted to 'Advances in Diabetes Therapy – Basic Science and Clinical Aspects.' Through these symposia, the Foundation aims to bridge the research endeavours taking place across the world and create a platform for knowledge sharing.

As a part of the group's outreach programmes, annual healthcare camps are organised at Moraiya and Dabhasa, near Vadodara. Leading specialists from Ahmedabad and Zydus employees, volunteer their services in organising these camps. So far, the group has organised general healthcare camps, diagnostic, dental-care, eye-care and paediatric camps.

The Ramanbhai Foundation is also committed to a number of special initiatives in the field of education. 'The Zydus School for Excellence' – a centre for learning where young minds are free to grow in relationship to his or her potential has been set up under the aegis of the Ramanbhai Foundation.

The Shri Ramanbhai B. Patel - AMA Centre for Excellence in Education which was inaugurated by His Excellency Dr. APJ Abdul Kalam in May 2002, provides a platform for parents, teachers and students to highlight the critical educational issues of the day. The centre conducts open house discussions, memorial lectures on excellence in education, progressive learning programmes for academicians and knowledge sharing forums, which study the successful learning models across the country.

Dedicated to the memory of the group's founder, Mr. Ramanbhai B. Patel, the IPA – Shri Ramanbhai B. Patel Foundation (IRF) has been set up jointly with the Indian Pharmaceutical Association. The IRF has been set up to recognise and award 'commitment and excellence' in the field of pharmacy.

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Zydus Cadila

- Zydus Cadila is a global healthcare provider and one of the top five pharma companies in India. The group was founded in 1952 by Late Mr. Ramanbhai B. Patel.
- The group has been listed as one of the 'Best Under a Billion' company from amongst 200 companies in Asia by Forbes. It is also ranked amongst the leading companies in the Indian pharmaceutical sector by Dun and Bradstreet India. (2006)
- Proven expertise in manufacturing and marketing of different dosage forms such as solid dosage forms, injectables, metered dose inhalers, dry powder inhalers, transdermal patches, suppositories and oncology formulations.
- Wide therapy coverage through three multi-therapy divisions and six speciality divisions – Zydus Cadila, Zydus Alidac, German Remedies, Zydus Medica, Zydus CnD, Zydus Biogen, Zydus Neurosciences, Evona and Respicare. The divisions are spearheaded by some of the stalwarts in the field of pharma marketing.
- A dedicated field force of 3000 reaches out to super specialists, specialists, surgeons, physicians and the rural markets.
- The group is a leader in cardiovascular, gastrointestinal and women's healthcare segments. Strong presence in the respiratory, pain management, anti-infective and oncology segments.
- Leading the way through new product introductions, the group was the first to launch Nucoxia (Etoricoxib), Nupatch (Diclofenac Patch), Pantodac (Pantoprazole), Mifegest (Mifepristone), Penegra (Sildenafil Citrate), Providac Techsules, Betaferon, Fludara and Novolizer in India. 11 of the group's brands feature amongst the top 300 pharmaceutical brands in India. (ORG, Oct. 2006)
- The group has a globally compliant manufacturing infrastructure comprising nine state-of-the-art facilities which support product launches not just in India but also in the regulated markets of U.S., Europe and Latin America.
- Three of the group's plants - the formulation plant at Moraiya, API plants at Ankleshwar and Dabhasa are approved by the USFDA.
- More than 500 professionals spearhead the group's research programme.
- Over 230 scientists are working on new molecular entity research at the Zydus Research Centre. The group has three NMEs – ZYH1 for treating dyslipidemia, ZYH2 for treating diabetes and ZYI1 for treating pain, in various stages of clinical trials. Also filed an IND for an anti-obesity drug – ZYO1.
- Zydus Cadila is a partner of choice for several global pharma majors such as Boehringer Ingelheim, Schering AG, Madaus AG and Altana Pharma of Germany, Mayne Pharma of Australia, Zambon of Italy, Bio Sidus of Argentina, Mallinckrodt of USA, to name a few.
- One of the most reputed pharma companies globally, Zydus Cadila aims to be one of the top ten global generic companies by 2010 and a global research-driven company by 2020.

Zydus Research Centre (ZRC)

Zydus Research Centre is the research arm of the Zydus Group. Founded in January 2000 at Ahmedabad in Western India, this state-of-the-art research centre sprawls over 2,60,000 sq. ft. The Centre is equipped with sophisticated equipment and infrastructure, necessary to carry out research in modern drug discovery and development and is recognised by the Department of Science and Industrial Research (DSIR), Government of India. Here, more than 230 research scientists conduct seminal research in diverse disciplines including Medicinal Chemistry, Biotechnology, Bio-Informatics, Genomics, Molecular & Cellular Biology, Pharmacology & Toxicology, Microbiology, Analytical Research, CMC Research, Clinical Research, and Novel Drug Delivery Research.

The Centre has three New Molecular Entities (NMEs) in various stages of clinical trials. ZYH1 for treatment of metabolic disorders is in Phase II clinical trials and NMEs - ZYI1 for treatment of inflammatory disorders and ZYH2 for the treatment of diabetes are in Phase I clinical trials. An IND has been filed for its NME - ZYO1 for treating obesity.

Zydus Research Centre aims to be the most admired pharmaceutical research centre for innovation in life science dedicated to alleviate human sufferings.

ZRC has complete infrastructure and facilities to take novel molecules/biologicals/formulations from concept to clinical evaluation stage in healthy human volunteers.

The research activities in the areas of Pharmacology, Toxicology, DMPK, Analytical Research, Clinical Research and CMC Research are to ensure compliance to GLP, GCP and cGMP specifications. Centre has OECD GLP/GCP accreditation by National GLP Compliance Monitoring Authority and ANVISA.

A number of patents have been filed from ZRC in India, US and other PCT countries. Several high quality research articles have been published in reputed international journals.

People are our strength - the Centre believes in teamwork and encouraging scientists to take up newer challenges and responsibilities. As a part of a growing organisation that continuously seeks to maintain a competitive edge through innovation, ZRC accords high value to diversity of thoughts, which is critical for arriving at the most innovative solutions to several problems and challenges confronting human healthcare.

For more details about Zydus Research Centre, please visit our website:
www.zyduscadila.com/R&D/r&d.asp.

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Day 1: February 1, 2007 (Pre-symposium Workshop)

10:00 - 10:30 hrs	**Spot Registration**
10:30 - 10:40 hrs	Opening Remarks
Dr. Mukul R Jain	Senior General Manager and Head, Department of Pharmacology & Toxicology, Zydus Research Center

10:40 - 11:25 hrs	"QSAR analyses of 3-(4-benzylpiperidin-1-yl)-N-phenyl-propylamine derivatives as potent CCR5 Antagonists"
Dr. Kunol Roy	Professor, School of Pharmacy, Jadavpur University Kolkata, India.
11:25 - 12:10 hrs	Demonstration of Accelrys products by Dr. Chandan Roy Chaudhari, Application Scientist, Accelrys Inc.
12:10 - 12:40 hrs	Tea Break

12:40 - 13:25 hrs	"Gene Expression Profiling with Dualchip Microarrays"
Dr. Muruganand	Application Manager, Eppendorf India Ltd
13:30 - 14:30 hrs	LUNCH
14:30 - 15:15 hrs	Demonstration of Eppendorf SilverQuant Microarray Scanner
Virendra Sharma	Eppendorf
15:15 - 15:45 hrs	Tea Break

15:45 - 16:30 hrs	Application of Taqman lowdensity array in diabetes research
Savita Bhosekar	Application Specialist, LabIndia
17:00 - 19:00 hrs	Social hour for all Delegates

Day 2: February 2, 2007

09.00 - 09.40 hrs — Inauguration ceremony

Session I
GLUCOSE METABOLISM AND ENERGY BALANCE

Chairpersons

- Dr. S. D. Sheth, Consultant, ICMR
- Dr. Richard DiMarchi, Indiana University

09.45 - 10.30 hrs	"An RNAi-based approach to understanding metabolic disease"
Dr. Michael Czech	Professor, Department of Biochemistry and Molecular Biology, and Director of the Program in Molecular Medicine University of Massachusetts, USA
10.30 to 11.00 hrs	Tea Break

11.00 to 11.35 hrs	"Glucose as a signal to control energy homeostasis"
Dr. Bernard Thorens	Professor of Physiology, Center for Integrative Genomics University of Lausanne, Switzerland

11.35 to 12.10 hrs	"Insulin and AMPK signalling in Skeletal Muscle: Validation of targets to prevent and treat Type 2 Diabetes Mellitus"
Dr. Juleen R. Zierath	Professor of Physiology, Department of Molecular Medicine and Surgery, Karolinska Institute, Sweden

12.10 to 12.45 hrs	"Forkhead transcription factors & Diabetes"
Dr. Markus Stoffel	Robert and Harriet Heilbrunn Professor, Rockefeller University, USA

12.45 to 13.15 hrs	"Cannabinoids and their regulation of metabolic syndrome"
Dr. Prasenjit Mitra	Group Leader, Zydus Research Centre, Ahmedabad, India.
13.15 to 15.35 hrs	Lunch, Poster & Networking

Session II
ISLETS AND ENDOTHELIAL DYSFUNCTION

Chairperson

• John H. Johnson, Ph.D., Director, Licensing and Development, Pfizer Inc.

15.35 to 16.10 hrs	"An Industry Perspective on New Therapeutic Approaches to Metabolic Disease"
Dr. David E. Moller, MD	Vice President, Endocrine and Cardiovascular, Research and Clinical, Investigation, Lilly Research Laboratories, USA

16.10 to 16.45 hrs	"AGPAT Isoforms and the Cellular Response to Fatty Acids"
Dr. Charles Burant, M.D., Ph.D.	Associate Professor, Metabolism, Endocrinology & Diabetes, University of Michigan, USA
16.45 to 17.05 hrs	Tea Break

17.05 to 17.35 hrs	"Spatial and temporal regulation of insulin granule exocytosis"
Dr. Susumu Seino, M.D.	Professor, Division of Cellular & Molecular Medicine, Kobe University School of Medicine, Japan
17.35 to 18.30 hrs	Panel Discussion. (Chairperson : Dr.Richard DiMarchi, USA)

Day 3: February 3, 2007

Session III
HORMONES, NUCLEAR RECEPTORS AND METABOLISM (ADIPOKINE, INCRETIN, INSULIN RESISTANCE, SIGNALING PATHWAYS, PPARs)

Chairperson

• Dr. C. M. Gupta, Director, CDRI, India
• Dr. Bernard Thorens, Professor of Physiology, Center for Integrative Genomics, University of Lausanne, Switzerland

09.15 - 10.00 hrs	"Integrated Neurohormonal Therapy for Obesity"
Dr. Alain Baron	Senior Vice President, Research, Amylin

10.00 - 10.35 hrs	"Cross-talk between nuclear receptors in metabolic control and cardiovascular disease"
Dr. Bart Staels	INSERM, Institut Pasteur de Lille, France
10.35 - 11.00 hrs	Tea Break

11.00 to 11.35 hrs	"Multifaceted role of PPAR gamma in the adipose tissue"
Dr. Walter Wahli	Director, Center for Integrative Genomics, Switzerland

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11.35 to 12.10 hrs	"Antiatherogenic properties of PPARgamma activators - novel effects beyond glucose control"
Dr. Nikolaus Marx	Professor, University of Ulm, Germany

12.10 to 12.45 hrs	"Therapeutic mechanisms of PPAR gamma modulators"
Dr. Silvia Corvera	Professor, Program in Molecular Medicine, University of Massachusetts, USA

12.45 to 13.20 hrs	"PPAR Based Therapy -How Do We Design Safer Compounds?"
Dr. Ashish Goel	Principal Scientist, NCE Discovery,Department of Cell Biology and Biochemistry,Zydus Research Centre, Ahmedabad, India.
13.20 to 15.00 hrs	Lunch, Poster & Networking

Session IV
ADVANCES IN TYPE 2 DIABETIC THERAPY

Chairperson

- Dr. P. Rama Rao, NIPER, India
- Dr. Michael Czech, University of Massachusetts, USA

15.00 to 15.45 hrs	"Depot-Specific Regulation of Human Adipose Tissue Adiponectin Secretion"
Dr. Robert R. Henry, M.D., FRCP (C) (Ed)	Professor of Medicine, University of California San Diego, Chief, Section of Diabetes, Endocrinology & Metabolism, Director, Center for Metabolic Research, VA San Diego Healthcare System, USA

15.45 to 16.20 hrs	"New avenues in the Treatment of Type 2 Diabetes: Targeting insulin resistance beyond HbA1c - PPARs and non PPARs"
Dr. Elena Sebokova, Ph.D., D.Sc.	F. Hoffmann La-Roche Ltd, Disease Area Head Metabolic Diseases, Basel, Swizerland
16.20 to 16.35 hrs	Tea Break

16.35 to 17.10 hrs	"Thiazolidinediones in Type 2 Diabetes: Indian Experience"
Dr. Anil Bhansali	Professor & Head, Endocrinology Postgraduate Institute of Medical Education & Research, India

17.10 to 17.45 hrs	"Therapeutic strategies to improve cardiovascular outcome in Type 2 Diabetes"
Dr. Satinath Mukherjee	Associate Professor, Department of Endrocrinology & Metabolism, Institute of Post Graduate Medical Education & Reasearch, Kolkata, India
17.45 to 18.30 hrs	Panel Discussion (Chairperson: Dr. Michael Czech, Ph.D., USA)
18.30 hrs	Cultural Evening

Day 4: February 4, 2007

Session V
DIABETES, DYSLIPIDEMIA AND RELATED COMPLICATIONS (NEPHROPATHY, NEUROPATHY, AND RETINOPATHY)

Chairperson

- Dr. Shaukat M. Sadikot, President, Diabetes India
- Dr. Alain Baron, Senior Vice President, Research, Amylin

09.00 - 09.45 hrs	"The emergence of chemical biotechnology and its application to endocrine proteins"
Dr. Richard DiMarchi	Retired Group Vice President, Eli Lilly Research labs. Professor of Chemistry and the Jack and Linda Gill, Distinguished Chair in Biomolecular Science, Indiana, University, US

09.45 - 10.20 hrs	"Pulmonary Methods of Delivery for Peptides and Proteins - Inhaled Insulin"
Dr. Viren Sarin	Senior Research Fellow, Eli Lilly & Co., Indianapolis, USA
10.20 - 10.40 hrs	Tea Break

10.40 to 11.15 hrs	"BI 1356, a novel potent and selective xanthine based DPP-IV inhibitor, exhibits a unique profile"
Dr. Michael Mark	Vice President, Metabolic Diseases Research, Boehringer-Ingelheim

11.15 to 11.50 hrs	"Trends and Opportunities in Diabetes and the Metabolic Syndrome"
Dr. John H. Johnson	Director, Licensing and Development, Pfizer Inc.
11.50 to 12.15 hrs	Best Poster Presentations (Best Poster 1&2 - 10 min. each)
12.15 to 13.30 hrs	Panel Discussion

Panel Discussion Participants

- Dr. C. M. Gupta, Director, Central Drug Research Institute, India
- Dr. Alain Baron, Senior Vice President, Research, Amylin
- Dr. Michael Czech, Ph.D., Professor, Department of Biochemistry and Molecular Biology, and Director of the Program in Molecular Medicine, University of Massachusetts, USA
- Dr. Richard DiMarchi , Jack and Linda Gill Distinguished Chair in Biomolecular Science, Indiana University, USA
- John H. Johnson, Ph.D., Director, Licensing and Development, Pfizer Inc.
- Dr Michael Mark Vice President, Metabolic Diseases Research, Boehringer-Ingelheim
- Dr. Elena Sebokova, Ph.D., D.Sc., F. Hoffmann La-Roche Ltd, Disease Area Head Metabolic Diseases, Basel, Swizerland

13.30 hrs	Vote of thanks & closing ceremony
13.45 hrs	Lunch

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Session I: Glucose Metabolism And Energy Balance

Introduction to the Chairpersons

Dr. Richard DiMarchi, Indiana University, US

Dr. DiMarchi was formerly Group Vice President for Biotechnology and Product Development at Lilly Research Laboratories, where he made major contributions to Lilly in biotechnology and endocrinology. Dr. DiMarchi was directly involved in the discovery and development of several Lilly drugs, including Humulin(R), Humatrope(R), Evista(R), Xigris(R), and Forteo(R). He was a co-inventor of Humalog(R), the first biosynthetic protein approved for human use. Additionally, at Lilly he championed the introduction and integration of cutting-edge biotechnologies, including genomics, proteomics, high-throughput screening, and combinatorial chemistry. Dr. DiMarchi is presently a Professor of Chemistry and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University. He currently serves as a co-founder and Board Chairman of Ambrx, Inc. He previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as such companies as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharmaceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, Kai Pharmaceuticals, Semafore Biotechnologies, 5AM.

Dr. S. D. Sheth, Consultant, ICMR

Dr. S.D. Seth was Professor of Pharmacology at All India Institute of Medical Science, New Delhi. Currently, He is the National Chair in Clinical Pharmacology, Indian Council of Medical Research, New Delhi. He is on the panel of Government Advisory Board and has lot of publication to his credit.

Speaker's profile

Dr. Michael Czech, Ph.D. Professor, Department of Biochemistry And Molecular Biology, and Director of the Program in Molecular Medicine University of Massachusetts, USA

Michael P. Czech, Ph.D., is currently Professor and Chair of the Program in Molecular Medicine, an academic department of the University of Massachusetts Medical School. His research program has focused on mechanisms of signal transduction and cell regulation, in particular insulin actions on glucose transport and other functions in adipocytes. He has also contributed to understanding the underlying mechanisms of insulin resistance in Type 2 diabetes and obesity.

Dr. Czech earned his doctorate in biochemistry in 1972 at Brown University, Providence, R.I. under the mentorship of Dr. John N. Fain, and was awarded a postdoctoral fellowship for further study at Duke University Medical Center. There, Dr. Czech discovered the inhibitory effect on fat cell glucose transport of cytochalasin B, a reagent that has become widely used to study glucose transport regulation. Dr. Czech became an Assistant Professor in 1974 at Brown University, where he attracted a talented group of colleagues and rose to the rank of full professor by 1980. In 1979, he developed an affinity crosslinking method to specifically label cell surface receptors, and deduced the disulfide-linked heterotetrameric subunit structure of the insulin receptor. In 1981 Dr. Czech moved to the University of Massachusetts Medical School as Professor and Chair of the Department of Biochemistry. Over the next several years, he and his colleagues identified the subunits of the IGF-I and II receptors and in collaboration with Dr. Axel Ullrich at Genentech cloned the IGF-II receptor. Dr. Czech established the concept that the IGF-I receptor tyrosine kinase mediates biological actions, while the IGF-II receptor mediates the degradation of the IGFs. More recently, Dr. Czech's group discovered GRP1, a novel target of the PI3-kinase signaling pathway. The implications of these results has helped provide the molecular framework for further exciting research on insulin and IGF-I receptor signaling.

Currently, Dr. Czech's lab is applying genomics and proteomics approaches to the goal of identifying novel components involved in the mechanisms of insulin action. His laboratory has pioneered the application of RNAi to silencing genes in adipocytes, and has discovered novel regulators of adipocyte function using RNAi screens. To date, he has co-authored more than 250 publications. He is a member of the editorial boards of several journals, including the Journal of Biological Chemistry and the American Journal of Physiology. He has served as a member of the National Institutes of Health Metabolism Study Section, the Endocrinology Study Section and the Diabetes Research and Training Center Panel. He has also served a term as member of the Cell Regulation Review Panel of the Howard Hughes Medical Institute.

Dr. Czech has received numerous awards for his research, including Outstanding Scientific Achievement Award of the American Diabetes Association in 1982; David Rumbough Scientific Award of the Juvenile Diabetes Foundation in 1985; MERIT Award, National Institutes of Health, 1997; the Elliot P. Joslin Medal in 1998, the CIIT Founder's Award, the 2000 Banting Medal and the 2004 Albert Renold Award of the American Diabetes Association.

Dr. Czech lives with his wife, Silvia Corvera, M.D., and their two children in Westborough, Massachusetts.

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Topic

An RNAi-based Approach to Understanding Metabolic Disease

Michael P. Czech
University of Massachusetts Medical School, Worcester MA, USA

Insulin resistance in muscle is a major syndrome in obese humans that contributes to the onset of diabetes. It is also established that adipose tissue is a major regulator of whole body metabolism through its ability to secrete peptides and control blood lipid levels, and can influence the insulin sensitivity of skeletal muscle. We have therefore sought to identify genes in adipose tissue that modulate insulin signaling and key metabolic pathways. Using siRNA-based screens, we identified the transcriptional corepressor RIP140 (Powelka et al JCI 116: 125, 2006) and the protein kinase MAP4k4(Tang et al PNAS 103:2087, 2006) as negative regulators of insulin-responsive hexose uptake and oxidative metabolism in 3T3-L1 adipocytes. Affymetrix GeneChip profiling revealed that RIP140 depletion upregulates the expression of clusters of genes in the pathways of glucose uptake, glycolysis, TCA cycle, fatty acid oxidation, mitochondrial biogenesis, and oxidative phosphorylation in these cells. RIP140-null mice, previously reported to resist weight gain on a high-fat diet, display enhanced glucose tolerance and enhanced responsiveness to insulin compared with matched wild-type mice. MAP4k4 depletion in adipocytes likewise increases many of the RIP140-sensitive genes and increases adipogenesis. The data available reveal that both RIP140 and MAP4k4 actions converge at PPARγ. The former directly represses PPARγ activity and the latter negatively controls PPARγ expression. We conclude that RIP140 and Map4k4 are novel negative regulators of adipose tissue oxidative metabolism and are potential therapeutic targets for controlling metabolic disease. These data also validate the power of RNAi screening for discovery of new therapeutic approaches to type 2 diabetes and obesity.

