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Essays in Biochemistry

The Biochemical Basis of the Health Effects of Exercise

Edited by A.J.M. Wagenmakers

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Abstract

Introduction

Biochemistry and function of the (micro)vasculature and skeletal muscle in healthy, physically active individuals

The consequences of the switch to a sedentary lifestyle in the second half of the 20th century

Metabolic and functional abnormalities in obese sedentary subjects and the metabolic syndrome

Further metabolic implications of impaired capillary recruitment by insulin

The metabolic network leading to insulin resistance in endothelial cells and skeletal muscle fibres

Impairments in flow (shear stress)-mediated increases in muscle perfusion

Loss of functional NO by superoxide anion production

Consequences of reduced NO production

The role of inflammation and atherogenesis in the communication between endothelium and VSM

Dual role of the NF-κB network in tissue repair and tissue damage

Complexity of the networks involved: added value of systems biology

Does underperfusion of skeletal muscle and the heart lead to an energy deficit?

The benefits of acute and regular exercise for patients

Conclusions

Summary

References
As recently pointed out in an excellent review by Chakravarthy and Booth [1], man in prehistoric times had a high daily energy expenditure, while the availability of food was irregular and restricted. Most of the men were hunters and most of the women food gatherers. Both activities required a disciplined lifestyle involving regular training sessions to practice the typical hunting skills (the equivalent to speed, strength and resistance training) or long days with heavy physical labour (equivalent to moderate-intensity endurance training). In order to develop successful survival strategies and earn the respect of fellow tribe members, individuals always had to maintain high fitness levels and a strong, lean and healthy constitution. Children followed the example of their parents and were carefully prepared and conditioned for their later tasks in life. It was in this period (50 000–10 000 BC) that evolution via the ‘survival of the fittest’ principle selected the genes that most of us still carry today [1].

Since the middle of the 20th Century, major and rapid changes have occurred in the mean physical activity of mankind; the introduction of automobiles, television, machines that take over manual labour in agriculture and industry, and the introduction of computers, computer games and the World Wide Web have grossly reduced the mean number of hours in which people are physically active. Children, until the 1960s, walked or cycled to school, had more hours of physical education (PE) at school than today and were heavily involved in post-school physical activities (both for fun and physical work). In urban areas, rapid increases in car use and traffic density since the 1960s and 1970s made walking and cycling into activities regarded to be increasingly dangerous by most of the parents [2]. Therefore, most parents bring their children by car to school and to all post-school activities, often not realizing how detrimental the lack of exercise is for the health of their children [3–6]. PE has nearly disappeared in the last two decades both from primary and secondary schools worldwide as academic learning is given higher priority. Many children have a minimal involvement in post-school sport and playing activities. Most of their time is spent watching television, behind a computer screen playing computer games or surfing the Internet. The American Paediatric Association recommends 60 minutes of moderate to vigorous exercise at least 5 days a week for school-aged children and fear that very few achieve this [3].

In addition to the decrease in physical activity, food and drinking habits have changed in recent decades and many children, adolescents and adults consume far too many calories for their low physical activity level. Excessive exposure to affluent amounts of energy-rich, but low-quality, food (e.g. via vending machines in schools, stations, public buildings and sport clubs) has greatly
increased the consumption of snacks between the three traditional main meals. Too little exercise and the consumption of too many calories are regarded as the main causes of the current epidemic increase in the frequency of obesity, type 2 diabetes and cardiovascular disease, both by expert committees [7] and the World Health Organization [8]. It is clear that the genes that we inherited from our prehistoric ancestors cannot cope with this abrupt change in lifestyle. Obesity, type 2 diabetes and atherosclerosis were regarded until recently as diseases of the elderly, but today frequently occur in children below the age of 10 years [4,5]. The increase in healthcare costs and reduction in quality of life of those affected and their families are already high and expected to increase much further when the present generation of obese children have reached adulthood [6,8].

