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24.19 Disorders of muscle CONTENTS 24.19.1 Structure and function of muscle 6304 Michael G. Hanna and Enrico Bugiardini 24.19.2 Muscular dystrophy 6310 Kate Bushby and Chiara Marini-Bettolo 24.19.3 Myotonia 6328 David Hilton-Jones 24.19.4 Metabolic and endocrine disorders 6334 David Hilton-Jones and Richard Edwards 24.19.5 Mitochondrial disease 6343 Patrick F. Chinnery and D.M. Turnbull 24.19.1 Structure and function of muscle Michael G. Hanna and Enrico Bugiardini ESSENTIALS The motor unit—the final common pathway for all voluntary muscle activity—is composed of an anterior horn cell, its peripheral axon, the axon terminal branches, the associated neuromuscular junctions, and the muscle fibres innervated. Muscle cells—these are multinucleate units with unique structures adapted for response to metabolic, nervous, and autocrine signals. Their key elements being (1) sarcolemma—complex structured pro- teins maintain the integrity of the muscle fibre membrane, which contains specialized regions (motor endplates) by which innervating nerves interact at synapses; (2) contractile components—biochemical interactions between actin and myosin filaments are initiated by cal- cium ions released from the sarcoplasmic reticulum; contraction is powered by chemical energy released by the hydrolysis of adenosine triphosphate, in globular regions of myosin, after they form crosslinks with actin. Different types of motor units—there are two biochemical variants (1) type 1—rich in mitochondria and specialized for oxidative me- tabolism of fat; (2) type 2—larger fibres with abundant glycogen that generate

energy by glycosis and are critical for short-lived muscle contraction. All muscles contain populations of both fibre types, but differ in their proportions and functions. Clinical perspective—knowledge of the underlying molecular cell biology, neurophysiology, and biochemical energetics of muscle provides a useful basis for understanding the symptoms, signs, and pathogenesis of clinical disorders affecting the muscles. Mutations in sarcolemmal proteins, such as dystrophin, cause diseases with widespread effects on skeletal muscle function, the heart, and survival. Basic anatomy of skeletal muscle We possess more than 150 voluntary (skeletal) muscles, most of which are attached to the skeleton at both ends through tendons. Complex voluntary movements of the body are achieved by inte- grated activity of different skeletal muscle groups. To the naked eye a transverse section of any skeletal muscle reveals small units known as muscle fascicles. Each skeletal muscle fascicle is com- posed of many basic structural units known as muscle fibres (Fig. 24.19.1.1). Muscle fibres are cylindrical structures that may be several centimetres long and 50–100 µm in diameter. A muscle fibre is a highly specialized cell. Similar to any other cell it has a mem- brane (the sarcolemma), contains cytoplasm (the sarcoplasm), and has an endoplasmic reticulum (the sarcoplasmic reticulum), as well as other subcellular organelles such as mitochondria. However, un- like cells from many other tissues, muscle cells are multinucleate. Typically, the nuclei are positioned at the edges of the muscle fibre. The sarcolemma of muscle fibres possesses specialized regions known as motor endplates. These endplate regions are the points at which the axon innervating a muscle fibre forms synapses. Release of acetylcholine from the presynaptic region trans- mits the axonal action potential to the muscle fibre membrane by binding to postsynaptic acetylcholine receptors located in the sarcolemma at the endplate. The sarcolemma is differentially per- meable to ions. This allows different concentrations of ions to be maintained inside and outside the membrane, and is critical in maintaining the resting membrane potential. A chain of important structural proteins maintains the integrity of the sarcolemma by linking intracellular muscle fibre cytoskeletal proteins to the extra- cellular matrix. These structural proteins include dystrophin (lo- cated in a subsarcolemmal distribution), the dystrophin-associated glycoprotein complex (a trans-sarcolemmal protein complex), and

