ADVANCED NEUROMUSCULAR EXERCISE PHYSIOLOGY

ADVANCED EXERCISE PHYSIOLOGY SERIES

Phillip F. Gardiner

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I dedicate this book to the most important people in my life—
my wife and best friend, Kalan; my sons, Patrick and
Matthew; and my mother and father, Verlie and Charles.

Series Preface

Having a detailed knowledge of the effects of exercise on specific physiological systems and under various conditions is essential for advanced-level exercise physiology students. For example, students should be able to answer questions such as these: What are the chronic effects of a systematic program of resistance training on cardiac structure and function, vascular structure and function, and hemostatic variables? How do different environments influence the ability to exercise, and what can pushing the body to its environmental limits tell us about how the body functions during exercise? When muscles are inactive, what happens to their sensitivity to insulin, and what role do inactive muscles play in the development of hyperinsulinemia and type 2 diabetes? These questions and many others are answered in the books in Human Kinetics' Advanced Exercise Physiology Series.

Beginning where most introductory exercise physiology textbooks end their discussions, each book in this series describes in detail the effects of exercise on a specific physiological system or the effects of external conditions on exercise. Armed with this information, students will be better prepared both to conduct the high-quality research required for advancing scientific knowledge and to make decisions in real-life scenarios such as the assement of health and fitness or the formulation of effective exercise guidelines and prescriptions.

Although many graduate programs and some undergraduate programs in exercise science and kinesiology offer specific courses on advanced topics in exercise physiology, there are few good options for textbooks to support those classes. Some instructors adopt general advanced physiology textbooks, but such books focus almost entirely on physiology without emphasizing *exercise* physiology.

Each book in the Advanced Exercise Physiology Series addresses the effects of exercise on a certain physiological system (e.g., cardiovascular or neuromuscular) or in certain contexts (e.g., in various types of environments). These textbooks are intended primarily for students, but researchers and practitioners will also benefit from the detailed presentation of the most recent research regarding topics in exercise physiology.

Preface

The field of neuromuscular exercise physiology is changing rapidly. A major part of this is due to the relatively young age of the field of neuroscience compared with the study of other physiological systems such as the cardiovascular and respiratory systems and even the study of muscle physiology. For example, we did not know the mechanisms involved in the generation of the action potential until the 1940s, and recordings from mammalian neurons did not occur until late into that decade. The Society for Neuroscience, whose annual meeting attracts more than 30,000 delegates, held its first meeting in 1971, with less than 1,400 delegates attending. Another important dimension of science that has changed our way of thinking about neuromuscular exercise physiology is molecular biology. We learned of the structure of DNA in the 1950s and have been systematically measuring mRNAs as an index of altered gene expression only since the 1980s. As a consequence, our ideas of how the nerves and muscles collaborate during acute and chronic exercise have evolved as our knowledge of the basic function of nervous and muscular systems has allowed us to understand exercise more thoroughly.

The basis for this text was formed some 30 years ago when, as a professor at the University of Montreal, I decided to create a graduate course titled Neuromuscular Aspects of Physical Activity, or, more precisely, Aspects neuromusculaires de l'activité physique (the course was in French, since Université de Montréal is a francophone institution). There was no available text on this subject at the time. The course material included excerpts from the neuroscience texts that were just becoming available as well as research articles relating to the effects of training and disuse and the causes of fatigue in the neuromuscular system. My postdoctoral years at UCLA, spent with Dr. Reggie Edgerton, had already sensitized me to the idea that physical activity is not merely an issue of turning entire muscles and muscle groups on and off and that the nervous system plays an extremely important and complicated role in recruiting subvolumes of muscle, with various patterns and intensities of recruitment of motor units of different types and sizes, to correspond to the needs of the task. This was a major shift in my thinking—my doctoral research at the University of Alberta involved stimulating entire dog hind-limb muscles to fatigue and determining the biochemical changes that might explain why force was decreasing. I still look on the 2 years in Edgerton's laboratory as a major epiphany in my research life.

