

eISBN: 978-1-68108-187-8  
ISBN: 978-1-68108-188-5

eISSN: 2210-2698  
ISSN: 2467-9615

# Anti-Obesity Drug Discovery and Development

Volume 3



Editors:

**Atta-ur-Rahman, *FRS***  
**M. Iqbal Choudhary**

Bentham  Books

# **Anti-Obesity Drug Discovery and Development**

*(Volume 3)*

**Edited By**

**Atta-ur-Rahman, *FRS***

*Honorary Life Fellow, Kings College, University of Cambridge,  
Cambridge, UK*

**&**

**M. Iqbal Choudhary**

*H.E.J. Research Institute of Chemistry, International Center for Chemical  
and Biological Sciences, University of Karachi, Karachi, Pakistan*

## **Anti-Obesity Drug Discovery and Development**

*Volume # 3*

Editors: Prof. Atta-ur-Rahman and Dr. M. Iqbal Choudhary

eISSN (Online): 2210-2698

ISSN (Print): 2467-9615

eISBN (Online): 978-1-68108-187-8

ISBN (Print): 978-1-68108-188-5

©2017, Bentham eBooks imprint.

Published by Bentham Science Publishers – Sharjah, UAE. All Rights Reserved.

First published in 2017.

## **BENTHAM SCIENCE PUBLISHERS LTD.**

### **End User License Agreement (for non-institutional, personal use)**

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: [permission@benthamscience.org](mailto:permission@benthamscience.org).

### **Usage Rules:**

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it. The following DRM (Digital Rights Management) policy may also be applicable to the Work at Bentham Science Publishers’ election, acting in its sole discretion:
  - 25 ‘copy’ commands can be executed every 7 days in respect of the Work. The text selected for copying cannot extend to more than a single page. Each time a text ‘copy’ command is executed, irrespective of whether the text selection is made from within one page or from separate pages, it will be considered as a separate / individual ‘copy’ command.
  - 25 pages only from the Work can be printed every 7 days.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

### ***Disclaimer:***

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided “as is” without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

### ***Limitation of Liability:***

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

## General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of the U.A.E. as applied in the Emirate of Dubai. Each party agrees that the courts of the Emirate of Dubai shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.
3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

### **Bentham Science Publishers Ltd.**

Executive Suite Y - 2

PO Box 7917, Saif Zone

Sharjah, U.A.E.

Email: [subscriptions@benthamscience.org](mailto:subscriptions@benthamscience.org)



# CONTENTS

<b>RTGHCEG</b> .....	i
<b>LIST OF CONTRIBUTORS</b> .....	iii
<b>CHAPTER 1 CURRENT STATUS OF MEDICAL THERAPY AND NEW TARGETS FOR ANTI-OBESITY DRUG DEVELOPMENT</b> .....	3
<i>Chihiro Okuma, Yukihito Ishii and Takeshi Ohta</i>	
<b>INTRODUCTION</b> .....	3
Approved Drugs .....	4
Phentermine .....	5
Mazindol .....	7
Fenfluramine/Dexfenfluramine .....	9
Orlistat .....	10
Shibutramine .....	12
Rimonabant .....	14
Qsymia .....	16
BELVIQ (Lorcaserin) .....	17
Contrave .....	19
New Drug Targets (Table 3) .....	20
<i>Late Phase Clinical Development</i> .....	21
<i>Early Phase Clinical Stage Development or Pre-Clinical Development Stage Late Phase Clinical Development</i> .....	27
Future Prospects .....	39
Obesity Animal Models .....	40
<i>ob/ob Mouse</i> .....	41
<i>db/db Mouse</i> .....	41
<i>KK-Ay Mouse</i> .....	41
<i>TSOD Mouse</i> .....	42
<i>SDT fatty Rat</i> .....	42
<i>ZF Rat</i> .....	42
<i>ZDF Rat</i> .....	43
<i>cp/cp Rat</i> .....	43
<i>WBN/Kob fatty Rat</i> .....	43
<i>DIO Models</i> .....	44
<b>CONFLICT OF INTEREST</b> .....	46
<b>ACKNOWLEDGEMENTS</b> .....	46
<b>REFERENCES</b> .....	46
<b>CHAPTER 2 UNRAVELLING POTENTIAL ANOREXIGEN EFFECTS OF NESFATIN-1: HOW HOMEOSTATIC MECHANISMS HELP BALANCE EXCESS CALORIES</b> .....	65
<i>Carmine Finelli</i>	
<b>INTRODUCTION</b> .....	65
Nesfatin-1/NUCB-2 and Anorexigenic Effect .....	67
The Oxytocin Pathway in Nesfatin-1's Inhibitory Effect on Food Intake .....	67
Nesfatin-1 and CRF .....	68
Nesfatin-1 and Anti-Obesity Treatment .....	69
Nesfatin-1 and Food Behaviour Control .....	70
Nesfatin-1 and Signaling Pathway .....	71
Nesfatin-1 and Eating Disorders .....	72
<b>CONCLUSIVE REMARKS</b> .....	73
<b>CONFLICT OF INTEREST</b> .....	74
<b>ACKNOWLEDGEMENTS</b> .....	74
<b>ABBREVIATIONS</b> .....	74
<b>REFERENCES</b> .....	75
<b>CHAPTER 3 PROTEOMICS IN THE CHARACTERIZATION OF NEW TARGET THERAPIES IN PEDIATRIC OBESITY TREATMENT</b> .....	80
<i>Gillian E. Walker, Marilisa De Feudis, Marta Roccio, Gianni Bona and Flavia Prodam</i>	
<b>INTRODUCTION</b> .....	80

<b>CHILDHOOD OBESITY: PATHOLOGICAL BASIS</b> .....	83
Genetic Considerations for Childhood Obesity .....	84
Energy Homeostasis Dysregulation .....	85
Pathophysiology of Adipose Tissue .....	87
<b>PROTEOMICS</b> .....	89
Gel Based Methods .....	90
Non Gel Based Methods: Mass Spectrometry (MS) .....	92
Chips .....	94
Challenges .....	95
<b>PROTEOMIC STUDIES OF ADIPOSE TISSUE</b> .....	96
WAT Depots .....	96
WAT Secretome .....	101
BAT .....	103
Stromal-Vascular Fraction (SVF) .....	106
<b>PROTEOMIC STUDIES IN ADIPOCYTES: STEM CELLS AND CELL LINES</b> .....	107
Adipogenesis: Adipo-proteomics .....	108
<i>Murine 3T3-L1 Preadipocytes</i> .....	108
<i>Adipocyte-Derived Stem Cells (ASCs)</i> .....	111
Adipocyte Secretome .....	111
Post-Translational Modifications (PTMs) .....	113
<b>PROTEOMIC PROFILING: TISSUES AND CIRCULATION</b> .....	114
Fetal Programming: Tissue-Specific Biomarkers .....	115
Circulating Biomarkers .....	116
Urine Biomarkers .....	119
<b>OUTLOOKS</b> .....	119
<b>CONFLICT OF INTEREST</b> .....	121
<b>ACKNOWLEDGEMENTS</b> .....	121
<b>ABBREVIATIONS</b> .....	121
<b>REFERENCES</b> .....	122

**CHAPTER 4 RELATIONSHIP BETWEEN HORMONAL MILIEU AND OXIDATIVE STRESS  
IN CHILDHOOD OBESITY: A PHYSIOPATHOLOGICAL BASIS FOR ANTIOXIDANT**

<b>TREATMENT AND PREVENTION OF CARDIOVASCULAR RISK</b> .....	149
<i>Antonio Mancini, Francesco Leo, Chantal Di Segni, Sebastiano Raimondo and Aurora Natalia Rossodivita</i>	
<b>INTRODUCTION</b> .....	150
<b>OBEILITY AND OXIDATIVE STRESS</b> .....	152
Hormones and Inflammatory Molecules Produced by or Related to Adipose Tissue .....	154
Oxidative Stress in Childhood Obesity .....	160
<b>HORMONAL REGULATION OF ANTIOXIDANT SYSTEMS AND THEIR DERANGEMENT IN CHILDHOOD OBESITY</b> .....	162
Growth Hormone (GH) .....	162
Thyroid .....	165
Adrenal Glands .....	168
Gonads .....	174
Adipose tissue (Leptin and Kisspeptin) .....	179
<b>ANTIOXIDANT-ENRICHED DIET AS A TREATMENT FOR OBESITY</b> .....	180
<b>CONCLUSION</b> .....	183
<b>CONFLICT OF INTEREST</b> .....	184
<b>ACKNOWLEDGEMENTS</b> .....	184
<b>REFERENCES</b> .....	184

**CHAPTER 5 THE ROLE OF GUT MICROFLORA IN OBESITY - DOES THE DATA PROVIDE  
AN OPTION FOR INTERVENTION?**

<b>TREATMENT AND PREVENTION OF CARDIOVASCULAR RISK</b> .....	204
<i>Parth J. Parekh, Edward C. Oldfield, IV, Amrit Lamba and David A. Johnson</i>	
<b>INTRODUCTION</b> .....	204
<b>OBEILITY AND THE MICROFLORA: A BRIEF OVERVIEW</b> .....	205
<b>DATA AND OPTIONS FOR INTERVENTION</b> .....	209
Antibiotics .....	210
Probiotics .....	213

Prebiotics .....	216
Synbiotics .....	218
The Role of Fecal Transplant .....	218
<b>CONCLUSION</b> .....	219
<b>CONFLICT OF INTEREST</b> .....	219
<b>ACKNOWLEDGEMENTS</b> .....	220
<b>REFERENCES</b> .....	220
 <b>SUBJECT INDEX</b> .....	 228



## PREFACE

An epidemic of obesity is among the most important global healthcare challenges of the 21<sup>st</sup> century, causing considerable morbidity and mortality in a large segment of human population. Obesity has been identified as the largest preventable cause of numerous diseases. Obese and overweight population are at risk for a number of conditions, including high cholesterol levels, high blood pressure, heart diseases, diabetes, bone problems, skin diseases, neurological and psychological disorders, and increased chances of various malignancies. At individual level, obesity adversely affects the state of health and the quality of life, whereas at national level, it is a significant burden on the current healthcare systems. Unfortunately existing anti-obesity drugs are associated with numerous side effects, and are only prescribed when the benefits of treatment outweigh their risks.