This volume of *Essays in Biochemistry* could not have been more timely, with the current epidemic increases in obesity, Type 2 diabetes and cardiovascular disease [7,8]. Each essay has been written by leading experts with complimentary expertise in human physiology and biochemistry. Both the metabolic impairments that occur in the human body as a result of inactivity and disease, and the beneficial effects of exercise in correcting these mechanisms and improving health, are described. Together, the essays give clear mechanistic insight into the multitude of enzymes, signalling pathways, tissues and bodily functions that benefit from relatively modest increases in physical activity. The volume compiles the hard, experiment-based evidence that shows how exercise improves human health and well-being. It covers the mechanisms that operate in muscle (endurance exercise in Chapters 1–4 and resistance exercise in Chapters 5 and 6), the metabolic interaction between muscle, liver and adipose tissue (Chapter 7), the effect of cytokines and inflammation (Chapter 8), the mechanisms that operate in the endothelium of the vascular wall (Chapters 9–12), the genetic differences between subjects in acquiring chronic diseases and the therapeutic effect of exercise upon it (Chapter 13). Finally, Chapter 14 integrates the metabolic effects in muscle and the cardiovascular effects of exercise.

Originally, it was my intention to aim this volume primarily at final-year undergraduate and postgraduate students and their teachers in the biological and medical sciences; however, I expect that the diversity of the topics covered also makes it interesting and stimulating reading for colleagues already active in the field. Finally, I do hope that it also will be an important and accessible source of information for the current generation of medical doctors, health professionals, dieticians and policymakers in public health. The quantity and diversity of the therapeutic effect of exercise seems to illustrate the acute need for active interference of governments and health agencies to make the current and future world populations as least as physically active as people were 100 years ago.
I would like to express my sincere thanks to all my colleagues for their excellent contributions and discussing their individual areas of expertise in a clear and erudite manner. I am also grateful to the many reviewers for their constructive comments and helpful suggestions for improvement of the submitted manuscripts. My thanks also go to Mike Cunningham and his colleagues at Portland Press Ltd for their hard work and diligence in ensuring the high quality of this book.

Anton J.M. Wagenmakers
Birmingham, UK
October 2006

References
Authors

John A. Hawley is currently Head of the Exercise Metabolism Research Group and Professor of Exercise Metabolism in the School of Medical Sciences at RMIT University, Melbourne, Australia. His research interests include the interaction of exercise training and dietary manipulations on glucose and lipid regulation in skeletal muscle, with a special interest in Type 2 diabetes; the regulation of carbohydrate and fat metabolism in skeletal muscle during exercise; and the molecular basis of training adaptation. He has published over 130 original research papers and review articles and has authored numerous book chapters for sports medicine/exercise biochemistry texts. In 1994, he became the first New Zealand researcher to be elected as a Fellow of the American College of Sports Medicine. Currently he holds editorial positions with several leading scientific journals. Mark Hargreaves is Professor in Physiology at The University of Melbourne, Australia. His research interests focus on the regulation of skeletal muscle carbohydrate metabolism in response to acute and chronic exercise, with a particular emphasis on GLUT4 expression. He has authored over 100 peer-reviewed articles and has editorial roles with the Journal of Applied Physiology, Exercise and Sport Sciences Reviews and Medicine and Science in Sports and Exercise. Juleen R. Zierath is head of the Section of Integrative Physiology, Department of Molecular Medicine at the Karolinska Institutet, Stockholm, Sweden. Her research focuses on cellular mechanisms underlying the development of insulin resistance in type 2 diabetes and she and has published over 140 original research papers and review articles. In 2001, Professor Zierath was awarded the prestigious Minkowski Prize from the European Association for the Study of Diabetes, and in 2005 she was a recipient of a Strategic Research Grant from the Foundation for Strategic Research, Sweden. In 2006, she was appointed to the Nobel Assembly at the Karolinska Institutet. She currently holds editorial positions with several leading scientific journals.