The text titled *Neuromuscular Aspects of Physical Activity,* authored by me and published by Human Kinetics in 2001, was prepared in order to allow students in my graduate course to have the material in text format as opposed to the 400+ pages of photocopied material that the course entailed by 2000. As it turned out, I taught the course only once using the text; I moved to the University of Manitoba in 2002. Since that time, my membership and research in the department of physiology at the Spinal Cord Research Center have extended my research horizons significantly. In particular, an appreciation for the complexities of

locomotion and other forms of voluntary movement has become a principal issue in my research, thanks to regular interaction with my colleagues in the Center, including the director David McCrea, Larry Jordan, Brian Schmidt, and Brent Fedirchuk.

This current text constitutes a significant extension of the 2001 text. An appreciable amount of material (in fact, several chapters) from research areas that have not evolved since 2001 has been removed. Perhaps more importantly, evidence emanating from important research advances since 2001 has been added and often highlighted in several text boxes in each chapter.

I start the text with a chapter on the relationships between motoneurons and the muscle fibers they innervate and the idea of motor unit types in order to demonstrate how the properties of each cell type seem to be matched appropriately. I also make reference to late adaptation as a phenomenon that might limit the excitability of motoneurons during prolonged exercise and bistability as a phenomenon by which the generation of self-sustaining currents might function to counteract this loss of excitability during exercise by supercharging motoneurons. This is followed by chapter 2, in which recruitment of different motor unit types during various types and intensities of movement is discussed. Here I describe the difficulties inherent in determining recruitment patterns during complex forms of exercise as well as the knowledge we have gained from well-controlled experiments. In this chapter I consider the possibilities that individuals might be able to rotate the recruitment of motor units to offset fatigue and that all individuals may or may not be actually capable of recruiting all of their motor units maximally during an all-out voluntary effort.

In chapter 3, muscle alone is the target. Here I present an overview of two issues that are currently of considerable interest in the research literature: the control of muscle blood flow and the metabolic pathways involved in control of metabolism, including AMP-activated protein kinase (AMPK), glucose sensitivity of muscle, and fatty acid transport into muscle. Special consideration is given to discussing what happens in type 2 diabetes, in which inactivity and obesity result in disruptions in glucose and fatty acid uptake and in fatty acid by-product accumulation in muscle. The effects of increased physical activity on these processes, including muscle blood flow, which is itself affected by type 2 diabetes, are discussed.

Fatigue is the topic of chapters 4 and 5. In chapter 4, I discuss the sites believed to be involved in the fatigue process that are more peripheral, such as the muscle fiber itself, the neuromuscular junction, and the motoneuron axon, with specific reference to the experimental evidence for their roles in fatigue. Chapter 5 is concerned with the currently available evidence that central fatigue, or physiological changes occurring at sites in the spinal cord level and above, contributes to decreased performance as exercise continues. Information in these two chapters suggests that there are many physiological processes that change during exercise and that no one site can be targeted as the single site of fatigue.

In chapters 6 and 7, the subject is aerobic endurance training. In chapter 6, I consider how endurance training changes the protein profiles of muscle fibers. Since whole-body endurance exercise is so complex, with different fibers in the same muscles being exposed to various degrees of relative overload, the use of the biopsy technique is problematic with respect to a mechanistic interpretation of results. For this reason, the literature on the effects of chronic electrical stimulation on muscle protein synthesis and degradation is referred to extensively. I consider the mechanisms and the metabolic signals involved in the changes in fiber phenotype that accompany

aerobic endurance training. Chapter 7 is devoted to the changes that occur in the nervous system in response to aerobic endurance training. In this chapter, most of the information is gleaned from the literature on actual increases in voluntary activity as opposed to chronic electrical stimulation. Of particular interest in this chapter is the applicability of the research information to the exercise rehabilitation of individuals with compromised nervous system function, such as spinal cord injury, other trauma, and neuromuscular disease.

