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Essays in Biochemistry

Drugs and Ergogenic Aids to Improve Sport Performance

Edited by C. E. Cooper and
R. Beneke

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Preface

Every athlete wants the 'edge' in competition over their opponents. This advantage can come from biochemistry, biomechanics, physiology or psychology. In this selection of essays we focus on the use of chemicals to enhance sport performance, whether they be legal ergogenic aids or illegal performance-enhancing drugs. As befits the *Essays in Biochemistry* series we have asked the authors to discuss detailed biochemical mechanisms of action, focusing on those chemicals they feel really benefit performance.

An extended opening chapter introduces the topic of chemical enhancement of sport performance and provides an overview of all the subsequent chapters. For those new to the topic this would be a good place to start. However, if you are only interested in one topic, e.g. stimulants or gene doping, the individual chapters are completely self-contained.

We would like to extend our thanks to our ex-colleague at the University of Essex, Dr Jerry Shearman (now at Christchurch Polytechnic Institute of Technology in New Zealand), for providing very helpful initial suggestions for this book. Finally we are indebted to the hard and efficient work of the Portland Press staff, in particular Clare Curtis and Michael Cunningham.

Chris Cooper and Ralph Beneke

January 2008

Authors

Chris Cooper did a BSc in Biochemistry at Bristol (1985) and subsequently studied mitochondrial bioenergetics at Brock University Canada, graduating with a PhD in 1989. His supervisor Peter Nicholls was David Keilin's last PhD student, so it is no surprise that his research career has revolved around the study of cytochromes and cell respiration. During a subsequent 3-year fellowship at King's College London, he studied a range of spectroscopic techniques and was co-ordinator of the interdisciplinary King's College Metals in Biology and Medicine Centre. He was keen to apply these *in vitro* techniques to the whole organism so that he might address questions at the interface between Biochemistry and Physiology/Pathophysiology. This ambition was realized by a very productive 3-year MRC (Medical Research Council) Research Fellowship in the Paediatric department at UCL (University College London), where he applied optical and magnetic techniques to the study of mitochondrial dysfunction and brain injury in the newborn infant. A Wellcome University Award took him to the University of Essex in 1995. In 1997 he was awarded the Melvin H. Knisely Award for outstanding achievements in research related to oxygen transport to tissue. In 1999 he was appointed to a Personal Chair in Biochemistry. Research in his group, funded by U.K. research councils [EPSRC (Engineering and Physical Sciences Research Council) and BBSRC (Biotechnology and Biological Sciences Research Council)], the European Union and the Wellcome Trust, relate primarily to three areas: (i) the mechanism of free-radical generation by myoglobin and haemoglobin in relation to oxidative stress-induced diseases and the safe design of novel haemoglobin-based blood substitutes; (ii) the role of nitric oxide as a mitochondrial signalling molecule via its reversible binding to cytochrome *c* oxidase; and (iii) the non-invasive measurements of blood flow, tissue oxygenation and mitochondrial energetics via NIRS (near infrared spectroscopy). He is a past Director of the Biochemical Society and Chair of the Inorganic Biochemistry Discussion Group of the Royal Society of Chemistry and he currently sits on the Executive Committees of the British Biophysical Society and the International Society on Oxygen Transport to Tissue.

Ralph Beneke, born in Hameln, Germany in 1958, studied Medicine and Sport and Exercise Science in Cologne. He has a doctoral degree in Medicine (Dr med., University Clinic Cologne, 1988) and habilitated in Sports Medicine and Physiology (Dr habil., University Clinic Berlin, 1999). Since 2002, he has been Professor for Biological Sciences at the University of Essex. His clinical experience includes working with transplant patients but also top athletes. He

has an extensive record of sport science support and coaching of world-class athletes with and without physical impairments. His research interests are modelling and computer-simulated analysis of energetics, regulation and kinetics of physiological measurements, cellular integrity and function with special attention to event, environmental conditions, age and health. **Dieter Böning**, born in Mönchengladbach, Germany in 1939, studied medicine from 1958 to 1964. He has a doctoral degree in Medicine (Dr med., University of Bonn, 1964). After an internship, he worked as a scientific assistant in Physiology (University of Cologne and Sports University Cologne). After graduating (Dr habil. for Physiology) he was appointed as a Professor for Sports Physiology at the Sports University of Cologne in 1974. In 1976 he became Head of the Department for Sports and Exercise Physiology at the Medical School in Hannover and in 1993 he was appointed Director of the Institute of Sports Medicine at the Free University Berlin. Research interests are blood volume regulation, gas transport, acid–base equilibrium and electrolytes during exercise and at altitude.