Anna-Maria Joseph is a fourth-year PhD student in the Biology Department at York University in Toronto, Canada. She completed her BSc and MSc degrees in Kinesiology and Health Science, also at York University, Toronto. Anastassia Litvintsev is a first-year PhD student in Kinesiology and Health Science at York University, Toronto; she also completed her BSc and MSc degrees in the same programme. Henriette Pilegaard is an Assistant Professor at the Institute of Molecular Biology and Physiology at University of Copenhagen. She has an MSc degree in biology (major) and exercise (minor) and did her PhD at the University of Copenhagen. The main focus of her current research is on the regulation of adaptive gene responses and
substrate choice within skeletal muscle. **Lotte Leick** is a first-year PhD student at the Institute of Molecular Biology and Physiology at the University of Copenhagen. She holds an MSc degree in biology (major) and exercise (minor). **David A. Hood** is a Professor in the School of Kinesiology and Health Science at York University, Toronto, and is crossappointed in the university's Department of Biology. He holds a Canada Research Chair in Cell Physiology, with an emphasis on the study of mitochondrial biogenesis in muscle, and the role of exercise.

**Jørgen F.P. Wojtaszewski** received his PhD from the University of Copenhagen in 1997. Postdoctoral positions at Joslin Diabetes Center and the Copenhagen Muscle Research Centre followed. In 2003, he obtained the prestigious Hallas Møller Research Stipend from the Novo Nordisk Foundation and in 2004 he also was appointed Associate Professor at the Copenhagen Muscle Research Centre, Institute of Exercise and Sports Science. He has published more than 60 original research papers and many reviews. **Erik A. Richter** is Professor of Physiology and Exercise Physiology at the Copenhagen Muscle Research Centre, Institute of Exercise and Sport Sciences, University of Copenhagen. He was one of the founders of the Copenhagen Muscle Research Centre and is currently head of the Department of Human Physiology, Institute of Exercise and Sport Sciences, University of Copenhagen. He has published more than 200 original research papers and many reviews.

**Arend Bonen** holds the Canada Research Chair in Metabolism and Health, and is a Professor in the Department of Human Health and Nutritional Sciences at the University of Guelph, Guelph Ontario, Canada. Work in his laboratory focuses on the molecular regulation of substrate transport and metabolism in skeletal muscle during exercise and in obesity and Type 2 diabetes. His research is supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario and the Natural Sciences and Engineering Research Council of Canada. **G. Lynis Dohm** is a Distinguished Research Professor of Physiology at the Brody School of Medicine, East Carolina University, Greenville, NC. His research focuses on the metabolic changes that occur in skeletal muscle in response to exercise, obesity and diabetes. His research group has identified factors that lead to the increase in muscle glucose transport and GLUT4 glucose transporter protein in response to exercise, and has worked towards an understanding the causes of muscle insulin resistance in obesity. His work has been supported by the National Institutes of Health (USA). **Luc van Loon** is an Assistant Professor in the Department of Movement Sciences at Maastricht University, The Netherlands. His research focuses on human skeletal muscle metabolism, namely the adaptation to endurance and resistance exercise and the use of combined physical activity and/or dietary interventions to improve health in chronic metabolic
diseases. He is also scientific co-ordinator of the Stable Isotope Research Center (SIRC) at the Academic Hospital Maastricht. His research is supported by The Netherlands Organization for Scientific Research (NWO), the Dutch Diabetes Research Foundation (DFN) and several industrial-research grants.

**Keith Baar** is the Director of the Functional Molecular Biology Laboratory and a lecturer in the Division of Molecular Physiology at the University of Dundee, Scotland, U.K. He received his PhD in Physiology from the University of Illinois Medical Center in Chicago before completing postdoctoral work at Washington University in St. Louis, University College London and the University of Michigan. His primary research goal is to understand how muscle size and phenotype are regulated and use this information to engineer functional heart and skeletal muscle *ex vivo*. **Gustavo Nader** is Research Associate in the Research Center for Genetic Medicine at the Children’s National Medical Center (CNMC) in Washington D.C. He received his PhD in Kinesiology from the University of Illinois, Chicago, and post-doctoral education in genomics at CNMC. His primary research interest is to develop a physiological genomics approach to understand skeletal muscle adaptation, specifically the mechanisms controlling ribosome biogenesis during skeletal muscle growth. **Sue Bodine** is a Professor in the Section of Neurobiology, Physiology and Behavior at the University of California, Davis. She returned to academia in 2003 after spending 7 years in the biotechnology industry at Regeneron Pharmaceuticals, Inc and Elixir Pharmaceuticals, Inc, pursuing the development of drugs to treat muscle atrophy. She received her PhD in Muscle Biology from the University of California, Los Angeles and began her academic career in the Department of Orthopedics at the University of California, San Diego. Her primary research interests are in understanding the mechanisms that regulate skeletal muscle size under growth and atrophy conditions.

