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The Biochemical Basis of the Health Effects of Exercise

Edited by A.J.M. Wagenmakers

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Contents

14 Integration of the metabolic and cardiovascular effects of exercise

Anton J.M. Wagenmakers, Natal A.W. van Riel, Michael P. Frenneaux and Paul M. Stewart

Preface

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 (50000–10000 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

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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
BH_4	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	N^{ω}-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

MHC	myosin heavy chain
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
MuRF	muscle ring finger protein
1-MX	1-methylxanthine
NEFA	non-esterified fatty acid
NF-κB	nuclear factor-κB
NHANES	National Health and Nutrition Examination Survey
nNOS	neuronal NOS
NO	nitric oxide
NOS	nitric oxide synthase
NRF	nuclear respiratory factor
OZR	obese Zucker rat
PCr	phosphocreatine
PDK	phosphoinositol-dependent protein kinase
PGC-1α	peroxisome proliferator activated receptor γ coactivator-1α
PGH	prostaglandin H_2
PI3K	phosphatidylinositol 3-kinase
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PPAR	peroxisome-proliferator-activated receptor
PS	capillary permeability-surface area product
PTEN	phosphatase and tensin homologue deleted on chromosome 10
PTP	protein tyrosine phosphatase
ROS	reactive oxygen species
S6K1	ribosomal S6 protein kinase
SH2	Src (Sarcoma virus protein) homology-2
SHIP	SH2-containing inositol phosphatase 2
siRNA	small interfering RNA
SRF	serum response factor
sTNF-R	soluble TNF-α-receptor
T2D	type 2 diabetes
TEA	tetraethylammonium chloride
Tfam	mitochondrial transcription factor A
TFB	mitochondrial transcription factor B
TG	triacylglycerol
TIM	translocases of the inner membrane
TNF	tumour necrosis factor

TOM	translocases of the outer membrane
5′TOP	5′ terminal oligopyrimidine tract
TORC	mTOR complex
TR	thyroid receptor
TxA_2	thromboxane A_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