For Notes:

Speaker's profile

Dr. Bernard Thorens
Professor of Physiology
Center for Integrative Genomics
University of Lausanne, Switzerland

Bernard Thorens studied biochemistry at the University of Geneva and received his Ph.D. from the same University for studies on the biosynthesis of immunoglobulins by pre-B lymphocytes carried in the laboratory of Pierre Vassalli. He then did a postdoctoral fellowship at the Whitehead Institute for Biomedical Research in Cambridge (USA) with Harvey Lodish. In 1991 he received a Career Development Award (START fellowship) from the Swiss National Science Foundation to establish his research group at the Department of Pharmacology and Toxicology of the University of Lausanne where he was then promoted as Associate professor. Since 2002 he is Professor of Physiology and member of the Center for Integrative Genomics at the University of Lausanne. Dr. Thorens has been working in the field of diabetes and obesity, with a major focus on pancreatic islet pathophysiology and more recently on the interaction between the central nervous system and the regulation of peripheral energy metabolism. His work encompasses both molecular studies, with the initial identification by molecular cloning of glucose transporters, including GLUT2, and of the gluco-incretin receptors for GLP-1 and GIP, and integrative physiology with various mouse models of diabetes and obesity.

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Topic

Glucose as a Signal to Control Energy Homeostasis

Bernard Thorens
Department of Physiology and Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, CH-1015

Food intake and energy expenditure need to be balanced to maintain body weight homeostasis. The equilibrium between these two physiological mechanisms is controlled, in great part, by nervous signals generated at the level of the hypothalamus. This structure integrates information on food absorption and the level of energy stored in adipose tissue. This information is delivered to the brain by hormones or nutrients, acting directly on sensitive hypothalamic neurons, or through activation of afferent neuronal pathways. Over the recent years, we have investigated the role that glucose plays as a signal to regulate feeding and energy homeostasis. We have tested the hypothesis that central glucose sensors share similarities with pancreatic beta cells, in particular that glucose uptake and metabolism is required for their function. In the beta-cells, glucose uptake is controlled by the glucose transporter GLUT2 and inactivation of its gene leads to suppressed glucose-stimulated insulin secretion. Using mice with global inactivation of the GLUT2 gene, but which express a transgenic glucose transporter in their beta-cells to normalize insulin secretion, we evaluated whether GLUT2-dependent central glucose sensors were involved in the control of feeding and energy expenditure. We showed that absence of GLUT2 expression in the brain led to deregulation of feeding behavior, reduced energy expenditure, abnormal adaptation to cold temperature and entry into torpor of fasted mice. The defect in heat production can be directly linked to a reduction in brown adipose tissue expression of UCP-1 and deiodinase-2. At the level of the hypothalamus, we demonstrated that absence of glucose sensing in GLUT2-null mice was associated with induction of leptin and insulin resistance, which was evidenced by absence of regulation of these hormone signaling pathways during the fast-to-refed transition as demonstrated by the absence of regulation of STAT-3 and Akt phosphorylation and by a persistent elevation in SOCS3 mRNA expression. Thus, central GLUT2-dependent signal is a critical regulator or feeding behavior and energy expenditure and is required for normal leptin and insulin sensitivity of the melanocortin pathway. Absence of central glucose sensing leads to a state of reduced energy expenditure and hypersensitivity to cold and fasting.

For Notes:

Speaker's profile

Dr. Juleen R. Zierath
Professor of Physiology
Department of Molecular Medicine and Surgery
Karolinska Institute, Sweden

Professor Juleen R. Zierath's research focuses on cellular mechanisms underlying the development of insulin resistance in Type 2 diabetes. She is head of the Section of Integrative Physiology, Department of Molecular Medicine at Karolinska Institute, Stockholm, Sweden and has published over 140 original research papers and review articles. In 2001, Professor Zierath was awarded the Prestigious Minkowski Prize from the European Association for the Study of Diabetes, in 2005 she was a recipient of a Strategic Research Grant from the Foundation for Strategic Research, Sweden. In 2006 she was appointed to the Nobel Assembly at Karolinska Institute. She currently holds editorial positions with several leading scientific journals and is a member of the scientific advisory board for the Keystone Symposia. Her research accomplishments have bane recognized at the National and International level. One accomplishment has been to develop methodology for translational studies to delineate molecular mechanism for insulin resistance in Type 2 diabetic patients. Her group provided the first evidence for physiological regulation of insulin signaling pathways and revealed key steps along this pathway are impaired in diabetic patients. Using genetically modified experimental models of insulin resistance; she has systematically revealed the contribution of specific genes to whole body and cellular physiology. Through functional genomics, she has validated AMP-kinase as a diabetes prevention target. Other important work was in the delineation of exercise-mediated effects on skeletal muscle glucose metabolism and gene expression. This is a clinically relevant discovery since people who exercise are protected against the development of Type 2 diabetes. The ultimate goal of her work is to identify and validate molecular candidates for pharmacological therapy to treat insulin resistance. Improving insulin sensitivity should alleviate diabetic complications and improve quality of life for the diabetic patient.

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Topic

Insulin and AMPK Signaling in Skeletal Muscle: Validation of Targets to Prevent and Treat Type 2 Diabetes Mellitus

Juleen R. Zierath,
Professor of Physiology, Karolinska Institutet, Stockholm, Sweden

Type 2 diabetes mellitus is one of the major causes of death and disability, due to the complications accompanying this disease. Thus, development of effective intervention strategies is essential in order to prevent and manage Type 2 diabetes. Physical exercise profoundly enhances substrate utilization and insulin sensitivity, which in turn lowers blood glucose and lipid levels. We have shown that muscle contraction increases protein expression and function of important components in the insulin signaling pathway (Proc Natl Acad Sci USA 97:38-43, 2000), pharmacological intervention with compounds designed to mimic the "exercise-response" may be efficacious in the management of metabolic abnormalities associated with Type 2 diabetes. AMP-activated protein kinase (AMPK) is considered a "master switch" in the regulation of key proteins in metabolic pathways known to control hepatic fatty acid oxidation and ketogenesis, lipogenesis and triglyceride synthesis, adipocyte lipolysis, modulation of insulin secretion from the pancreatic β-cells, and skeletal muscle fatty acid oxidation (Am J Physiol 277:E1-E10, 1999). AMPK is an important mediator of muscle contraction-induced glucose transport and a target for pharmacological intervention to treat altered glucose homeostasis associated with Type 2 diabetes and obesity (Diabetologia 44:2180-2186, 2001; Diabetologia 45:56-65, 2002). AMPK is a heterotrimeric protein, composed of one catalytic (α) and two non-catalytic (β and γ subunits and is activated by cellular stress associated with ATP depletion (Am J Physiol 277: E1-E10, 1999). A single amino acid mutation (RNA) in the muscle-specific γ3 subunit of AMPK increases glycogen content in skeletal muscle from Hampshire pigs and this isoform provides a biological entry-point into tissue-specific metabolic regulation. 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) is an adenosine analog that can be taken up into intact hepatocytes, adipocytes and skeletal muscle and is phosphorylated to form 5-aminoimidazole-4-carboxamide ribonucleotide (ZMP), the monophosphorylated derivative that mimics the effects of AMP on AMPK (FASEB J 9:541-546, 1995). We have shown AICAR-treatment leads to a striking normalization of blood glucose levels and glucose tolerance in KKAy-CETP and ob/ob mice after in vivo treatment. Collectively, these results support a pivotal role of AMPK in the regulation of glucose homeostasis and provide evidence that targeting the AMPK pathway is effective to improve metabolic defects in diabetes. The improvements in glucose homeostasis are accompanied by increased protein expression of GLUT4 and hexokinase II due to increased MEF2 DNA binding activity (Diabetologia 45:56-65, 2002) implicating a role for AMPK in gene regulatory responses similar to that observed in response to physical exercise. This lecture will review new developments to validate AMPK as a diabetes prevention and treatment target.

For Notes:

Speaker's profile

Dr. Markus Stoffel
Director, Laboratory of Metabolic Diseases
Eidgenössische Technische Hochschule (ETH)
Zürich, Switzerland

Markus Stoffel received his medical training at Bonn University in Germany, and Fitzwilliam College at Cambridge University in Great Britain. He did his internship at the V.A. Hospital in New York and residency at the University Medical Center in Hamburg, Germany. Following Postdoctoral Fellowships at the Heinrich-Pette Institute in Hamburg (1989-1992) and the University of Chicago (1991-1993), he joined the faculty at the University of Chicago in 1993. In 1995, he was appointed Head of the Laboratory of Metabolic Diseases at the Rockefeller University in New York. And in 1999 he was appointed full Professor. In 2006 he moved to the Eidgenössische Technische Hochschule (ETH) in Zürich, Switzerland, where he is the Director of the Laboratory of Metabolic Diseases. His honors include: Irma T. Hirschl Career Scientist Award (1996), Pew Scholar Award in Biomedical Sciences (1996), Career Development Award, American Diabetes Association (1997); Robert and Harriet Heilbrunn Professorship (1998), Bristol Myers Squibb Unrestricted Grant Award (Metabolism) (2002), Ernst Klenk Award (2002), the Mary Jane Kugel Award (2002), the Dorothy Hodgkin Award (Diabetes UK, 2005) and the Oustanding Scientific Research Award from the American Diabetes Association (2006), the highest recognition for a scientist at the age below 45. In 2006 he was elected member of the Leopoldina Academy. Dr. Stoffel's research interests focus on the identification and characterization of genes involved in pathological states of insulin secretion and sensitivity in early- and late-onset non-insulin-dependent diabetes mellitus. He utilizes genetic approaches to identify and characterize diabetes susceptibility genes and drug targets for therapeutic intervention in type 2 diabetes. More recent studies have also led to the discovery of novel micoRNAs and their role in metabolism.

Together we can fight diabetes

Topic

Forkhead Transcription Factor and Diabetes

Markus Stoffel
Laboratory of Metabolic Diseases Eidgenössische Technische Hochschule (ETH) Zürich, Switzerland

Insulin resistant states are commonly associated with hepatic steatosis, hyperinsulinemia and dyslipidemia that is characterized by low HDL levels and elevated plasma triglyceride concentrations. Together with impaired glucose metabolism they are believed to significantly contribute to the etiology of type 2 diabetes. The most fundamental defect in these patients is resistance to cellular actions of insulin. Insulin insensitivity appears to cause hyperinsulinemia, increased gluconeogenesis and glucose output from the liver, reduced suppression of lipolysis in adipose tissue leading to a high free fatty acid flux, and increased hepatic very low density lipoprotein (VLDL) secretion causing hypertriglyceridemia and reduced plasma levels of high density lipoprotein (HDL) cholesterol. Emerging evidence suggests that insulin resistance and its associated metabolic dyslipidemia result from perturbations in the insulin-signaling pathway, thereby leading to a state of mixed hepatic insulin resistance and sensitivity. Several molecular pathways that link hyperinsulinemia to the development of hepatic insulin resistance and dyslipidemia are emerging: The forkhead transcription factor Foxa2 and its coactivator PGC1β are powerful activators of β-oxidation. Insulin inhibits Foxa2 through a mechanism that involves threonine phosphorylation at amino acid position T156 and nuclear exclusion. In hyperinsulinemic rodent animal models Foxa2 is permanently inactivated, thus leading to hepatic steatosis and insulin resistance. Foxa2 also is a potent transcriptional activator of apoM, a critical apolipoprotein for prebeta-HDL formation and determinant of plasma HDL levels. Thus, Foxa2 is a critical mediator of the state of mixed response to hepatic insulin resistance and sensitivity observed in type 2 diabetic subjects.

For Notes:

Speaker's profile

Dr. Prasenjit Mitra
Group Leader
Zydus Research Centre,
Ahmedabad, India

Prasenjit Mitra did his PhD from Indian Institute of Chemical Biology, Calcutta, India in 1998. He was a Postdoctoral Fellow at UMASS Medical School from 1998-2002 and served as an Instructor in Molecular Medicine at UMASS until 2005. He discovered a novel pathway of synthesis of Phosphatidylinositol (3, 4, 5) P3, a key player in signaling pathways involved in diabetes and cancer. Dr Mitra at present is a Group Leader in Discovery Biology division at Zydus Research Centre, India.

Together we can fight diabetes

Topic

From Appetite Regulation to Insulin Resistance: An Endocannabinoid Way of Modulation of Metabolic Syndrome

Prasenjit Mitra
Zydus Research Centre, Moraiya, Ahmedabad

The cannabinoid receptors, endocannabinoids and the proteins catalyzing their biosynthesis and degradation constitute a unique signaling system which has recently afforded an entirely new class of drugs for the treatment of obesity. Role of endocannabinoid system in regulating energy intake was well documented in literature. More recently, experimental evidences from our group as well as others emphasized on the role of endocannabinoids and their receptors in regulating energy homeostasis in peripheral organs. The present lecture will focus on endocannabinoid system as a central regulator of energy metabolism dysfunction of which has its sequel in the development of abdominal obesity, dyslipidemia, hyperglycemia, hyperinsulinemia and other clinical manifestations of metabolic syndrome.

For Notes:

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Session II: Islets And Endothelial Dysfunction

Introduction to the Chairperson

Dr. John H. Johnson,

Director, Licensing and Development, Pfizer Inc.

Wick Johnson received his PhD at Oklahoma State University in Cell Biology. After an NIH Postdoctoral Fellowship in Biochemistry at Cornell University, he joined the faculty of the University of Texas Southwestern Medical School where he became Professor of Internal Medicine and Physiology. He subsequently joined Warner-Lambert Parke-Davis as an Associate Research Fellow. Following the acquisition of Warner-Lambert by Pfizer, he has been Director of Metabolic and Endocrine Diseases in World -Wide Business Development for Pfizer.

Speaker's profile

Dr. David E. Moller, MD

Vice President, Endocrine and
Cardiovascular Research and Clinical Investigation
Lilly Research Laboratories, USA

David Moller is a graduate of Brown University; he received his medical degree from the University of Cincinnati followed by training in Internal Medicine and Endocrinology at George Washington University and Harvard Medical School. Following his clinical and research training at Harvard, David was an Assistant Professor at Harvard from 1989-1995; during this time, his laboratory research yielded several important clues to the molecular pathogenesis of obesity and diabetes, including the discovery of novel mutations in the insulin receptor gene which were causative for inherited insulin resistance.

Recently, Dr. Moller joined Eli Lilly and Company in November 2005 as Vice President of Endocrine and Cardiovascular Research and Clinical Investigation. In this new position, he oversees discovery and early clinical development efforts in Diabetes, Obesity, Atherosclerosis, and Musculoskeletal research.

Prior to joining Lilly, Dr. Moller worked at Merck Research Laboratories as Vice President, Metabolic Disorders and assumed responsibility for oversight and coordination of global diabetes and obesity research efforts. Dr. Moller's research team delivered several important additions to the pipeline including Sitagliptin (Januvia™), a first-in-class DPP-4 inhibitor (NDA now filed) and several additional diabetes and obesity mechanisms which are progressing in clinical development.

Dr. Moller has greater than one hundred peer-reviewed papers to his credit and has spoken at many national and international meetings. He has served on the editorial board of several journals; in addition to receiving several awards. He is a member of various professional and honorary societies, and was elected as a member of the American Society of Clinical Investigation in 1996. Dr. Moller was also recently appointed as an adjunct (honorary) professor at the Karolinska Institute in Stockholm.

Together we can fight diabetes

Topic

An Industry Perspective on New Therapeutic Approaches to Metabolic Disease

David E. Moller
Endocrine and Cardiovascular Research and Clinical Investigation, Lilly Research Laboratories, USA

For Notes:

Speaker's profile

Dr. Charles Burant, M.D., Ph.D.

Associate Professor
Metabolism, Endocrinology & Diabetes
University of Michigan, USA

Charles F. Burant, MD, Ph.D. is Professor of Internal Medicine at the University of Michigan Health System in Ann Arbor, Michigan. He currently is the Robert C. and Veronica Atkins Professor of Metabolism and directs the Michigan Metabolics and Obesity Center. His research interests are in the areas of the molecular and cellular biology of insulin resistance and the effect of insulin resistance on β-cell function as well as lipid and glucose metabolism. His clinical interests are focused on type 2 diabetes, insulin resistance, and the metabolic syndrome.

Dr. Burant is an Associate Editor for the American Journal of Physiology-Endocrinology and Metabolism. He is active in the American Diabetes Association, serving on the Research Policy Committee and the Board of Directors of the Research Foundation.

Dr Burant received his medical degree and doctorate of philosophy in Molecular and Cellular biology from the Medical University of South Carolina in Charleston. His internship and residency were served at the University of California in San Francisco, and Dr Burant completed his fellowship in the Department of Medicine, Endocrinology Section, at the University of Chicago.

Together we can fight diabetes

Topic

Fatty acids, AGPAT1 and AGPAT2 and the Modulation of Insulin Signaling

Angela R. Subauste and Charles F. Burant
Department of Internal Medicine, University of Michigan, Ann Arbor, MI.

Congenital Generalized Lipodystrophy (CGL) is an autosomal recessive disorder characterized by the total lack of fat since birth. Homozygous or compound heterozygous mutations in 1-acylglycerol-3-phosphate-O-acyltransferase 2 (AGPAT2) is responsible for CGL in a subgroup of patients. We found that muscle derived stem cells (MDSC) from CGL were incapable of differentiating into adipocytes while retaining myogenic potential. Adipogenesis can be rescued by AGPAT2, but not AGPAT1 overexpression. Induction of adipogenesis in GCL MDSC resulted in a significant increase in apoptosis which could be reproduced using siRNA-mediated knockdown of AGPAT2 in 3T3-L1 preadipocytes. The decrease in cell survival correlated with a downregulation of Akt phosphorylation at Ser 473 together with a decreased phosphorylation of its downstream targets p70S6K1 and FoxO1. The inhibition of adipogenesis after AGPAT2 knockdown was rescued by constitutively active Akt (myr-Akt), suggesting the adipogenic failure is due to defective Akt signaling in preadipocytes. Overexpression of AGPAT2, but not AGPAT1, increased mTOR (TORC2) dependent Akt Ser 473 phosphorylation and this effect was enhanced by fatty acids. In contrast, overexpression of AGPAT1 increased TORC1-mediated phosphorylation of p70S6K1 which was also enhanced by fatty acids. In C2C12 muscle cells, AGPAT1 and fatty acids increased phosphorylation of IRS-1 on S307 and caused a down-regulation of the protein. The results suggest that fatty acids have a dual effect on insulin signaling which are mediated in part by the generation of phosphatidic acid or derivatives.

For Notes:

Speaker's profile

Dr. Susumu Seino, M.D. D. M. Sci.

Professor Division of Cellular & Molecular Medicine,
Kobe University School of Medicine, Japan

2003 to present Professor, Division of Cellular and Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, JAPAN

1991 Professor, Division of Molecular Medicine, Center for Biomedical Science, Chiba University School of Medicine, Chiba, JAPAN

1991 Associate Professor, Department of Medicine, Section of Endocrinology, The University of Chicago, Chicago, U.S.A.

1986 Associate, Howard Hughes Medical Institute, University of Chicago

1982 Postdoctoral Fellow , Department of Internal Medicine, Division of Endocrinology and Metabolism, The University of Michigan, Ann Arbor, U.S.A.

1982 Doctor of Medical Science (D. M. Sci., Ph.D) received, Kyoto University School of Medicine, Kyoto, Japan

1974 Doctor of Medicine (M.D.) received, Kobe University School of Medicine, Kobe, JAPAN

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Topic

Spatial and Temporal Regulation of Insulin Granule Exocytosis

Susumu Seino
Kobe University Graduate School of Medicine, Japan

Insulin, a central hormone of glucose homeostasis, is secreted from pancreatic β-cells. Insulin secretion is regulated by various intracellular signals, including calcium, ATP, cAMP, and GTP-binding proteins. Among them, cAMP is known to play an important role in the potentiation of insulin secretion. We recently have found that cAMP potentiates insulin granule exocytosis by PKA-independent as well as by PKA-dependent mechanisms. The PKA-independent mechanism is mediated by the cAMP-binding protein cAMP-GEFII (also called Epac2). cAMP-GEFII-mediated insulin granule exocytosis requires the interaction of cAMP-GEFII with Piccolo and Rim2. cAMP signals are now known to be localized in distinct microdomains or functional compartments (cAMP compartmentation). G-protein coupled receptors, GTP-binding proteins, adenylyl cyclase isoforms, PDE isoforms, phosphoprotein phosphatases, AKAP isoforms, and PKA substrates all contribute to cAMP compartmentation associated with PKA signaling, as proposed for cardiomyocytes. We hypothesize that cAMP-GEFII resides in a cAMP compartment distinct from that containing PKA. Because cAMP-GEFII has a lower affinity for cAMP than for PKA, a much higher concentration of cAMP might accumulate in the cAMP compartment in which cAMP-GEFII-mediated signaling occurs. We are currently investigating the temporal and spatial regulation of insulin granule exocytosis, using yellow fluorescence protein (Venus) fused with insulin (insulin-Venus) in combination with total internal reflection fluorescence (TIRF) microscopy. In this symposium, I will discuss the role of cAMP signaling in the temporal and spatial regulation of insulin granule exocytosis.

For Notes:

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Session III: Hormones, Nuclear Receptors And Metabolism (Adipokine, Incretin, Insulin Resistance, Signaling Pathways, PPAR's)

Introduction to the Chairpersons

Dr. C. M. Gupta, Director,
Central Drug Research Institute, India

C.M. Gupta was born in Rajasthan in the year 1944 and received his Ph.D. degree from Central Drug Research Institute (CDRI), Lucknow in 1969. Subsequently, he worked first as a Post Doctoral Fellow at Syntex Research Centre at Palo Alto, California, U.S.A. and then at M.I.T., Cambridge, USA as a Research Associate under the supervision of Prof. H. Gobind Khorana. After returning to India in 1978, he established a very vibrant research group in Membrane Biology at CDRI. In 1992, he moved to the Institute of Microbial Technology, Chandigarh as its Director and then in 1997, he took over the charge as the Director, Central Drug Research Institute, Lucknow where he still continues to work in the same capacity. Dr. Gupta received several prizes and awards including Shanti Swarup Bhatnagar Prize in Biological Science and elected to the fellowships of all the three science academies of India as well as National Academy of Medical sciences and Third World Academy of Sciences.