The last three chapters are concerned with resistance training. Chapter 8 summarizes the current knowledge regarding the molecular mechanisms that promote increased muscle mass and associated strength. While aerobic endurance training signals seem to be primarily metabolic, many resistance training signals have to do with mechanical perturbations associated with the acute exercise challenge. The signaling discussed here includes the production of insulin-like growth factor 1 (IGF-1); activation of the Akt and mTOR pathway; activation of phospholipases A and C (PLA and PLC); and activation of the kinase systems protein kinase C (PKC), focal adhesion kinase (FAK), and mitogen-activated protein kinase (MAPK). In chapter 9, I present the phenotypic responses of muscles to resistance training. This discussion includes the specific changes that occur with different forms of resistance training, including isometric, slow isotonic, lengthening, and plyometric types of training. Finally, chapter 10 constitutes an overview of the effects of resistance training on the nervous system, with discussion on the strength of each piece of evidence as it is presented. The clinical implications are obvious and are discussed within that chapter.

I cannot pretend that this book includes every piece of literature relating to the neuromuscular system and exercise that has ever been published. Indeed, I know full well that I have omitted many important and elegant pieces of research in each chapter, and I apologize if it is your work. Much of the information in this text is also based on opinion—in choosing to present research literature on the effects of chronic electrical stimulation of muscle as representative of aerobic endurance training, for example, I am expressing my opinion that the commonalities are more important than the differences between these two models of increased muscle activity. I hope that you appreciate my thought processes as you progress through the text. Please contact me if you have any thoughts about the material that is included or that is absent and that you think should be included or any thoughts about my interpretations, which might not always be correct.

Acknowledgments

Like everyone else, I am a product of my environment, and my life trajectory has been redirected by people whom I have interacted with along the way.

I would like to acknowledge the wisdom and patience of my mentors at the University of Windsor, where I began my university training and awakened to the possibility of research as a career path; at the University of Alberta, where I honed important research skills and attitudes; at the University of California, Los Angeles, where I learned from a master and was allowed and encouraged to develop research independence and confidence; and at the University of Amsterdam, where I attained a new level of appreciation for the absolute and indescribable beauty of the experimental process. I have been extremely fortunate to have had the opportunity to cross paths with these exceptional individuals.

I must acknowledge the trainees whom I have worked with during my career, ranging from undergraduate students to postdoctoral fellows. I remember each one of them (they number more than 100 now) for their energy, enthusiasm, and youthful optimism, and I cannot help but think that I have been, in the long run, the major beneficiary of my contact with each one of them, which now in many cases seems sadly evanescent.

I have enjoyed very much the collegial relationships with my colleagues at the Université de Montréal and the University of Manitoba during my 30-plus-year career. I cannot think of a better environment in which one can spend one's working life, interacting daily with individuals who are kindred spirits in their appreciation of the importance of the pursuit of knowledge and truth.

Finally, I would like to acknowledge the assistance of Maria Setterbom for the artwork in the book, and also for the many times that she has blessed us all at the Spinal Cord Research Center with her genius in graphics. Thanks, Maria!

Credits

Chapter 1

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Contents

Series Preface ix
Preface xi
Acknowledgments xiv
Credits xv

Chapter 1 **Muscle Fibers, Motor Units, and Motoneurons 1**
Muscle Heterogeneity 2
Orderly Motor Unit Recruitment 7
Smaller Motoneurons Are More Excitable. 9
Membrane Resistivity and Motoneuron Size 9
Other Factors Determining Action Potential Generation 11
Minimal Firing Rates and Afterhyperpolarization Durations. . . . 12
Motoneuron Current–Frequency Relationship and Excitability. . . 15
Late Adaptation. 17
Motoneuron PICs 20
Summary 23