The regulation of body weight is a complex process which involves cascades of mechanisms, including a variety of neuropeptides and transmitters in the brain, and endocrine and metabolic signalling molecules. Many of these processes are only superficially understood and extensive research is being conducted to decipher the complex biomolecular pathways behind the obesity syndrome. Understanding these inherent pathways, as well as the role of other factors, such as dietary habits, physical activities, gut microflora, *etc.* is critically important in devising successful strategies to combat obesity epidemics, including the discovery and development of improved treatments.

The 3<sup>rd</sup> volume of the book series entitled “*Anti-Obesity Drug Discovery and Development*” presents the most exciting recent developments in the field of obesity and its treatment. This book comprises five authoritative reviews ranging from identification of new drug targets to novel pharmacological and non-pharmacological interventions.

The first chapter by Ohta *et al.* presents a comprehensive account of recent literature on various treatment options available for obesity. Primary treatment of obesity disorder involves dietary restrictions, and exercise. However, in many cases, pharmacotherapy is imperative. The authors have categorised anti-obesity drugs into three classes, *i.e.* appetite suppressors, agents which inhibit nutritional absorptions, and drugs which accelerate energy expenditures. Various molecular targets in all three categories have been described, with merits and demerits of drugs developed against them.

Nesfatin-1 is a peptide which has attracted considerable attention as a possible antibody treatment of obesity. Nesfatin-1 is secreted by peripheral tissues, central and peripheral nervous system and it can pass the blood-brain barrier. It is involved in the regulation of energy homeostasis related with food regulation and water intake. It suppresses the urge for food independently from the leptin pathway and increases insulin secretion of the pancreatic beta islet cells. The use of Nesfatin-1 for the treatment of obesity has been widely investigated. Finelli has contributed a comprehensive review in chapter 2 on the potential of Nesfatin-1 as a new treatment for obesity and related disorders, its effects on other physiological parameters and the proposed mechanisms of action.

In chapter 3, Walker *et al.* focus on obesity in children, and identification of appropriate drug targets. Paediatric obesity is a growing menace with increasing prevalence globally. Overweight and obese children are at high risk of becoming overweight adolescents and adults, developing chronic diseases, such as heart disease and diabetes later in life. They are also more prone to develop stress, sadness, and low self-esteem. Adipose tissues (AT) play an important role in obesity. AT dysfunction leads to chronic inflammation, weight homeostasis,

*ik*

and insulin resistance. Understanding AT dysfunction at receptors and secondary messenger pathways is critically important in understanding the unique features of paediatric obesity at molecular levels. The authors have reviewed recent advances in the field of proteomics technologies with reference to their use in identifying key components of adipose proteome. This helps in understanding the pathogenesis of adipose tissue dysfunction in obesity

Mancini *et al.* have contributed a chapter on vascular, histopathological and metabolic changes that occur in obese children, which in many cases lead to metabolic syndrome, such as insulin resistance, type 2 diabetes, dyslipidemia, endothelial dysfunctions and cardiovascular disorders. The authors have focussed on the role of neuroendocrine peptides and cytokines in chronic inflammation and oxidative stress (OS). These mediators of chronic inflammation and OS are produced in adipose tissues, and are thus, directly responsible for endothelial dysfunction and insulin resistance. An extensive commentary on the role of oxidative stress in the onset of various obesity related diseases, such as atherogenesis and diabetes, is presented. Based on this, the authors have moved on to discuss the strategies to lower the chronic inflammation and oxidative stress in childhood obesity in order to prevent metabolic syndrome.

Gut microflora are perceived to play an important role in the prevention of various diseases, including obesity. Comparative studies have been conducted on bacterial flora of obese and lean individuals, and substantial differences were recorded. The disequilibrium in the composition of microorganisms that inhabit the human body can cause various diseases. High-throughput sequencing techniques and new tools used in bioinformatics have indicated strong relationships between the gut microbiota, and host's physiology. Disruption of the ecological equilibrium in the gut is called dysbiosis. Diet is a strong determinant of gut microbial balance. In chapter 5, Johnson *et al.* present a comprehensive discussion on state-of-the-art understanding of the role of intestinal dysbiosis in the on-set of obesity disorder. They reviewed the most recent literature on the restoration of microflora in gut as a novel therapeutic option against the obesity epidemics. Strategies for the manipulation of intestinal microflora, such as antibiotic therapy against xenobiotic flora, supplementation of normal flora through probiotics and prebiotics and symbiotics (combination of probiotics and prebiotics), fecal microbiota transplant, *etc.* have been discussed. The role of intestinal microflora in metabolic programming is also extensively discussed.

In brief, the above cited reviews contributed by leading researchers in the field make this volume an interesting and useful reading for scientists and graduate students. We wish to express our felicitation and gratitude to all the authors for their excellent and scholarly contributions for the 3rd volume of this reputed series. We also greatly appreciate the efforts of the entire team of Bentham Science Publishers for efficient processing and timely management of the publication. The efforts of Ms. Faryal Sami (Assistant Manager Publications), Mr. Shehzad Naqvi (Senior Manager Publications) and the leadership of Mr. Mahmood Alam (Director Publications) are specially praiseworthy. We hope that like the previous volumes of this internationally recognized book series, the current compilation will also receive a wide readership and appreciation.

**Prof. Dr. Atta-ur-Rahman FRS**  
Honorary Life Fellow  
Kings College  
University of Cambridge  
Cambridge  
UK

**Prof. Dr. M. Iqbal Choudhary**  
H.E.J. Research Institute of Chemistry  
International Center for Chemical  
and Biological Sciences, University of Karachi  
Karachi  
Pakistan

## List of Contributors

<b>Antonio Mancini</b>	Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy
<b>Aurora Natalia Rossodivita</b>	Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy
<b>Amrit Lamba</b>	Department of Internal Medicine, Tulane University, New Orleans, USA
<b>Chantal Di Segni</b>	Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy
<b>Carmine Finelli</b>	Department of Emergency and Internal Medicine, S. Maria della Pietà Nola's Hospital, <i>Via della Repubblica</i> 1, 80035 Nola (Na), Italy
<b>Chihiro Okuma</b>	Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, Japan
<b>David A. Johnson</b>	Department of Internal Medicine, Division of Gastroenterology and Hepatology, Eastern Virginia Medical School, Norfolk, USA
<b>Edward C. Oldfield</b>	Department of Internal Medicine, Eastern Virginia Medical School, Norfolk, USA
<b>Francesco Leo</b>	Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy
<b>Flavia Prodam</b>	Division of Pediatrics, Department of Health Sciences, Università Del Piemonte Orientale, Novara, Italy
<b>Gianni Bona</b>	Division of Pediatrics, Department of Health Sciences, Università Del Piemonte Orientale, Novara, Italy
<b>Gillian E. Walker</b>	Laboratory of Clinical Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, <i>Via Solaroli</i> , Italy
<b>Marilisa De Feudis</b>	Laboratory of Clinical Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, <i>Via Solaroli</i> , Italy
<b>Marta Roccio</b>	Laboratory of Clinical Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, <i>Via Solaroli</i> , Italy
<b>Parth J. Parekh</b>	Department of Internal Medicine, Division of Gastroenterology and Hepatology, Tulane University, New Orleans, USA
<b>Sebastiano Raimondo</b>	Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy
<b>Takeshi Ohta</b>	Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, Japan
<b>Yukihito Ishii</b>	Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, Japan

## CHAPTER 1

# Current Status of Medical Therapy and New Targets for Anti-Obesity Drug Development

**Chihiro Okuma, Yukihito Ishii and Takeshi Ohta\***

*Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, 569-1125 Osaka, Japan*

**Abstract:** Obesity is considered to be caused by an imbalance in individual energy. The basic therapies for obesity are appropriate dietary restriction for the purpose of decreasing energy intake and effective exercise for the purpose of promoting energy expenditure. At present, drug therapies for obesity are secondary treatments. Therapeutic strategies using pharmacotherapy are divided into the following three types: 1) suppressing appetite, 2) inhibiting nutritional absorption, and 3) accelerating energy expenditure. Mazindol and Phentermine have long been recognized as drugs for increasing satiety, and Orlistat and Cetilistat have been developed as drugs that inhibit lipid absorption from the intestine. Moreover,  $\beta$ 3 agonists have been developed to accelerate energy combustion. In this chapter, we first introduce drugs that are on the market, after which drugs that are in clinical or preclinical stages of development will be introduced. Furthermore, obese animal models that are now available will be introduced in the last section.

**Keywords:** Animal model, Anti-obesity drug, DGAT inhibitor, MGAT inhibitor, MTP inhibitor, Obesity.

## INTRODUCTION

The number of obese patients is rapidly increasing all over the world due to changes in lifestyle, such as habits of consuming high calorie diets and sedentary lifestyles. Obesity and obesity-related diseases, such as diabetes mellitus, dyslipidemia, and hypertension, deteriorate the quality of life (QOL) of patients and result in high medical expenses [1 - 3].

Energy homeostasis in the body is maintained by a balance between energy intake and energy expenditure. When the former exceeds the latter, overt energy is accumulated in adipose tissues, resulting in obesity. Regulating food intake and

---

\* **Corresponding author Takeshi Ohta:** Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, 569-1125 Osaka, Japan; Tel: +81-72-681-9700; Fax: +81-72-681-9722; takeshi.ota@jt.com

energy expenditure and integrating this balance is important in preventing obesity [4, 5]. Lifestyle modifications, such as diet therapy and exercise, as well as medications, chiefly occupy the treatments for obesity and related diseases; however, bariatric surgery is sometimes performed on patients with overt obesity (ex. Body mass index (BMI) over 35) [6 - 8].

Basically, medical therapy is a pivotal step in reducing excess fat accumulation. To reduce excess fat accumulation and excess body weight, several anti-obesity drugs that reduce appetite or lipid absorption in the intestine have been developed. Mazindol is now available only in Japan [9]. In the 1990s, another type of anti-obesity drug, Orlistat, was approved in the U.S. and Europe. Orlistat inhibits lipid absorption in the intestine and is now also available [10, 11]. Thereafter, Sibutramine and Rimonabant were developed; however, both drugs were withdrawn because of adverse effects [12]. Drug combinations, including Qsymia and Contrave, have been developed [13] and serotonin (5HT<sub>2c</sub>)-R agonist Lorcaserin was approved by the FDA in 2012 [14].