Dr. Bernard Thorens
Professor of Physiology
Center for Integrative Genomics
University of Lausanne, Switzerland

Bernard Thorens studied biochemistry at the University of Geneva and received his PhD from the same University for studies on the biosynthesis of immunoglobulins by pre-B lymphocytes carried in the laboratory of Pierre Vassalli. He then did a postdoctoral fellowship at the Whitehead Institute for Biomedical Research in Cambridge (USA) with Harvey Lodish. In 1991 he received a Career Development Award (START fellowship) from the Swiss National Science Foundation to establish his research group at the Department of Pharmacology and Toxicology of the University of Lausanne where he was then promoted as Associate professor. Since 2002 he is Professor of Physiology and member of the Center for Integrative Genomics at the University of Lausanne. Dr. Thorens has been working in the field of diabetes and obesity, with a major focus on pancreatic islet pathophysiology and more recently on the interaction between the central nervous system and the regulation of peripheral energy metabolism. His work encompasses both molecular studies, with the initial identification by molecular cloning of glucose transporters, including GLUT2, and of the gluco-incretin receptors for GLP-1 and GIP, and integrative physiology with various mouse models of diabetes and obesity.

Speaker's profile

Dr. Alain Baron
Senior Vice President, Research
Amylin

Dr. Baron is currently serving as Senior Vice President of Research since September 2004 after having served as Vice President of Clinical Research from December 1999, and as Senior Vice President of Clinical Research from June 2002. He is currently responsible for early development of all drug candidates at Amylin Pharmaceuticals. Previously, Dr. Baron worked for the Indiana University School of Medicine in Indianapolis, where he served as Professor of Medicine and Director, Division of Endocrinology and Metabolism. Prior to this position at Indiana, Dr. Baron held academic positions in the Division of Endocrinology and Metabolism at University of California, San Diego, and the Veterans Administration Medical Center in San Diego. He is the recipient of several prestigious awards for his research in diabetes and vascular disease, including the 1996 Outstanding Clinical Investigator Award from the American Federation for Medical Research, and is a past National Institutes of Health ("NIH") MERIT award recipient. He is co-editor of the Ellenberg & Rifkin Text book of Diabetes. He earned his M.D. from the Medical College of Georgia, Augusta, and completed postdoctoral studies at the University of California, San Diego.

Topic

Integrated Neurohormonal Therapy for Obesity

Alain D. Baron, Amylin

The incidence of obesity is currently at pandemic levels, and represents one of the highest unmet medical needs as it is associated with increased morbidity and mortality. Therapeutic modalities, exclusively small molecules to date, have not performed in a satisfactory manner on either efficacy or safety. Peptide and protein hormones are generally both safe and potent. These hormones have typically been studied for their individual activities and pharmacologies. As single agents, gut, islet, and fat cell derived hormones have shown moderate efficacy in rodent models of obesity, in particular the diet induced obese or DIO rat model. Here we present data supporting an integrated multihormonal approach to the therapy of obesity, both rodent and human data will be shared.

For Notes:

Speaker's profile

Dr. Bart Staels

INSERM
Institut Pasteur de Lille, France

Bart Staels, PhD., is professor in the faculty of pharmacy at the University of Lille 2, Lille, France. He is also research group leader in the Department of Atherosclerosis at the Institut Pasteur de Lille, Inserm UR545, France.

Pr. Staels earned his doctorate at the Institute for Pharmaceutical Sciences, University of Leuven, Belgium. He completed postdoctoral work at the Metabolic Research Unit, University of California, San Francisco and was postdoctoral research fellow of the Reverse Cholesterol Transport/Atherosclerosis Project, BioAvenir, Vitry sur Seine, France.

Pr. Staels is a member of learned societies such as the European and International Atherosclerosis Societies, the Nouvelle Société Française d'Athérosclérose, the American Heart Association and the American Diabetes Association.

The recipient of numerous grants, awards, and scientific prizes, Pr Staels has been awarded the Young Investigator Award of the European Atherosclerosis Society, the Bronze Medal of the CNRS and the Lifetime Achievement Award of the British Atherosclerosis Society.

Pr. Staels' research has focused on molecular pharmacology of cardiovascular and metabolic diseases. He studied particularly the role of nuclear receptors (such as the PPARs, FXR, Rev-erbα and RORα) in the control of inflammation and lipid and glucose homeostasis as well as the transcriptional mechanisms involved. Pr. Staels was the first to identify a crucial role for the nuclear receptor PPARα in the control of lipid and glucose metabolism as well as cardiovascular function in humans. He elucidated the action mechanism of the fibrate class of drugs that are currently used in the treatment of lipid disorders and worked also on the action mechanism of the glitazones, a very recently developed class of anti-diabetic drugs. His work has identified the PPAR transcription factors as potential drug targets for the treatment of diabetes, dyslipidemia and cardiovascular disease, which contributed to the development of several novel therapeutic compounds currently in different stages of clinical development.

To date, Pr. Staels has published more than 180 original papers and more than 100 abstracts. He has also authored 80 review articles and contributed several book chapters. Pr. Staels is also reviewer for numerous international journals and has been invited speaker at many prestigious international meetings.

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Topic

Cross-talk Between Nuclear Receptors in Metabolic Control and Cardiovascular Disease

B. Staels, U545 INSERM, Département d'Athérosclérose, Institut Pasteur de Lille, and Université de Lille II, Lille, France.

Cardiovascular disease is significantly increased in patients with the metabolic syndrome and type 2 diabetes. A clustering of risk factors, including dyslipidemia, insulin resistance, hypertension, inflammation and coagulation disorders result in an increased risk for cardiovascular events in these patients. The Farnesoid X Receptor (FXR) and peroxisome proliferator-activated receptor (PPAR) α are members of the nuclear receptor superfamily. Whereas PPARα is activated by fatty acids, FXR has recently been identified as a bile acid-activated nuclear receptor. FXR not only controls bile acid synthesis, conjugation and transport, but also lipid and glucose metabolism. Activation of PPARα represents one important pathway that influences vascular function both directly and indirectly. PPARα activation induces beneficial effects not only on lipid metabolism, but also influences glucose homeostasis, endothelial function and vessel wall inflammation. PPARα agonists in clinical use, such as fibrates, may alter the process of atherosclerosis, especially in subjects with the metabolic syndrome and type 2 diabetes. This presentation will highlight the molecular mechanisms of FXR and PPARα action in the prevention and treatment of the metabolic syndrome and atherosclerosis.

For Notes:

Speaker's profile

Dr. Walter Wahli

Director, Center for Integrative Genomics & National Research Centre, University of lausanne, Switzerland

Walter Wahli received his PhD in Bern in 1977. He carried out a postdoctoral fellowship with Dr. Igor Dawid at the Department of Embryology, Carnegie Institution of Washington in Baltimore. He then was at the Department of Biochemistry of the National Cancer Institute, NIH, in Bethesda, as visiting fellow and visiting associate. He moved to Lausanne in 1980, where he was appointed Professor of biology and Director of the Institute of Animal Biology of the University. He was Vice-rector for Research and Postgraduate Education of the Lausanne University between 1999 and 2003 and Founding Director of the Center for Integrative Genomics. In 1996, he was elected member of the Research Council of the Swiss National Science Foundation and was President of its Biology and Medicine Division between 2004 and 2006.

One major research interest of Walter Wahli is the role of nuclear hormone receptors. In recent years, he worked mainly on receptors that he co-discovered, the Peroxisome Proliferator-Activated Receptors (PPARs). Their dysfunction has been implicated in the manifestation of many diseases, ranging from obesity to cancer. Currently, his activities concentrate on the unveiling of new functions of PPARs in both coordinating the roles of different organs in energy homeostasis and regulating tissue repair mechanisms, including cell survival, proliferation and migration. Walter Wahli's many career honors and awards include the prestigious Otto Naegeli Price and the Euro Fed Lipid Research Award.

Topic

Multifaceted Role of PPAR gamma in the Adipose Tissue

Silvia I Anghel, Jérôme Feige, Daniel Rossi, Jennifer Rieusset, Béatrice Desvergne and Walter Wahli.
Center for Integrative Genomics and National Research Centre "Frontiers in Genetics", University of Lausanne, Switzerland

PPAR gamma plays a key role in adipocyte differentiation and insulin sensitivity. Its synthetic ligands, the thiazolidinediones (TZD), are used as insulin sensitizers in the treatment of type 2 diabetes. PPAR gamma is mostly expressed in adipose tissue and to a much lesser extent in other organs. It serves as an essential regulator of adipocyte differentiation, lipid storage in mature adipocytes, as well as their maintenance and survival in the adipose tissue of the adult. Deregulations of PPAR gamma functions in adipocytes are suggested to account for diseases such as obesity and diabetes although deletion of only one allele of PPAR gamma or partial inhibition of its activity in mouse models seems to improve insulin sensitivity. It was also shown that a tissue-specific deletion PPAR gamma in skeletal muscle causes insulin resistance.

Comparison of the gene expression profiles in the adipose tissue of wild type and heterozygous PPAR gamma mice enabled us to better understand the role of this nuclear receptor isotype in the adult adipocyte. Deletion of one PPAR gamma allele not only affects different metabolic pathways, such as lipid synthesis, pentose phosphate shunt, lipolysis, and glycerol export, but also, more surprisingly, networks of genes involved in IR/IGF-1 signaling, cellular integrity, detoxification, and inflammation/immunity. Whereas most of these pathways are not affected in heterozygous skeletal muscle cells, there is a remarkable correlation with affected expression pathways in a cellular model (3T3-L1) of adipocyte differentiation in response to TZD. In addition, this model reveals the specific actions of PPAR gamma on adipokines in adipocytes versus other cell types of the adipose tissue. Altogether, these results unveil novel roles of PPAR gamma in the adipose tissue and underscore the multifaceted action of this PPAR isotype in the fine-tuned functioning of this major tissue in the healthy and diseased organism.

For Notes:

Speaker's profile

Dr. Nikolaus Marx

Professor
University of Ulm, Germany

Nikolaus Marx is Professor of Medicine at the University of Ulm in Germany. He received his medical training at the Universities of Mainz, Genf (Switzerland) and Düsseldorf, obtaining his MD in 1994. His thesis on growth regulation in human renal cancer cell lines was completed at the laboratory of Professor Gerharz at the Institute of Pathology, University of Mainz.

After a post-doctoral fellowship at Brigham and Women's Hospital, Harvard Medical School, Nikolaus Marx later became a board-certified internist, then cardiologist, before specializing in intensive care medicine in internal medicine at the University of Ulm, where he was appointed Professor of Medicine earlier this year.

Professor Marx is a member of several organizations within the field of diabetes and the vasculature, including the European Society of Cardiology, American Heart Association (AHA), German Diabetes Association and the European Association for the Study of Diabetes. In addition to reviewing submitted manuscript to numerous journals, including Circulation, Diabetologia, Diabetes, Diabetes Care, the Journal of Immunology and The Lancet, he is currently Assistant Editor for Diabetes and Vascular Disease Research. Professor Marx was awarded the Servier Young Investigators Award in 1999 at the First European Meeting on Vascular Biology and Medicine more recently was winner of the Poster Award Competition in Epidemiological Science at AHA 2002, the 2004 Morgagni Young Investigator Award as well as the Rising Star Award 2005 of the European Association for the Study of Diabetes (EASD).

Topic

Antiatherogenic Properties of PPARγ Activators - Novel Effect Beyond Glucose Control

Nikolaus Marx
University of Ulm, Germany

Patients with type 2 diabetes mellitus and insulin resistance exhibit an increased propensity to develop arteriosclerosis with its sequelae acute myocardial infarction and stroke. Therapeutical strategies to modulate the increased cardiovascular risk of these patients is one of the major task in vascular biology these days. Among such approaches, anti-diabetic, PPARγ activating, thiazolidinediones (TZDs, glitazones) are very promising with respect to their anti-atherogenic properties.

Peroxisome proliferator-activated receptor-gamma (PPARγ) is a nuclear transcription factor, controlling gene expression in response to their ligands. PPARγ can be activated by antidiabetic glitazones, thus regulating genes involved in glucose homeostasis and adipogenesis. In addition to these metabolic effects, various groups were interested to examine the effect of PPARγ activators on mechanism involved in atherogenesis. First, the expression of PPARγ in the vessel wall in arteriosclerotic lesions has been demonstrated and it has been shown that anti-diabetic PPARγ-activating TZDs exhibit anti-inflammatory and anti-atherogenic properties in vascular cells. As such, we and others found inhibitory effects on endothelial cell and T-cell activation, modulatory function on the release of matrix-degrading enzymes from human monocytes / macrophages, as well as a reduction of smooth muscle cell migration by PPARγ activation. Given the critical role of these processes in lesion development, these in-vitro data suggested that anti-diabetic PPARγ activators may modulate the inflammatory response in the vessel wall and as such provide a potential novel therapeutical option to influence vascular disease in the high risk population of type 2 diabetic patients. Subsequently, clinical studies showed that treatment of patients with diabetes mellitus type 2 and coronary artery disease with PPARγ-activating TZDs reduces serum levels of novel inflammatory biomarkers of arteriosclerosis, improves endothelial function, and reduces restenosis after coronary stenting in non-diabetic subjects, suggesting that this concept of anti-inflammatory effects of TZDs holds true in treated patients.

For Notes:

Speaker's profile

Dr. Silvia Corvera

Professor
Program in Molecular Medicine
University of Massachusetts, USA

Silvia Corvera received her MD degree from the National University of Mexico in 1981, and a MSc in Biochemistry at the same institution in 1984. She received a Fogarty International Fellowship from the National Institutes of Health to perform Postdoctoral studies at the University of Massachusetts Medical School. Prior to joining the faculty at UMMS, she held the position of Assistant Professor of Pathology and Laboratory Medicine at the University of Pennsylvania.

Together we can fight diabetes

Topic

Therapeutic Mechanisms of PPAR gamma Modulators

Dr. Silvia Corvera

Program in Molecular Medicine, University of Massachusetts, USA

For Notes:

Speaker's profile

Dr. Ashish Goel

Principal Scientist
NCE Discovery
Department of Cell Biology and
Biochemistry
Zydus Research Centre

Dr. Goel is currently serving as Principal Scientist for PPAR NCE Discovery group at Zydus Research Centre (ZRC) since 2006. He joined ZRC as Senior Scientist in 2003 and has been responsible for setting up in vitro screening assays for various metabolic disorder targets like diabetes, dyslipidemia and obesity. He is currently serving as Project Manager for PPARs as a target for diabetic dyslipidemia. Dr. Goel earned his doctorate in Biochemistry in 2000 at All India Institute of Medical Sciences, New Delhi. His work on the gene regulation of human cathepsin L in malignant cells was done under the guidance of Dr. Shyam Chauhan (AIIMS) and Dr. Michael M. Gottesman (NCI, NIH). Thereafter he moved to Johns Hopkins University, School of Medicine to complete postdoctoral studies with Prof. Peter Pedersen in the filed of Epigenetic regulation of Hexokinase Type II in highly malignant hepatoma. He has published many papers in peer reviewed journals of national and international repute. He is the recipient of many fellowships and awards including the prestigious Daniel M. Lane postdoctoral award at Johns Hopkins University, School of Medicine. His current interest lies in designing, molecular profiling and toxicogenomics of PPAR compounds for the treatment of diabetic dyslipidemia.

Topic

PPAR Based Therapy - How Do We Design Safer Compounds?

Ashish Goel, Ph.D

NCE Discovery, Department of Cell Biology and Biochemistry, Zydus Research Center, Ahmedabad, India

Peroxisome Proliferator-Activated Receptors (PPARs) are ligand activated transcription factors of nuclear receptor superfamily. They form heterodimers with RXR and transactivate target genes involved in metabolic pathways such as insulin signaling, glucose metabolism and adipocyte differentiation. Ligands for PPARs have been implicated in the treatment of various metabolic disorders like diabetes and dyslipidemia. However these ligands have also been associated with several side effects such as weight gain, edema and liver toxicity.

It has been well established that each ligand confers a unique conformational change in the nuclear receptor, which in turn leads to displacement and recruitment of a specific set of co-repressors and co-activators. Such differential co-regulator recruitment leads to modulation of different physiological pathways, tissue selective effects and side effects. We have utilized this ligand specific co-regulator recruitment property of these nuclear receptors and developed a Co-regulator Interaction Database (CoID) for screening and selecting compounds with safer toxicity profile in a high throughput screening (HTS) system. This presentation will present data of various compounds that show PPAR activation, related with differential interaction with co-regulators, which in turn might influence the pharmacodynamic activities arising from these compounds as well as toxicological effects related with such co-regulator interaction.

For Notes:

Together we can fight diabetes

Session IV: Advances In Type 2 Diabetic Therapy

Introduction to the Chairpersons

Dr. Michael Czech, University of Massachusetts, USA

Michael P. Czech, Ph.D., is currently Professor and Chair of the Program in Molecular Medicine, an academic department of the University of Massachusetts Medical School. His research program has focused on mechanisms of signal transduction and cell regulation, in particular insulin actions on glucose transport and other functions in adipocytes. He has also contributed to understanding the underlying mechanisms of insulin resistance in Type 2 diabetes and obesity.

Dr. Czech earned his doctorate in biochemistry in 1972 at Brown University, Providence, R.I. under the mentorship of Dr. John N. Fain, and was awarded a postdoctoral fellowship for further study at Duke University Medical Center. There, Dr. Czech discovered the inhibitory effect on fat cell glucose transport of cytochalasin B, a reagent that has become widely used to study glucose transport regulation. Dr. Czech became an Assistant Professor in 1974 at Brown University, where he attracted a talented group of colleagues and rose to the rank of full professor by 1980. In 1979, he developed an affinity crosslinking method to specifically label cell surface receptors, and deduced the disulfide-linked heterotetrameric subunit structure of the insulin receptor. In 1981 Dr. Czech moved to the University of Massachusetts Medical School as Professor and Chair of the Department of Biochemistry. Over the next several years, he and his colleagues identified the subunits of the IGF-I and II receptors and in collaboration with Dr. Axel Ullrich at Genentech cloned the IGF-II receptor. Dr. Czech established the concept that the IGF-I receptor tyrosine kinase mediates biological actions, while the IGF-II receptor mediates the degradation of the IGFs. More recently, Dr. Czech's group discovered GRP1, a novel target of the PI3-kinase signaling pathway. The implications of these results has helped provide the molecular framework for further exciting research on insulin and IGF-I receptor signaling.

Currently, Dr. Czech's lab is applying genomics and proteomics approaches to the goal of identifying novel components involved in the mechanisms of insulin action. His laboratory has pioneered the application of RNAi to silencing genes in adipocytes, and has discovered novel regulators of adipocyte function using RNAi screens. To date, he has co-authored more than 250 publications. He is a member of the editorial boards of several journals, including the Journal of Biological Chemistry and the American Journal of Physiology. He has served as a member of the National Institutes of Health Metabolism Study Section, the Endocrinology Study Section and the Diabetes Research and Training Center Panel. He has also served a term as member of the Cell Regulation Review Panel of the Howard Hughes Medical Institute.

Dr. Czech has received numerous awards for his research, including Outstanding Scientific Achievement Award of the American Diabetes Association in 1982; David Rumbough Scientific Award of the Juvenile Diabetes Foundation in 1985; MERIT Award, National Institutes of Health, 1997; the Elliot P. Joslin Medal in 1998, the CIIT Founder's Award, the 2000 Banting Medal and the 2004 Albert Renold Award of the American Diabetes Association.

Dr. P. Rama Rao, NIPER, India

Prof. P Ramarao is currently director NIPER, Mohali, India. Ramarao is known to have successfully established the Pharmacology & Toxicology department and has also been instrumental in shaping other facilities at the Institute viz., Computer Centre, Library and Central Animal Facility. In a multidimensional career spanning over 25 years, Prof. Ramarao has held various positions of responsibility. He is a member of several national committees. Prof. Ramarao completed his pharmacy education (B.Pharm. and M.Pharm.) from Banaras Hindu University, Varanasi in 1979 and worked for a short period in Analytical Testing Services, New Delhi. He joined his Alma mater in 1980 as lecturer, and obtained his Ph.D in the year 1986. Subsequently, during 1987-1990, he worked in Department of Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago and Department of Surgery, Beth Israel Hospital & Harvard Medical School, Boston. Prof. Ramarao on his return joined as Reader in Pharmacology at his parent department. While working at this department he was offered UGC Career Development award in 1995 (which he did not avail) and opted to join NIPER to establish the Department of Pharmacology & Toxicology. Dr. Ramarao's research interests are determination of cause and effect relationship of diabetic complications especially hypertension, inhibition of opioid tolerance and dependence and G-protein coupled characterization and their transmembrane signal mechanisms. Dr. Ramarao has published several papers in international journals of high repute.

Speaker's profile

Dr. Robert R. Henry, M.D., FRCP (C) (Ed)

Professor of Medicine
University of California San Diego
Chief, Section of Diabetes,Endocrinology & Metabolism
Director, Center for Metabolic Research,
VA San Diego Healthcare System, USA

Robert R. Henry, MD, is Professor of Medicine at the University of California, San Diego. He is also Chief of both the Section of Endocrinology, Metabolism & Diabetes and the Center for Metabolic Research at the VA Medical Center in San Diego.

Dr Henry received his medical degree from the University of Manitoba Medical School, Manitoba, Canada, where he also completed his residency in internal medicine and fellowship in endocrinology. He has been Visiting Assistant Professor of Medicine, Diabetic Research Unit, at the University of Colorado Health Sciences Center, Visiting Assistant Research Endocrinologist at the University of California, San Diego, and Visiting Professor of Medicine at the University of Edinburgh, Royal Infirmary.

He is a member of several professional societies, including the American Diabetes Association, the European Association for the Study of Diabetes, the North American Association for the Study of Obesity, the Endocrine Society, the Royal College of Physicians and Surgeons of Canada and Edinburgh, and the American Federation for Clinical Research. His research is funded by the National Institutes of Health-NIDDK, the Department of Veterans Affairs and numerous pharmaceutical grants. Recent awards include the Distinguished Clinical Scientist Award from the American Diabetes Association, the Mary Jane Kugal Award of the Juvenile Diabetes Research Foundation International, the Pfizer Visiting Professorship in Diabetes and the Robert H. Williams-Rachmiel Levine Award from the Western Metabolism Club.