**Michael Kjaer** received an MD from the University of Copenhagen in 1984, after which his doctoral thesis (1988) investigated hormonal regulation during exercise. He has been Professor of Sports Medicine at the University of Copenhagen since 1998 and is head of a research group investigating the responses of muscle and connective tissue to exercise. **Flemming Dela** MD, DMSc. is Professor in the Pathophysiology section at the Department of Medical Physiology, University of Copenhagen, Denmark. He has published 67 peer-reviewed original papers and 11 book chapters. Keywords to his main field of research are: exercise physiology, metabolism, diabetes, skeletal muscle and mitochondria.

**Keith Frayn** is Professor of Human Metabolism at the University of Oxford. He graduated from the University of Cambridge and studied for his PhD at St Bartholomew’s Medical College, London, before working with the MRC Toxicology Unit and later the MRC Trauma Unit. He has
been in Oxford since 1986, where he leads a research group with interests in fat metabolism in humans, studying both basic physiology and the pathophysiology of obesity, insulin resistance and Type 2 diabetes. Professor Frayn is author of the textbooks *Lipid Biochemistry: an Introduction* (5th edition, with M.I. Gurr and J.L. Harwood, Blackwell Science, 2002) and *Metabolic Regulation: a Human Perspective* (2nd edition, Blackwell Publishing 2003). **Peter Arner** is Professor of Medicine at Karolinska Institutet, from where he also graduated and studied for his PhD. He received specialist training as an MD at Karolinska University Hospital, Stockholm, Sweden, where he currently is senior physician in endocrinology and deputy chairman at the Department of Medicine. He has been at the Karolinska Institutet since 1963, and he leads a research group with interest in human adipose tissue, studying both basic mechanisms and pathophysiology of obesity, insulin resistance, Type 2 diabetes and dyslipidaemia. Professor Arner has published over 300 original research articles and is one of the most cited scientists in the obesity field according to the Institute of Scientific Information. **Hannele Yki-Järvinen** is Professor of Medicine at the Department of Medicine, University of Helsinki. She leads a research group with interest in causes and consequences of insulin resistance in humans. She has received several major international science awards and published over 200 original research articles and is author of textbook chapters in *International Textbook of Diabetes Mellitus* (3rd edition, John Wiley & Sons, 2004) and in *Textbook of Diabetes* (3rd edition, Blackwell Publishing, 2003).

**Bente Klarlund Pedersen** is a Professor at the University of Copenhagen and senior consultant at Rigshospitalet, Copenhagen. She is the director of The Danish National Research Foundation Centre of Inflammation and Metabolism (CIM), where the main area of research is the molecular mechanisms involved in physical activity and how these benefit human health. Professor Pedersen has written more than 350 scientific articles and books, and appears as guest professor all over the world. She is President of the Research Council of Rigshospitalet, University of Copenhagen, leader of the Muscle Cluster at the Faculty of Health Sciences, University of Copenhagen and Chair of the National Council for Public Health.

**Richard M. McAllister** earned his BSc in Kinanthropology from the University of Ottawa, Ontario, Canada, his MA in Exercise Physiology from Ball State University in Muncie, IN, USA, and his PhD in Physiology from the State University of New York Health Science Center in Syracuse, NY, USA. After post-doctoral training at the University of Missouri, he moved to Kansas State University, where he attained the rank of Associate Professor in the Departments of Kinesiology and of Anatomy and Physiology. He then returned to the University of Missouri, where he is currently a Research Associate Professor in the Department of Biomedical Sciences.
M. Harold Laughlin earned his BA in Biology and Chemistry from Simpson College in Indianola, IA, USA and his PhD in Physiology and Biophysics from the University of Iowa College of Medicine in Iowa City. After post-doctoral training at the University of Iowa, he moved to the US Air Force School of Aerospace Medicine in San Antonio, TX. He then moved to Oral Roberts University in Tulsa, OK, where he attained the rank of Associate Professor of Physiology. He subsequently moved to the University of Missouri, where he is currently Professor and Chair of the Department of Biomedical Sciences.

