WJPR
World Journal of Pharmaceutical Research

BETATROPHIN: A NOVEL MEDICAL ADVANCE

*Dr. Moumita Hazra

Published By
Editor in Chief
WJPR

BETATROPHIN: A NOVEL MEDICAL ADVANCE

***Author, Editor**
Dr. Moumita Hazra

MBBS, DCP, MD, MBA, PGDCR

Associate Professor of Pharmacology and Clinical Pharmacology for MBBS, MD, MS, DM, MCh, Dental, MSc, MPhil, PhD, Nursing, Paramedical and Pharmacy Students.

Published By:
WJPR
2022

PREFACE

The present edition is the first edition of this academic medical book on “Betatrophin: A Novel Medical Advance”. This book is being published with an immense delight, addressing the latest advances in anti-diabetic pharmacotherapeutics, and the medical developments involving betatrophin. The chapters have been meticulously scripted, with an arduous effort to brighten up the infinite horizons of these interesting novel advance in Medical Pharmacotherapeutics, termed, Betatrophin.

Dr. Moumita Hazra
Author and Editor

CONTENT

CHAPTER 1: BETATROPHIN: A NOVEL MEDICAL ADVANCE

Dr. Moumita Hazra

Betatrophin: Betatrophin is a protein of 198 amino acids. In humans, it is encoded by C19orf80 gene.

Angiopoietin-like protein (ANGPTL)8(TD26, RIFL, Lipasin, Betatrophin), located in the corresponding intron of *DOCK 6*, is a newly recognised ANGPTL family member that is expressed mostly in liver and adipose tissue, and is markedly upregulated by feeding and suppressed by fasting. It has been implicated in both triglyceride and glucose metabolism. Hepatic overexpression of ANGPTL8 promotes proliferation of pancreatic β cells, causes hypertriglyceridemia, increased insulin secretion and contributes to glucose homeostasis. Co- expression of ANGPTL8 and ANGPTL3 increased plasma triglyceride level more than 10-fold,suggesting that the two proteins act together, and co-ordinate the transport of triglycerides to tissues in response to food intake. ANGPTL8, a paralog of ANGPTL3 that arose through duplication of ancestral *DOCK* gene, regulates post-prandial TAG and fatty acid metabolism by controlling activation of its progenitor, and perhaps other ANGPTLs. Inhibition of ANGPTL8 provides a new therapeutic strategy for reducing plasma lipoprotein levels.

Gene for betatrophin: The gene for betatrophin is located on mouse chromosome 9 (gene symbol: Gm6484), andon human chromosome 19 (gene symbol: C19orf80).

Discovery: The link between betatrophin and islet cell proliferation, was discovered by Douglas Melton and Peng Yi from the Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, USA in 2013. The earlier names of betatrophin were TD26, RIFL, Lipasin, and ANGPTL8. Betatrophin is a member of angiopoietin-like gene family and shares extensive homology with ANGPTL4 and ANGPTL3.[1, 2, 3, 4, 5, 6]

CHAPTER 2: BETATROPHIN: PHARMACODYNAMICS, PHARMACOKINETICS ANDMOLECULAR PHARMACOLOGY

Dr. Moumita Hazra

Functions

Betatrophin acts as a putative peptide hormone found in mice. It causes dramatic pancreatic beta cell proliferation and beta cell mass expansion. On parenteral administration of betatrophin cDNA in mice, it initiates its action at pancreas, for lowering the blood sugar level. The encoded 22kDa protein contains N-terminal secretion signal and two coiled-coil domains, and lacks C-terminal fibrinogen-like domain (unlike other angiopoietin-like proteins), like ANGPTL4 and ANGPTL3. It inhibits lipoprotein lipase and elevates the circulating triglyceride levels in mice. Mice lacking betatrophin/ANGPTL8 exhibits markedly decreased uptake of VLDL-derived fatty acids into adipose tissue and improves glucose tolerance in mice. The antidiabetic drugs or subcutaneous insulin injection (a) do not provide same degree of glycaemic control as functional pancreatic beta cells, and (b) do not prevent debilitating consequences of the disease. Betatrophin causes (a) long-term restoration of normal glycaemic control, and (b) potentially curative therapy.