Dr Henry has published more than 250 journal articles and abstracts. His current research interests involve the metabolic and cardiovascular effects of human adipose tissue secretory products including adiponectin, signal interactions between skeletal muscle and adipose tissue and defects of insulin signal transduction in these tissues of obese and type 2 diabetic patients.

Together we can fight diabetes

Topic

Depot-Specific Regulation of Human Adipose Tissue Adiponectin Secretion

Dr. Robert R. Henry
University of California San Diego; Section of Diabetes,Endocrinology & Metabolism,

Obesity and type 2 diabetes are increasingly significant health care concerns. Excess adipose tissue is highly correlated with and may contribute to insulin resistance. Studies have suggested that greater insulin resistance and metabolic dysfunction results from accumulation of visceral rather than subcutaneous adipose tissue. One possible contributing factor is adiponectin, an adipocyte-specific insulin-sensitizing secreted protein. Circulating adiponectin levels are reduced in obesity and type 2 diabetes and elevated in response to thiazolidinedione treatment. We have evaluated adiponectin release from subcutaneous and visceral adipose tissue maintained in organ culture over a seven-day period. Over 0-48 hours in culture subcutaneous adipose tissue from healthy subjects released more adiponectin than from type 2 diabetic subjects, reflecting the situation seen in vivo. In that same period, adiponectin secretion from human subcutaneous fat was greater than that from visceral fat. Adiponectin release decreased with time in culture but this depot difference was still present at 6 days for healthy non-diabetic subjects. In contrast, there were no differences in adiponectin release between diabetic subcutaneous or visceral fat, either at 48 hourr or later times. Unlike the case for secretion, the adiponectin content of isolated adipocytes, normalized to cell protein, was similar in subcutaneous and visceral fat. Pioglitazone (2-10 uM) treatment resulted in an approximate 2-fold increase in adiponectin secretion from subcutaneous fat from both non-diabetic and type 2 diabetic subjects. Greater than 48 hr was needed for the effect to appear. Visceral fat from both non-diabetic and diabetic subjects showed little or no change in adiponectin secretion in response to pioglitazone. However, pioglitazone treatment did increase the adiponectin content of adipocytes from both subcutaneous and visceral fat. Increasing the amount of subcutaneous fat in the culture system resulted in a reduction of adiponectin secretion normalized to tissue weight, similar to the lower levels seen with increasing adiposity in vivo. Potential mediators of this effect, whose secretion increased under these conditions include: IL-6, IL-8, and MCP-1. The organization of adiponectin into multimeric forms changed with time in culture, shifting from high molecular weight (HMW) oligomers to low molecular weight (LMW) trimers over 6 days, for both intracellular and secreted adiponectin. Pioglitazone treatment did not alter this change in multimerization. Adipose tissue maintained in organ culture reveals several features of adiponectin synthesis and secretion, including augmented release from non-diabetic subjects. In summary/conclusion: 1) subcutaneous fat from non-diabetic subjects display augmented adiponectin release. 2) This depot-specific benefit is lost in diabetic subjects. 3) Differences in adiponectin secretion between non-diabetic and diabetic subcutaneous fat, in light of comparable tissue adiponectin content, suggests independent regulation of adiponectin synthesis/accumulation and secretion. 4) Further support for such dissociation is provided by the ability of pioglitazone to increase cellular adiponectin in subcutaneous and visceral fat but augment secretion only in subcutaneous. 5) Adipose tissue mass is sufficient to induce obesity-related reductions in adiponectin secretion. There are adipose tissue depot-specific differences in adiponectin secretion and thiazolidinedione responsiveness that may contribute to insulin resistance in obesity and type 2 diabetes.

For Notes:

Speaker's profile

Elena Sebokova, Ph.D., D.Sc

F. Hoffmann La-Roche Ltd
Disease Area Head Metabolic Diseases,
Basel, Switzerland

Elena Sebokova, is a Disease Area Head of Metabolic Diseases in Pharma Research at the F. Hoffman La Roche Ltd in Basel, Switzerland. Before joining the industry her academic carrier was devoted to research professorship in physiology at the Institute of Endocrinology and to the DNA diagnosis of monogenic forms of diabetes at the Diabgene Laboratory in Bratislava, Slovakia.

Dr. Sebokova graduated from Technical University in Bratislava, where she also received her postgraduate training in biochemistry followed by further studies in biological sciences. Her research expertise in metabolism and diabetes was launched during postdoctoral fellowship at the Department of Medicine at the University of Alberta, Edmonton Canada, as well as at the Diabetes and Metabolism Unit of Boston University Medical Center, MA, USA. All-together she has spent three decades in basic and clinical research in integrated physiology, genetics, diagnostics and treatment of diabetes, metabolic and endocrine diseases.

Dr. Sebokova has authored more that 120 in extenso papers in national and international journals, and also noteworthy number of book chapters and editorials. In addition to holding membership in several professional societies such as the American Diabetes Association, European Association of the Study of Diabetes etc., Dr. Sebokova served as a Lecturer in the field of diabetes, insulin resistance and metabolic syndrome, guest co-editor of the Annals of the new York Academy of Sciences, and EU Expert in the Life Sciences – Diabetes.

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Topic

New Avenues in The Treatment of Type 2 Diabetes – Targeting Insulin Resistance Beyond HbA1c - PPAR and non-PPAR Approaches

Elena Sebokova and Jacques Mizrahi

Pharmaceutical Division, F. Hoffman La Roche Ltd, PRBD-M, Basel, Switzerland

Type 2 diabetes is a chronic and progressive metabolic disease, characterized by the presence of both fasting and postprandial hyperglycemia. Insulin resistance, resulting from defects in either insulin secretion, insulin action or both, is considered to be the primary contributor to disease development. Even before the appearance of overt hyperglycemia, insulin resistance is associated with several abnormalities, including obesity, dyslipidemia and hypertension, that together, increase cardiovascular disease risk. Therefore, a more effective oral anti-diabetic agent should be able, not only to impact HbA1c levels, but also to positively modulate one or more of these additional risk factors. In this regard, novel therapeutic approaches, currently at various stages of maturity, will be discussed.

Peroxisome proliferator-activated receptors (PPARs) are powerful insulin sensitizers. PPARα agonists specifically regulate lipid homeostasis by altering the expression of genes involved in lipid uptake, storage and metabolism, and insulin action in adipocytes. PPARγ agonists improve glycemic control, primarily by enhancing the sensitivity of peripheral tissues such as skeletal muscle, liver and adipose tissue to the actions of insulin. Moreover, PPARγ agonists improve β-cell function. Glitazars, dual agonists of PPARα and PPARγ, may provide a more effective therapy targeting not only hyperglycemia and insulin resistance, but also the associated lipid abnormalities, particularly low HDL-C and high triglycerides.

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is the key enzyme in the conversion of inactive cortisone to active cortisol. This serves as the pivotal switch in the activation of glucocorticoids, which have been shown to play key roles in metabolic disorders such as diabetes and obesity. Mounting evidence, emerging from both preclinical and clinical studies, support the hypothesis that inhibition of liver and adipose 11β-HSD1 activity may provide effective therapeutic benefit via the improvement of insulin action, lipid metabolism and also decreasing body weight.

These emerging novel therapies, that target multiple risk factors, may provide exciting new approaches to address the current unmet medical need in combating the pandemic of type 2 diabetes and its cardiovascular consequences.

For Notes:

Speaker's profile

Dr. Anil Bhansali

Professor & Head, Endocrinology
Postgraduate Institute of Medical
Education & Research, India

Dr. Bhansali is the Professor and Head of Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India. His areas of interest are adrenals, gonads and T2DM. His current research is in childhood Cushing's: clinical profile and outcome, childhood Addison's: clinical profile and outcome, mortality data in T2DM, Hypogonadotropic – hypogonadism: Profile and outcome of 150 patients. His honors include visiting professorship to LKM University, Graz, Austria Vienna. He is a member of many professional bodies like: Endocrine Society of India, American Endocrine Society, American Diabetes Association, Association of Physicians of India, Research Society for Study of Diabetes in India, Indian Menopausal Society, Executive Member of Endocrine Society of India.

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Topic

Thiazolidinediones in Type 2 Diabetes: Indian Experience

Dr. Anil Bhansali, Professor & Head, Endocrinology
Postgraduate Institute of Medical Education & Research, India

For Notes:

Speaker's profile

Dr. Satinath Mukherjee

Associate professor, Department of Endocrinology & Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata

He has been trained in research methodology and bio statistics under the aegis of the Steno Diabetes Center, Copenhagen, Denmark.

As an Assistant Research Officer (clinical) in the "Collaborative Study on NIDDM", he conducted clinical and epidemiological research involving 500 diabetic subjects for six years. He is familiar with basic medical statistics and laboratory procedures. He participated in research works on platelet function in insulin dependent diabetes, anthropometric indices of adiposity and plasma lipid profile in NIDDM and ischemic heart disease, correlative study on glycemic control and plasma lipid profile in NIDDM, neuro-electro-physiological study to assess central nervous system involvement in diabetes and study of left ventricular mass in diabetes. Recently, he completed a prevalence study of diabetes in India.

As a postgraduate trainee in medicine, he conducted regular bedside classes for the undergraduates at Calcutta Medical College. He delivered lectures regularly at the continuing medical education programme of the Association of Physicians of India, Diabetic Association of India, Research Society for the Study of Diabetes in India (RSSDI), Indian Medical Association and Endocrine Society of India. He worked as postdoctoral fellow (equivalent to lecturer) in the Department of Endocrinology and Metabolism at the Institute of Postgraduate Medical Education and Research, Calcutta for three years (1994-1997).

Topic

Therapeutic Strategies to Improve Cardiovascular Outcome in Type 2 Diabetes

Dr. Satinath Mukherjee
Associate professor, Department of Endocrinology & Metabolism, Institute of Post Graduate Medical Education and Research, Kolkata

In the recently published "Prevalence of Diabetes in India Study (PODIS)", we reported that Type2 Diabetes is a major public health problem in India. In this study involving 108 centers (49 urban ; 59 rural) and 41,270 subjects ≥ 25years of age, the prevalence of the different diabetic and prediabetic states in the urban and rural areas were as follows: Type2 Diabetes (T2D)- Urban 5.9%, Rural 2.7%; Impaired Glucose Tolerance (IGT)- Urban 6.3%, Rural 3.7% and Impaired Fasting Glucose (IFG)- Urban 4.8%, Rural 2.5%. In a sub-study involving 18 363 subjects (Male 9008; Female 9355), we also documented a high incidence of new onset T2D: 581 by WHO and 437 by ADA criteria. (Ref.1.PODIS: The burden of diabetes and Impaired Glucose Tolerance in India. 2. PODIS: The burden of diabetes and Impaired Fasting Glucose in India. 3. PODIS: Comparing the ADA 1997 & the WHO 1999 criteria. S.M. Sadikot., A. Nigam, S. Mukherjee, et. al. Diab. Res. & Clin. Prac. 2004. 66: 293-300, 301- 307, 309- 315).

Although microangiopathic complications like retinopathy and nephropathy are considered specific to diabetes, 80% of them ultimately succumb to cardiovascular disease (CVD). So strong has been the association between T2D and CVD that T2D has been redefined as "a state of premature cardiovascular death which is associated with chronic hyperglycemia" (B M Fisher). In the ICMR Collaborative Study on NIDDM, we documented a high prevalence of CVD (27%) at presentation (Diabetes Bulletin, 1993). The UK Prospective Diabetes Study (UKPDS) also reported a similar prevalence of CVD. Although several studies documented significant risk reduction for retinopathy and nephropathy with intensive treatment, the risk reduction for CVD was not impressive. Some believe that the glycemic control achieved in those studies, although sufficient to prevent retinopathy or nephropathy, was not tight enough to prevent CVD. In fact, we probably need to renormalize blood glucose levels in order to improve cardiovascular outcome, as shown by the high prevalence of CVD in prediabetic subjects, who do not have retinopathy or nephropathy. With the availability of insulin analogs, glitazones, alpha glucosidase inhibitors, meglitinides, GLP-1 analogs, insulin delivery systems and glucose monitoring devices, the clinicians are now in a better position to treat their patients more intensively, without significantly increasing the risk of hypoglycemia. Some ongoing trials are looking at the impact on CVD of intensive glucose control strategies with the aim of maintaining glycated hemoglobin (HbA1c) level at 6% or even lower. The results of these studies are going to tell us whether such strategies are effective and can be implemented in clinical practice. If they prove ineffective, we shall have to pay more attention to the non glycemic risk factors such as hypertension, dyslipidemia, smoking, hyperhomocysteiemia and oxidative stress, in order to reduce the burden of CVD in T2D.

For Notes:

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Session V: Diabetes, Dyslipidemia And Related Complications (Nephropathy, Neuropathy, And Retinopathy)

Introduction to the Chairpersons

Dr. Shaukat M. Sadikot, President, Diabetes India

Dr. Shaukat M. Sadikot, is currently the President of DiabetesIndia. Presently working as a Consultant in Endocrinology at the Jaslok Hospital and Research Center, Mumbai. He has been actively involved with the cause of diabetes and associated metabolic disorders for the past 30 years. He received his M.D. degree from the Grant Medical College, Bombay University and then underwent further training in Endocrinology and Metabolic Disorders as a Visiting Colleague at the Royal Postgraduate Medical School and the Hammersmith Hospital, London, U.K.

Dr. Sadikot has worked as a Senior Research Fellow of the Indian Council of Medical Research where he worked on the role of fibers in diabetic diets as well as the role of EFAs in Indian diets. He has had short term training in aspects of islet cell physiology and implants at the Institute of Transplantology and Artificial Organs, Moscow, Russia.

Dr. Sadikot is a Fellow of the All India Institute of Diabetes and the International College of Nutrition. He is a member of DiabetesIndia, Diabetic Association of India, International Diabetes Federation, Endocrine Society of India, Research Society for the Study of Diabetes in India and has been awarded a Hon. Membership of the British Diabetes Association.

He has been the Chief Co-ordinator of three Indian Consensus Guidelines for the Management of Diabetes (1991, 1998 and 2003) with a special focus on helping primary care physicians (who look after more than 99% of India's diabetes population) in their day to day management of diabetes. Under his Presidentship, DiabetesIndia pioneered the first ever truly national survey for the prevalence of diabetes as well as the Metabolic Syndrome in India. The latter is an ongoing process with evaluation of the novel risk factors and their role and importance in the Indian context.

He has been closely associated with the activities of the IDF for many years and is a member of the IDF task Force on Insulin, Test strips and other diabetes supplies, a member of the IDF Consensus group on the Prevention of Prediabetes, Diabetes and the Metabolic Syndrome, as well as the IDF group on Diabetes and Obstructive Sleep Apnoea.

His main research area is in the area of diabetes and its association with vascular disease and has written four books and has numerous publications to his credit, both original papers as well as solicited articles. .

He is currently heading a team which is evaluating the role of guidelines and mechanisms for the prevention of diabetes and obesity, especially childhood and juvenile obesity, through lifestyle interventions valid in the Indian and developing country scenarios. He is also co-ordinating the Indian Consensus on the Metabolic Syndrome with a special emphasis on the prevention aspects of diabetes and early onset atherosclerotic cardiovascular disease.

Dr. Alain Baron, Senior Vice President, Research, Amylin

Dr. Baron is currently serving as Senior Vice President of Research since September 2004 after having served as Vice President of Clinical Research from December 1999, and as Senior Vice President of Clinical Research from June 2002. He is currently responsible for early development of all drug candidates at Amylin Pharmaceuticals. Previously, Dr. Baron worked for the Indiana University School of Medicine in Indianapolis, where he served as Professor of Medicine and Director, Division of Endocrinology and Metabolism. Prior to this position at Indiana, Dr. Baron held academic positions in the Division of Endocrinology and Metabolism at University of California, San Diego, and the Veterans Administration Medical Center in San Diego. He is the recipient of several prestigious awards for his research in diabetes and vascular disease, including the 1996 Outstanding Clinical Investigator Award from the American Federation for Medical Research, and is a past National Institutes of Health ("NIH") MERIT award recipient. He is co-editor of the Ellenberg & Rifkin Text book of Diabetes. He earned his M.D. from the Medical College of Georgia, Augusta, and completed postdoctoral studies at the University of California, San Diego.

Speaker's profile

Dr. Richard DiMarchi

Retired Group Vice President, Eli Lilly Research labs.
Professor of Chemistry and the Jack and Linda Gill Distinguished Chair in Biomolecular Science, Indiana University, US

Dr. DiMarchi was formerly Group Vice President for Biotechnology and Product Development at Lilly Research Laboratories, where he made major contributions to Lilly in biotechnology and endocrinology. Dr. DiMarchi was directly involved in the discovery and development of several Lilly drugs, including Humulin(R), Humatrope(R), Evista(R), Xigris(R), and Forteo(R). He was a co-inventor of Humalog(R), the first biosynthetic protein approved for human use. Additionally, at Lilly he championed the introduction and integration of cutting-edge biotechnologies, including genomics, proteomics, high-throughput screening, and combinatorial chemistry. Dr. DiMarchi is presently a Professor of Chemistry and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University. He currently serves as a co-founder and Board Chairman of Ambrx, Inc. He previously served as a board member to the biotechnology trade group BIO and the American Peptide Society, as well as such companies as Millennium Biotherapeutics and Inproteo. He currently serves as Board member to Isis Pharmaceuticals, and scientific advisor to Alba Inc., Epitome Biosciences, Kai Pharmaceuticals, Semafore Biotechnologies, 5AM.

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Topic

The Emergence of Chemical Biotechnology and Its Application to Endocrine Proteins

Richard DiMarchi, Department of Chemistry and Biomolecular Science, Indiana University, US

The recent emergence of new technologies in protein biosynthesis is dramatically enlarging the structural space that can be utilized by protein medicinal chemists. The simultaneous mutation of tRNAs and the tRNA-Synthetases has demonstrated that amino acids previously restricted to chemical synthetic approaches can now be successfully utilized in rDNA-based biosynthesis. This period in protein chemistry is quite analogous to the advent of rDNA-based synthesis when the first natural sequenced proteins were produced and the foundation for the delivery of structurally optimized proteins was established. The integration of this new synthetic technology with more conventional synthetic methodologies is dramatically enhancing the academic and commercial opportunities in protein chemistry. The application of chemical biotechnology to peptides and proteins of importance in endocrine diseases will be presented.

For Notes:

Speaker's profile

Dr. Viren Sarin

Senior Research Fellow, Eli Lilly & Co.,
Indianapolis, USA

Dr. Viren is a Senior Research Fellow in the Bioproduct Research and Development, PR&D at Eli Lilly and is responsible for Alternate Drug Delivery efforts like pulmonary, oral, depot, etc. and external collaborations. Dr. Viren provided leadership to the development, global regulatory submission and approval of Lilly's therapeutic protein efforts like Forteo, Xigris and Byetta, which is developed in collaboration with Amylin. He was a member of the CDC, and as such, provided leadership in a cross organizational committee to help Lilly meet its portfolio deliverables. He was instrumental in the establishment and implementation of Lilly's pulmonary strategy for systemic delivery of therapeutically active molecules, in particular peptides and proteins. He has also established and implemented the outsourcing strategy at the Bioproduct Research and Development organization, which culminated in establishing synthetic peptides and ASO's development strategy.

Before joining Lilly, Dr. Viren worked at Abbott Laboratories for about 16 years in Discovery and Product development organizations. His research included development of Lung Surfactant Proteins, a variety of recombinant proteins and use of peptide antibodies for diagnostics purposes. Earlier to joining Abbott, Dr. Viren researched at The Rockefeller University in Prof. Bruce Merrifield laboratory in the field of Peptide and Protein chemistry.

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Topic

Pulmonary Methods of Delivery of Peptides and Proteins - Inhaled Insulin

Viren Sarin, Eli Lilly & Co., Indianapolis, IN

Drug delivery is an integral part of Pharmaceutical product development, especially for biomolecules. It plays a role not only in life cycle management of a molecule, but is critical in many instances in enabling the pharmacology of a molecule. One of the challenges in biomolecules therapy is their mode of delivery i.e. peptides and protein drugs are usually delivered via an injectable route. In order to make these therapies more patient friendly and hence increase their compliance, alternate routes of delivery are developed. At Lilly, we have chosen systemic delivery of biomolecules via lung as a delivery platform. In this presentation, pulmonary delivery technology using dry powder inhalers and its application to delivery of Insulin will be discussed.

For Notes:

Speaker's profile

Dr. Michael Mark

Vice President, Metabolic Diseases Research,
Boehringer-Ingelheim Pharma GmbH & Co KG Biberach,
Germany

Currently Vice President Metabolic Diseases at Boehringer Ingelheim Pharma GmbH&Co KG in Biberach Germany. Head of a department being responsible for discovery activities in Metabolic Diseases i.e Diabetes type 2, Obesity and Dyslipidaemia/Atherosclerosis.

Educated as pharmacist I am holding a Ph.D. degree in Pharmacology from the University of Tuebingen in Germany. Focus of that work was the mechanism of insulin secretion especially the ion fluxes. After a PostDoc period I am now over 20 years in the pharmaceutical industry. I started the industrial career as Principal scientist in the labs of Dr. Karl Thomae GmbH being then involved in the Discovery and Development of repaglinide, a now approved therapy for the treatment of type 2 diabetes. Further projects at that time were the ß3 receptor agonists for the treatment of obesity and also insulin sensitizers. Switched then research focus towards dyslipidemia and spearheaded the research of squalenecyclase inhibitors a novel opportunity for treatment of lipid disorders. After that till now I have broader responsibility for Metabolic research in Boehringer Ingelheim covering the full spectrum of the above mentioned subindications.

Together with the team developed a competitive portfolio with various preclinical and several clinical developments projects currently ongoing.

Contributed to numerous patents, being also author of several publications, many meeting contributions and also various book chapters.