 laminin (located extracellularly). These important proteins may be dysfunctional in certain forms of genetic muscle diseases (see Chapter 24.19.2). After staining, or if suitably illuminated, muscle fibres are seen to have regular cross-striations that extend right across the inside of the fibre, dividing it up into sarcomeres (see Fig. 24.19.1.1). The parts of the cross-striations are identified by letters: the light I band is divided by the dark Z line and the dark A band has the lighter H zone in its centre. The region between two ad- jacent Z lines is called a sarcomere. The cross-striations are due to the presence of the principal contractile filamentous proteins, actin, and myosin, in the sarcoplasm. These filamentous proteins are arranged in rod-like structures known as myofibrils. A single myofibril contains many protein filaments. In life, myofibrils are transparent on routine light microscopy, but, if viewed with a po- larizing microscope, a typical pattern of cross-striations can be seen within individual myofibrils. The correct understanding of the basic microscopic anatomy of this pattern of cross-striations was critical to the discovery of the sliding filament theory of skel- etal muscle contraction. The sliding filament theory of skeletal
muscle contraction The protein filaments contained within myofibrils are of two types: the thin filaments are composed of actin, tropomyosin, and troponin, and the thick filaments of myosin (Fig. 24.19.1.2). The thick filaments are approximately twice the diameter of the thin filaments. The

thick filaments are lined up to form the A bands, whereas the array of thin filaments forms the less dense I bands. The lighter H bands in the centre of the A bands are the regions where, when the muscle is relaxed, the thin filaments do not overlap the thick fila- ments. The Z lines transect the myofibrils and connect to the thin filaments. If a transverse section through the A band is examined under the electron microscope, each thick filament is found to be surrounded by six thin filaments in a regular hexagonal array (see Fig. 24.19.1.2). The myosin molecules have large globular heads at their C-terminal portions (Fig. 24.19.1.3), and the heads contain an actin-binding site that hydrolyses adenosine triphosphate (ATP). During muscle contraction, cross-linkages occur between the heads of the myosin and the actin molecules (Fig. 24.19.1.3). The thin filaments are composed of two chains of actin that form a long double helix. Tropomyosin molecules are long filaments lo- cated in the groove between the two chains of actin. Troponin molecules are small globular units located at intervals along the tropomyosin molecules. Troponin has three components: troponin T, responsible for binding to tropomyosin; troponin I, which in- hibits the interaction of actin and myosin; and troponin C, which contains the binding sites for the Ca2+ ions that initiate contraction (see Fig. 24.19.1.3). The process by which shortening of the contractile elements of muscle is brought about is sliding of the thin filaments over the thick filaments. The width of the A band is constant, whereas the Z lines move closer together when the muscle contracts and further (a) Tendon 50–100 µm 1–2 µm 0–8 µm 1–5 µm 0–8 µm Muscle fibre Tendon Whole muscle (b) Muscle fibre Fibrils (c) Isolated myofibril (d) I band A band I band Z line H zone Z line Myofibril showing band-pattern at resting length Diameter 50 Å (5 nm) Diameter 100 Å (10 nm) (e) Muscle filaments on same scale at myofibril in (d) Fig. 24.19.1.1 The dimensions and arrangement of the contractile components in a muscle. The whole muscle (a) is made up of fibres (b) that contain cross-striated myofibrils (c, d). These are constructed of two types of protein filaments (e), put together as shown in Fig. 24.19.1.2. I Z I Z A H Fig. 24.19.1.2 Diagram illustrating the arrangement of the different kinds of protein filament (thick filaments: myosin; thin filaments: actin) in a myofibril. At the top are three sarcomeres drawn as they would appear in longitudinal section. Below are transverse sections through the H zone and other parts of the A band where the thick and thin filaments interdigitate. The plane of section determines whether, in electron micrographs, there seem to be one or two thin (actin) filaments between two thick (myosin) ones. Reprinted from Huxley and Hanson (1972),