Mechanism of Action

The liver-specific deletion of insulin receptor, causes a compensatory increase in pancreatic beta cell replication (Michael *et al*, 2000). The overexpression of constitutively active MEK1 (mitogen-activated or extracellular signal–regulated protein kinase) kinase in mouse liver increases replication rate in pancreatic beta cells and improves glucose tolerance through innervation-dependent mechanism (Imai *et al*, 2008). Although, it is unknown how liver signals pancreatic beta cells to proliferate is unknown. The recent work by Kulkarni's group indicated at the possibility that liver cells secrete a protein that acts directly on the islet cells (El Ouaamari *etal*, 2013; Flier *et al*, 2001).

Molecular Mechanisms

The molecular mechanisms by which ANGPTL8/betatrophin regulates glucose metabolism are poorly understood in human. Two sub-clones of HepG2 cells, ANGPTL8/betatrophin knockouts and ANGPTL8/betatrophin over-expressors, were

established using TALENs (transcription activator-like effector nucleases) and through stable transfection, respectively.

Over-expression of ANGPTL8/betatrophin enhanced the insulin-stimulated activation of the Akt-GSK3β or Akt-FoxO1 pathway, no matter whether the cells were present with insulin resistance or not. In contrast, knockout of ANGPTL8/betatrophin did not affect the Akt-GSK3βor Akt-FoxO1 pathway unless the HepG2 cells were preset with insulin resistance.

ANGPTL8/betatrophin might play an important role in glucose metabolism in the context ofinsulin resistance.

Secretion

Betatrophin is secreted by liver, in the mice, and by white adipose tissue and brown adipose tissue, in the humans. It is reduced by fasting and elevated upon insulin resistance and during pregnancy.[1, 2, 3, 4, 5, 6]

CHAPTER 3: BETATROPHIN: CLINICAL PHARMACOLOGY

Dr. Moumita Hazra

Clinical Significance: Betatrophin treatment augments or replaces insulin injections by increasing the number ofendogenous insulin-producing cells in diabetics. It is also therapeutically used in the treatment for type II diabetes, and perhaps even type I diabetes.

Clinical Preparations

The clinical preparations are as follows: Betatrophin (human): Fc (human) (rec.) AG-40B-0145-C010 10 µg.

AG-40B-0145-3010 MultiPack 3 x 10 µgBetatrophin (mouse) (rec.)

AG-40B-0144-C010 10 µg

AG-40B-0144-3010 MultiPack 3 x 10 µgBetatrophin (mouse): Fc (human) (rec.) AG-40B-0142-C010 10 µg

AG-40B-0142-3010 MultiPack 3 x 10 µg[1, 2, 3, 4, 5, 6]

ACKNOWLEDGEMENTS

My gratitude to my dear family, as well as, the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Pharmacovigilance, Rational Pharmacotherapeutics, Pharmacogenomics, Medical Education, Clinical Pathology, Pathology, Molecular Diagnostics, Clinical Medicine, Respiratory and Chest Medicine, Obstetrics and Gynaecology, Infertility and Reproductive Endocrinology, Neonatology, Clinical Research, Medical Administration and Management, at Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Dr. Moumita Hazra's World Enterprises, West Bengal, India, World; Mamata Medical College and Hospitals, Khammam, Telangana, India; Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India; Hi-Tech Medical College and Hospital, Odisha, India; Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, West Bengal, India; Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, India; K.D. Medical College Hospital and Research Center, Uttar Pradesh, India; J. J. M. Medical College and Hospitals, Chigateri General Hospital, Karnataka, India; Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, Karnataka, India; Medical Schools, USA, UK, World; Hi-Tech College of Nursing, Odisha, India; Symbiosis Centre of Health Care, Symbiosis International University (DE), Maharashtra, India, World; Presidency College, Presidency University, West Bengal, India; All India Institute of Medical Sciences, New Delhi, India; Mahuya Diagnostic Centres and Doctors' Chambers, West Bengal, India; Indus Nursing Home and Indus Diagnostic Centres, West Bengal, India; Sikkim Manipal University (DE), India, World; Fortis Hospitals, India; GIOSTAR IRM Institutes, Hospitals and Laboratories, New Delhi, India, USA, World; and National and International Publications, with special thanks to the World Journal of Pharmaceutical Research, for the successful completion of this book publication.