Stephen Rattigan earned his degrees in biochemistry from the University of Western Australia, Perth. He then worked as a post-doctoral fellow at the Commonwealth Scientific and Industrial Research Organisation’s (CSIRO) Division of Human Nutrition in Adelaide, South Australia, before moving to the Biochemistry Department, University of Tasmania, Hobart, as a research fellow. He spent three years as a visiting research scientist at the University of Virginia, Charlottesville, USA, and after returning to the University of Tasmania is now an Associate Professor and Australian Heart Foundation Career Fellow in Hobart. Eloise Bradley earned her degree at the University of Tasmania, where she is presently a research associate and post-graduate student. Stephen M. Richards earned his degrees in biochemistry from the University of Tasmania. He then worked as a post-doctoral fellow at the Baker Heart Research Institute and The Alfred Hospital in Melbourne, INSERM Unit 390 in Montpellier, France, and returned to Australia under a National Health and Medical Research Council (Australia) Howard Florey Centenary Research Fellowship, joining the Department of Physiology, University of Melbourne. He returned to University of Tasmania to take up a tenured lectureship in 1999. Michael G. Clark earned his degrees in biochemistry from the University of New South Wales. He then worked at the University of Wisconsin, Madison, as postdoctoral fellow before returning to Australia, first as Senior Lecturer at Flinders Medical School, Adelaide, then as Section Head of the CSIRO Division of Human Nutrition, Adelaide. He is currently the Professor and Head of the Biochemistry, University of Tasmania, and has been in this role since 1985.

Jefferson C. Frisbee is an Assistant Professor in the Department of Physiology and Pharmacology and is a core member of the Center for Interdisciplinary Research in Cardiovascular Sciences at West Virginia University School of Medicine. His research is currently funded by the National Institutes of Health and the American Heart Association, and focuses on the evolving impairments to vascular structure and function in the metabolic syndrome, the mechanistic bases of these myriad dysfunctions and how these impact the integrated regulation of blood flow control. His most recent work focuses on the regulation of microvessel density in the metabolic syndrome. Michael D. Delp is a Professor in the Division of Exercise Physiology.
and the Center for Interdisciplinary Research in Cardiovascular Sciences at West Virginia University School of Medicine. His research, funded by NASA and NIH, has focused on how physical deconditioning associated with old age, microgravity and diabetes alters smooth muscle and endothelial cell function of resistance arteries and, correspondingly, control of arterial pressure and tissue perfusion. In addition, the effects of how exercise training alters vascular cell signaling mechanisms to improve endothelial function and tissue blood flow are being investigated.

**Gang Hu** is a Senior Researcher and Docent at the Department of Epidemiology and Health Promotion of the National Public Health Institute, Helsinki, Finland, and at the Department of Public Health, University of Helsinki. **Timo A. Lakka** is a Professor of Medical Physiology, a Specialist in Internal Medicine and an Academy Research Fellow at the Institute of Biomedicine, Department of Physiology, University of Kuopio, Finland. He is also an Adjunct Associate Professor at Pennington Biomedical Research Center, Louisiana State University, USA. **Jaakko Tuomilehto** is a Professor at the Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, and Professor of Public Health at the Department of Public Health, University of Helsinki. **Jesús Rico-Sanz** is an Associate Professor at the School of Human Performance and Recreation, School of Health of the University of Southern Mississippi. He obtained a BS in Exercise Physiology and MS in Exercise Science at the University of California at Davis, USA. His PhD in exercise physiology is from the August Krogh Institute, University of Copenhagen, Denmark. After completing his PhD, he held research positions at the Hammersmith Hospital, Imperial College London, UK, the University Autonoma of Barcelona, Spain, Pennington Biomedical Research Center in Louisiana, USA, the National Public Health Institute in Helsinki and the Department of Medicine at University of Kuopio. During the past 5 years, Dr Rico-Sanz has been involved in human genetic studies. He has performed genome scans on exercise capacity phenotypes as well as association studies of candidate genes with metabolic and disease marker phenotypes. His current research interests are the interactions of genes and exercise on the development of Type 2 diabetes, obesity and the metabolic syndrome.