Main research interests currently: ß-cell destruction, metabolic syndrome and the regulation of food intake and appetite

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Topic

BI 1356, a Novel Potent and Selective Xanthine Based DPP-IV Inhibitor, Exhibits a Unique Profile

Michael Mark, Frank Himmelsbach, Leo Thomas, Matthias Eckhardt, Elke Langkopf, Klaus A. Dugi, Ulrike Graefe-Mody

Boehringer Ingelheim Pharma GmbH & Co KG, Biberach Germany

BI 1356 is a potent and selective DPP-IV inhibitor derived from the xanthine class, having been selected for further development based on its in vitro and in vivo pharmacodynamic properties, as well as its specific compound characteristics. Here we have compared the in vitro and in vivo preclinical properties of BI 1356 with that of sitagliptin and vildagliptin.

The in vitro DPP-IV inhibitory activity (IC50 1 nM) was superior when compared to sitagliptin or vildagliptin (19 and 62 nM respectively) whilst all 3 compounds exhibited high selectivity over other human proteases including DPP 8 and 9.

In vivo efficacy of BI 1356 was studied in several animal models such as mice, rats, dogs, and nonhuman primates. A strong and dose-dependent inhibition of plasma DPP-IV activity was observed in rats. Effects of BI 1356 on glucose tolerance were compared to sitagliptin and vildagliptin under 2 different experimental conditions in C57Bl/6J mice: oral administration of test compounds was either (A) 45 min before a 2 g/kg glucose challenge or (B) 16 h before the glucose load. Whereas under conditions (A) all 3 compounds reduced glucose AUC (0-120 min) to a similar extent (-45 %, -53 %, -47 %), a positive effect under conditions (B) was only shown for BI 1356, when using the same dose as under (A) (1 mg/kg) (AUC -18 % to -29 %). Whereas sitagliptin improved glucose tolerance when a higher dose (10 mg/kg) was applied (AUC -20 %), vildagliptin even with that dose was without effect.

Based on these results we conclude that BI 1356 is superior to both sitagliptin and vildagliptin due to its in vitro potency, and its longer duration of action in vivo in the models described. Therefore, BI 1356 appears to be a truly once daily DPP-IV inhibitor. Strong DPP-IV inhibition over 24 hours has been observed also in clinical studies with low doses of BI 1356 which resulted in significant glucose reductions in type 2 diabetic patients. Currently, the compound is in Phase IIb clinical development to further confirm this unique profile.

For Notes:

Speaker's profile

Dr. John H. Johnson,

Director, Licensing and Development,
Pfizer Inc.

John Johnson received his Ph.D at Oklahoma State University in Cell Biology. After an NIH Postdoctoral Fellowship in Biochemistry at Cornell University, he joined the faculty of the University of Texas Southwestern Medical School where he became Professor of Internal Medicine and Physiology. He subsequently joined Warner-Lambert Parke-Davis as an Associate Research Fellow. Following the acquisition of Warner-Lambert by Pfizer, he has been Director of Metabolic and Endocrine Diseases in World -Wide Business Development for Pfizer.

Topic

Trends and Opportunities in Diabetes and the Metabolic Syndrome

John H. Johnson Licensing and Development, Pfizer Inc.

Trends and opportunities in diabetes and the Metabolic Syndrome will be discussed. These include emerging technologies and new therapeutic strategies in both areas. These include advances in insulin therapy, new strategies in cell-based therapy and new strategies for gene therapy. In addition, the differences in Metabolic Syndrome definitions as well as similarities in recognition by physicians of the individual components of the Metabolic Syndrome in the seven major markets of the world will be shown. New data, and their implications on Metabolic Syndrome definitions, presented at the IDF meeting on the Rimonabant® SERENADE trial will be discussed.

For Notes:

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Scientific Poster Presentations

PS1: Gene Expression Profiling of Human Adipogenesis - An Insight Into the Mechanism

Anandharajan R*, Debarshi Chakrabarti, Arvind Thakkar, Prabha Mishra, Somesh Sharma, Muralidhara Padigaru

Nicholas Piramal Research Centre, 1, Nirlon Complex, Off Western Express Highway, Goregaon East, Mumbai-400063

Presence of excess adipose tissue in obesity is associated with increased risk of insulin resistance. Study of mechanism of adipogenesis may help in understanding the process of obesity. To address this question, we undertook a comprehensive gene expression profiling of adipogenesis using primary human pre-adipocytes in presence of rosiglitazone. Subcutaneous human pre-adipocyte is used for our study. Pre-adipocyte at confluence is used as common control and progression of adipogenesis was studied for a period of 17 days on alternative days by microarray based gene expression profiling. After extensive statistical analysis approximately 600 genes are grouped into specific clusters based on the expression pattern and biological functions, which is further, validated by gene expression data obtained from public database for clinically relevant patients sample. Our findings clearly demonstrated an expression pattern that is reflective of presence of rosiglitazone in the culture medium thus validating our data. Significant up-regulation of established markers like FABP4, LPL, LIPE, PLN, PPARγ APM1, and CD36 and down-regulation of DKK1, CIDE-3 clearly demonstrated the already established adipogenesis pattern in our system. Most interestingly we have identified several new genes with biologically significant expression profile as candidate drug targets for obesity. We also identified genes, which can be developed into potential diagnostic/prognostic markers to understand the physiology of obesity and insulin resistance in human. Currently we are in the process of validating these findings using tools such as protein expression and siRNA technology. We hope to use information derived from this study to develop new assays to screen our ~ 40,000 natural products and herbal extract library and find lead molecules for treatment of obesity and diabetes.

PS2: Development of a Trimarker Panel: Proinsulin, Insulin, C-Peptide

Anil T. M1, Smitha P.K.[1], Sujan Kr. Dhar1, Anjali Karande[2] and Manjula Das[1]

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Objective: Insulin, proinsulin and C-peptide are measured in the investigation of hypoglycemia and diabetes mellitus. In addition to measuring the individual concentrations in DM, hyperinsulinism etc, comparison of the three is essential for various diagnosis. (1) In hypoglycemia, elevated insulin concentration is normalized by elevated C-peptide concentration to confirm the presence of abnormal endogenous insulin. (2) The same normalization is useful in insulin-treated diabetes to avoid the interference of exogenous insulin or anti-insulin antibodies. (3) The ratio of proinsulin to processed-insulin is measured to predict Beta-cell dysfunction, familial hyperinsulinaemia and progression of DM2. The measurement of C-peptide may be used in all these clinical situations for normalization. (4) Islet cell adenomas secrete proinsulin and insulin in varying concentration at different stages of progression of tumor. Abexome is developing an immunodiagnostic panel where in a single test all the three markers can be measured and compared.

Methodology: Monoclonal antibodies specific for insulin, proinsulin and C-peptide are used in single ELISA kits.

Results: Abexome has already produced a monoclonal antibody, which is specific to insulin but does not react to proinsulin. MAb for measuring the concentration of proinsulin has also been successfully developed. The MAb to C-peptide is in progress. We are trying to develop a semi-quantitative point of care (POC) kit also.

PS3: Studies on Hypolipidemic Potential of *Enicostemma littorale* Blume on Zucker Fatty and Alloxan-Induced Diabetic Rat Models

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Hyperlipidaemia has been implicated in atherosclerosis, which is the leading cause of death among world population. Decreased physical activity and increased consumption of calories and saturated

fat result in abdominal obesity, insulin resistance, and atherogenic dyslipidaemia. Hyperlipidaemia is associated with diabetes and venous thrombosis, which further increases the incidence of coronary heart disease. Many plant extracts are being used in treatment of dislipidaemia, which is one of the consequences of diabetes. Our previous study on one of the gentianaceae plant *Enicostemma littorale* Blume showed that, aqueous extracts of E. littorale to cholesterol fed rats significantly reduces serum cholesterol, triglycerides, LDL and VLDL cholesterol along with significantly increasing HDL cholesterol levels. In the present study, hypolipidaemic activity of aqueous extract *E. littorale* has been evaluated in obese zucker fatty rats. There was significant decrease in serum triglyceride and cholesterol levels as compared to control. There is significant increase in fasting insulin level. However, there is no significant difference in AUC glucose levels. It dose not produce any significant decrease in serum NEFA levels and LDL-C levels as compared to control. It dose not produce any increase in fasting HDL-C levels. Further in another set of experiment alloxan-induced diabetic rats were treated with methnolic extract of *E. littorale* for six weeks. Blood coagulation parameters like PT, APTT and platelet aggregation along with lipid profile were monitored. We found ameliorating effect of E. littorale on this parameter as compared to diabetic control rats. Thus, result from both the experiment certainly demonstrate beneficial role of E littorale in reducing diabetic complications

PS4: Comparison of Chronic Anti-Inflammatory Activity of *Pongamia Pinnata* with Aspirin in Cotton Pellet Granuloma Model in Rats

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Pongamia pinnata (Karanj) is an important shade tree of India, claimed to possess anti-inflammatory activity. The present study was undertaken to evaluate anti-inflammatory potential of *Pongamia pinnata* in cotton pellet granuloma test in rats. 18 Wistar rats were randomly divided into three groups, each group comprising 6 rats. Sterilized cotton pellets weighing 10 mg were surgically implanted subcutaneously in both groins of each rat under ether anaesthesia. Alcoholic extract of *Pongamia pinnata* seeds was administered at dose rate of 300 mg/kg body weight by oral gavage once daily for seven days. Aspirin was administered as reference drug at the dose rate of 300 mg/kg body weight orally for seven days. Control group was treated with vehicle orally for seven days. On eighth day, cotton pellets were removed, dried and weighed. The percent inhibition of granulation (chronic inflammation) in *Pongamia pinnata* and aspirin treated group was 26.08 % and 48.97 %, respectively, as compared to control group. Aspirin produced more potent anti-inflammatory activity as compared to Pongamia pinnata.

PS5: Focal Adhesion Kinase (FAK) Regulates Glut-4 Translocation Mediated by Actin Remodeling

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Using RNA interference approach we have recently reported that Focal Adhesion Kinase (FAK) silencing results into impaired insulin signaling and glucose uptake in skeletal muscle. However the underlying mechanism for glucose transporter 4 (Glut-4) translocation remains unknown. Insulin causes a rapid and dynamic remodeling of actin filaments into a cortical mesh, which is required for Glut-4 translocation and glucose uptake. Therefore our hypothesis was to determine whether FAK regulates Glut-4 translocation by actin remodeling in skeletal muscle. In the present study, we have investigated the effect of FAK modulation on actin remodeling and glucose transport in differentiated mouse C2C12 skeletal muscle cells. Although C2C12 cells expresses less Glut-4 molecules but was recently reported to have basic Glut-4 translocation machinery that can be activated by insulin. In order to study the involvement of FAK in Glut-4 translocation we have developed C2C12 cells overexpressing GFP-tagged Glut-4. Using Z-scan confocal microscopy we revealed a spatial colocalization of Glut-4 with actin after insulin stimulation. Overexpression of FAK under insulin resistant condition results into enhanced actin remodeling compared to untransfected cells that might be responsible for the observed Glut-4 translocation and glucose uptake. Therefore our data proves that, overexpression of FAK caused actin remodeling accompanied by an increase in Glut-4 translocation and glucose uptake after insulin stimulation suggesting that FAK plays a key role in insulin-mediated glucose metabolism in skeletal muscle cells. Taken our previous study and the present together established that FAK could be a potential therapeutic target against insulin resistance.

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PS6: Stability Indicating Method Development for ZYXX01, an Antidiabetic Compound, by Reversed Phase Liquid Chromatograph by Using Diode Array Detection

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Stability-indicating high-performance liquid chromatography analytical procedures were developed for determination of potential impurities during degradation under peroxide and accelerated acid/alkali conditions. The chromatographic conditions were developed so that the drug peak was well separated from the peaks of the degradation products. Peak homogeneity of the resolving drug peak was assessed by the shape of the ratio chromatogram. Good and reproducible separations were achieved on a reversed-phase column using a mobile phase consisting of acetonitrile and a solution of acetate buffer in water. Optimal separations for all potential impurities were achieved. The detection wavelengths were 305 nm and diode array detection. The stability-indicating nature of the methods was confirmed by the generating potential impurities. No significant interference in the analysis of degradation products and impurities was observed.

PS7: Design and Synthesis of Novel Thiazolidinedione Derivatives as PPARγ Activators

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Type 2 diabetes, also known as noninsulin-dependent diabetes mellitus (NIDDM), is a chronic and multifactorial disease characterized by insulin resistance in the liver and peripheral tissues and impaired insulin secretion from pancreatic-cells. Hyperglycemia in type II diabetes leads to a gradual progression of complications, including neuropathy, nephropathy, retinopathy, arteriosclerosis, and coronary artery disease. Thus, insulin sensitivity enhancer represents an attractive approach to the treatment of type 2 diabetes. Clofibrate is the first such compound found to improve insulin resistance. It was followed by the discovery of thiazolidinediones (TZD), which are a class of oral insulin-sensitizing agents that improve glucose utilization without stimulating insulin secretion. Although the precise mechanism of action of TZDs remains unknown, a number of reports suggest that TZDs are high-affinity ligands of peroxisome proliferator activated receptor-γ (PPARγ). PPARs are members of the nuclear hormone receptor superfamily that consists of three members, PPAR-α, -γ, and -δγ and acts as ligand-activated transcription factors, which play a major role in the regulation of lipid metabolism and storage. To date, a large number of compounds containing TZD moiety have been synthesized to produce new antidiabetic agents. Among them, troglitazone was launched first in the market, but had been withdrawn due to its liver toxicity. Nowadays, rosiglitazone and pioglitazone, the second and third TZDs marketed are clinically used. However, even these drugs have been associated with liver, cardiovascular, hematological toxicity and body weight gain. Therefore, improvement of the TZD class of antidiabetic agents is still worth pursuing. In this research we describe the design and synthesis and evaluation of novel tetrahydroquinoline-linked TZD derivatives based on the structure of rosiglitazone as a lead compound. We modified the lipophilic tail of rosiglitazone into a series of tetrahydroquinolines, in which the nitrogen on the spacer of rosiglitazone is included, leading to conformationaly-constrained analogs. Here, we report novel selective PPARγ activators, tetrahydroquinoline-TZDs, as candidate leads for the potential treatment of type 2 diabetes.

PS8: Validation of Novel Exercise-Responsive Phospho-Proteins in Skeletal Muscle

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AMP-activated protein kinase (AMPK) is a heterotrimeric protein that regulates glucose transport mediated by exercise, cellular stress or pharmacological agonists such as 5-aminoimidazole-4-carboxamide 1 ß-D-ribonucleoside (AICAR). AS160, a Rab GTPase activating protein, provides a mechanism linking AMPK signaling to glucose uptake. AICAR increased AMPK, acetyl-CoA carboxylase and AS160 phosphorylation by an insulin-independent and time-dependent manner in skeletal muscle ($P<0.05$). Recombinant AMPK heterotrimeric complexes ($\alpha1\beta1\gamma1$ and $\alpha2\beta2\gamma1$) phosphorylate AS160 in a cell-free assay ($P<0.05$). In mice deficient in AMPK signaling ($\alpha2$ AMPK knockout (KO), $\alpha2$ AMPK

kinase dead (KD) and γ3 AMPK KO, the AICAR effects on AS160 phosphorylation were severely blunted (P<0.01), highlighting complexes containing α2 and γ3 are necessary for AS160 phosphorylation in skeletal muscle. Contraction-mediated AS160 phosphorylation was impaired in α2 AMPK KO and KD (P < 0.01), but not γ3 AMPK KO mice. We also determined the exercise effects on phosphorylation of Akt and downstream substrates in human skeletal muscle. Akt Ser473 phosphorylation was increased (1.8-fold; P=0.011) after exercise. Exercise-responsive phosphoproteins (pp) pp160 and pp300 were identified as AS160 and filamin A; providing a potential mechanism for exercise-induced metabolic responses. Our results in AMPK KO mice directly link AMPK and AS160 signaling in skeletal muscle.

PS9: Design and Synthesis of Stilbene Derivatives as FXR Specific Ligands

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Farnesoid X receptor (FXR) is a member of the nuclear hormone receptor superfamily. FXR play important roles in maintaining cholesterol and bile acid homeostasis as a result of the regulation of hepatic genes controlling both the catabolism of cholesterol to bile acids and the subsequent secretion of bile acids into the bile. Additionally, it has been reported that activation of FXR lowers plasma triglyceride levels. Due to its role in the regulation of cholesterol and bile acid homeostasis and glucose metabolism, FXR is a potential drug target for treatment of dyslipidemia, cholestasis and diabetes mellitus. The known endogenous ligands for FXR are bile acids that are poor reagents for characterizing FXR functions due to their multiple receptor independent properties. Therefore, the development of selective FXR ligands is necessary for therapeutic purposes. We report the design and synthesis of FXR specific ligands. A preliminary lead was obtained through the screening of a set of library compounds and then modification of the lead was performed. Several stilbene analogs were synthesized by Still coupling or addition of Grignard reagent to carbonyl of 2-(4-bromophenyl)-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-ethanone as a key step.

PS10: Pharmacological Profile of Novel Highly Potent and Balanced PPARα/γ Dual Agonist

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Background: PPARs play a major role in regulating the storage and catabolism of lipids in both animals and humans. There are three PPAR subtypes, like α, γ and δ or β. PPARα agonists, fibrates effectively improve dyslipidemia profile but has side effects like hepatotoxicity and skeletal myopathy. PPARγ agonists are effective anti-diabetic agent but have side effects like gain in body weight and edema, which may aggravate the congestive heart failure. In view of need to control both glucose and lipid levels in type 2 diabetes condition, ligands that binds and activate both PPARα and PPARγ may provide desired therapeutic effect with minimal side effect liability. Though many dual PPARα/γ agonists are reported in literature, they have not met the success criteria. Hence, there is need for identification of an "evenly balanced" dual agonist possessing sufficient anti hyperglycemic and hypolipidemic effect and improved side effect profile.

Aim: The purpose of this study was to characterize a novel alkoxy acid derivative (ZY20169) for its anti-diabetic & hypolipidemic potential in relevant pre-clinical models.

Methods and Results: ZY20169 has shown potent PPARα and γ transactivation (EC50 α is 0.0003nM and for γ is 0.0018nM) in the assay carried out using HepG-2 cells. ZY20169 has shown dose dependent reduction in serum triglyceride (ED50-0.0007mg/kg) and significant improvement in glucose tolerance after 14 days of treatment in Zucker fa/fa rats. In euglycemic-hypertriglyceridemic Swiss albino mice, 6-days treatment with ZY20169 has exhibited dose dependent reduction in triglyceride (maximum 83% @ 3mg/kg, ED50 0.01mg/kg) and total cholesterol (maximum 62% @3mg/kg, ED50 0.23mg/kg). In db/db mice, a model of Type2 diabetes, this molecule showed dose dependent reduction in triglyceride (maximum 64 % @ 1mg/kg, ED50 0.024mg/kg) & significant improvement in glucose tolerance after 6-days treatment. In high cholesterol-fed Sprague Dawley rats, 4-days treatment of ZY20169 showed 50 & 40 % reduction in cholesterol & triglyceride, respectively. In ob/ob mouse model of insulin resistance and obesity, the molecule showed significant reduction in triglyceride & improved glucose tolerance along with reduction in body weight gain (23% @ 3mg/kg for 28 days) as compared to pioglitazone which showed similar profile but 7% increase in body weight gain. At the same time, ZY20169 showed

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induction of liver ACO and LPL m-RNA levels indicating its PPARα agonistic activity. In repeat dose oral toxicity study for 10 days in male Wistar rat (up to 500 mg/kg), ZY20169 dose not show significant increase in body weight gain and no significant decrease in hematocrit. Also there was no significant increase in serum AST, ALT, total bilirubin (liver enzymes) and creatinine levels.

Conclusion: In conclusion, ZY20169, a novel alkoxy acid derivative, a potent dual activator of PPAR α and PPARγ is an interesting NCE for the management of metabolic disorder and associated comorbidities.

PS11: Comparison of Plasma Volume Expansion Potential of Pioglitazone and Rosiglitazone

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TZD's, PPAR γ ligands, have demonstrated a great potential in treatment of Type 2 diabetes. However their clinical applicability is limited due to their common and serious side effect of edema. Although commercially available glitazones, pioglitazone & rosiglitazone, are well tolerated but they produce modest weight gain in a sub-population of patients. Insulin sensitization and a resultant increase in adipogenesis may contribute to weight gain. However, an increase in plasma volume and fluid retention has also been reported. In the present study, we evaluated plasma volume expansion potential of Pioglitazone & rosiglitazone in Sprague-Dawley rats. Animals were treated with very high doses of pioglitazone (300mg/kg/day) and Rosiglitazone (80mg/kg/day) for 14 days. Evan's blue dye dilution technique was used for estimation of plasma volume. Pioglitazone induced 16% increase in plasma volume expansion whereas rosiglitazone showed 31% increase. These observations were accompanied by 3 & 9% decrease in hematocrit (HCT) in pioglitazone and rosiglitazone treated animals respectively and are suggestive of haemodilution. Rosiglitazone caused a significant increase in plasma sodium & chloride ion concentration, which was not evident in pioglitazone. In addition, rosiglitazone also showed significant cardiomegaly compared to pioglitazone treatment. These change in plasma electrolytes and plasma volumes were accompanied by an increase in renal m-RNA levels of ENaC and Na+K+ATPase. In summary, these results suggested that rosiglitazone produces a more pronounced plasma volume expansion as compared to pioglitazone.

PS12: Synthesis and Biological Activity of Azetidine Analogues for Appetite Suppression Having CB-1 Antagonists Like Activity

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Obesity is one of the greatest health threats of the modern society. Obesity increases the risk of type 2-diabetes, cardiovascular morbidity & cancer. Controlled diet & exercise as the treatment of obesity are successful to a very small extent. Hence, there is a clear need of effective pharmaceutical intervention. It has been demonstrated that, the cannabinoid-1 (CB1) receptors significantly regulate the feed intake behavior. These receptors are present mainly in the brain. Hence, compounds targeting at the anorexgenic property of CB1 receptors are worth investigating. In continuation of our efforts in this direction, we have synthesized various azetidine based novel compounds. These compounds were synthesized by coupling 3-diarylmethoxyazetidine with methyl-aryl-carbamates under modified conditions as the key step. These compounds were screened in vivo for CB1 antagonist like activity in Sprague Dawley rats. The study revealed that the analogues (1a), (1d), (1e), (1f), (1j) showed promising reduction in the intake of palatable sucrose solution in Sprague Dawley rats.