BIBLIOGRAPHY

1. Wang Y, Quagliarini F, Gusarova V, Gromada J, Valenzuela DM, Cohen JC, Hobbs HH. Mice lacking ANGPTL8 (Betatrophin) manifest disrupted triglyceride metabolism without impaired glucose homeostasis. Proc Natl Acad Sci USA, 2013; 110(4): 16109-16114.
2. Yi P, Park J-S, Melton DA. Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell, 2013; 153(4): 747-758.
3. Quagliarini F, Wang Y, Kozlitina J, Grishin NV, Hyde R, Boerwinkle E, Valenzuela DM, Murphy AJ, Cohen JC, Hobbs HH. Atypical angiopoietin-like protein that regulates ANGPTL3. Proc Natl Acad Sci USA, 2012; 109(48): 19751-19756.
4. Ren G, Kim JY, Smas CM. Identification of RIFL, a novel adipocyte-enriched insulintarget gene with a role in lipid metabolism. Am J Physiol Endocrinol Metab, 2012; 303(3): E334-E351.
5. Zhang R. Lipasin, a novel nutritionally-regulated liver-enriched factor that regulatesserum triglyceride levels. Biochem Biophys Res Commun, 2012; 424(4): 786-792.
6. Rong Guo X, Li Wang X, Chen Y, Hong Yuan Y, Mei Chen Y, Ding Y, Fang J, JiaoBian L, Sheng Li D. ANGPTL8/betatrophin alleviates insulin resistance via the Akt- GSK3β or Akt-FoxO1 pathway in HepG2 cells. Exp Cell Res, 2016; 345(2): 158-167.

INDEX

SHORT BIOGRAPHY

Dr. Moumita hazra

Author and Editor:

Betatrophin : A Novel Medical Advance

Qualifications :

MBBS (Medicine),

DCP (Clinical Pathology),

(Haematology, Cytopathology, Molecular Diagnostics),

MD (Pharmacology),

(Clinical Pharmacology, Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Medical Education, Obstetric and Gynaecological Reproductive Endocrinological Pharmacology, Diabetological Endocrinological Pharmacology, Neonatal Pharmacology, Respiratory Pharmacology, Clinical Medical Pharmacology),

MBA (Hospital Management),

PGDCR (Clinical Research),

(Medical Research Methods, Clinical Research Ethics).

FIAMS (Pathology); Associate MRCP (Clinical Medicine), Associate MRCOG (Obstetrics and Gynaecology);

MIPS (Pharmacology), MISRPT (Rational Pharmacotherapeutics, Pharmaco-Haemo-MaterioVigilance), MCCP (Chest Medicine), MIAC (Cytology and Cytopathology), MIAPM (Pathology), MKCIAPM (Pathology), MIMA (Medicine).

Affiliations :

Associate Professor of Pharmacology and Clinical Pharmacology for MBBS, MD, MS, DM, MCh, Dental, MSc, MPhil, PhD, Nursing, Paramedical and Pharmacy students.

Consultant Multi-Specialist Clinical Pharmacological Physician, Consultant Clinical Pathologist, Medical Director, Medical Superintendent, Consultant Rational Pharmacotherapeutic Physician, Consultant Drug Safety and Quality Physician, Pharmaco-Haemo-Materio-Vigilance Specialist, Medical Academics and Clinical

Research Director, Managing Director, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Dr. Moumita Hazra's World Enterprises, West Bengal, India, World;

Associate Professor, Head of Department In Charge, Department of Pharmacology, Pharmaco-Haemo-Materio-Vigilance Specialist, Pharmacovigilance Committee, Mamata Medical College and Hospitals, Khammam, Telangana, India;

Pharmacology Guest Faculty, Head of Department, Hi-Tech College of Nursing, Odisha, India;

Consultant Pathologist, Laboratory Supervisor, Mahuya Diagnostic Centres and Doctors' Chambers, West Bengal, India;

Medical Editor-In-Chief, Medical Editorial Board Member, Medical Editor, Medical Reviewer, Medical Author, National and International Publications, World;