 apart when it is stretched. The sliding during muscle contraction is produced by breaking and reforming the cross-linkages between actin and myosin. The immediate source of energy for contraction is hydrolysis of ATP localized to the myosin head. Neural activation of muscle fibres—the motor unit The motor unit is the final common pathway for all voluntary muscle activity. It is composed of an anterior horn cell (located within the spinal cord), its peripheral axon, the axon terminal branches, the associated neuromuscular junctions, and the muscle fibres innerv- ated. The muscle fibres of a single motor unit are spatially dispersed throughout a muscle and only a few fibres innervated by the same anterior horn cell are contiguous. The number of motor units varies greatly between muscles, from approximately 1000 in leg muscles to 100 in intrinsic hand muscles. The number of muscle fibres per motor unit also varies greatly, and motor units differ in physiological and biochemical characteristics. Two main types of motor units are recognized, each composed of a single muscle fibre type. Type 1 muscle fibres contain many mitochondria and are slightly smaller than type 2 muscle fibres because they contain myofibrils, which are more slender. Type 1 fibres contain a high concentration of oxida- tive enzymes and more fat; type 2 fibres are larger, contain fewer mitochondria, but have a higher

concentration of glycogen and en- zymes involved in anaerobic metabolism such as myophosphorylase. All skeletal muscles contain a mixture of both fibre types, typically in a chequerboard pattern when stained appropriately (with the myofibrillar ATPase reaction) and visualized under light micros- copy (Fig. 24.19.1.4). Type 1 fibres are also known as slow fibres because they contract and relax slowly and are abundant in muscles concerned mainly with maintaining posture. In contrast, type 2 fibres contract and relax quickly and are also known as twitch fibres. Type 2 fibres can be further subdivided into type 2a and 2b based on their intensity of staining with myofibrillar ATPase reaction at different pH values (Table 24.19.1.1). Normally muscle fibres do not contract in isolation; rather the muscle fibres that comprise the motor unit contract together in re- sponse to depolarization of an anterior horn cell. Such depolariza- tion is transmitted along the axon until it invades the nerve terminal. This results in opening of voltage-gated calcium channels located in the presynaptic membrane. Calcium enters the nerve terminal down an electrochemical gradient. The resulting increase in presynaptic calcium concentration promotes fusion of acetylcholine-containing vesicles normally present in the nerve terminal with the presynaptic membrane. Quanta of acetylcholine are released into the synaptic cleft and diffuse to the postsynaptic membrane to bind to and acti- vate acetylcholine receptors. Acetylcholine binding causes opening of its receptor channel, allowing cations to enter the muscle fibre in the endplate region. This cation flux depolarizes the postsynaptic membrane, resulting in a mini-endplate potential. The summation of endplate potentials results in the excitation of the postsynaptic membrane, which is then conducted along the muscle fibre mem- brane. The excitation is transmitted into the muscle fibre by invagin- ations of the sarcolemma known as the T-tubule system. Activation of calcium channels in the T-tubule system membrane results in opening of calcium channels in the sarcoplasmic reticulum. Calcium is then released into the muscle fibre cytoplasm, initiating muscle contraction. Myosin I Cross-bridge Tropomyosin Troponin C T Actin ADP + Pi Ca2+ ATP Ca2+ Ca2+ Ca2+ Myosin I C T Fig. 24.19.1.3 Initiation of muscle contraction by Ca2+ ions. The cross-bridges (heads of myosin molecules) attach to binding sites on actin (striped areas) and swivel when tropomyosin is displaced laterally by binding of Ca2+ ions to troponin C. Source data from Katz AM, 1975, Congestive heart failure. New England Journal of Medicine 293, 1184; 1184–1191. Fig. 24.19.1.4 A transverse section of human skeletal muscle obtained by biopsy from a patient with spinal muscular atrophy stained for the myofibrillar ATPase reaction after preincubation at pH 4.6. There is extensive evidence of fibre type grouping, particularly of the type 1 fibres, resulting from reinnervation. Magnification ×150. Kindly supplied by Dr Margaret Johnson.