S.R.	Compound	R1	R2	R3	R4	R5	5%Sucrose intake in 4h(g)	% Decrease in Sucrose intake
1.	Control						25.3±5.6	--
2.	1a	4'-Cl	2-Cl	H	Cl	Me	16.3±3.4	-35.4 ±13.3
3.	1b	4'-Cl	2-CF_3	H	Cl	Me	21.3±2.8	-15.8 ± 11.2
4.	1c	4'-Cl	4-Cl	H	Cl	Me	16.3±1.5	-3.2 ± 9.1
5.	1d	H	2-Cl	4-Cl	Cl	Me	9.7±2.4	-50.6 ± 12.5
6.	1e	H	4-Cl	H	Cl	Me	14.7±2.9	-25.2 ±14.6
7.	1f	H	4-F	H	Cl	Me	10.4±2.4	-44.8 ± 12.5
8.	1g	H	4-CF_3	H	Cl	Me	24.6±2.8	-1.6 ± 18.5
9.	1h	H	4-Cl	H	Cl	Cy-C_6H_{11}	18.0±2.5	-5.1±13.0
10.	1i	H	H	H	H	Me	16.1±1.4	-15.1±7.5
11.	1j	H	2-Cl	3-Cl	Cl	Cy-C_6H_{11}	8.7±2.3	-53.9±12.0
12.	1k	H	2-Cl	3-Cl	Cl	Me	16.4±4.1	-13.3±21.4
13.	1l	H	H	H	CF_3	Cy-C_6H_{11}	13.9±3.1	-26.5±16.6
14.	1m	H	H	H	CF_3	Me	10.8±2.8	-42.9±15.1
15.	Rimonabant						8.0±1.2	-68.4±4.8
16.	(±)-SLV-319						6.1±1.3	-60.1±8

Table 1: Effect of azetidine analogues on consumption of 5% sucrose solution in male Sprague Dawley rats (mean+SEM, n =6)

PS13:

Synthesis and Activity of 5-Substituted Thiadiazole Class of Compounds as TACE and MMP Inhibitors

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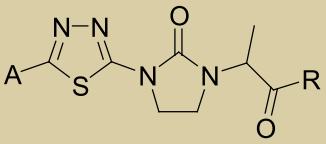
The commercial success of biologics, including Enbrel and Remicade, that modulate levels of both membrane-bound 26 kDa TNF and the soluble 17 kDa form of this pro-inflammatory cytokine has led to an intensive search for orally active small molecules that might be similarly effective in the treatment of rheumatoid arthritis (RA). One attractive approach for affecting TNF-α level is the inhibition of TNF-α converting enzyme (TACE/ADAM-17), the metalloprotease responsible for the shedding of membrane bound TNF-α there by reducing circular level of soluble TNF-α. The 5-substituted thiadiazole derivative (1) was synthesized starting from corresponding aldehyde and thiosemicarbazide in 8 different synthetic steps. Synthesized compound showed comparable in vitro TNF-α inhibition.



R = OH, OCH_3, NHOH

(1)

PS14:

Synthesis and Biological Activity of Pyrrolidine and Piperidine Analogues for Appetite Suppression as Probable CB-1 Antagonists

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Excess energy intake leading to obesity has emerged as a major health threat. Obese individual have greater chances of developing type 2 diabetes, hypertension, heart diseases, stroke, cancer and arthritis. With the percentage of the population considered to be obese increasing annually there is a need to address this issue. It has been demonstrated that, endocannabinoids in the hypothalmus tonically activate CB1 receptors to maintain food intake and to sustain over eating in obese animals. Hence, to synthesize CB1 antagonist is a logical way to treat obesity. In continuation of our efforts in this direction, we have synthesized various novel analogues of pyrrolidine and piperidine. These compounds were synthesized by coupling substituted 3-diarylmethoxypyrrolidine with methyl aryl carbamates under modified conditions as the key step. These compounds were screened in vivo for CB1 antagonist like activity in Sprague Dawley rats. The study revealed that the analogues (1a), (1b), (1f), (1h), (1i) showed promising reduction in the intake of palatable sucrose solution in Sprague Dawley rats.

Sr.No.	Compound	R1	R2	% Decrease in Sucrose intake
1.	Control			--
2.	1a	C_6H_5	2-F-C_6H_4	-47.8 ± 12.1
3.	1b	C_6H_5	2-Cl-C_6H_4	-34.2 ± 7.6
4.	1c	C_6H_5	C_6H_5	-9.8 ± 17.5
5.	1d	C_6H_5	2,3-diCl-C_6H_3	1.8 ± 14.3
6.	1e	C_6H_5	4-F-C_6H_4	ND
7.	1f	4-Cl-C_6H_4	2-CF3-C_6H_4	-38.8 ± 12.3
8.	1g	4-Cl-C_6H_4	2,4-diCl-C_6H_3	10.7 ± 21.0
9.	1h	C_6H_5	2-CF3-C_6H_4	-37.1 ± 12.4
10.	1i	C_6H_5	2,4-diCl-C_6H_3	-29.6 ± 13.1
11.	Rimonabant			-68.4 ± 4.8
12.	(±)-SLV-319			-60.1 ± 8

Table 1: Effect of the pyrrolidine analogues on consumption of 5% sucrose solution in male Sprague Dawley rats (mean+SEM, n =6),

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PS15: Near Normalization of Metabolic Control in Type-1 DM Using Conventional Insulin Therapy And A 13-Point Method Designed to Enhance Compliance

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Objective: To determine if adequate compliance improves metabolic control in Type-1 DM using conventional insulin therapy (CIT) because of its lower cost and safety profile.

Methods: A Stabilization Phase (SP) was implemented in Type-1 DM subjects (17M; 8F); Age 28.6y (9.0); Height 164.8cm (8.53); Weight 62.4kg (8.68); BMI 22.9 (1.97); Duration of DM 9.7 (5.1). During SP all subjects received standard therapy with basal s.c. twice daily (BID) isophane insulin (BID-NPH) and 3 pre-prandial s.c. injections of regular insulin (TID-RI). After SP, subjects entered a 2-cohort 99-d Comparison Phase (CP) with basal BID-NPH and two different modalities of prandial regular insulin administration (Od to +99d). Fructosamine and glycated hemoglobin were measured every two weeks. A simple 13- Point method (13-pm) made of clinical measures designed to enhance compliance and self control was prospectively applied.

Conclusion: Near normalization of parameters of DM metabolic control was achieved using CIT and a 13-PM designed to enhance compliance. The combination of CIT, enhanced compliance and self-control might help to appropriately control type-1 DM.

PS16: Metformin Gum: An Alternative Method for Delivery of Biguanides

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Metformin (Met) is widely used in the treatment of Diabetes Mellitus due to its efficacy comparable to that of sulfonylureas but devoid of side effects such as weight gain and hypoglycemia. Despite its beneficial actions, approximately 30% of Met users devlelop gastrointestinal (GI) adverse effects. The aim of this study was to compare the pharmacokinetic (PK) profile of Met administered by tablets and by an alternative presentation (Met-Gum), that supposedly diminish Met GI adverse effects. Met PK was determined in 10 healthy volunteers (6M, 4F) afe 30/29.8; BMI 23.9/21.49.850 mg Met tablets and Met-Gum/214.5 mg unit were administered and Met PK was subsequently evaluated at: a) 12-hour period after 429 tablet (fraction of the larger tablet) administration. Plasma Met concentration was determined by HPLC (HPLC time; 6 minutes; retention time of Met and internal standard atenolol: 3.4 and 2.9 minutes respectively. Frozen (-70°C) experimental specimens were thawed for 1 hour before the assay. Removal of proteins and lipids from the biological matrix were achieved prior to HPLC.

Conclusion: The Metformin Gum displays a PK profile similar to that of tablets and shows promise as an alternative method for delivery of this biguanide.

PS17: Generex Oral-Lyn™ At Lunchtime in Juvenile Type-1 DM Subjects Maintained on Basal Glargine Insulin and Pre-Breakfast and Pre-Dinner Regular Insulin

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Adolescent DM is associated with dramatic changes that make control difficult. Injection at lunchtime is frequently missed.

Objective: To replace lunch -time insulin injected dose for Generex Oral-lyn™

Method: 24 adolescents (12M; 12F) and 5 young adults (2M;3F) Age 15.7y(3.0); Bone Age 14.9(2.7); Height 155.1 cm(10.2);Weight 53kg(10.8) BMI 21.9(3.0);DM duration 6.8(2.6) were included into a 21-days stabilization period with Standard therapy (ST): s.c. BID insulin analogue + 3 pre-prandial s.c. regular insulin injections (RI) followed by a 28-days ST Comparision Phase. Thereafter, Generex Oral-lyn™ replaced lunch-time injection for 6 months. At study end, 6 evaluators blinded to biochemical results assessed compliance using a 9-parameter method.21 subjects had good compliance (GC); 8 subjects had very poor compliance (PC). GC score; 51.86(14.97) vs. PC score 14(10.87) $p<0.001$.

Conclusions: 29 juvenile Type-1 DM subjects replaced lunchtime injection of RI with Generex Oral-lyn™ for 6 months. Metabolic control corresponded to compliance.

PS18: Pre-Prandial S.C. Regular Insulin versus Prandial Generex Oral-Lyn™ in Type-1 DM Subjects Maintained in Basal S.C. Twice Daily Isophane Insulin (NPH)

Jaime Guevara-Aguirre, Marco Guevara, Jeannette Saavedra

Institute of Endocrinology IEMYR, Quito, Ecuador

Objective: study safety and efficacy of meal time Generex Oral-Lyn™ replacing s.c. injected insulin

Methods: 25 Type-1 DM subjects (17M; 8F); age 28.6y(9.0); Height 164.8cm (8.53); Weight 62.4kg (8.68);BMI 22.9 (1.97); BMI 23.8 (2.0). Duration of DM 9.7 (5.1) years were included into an initial Stabilization period where subjects received standard therapy (ST) with basal s.c. twice daily (BID) isophane insulin (BID-NPH) and 3 pre-prandial s.c. injections of regular insulin (TID-RI) in addition to encouragement to self-control. Subsequent to SP subjects were allocated to 2 cohorts; 11 subjects (5mM; 6F0 in the Control Group (CG) and 14 subjects (14M; 2F) in the Treated Group (TG). Subjects in the CG continued receiving BID-NPH and TID-RI. Subjects in the TG received BID-NPH and TID prandial split doses of Generex Oral-lyn™ (OI). Comparision Phase (CP) lasted 99 days. Fructosamine (F) and Glycated Hemoglobin (HbA1c) were determined every 14 days.

Conclusion: Near normalization of parameters of DM metabolic control was achieved in each and all subjects as reflected by continuous improvement in F and HbA1c concentrations documented every 2 weeks. Direct comparison of HbA1c concentration during CP demonstrate a superior effect of Generex Oral-lyn™ over injected regular insulin.

PS19: Design, Synthesis and Characterization of α,β-dehydrophenylalanine Containing Peptide Based Inhibitors of Human Islet Amyloid Polypeptide Fibrillogenesis

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Amyloid fibrils are the hallmark of a range of debilitating diseases of unrelated origin, including the deadly Alzheimer's disease and type II diabetes. A key step in amyloid formation is the transition of a protein from its native structure to a β-sheet arrangement, suggesting that prevention of the ability of amyloidogenic proteins to adopt a β-sheet conformation would be useful in interfering the amyloid formation. The use of β-breaker residues can thus be a useful approach to the development of peptide based fibrilization inhibitory drugs. In this context, we have tried to harness the potential of a non-natural amino acid, α,β-dehydrophenylalanine (ΔPhe), as a β-sheet breaker residue. The extended conjugation of π clouds of ring and the double bond between Cα-Cβ atoms in ΔPhe makes it a planar residue. ΔPhe induces β-turns in shorter peptides and 3-10-helices in medium and longer sized peptides. Human islet amyloid polypeptide (IAPP) is the major component of amyloid deposits found in the pancreas of over 90% of all cases of type-II diabetes. One of the major consequences of type-II diabetes is the loss of the functional β-cell mass and the replacement of pancreatic islet cells with deposits of insoluble amyloid. Peptide fragments of hIAPP14-20 have been found to be highly amyloidogenic. We designed two peptide inhibitors by strategically incorporating ΔPhe residue in the sequences 13-20 and 13-17 of hIAPP. Congo red birefringence, CD, and FT-IR studies revealed the absence of fibrillar aggregates in peptide inhibitors as compared to that of the native peptides. The successful exploration of ΔPhe residue as a β-breaker in short peptide sequences is likely to be a starting point for future designing of peptide based anti-fibrilizing drugs.

PS20: CYP3A a Major Drug Metabolizing Enzyme for Oral Hypoglycemic Agents- Status of Gujarat population

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Background: Insulin exerts different effects on the various P450 subfamily members. Insulin has down-regulatory effect on CYP3A. Thiazolidinediones compounds are known to be substrates for CYP3A4. CYP3A4 has been identified as an important enzyme in the in vitro metabolism of repaglinide.

Objective: Atorvastatin is exclusively metabolized by CYP3A. Statins have been accepted sensitive probe drug for CYP3A4 activity by the U.S.Food and Drug Administration. Thus atorvastatin was used

as a probe to study phenotyping in Gujarati subjects and look into the metabolizing status of Gujarati population.

Method: The subjects chosen for the study were 20- to 35-year-old men and women and were residents of Gujarat. For phenotyping, each healthy Gujarati volunteer was given 20 mg atorvastatin (Zivast. FDC.India) orally, with 250 ml water after an overnight fasting. Atorvastatin, o-hydroxyatorvastatin and p-hydroxyatorvastatin in plasma were estimated using HPLC-MS/MS method of analysis. Metabolic ratio (MRs) of atorvastatin/ortho hydroxyatorvastatin were calculated in a 2-h plasma sample. Analysis of interindividual variations in the metabolism of atorvastatin was expressed by a probit plot and a frequency distribution histogram between log MR on the abscissa and the number of the subjects on the ordinate. The Kolmogorov-Smirnov test was performed to estimate Normality of the population.

Result: The data of Gujarat (West Indian) subjects shows a bimodal distribution with respect CYP3A metabolizing enzyme. Interindividual differences of drug metabolism expressed as log MR. It was inferred that there were 3 poor metabolizers and 122 extensive metabolizers of atorvastatin.

Conclusion: These observations showed that frequency of occurrence of poor metabolizer phenotype is 2.4 % in the Gujarat (West Indian) subjects. Thus the chances of hypoglycemia due to drugs like thiazolidinediones and repaglinide due to a poor metabolizing phenotype are about 2-3% in Gujarati population

PS21: Rimonabant, a CB-1 Antagonist, and LHRH Show Anxiolytic-like Activity in Marble Burying Behavior in Mice

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Cannabinoids (CBs) are known to suppress gonadal function by reducing LH secretion. The LH-inhibitory action of cannabinoids may be attributed their effects on LHRH secretion. While LHRH is known to regulate the reproductive functions, abnormalities of LHRH release have been observed in various psychiatric disorders. LHRH agonists are known to influence the centrally mediated behaviors like anxiety, catalepsy and analgesia. Rimonabant, a CNS acting CB-1 antagonist and inverse agonist, is also known to modulate anxiety. Since the negative modulation of LHRH release by endocannabinoid is documented, the objective of the current wok is to probe into the modulation of anxiety-related behavior of LHRH by CB-1 blockade. The marble-burying behavior test in male Swiss albino mice was used to test the anxiolytic activity of Rimonabant and LHRH. Rimonabant (1,3, and 10 mg/kg, i.p.) caused a dose-dependent inhibition of marble-burying behavior. Similar effect was also observed with LHRH agonist (25, 50, and 100µg). Combination of sub-optimal dose (50 µg) of LHRH agonist with Rimonabant (0.3, 1, 3 mg/kg) showed additive effect in marble-burying behavior, without producing hypomotility. Whereas, the anxiolytic-like behavior of rimonabant was significantly attenuated by the central administration of LHRH antagonist. While LHRH and Rimonabant showed similar effects on anxiety behaviour, their effects on catalepsy may be mediated by different circuitry. LHRH is known to show catalepeptogenic effects whereas rimonabant does not show catalepsy. On the other contrary, rimonabant antagonize the catalepsy caused by cannabinoids. In view of these opposite effects of Rimonabant and LHRH, a group of animals were given treatment of LHRH and Rimonabant. In this study, Rimonabant (1, 3, and 10mg/kg) was unable to block the catalepsy shown by higher doses of LHRH agonist (200, 300 µg), though it has shown a significant blockade of CB-1 agonist (WIN55212-2, 3mg/kg)-induced cataleptogenic effect. These results suggest that Rimonabant, a CB-1 antagonist shows significant anxiolytic-like behavior that may be mediated by LHRHergic mechanism. However, rimonabant and LHRH may involve independent pathways for exerting their effects on catalepsy behaviour.

PS22: Synergistic Antiobesity Activity of CB1 Antagonist Rimonabant and T3 in Zucker fa/fa Rats

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The Endocannabinoid system (ECS) as well as thyroid hormones has been implicated in regulation of energy homeostasis. The antagonists of ECS acting via CB-1 receptor are believed to act primarily through appetite suppression whereas thyroid hormones affect the energy homeostasis by increasing the basal metabolic rate. Whether these two distinct approaches for controlling obesity would

complement each other is not known. In this study, we attempted to understand the interaction between cannabinoid antagonism and thyroid agonism in reduction of body weight in obese rats. Male Zucker fa/fa rats of 8-10 week age were treated with either Rimonabant (10mg/kg, p.o.), T3 (triiodothyronine, 20.6nM/kg, p.o.) or the combination of Rimonabant and T3. The combination of Rimonabant (10mg/kg) and T3 (20.6 nM) was found to significantly improve the antiobesity action of Rimonabant or triiodothyronine alone. T3 showed slight increase whereas Rimonabant resulted in prominent decrease in the feed intake. On the other hand combination of Rimonabant and T3 treatment showed similar anorectic effect as that of Rimonabant alone. The hyperphagic effect of T3 were seen during entire 28 days treatment period whereas the anorectic effect of Rimonabant or of the T3-Rimonabant combination showed tolerance after 14 days. Apart from effects on body weight, the combination showed significant additive effect in reduction of serum triglyceride, fasted glucose, and LDL cholesterol also. An increase in the heart weight suggesting cardiac hypertrophy was seen in case of treatment with T3 alone. Co-administration of Rimonabant with T3 had no protection against this increase. Lastly, the liver mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH) activity was increased in both T3 as well as Rimonabant treated group while the combination had additive effect on this parameter. In conclusion, the combination of Rimonabant and triiodothyroine produced synergistic antiobesity effect in genetic animal model of obesity.

PS23: Comparison of Acute and Chronic Antiobesity Effects of Two CB-1 Receptor Antagonists: Rimonabant and SLV-319

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CB1 receptor antagonists represent a promising approach for reducing body weight, and decreasing the co-morbidities associated with excessive adiposity. Rimonabant is the first therapeutically relevant, potent and selective CB1 receptor antagonist for antiobesity activity. SLV-319 is another molecule of CB1 antagonist category, which has shown potent in vitro activity and selectivity. However, the antiobesity activity of SLV-319 is not reported. In view of this, the antiobesity activity of Rimonabant and racemic SLV-319 were evaluated in acute models of appetite suppression, and in genetic as well as diet-induced obesity model in rats. The in vivo cannabinoid antagonistic activity was evaluated in mouse tetrad model. The appetite suppressant effect of a single dose of Rimonabant (10mg/kg) or SLV-319 (10mg/kg) was measured using 5% sucrose intake model in non-deprived and fasting-induced feed intake in Sprague Dawley rats. In view of similar efficacy of both the compounds in acute appetite suppressant models, the antiobesity activity of both the compounds were evaluated in high sucrose-fed Sprague Dawley rats and obese Zucker fa/fa rats in chronic dosing schedule. Similar efficacy was observed with both the compounds in acute appetite suppression. However, the chronic dosing effect of SLV-319 indicated lesser effect on body weight reduction in both Zucker fa/fa rats as well as in diet-induced obesity model. This decrease in efficacy could be related to the early extinction of the anorectic effect of SLV-319 as compared to that of Rimonabant. In view of this, the activity of Rimonabant and SLV-319 were evaluated to detect their ability to synergize LiCl-induced malaise using conditioned aversion test. SLV-319 had lesser tendency to synergize LiCl-induced conditioned aversion as compared to Rimonabant. The apparent discrepancy in the antiobesity profile of the two compounds in chronic dosing schedule could be correlated with decreased appetite suppression.

PS24: Rimonabant, a CB-1 Receptor Antagonist, Potentiates LPS- and LiCl-induced Anorexia Independent of the Metabolic Status of the Animals

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Rimonabant, a CB-1 receptor antagonist exerts its anorectic effects through central and peripheral mechanisms. Evidences indicate that one of the mechanisms by which Rimonabant causes anorexia is by taste aversion or malaise. The present research compared the effect of this anorectic agent in pathological anorexia in two paradigms, namely, LPS (lipopolysaccharide)-induced anorexia and LiCl-induced visceral illness. Three different groups of male Wistar rats - overnight fasted, partially satiated and satiated were used in the study. The anorectic effects of LPS (250µg/kg, i.p.) as well as LiCl (0.15M, i.p.) were potentiated by rimonabant (10mg/kg, i.p.). The degree of potentiation of the anorexia was similar in all the groups, irrespective of the nutritional status of the animals. The body weight changes over the period of study correlated with the appetite changes, however the biochemical parameters like glucose, triglycerides, and free fatty acids were unaffected. LPS as well

as LiCl, both produced hypothermia that was potentiated by Rimonabant, but it had no effect on the LPS-induced hyperthermia that follows early hypothermia. Moreover, the inhibitory effects of LPS and LiCl on gastric motility were significantly enhanced by rimonabant in fasted rats. Neither of the combination or single treatment or combination had produced hypoalgesia or hyperalgesia throughout the 24 hours duration of the study. These data showed that Rimonabant could potentiate the anorectic effects of LiCl as well as LPS. These effects seem to be independent of the metabolic status of the system, though they involve modulation of distinct central as well as peripheral pathways of appetite control.