In addition, a variety of drugs with various mechanisms, such as microsomal triglyceride transfer protein (MTP) inhibitors, diacylglycerol acyltransferase 1 (DGAT1) inhibitors, monoacylglycerol acyltransferase (MGAT) inhibitors, and protein tyrosine phosphatase 1B (PTP1B) inhibitors, have been investigated in clinical and basic research stages of development [15 - 20]. Several anti-obesity drugs were withdrawn because of adverse effects; however, a tremendous amount of research to develop novel anti-obesity drugs is still ongoing all over the world. In this chapter, we focus on the effects of these drugs and will introduce preclinical and clinical data.

### **Approved Drugs**

Anti-obesity drugs launched in the past years are shown in Table 1. Ten drugs have been launched to date, but the six drugs were withdrawn because of the severe side effects. The drug properties, including efficacy and adverse events, are shown in Table 2. Efficacy indexed by body weight change was approximately 5-10 kg decrease in body weight. Mazindol showed pronounced clinical efficacy, -14.2 kg, whereas the decrease in BELVIQ, -5.8 kg, was mild as compared with the other drugs. Adverse events related to the central nervous system, such as nervousness, anxiety, and dizziness, were observed as responses to TAAR1 agonists, monoamine-reuptake inhibitors, and serotonin receptor agonists. Moreover, digestive symptom, such as, oily stool, faecal urgency, and oily spotting was observed in orlistat. Detailed features of each anti-obesity drug are included in Table 2.

**Table 1. Anti-obesity drugs launched in the past years.**

Drug	Mechanism of action	History in USA	History in EU
Phentermine	Trace amine-associated receptor 1 (TAAR1) agonist	1959:Approval	1999:Withdrawn
Mazindol	Monoamine-reuptake inhibitor	1973:Approval Withdrawn	Withdrawn
Fenfluramine	Serotonin receptor (5-HT <sub>2B</sub> ) agonist	1973:Approval 1997:Withdrawn	1997:Withdrawn
Dexfenfluramine	Serotonin receptor (5-HT <sub>2B</sub> ) agonist	1996:Approval 1997:Withdrawn	1997:Withdrawn
Orlistat	Lipase inhibitor	1999:Approval	1998:Approval
Sibutramine	Monoamine-reuptake inhibitor	1997:Approval	2001:Approval 2010:Withdrawn
Rimonabant	Cannabinoid receptor antagonist	Disapproval	2006:Approval 2008:Withdrawn
Qsymia (Qnexa)	Phentermine/topiramate	2012:Approval	Disapproval
BELVIQ (lorcaserin)	Serotonin receptor (5-HT <sub>2C</sub> ) agonist	2012:Approval	Disapproval
Contrave	Bupropion/naltrexone	2014:Approval	2015:Approval

## Phentermine

Phentermine is a sympathomimetic amine (Fig. 1A) and anorectic agent that is used for short-term therapy of obesity (less than 12 weeks) in combination with behavioral modification, caloric restriction and exercise. In 1959, phentermine received approval from the FDA as an appetite-suppressing drug, after which a hydrochloride form of the drug became available in the early 1970s. In 1999, phentermine was removed from the market in the EU; however, the drug is also currently sold as a generic in the U.S., and is still available in most countries, including the U.S [21, 22].

**Table 2. Clinical efficacy and adverse events in anti-obesity drugs.**

Drug	Body weight change (Administration period)	Adverse events
Phentermine	- 11.7 kg (24 weeks)	Insomnia, Irritability, Agitation, Nervousness, Anxiety
Mazindol	- 14.2 kg (64 weeks)	Dry mouth, Constipation, Stomach discomfort, Nausea, Sleep disturbance, Dizziness

## **Unravelling Potential Anorexigen Effects of Nesfatin-1: How Homeostatic Mechanisms Help Balance Excess Calories**

**Carmine Finelli\***

*Department of Emergency and Internal Medicine, S. Maria della Pietà Nola's Hospital, Via della Repubblica 1, 80035 Nola (Na), Italy*

**Abstract:** In this chapter, we review the current concepts about Nesfatin-1 as a new anti-obesity treatment and evaluate the existing issues about this knowledge and the available literature. The intent is to inform clinicians about Nesfatin-1 as a new kind of anti-obesity treatment and make a rational decision based on this perspective as possible clinical application. It can be potentially helpful in the therapy of metabolic disorders and obesity of various origins. In fact, the details of nesfatin-1 physiology could be clarified, and it may be considered suitable in the future as a potential drug in the pharmacotherapy of obesity, due to its anorexigenic effects, and as a new potential modulator of appetite in the therapy of eating disorders such as anorexia nervosa by using selective nesfatin-1 antagonists. Therefore, further progress of pharmacological researches in this field is still very limited. Further research on this topic certainly merit attention.

**Keywords:** Drug treatment, Eating disorders, Feeding behaviour, Nesfatin-1, Obesity.

### **INTRODUCTION**

Nesfatin-1 is an 82-amino-acid peptide originated from post-translational processing of the terminal fragment of nucleobindin 2 (NUCB2), a 396-amino-acid protein exceptionally conserved across mammalian species [1]. The structure of NUCB2 appears to predict the post-translational cleavage by nesfatin-2 fragment (85–163) and nesfatin-3 fragment (166–396) in addition to nesfatin-1 [1]. Pharmacological studies in rats [1] suggest that nesfatin-1 (named as acronym for NEFA/nucleobindin2-encoded satiety- and fat-influencing protein) might have physiological importance in regulating food intake.

---

\* **Corresponding author Carmine Finelli:** Department of Emergency and Internal Medicine, S. Maria della Pietà Nola's Hospital, Via della Repubblica 1, ASL Napoli 3 Sud, 80035 Nola (Na), Italy; Tel: +39 349/8667338; Fax: +39 081/0322199; E-mail: carminefinelli74@yahoo.it

In fact, nesfatin-1 injected into the third brain ventricle reduced food intake during the dark phase, while nesfatin-2 or nesfatin-3 had no effect [1]. In the same way, continuous infusion of nesfatin-1 (5 pmol/day for 10 days into the third brain ventricle) decreased food intake significantly and body weight gain. Conversely, third ventricle infusion of a NUCB-2 antisense oligonucleotide increased food intake and body weight gain compared with a mis-sense NUCB-2 oligonucleotide [1]. Additionally, a 24-h fast decreased the expression of NUCB-2 in the paraventricular nucleus (PVN) [1].

Some studies [2 - 4] showed high expression level of nesfatin-1/NUCB-2 in hypothalamic and medullary sites implicated in feeding regulation in rats. The localisation on arcuate nucleus, PVN, and the nucleus of the solitary tract (NTS) further support the evidence that nesfatin-1 is involved in food intake regulation.

Nesfatin-1, a neuropeptide produced in the hypothalamus of mammals, is co-expressed with Melanin-Concentrating Hormone (MCH) in neurons from the tuberal hypothalamic area (THA), being both recruited during sleep states, especially paradoxical sleep [5]. To help decipher the contribution of this contingent of THA neurons to sleep regulatory mechanisms, Jergo *et al.* investigated whether the co-factor Nesfatin-1 is also endowed with sleep-modulating properties in rats [5]. Jergo *et al.* found that disruption of the brain Nesfatin-1 signaling, achieved by intracerebroventricular administration of Nesfatin-1 antiserum or antisense against the nucleobindin2 (NUCB2) prohormone, suppressed PS with little, if any alteration of slow wave sleep (SWS) [5]. Additionally, the infusion of Nesfatin-1 antiserum after a selective PS deprivation, designed for elevating PS needs, severely prevented the ensuing expected PS recovery [5]. Strengthening these pharmacological data, Jergo *et al.* demonstrated by using c-Fos as an index of neuronal activation that the recruitment of Nesfatin-1-immunoreactive neurons within THA is positively correlated to PS but not to SWS amounts experienced on rats previously to sacrifice [5]. In conclusion, this work supports a functional contribution of the Nesfatin-1 effects, which are managed by THA neurons, to PS regulatory mechanisms [5]. Jergo *et al.* proposed that these neurons, maybe releasing MCH as a synergistic factor, constitute an appropriate lever through which the hypothalamus may integrate endogenous signals to adapt the ultradian rhythm and maintenance of PS in a manner dictated by homeostatic needs [5]. This could be done through the inhibition of downstream targets comprised primarily of the local hypothalamic wake-active orexin- and histamine-containing neurons [5].

The corticotropin-releasing factor (CRF)/urocortin family of neuropeptides and receptors constitute an affective regulatory system due to the integral role it plays in controlling neural substrates of arousal, emotionality, and aversive processes



[6]. Activation of brain CRF signaling pathways by CRF acting on CRF1 and CRF2 receptors and by selective endogenous CRF2 agonists urocortin 2 or 3 [6] inhibits food intake [7]. Nesfatin-1 injected intracerebroventricularly significantly decreased gastric emptying [8]. Goebel-Stengel *et al.* showed that NUCB2/nesfatin-1 immunoreactivity is distributed in mouse brain areas involved in the regulation of stress response and visceral functions are activated by an acute psychological stressor, suggesting that nesfatin-1 might play a role in the efferent component of the stress response [8].

### **Nesfatin-1/NUCB-2 and Anorexigenic Effect**

Peptides that often regulate food intake act in concert or in series with other neurotransmitters to exert their actions [9]. Nesfatin-1/NUCB-2 is co-localized with a number of hypothalamic peptides regulating food intake [10 - 16]. Several interactions have been described to underlie the central anorexic effect of nesfatin-1 [17]. In situ hybridization and immunohistochemical researches have evaluated the expression of nesfatin-1 throughout the brain and, particularly, in the medullary autonomic gateway known as NTS [18].

Two proteins have been localized in the arcuate nucleus (ARC) and implicated in the regulation of food intake: the serine-threonine-kinase mammalian target of rapamycin (mTOR) as part of the TOR signaling complex 1 (TORC1) that integrates signals from multiple pathways, including nutrients (*e.g.*, amino acids and glucose), growth factors (*e.g.*, insulin and insulin like growth factor 1), hormones (*e.g.*, leptin), and stresses (*e.g.*, starvation, hypoxia, and DNA damage) to regulate a wide variety of eukaryotic cellular functions, such as translation, transcription, protein turnover, cell growth, differentiation, cell survival, metabolism, energy balance, and stress response, and nesfatin-1 derived from the precursor protein nucleobindin2, as reported by Inhoff *et al.* [19]. In fact, nesfatin-1 is not only intracellularly co-localized with cocaine- and amphetamine-regulated transcript (CART) peptide as reported before, but also with phospho-mTOR (pmTOR) and neuropeptide Y (NPY) in ARC neurons [19]. This data could also confirm results from previous studies, showing that the majority of nesfatin-1 neurons are also positive for CART peptide, whereas most of the pmTOR is co-localized with NPY and only to a lesser extent with CART [19].