Medical Academic Scholar, Medical Schools, USA, UK, World;

Former Associate Professor, Head of Department In Charge, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India;

Former Assistant Professor, Head of Department, Department of Pharmacology, Hi-Tech Medical College and Hospital, Odisha, India;

Former Deputy Medical Superintendent, Department of Medical Administration, Assistant Professor, Head of Department In Charge, Department of Pharmacology, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, West Bengal, India;

Former Assistant Professor, Head of Department, Department of Pharmacology, Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, India;

Former Assistant Professor, Head of Department, Department of Pharmacology, K.D. Medical College Hospital and Research Center, Uttar Pradesh, India;

Former Resident and Tutor, Departments of Pharmacology and Pathology, J. J. M. Medical College and Hospitals, Chigateri General Hospital, Karnataka, India;

Former Resident, Medical and Surgical Departments, Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, Karnataka, India;

Former Academic and Research Scholar, Department of Clinical Research, Symbiosis Centre of Health Care, Symbiosis International University (DE), Maharashtra, India, World;

Former Academic and Research Scholar, Departments of Zoology, Physiology and Chemistry, Presidency College, Presidency University, West Bengal, India;

Former Laboratory Director, Consultant Pathologist, Indus Nursing Home and Indus Diagnostic Centres, West Bengal, India;

Former Academic and Research Scholar, Department of Business Administration, Sikkim Manipal University (DE), India, World;

Former Manager, Clinical Excellence and Quality Management, Fortis Hospitals, India;

Former Assistant Medical Director, Medical Editor, GIOSTAR IRM Institutes, Hospitals and Laboratories, New Delhi, India, USA, World.

Significant literary contributions in :

Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Pharmaco-Haemo-Materio-Vigilance, Rational Pharmacotherapeutics, Evidence Based Medicine, Pharmacological Quality and Safety, Pharmacology and Clinical Pharmacology undergraduate, postgraduate, doctorate and postdoctorate Professing, Pharmacology and Clinical Pharmacology Education, Medical undergraduate, postgraduate, doctorate and postdoctorate Professing, Medical Education, Medical Advisory Board and Faculty, Competency Based Medical Education : Competencies, Objectives, Teaching Learning Methods, Alignment and Integration in Medical Education, Assessment Methods, Aligned and Integrated Assessment Methods, Pharmacology Professing Methods, Clinical Pharmacology Professing Methods, Medical Professing Methods, Medical Academic and Education Management, Academic Directorialship, Pharmacology Research Methods, Clinical Pharmacology Research Methods, Clinical Research Methods, Pharmacology Education Research Methods, Clinical Pharmacology Education Research Methods, Medical Education Research Methods, Dermatopharmacology, Respiratory Pharmacology, Drug Delivery Systems, Pharmacology of Antibiotics, Pharmacology of Retinoids, Ocular Pharmacology, Gynaecological and Obstetric Pharmacology, Endocrine Pharmacology, Endocrine Onco-Pharmacology, Reproductive Endocrinology, Pharmacology of Vitamins and Antioxidants, Onco-Molecular Pharmacology, Therapeutic Onco-Vaccines, Pharmaco-Immuno-Onco-Therapeutics, Molecular Therapeutics, Pharmacogenetics, Pharmacogenomics, Epigenetics, Pharmacoepidemiology, Pharmacoeconomics, Pharmacodynamics, Pharmacokinetics, Personalised Medicine, Clinical Medicine,

Stem Cell Therapeutics and Research, Regenerative Medicine, Haematology, Haemato-Oncology, Endocrine Onco-Pathology, Onco-Molecular Pathology, Cytopathology, Cytology, Molecular Diagnostics, Medical Directorship, Hospital Management, Hospital Administration, Medical Administration, Medical Directorship of Global Medical Universities, Institutions, Hospitals and Laboratories, Management of Government Universities, Institutions and Hospital Establishments, Corporate Strategies, Planning and Advisory, Brand Management, Corporate Project Improvisation, Clinical Research, Clinical Research Methods, Clinical Research Authorship and Reviewing, Clinical Research Publications Editing, Medical Editing, Clinical Trials Management, Medical and Clinical Research Directorship.