PS25: Cannabinoid Agonism in Human Preadipocytes & Mouse Adipocytes

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Peripheral endocannabinoid overactivity has been reported to be associated with obesity and insulin resistance. In the present study we explored the cannabinoid signaling pathway in cultured adipocyte system. Activation of cannabinoid receptors in human preadipocytes and mouse adipocytes attenuates cyclic AMP, which is reversed by standard inverse agonists. Moreover, cannabinoid agonism decreases basal and insulin stimulated glucose uptake establishing the mechanistic relationship between elevated endocannabinoid activity and reduced glucose uptake in obese animals and humans.

PS26: Role of Serum Adipocytokines and Insulin Resistance in Asian Indian Subjects with Metabolic Syndrome

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Aims & Objectives: In the present study we detected serum levels of adipocytokines and evaluated role of serum adipocytokines and insulin resistance in Asian Indian subjects with metabolic syndrome (MS).

Methods: A total of 160 subjects including 96 normal-glycemic subjects without MS and 64 abnormal glycemic subjects with MS were recruited in this study. Elisa technique was employed to determine serum adipocytokines and hsCRP concentration. Serum insulin was measured by radioimmunoassay. Association between variables was studied by univariate regression analysis.

Results: The prevalence of the Adult treatment panel III MS was 40%. Subjects with metabolic syndrome shows significantly increased leptin and reduced adiponectin. HOMA-IR was common in the MS group and significantly associated with the components of MS ($p < 0.001$). Among the adipocytokines only adiponectin is significantly correlated with components of MS like Waist, SBP, Triglyceride, HDL Cholesterol and also with HOMA-IR.

Conclusions: The association of Adiponectin and HOMA-IR with the components of MS suggest that they may take part in the development of MS. Among the adipocytokines only adiponectin is reduced in the metabolic syndrome hence the adiponectin replacement might became a new pharmacological approach for the management of MS.

PS27: Beneficial Effects of Coenzyme Q10 in Streptozotocin Induced Type-I Diabetic Rats

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The present investigation was undertaken to study the beneficial effects of Coenzyme Q10 in streptozotocin (STZ)-induced type I diabetic rats. STZ-diabetes produced a significant increase in fasting glucose levels that was associated with decrease in serum insulin levels. STZ also produced hypercholesterolemia, hypertriglyceredemia, increase lipid peroxidation and decrease in high-density lipoprotein (HDL) levels. Treatment with Coenzyme Q10 produced a significant decrease in fasting glucose levels without affecting insulin levels. Coenzyme Q10 was also found to decrease significantly AUCglucose and no significant change in AUCinsulin values in STZ-diabetic rats. Treatment with

Coenzyme Q10 also caused decrease in serum cholesterol, serum triglyceride levels and an increase in HDL levels. Coenzyme Q10 treatment also reduced the lipid peroxidation in diabetic rats. The elevated blood pressure in diabetic rats was also lowered. Our data suggest that Coenzyme Q10 has beneficial effects in diabetes-induced complications.

PS28: Evaluation of Hypoglycemic Effect of *Morus Alba* on Diabetes Induced Animal Model-Wistar Rat

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Diabetes mellitus is a chronic disease characterized by elevated blood glucose levels and disturbances in carbohydrate, fat and protein metabolism. These metabolic abnormalities result in part from deficiency of blood sugar lowering hormone insulin (Type-1 diabetes-IDDM). Type-2 diabetes or NIDDM is a result of hyperglycemia caused by overproduction of glucose at hepatic level, or abnormal β cell function or insulin resistance at target cells. Therefore knowledge of how to stimulate growth and differentiation of islet β cells is critical for developing new therapies. Despite lack of scientific evidences to support therapeutic efficacy the use of herbal supplement has increased. The objective of the present investigation was to evaluate therapeutic efficacy of mulberry leaves on diabetes induced animal model Wistar rat. Experimental animals were grouped as control, control diabetic group with mulberry leaf extract Treated with 400 mg and 600 mg/kg body wt. Blood glucose, glycosylated hemoglobin, triglyceride, LDL, VLDL, HDL, blood urea and cholesterol were measured at the beginning and termination of experiments. Blood glucose level and other parameters were elevated in diabetic group except HDL and were brought to control group level in diabetic group treated with mulberry leaf extract with 600 mg /kg body wt. Results are discussed comparing similar studies using different plant extracts.

PS29: A PPAR-Gamma Agonist Increases Insulin Sensitivity in Diabetic Animals (db/db) By a Visfatin Independent Mechanism

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Backgound: Insulin resistance is a fundamental defect that precedes the development of the full insulin resistance syndrome as well as beta cell failure and type 2 diabetes. Here we investigated how a PPAR-γ agonist (pioglitazone) treatment, enhanced insulin sensitivity in diabetic mice via the regulation of adipocytokines e.g. visfatin, adiponectin, resistin and TNF-α levels.

Methods and Results: Female db/db mice were dosed with 3 and 30 mg/kg pioglitazone for 14 days. At the termination of the study white adipose tissue (WAT) was collected and flash frozen for later RT-PCR analysis. Later, tissue was homogenized and RNA was extracted using Trizol reagent. cDNA was synthesized using High-Capacity cDNA Archive Kit, (ABI, USA) which was followed by Real Time PCR. Blood was collected, serum separated glucose was measured and stored at -70°C until resistin levels was measured using ELISA method. In db/db mice, visfatin and adiponectin mRNA expression in the WAT were found to be significantly lower in comparison to normal control, C57 mice indicating conditions of insulin resistance. On the other hand, in the same tissues, resistin and TNF-α mRNA levels, which are produced under conditions of insulin resistance, were found to be significantly higher than the c57 control mice. Pioglitazone showed a significant decrease in blood glucose at a dose of 30mg/kg. While the treatments did not alter tissue visfatin levels at either of the doses tested, there was dose dependent increase in adiponectin levels. Both resistin and TNF-α tissue levels were lowered by pioglitazone. Circulatory resistin levels were also lowered dose dependently by pioglitazone, which correlated well with the tissue resistin mRNA levels.

Conclusion: Pioglitazone treatment increased insulin sensitivity in diabetic animals in a visfatin independent mechanism by restoring adiponectin levels and downregulating resistin and TNF-α levels.

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PS30: Role of Resistin in Leptin Mediated Regulation of Inflammatory Cytokines

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Background: Obesity is an epidemic health hazard in industrialized countries and is strongly associated with increased prevalence of type 2 diabetes, hypertension, dyslipidemia, and atherosclerosis. Although many epidemiological studies have suggested that increased adiposity is associated with chronic low-grade inflammation, as indicated by increased levels of the inflammatory markers, the molecular mechanisms underlying this connection still remain unknown. Here we investigated the correlation of leptin with the inflammatory markers and the relation of resistin levels with the inflammatory state. This was studied using leptin deficient models to validate the resistin regulation.

Methods and Results: Female db/db, ob/ob mice and their age-matched C57BL/6J littermates were used in this study. Serum cytokines TNF-α, IL-1β, resistin and leptin were measured by ELISA. LPS challenge led to a significant alteration in the serum proinflammatory cytokine TNF–α and IL-1β levels. Both TNF- α and IL-1β levels were significantly increased in ob/ob, db/db mice as compared to C57 control mice. This clearly indicated that LPS sensitivity was increased in the obese condition associated with the absence of intact leptin signaling mechanism. Parallely, serum resistin levels were decreased in C57 mice while they rose dramatically in ob/ob and db/db mice. DPC-333, a TNF-α release inhibitor and Anakinra, a IL-1β receptor antagonist attenuated the increase in resistin level in ob/ob & db/db mice, C57 showed decreasing trends in resistin levels after LPS challenge which was not significantly altered by the drug treatments.

Conclusion: These findings clearly indicate that leptin is an important regulator for mediating the inflammatory response to LPS by altering intermediate serum resistin levels.

PS31: Low Level Quantification of Polymorph – II in Polymorph – I by Powder X-ray

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Polymorphism (or crystal polymorphism) is a phenomenon related to the solid state. It is the ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition. Substances that exist in a non-crystalline solid state are said to be amorphous. Where a monograph indicates that a substance shows polymorphism, this may be true crystal polymorphism, occurrence of solvates, allotropy or occurrence of the amorphous form. The identity of chemical composition implies that all crystalline and amorphous forms of a given species have the same chemical behavior in solution or as a melt; in contrast, their physico-chemical and physical characteristics (solubility, hardness, compressibility, density, melting point, etc.), and therefore their reactivity and bioavailability may be different at the solid state. Techniques used to study polymorphism include X-ray diffraction of powders, X-ray diffraction of single crystals, Thermal analysis (differential scanning calorimetry, thermogravimetry, thermomicroscopy), microcalorimetry, Moisture absorption analysis, Optical and electronic microscopy, Solid-state nuclear magnetic resonance, Infrared absorption spectrophotometry, Raman spectrometry, Measurement of solubility and intrinsic dissolution rate and Density measurement. These techniques are often complementary and it is indispensable to use several of them, however, by far, the most powerful tool has been the X-ray Diffractometry (XRD). A highly sensitive XRD method was developed and validated for estimation of Form – II of a blockbuster drug as a Polymorphic Impurity in the desired Form – I of that drug to a level as low as 0.2%.

PS32: Bioisosteric Replacement of Dihydropyrazole of SLV-319: Synthesis, Structure Activity Relationship of Imidazoles and Oxazoles as CB1 receptor antagonist

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Bioisosteric replacement of dihydropyrazole nucleus of SLV-319 (a potent CB1 receptor antagonist) by imidazole and oxazole congeners resulted compounds, which did not exhibit CB1 receptor antagonistic activity in pharmacological animal models. The conformational changes of these congeners were found to be unfavorable in the molecular modeling studies, which are attributed for loss of CB1 antagonistic activity.

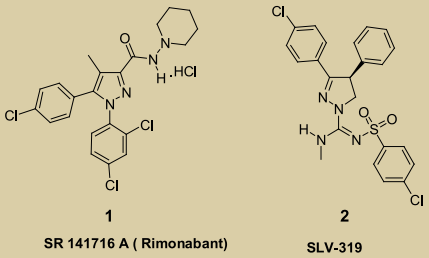

Figure 1.

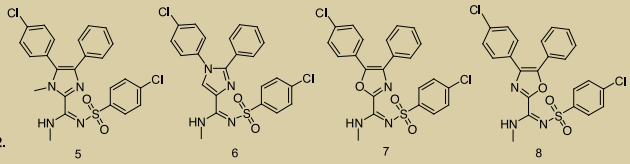

Figure 2.

PS33: Pioglitazone Acts as a Selective Partial Agonist for Human PPAR

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Pioglitazone (Actos ™), a thiazolidinedione (TZD) derivative, is an anti-diabetic agent that improves hyperglycemia and hyperlipidemia in obese and diabetic animals via a reduction in hepatic and peripheral insulin resistance. The TZDs including Pioglitazone have been identified as high affinity ligands for peroxisome proliferator-activated receptor (PPAR) gamma. In our study we observed that Pioglitazone is a selective PPAR gamma agonist with partial activity for PPAR alpha subtype also. We compared the efficacy of Pioglitazone by in vitro trans-activation assays using full length PPAR alpha and a PPRE driven luciferase construct. It was observed that the efficacy of Pioglitazone did not reach to the same level as that of WY-14,643. The Emax was 32 % that of standard PPAR alpha compound (WY-14,643). We show that Pioglitazone is a selective PPAR alpha modulator, wherein it acts as an antagonist for PPAR alpha agonist in cell based transactivation assays and has its Emax less than 50% of that of the full agonist. Also in co-regulator recruitment assays, Pioglitazone shows recruitment profile indicative of a partial agonist as compared to a full agonist (Farglitazar). In clinical trials, compared with placebo, Pioglitazone significantly decreased mean triglycerides levels and increased mean HDL-cholesterol levels in both monotherapy and in combination with sulfonylureas, metformin or insulin. These preferable lipid effects of Pioglitazone could be at least partly mediated due to partial PPAR alpha activity.

PS34: Protein Kinase C Inhibition Attenuates Augmented Responses to H_2O_2 and Angiotensin II In Thoracic Aorta of Streptozotocin Induced Diabetic Rats

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Hyperglycemia, hallmark of diabetes, contributes to micro and macro vascular complications of diabetes. The effects of hyperglycemia can be mediated by several pathways: (a) production of Reactive Oxygen Species; (b) accumulation of sorbitol; (c) nonenzymatic glycoxidation of macromolecules; and (d) direct activation of protein kinase C. Among these hypotheses, the involvement of PKC may be one of the most relevant. Initial studies of PKC activation in diabetes focused on microvascular complications like retinopathy, neuropathy and nephropathy but increasing evidence also supports that PKC plays a role in several mechanisms promoting atherosclerosis. We propose the hypothesis that hyperglycemia induced PKC activation is responsible for hypertension in diabetes. We found leftward shift as well as higher amplitude of cumulative concentration response curves to H_2O_2 (10-6 M to 10-3 M) and Angiotensin II (10-10 to 10-6 M) in the aortic spiral preparations obtained from STZ induced diabetic rats when compared to those of age matched control rats, which was reflected in increased pD2 value as well as Emax of H_2O_2 and Ang-II in diabetic aorta than in control. H_2O_2 and Ang-II mediated contraction were higher in endothelium denuded aortic spiral preparations obtained from age matched control rats but not in those of diabetic rats because there is already endothelial dysfunction in diabetes. PKC inhibitors like chelerithrine, staurosprine and rottlerin decreased H_2O_2

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and Ang-II induced vascular responses in thoracic aorta obtained from both age matched control and diabetic rats in concentration dependent manner, but the concentration of inhibitor required to inhibit vascular responses to H_2O_2 and Ang-II in thoracic aorta of diabetic rats were higher as compared to those of control which is very well evident by observing increase in IC50 value of inhibitors in diabetic aorta as compared to those of control. So from above results, it is reasonable to conclude that over activation of PKC is one of the main mediators for augmented vascular responses to H_2O_2 and Ang-II in diabetic condition, which may be an important culprit for vascular dysfunction like hypertension in diabetes.

PS35: Comparative Evaluation of Muraglitazar and Tesaglitazar for Toxicological Effects and Efficacy in Different Animal Models of Dyslipidemia and Insulin Resistance

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Pharmacological effects of muraglitazar and tesaglitazar were evaluated in various animal models of dyslipidemia, diabetes and obesity. Both muraglitazar as well as tesaglitazar treatment produced a significant reduction in circulating triglyceride, free fatty acid, LDL-C and body weight in HF-HC fed Golden Syrian hamsters. However, all these effects were markedly higher in tesaglitazar treated animals as compared to muraglitazar group. In db/db and ob/ob mice, muraglitazar and tesaglitazar both showed reduction in serum glucose and improvement in glucose tolerance and tesaglitazar was superior in all these parameters. Interestingly, tesaglitazar treatment produced a dose dependent reduction in circulating triglyceride levels in Swiss albino mice whereas no such effect was noted with muraglitazar treatment. Muraglitazar treatment resulted in 1.12, 1.45 & 1.25 fold increase of liver CPT, LPL & PEPCK mRNA levels and 1.13 & 1.36 fold increase of muscle CPT & LPL levels in ob/ob mice. On the other hand, tesaglitazar treatment showed much higher 15.7, 10.0 & 1.22 fold increase of liver CPT, LPL & PEPCK mRNA and 1.39 & 1.47 fold increase of muscle CPT & LPL mRNA level. In 14 days oral toxicity (single dose) study, muraglitazar did not show any significant change in body weight, vital organ weight, hematological and biochemical parameters but tesaglitazar treatment showed significant reduction in total red blood cell count & hemoglobin concentration and significant increase in serum alkaline phosphatase levels and relative liver weight. Based on this data, it may be suggested that muraglitazar is less potent and less toxic as compared to tesaglitazar, and may be safer to use in the treatment of dyslipidemia, diabetes and obesity.

PS36: Effect of Different Kind of PPAR Agonists on Changes in Plasma Volume and Biochemical Markers of Hepatotoxicity

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PPAR -γ agonists have been shown to have significant therapeutic benefits in Type 2 diabetic patients, however these agents may cause fluid retention in susceptible individuals. PPAR-α agonists are used for dyslipidemia treatment but potent PPAR-α activators may cause hepatotoxicity, particularly in rodents. Whereas, compounds like Muraglitazar, which is a dual PPAR-α/γ dual agonist, show beneficial effects in controlling lipids as well as hyperglycemia due to strong PPAR-γ agonistic and moderate PPAR-α agonistic effects. We have evaluated the plasma volume expansion potential as well as hepatotoxicity of potent PPAR-α agonist (NS-220) and PPAR-γ agonist (Farglitazar) induced fluid retention and compared these effects with dual PPAR-α/γ agonist (Muraglitazar). Sprague Dawley rats were treated with NS-220 (30mg/kg/day), Muraglitazar (30mg/kg/day) and Farglitazar (40mg/kg/day) for 14 days. PPAR-α agonist (NS-220) caused 3-5 fold elevation of liver enzyme along with hepatomegaly. Farglitazar, a potent PPAR-γ agonist induced a significant plasma volume expansion as measured by Evan's blue dye dilution technique, along with small but significant increase in plasma sodium and chloride ion concentration. Farglitazar also caused significant reduction in hematocrit. On the other hand, PPAR-α/γ agonist (Muraglitazar) showed significant plasma volume expansion which was less severe than Farglitazar and did not show any hepatotoxicity which was evident in PPAR-α agonist (NS-220) treated animals. Gene expression studies showed ENaC-α is positively correlated with plasma volume expansion. The studies indicate that hepatotoxicity & plasma volume expansion potential of PPAR molecules may be correlated with the potency of molecule in PPAR alpha or gamma transactivation assay.

PS37: Converting Dual PPAR α/γ Agonist to Selective α Agonist: Design and Synthesis.

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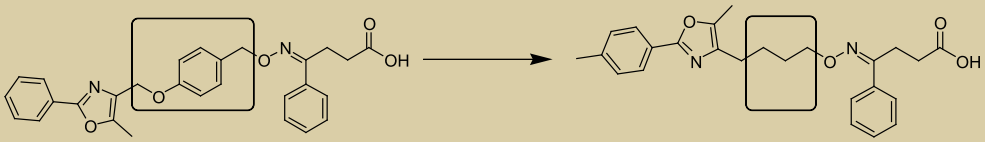
*Department of Medicinal Chemistry, Department of Cell and Molecular Biology, Zydus Research Centre, Ahmedabad

In view of unsuccessful intensive efforts within the pharmaceutical industry to develop PPAR α/γ dual agonists based on the hypothesis that PPAR α/γ dual agonism provides an additive, and possibly synergistic, pharmacology and recent finding that activation of PPAR α is known to lower triglycerides, elevate HDL and exert insulin-sensitizing effects which suggests that even chronic administration of selective PPAR α agonist will serve as a better remedy for the treatment of metabolic disorder we intended to develop selective and potent PPAR α agonist. Imiglitazar, a PPAR α/γ dual agonist was converted to a highly selective PPAR α agonist by replacing the aromatic spacer with an aliphatic chain without modifying pharmacophore.



Imiglitazar

PPAR α/γ dual agonist

ZY-3266

PPAR α agonist

PS38: Gastro Retentive Dosage Form of Metformin HCl: Effect of Hydrophilic and Hydrophobic Polymers

Pritam D.K, Venkatesan N., Shreejit M and Murali Krishna

Department of Novel Drug Delivery Systems, Zydus Research Centre, Ahmedabad

The aim of present study was to develop and optimize controlled delivery system of a biguanide anti-diabetic drug, Metformin using Gastro Retentive Dosage Form (GRDF) and study the effect of gas generating agent [Sodium bicarbonate (SB)], hydrophilic polymer [Hydropropyl methylcellulose (HPMC K15M)] and hydrophobic polymer [Ethyl cellulose (EC)] at various ratios on floating time and in-vitro dissolution studies. Metformin has short elimination half-life (~3 h), has poor bioavailability (~50%) and oral absorption of metformin is confined to upper part of intestine. Hence there is a strong clinical need for delivery of metformin in site specific and controlled delivery. The matrix formulations were prepared mainly considering the solubility characteristics of the drug. The in-vitro release studies were carried out using US Pharmacopoeia (USP) Type II apparatus and simulated gastric fluid (SGF) as dissolution media. The formulations giving floating lag time of less than 30 sec and floating time of about 12 h were further optimized. The study revealed that concentration of HPMC and SB was directly proportional to floating time and drug release up to certain level and was optimized (102 mg and 240 mg of SB and HPMC respectively) to achieve the desired release. Presence of SB reduced the hydration rate of HPMC and hence reduction of release rates. The partial replacement of hydrophilic polymer (HPMC) with hydrophobic polymer (EC) did not affect the floating behavior but enhanced the release rate. From mathematical models, it was concluded that the release rate followed first order and non-fickian mechanism of drug release.