Lawrence L. Spriet, PhD, is a Professor in the Department of Human Health and Nutritional Sciences at the University of Guelph, Ontario, Canada. His major research focus examines the regulation of skeletal muscle mitochondrial, fat and carbohydrate metabolism during aerobic and sprint exercise in untrained and trained human beings. He also conducts practical research examining the efficacy of purported ergogenic aids in athletes during exercise and examines the hydration and nutritional status of athletes during practices and games. **Christopher Perry** is a PhD candidate in the Department of Human Health and Nutritional Sciences at the University of Guelph, Ontario, Canada. He obtained his BSc and MSc degrees in the same department. His doctoral research focuses on the skeletal muscle mitochondrial and metabolic adaptations that occur following high-intensity interval training in humans. **Jason Talanian** is a PhD candidate in the Department of Human Health and Nutritional Sciences at the University of Guelph, Ontario, Canada. He completed his BSc degree in Biology and MSc in Exercise Physiology at the California State University of Sacramento, California, U.S.A. His doctoral research examines the effects of exercise training on skeletal muscle fat metabolism and his broad research interests include studying the effects of exercise training and ergogenic aids on fat metabolism and exercise performance.

Ceri Nicholas is currently a Senior Lecturer and Area Leader in sport and exercise physiology in the Department of Sport and Exercise Sciences at the University of Chester. Prior to that appointment she lectured in the Centre for Sport and Exercise Science at the University of Essex (2003–2006), was a Research fellow at Loughborough University (1996–2003) and a lecturer at the University of Wales Institute, Cardiff (1995–1996). She completed her PhD on the 'Influence of nutrition on muscle metabolism and performance during intermittent

high-intensity running in man' at Loughborough University in 1996. Her research interests include the physiology of intermittent, high-intensity exercise, fluid ingestion and performance and recovery of performance.

Kevin Tipton is a Senior Lecturer in Exercise Metabolism in the School of Sport and Exercise Sciences at The University of Birmingham. Prior to his appointment in Spring 2005, he was an Assistant Professor in the Department of Surgery at UTMB (University of Texas Medical Branch) in Galveston. His postdoctoral work was under the supervision of Professor Robert Wolfe at UTMB. His research focuses on the interaction of nutrition and exercise on muscle protein metabolism in humans. **Arny Ferrando** is a Professor of Geriatrics and Assistant Director for the Center for Translational Research in Aging and Longevity at the University of Arkansas for Medical Sciences. Prior to his relocation to Little Rock in August of 2006, he was a Professor of Surgery at the UTMB in Galveston. His research focus is on the amelioration of muscle wasting states with nutritional and hormonal interventions.

Henning Wackerhage is a Senior Lecturer and **Aivaras Ratkevicius** is a Lecturer in the School of Medical Sciences at the University of Aberdeen. Their research interests are signal transduction pathways that regulate muscle adaptation to exercise and other environmental stimuli.

Gareth Jones is a teaching fellow at the Centre for Sports and Exercise Science, University of Essex, with interests in Exercise Biochemistry since 1995. His particular interests include the mechanism of action of caffeine and alcohol in sport performance. He is currently examining the effects of these drugs on skill acquisition relating to sport.

