Neurobiology of Obesity

Obesity is one of the prime contributors to ill health in modern society, affecting around 20–25% of the population. It can cause or exacerbate a variety of health problems and is often associated with several other diseases including type 2 diabetes, coronary heart disease and certain types of cancer. Significant progress has been made in understanding the role of the nervous system and, in particular, the complex interplay between a range of orexigenic and anorectic agents within specific hypothalamic nuclei in the regulation of energy balance, appetite and adiposity. Several different neuronal pathways, neurotransmitters and hormones have been identified as major players in the regulation of feeding behavior and body weight and these are now being targeted as having therapeutic potential. Written for academic researchers and graduate students, *Neurobiology of Obesity* is a concise overview of recent developments in this field, written by leading international experts.

Jenni Harvey is currently a Wellcome Research Career Development Fellow in the Department of Pharmacology and Neuroscience at the University of Dundee. The main focus of her research is to investigate the role of the endocrine peptides, leptin and insulin, in both normal and pathological function in extrahypothalamic regions of the brain, including the hippocampus and cerebellum.

Dominic J. Withers is Professor of Diabetes and Endocrinology at the Centre for Diabetes and Endocrinology at University College London. His research interests include the role of hormone and nutrient-sensing signaling pathways in the regulation of energy homeostasis by the central nervous system and in pancreatic beta cell function.

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Jenni Harvey
Department of Pharmacology and Neuroscience, University of Dundee

Dominic J. Withers
Centre for Diabetes and Endocrinology, University College London

CAMBRIDGE UNIVERSITY PRESS

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Shaftesbury Road, Cambridge CB2 8EA, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre, New Delhi – 110025, India

103 Penang Road, #05–06/07, Visioncrest Commercial, Singapore 238467

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www.cambridge.org
Information on this title: www.cambridge.org/9780521860338

First published 2008

A catalogue record for this publication is available from the British Library

ISBN 978-0-521-86033-8 Hardback

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Preface

In the twenty-first century, obesity affects around 20–25% of the population and it is now one of the prime contributors to ill health in modern society. Obesity can cause or exacerbate a variety of health problems and it is often associated with a number of other diseases including type II diabetes mellitus, coronary heart disease and certain types of cancer. The incidence of obesity and related diseases is steadily increasing such that obesity is now regarded as a global epidemic. In recent years, major advances have been made in determining the role of the central nervous system, in particular specific hypothalamic nuclei, in regulating energy balance. From such studies it is apparent that a highly intricate neural system involving a complex interplay between a range of orexigenic and anorectic agents controls food intake and body weight. Thus, a greater understanding of the key neurotransmitter molecules, their related signal transduction pathways and molecular targets, as well as the neuronal pathways that control release of these neurotransmitters is vital if novel therapeutic targets for the treatment of obesity and related diseases are to be uncovered. This book provides a concise overview of recent developments in this field. As an introduction, Professor Bloom gives an outline of the factors that are known to play a key role in regulating energy balance and the development of obesity in humans. Professor Clement considers the genetics of human and rodent body weight regulation as the use of genetic technologies has markedly increased our understanding of dysfunctions in body weight regulation. The hypothalamus is a key region of the brain that adjusts both the drive to eat and energy expenditure in response to a range of signals. Professor Ahima reviews the role of particular medial hypothalamic structures in this regulatory process, and introduces the concept that a range of distinct, but molecular signals interact to control food intake. In the following chapter, Dr Niswender reviews the evidence implicating leptin and insulin as key hormones that provide afferent information to the brain as well

as the recent advances made in determining the sites and mechanisms of action of these adipostats. This aspect is expanded on by Dr Sutherland and Professor Ashford, who provide an overview of the signaling capability of leptin and insulin receptors and discuss how specific signaling pathways may impact on feeding behavior. The potential development of specific therapeutic agents directed against signaling pathways regulated by leptin and insulin for the treatment of obesity is also discussed. This is followed by a detailed review by Dr Strack and Professor Levin of various animal models of diet-induced obesity and how these compare with human obesity. In addition to leptin and insulin, findings from both genetic and pharmacological studies have implicated melanocortins, opiates and the gut hormone ghrelin in hypothalamic regulation of energy homeostasis. The role of these agents is dealt with in depth in reviews by Professors Low, Levine and Horvath, respectively. Drs Della-Fera and Baile discuss the role of the CNS in regulating the levels of adipose tissue, whereas in the final review, Dr Halford provides a detailed overview of the therapeutic strategies to treat obesity.

Contributors

Rexford S. Ahima
University of Pennsylvania School of Medicine
Department of Medicine
Division of Endocrinology, Diabetes and Metabolism
Philadelphia
Pennsylvania 19104
USA

Mike Ashford
Division of Pathology and Neurosciences
University of Dundee
Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

Clifton A. Baile
University of Georgia
444 Animal Science Complex
Athens
GA 30602–2771
USA

Stephen R. Bloom
Department of Metabolic Medicine
Division of Investigative Science
Imperial College London
Hammersmith Campus
Du Cane Road
London W12 0NN
UK

Richard J. Bodnar
Department of Psychology and
Neuropsychology Doctoral Sub-Program
Queens College
City University of New York
USA

Karine Clément
Hôtel-Dieu Service de Nutrition
Place du Parvis Notre-Dame
75004 Paris
France

Mary Anne Della-Fera
University of Georgia
444 Animal Science Complex
Athens
GA 30602–2771
USA

Benjamin C. T. Field
Department of Metabolic Medicine
Division of Investigative Science
Imperial College London
Hammersmith Campus
Du Cane Road
London W12 0NN
UK

Jason C. G. Halford
School of Psychology
Eleanor Rathbone Building
Bedford Street South
University of Liverpool
Liverpool, L69 7ZA
UK

Mark W. Hamrick
Medical College of Georgia
Augusta
GA 30912–2000
USA

Tamas Horvath
Department of Obstetrics, Gynecology and Reproductive Sciences
Yale University School of Medicine
New Haven
Connecticut 06520
USA

Barry E. Levin
Neurology Service (127C)
Veterans Affairs Medical Center
385 Tremont Avenue
East Orange
New Jersey 07018–1095
USA

Allen S. Levine
Minnesota Obesity Center
Department of Food Sciences and Nutrition
University of Minnesota
St. Paul
MN 55108
USA

Malcolm J. Low
Center for the Study of Weight Regulation
Mail code L481
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland
OR 97239–3098
USA

Kevin D. Niswender
Diabetes, Endocrinology and Metabolism
715 Preston Research Building
Vanderbilt University Medical Center
2220 Pierce Avenue
Nashville
TN 37232–6303
USA

Neel S. Singhal
University of Pennsylvania School of Medicine
Department of Medicine
Division of Endocrinology, Diabetes and Metabolism
Philadelphia
Pennsylvania 19104
USA

Caroline J. Small
Department of Metabolic Medicine
Division of Investigative Science
Imperial College London
Hammersmith Campus
Du Cane Road
London W12 0NN
UK

Alison M. Strack
Neurology Service (127C)
Veterans Affairs Medical Center
385 Tremont Avenue
East Orange
New Jersey 07018–1095
USA

Calum Sutherland
Division of Pathology and Neurosciences
University of Dundee
Ninewells Hospital and Medical School
Dundee DD1 9SY
UK

Virginie Tolle
UMR. 549 INSERM-Université Paris V
IFR Broca Ste-Anne
Paris
France