PS39: Apoptosis Plays Crucial Role in Diabetic Stroke Damage

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Diabetes mellitus is a well-recognized risk factor for acute stroke and estimated to increase stroke incidence by more than two folds with high impact on neurological ability. Present study was aimed to delineate the effect of varying degree of cerebral ischemia/reperfusion (I/R) ranging 0.5h, 1.0h and 2.0h of ischemia and 24h of reperfusion on cellular damage in STZ-diabetic and normoglycemic rats. Further, cytochrome c, apoptosis inducing factor (AIF), PARP and caspase-3 expressions were investigated to explore the molecular alterations at shorter time periods (1.0h/3.0h and 1.0h/6.0h) of

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I/R injury. Diabetes resulted into pronounced decrease in neurological function, GSH and significant increase in malondialdehyde (MDA) in diabetic ischemic rats as compared to normoglycemic ones with increasing I/R. Moreover, TTC demonstrated infarction at 0.5h/24h of I/R in diabetic, which was not seen in normoglycemic subjects and further the infarct size at each time point of I/R was comparatively larger in diabetic as compared to normoglycemic rats. The cellular alterations revealed by H&E staining showed necrotic as well as apoptotic damage. The apoptotic cell density, demonstrated by TUNEL, was more pronounced in diabetic in comparison to normoglycemic ischemic animals. Additionally, caspase-3 immunoflourescence further confirmed the role of apoptosis following I/R insult in diabetes. However, at shorter time point of I/R, cytochrome c and AIF was conspicuously increased in cytosolic fraction in cortex and striatum in diabetic animals as compared to normoglycemic ischemic subjects following I/R injury. Moreover, increased level of AIF and early increase in PARP expression in nucleus of diabetics following I/R injury suggest its involvement in cell damage, but, the caspase-3 expression was not detectable at these time points.Hence, the results suggest that diabetes enhanced the development and progression of cell damage with significant contribution of apoptotic process.

PS40: Cannabinoid Receptor Agonism in Rat Insulinoma Cells Stimulate Insulin Secretion

Nisha Sadhwani, Sunil Metiya, Shital Shah, Sachin Jain, Dipesh Kanani, Purvi Pandya & Prasenjit Mitra

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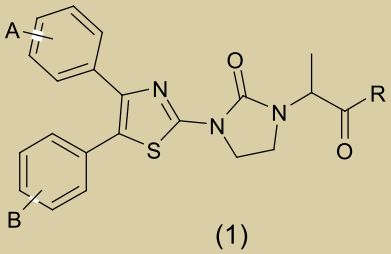
Cannabinoid receptor inverse agonism has been reported to regulate body weight and hyperinsulinemia in obese animals and humans. In our present study, we explored for the existence of functional cannabinoid receptor in cultured rat insulinoma cell line. Type 1 cannabinoid receptor has been detected in RIN M5F beta cells. Surprisingly cannabinoid receptor agonism by synthetic cannabinoid stimulates cyclic AMP in RIN M5F beta cells, which is attenuated by inverse agonist activity of the receptor. Cannabinoid signaling in cultured rat insulinoma cells stimulates insulin secretion under normoglycemic condition providing first concrete evidence of relationship between endocannabinoid hyperactivity and elevated insulin secretion.

PS41: Synthesis and activity of 4,5-Diaryl Thiazole Class of Compounds as TACE and MMP Inhibitors

Kiran Shah, Jigar Desai, Anil Argade, Sanjay Gite, Laxmikant Pavase, Jogeswar Mahapatra*, Mukul R Jain* and Pravin Thombare

Department of Medicinal Chemistry, *Department of Pharmacology, Zydus Research Centre, Ahmedabad

TNF-α converting enzyme, a member of ADAM family of enzyme is responsible for the cleavage of membrane bound TNF in to soluble. It has been postulated that agent that inhibit TACE and thereby reduced level of soluble TNF-α, might offer an effective treatment for RA. Herein we report the synthesis and biological activity of 4,5-diaryl thiazole class (1) of TACE and MMP inhibitor. These inhibitors were synthesized from phenyl acetic acid derivatives in 9 different synthetic steps. We observed that hydroxamic acid based inhibitors were more potent than its corresponding carboxylic acid and ester analogues.



R = OH, OCH_3, NHOH

(1)

PS42: A Cell Based Assay System For Measurement of Cortisol Generation

Shital Shah, Dipesh Kanani, Sunil Metiya, Rajendra Kharul*, Ajay Sharma#, Purvi Pandya, Sachin Jain, Nisha Sadhwani & Prasenjit Mitra

Department of Cell and Molecular Biology, *Department of Medicinal Chemistry, #Department of Pharmacology, Zydus Research Centre, Ahmedabad

The epidemic spread of obesity and metabolic syndrome has heightened the necessity for the development of new and effective treatment. Although circulating cortisol concentrations are not

elevated in obesity and metabolic syndrome, regulation of tissue specific generation of cortisol has been postulated as an effective screening strategy. In our present study we employed a screening platform based on competitive ELISA to measure cortisol generation in cultured cell system. Our screening format can distinguish between differential cortisol generation in mouse and human cell system as is evidenced by differential inhibitory profile of particular small molecule inhibitors.

PS43: Validation of Non-isotopic Methodology for Monitoring the Tissue Production of Cortisol Before and After Treatment with 11-β-Hydroxysteroid Dehydrogenase Type 1 Inhibiting Drugs

Ravinder J. Singh

Mayo Clinic, USA

Hypercortisolism is not only associated with rare disease known as Cushing's but has also been linked to hypertension, diabetes, obesity and pseudo-Cushing's. Analysis of free cortisol in serum/plasma, urine and saliva is used for the diagnosis of hypercortisolism. Various clinical laboratories are now using LC-MS/MS methodology which not only provides simultaneous analysis of free cortisol and cortisone but also has high throughput with least interferences. Cortisone is an inactive metabolite of cortisol formed by an enzyme 11-β-HSD-II, which is converted back to cortisol by 11-β-HSD-I. Recently, various publications have indicated that direct cortisol/cortisone ratio is a better indicator of 11-β-HSD activity than the ratio of urinary metabolites of cortisol and cortisone. Simultaneous analysis of free cortisol and cortisone by the LC-MS/MS method is being used an index for 11-β-HSD activity. 11-β-HSD is expressed in various organs and tissues, thus cortisol and cortisone levels in systemic blood circulation are not a specific index for the organ/tissue 11-β-HSD activity. Various studies have demonstrated that 11-β-HSD-I activity is increased in subcutaneous adipose tissue, implying the link between obesity and other features of the metabolic syndrome. Inhibition of 11-β-HSD-I has become a major therapeutic target in metabolic syndrome. Preclinical results with novel selective 11-β-HSD-I inhibitors are encouraging. It has been shown that the infusion of non-isotopic cortisol can be used to monitor the systemic 11-β-HSD activity. The methodology for monitoring the adipose tissue activity involving infusion of d4-cortisol, clamping and monitoring the levels of the metabolites of d4-cortisol by LC-MS/MS will be presented.

PS44: Antidiabetic Potential of *Rubia cordifolia* in Diabetic Animals

Rahul Somani[a], Kishor Jain[a] and Abhay Kumar Singhai [b]

a. Sinhgad College of Pharmacy, Pune-411 041 (MS), India. b. Dept. of Pharm. Sci., Dr. HS Gour University, Sagar-470 003 (MP), India.

Diabetes mellitus remains one of the oldest diseases all over the world and is the major cause of morbidity and mortality in human populations. The pathophysiology is a consequence of insulin or resistance to insulin, resulting in an increase in blood glucose levels.*Rubia cordifolia* is a commonly used herb in Ayurvedic system of medicine. The present study was carried out with ethyl acetate fraction (RCEAF) of alcoholic extract (RCAE) of roots of *Rubia cordifolia* (RC) on normal fasted, streptozotocin- induced diabetic and fructose- induced hyperinsulinemic rats. A single dose of RCEAF (200 mg/kg, p.o.) significantly ($P<0.05$) decreased blood glucose in normal fasted and streptozotocin-induced diabetic rats at 6h after treatment. Repeated two weeks administration of RCEAF (200 mg/kg, p.o.) decreased ($P<0.05$) blood glucose level, serum cholesterol and triglyceride and increased ($P<0.05$) serum HDL- cholesterol, albumin and insulin as compared to diabetic control rats. Concurrent histological studies of the pancreas of these animals showed comparable regeneration by RCEAF, which were earlier necrosed by streptozotocin. The two weeks treatment of RCEAF (200 mg/kg, p.o.) significantly ($P<0.05$) prevented hyperglycaemia, hypertriglyceridaemia and hyperinsulinaemia as compared to fructose fed rats. According to these results, ethyl acetate fraction (RCEAF) of alcoholic extract of roots of *Rubia cordifolia* might be useful in the treatment of insulin resistance and diabetic complications.

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PS45: Comparative Effect of Tiplaxtinin, PAI Inhibitor, With Other Anticoagulants in Animal Model of Arterial Thrombosis

Hitesh Soni, Ajay Sharma, Mukul R Jain

Department of Pharmacology and Toxicology, Zydus Research Centre, Ahmedabad

Fibrinolysis is a repair mechanism that restores blood flow by degrading fibrin and thereby removing intravascular thrombi. Proenzyme plasminogen and its activators tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), are the key components of fibrinolytic system. Activity of tPA and uPA is negatively regulated by a serine protease inhibitor (SERPIN) named plasminogen activator inhibitor-1 (PAI-1). Platelets contain high amount of PAI-1 and release of PAI-1 from activated platelets may lead to its high local concentration. This may lead to thrombi formation, which are resistant to dissolution by tPA. Therefore, the present study was designed to evaluate the effect of tiplaxtinin, a PAI inhibitor, in animal model of arterial thrombosis. Arterial thrombosis was produced by $FeCl_3$ induced chemical injury in carotid artery and time to occlusion (TTO) after $FeCl_3$ application was noted down. Tiplaxtinin (10, 50 and 200 mg/kg) was administered orally 90 minutes prior to $FeCl_3$ injury. Two separate groups of animals received either clopidogrel (10 & 50 mg/kg, p.o.) or enoxaparin (5 mg/kg & 30 mg/kg, s.c.) respectively. $FeCl_3$ injury lead to thrombus formation in 16-20 minutes in vehicle treated animals. Pretreatment with clopidogrel completely prevented thrombus formation at both the dose levels. A significant delay in thrombus formation was noted with 5 mg/kg dose of enoxaparin whereas high dose completely prevented the thrombus formation. On the other hand, tiplaxtinin did not show any such effect at any of the dose levels. Based on these results, it may be suggested that PAI inhibition by tiplaxtinin does not prevent clot formation in arterial model of thrombosis.

PS46: Local Lymph Node Assay –A Method Validation Study

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Jai Research Foundation, Vapi 396 195 (Gujarat)

The Principle of 3 Rs (i.e. reduction, refinement and replacement) promoted us to validate alternate method for the evaluation of allergic contact dermatitis potential of chemicals instead of conventional guinea pig methods (M&K and B-uheler test), which is well accepted by regulators across the globe i.e. Local Lymph Node Assay (LLNA). The study was undertaken using 2- Mercaptobenzothiazole and Hexylcinnamaldehyde (HCA), well-known skin sensitizers. A volume of 25 µL of test substances was applied on dorsum of the both ears of CBA/Ca Mice for 3 consecutive days (day 0, 1 and 2) at the various dose concentrations. On day 5, 250 µL of phosphate buffered saline containing of 3H-methyl thymidine was injected into all test and control mice via the tail vein. At 5 hour post injection, auricular lymph nodes were excised and single cell suspension was prepared. Incorporation of 3H-methyl thymidine in draining lymph node as disintegration per minute (DPM/Node) was measured using Liquid Scintillation Analyzer. Results showed more than 3 fold increase in Stimulation index (SI value) at 30% (w/v) dose concentration of 2-Mercaptobenzothiazole and at all dose concentration of Hexylcinnamaldehyde. EC3 value was calculated and found to be 12.82 for Mercaptobenzothiazole and 8.9 for Hexylcinnamaldehyde. Results indicate sensitization potential of test material as well as sensitivity and reproducibility of the method. We feel confident that this method should help in furthering the cause of 3 'R's.

PS47: NAD(P)H Oxidase Inhibitor Apocynin Prevents the Development of Insulin Resistance Syndrome.

Banappa S Unger, Basanagouda M Patil, Thippeswamy BS, Veeresh babu SV, Veeresh B

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Background: Oxidative stress has been proposed as the root cause underlying the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance and type 2 diabetes. Recent findings have suggested the pivotal role for NAD(P)H oxidase activation and ROS generation in inhibition of insulin signaling.

Objective: The purpose of the present study was to investigate the effect of Apocynin (NAD(P)H oxidase inhibitor) in rats fed a high fructose diet, an animal model of insulin resistance syndrome associated with oxidative stress.

Methods: Male SD rats of 10 weeks old were randomly divided in to four groups: 1) Control(C); received standard chow diet, 2) Fructose-fed (F); received High fructose (60%) diet , 3) Fructose + Apocynin; received high fructose (60%) diet and Apocynin in drinking water (1.5mM), 4) Control + Apocynin (C); received standard chow diet and Apocynin in drinking water (1.5mM). The specified diet and drinking water with or without Apocynin were provided ad libitum for seven days. Systolic blood pressure (SBP) was measured indirectly by tail cuff method. At the end of the study fasting plasma glucose, insulin triglycerides, thiobarbituric acid reactive substances (TBARS) were measured. Glucose tolerance and insulin secretion in response to oral glucose load were measured.

Results: Fructose feeding in rats lead to impaired fasting glucose (IFG), hypertriglyceridemia, increased oxidative stress as indicated by increased TBARS, impaired gucose tolerance (IGT) and defective early insulin secretion (β-cell dysfunction) and mild elevation in SBP. Treatment with NAD(P)H oxidase inhibitor prevented these fructose induced metabolic abnormalities and oxidative stress as well as elevation of SBP.

Conclusion: Results of the present study suggest the critical role for NAD(P)H oxidase mediated oxidative stress in the development of insulin resistance syndrome.

PS48: Protective Effect of Celecoxib (a selective COX-2 inhibitor) Treatment on Diabetes Induced Vascular Complications in Streptozotocin Diabetic Rats

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Department of Pharmacology and Toxicology, KLES's College of Pharmacy, J N Medical College Campus, Nehru Nagar, Belgaum-590010. Karnataka, INDIA

To study the effect of celecoxib treatment on enhanced contractility and endothelial dysfunction in streptzotocin (STZ) diabetic rats. Male wistar rats were divided into three groups: Control (NC), diabetic control (DC) and diabetic treatment (DT). 1ml of 1% Sod CMC to NC and DC and celecoxib (10 mg/kg) to DT groups were given for 8 weeks by oral gavage. Thoracic aorta was isolated and isometric contraction and relaxations were carriedout. Dose response curve (DRC) to phenylephrine (PE) induced contraction in presence and absence of SQ29548 (an PGH2/TXA2 receptor blocker) was recorded in endothelium intact (E+) and endothelium denuded (E-) aortic rings. The DRC of acetylcholine (Ach) induced relaxation in presence and absence of SQ29548 was recorded in E+ aortic rings. DC group aortic rings shows significant increase and decrease of sensitivity (pD2) and maximum response (Emax) to PE (in both E + and E -) and Ach respectively when compared to NC group. Celecoxib treatment significantly inhibits enhanced PE contraction and improves decreased Ach relaxation when compared to DC group. Preincubation with SQ29548 significantly decrease and increase of pD2 and Emax to PE (in both E + and E -) and Ach in DC group respectively and these changes was not observed in NC and DT group when compared with respective pD2 and Emax before incubation. In conclusion, these results suggest that COX-2 mediated smooth muscle and endothelium derived vasoconstricting prosatnoids could be responsible for diabetic vascular complication and treatment with celecoxib will give the beneficial effects for these complications.

PS49: Chronic Treatment with Celecoxib (a Selective COX-2 Inhibitor) Increases Atherogenic Diet Induced Systolic Blood Pressure and Renal Complications in Rats

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Objective: To investigate the effect of celecoxib treatment on systolic blood pressure and renal function in atherosclerotic rats.

Methods: Male wistar rats were divided into three groups: Control (NC), atherogenic control (AC) and atherogenic treatment (AT). 1ml of 1% Sod CMC to NC and AC and celecoxib (10 mg/kg) to AT groups were given for 8 weeks by oral gavage. Systolic Blood Pressure (SBP) was measured weekly interval by tail cuff method. At the end of the treatment blood sample was collected from over night fasted rats for estimation of serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) creatinine (Cr) and blood urea nitrogen (BUN).

Results: Induction of atheorsclerosis significantly raised the SBP from 6th week onwards when compared to NC group. Treatment with celecoxib further raised the SBP from 4th week onwards when

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compared to AT group. Significant rise in TC and TG and decrease in HDL was found in both AC and AT group when compared to NC group. In AC group the Cr and BUN was significantly raised when compared to NC group. Celecoxib treatment further raised Cr and BUN when compared to AC group.

Conclusion: In conclusion the results suggest that, altered renal function may be the causal factor for further increase in SBP in celecoxib treated atherosclerotic rats.

PS50: *Tinospora Cordifolia* Root Extract Prevents Development of Insulin Resistance and Hypertension in Fructose Fed Rats

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Objectives: To evaluate the effect of aqueous extract of *Tinospora cordifolia* roots (TCE) on hypertriglyceridemia, insulin resistance and hypertension in fructose fed rats.

Methods: Male Sprague Dawley rats were divided into four groups: control (C), fructose (F), control treated (C-T), and fructose treated (F-T). Control and C-T animals were fed with standard chow and F and F-T groups were fed with 60% fructose diet for 4 weeks. TCE (400 mg/kg/p.o./day) was given to C-T and F-T groups for 4 weeks. Systolic blood pressure (SBP) was measured by indirect tail cuff plethysmography. Oral glucose tolerance test was performed on 26th day of the experiment. At the end of experiment, biochemical estimations were performed and Insulin resistance index was calculated by Homeostasis model of assessment (HOMA-IR).

Results: Chronic fructose feeding in rats lead hyperglycaemia ($P<0.05$), hyperinsulinemia ($P<0.001$), hypertriglyceridemia ($P<0.001$), glucose intolerance (Total AUC of glucose: 21310±991.4, $P<0.01$) and hypertension ($P<0.001$) compared to control group. Treatment with TCE significantly prevented the development of hyperglycaemia ($P<0.05$), hyperinsulinemia ($P<0.001$), glucose intolerance (Total AUC of glucose: 16318±708.9, $P<0.001$) and hypertension ($P<0.001$) and significantly reduced the elevation in triglycerides ($P<0.001$) in fructose fed rats. Degree of insulin resistance (HOMA-IR) was significantly higher in F rats ($P<0.001$) compared to control rats and it was significantly lower in F-T rats ($P<0.01$) compared to F rats. No change in above parameters was found between C-T and control rats.

Conclusions: Results indicate the insulin sensitizing effect of OSE in fructose induced insulin resistance

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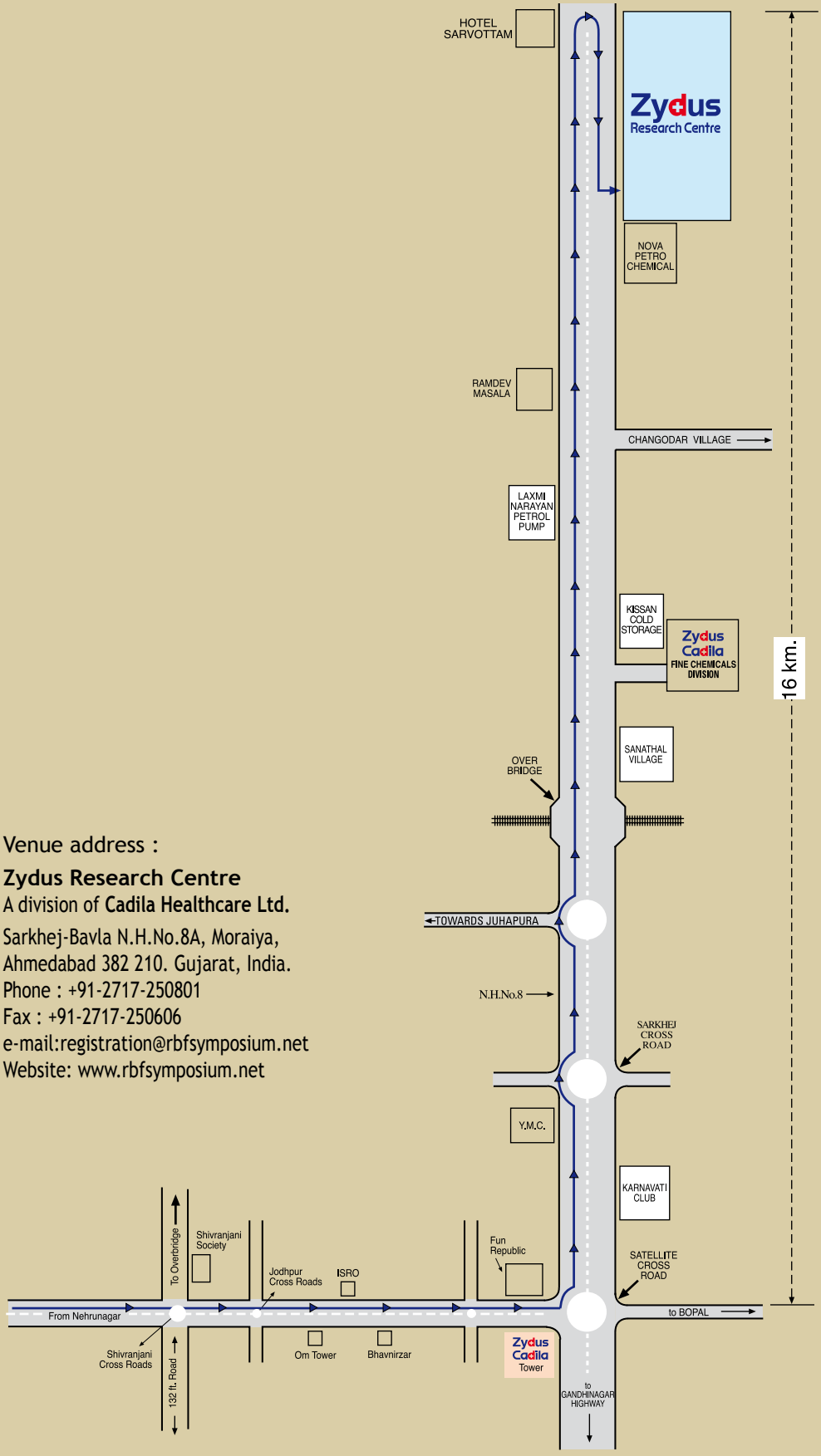

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