### **The Oxytocin Pathway in Nesfatin-1's Inhibitory Effect on Food Intake**

Oxytocin is a hormone secreted by the posterior lobe of the pituitary gland, a pea-sized structure at the base of the brain. The oxytocin injected into the 3v reduces food intake *via* a leptin-independent mechanism [12] and nesfatin-1 injected into the 3v activates oxytocin-positive neurons in the magnocellular part of the PVN as assessed by double labelling for Fos/oxytocin immunoreactivity. Furthermore,

## Proteomics in the Characterization of New Target Therapies in Pediatric Obesity Treatment

Gillian E. Walker<sup>1,\*</sup>, Marilisa De Feudis<sup>1</sup>, Marta Roccio<sup>1</sup>, Gianni Bona<sup>2</sup> and Flavia Prodam<sup>2</sup>

<sup>1</sup> *Laboratory of Clinical Pediatrics, Department of Health Sciences, Università Del Piemonte Orientale, Novara, Italy*

<sup>2</sup> *Division of Pediatrics, Department of Health Sciences, Università Del Piemonte Orientale, Novara, Italy*

**Abstract:** Adipose tissue (AT) with a central role in body weight homeostasis, inflammation and insulin resistance, is a highly orchestrated tissue involving receptor and second messenger pathways with steps and passes that influence hyperplasia, hypertrophy, adipocyte differentiation, turnover, lipolysis, free-fatty acid (FFA) metabolism, lipogenesis and the secretome profile. Due to the limitations of the classical molecular biological methods only pieces of the puzzle have been studied, with studies failing to consider the global, time-resolved changes that are evident in this highly plastic organ. “Proteomics”, first coined in 1995 is a large-scale characterization of the entire protein profile of a cell line, tissue, or organism not only from the perspective of expression but also post-translational modifications. As such proteomic technologies offer powerful tools for identifying key components of the adipose proteome, which may contribute to the pathogenesis of adipose tissue dysfunction in obesity. In this review, we plan to address the recent advances in the proteomic characterization of pediatric obesity, in particular the newly identified proteins that potentially play relevant roles and offer targets for novel therapies.

**Keywords:** Adipose tissue, Biomarkers, Circulation, Lifestyle, Obesity, Pediatric, Proteomic, Secretome, Therapy.

### INTRODUCTION

According to the World Health Organization (WHO), obesity is now the most important contributor to ill health and expenditure worldwide, with the pediatric population paralleling adults. In 2014, WHO estimated that globally over 2 billion people were overweight, with 43 million children < 5 years overweight or obese.

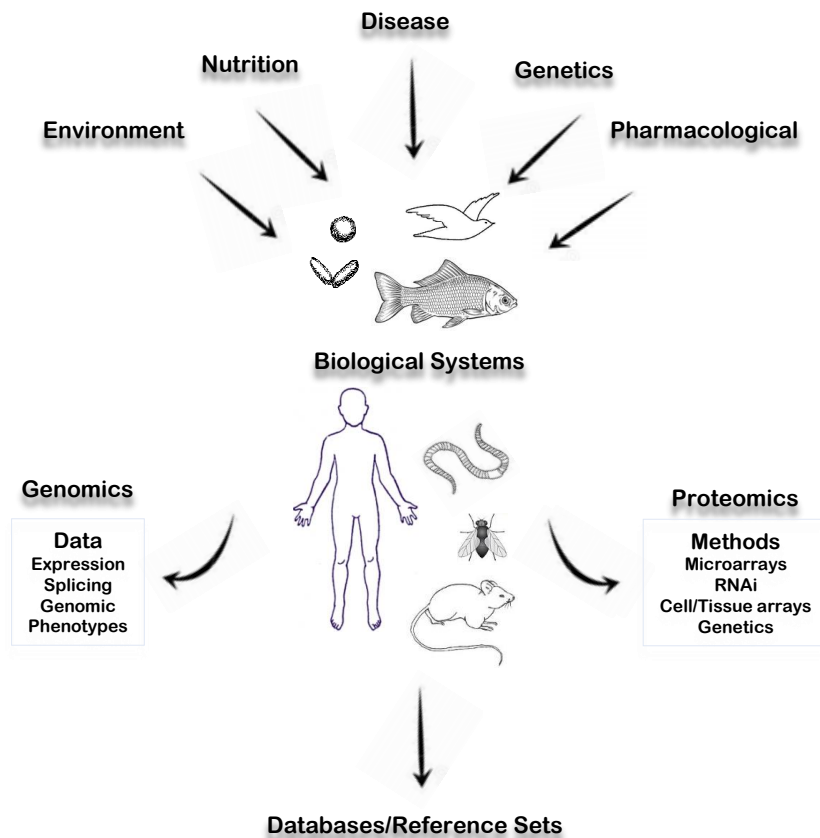
\* **Corresponding author Gillian E. Walker:** Department of Health Sciences, Università del Piemonte Orientale, Via Solaroli, 17 Novara, 28100 Italy; Tel: +39 0321 660 647; Fax: +39 0321 3733598; E-mail: gillian.walker@med.uniupo.it

While the prevalence rates are highly variable between countries, a clear growth has been seen in developed countries [<http://www.who.int/topics/obesity/en/>]. The most recent OECD “Health Behavior in School Children Survey” demonstrates overweight prevalence rates based on measured height and weight in children in the European Union of approximately 23% and 21% for 15 year old boys and girls, respectively, with a steady increase observed from the year 2000 [<http://www.oecd.org/els/health-systems/Health-at-a-Glance-2013>]. To address these alarming statistics, a growing number of countries have adopted and invested in health and awareness policies such as “Fit not Fat”, with obesity trends in recent years stabilizing [1; <http://www.who.int/topics/obesity/en/>]. It remains, however, that in countries such as Greece, Italy, Slovenia, New Zealand and the United States, over 30% of the pediatric population are overweight or obese [<http://www.oecd.org/health/obesity-update.htm>]. The WHO estimates that if current trends continue the number of overweight or obese children globally will increase to 70 million by 2025.

Because obesity is a chronic disorder requiring continuous management, the impact of these statistics highlights a more important issue: the economic stress to National Health Care Systems. Obesity has been shown to decrease life expectancy by 7 years by the age of 40, if subjects were obese during their childhood [2]. This is because obesity in adults is closely associated with type 2 diabetes mellitus (T2D), cardiovascular disease (CVD), hypertension, non-alcoholic fatty liver disease (NAFLD), vitamin D deficiency, degenerative joint disease and certain types of cancer [3]. Further, obesity has also been demonstrated to impact an individual’s functional capacity, with a higher prevalence of disability observed in obese as opposed to normal-weight individuals [4]. Even in early infancy, obesity has been demonstrated to be most strongly associated to insulin resistance [5], with childhood obesity predicting the long-term risk of adult diabetes [6]. Most alarming is the high likelihood that without intervention an obese child at puberty will likely remain obese into adulthood, further compounding the economic burden with obesity-related problems [7, 8].

The cause of obesity is a chronic imbalance between energy input and output, with a long-term energy imbalance inducing an accumulation of adipose tissue (AT) [9]. Energy homeostasis is critical for survival, where species have evolved highly complex mechanisms integrating AT, the central nervous system (CNS) and peripheral organs and tissues to maintain a tight energy balance. Simply put the accumulation of energy during periods of “feast” to be used during periods of “famine” for survival. In humans, however, this balance is easily influenced not only by our genotype but also by exogenous stimuli [9]. Known risk factors in pediatric obesity which can tip the balance include genetics, environmental and

neighborhood factors, increased intake of sugar-sweetened beverages, fast-food and processed snacks, decreased physical activity, a shorter sleep duration, parental obesity and prenatal events, as well as increased individual stress [10]. While genetic alterations and the “thrifty gene hypothesis” may be the basis of obesity [11 - 13], it is now well accepted that obesity has a multifactorial etiology with diet, lifestyle and environmental factors key players in its development [13 - 15].



**Fig. (1).** Proteomics in hand with genomics offer global perspectives to complex biological systems.

Investigations in monogenic models of obesity and studies evaluating the molecular mechanisms of energy homeostasis [16 - 20], as well as the recognition that AT is an endocrine organ that secretes “adipokines” into the circulation which can impact peripheral tissues [21, 22], have improved our understanding of body weight control at the central and peripheral level [23, 24]. Despite these findings, however, no clear “central regulators” of metabolism, energy

## CHAPTER 4

# Relationship Between Hormonal Milieu and Oxidative Stress in Childhood Obesity: A Physiopathological Basis for Antioxidant Treatment and Prevention of Cardiovascular Risk

**Antonio Mancini\***, Francesco Leo, Chantal Di Segni, Sebastiano Raimondo and Aurora Natalia Rossodivita

*Departments of Medical Sciences and Pediatrics, Catholic University of the Sacred Heart, Rome, Italy*

**Abstract:** The thrifty genotype, exposed to modern and industrialized societies, characterized by food availability and reduced physical activity, recently culminated in an epidemic obesity of giant proportions. Even more alarming than the figures regarding adult obesity is the increasing rate of obese children that has augmented almost 3-fold within the last 3 decades.

Obesity is associated with significant adverse effects on health, including metabolic, endocrine, cardiovascular, gastrointestinal, respiratory, neurologic, psychiatric, hematologic, and skeletal complications, and development of some types of malignancies. Studies strongly suggest that vascular, histopathological and metabolic changes begin in childhood. The development of metabolic problems associated with obesity during childhood track into adulthood increases the risk for type 2 diabetes, dyslipidemia and early cardiovascular disease.

In this paper, firstly we examine the numerous links between neuroendocrine peptides and cytokines, which contribute to inflammation and oxidative stress (OS) in obesity. A number of cytokine, mediators of inflammation, are produced by adipose tissue. In obese patients, increase in IL-6, C reactive protein (CRP), TNF-alpha and decrease in adiponectin and IL-10, induce pro-inflammatory stage, resulting in insulin resistance and endothelial dysfunction. Decreasing the levels of chronic inflammation and OS in childhood may prevent subsequent metabolic derangement along with increased cardiovascular morbidity and mortality in adulthood. OS has been proposed to be a potential mechanism linking obesity and endothelial dysfunction. In fact, oxidative reactions are critical in all the events which lead to atherogenesis. OS plays an important role in the pathogenesis of vascular alterations by either triggering exacerbating the biochemical processes accompanying endothelial dysfunction.