 Energy production in skeletal muscle Resting skeletal muscle requires remarkably little energy, but the need for energy production may increase dramatically in response to ex- ercise, because energy is required for muscle contraction. ATP is the main source of energy in muscle. It is required for shortening of the contractile filaments and for the active reuptake of calcium into the sarcoplasmic reticulum after each muscle contraction. Maintenance of electrochemical gradients across the sarcolemma also requires ATP. Resynthesis of ATP from adenosine diphosphate (ADP) is es- sential for normal muscle function. The two main energy-producing pathways in muscle are glycolysis in the sarcoplasm and oxidative phosphorylation in the mitochondria. Resynthesis of ATP from ADP is also aided by phosphocreatine and the creatine kinase reaction. Creatine kinase catalyses the transfer of high-energy phosphate from phosphocreatine to ADP in circumstances in which ATP demand may outstrip ATP production (e.g. at the very start of exercise be- fore oxidative phosphorylation or

glycolysis is activated). Glycolysis is the main pathway of ATP synthesis in anaerobic conditions and results in the generation of lactate. Oxidative phosphorylation is the major ATP-generating pathway in aerobic conditions. The main fuel sources in skeletal muscle are glucose, glycogen, and fatty acids. In anaerobic conditions, glycogen is the main energy source. In aerobic exercise, glycogen and glucose are utilized initially, but, after approxi- mately 30 min, fatty acids are the main energy source. In resting aer- obic muscle, fatty acids provide the principal source of fuel. Several muscle diseases are recognized in which energy metabolism is im- paired; these are known as the metabolic myopathies. Diseases of human skeletal muscle: overview Human muscle diseases may be conveniently divided into those that are genetically determined and those that are acquired (Box 24.19.1.1). The clinical history in muscle diseases Although a muscle biopsy is usually needed to determine the exact type of muscle disease, the clinical history and examination are usu- ally sufficient to determine whether a muscle disease is present or absent. As many muscle diseases are genetically determined, it is particularly important to consider the family history. A careful drug history is also essential. Although many diseases may affect skeletal muscle (see Box 24.19.1.1), there are three main symptoms with which patients may present: muscular pain, muscular weakness, and fatigability. A further important but less common symptom is darkening of the urine (pigmenturia) due to release of myoglobin from damaged muscle, which occurs particularly in the metabolic myopathies. Unless pigmenturia has been dramatic, patients may not volun- teer this symptom. Muscle pain is a common symptom, but in only about a third of patients presenting with this symptom will an underlying muscle disease be identified. In those without a defin- able muscle disease, many are considered to have a psychogenic Table 24.19.1.1 Histochemical and physiological characteristics of the three major types of muscle fibre Fibre type 1 2A 2B Enzyme reactions NADH–tetrazolium reductase and SDH +++ ++ + Myofibrillar ATPase: pH 9.4 + +++ +++ pH 4.6 +++ – +++ pH 4.3 +++ – – Phosphorylase + +++ +++ Physiological properties Twitch speeds Slow Fast Fast Fatigue resistance +++ ++ + Nomenclature Peter et al. (1972) Slow twitch Fast twitch Fast twitch Oxidative Oxidative–glycolytic Glycolytic Burle et al. (1971) S (slow contracting) FR (fast contracting, fatigue resistant) FF (fast contracting, fast fatigue) From Walton JN, Mastaglia FL (1980). Box 24.19.1.1 A simple classification of human muscle diseases Genetically determined muscle diseases • Muscular dystrophies, such as Duchenne/Becker • Congenital myopathies, such as nemaline • Muscle ion channel disorders, such as hyper-/hypokalaemic periodic paralysis • Metabolic myopathies, such as McArdle’s disease (myophosphorylase deficiency) and mitchondrial myopathies Acquired muscle diseases • Inflammatory muscle diseases, such as polymyositis/dermatomyositis • Degenerative muscle diseases, such as inclusion body myositis • Endocrine muscle diseases, such as hyper-/hypothyroid myopathies • Toxic and drug-induced muscle diseases, due to alcohol/corticosteroids

section 24 Neurological disorders 6308 cause for their muscle pain, although some may have as yet un- defined disorders of muscle metabolism. Sometimes it can be difficult for the patient and the phys- ician to distinguish between pain originating in muscle and that originating in joints or bones. Certain rheumatological diseases may result in joint pain as well as muscle pain (e.g. systemic lupus erythematosus may cause arthritis and polymyositis). Muscle pains may take the form of cramps, which are involuntary con- tractions of muscle groups. Simple muscle cramps are not un- common in older people and frequently occur at night. There is usually no underlying muscle disease but drugs such as diuretics (which induce hypokalaemia) may be implicated. In younger pa- tients, muscle cramps may be the presenting feature of a metabolic muscle disease such as McArdle’s disease. Muscle pain brought on by exertion is a particular feature of the