In 1993, **Erik Serné** obtained his MD at the Vrije Universiteit in Amsterdam. He finished his thesis ‘Essential hypertension and insulin resistance: role for microcirculatory function? in 2001’ at the Vrije Universiteit Medical Centre (VUmc). He completed his specialization in internal medicine in 2006 and is presently working as a staff member of the Department of Internal Medicine. His field of expertise is the microvasculature and its role in the metabolic syndrome and cardiovascular disease. **Renate de Jongh** studied medicine at the Vrije Universiteit in Amsterdam, from where she graduated with honours in 2001. The subject of her subsequent research is microvascular
function as a possible link in relationships among obesity, hypertension and insulin resistance, under the supervision of Coen Stehouwer at the VUmc. In 2004, she began her training in internal medicine. Etto Eringa studied biology at the University of Groningen, The Netherlands, graduating in 1999. Afterwards he worked at the Institute for Cardiovascular Research, Vrije Universiteit in Amsterdam, on insulin signalling in vascular endothelium and rat models of insulin resistance. In 2004, he was awarded a PhD by Vrije Universiteit for his thesis on ‘Selective insulin resistance in the microcirculation: a new concept for studying microvascular function and insulin sensitivity’. Since then he has worked as a junior researcher in the Laboratory for Physiology at the same institute on physiological regulation of insulin signalling in vascular endothelium and regulation of blood pressure by phosphatidylinositol 3-kinase. Richard G. Ijzerman studied at the Vrije Universiteit in Amsterdam and he acquired his MD with honours in 1997. In 2004, he obtained a PhD at VUmc, the subject of which was ‘Birth weight, microvascular function and cardiovascular risk factors’. In 2004, he started his residency in internal medicine at the VUmc. His particular field of interest relates to the subject of his thesis and also consists of the study of the role of genetic and/or intrauterine factors in cardiovascular risk factors. Michiel de Boer studied medicine at the Vrije Universiteit in Amsterdam and received his MD in 2003. Subsequently, he worked as a house officer in pulmonology at the Medical Center in Alkmaar, The Netherlands, and in internal medicine at the Westfries Gasthuis Hospital in Hoorn, The Netherlands. In 2005, he started research for a PhD on insulin’s actions on skin and muscle microcirculation in hypertensive, obese and healthy subjects: a role for endothelin-1? Coen Stehouwer obtained his MD with honours at the Erasmus University in Rotterdam in 1985. After registering as an internist in 1990, he was awarded a PhD at VUmc in 1992 for his thesis ‘Albuminuria and endothelial function in diabetes’. He was appointed Professor of Medicine at VUmc in 2000. From 1992 to 2004, he led the Diabetes and Vascular Medicine Research Programme at VUmc’s Institute of Cardiovascular Research. In 2004, he was appointed Professor and Chair of Medicine at the University Hospital in Maastricht. His field of expertise is in the vascular complications of metabolic diseases, with particular emphasis on diabetes, hypertension and hyperhomocysteinemia.