---

\* **Corresponding author Antonio Mancini:** Department of Medical Sciences, Catholic University of the Sacred Heart, Rome, Italy; Tel: +39-06-30154440; Fax: +39-06-30157232; E-mail: mancini.giac@mcclink.it

The production of Radical Oxygen species (ROS) and Radical Nitrogen Species (RNS) can occur at the cellular level in response to metabolic overload caused by an overabundance of macronutrients. Excessive generation of ROS in adipose tissue occurs by several interrelated pathophysiologic mechanisms, including nutrient metabolic overload, mitochondrial dysfunction, and endothelial reticulum stress. ROS generation is maintained by an inflammatory response, sustaining a vicious cycle. Puberty alters some of the inflammatory markers associated with endothelial dysfunction (adipocytokine levels, OS and insulin sensitivity) in obese children.

However, other than to inflammation, OS can be related to hormonal derangement in a reciprocal way. Some hormones influence antioxidant levels, but OS also can modify synthesis, activity and metabolism of hormones. Therefore, in the second section we examine some hormonal patterns which are influenced by obesity and their role in the regulation of antioxidant systems. In conclusion it seems that oxidative stress is certainly related to systemic inflammation but also to hormonal derangement.

Aside from the excess energy intake, nutrients have a specific role in the development of inflammation via the regulation of adipokine gene expression and secretion. In this way, it is possible to choose “non-inflammatory” or “anti-inflammatory” foods to minimize postprandial OS and inflammation. Therefore, lifestyle modifications, consisting in a reduction of caloric intake, a diet focused on particular macronutrient or micronutrient intake, and the encouragement of a regular exercise program with a personalized format, type and duration may reduce the consequences of childhood obesity. In particular we review the role of natural antioxidant in diet, as well as the administration of pharmacological antioxidants. Whether this approach is effective in improving vascular function in the short-term, but also in adult life remains to be established.

**Keywords:** Antioxidants, Childhood, Metabolic syndrome, Obesity, Oxidative stress.

## INTRODUCTION

Obesity is a disease of body composition determined by a relative or absolute excess of body fat [1], which usually leads to an increase in body weight. The definition of overweight and obesity in childhood is still under debate. To date the definition of overweight and obesity in children is not based on the absolute value of body mass index (BMI), since it changes according to age, sex, height and weight of the child. Therefore to have an objective parameter, which is independent of age, the conditions of overweight and obesity in children are defined on the basis of the standard deviation of BMI.

The largest epidemiological transition of the 20<sup>th</sup> century concerned the shift of mortality and morbidity from infectious diseases to chronic diseases, particularly cardiovascular disease. This transition was primarily attributed to changes in social, economic and public health that occurred in the US during the first half of

the century. The abundance of food brought not only better nutrition and improved health, but also an excess of positive energy balance, associated to a parallel increase of sedentary lifestyles in the population.

At the beginning of the millennium an augmented prevalence of obesity was thus generated with a consequential increase in related chronic disease [2]. Many studies in adults have shown the relationship between obesity and serious complications causing an increased risk of premature death in chronic diseases, such as diabetes mellitus type 2 (DM2), cholelithiasis, dyslipidemia, insulin resistance (IR), sleep apnea, coronary artery disease, hypertension and so on.

This phenomenon, spreading like wildfire across the planet, began to affect people more and more young, until obesity-related diseases appeared even in childhood.

Obesity is constantly increasing; in United States it progressed from 15% of overweight children in 1970 to nearly 30% in 2014. In Europe the percentage of overweight and obese children is slightly lower than in US. The difference can be seen especially in the age between 10 and 17, while 20% of overweight children in Europe are well below the 29% of American children. This does not reduce, however, the seriousness of a widespread problem, which is continuously increasing also in Europe: in particular the countries with higher prevalence of obese children are Greece (44% of obese males and 37% females), Italy (37% of obese males and 34% of females) and Spain (32% and 29%).

In Italy there are important differences between the North and the South of the country, in particular there is an higher prevalence in the South and in the islands, and also between different regions [3].

“Tracking” phenomenon is well known in pediatrics. It indicates any alteration occurred in childhood which is inclined to be present in adulthood. Therefore, when tracking occurs, like in obesity, it is useful to start a therapy to limit its future consequences as early as possible.

There are, in fact, clear epidemiological evidences of the risk of persistence of obesity of childhood onset into adulthood, with the worsening circumstance of a real storm of anticipation throughout the plethora of cardiovascular and metabolic complications (hyperlipidemia, DM 2, gallstones, liver disease) that characterize the status of adult obesity. It is not rare to find, in severely obese children, IR was very similar to that of an adult that anticipate, in effect, a state of full-blown diabetes.

The phenomenon of tracking appears to be related to several factors. First, the age in which obesity develops [4]. In fact, approximately 82% of males and 62% of

## The Role of Gut Microflora in Obesity - Does the Data Provide an Option for Intervention?

Parth J. Parekh<sup>1</sup>, Edward C. Oldfield, IV<sup>2</sup>, Amrit Lamba<sup>3</sup> and David A. Johnson<sup>4,\*</sup>

<sup>1</sup> Department of Internal Medicine, Division of Gastroenterology and Hepatology, Tulane University, New Orleans, LA, USA

<sup>2</sup> Department of Internal Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

<sup>3</sup> Department of Internal Medicine, Tulane University, New Orleans, LA, USA

<sup>4</sup> Department of Internal Medicine, Division of Gastroenterology and Hepatology, Eastern Virginia Medical School, Norfolk, VA, USA

**Abstract:** The obesity epidemic has proven to have a significant burden on the current of state of healthcare. At an individual level, obesity and its sequelae have numerous effects on the state of health and quality of life. On a global perspective, treatment of obesity and its sequelae come at a high cost. Obesity, in terms of intestinal dysbiosis, is a complicated disequilibrium that offers many unclear complications. Thus, restoration of the commensal microflora serves a potential therapeutic option in combatting the obesity epidemic be it *via* antibiotic therapy, probiotics, prebiotics, symbiotics (combination of prebiotic and probiotic therapy), or fecal microbiota transplant. This manuscript will review the role of intestinal dysbiosis in the pathogenesis of obesity and the potential role for microflora manipulation as therapy.

**Keywords:** Antibiotics, Butyrate, Dysbiosis, Fecal Microbiota Transplant, FFAR, Fiaf, Metabolic Endotoxemia, Microbiota, Obesity, Prebiotics, Probiotics, Propionate, SCFAs, Symbiotics.

### INTRODUCTION

The commensal microbiota is the largest immune system in the body, which is host to approximately  $10^{14}$  microorganisms and comprised of greater than 1,000 distinct bacterial species [1]. The gut microbiota is also thought to play a pivotal role in metabolic programming, and thus recent research efforts have focused on the role of intestinal dysbiosis in the pathogenesis of obesity [1, 2].

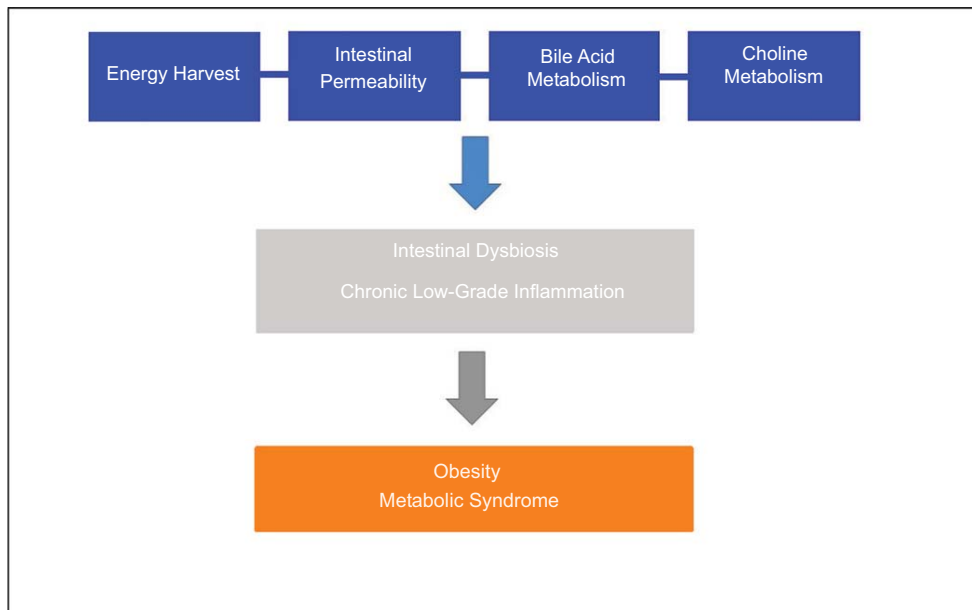
\* Corresponding author David A. Johnson: Division of Gastroenterology and Hepatology, Eastern Virginia Medical School, Norfolk, VA 23510, USA; Tel: (757)466-0615; Fax: (757) 466-9082; E-mail: dajevms@aol.com



Through recent advances in pyrosequencing technologies, researchers have gained further insight into the symbiotic relationship between the intestinal microbiota and the mammalian host, and how this dynamic interrelationship can have significant impact on regulating metabolic function. This then raises the question as to whether or not manipulating the commensal microbiota is potential for therapy in combating the obesity epidemic, which currently afflicts more than 1/3 of the adult population in the United States [1]. Here, we review the current literature relating to the gut microbiota, provide an overview on the role of intestinal dysbiosis on the pathogenesis of obesity, and discuss approaches to manipulate this symbiotic relationship as a potential for therapy.

### OBESITY AND THE MICROFLORA: A BRIEF OVERVIEW

Initial studies in mice demonstrated that transfer of gut microflora from conventionally raised, genetically obese mice into germ-free mice resulted in phenotypically obese mice, suggesting obesity is a transmissible trait through the microbiota [3 - 6]. These studies led to further investigation into the underlying mechanisms at play. There are several ways by which the commensal microflora is thought modulate host energy metabolism, which ultimately contribute to the pathogenesis of obesity. These include bile acid metabolism, fermentation of dietary polysaccharides, and chronic inflammation (see Fig. 1).