metabolic muscle dis- eases. Muscle contractures may also be a source of muscle pain in patients with metabolic myopathies. Patients experience a pain similar to a cramp, but, unlike a cramp, electromyography reveals that a contracture is electrically silent. Muscle weakness is a common feature of muscle diseases and the distribution of weakness in most of these diseases is in the prox- imal limb muscles. Patients may complain of difficulty performing tasks that involve lifting their arms up to or above the head, such as brushing hair. Proximal lower limb muscle weakness causes diffi- culties getting out of low chairs and in climbing stairs. Muscle dis- eases often affect the limb musculature symmetrically, although there are important exceptions to this (e.g. one of the common autosomal dominant muscular dystrophies), fascioscapulohumeral muscular dystrophy, often affects the limb muscles in an asymmet- rical fashion. Some muscle diseases may affect the facial muscu- lature as well as that of the limb. Symptoms may include difficulty in whistling, closing the eyes, or articulating. Respiratory muscle disease may cause breathlessness. It is important to determine the natural history of muscle weakness. In most genetically determined muscle diseases, weakness progresses slowly over years; occasionally patients may experience attacks of weakness separated by periods when they seem to have normal strength, as in the periodic par- alyses. The muscle weakness in the inflammatory muscle diseases usually develops more rapidly. Fatigability is defined as an increase in weakness with exer- cise. Patients may say that they can start a particular physical ac- tivity but the longer they continue the weaker they become. They may also complain that they become weaker as the day goes on. Myasthenia gravis, a disorder of neuromuscular transmission, is the principal cause of fatigability. In patients with myasthenia gravis, fatigability can usually be demonstrated at the bedside. Patients with metabolic muscle diseases may also experience fatigability. The physical examination in muscle disease The examination may be broadly divided into two aspects: first, an examination is made to establish whether there are any clues to the cause of the muscle disease. In this context, the general phys- ical examination is very important. Particular attention is paid to eliciting signs that might indicate an underlying endocrine or rheumatological disorder (e.g. signs of hyper-/hypothyroidism, Cushing’s syndrome, or rheumatological disorders such as systemic lupus erythematosus). Inspection of the skin may reveal the appear- ances of dermatomyositis. The second part of the examination in- volves examining the muscular system to determine the extent and severity of the condition; this may also give further clues to the aeti- ology. The muscles are inspected for any atrophy or hypertrophy (as occurs in some muscular dystrophies) or for any spontaneous ac- tivity of the muscle fibres (such as fasciculation, which might indi- cate an anterior horn cell disorder). The muscles should be palpated for any tenderness or swelling, which may occur in inflammatory muscle diseases. Myotonia is a delayed relaxation of muscle after contraction, and may be ob- served by asking the patient to clench the fist and then open it rap- idly. A patient with myotonia is unable to open the clenched fist rapidly due to an inability to relax the contracted muscles quickly. Myotonia may also be evident on percussion of muscle. The exam- ination of muscle power is carried out systematically, starting with the cranial musculature before proceeding to the arms and legs. The degree of weakness is assessed with reference to the Medical Research Council grading scale (0 to 5). The distribution of weak- ness is also noted, because different muscle diseases have charac- teristic patterns of weakness. Bedside assessment of respiratory muscles including the diaphragm is also important, although detailed assessment of these muscles requires formal spirometry. Finally, the tendon reflexes are elicited. These are generally pre- served in acquired muscle diseases, except when there is advanced weakness; however, they may be lost relatively early in the course of dystrophies. Investigating the patient with muscle disease Investigations are generally instituted only when the history and examination have provided clear evidence that the