Anton Wagenmakers is Professor of Exercise Biochemistry in the School of Sport and Exercise Sciences, University of Birmingham, UK and occupies a chair at Eindhoven University of Technology to work on integrative mathematical models of metabolic regulation mechanisms. His main scientific interests are the therapeutic effect of exercise and lifestyle changes on metabolism and cardiovascular physiology in chronic diseases. He serves on the Executive Committee of the International Research Group of the Biochemistry of
Exercise and is member of the Scientific Board of the European College of Sport Sciences. Natal van Riel is Assistant Professor in the Department of Biomedical Engineering at Eindhoven University of Technology. He leads the Bioregulation and Systems Biology research programme, which is an inter-departmental programme involving the Departments of Biomedical Engineering and Electrical Engineering. He is a principal investigator with the Eindhoven Biomedical Systems Biology Platform. Michael Frenneaux is British Heart Foundation Chair of Cardiovascular Medicine at the University of Birmingham UK. He is a clinical cardiovascular physiologist whose main research focus on heart failure and heart-muscle diseases. His current research interests include cardiac energetic impairment in heart failure and insulin resistance, the consequences of metabolic modulation in heart failure, cardiomyopathies and insulin resistance, diastolic ventricular interaction, the physiological control of capacitance vessels, the pathophysiology of heart failure with normal left ventricular ejection fraction, and the mechanisms responsible for increased cardiovascular risk in depression. Paul Michael Stewart is Professor of Medicine in the Department of Medicine, joint director of The Wellcome Trust Clinical Research Facility and Associate Dean for Clinical Research at the University of Birmingham’s Medical School. His research specialties include reproductive endocrinology, steroid hormone metabolism, mineralocorticoids, glucocorticoids and endocrine hypertension. Specifically, Professor Stewart is head of a research group that explores the hypothesis that altered cortisol metabolism might underpin diverse diseases, including hypertension, obesity-glucose tolerance, glaucoma, malignancy and bone disease, and may cause foetal problems, such as growth restriction. Professor Stewart serves on committees for the Medical Research Council, The Wellcome Trust and the British Heart Foundation.
Abbreviations