**Fig. (1).** Intestinal dysbiosis and the underlying mechanisms in the pathogenesis of obesity and the metabolic syndrome [1, 7 - 9].

Recent studies have demonstrated that microbiota-mediated changes in the bile acid metabolism contribute to the pathogenesis of obesity [7 - 9]. Bile acids are signaling molecules that act as a natural ligand for nuclear hormone receptors, namely farnesoid X receptor (FXR), which are expressed at high levels in the intestine [10]. Most recently, Parséus *et al.* investigated the role of the gut microflora in modulating obesity and associated phenotypes through FXR [11]. Germ-free mice, conventionally raised wild-type, and FXR *-/-* mice were fed a high-fat diet for 10 days, during which their weight gain, glucose metabolism, gut microflora composition, and bile acid composition were closely monitored. In addition, gut microflora was transferred from wild-type and FXR *-/-* mice to germ-free mice. After a 10-week high-fat diet, conventionally raised wild-type mice gained significantly more weight than germ-free mice, which occurred in association with increased fasting glucose and insulin levels in addition to impaired glucose and insulin tolerance. In the absence of intact FXR signaling, the gut microflora did not affect weight gain, however these mice did exhibit increased fasting glucose and insulin levels and impaired glucose and insulin tolerance similar to that seen in conventionally raised wild-type mice. Conversely in FXR *-/-* mice, the presence of the gut microflora did not affect fasting insulin or insulin tolerance. They also noted that the bile acid composition differed between FXR *-/-* and wild-type mice. Pyrosequencing demonstrated decreased levels of *Firmicutes* and increased levels of *Bacteroidetes* in FXR *-/-* mice compared to wild-type mice after being fed a high-fat diet for ten weeks. Lastly, the authors investigated the role of altered gut microbiota and its impact on metabolic differences between conventionally raised wild-type mice and FXR *-/-* mice. Microflora from FXR *-/-* mice fed a high-fat diet and conventionally raised wild-type mice were transferred into germ-free mice and after ten weeks on a high-fat diet, mice colonized with the microflora from FXR *-/-* gained less weight than mice that were colonized with microflora from conventionally raised wild-type mice. This led the authors to conclude that intestinal dysbiosis promotes diet-induced obesity through FXR and that FXR alters the microbial composition, which may contribute to increased adiposity.

Another way by which the gut microflora contributes to the pathogenesis of obesity is through its role in energy harvest, namely the fermentation of dietary polysaccharides [2, 6]. Through a complex process involving methanogens in the gut (primarily the distal small intestine), the commensal microflora ferments dietary polysaccharides to form its metabolites, namely monosaccharides and short chain fatty acids (SCFAs), which regulates energy homeostasis in the host [2]. The three main SCFAs produced are acetate, propionate, and butyrate, all of which have been shown to have protective effects against diet-induced obesity and insulin resistance; acetate and propionate are the main metabolites produced by *Bacteroidetes*, whereas butyrate is the main metabolite produced by *Firmicutes*

## SUBJECT INDEX

### A

Abnormal adipose tissue enlargement 41  
 Abnormalities, valvular 9  
 Adeno-associated virus (AAV) 74  
 Adipocyte differentiation 80, 96, 108, 110, 120  
 Adipogenesis 99, 104, 108, 109, 110, 111, 113, 114  
 Adipokines 69, 73, 82, 108, 111, 112, 114, 118, 120, 153, 157, 161, 169  
   novel 112  
 Adiponectin 102, 105, 106, 108, 109, 110, 111, 117, 149, 154, 155, 156, 157, 159, 173  
   secretion of 105, 109, 155  
 Adipose tissue 3, 11, 14, 17, 21, 31, 32, 33, 39, 40, 41, 69, 71, 80, 81, 87, 88, 96, 97, 101, 118, 120, 149, 150, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 164, 168, 173, 179, 207, 213, 214, 215  
   dysfunctional 153  
   tissue nesfatin-1/NUCB-2 expression 69  
   visceral 39, 87, 164  
   white 40, 41, 155, 159, 160, 213  
 Adiposity, truncal 164  
 Adrenalectomy 170  
 Adrenal glands 6, 14, 154, 159, 168, 170, 172  
 Aldosterone concentrations 169  
 Amoxicillin 212  
 AMP-activated protein kinase 107, 207  
 Amphetamine 6, 7, 9, 13  
 Androgens 168, 174, 178, 179  
   free 179  
 Annexin 118  
 Anorexia nervosa 65, 72, 74  
 Anorexigenic effects 65, 67, 70, 73, 74, 207  
 Antibiotics 120, 204, 210, 211, 212, 213, 219  
   effects of 210, 212  
   role of 210, 212, 213  
   use of 210, 212  
 Antibiotic stewardship 212  
 Anti-obesity agent 10  
 Anti-obesity drugs 3, 4, 5, 20, 28, 33, 40, 69  
   candidate 69

  novel 4, 40  
 Anti-obesity effects 8, 11, 15, 19, 21, 22, 23, 28, 31, 32, 36, 38, 39  
 Anti-obesity treatment 65, 69, 74  
 Antioxidants 150, 161, 166, 169, 170, 175, 176, 177, 178, 179, 180, 181, 182, 184  
   natural 150, 181, 183, 184  
 Antioxidant systems 150, 157, 162, 163, 165, 170, 181  
 Apolipoprotein A-IV 118  
 Apoptosis 99, 112, 114, 116, 117, 162, 209  
 Appetite suppression 8, 12, 13, 14, 156  
 Atherosclerosis 11, 31, 44, 113, 157, 158, 166, 175, 176

### B

Bacteroidetes 206, 209, 217  
 BAT 100, 105  
   mitochondria 105  
 Beloranib 27, 28  
   effects of 27  
 Blood-brain barrier 156  
 Blood glucose levels 43  
 Body mass index (BMI) 4, 7, 17, 25, 27, 71, 72, 83, 85, 98, 101, 108, 119, 150, 152, 154, 161, 167, 182, 214, 216, 218, 219  
 Body weight loss 9, 17, 28  
   induced sustained 9  
   significant 17  
 Body weight 26, 86, 101, 117, 181  
   reductions 26, 181  
   regulation 86, 101, 117  
 Brain-derived neurotrophic factor (BDNF) 24  
 Brain ventricle 66  
 Brown adipose tissues 40, 211  
 Buffers, rehydration 96, 97  
 Bupropion 19, 20, 22, 23  
 Butyrate 204, 206, 207, 212, 214

### C

Caloric restriction 5, 7, 118, 162

Canagliflozin 38, 39  
 Carbonic anhydrases 23, 106  
 Cardiovascular 12, 14, 81, 87, 106, 107, 113,  
   116, 149, 150, 157, 160, 169, 171, 174,  
   180, 183  
   disease (CVD) 12, 81, 87, 106, 107, 113,  
   116, 149, 150, 157, 169, 171, 180, 183  
   risk 12, 160, 174, 180  
 Catalase 165, 166, 176, 177, 180, 181  
 Catecholamines 6, 13, 155, 169  
 Catecholestrogens 176  
 CB1 receptor 14, 15  
   antagonists, selective 14  
 Ceftazidime 210, 212  
 Cerebro-spinal fluid (CSF) 69, 156  
 Cetilistat 3, 21, 22  
   administration group 21  
   treatment 21, 22  
   treatment groups 22  
 Characteristics, phenotypic 84, 85, 173  
 Chemical derivatization 93, 94  
 Childhood obesity 81, 83, 84, 86, 87, 109,  
   116, 119, 150, 152, 160, 162, 167, 172,  
   173, 174, 182, 183, 208, 211  
   examining 116  
   oxidative stress in 160, 183  
 Children and adolescents 96, 101, 103, 104,  
   118, 219  
 Chip array technologies 91  
 Cholesterol, total 12, 45, 166  
 Chronic sibutramine treatment 13  
 Chylomicrons 34, 208  
 Circulation, hepatic portal 207  
 Combination therapies 17, 19, 39, 121  
 Co-morbidities 44, 87, 89, 97, 100, 101, 104,  
   106, 108, 111, 115  
   associated 44, 104, 106, 108, 111, 115  
   obesity-associated 87, 89, 97, 100, 101  
 Composition, bile acid 206  
 Computed tomography (CT) 44, 45, 103  
 Copy number variation (CNV) 85  
 Coronary artery disease (CAD) 151, 174, 175  
 Cortex, adrenal 169  
 Corticotropin-releasing factor (CRF) 66, 67,  
   68  
 Cortisol 156, 169, 170, 171, 172, 173  
   associations of 173  
 C-reactive protein (CRP) 101, 149, 172

CRF2 67, 68  
   antagonist 68  
   receptors 67, 68  
 CRF neurons 68, 69  
 Cushing's syndrome (CS) 170, 171, 172, 173  
 Cysteines 114  
 Cytokines 111, 116, 149, 153, 154, 157, 158,  
   160, 165, 169, 172, 173, 209, 217  
   pro-inflammatory 111, 153, 154, 157, 209,  
   217

## D

Damage, endothelial 158, 160, 161  
 Dapagliflozin 39  
 Dexfenfluramine 5, 6, 9, 10  
 D-fenfluramine 9  
 DGAT1 21, 31, 32, 33  
   inhibitors 21, 31, 32, 33  
 DGAT inhibitor 3, 33  
 Diabetes mellitus 3, 42, 72, 81, 157, 171  
 Diet 10, 17, 23, 25, 34, 44, 45, 46, 82, 119,  
   150, 154, 167, 178, 180, 181, 182, 183,  
   184, 209, 219  
   enriched 180, 181  
   high-fat/sucrose 44, 45, 46  
 Dietary 32, 33, 34, 182, 205, 206  
   fat content 32, 33, 34  
   fibers 182  
   polysaccharides 205, 206  
 Diet-induced obesity (DIO) 8, 34, 36, 40, 44,  
   181, 206, 207, 210, 213, 215, 217  
   high-fat 34  
   high-fat western 207  
 Discoveries, biomarker 95, 115, 116  
 Diseases 3, 44, 119, 151, 219  
   obesity-associated renal 119  
   obesity-related 3, 44, 151, 219  
 DNA microarrays 94  
 Drugs 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 17, 19,  
   20, 21, 22, 23, 24, 27, 28, 29, 36, 38, 39,  
   40, 94, 104, 119  
   anti-diabetic 36  
   anti-epileptic 16  
   combination 19, 22  
 Dysbiosis 204, 205, 206, 208, 209, 210, 212,  
   219