Stephen Harridge obtained his PhD from the University of Birmingham, U.K. Following postdoctoral research at the Karolinska Institute, Stockholm, the Copenhagen Muscle Research Centre, Denmark and at the University of Pavia, Italy, he was appointed Lecturer in Human and Applied Physiology at the Royal Free Hospital Medical School, London. He subsequently spent 7 years as a member of the Department of Physiology at UCL (University College London), before being appointed Professor of Human and Applied Physiology at King's College London in 2005. His research integrates molecular, cellular and *in vivo* approaches to human muscle function and plasticity. **Cristiana Velloso** is a graduate of the University of Rome in biological sciences. She obtained a PhD from UCL in Biochemistry and Molecular Biology while studying skeletal muscle as a source of cells for limb regeneration in newts. Since then, she has been working as a postdoctoral fellow, first at UCL and now at King's College London, on the mechanisms of skeletal muscle hypertrophy in cultured cells and in humans, in particular as regards the roles of growth hormone and insulin-like growth factor.

David Cowan is the Head of Department of Forensic Science and Drug Monitoring and is co-founder and Director of the Drug Control Centre

at King's College London, which is accredited by the World Anti-Doping Agency and the United Kingdom Accreditation Service to ISO 17025. He holds a personal chair in Pharmaceutical Toxicology and is a Fellow of the Royal Pharmaceutical Society of Great Britain.

Abbreviations

ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ACTN-3	actinin 3
AMPK	AMP-activated protein kinase
Andro	androstenedione
Balco	Bay Area Laboratory Co-operative
BCAA	branched-chain amino acid
CAT	carnitine acetyltransferase
CES	carbohydrate–electrolyte solutions
CFTR	cystic fibrosis transmembrane conductance regulator
CFU-E	erythroid colony-forming unit
CHO	carbohydrate
CPT	carnitine palmitoyltransferase
DA	dopamine
DARPP-32	dopamine and cAMP-regulated phosphoprotein
DHEA	dehydroepiandrosterone
EAA	essential amino acid
4E-BP1	eIF-4E-binding protein 1
eIF-4E	eukaryotic initiation factor 4E
EPO	erythropoietin
FAT/CD36	fatty acid transport protein
FDA	Food and Drug Administration
FiO ₂	inspired fraction of oxygen
f-TRP	free tryptophan
GH	growth hormone
GP	glycogen phosphorylase
HBOC	haemoglobin-based oxygen carrier
hCG	human chorionic gonadotropin
HES	hydroxyethyl starch
HIF	hypoxia-inducible factor
IGF 1	insulin-like growth factor 1
IOC	International Olympic Committee
IRMS	isotope ratio MS
IRS	insulin receptor substrate
LCFA	long-chain fatty acid
LC-MS/MS	liquid chromatography–tandem MS
MCT	medium-chain triacylglycerol
MGF	mechano-growth factor

MHC	myosin heavy chain
MPB	muscle protein breakdown
MPS	muscle protein synthesis
mTOR	mammalian target of rapamycin
NBAL	net muscle protein balance
NEFA	non-esterified fatty acid
NFAT	nuclear factor of activated T cells
NF κ B	nuclear factor κ B
p70 S6K	70 kDa ribosomal S6 kinase
PDE	phosphodiesterase
PDH	pyruvate dehydrogenase
PDK1	PIP ₃ -dependent protein kinase 1
PEG	poly(ethylene glycol)
PFC	perfluorocarbon
PFK2	6-phosphofructo-2-kinase
PGC1 α	PPAR γ co-activator
PH	pleckstrin homology
PI	phosphoinositide
PI3K	phosphoinositide 3-kinase
PIIIP	procollagen III peptide
PIP ₃	phosphatidylinositol (3,4,5) triphosphate
PKA	protein kinase A; cAMP-dependent protein kinase
PKB	Akt; protein kinase B
PLD	phospholipase D
PPAR	peroxisome-proliferator-activated receptor
rEPO	recombinant EPO
RER	respiratory exchange ratio
rHuEPO	recombinant human EPO
rHuGH	recombinant human growth hormone
ROS	reactive oxygen species
RSR13	right-shifting reagent 13/faproxiral
SBE	Smad-binding elements
SIAB	Science and Industry Against Blood Doping
SR	sarcoplasmic reticulum
TCA	tricarboxylic acid
TGF- β	transforming growth factor- β
THG	tetrahydrogestrinone
TSC2	tuberous sclerosis complex protein 2
VEGF	vascular endothelial growth factor
$\dot{V}O_{2,max}$	maximum oxygen uptake
WADA	World Anti-Doping Agency