ACC acetyl-CoA carboxylase
ACE angiotensin I-converting enzyme
ADR adrenergic receptor
AGE advanced glycation end-products
AICAR 5'-aminoimidazole-4-carboxamide-1-β-D-ribonucleoside
Akt/PKB protein kinase B
AMPK AMP-activated protein kinase
ANF atrial natriuretic factor
APS adaptor proteins
AS160 Akt substrate of 160 kDa
ATGL adipose triglyceride lipase
BAT brown adipose tissue
BH₄ tetrahydrobiopterin
BMI body mass index
BNF brain natriuretic factor
CaMK calcium/calmodulin-dependent protein kinase
CAP c-Cbl associated protein
CARDIA Study Coronary Artery Risk Development in Young Adults
cdk cyclin-dependent protein kinase
CEU contrast-enhanced ultrasound
COX cytochrome c oxidase
CPT carnitine palmitoyltransferase
CRE cAMP response element
CREB cAMP response element-binding protein
CRP C-reactive protein
DDP deafness/dystonia peptide
DNL de novo lipogenesis
DPP Diabetes Prevention Program
DPS Diabetes Prevention Study
Drp-1 dynamin-related protein 1
4E-BP eIF4E binding protein
E1 ubiquitin-activating enzyme
E2 ubiquitin-conjugating enzyme
E3 ubiquitin ligase
EDHF endothelium-derived hyperpolarizing factor
EGP  endogenous glucose production
eIF  eukaryotic initiation factor
eNOS  endothelial NOS
ERK  extracellular signal-related kinase
ET  endothelin
FABP  fatty acid binding protein
FABPpm  fatty acid binding protein in the plasma membrane
FAT  fatty acid translocase
FATP  fatty acid transport protein
Fis-1  mitochondrial fission protein
FOXO  forkhead transcription factor
GAP  GTPase-activating protein
GH  growth hormone
GLUT4  glucose transporter 4
GMEB  glucocorticoid modulatory element binding protein
GS  glycogen synthase
GSK3  glycogen synthase kinase 3
HbA1c  haemoglobin A1c
HDL  high-density lipoprotein
HK  hexokinase
HL  hepatic lipase
HSL  hormone-sensitive lipase
IGF-1  insulin-like growth factor-1
IL  interleukin
IL-6R  IL-6 receptor
IL-1ra  interleukin-1 receptor antagonist
IMCL  intra-myocellular lipid
iNOS  inducible NOS
IR  insulin receptor
IRS-1  insulin receptor substrate-1
IκK  IκB kinase
JNK  c-Jun N-terminal kinase
LAR  leukocyte antigen related phosphatase
LDL  low-density lipoprotein
LEPR  leptin receptor
L-NAME  Nω-nitro-l-arginine methyl ester
LPL  lipoprotein lipase
MAFbx  muscle atrophy F-box protein/atrogen-1
MAPK  mitogen-activated protein kinase
MEF2  myocyte enhancer factor 2
Mfn  mitofusin
MGF  mechano growth factor
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC</td>
<td>myosin heavy chain</td>
</tr>
<tr>
<td>mtDNA</td>
<td>mitochondrial DNA</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>MuRF</td>
<td>muscle ring finger protein</td>
</tr>
<tr>
<td>1-MX</td>
<td>1-methylxanthine</td>
</tr>
<tr>
<td>NEFA</td>
<td>non-esterified fatty acid</td>
</tr>
<tr>
<td>NF-κB</td>
<td>nuclear factor-κB</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>nNOS</td>
<td>neuronal NOS</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
</tr>
<tr>
<td>NRF</td>
<td>nuclear respiratory factor</td>
</tr>
<tr>
<td>OZR</td>
<td>obese Zucker rat</td>
</tr>
<tr>
<td>PCr</td>
<td>phosphocreatine</td>
</tr>
<tr>
<td>PDK</td>
<td>phosphoinositol-dependent protein kinase</td>
</tr>
<tr>
<td>PGC-1α</td>
<td>peroxisome proliferator activated receptor γ coactivator-1α</td>
</tr>
<tr>
<td>PGH</td>
<td>prostaglandin H$_2$</td>
</tr>
<tr>
<td>PI3K</td>
<td>phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>PIP3</td>
<td>phosphatidylinositol-3,4,5-trisphosphate</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase A</td>
</tr>
<tr>
<td>PKB</td>
<td>protein kinase B</td>
</tr>
<tr>
<td>PKC</td>
<td>protein kinase C</td>
</tr>
<tr>
<td>PPAR</td>
<td>peroxisome-proliferator-activated receptor</td>
</tr>
<tr>
<td>PS</td>
<td>capillary permeability-surface area product</td>
</tr>
<tr>
<td>PTEN</td>
<td>phosphatase and tensin homologue deleted on chromosome 10</td>
</tr>
<tr>
<td>PTP</td>
<td>protein tyrosine phosphatase</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>S6K1</td>
<td>ribosomal S6 protein kinase</td>
</tr>
<tr>
<td>SH2</td>
<td>Src (Sarcoma virus protein) homology-2</td>
</tr>
<tr>
<td>SHIP</td>
<td>SH2-containing inositol phosphatase 2</td>
</tr>
<tr>
<td>siRNA</td>
<td>small interfering RNA</td>
</tr>
<tr>
<td>SRF</td>
<td>serum response factor</td>
</tr>
<tr>
<td>sTNF-R</td>
<td>soluble TNF-α-receptor</td>
</tr>
<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>TEA</td>
<td>tetraethylammonium chloride</td>
</tr>
<tr>
<td>Tfam</td>
<td>mitochondrial transcription factor A</td>
</tr>
<tr>
<td>TFB</td>
<td>mitochondrial transcription factor B</td>
</tr>
<tr>
<td>TG</td>
<td>triacylglycerol</td>
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<tr>
<td>TIM</td>
<td>translocases of the inner membrane</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
</tbody>
</table>
Abbreviations

TOM  translocases of the outer membrane
5'TOP  5' terminal oligopyrimidine tract
TORC  mTOR complex
TR  thyroid receptor
TxA\textsubscript{2}  thromboxane A\textsubscript{2}
TZD  thiazolidinedione
UBF  upstream binding factor
UCP1  uncoupling protein 1
VCAM-1  vascular cell adhesion molecule-1
VDR  vitamin D receptor
VLDL  very-low-density lipoprotein
VNTR  variable number of tandem repeats
VSM  vascular smooth muscle
WAT  white adipose tissue