Dyslipidemia 3, 12, 15, 16, 17, 43, 44, 149, 151, 152, 157  
Dysregulation 114, 116, 120, 153, 172

## **E**

Electron 91, 93, 94  
  capture dissociation (ECD) 94  
  spray ionization (ESI) 91, 93  
Elevation, catecholamine 6  
Endocannabinoids 14  
Endothelial dysfunction 149, 150, 161, 169, 170  
Endotoxemia 204, 208, 217  
  metabolic 204, 208  
Energy 3, 4, 6, 8, 11, 12, 13, 14, 21, 27, 30, 31, 36, 39, 69, 70, 73, 81, 82, 85, 86, 102, 103, 104, 113, 156, 160, 179, 206, 207, 208, 209, 213, 218, 219  
  consumption 31, 39  
  expenditure 3, 4, 6, 8, 13, 27, 30, 36, 39, 69, 70, 85, 86, 103, 104, 156, 213  
  harvest 206, 208, 209, 218  
  homeostasis 3, 14, 73, 81, 82, 85, 86, 102, 113, 160, 179, 206, 207, 208, 213, 219  
  intake 3, 11, 12, 21, 39, 85  
Energy balance 34, 67, 69, 70, 81, 85, 86, 120, 154, 155, 159, 162, 167  
  long-term 154  
Enterocytes 28  
Enzymatic digestion 93  
Enzyme-linked immuno sorbent assay (ELISA) 93  
Epidermal growth factor receptor (EGFR) 169  
Estrogens 168, 174, 175, 176, 177, 178  
Extended-spectrum beta-lactamases (ESBL) 212

## **F**

FABP4 for pediatric obesity 100  
Fat 32, 33, 108  
  cell numbers 108  
  energy content diet 32, 33  
Fat absorption 10, 21, 22, 31, 32, 33  
Fatty acid binding protein 98  
Fecal microbiota transplant (FMT) 204, 219

Fenfluramine 5, 6, 9, 10, 13  
  effects of 9, 10  
Fenfluramine treatment 10  
Fetal programming 114, 115, 116  
Fiaf expression 207  
Follicle-stimulating hormone (FSH) 179  
Food intake 7, 8, 9, 10, 15, 17, 18, 25, 26, 29, 36, 37, 38, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 108, 159, 179, 211  
  normal 9, 10  
  reduced 15, 17, 18, 66  
  regulating 3, 65, 67, 71  
Fourier-transform ion-cyclotron resonance (FTICR) 93  
Free-fatty acid (FFAs) 80, 87, 204, 207, 217  
  receptors (FFAR) 204, 207, 217

## **G**

Gamma-amino butyric acids (GABAs) 16  
Geldanamycin derivatives 99  
Genes 40, 42, 85  
  obesity-associated 85  
  yellow obese 40, 42  
Genome-wide association studies (GWAS) 85  
Gestation 115, 155  
GH, maximal secretory capacity of 164  
GH concentrations, lower 164  
GH secretion 164, 165  
Glomerular hyper filtration 101  
Glucocorticoids 86, 108, 110, 155, 156, 168, 171  
Gluconeogenesis 157, 158, 181, 207  
Glucose 12, 22, 26, 30, 38, 42, 44, 46, 67, 120, 155, 156, 158, 159, 206  
  impaired 30, 206  
  urinary 42  
Glucose homeostasis 72, 87, 88, 59, 100, 160  
  normal 87, 88, 100  
Glucose tolerance, impaired 43, 44  
Glutathione peroxidase (GPx) 163, 181  
Glutathione-reductase (GR) 171  
Glutathione S-transferase (GST) 171  
Glyceroneogenesis 105  
Growth hormone (GH) 28, 32, 154, 156, 162, 163, 164, 165, 217  
Gut microbiome 210, 212, 213, 217

Gut microbiota 120, 121, 204, 205, 208, 209, 212, 216, 218, 219

## H

Haptoglobin 117  
 Heat shock proteins (HSPs) 98, 99, 111  
 Hepatocytes 28, 158, 160  
 Hepatotoxicity 28, 176  
 High density lipoprotein (HDL) 87, 97, 178  
 High fat diet (HFD) 99, 102, 214, 215  
 Hirsutism 178, 179  
 Hormonal derangement 150  
 Hormones, adrenal 170, 171, 172  
 Hormone sensitive lipase (HSL) 105  
 Hydroperoxides 165  
 Hyperglycemia 38, 41, 42, 43, 72, 98, 152  
 Hyperinsulinemia 32, 38, 41, 42, 43, 44  
 Hyperlipidemia 7, 15, 32, 38, 42, 44, 46, 151  
 Hyperphagia 41, 42  
 Hyperplasia 89, 107, 108  
 Hyperthyroidism 165, 166, 172  
   secondary 172  
 Hypocaloric diet 12, 22, 181, 182  
 Hypogonadism 84, 174, 175  
 Hypothalamic-hypophyseal-adrenal (HHA) 171  
 Hypothalamus 7, 9, 14, 17, 18, 26, 36, 66, 69, 70, 71, 72, 73, 86, 154, 155, 156, 159  
 Hypothyroidism 165, 166, 167, 172  
   overt 166  
   subclinical 166, 167

## I

Immobilized metal affinity chromatography (IMAC) 113  
 Immobilized pH gradient (IPG) 91  
 Impaired glucose tolerance (IGT) 43, 44, 87, 88, 100  
 Inflammation, obesity-induced adipose 101  
 Inhibition of lipid absorption 20, 21  
 Injection, intracerebroventricular 68, 70  
 Insomnia 6, 7, 17, 23, 25  
 Insulin 12, 16, 32, 41, 43, 44, 80, 81, 83, 88, 97, 98, 99, 101, 102, 107, 109, 112, 113, 114, 115, 117, 120, 149, 150, 151, 153,

154, 155, 157, 158, 159, 160, 162, 167, 173, 174, 178, 180, 181, 206, 210, 212, 214, 215, 217, 219  
 levels 12, 44, 154, 206  
 receptor 157, 158, 160  
 -related substrate (IRS) 181  
 resistance 16, 32, 41, 43, 44, 80, 81, 83, 88, 97, 98, 99, 101, 102, 107, 109, 112, 113, 114, 115, 117, 120, 149, 151, 153, 155, 158, 159, 160, 162, 167, 173, 174, 178, 206, 210, 217  
 sensitivity 83, 112, 150, 154, 158, 159, 160, 180, 212, 214, 215, 219  
 sensitivity improving 214, 215  
 sensitivity systemic 159, 160  
 stimulation 113, 114  
 tolerance 206  
 treatments 102, 113, 162  
 Intestinal dysbiosis 204, 205, 206, 208, 210, 212, 219  
 Isotope-coded affinity tags (ICAT) 94

## J

Janus Kinase (JAK) 104

## K

Key anti-obesity strategy 108, 110  
 Kidney disease 101, 119  
   obesity-induced chronic 101

## L

Lactation 86, 87, 115  
 Lateral hypothalamic area (LHA) 70  
 Lepob mutations 41  
 Leptin 3, 4, 6, 17, 20, 21, 22, 36, 40, 41, 43, 67, 70, 73, 74, 86, 101, 106, 111, 154, 155, 156, 157, 160, 161, 168, 178, 179, 182, 210  
 levels 6, 22  
 receptor dysfunction 40, 41  
 receptors 17, 43, 156, 168  
 secretion 155, 156, 168  
 treatment 36  
 absorption 3, 4, 20, 21

Lipid peroxidation 163, 165, 170, 174, 176  
 reduced 163  
 Lipogenesis 80, 96, 106, 120, 154, 216, 217  
 Lipoperoxides 163  
 Lipoxins 101  
 Liraglutide treatment 26  
 Long-evans tokushima otuska (LETO) 27  
 Lorcaserin treatment 18  
 Lorcaserin treatment groups 18  
 LPL activity in adipose tissue 207  
 Luteinizing hormone (LH) 178, 179  
 Lymphocytes 106, 153, 157, 158, 162

## M

Macrophages 106, 153, 157, 158, 160, 177, 209  
 Magnetic resonance imaging (MRI) 103  
 Markers, fetal-programming-related obesity 116  
 Mass spectrometry (MS) 90, 92, 93, 94, 96, 97, 105, 120, 161, 180  
 Maternal food restriction 115, 116  
 Matrix-assisted laser desorption ionization (MALDI) 93  
 Mazindol treatment 8  
 Mechanisms 4, 5, 10, 21, 23, 24, 39, 66, 67, 69, 71, 74, 86, 112, 156, 161, 163, 165, 168, 169, 171, 178, 181, 205, 207, 208, 209, 213, 218, 219  
 leptin-independent 67, 69  
 potential 213, 218  
 regulatory 66, 207  
 underlying 205  
 Melanin-concentrating hormone (MCH) 66  
 Metabolic 34, 65, 155, 156, 179, 180, 207  
 disorders 34, 65  
 functions 155, 156, 207  
 Kisspeptin actions 179, 180  
 Metabolism, bile acid 205, 206  
 Metformin 22, 104, 181  
 MGAT2 inhibitors 21, 34, 35  
 MGAT inhibitor 3  
 Microbiota 120, 204, 205, 208, 218, 219  
 commensal 204, 205, 208  
 Microbiota transplant, fecal 204, 219

Microflora 204, 205, 206, 208, 209, 211, 214, 215, 217  
 commensal 204, 205, 209, 211, 214, 217  
 Mitochondrial respiratory chain 161, 166, 168  
 Mitogen-activated protein kinase (MAPK) 169  
 Monoacylglycerol 11, 33  
 Monoamine-reuptake inhibitor 4, 5  
 Monogenic obesity 84, 85  
 non-syndromic 84  
 Motility, gastroduodenal 70, 71  
 mRNA levels 17  
 MTP inhibitors 3, 20, 28, 29, 31, 39