patient has symp- toms and/or signs of muscle disease. The investigations are aimed primarily at determining the exact type of muscle disease because it is essential to establish whether the patient has a treatable muscle disease, such as an inflammatory myopathy. Many investigations of increasing complexity and invasiveness are available. Simple blood tests allow an assessment of the endocrine and nutritional status of the patient (such as thyroid function, the consumption of excess alcohol, or the presence of vitamin D de- ficiency). Measurement of blood creatine kinase is important be- cause this can be an indicator of the degree of muscle fibre damage or necrosis. Creatine kinase is generally elevated in inflammatory muscle diseases and in many of the muscular dystrophies. Increasingly, DNA-based testing is available from simple blood samples. This can be particularly helpful and in some situations may obviate the need for further more invasive tests, such as a muscle biopsy (e.g. if analysis of the dystrophin gene on the X chromosome identifies a pathogenic mutation known to associate with Duchenne muscular dystrophy, the diagnosis is confirmed). The expanding use of the genetic techniques has revealed that gen- etic muscle disorders are heterogeneous and several genes may be associated with the same disease. For example, congenital myop- athies are caused by mutations of more than 20 genes. To face this genetic heterogeneity it is now possible to test simultaneously all the genes associated with a specific phenotype (‘genetic panel’) allowing a quick and cost-effective approach to several genetic muscle diseases.

24.19.1 Structure and function of muscle 6309 The diagnosis of metabolic muscle diseases may be achieved by specific dynamic tests (e.g. McArdle’s disease can be diagnosed using the ischaemic lactate test), and mitochondrial disease may be suspected on the basis of subanaerobic exercise tests (both these tests are described in the relevant section). Detailed nerve conduction studies and electromyography (EMG) are useful in determining whether a patient has a neuropathy, a de- fect in neuromuscular junction transmission, or a myopathy. EMG is useful in characterizing any spontaneous activity of muscle, such as fasciculations or myotonia. Although EMG is generally useful in confirming the presence of a myopathy, it is less useful in determining the cause. Muscle MRI is increasingly being recognized as a diagnostic tool in muscle diseases. MRI detects inflammatory and dystrophic changes and may reveal specific pattern of muscle involvement nar- rowing the differential diagnosis. Furthermore, quantitative MRI methods may be used as a marker of disease progression. Muscle biopsy allows a detailed analysis of the internal archi- tecture of muscle and is an extremely valuable and safe investiga- tion in carefully selected patients. Using a range of histochemical stains, histochemical enzyme reactions, and immunological tech- niques on frozen muscle biopsy sections, much information of diagnostic use can be obtained. Different muscle diseases often reveal characteristic patterns of abnormalities, which are usually identified by light microscopic techniques. Using basic histochem- ical stains, the features of different muscular dystrophies are gen- erally similar, the most common features being marked variations in fibre diameter, internal nuclei, fibre splitting, fibre necrosis and regeneration, and increase in connective tissue. However, a more precise diagnosis of the type of muscular dystrophy can now be obtained by immunostaining techniques. Antibodies that are raised against specific membrane proteins allow quantitative ana- lysis (e.g. staining using antibodies directed against dystrophin re- veals no or very little dystrophin in cases of Duchenne muscular dystrophy). Prominent inflammatory infiltrates are typically seen in muscle sections from patients with inflammatory myopathies. Figs. 24.19.1.5, 24.19.1.6 and 24.19.1.7 show the muscle biopsy features of some of the metabolic myopathies. In some cases, the changes seen on the biopsy clearly indicate a myopathic process, but it is not possible to be more specific in the absence of typical immunological, inflammatory, or metabolic changes. Fig. 24.19.1.5 A transverse section of human

skeletal muscle obtained from a patient with carnitine deficiency and stained with Sudan black B. The massive accumulation of neutral fat, especially with the type 1 fibres, is evident. Magnification ×196. Fig. 24.19.1.6 A transverse section of skeletal muscle obtained from a patient with mitochondrial myopathy, stained for the MADH-TR reaction. The type 1 fibres are darkly stained and show the typical reticulated appearance of so-called ‘ragged-red fibres’ with massive mitochondria, particularly in many fibres just deep to the sarcolemma. Magnification ×384. Kindly supplied by Dr Margaret Johnson. Fig. 24.19.1.7 A transverse section of a biopsy specimen obtained from one quadriceps muscle in a patient with mitochondrial myopathy, showing arrays of paracrystalline inclusions in the damaged mitochondria. Bar = 1 μm. Kindly supplied by Dr Michael Cullen.

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