Chapter 2 **Motor Unit Recruitment During Different Types of Movements 25**
Measuring Human Motor Unit Recruitment 25
Influence of Task 27
Slow-Ramp Isometric Contractions 28
Maintained Isometric Contractions 32
Isometric Contractions in Various Directions 34
Isometric Contractions Versus Movements 35
Lengthening Contractions. 38
Cocontraction of Agonists and Antagonists 40
Unilateral Versus Bilateral Contractions 40
Rhythmic Complex Contractions 41
Maximal Voluntary Contractions 42
Summary 44

Chapter 3 **Muscle Blood Flow and Metabolism. 46**
Muscle Blood Flow 46
Muscle Metabolism 53
Summary 60

Chapter 4 **Peripheral Factors in Neuromuscular Fatigue. 63**
Intramuscular Factors and Muscle Force 64
Involvement of Structures Other Than Muscle 67
Research From Animal Experiments. 77
Summary 80

Chapter 5 **Central Factors in Neuromuscular Fatigue 83**
Motoneuron Activity During Sustained Contractions 83
Isometric Versus Anisometric Tasks. 98
Rotation of Motor Units? 99
Summary 99

Chapter 6 **Muscular Mechanisms in Aerobic Endurance Training 101**
Chronic Muscle Stimulation 102
Coordination of Muscle Protein Systems 104
Pretranslational Control 106
Translational Control. 109
Posttranslational Modifications 110
Simultaneous Expression of Isoforms 112
Adaptations Can Occur Ex Vivo. 112
Adaptations Appear in a Specific Sequence 112
Thresholds of Activity for Adaptation 114
Chronic Stimulation and Atrophy 115
Metabolic Signals and the Adaptive Response 117
Degenerative and Regenerative Processes 122
Summary 122

Chapter 7 **Neural Mechanisms in Aerobic Endurance Training 125**
Adaptation of the Neuromuscular Junction 125
Responses of Motoneurons 130
Adaptations of Spinal Cord Circuits 134
Summary 139

Chapter 8 **Muscle Molecular Mechanisms in Strength Training 141**
Acute Responses in Protein Synthesis and Degradation 142
Connective Tissue Responses 155
Role of Muscle Damage 156
Role of Dietary Supplements 157
Summary 158

Chapter 9 **Muscle Property Changes in Strength Training 161**
Increased Muscle Fiber Cross-Sectional Area 161
Fiber Type Composition. 162
Muscle Fiber Number 163
Muscle Composition 165
Muscle Architecture 166
Muscle Fiber Ultrastructure 166
Evoked Isometric Contractile Properties 167
Changes in Muscle Force, Velocity, and Power. 169
Fatigue Resistance 171
Role of Eccentric Contractions 171
Summary 173

Chapter 10 **Neural Mechanisms in Strength Training 175**
Gains in Strength Versus Muscle Girth 175
Strength Gains Show Task Specificity 176
Surface EMG Response During MVC 178
Imaginary Strength Training 179
Reflex Adaptations 179
Cross Education 181
Decreased Activation of Antagonists 183
Changes in Motor Unit Recruitment 183
Changes in Motor Cortex 186
Summary 186

References 189
Index 225
About the Author 229

CHAPTER 1

Muscle Fibers, Motor Units, and Motoneurons

In this chapter, we discuss how muscle fibers, motor units, and motoneurons take part in voluntary movements and how the variability in their properties allows for variability in these movements. Muscle fibers demonstrate a coordinated set of biochemical and functional properties that are used to divide them into several types. The most frequently used nomenclature for distinguishing fiber types classifies the types according to their myosin heavy chain (MHC) composition, and we use that nomenclature in this chapter when referring to different muscle fiber types. The motor unit (muscle unit and its innervating motoneuron) exhibits a set of specific properties that provides a logical recruitment blueprint for the performance of simple isometric contractions. This is facilitated by the fact that all muscle fibers in the muscle unit have the same properties; therefore, heterogeneity at the muscle fiber level is transferred to the muscle unit, and thus motor unit, level. This recruitment blueprint is known as the *size principle,* which dictates that small, more excitable motoneurons are recruited before large, less excitable ones are recruited. For the motoneuron, properties that vary systematically among the motor units include rheobase current, input resistance, afterhyperpolarization duration, and propensity for late adaptation. Motoneurons also exhibit active properties such as self-sustained firing, which is modulated by several monoamines and peptides. These properties can acutely increase the excitability of the motoneuron—and thus the propensity of the motor unit to fire— and modulate its firing patterns once activated.