## N

Naltrexone 19, 20  
 Nesfatin 69, 71, 73  
 Nesfatin-1 68  
 Nesfatin-1 66, 67, 68, 69, 71, 72, 73  
 and anti-obesity treatment 69  
 anorexigenic effect of 68  
 antiserum 66  
 intracerebroventricular 68  
 levels 72  
 neurons 67, 71, 72, 73  
 Neurons 6, 66, 68, 69, 70, 156  
 central 69  
 Neuropeptide 6, 66, 67, 70, 73  
 Neurotransmitters 6, 12, 14, 16, 67  
 Neutrophil granulocytes, human 177  
 Next generation sequencing (NGS) 85, 122  
 Noradrenaline 12, 24  
 Nuclear factor- $\kappa$ B 208, 209  
 Nucleobindin 65, 66  
 Nucleus 26, 66, 67, 68, 71, 73, 154, 156, 157  
 arcuate 26, 66, 67, 157  
 paraventricular 66, 71, 73  
 Nutrition, maternal 114, 115

## O

Obese 154, 156, 207, 208  
 adolescents 154, 156  
 cohorts 207, 208  
 Obesity 8, 13, 26, 82, 83, 85, 86, 87, 98, 102, 104, 107, 114, 115, 149, 152, 153, 156, 161, 205, 206

- abdominal 98, 152, 156, 161
  - adolescent 152
  - ameliorated impaired 13, 26
  - android 87
  - central nervous system-induced 8
  - developing 83, 102
  - epidemic 149
  - global 85
  - hyperplastic 153
  - hypertrophic 107
  - maternal 86, 115
  - modulating 206
  - morbid 104
  - parental 82, 83, 114
  - phenotypes 85
  - polygenic 85
  - potential mechanism linking 149
  - prevention 83
  - /proteomics 96
  - related disorders 112
  - related problems 81, 83
  - resistance 89
  - severe 152
  - suggesting 205
  - therapy 106
  - treatment 25
  - trends 81, 85
  - Omentin 107
  - Orlistat 3, 4, 5, 6, 10, 11, 12, 20, 21, 119
    - effect of 11, 12
  - Orlistat treatment 12
  - Orphan G-protein-coupled-receptor 159
  - OSBP-related proteins (ORPs) 111
  - Ovariectomy 169, 176, 177
  - Overweight adolescents 112, 164, 173
  - Oxidative stress 97, 113, 116, 149, 150, 152, 165, 170, 172, 180, 183
  - Oxytocin 67, 68, 73
- P**
- Pancreatic lipases 11, 21
  - Pediatric obesity 80, 81, 83, 84, 96, 99, 100, 102, 103, 106, 107, 108, 113, 114, 115, 116, 117, 119, 120, 121, 208
    - parallels adults 96
    - prevalence rates 119
    - proteomic characterization of 80, 120
  - Pediatric population 80, 81, 83, 97, 112, 116
  - Peritoneum 87
  - Peroxisome proliferator-activated receptor (PPAR) 40, 99, 165, 180, 214, 215
  - Phentermine 3, 5, 6, 7, 9, 13, 16, 17
    - /topiramate 5, 16, 17
  - Phentermine treatment 7
  - Phosphorylation 17, 89, 113, 158, 160
    - inhibiting secondary protein 17
  - Pigment epithelium-derived factor (PEDF) 112
  - Pioglitazone treatment group 38
  - Plasma proteome 116, 117
  - Post translational modifications (PTMs) 89, 90, 92, 94, 95, 113, 114, 120
  - Preadipocytes 88, 96, 106, 108, 111, 112, 153, 154, 173
  - Prebiotics 120, 204, 210, 211, 213, 216, 217, 218, 219
  - Prebiotic supplementation 217
  - Prepubertal children 161, 173
  - Proapolipoprotein A-1 97
  - Probiotics 120, 204, 210, 213, 214, 215, 216, 218, 219
  - Production 16, 18, 42, 69, 150, 153, 157, 158, 159, 160, 161, 162, 177, 207, 213
    - hepatic glucose 157, 158
    - superoxide anion 177
  - Pro-inflammatory cascade 208, 209
  - Propionate 204
  - Protective effects 162, 174, 178, 179, 180, 206
  - Protein 4, 14, 36, 90, 91, 92, 93, 94, 95, 98, 99, 105, 113, 114, 122
    - carbonylation 114
    - coupled receptor family 14
    - detection 91, 92
    - expression 93, 94
    - expression profile 90
    - kinase 99, 105, 113, 122
    - kinase A (PKA) 105, 122
    - synthesis 95, 98
    - tyrosine phosphatase 4, 36
  - Protein modifications 90, 113, 162
    - oxidative liver 162
  - Protein-protein interactions 95, 100



Proteins 4, 17, 28, 71, 80, 83, 97, 99, 100, 101, 102, 103, 105, 108, 111, 114, 115, 116, 118, 149, 165, 172, 173  
 adipocyte 97, 114  
 candidate 118  
 cytoskeletal 111, 114  
 diet-associated 118  
 domain-containing 108  
 identified 71, 80, 83, 105  
 identifying 97, 115  
 microsomal triglyceride transfer 4, 28  
 mitochondrial 105, 165  
 reactive 149, 172  
 serum 102, 116  
 target 97, 100, 101  
 uncoupling 17, 103, 165, 173  
 zinc finger 99  
 Proteome 83, 89, 90, 95, 97, 104, 105, 106  
 mitochondrial 104  
 Proteome profiling 97  
 Proteomic(s) 80, 82, 83, 89, 90, 93, 96, 100, 101, 102, 104, 107, 109, 114, 115, 116, 120, 121  
 investigations 115, 116  
 profiling 114, 115  
 shotgun 93  
 Pyruvate carboxylase 110

## R

Radical nitrogen species (RNS) 150, 153  
 Radical oxygen species (ROS) 122, 150, 153, 168, 169, 171, 176  
 Reactive oxygen intermediate (ROI) 162  
 Receptors, amine-associated 5, 6  
 Reduced white adipose tissue 215  
 Regenerating system 169  
 Regulating nascent protein folding 99  
 Relationship, symbiotic 205  
 Resistance 99, 120, 212  
 antibiotic 212  
 obesity-related insulin 120  
 particular obesity-associated insulin 99  
 Retinol binding protein (RBP) 102, 159, 160  
 Rimonabant 4, 5, 6, 14, 15, 16, 24

effects of 15  
 in obesity (RIO) 15  
 treatment 15, 16  
 RIO-diabetes 15, 16  
 Rosiglitazone 104

## S

SCFAs, production of 214  
 Search tool for the retrieval of interacting genes/proteins (STRING) 102  
 Secretomes 80, 101, 102, 103  
 Serotonin receptor 5, 9  
 Sex hormone binding globulin (SHBG) 179  
 SGLT2 Inhibitors 21, 38, 39  
 Short chain fatty acids (SCFAs) 204, 206, 207, 216, 217  
 Sibutramine cardiovascular outcomes (SCOUT) 14  
 Sibutramine treatment 12, 13, 14  
 Signal transducer and activator of transcription (STAT) 104  
 Slow wave sleep (SWS) 66  
 Sodium-dodecyl sulphate (SDS) 90, 91  
 Stem cells 107, 111  
 Steroids, gonadal 174, 175

Stress 67, 98, 171, 172  
 hormones 171, 172  
 response 67, 98, 172  
 Syntaxins 111  
 Systemic inflammation 117, 150, 152, 183  
 obesity-associated 117

## T

Tesofensine 24, 25  
 treatment 25  
 Testosterone 174, 175, 177, 179  
 TG-rich lipoproteins 28  
 TG synthesis 31, 33, 34  
 THA neurons 66  
 Therapy 10, 16, 22, 40, 65, 74, 80, 109, 151, 204, 205, 210, 212, 213  
 antibiotic 204, 212, 213  
 anti-obesity 16

obesity-associated 109  
Thiazolidinediones 103, 104  
Thyroid hormones 155, 161, 165, 166, 167,  
168, 172, 182, 183  
Tomography, computed 44, 45, 103  
Total 12, 45, 166, 172, 175, 180, 181  
    antioxidant capacity (TAC) 166, 172, 175,  
    180, 181  
    antioxidant status (TAS) 166  
    cholesterol (TC) 12, 45, 166  
Transthyretin 117  
Triglycerides 11, 15, 21, 23, 28, 31, 45, 89,  
155, 160, 163, 166, 174, 207  
Tsumura suzuki obese diabetes (TSOD) 40, 42  
Tuberal hypothalamic area (THA) 66  
Tumor necrosis factor (TNF) 101, 153, 209

## **U**

Uncoupling protein (UCP) 17, 103, 165, 173  
Unsaturated fatty acids (UFAs) 115

## **V**

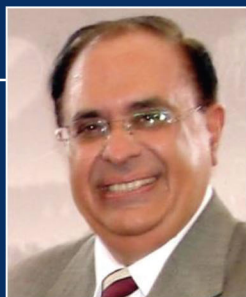
Vancomycin 210, 212  
    oral 212  
Vancomycin resistant enterococci (VRE) 212  
VAT 97, 98, 100  
    depots 97, 98, 100  
    overexpression of heat shock proteins 98  
Very low-density lipoprotein (VLDL) 28  
Visceral 39, 40, 44, 87, 97, 98, 99, 100, 101,  
102, 103, 106, 111, 164, 178  
    adipose tissue (VAT) 39, 87, 97, 98, 99,  
    100, 101, 102, 103, 106, 111, 164  
    obesity 40, 44, 178  
Vitamin D binding protein (VDBP) 103, 117  
VMH obesity 8

## **W**

Weight loss effects 7, 8, 10, 38, 107

## **Z**

Zonisamide 22, 23, 107  
Zucker diabetic fatty (ZDF) 40, 41



## PROF. DR. ATTA-UR-RAHMAN, FRS

---

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1080 international publications in several fields of organic chemistry including 751 research publications, 37 international patents, 69 chapters in books and 221 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 54 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean



## PROF. DR. M. IQBAL CHOUDHARY

---

Dr. M. Iqbal Choudhary is a Professor of Organic/Bioorganic Chemistry and Director at the International Center for Chemical and Biological Sciences (H. E. J. Research Institute of Chemistry and Dr. Panjwani Center for Molecular Medicine and Drug Research). He is among the most prominent scientists of Pakistan, recognized for his original contributions in the fields of natural products and bioorganic chemistry. He has written and edited 27 books, most of which have been published in USA and Europe. He is also the author of over 900 research papers and chapters in top international science journals of the West as well as 27 US patents. He is the Volume Editor of many international book series and journals. He has served as a visiting faculty in many prestigious universities of the world including Cornell University (New York), Purdue University (Indiana), Pennsylvania State University (Pennsylvania), Scripps Institution of Oceanography (San Diego, California), The University of Rhode Island (Rhode Island), and other top Universities.