MUSCLE HETEROGENEITY

In a book about neuromuscular exercise physiology, an important first step is to discuss the ways in which contractile units (the motor units) combine to produce voluntary movements. This chapter assumes that in previous courses, you have learned about

the basic mechanics of muscle function. You should already know the sliding filament theory of muscle contraction; the basic structure of skeletal muscles and typical muscle cells, or fibers; the mechanisms by which action potentials are transduced into chemical, and then mechanical, events during excitation–contraction coupling; the twitch, unfused tetanic, and tetanic mechanical responses that take place when muscles are stimulated; and the events that take place at the neuromuscular junction. These topics have been covered very well in a variety of texts currently available, and you should consult these references if questions arise. Assuming that you already have this knowledge base allows us to delve more deeply into more timely issues surrounding our knowledge of muscle contribution to exercise in a variety of situations.

The gross anatomy of muscles is another factor that plays a major role in the patterns of movement the crossed joints are capable of producing. Factors such as muscle size and the point of origin and insertion of the muscle relative to the axis of rotation of the joint affect the strength and speed of movement. Muscles that have a pennate arrangement of short muscle fibers (meaning that the fibers are arranged at an angle not completely in line with the angle of force generation between the proximal and distal attachments of the muscle) are potentially stronger, albeit slightly slower in shortening speed, than muscles of the same weight in which fibers are fusiform (run the entire length of the muscle along its line of force generation). This is because fibers in a pennate muscle are shorter and more numerous. This arrangement allows for more fibers in parallel for force generation that are slower in shortening distance per unit time because of their shorter length. Human muscles vary widely in their degree of pennate arrangement, ranging from the fusiform (e.g., the sartorius) to the highly pennate (e.g., the quadriceps femoris, which is multipennate). This chapter assumes that you are familiar with the importance of these macrostructural anatomical issues, and they will be referred to in this chapter, and throughout the text, with this assumption.

Our understanding of how muscles respond during exercise would be greatly simplified if muscles always contracted isometrically, via a twitch contraction or a maximal tetanic contraction (which are the types of contractions usually shown in textbooks), with all fibers responding simultaneously. Alas, they do not. In addition, often during exercise only some of the fibers in the muscle are used, with the proportion of maximal force generated among those recruited fibers ranging from low to high (relative to their maximum), and with contractile forces of individual fibers not synchronized, such that voluntary contractions are a combination of twitch, semifused tetanic, and tetanic contractions, all occurring out of synchrony. With respect to examining what is occurring in exercising muscles, the interpretation of data using techniques such as the muscle biopsy, in which samples are taken from the muscle belly to measure metabolic changes in the working muscle fibers, becomes problematic, especially when exercise is submaximal in intensity. The force of the recruited fibers also depends on the velocity at which they are shortening, or lengthening, according to the force–velocity relationship that you have learned previously. Finally, we know that all muscle fibers are not the same, which leads us to our currently used terminology of fiber types, and that there are systematic (as opposed to random or unorganized) ways in which these fibers are recruited during exercise.

One indication of the importance of muscle heterogeneity in the contractile performance of the whole muscle is the relationship between muscle fiber type composition and contractile performance during voluntary and stimulation-evoked contractions. Data from the literature describing this relationship are summarized in table 1.1.