Exercise and Fatigue

Wim Ament[1] and *Gijsbertus J. Verkerke*[2,3]

1 Department of Biometrics, Faculty of Health and Technology, Zuyd University, Heerlen, the Netherlands
2 Department of Biomedical Engineering, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
3 Department of Biomechanical Engineering, University of Twente, Enschede, the Netherlands

Contents

Abstract

Physical exercise affects the equilibrium of the internal environment. During exercise the contracting muscles generate force or power and heat. So physical exercise is in fact a form of mechanical energy. This generated energy will deplete the energy stocks within the body. During exercise, metabolites and heat are generated, which affect the steady state of the internal environment. Depending on the form of exercise, sooner or later sensations of fatigue and exhaustion will occur. The physiological role of these sensations is protection of the exercising subject from the deleterious effects of exercise. Because of these sensations the subject will adapt his or her exercise strategy. The relationship between physical exercise and fatigue has been the scope of interest of many researchers for more than a century and is very complex.

The exercise intensity, exercise endurance time and type of exercise are all variables that cause different effects within the body systems, which in turn create different types of sensation within the subject's mind during the exercise.

Physical exercise affects the biochemical equilibrium within the exercising muscle cells. Among others, inorganic phosphate, protons, lactate and free Mg^{2+} accumulate within these cells. They directly affect the mechanical machinery of the muscle cell. Furthermore, they negatively affect the different muscle cell organelles that are involved in the transmission of neuronal signals.

The muscle metabolites produced and the generated heat of muscle contraction are released into the internal environment, putting stress on its steady state. The tremendous increase in muscle metabolism compared with rest conditions induces an immense increase in muscle blood supply, causing an increase in the blood circulatory system and gas exchange. Nutrients have to be supplied to the exercising muscle, emptying the energy stocks elsewhere in body. Furthermore, the contracting muscle fibres release cytokines, which in their turn create many effects in other organs, including the brain. All these different mechanisms sooner or later create sensations of fatigue and exhaustion in the mind of the exercising subject. The final effect is a reduction or complete cessation of the exercise.

Many diseases speed up the depletion of the energy stocks within the body. So diseases amplify the effect of energy stock depletion that accompanies exercise. In addition, many diseases produce a change of mind-set before exercise. These changes of mind-set can create sensations of fatigue and exercise-avoiding behaviour at the onset of an exercise. One might consider these sensations during disease as a feed-forward mechanism to protect the subject from an excessive depletion of their energy stocks, to enhance the survival of the individual during disease.

For more than a century, exercise-induced fatigue and exhaustion have been an area of interest for many physiologists. A comprehensive review, including history, is given by Gandevia.[1]

Although most exercise-related studies focus on the neuromuscular system, in fact all organs are involved. Not only the neuromuscular system but other organs also react to the individual's exercise

capacity. It is well known that this exercise capacity is reduced during illness. Chronic illness, such as end-stage renal failure, has an immense impact on exercise capacity.

Fatigue caused by exercise is a common sensation, which everybody has experienced. During exercise the workload may create such an intense sensation that one has to reduce the workload or even stop the exercise. Any physical exercise is an energy-consuming activity, which will sooner or later empty the energy stocks within our body. An unlimited consumption of these stocks without re-supply would have deleterious effects on our physical health. Therefore, the sensations of fatigue and exhaustion are most likely essential for maintaining our physical integrity. The sensations of fatigue and exhaustion represent psychological entities, which will sooner or later introduce changes in behaviour. The accompanying physical and biochemical changes during exercise are physiological entities. The phenomena of fatigue and exhaustion during exercise are fields of interest of different scientific disciplines, especially physiology and psychology.

The physical and biochemical changes during exercise are physiological effects. In exercise physiology these effects are defined as 'fatigue', and can be monitored objectively. However, 'fatigue' is also a psychological entity, which represents a subjective and mental variable. Besides fatigue, 'exhaustion' is another psychological entity that is related to physical exercise. Despite the constant motor output during exercise, the 'sense of effort' may increase gradually.[2] Sometimes this sense of effort can be so intense that it topples one's willpower to maintain the motor output and forces the subject to reduce or even stop his/her workload. In this article, this moment is defined as 'exhaustion'. This is in contrast to the definition stated during the CIBA Foundation Symposium 82 of 1981 (Chairman RHT Edwards),[3] where 'fatigue' was defined as the moment when a subject is unable to maintain the required muscle contraction or performed workload. In this article 'exhaustion' has the same quality as the definition of 'fatigue' given at the CIBA Symposium. The 'sense of effort' is not the same as the 'sense of perceived exertion'. The sense of perceived exertion reflects more or less all the subjective sensations accompanied during an exercise performance. Borg[4] has introduced a psychophysical ratio scale for perceived exertion.

In exercise, the performed motor output can be measured. Motor output is the mechanical output produced by the contractile properties of the skeletal muscle, which can be measured objectively as contraction force (in newtons [N]) or as power (in watts [W]). In this article the neuronal output of the motor cortex is defined as motor drive. The motor drive of the motor cortex is the final result of many centres in the CNS, which act on the motor cortex. These centres are situated in the cerebral cortex, in subcortical nuclei and in nuclei situated in the brain stem. The CNS and the motor units together form the neuromuscular system. For a proper functioning of this system, it is embedded in the internal environment, which has a physical and chemical equilibrium. This equilibrium, the steady state of the internal environment, is maintained by the other organs. Exercise affects the neuromuscular system as well as the internal environment at many levels. Exercise is accompanied by psychological phenomena. Different types of exercise create different kinds of sensations. Furthermore, disease alters the exercise capacity. All these different aspects of exercise are reviewed in this article. A synopsis of the different causes is shown in table I.

1. Physiological Aspects of Exercise

1.1 Effects of Exercise on the Motor Unit

1.1.1 Biomechanical Consequences of the Accumulation of Metabolites within Muscle Fibres

The energy source for the contraction of muscle fibres (muscle cells) is adenosine triphosphate (ATP).[5,6] In the muscle cell, the major pathways for ATP production include:[6]

1. A rapid production of ATP from sarcoplasmic stores of creatine phosphate.
2. A somewhat slower production using anaerobic glycolysis. The enzymes and fuel (i.e. glycogen) for these reactions are located in the sarcoplasm.

Table I. Overview of possible sites of exercise-associated fatigue

I. Peripheral fatigue

A. Exercise-related changes in the internal environment

During exercise workloads above the point of increased blood lactate accumulation (OBLA), changes in the internal environment (blood, extracellular fluid) include:

1. Accumulation of lactate and hydrogen ions (protons). The accumulation of hydrogen ions is partly buffered such that there is an increased liberation of carbon dioxide from bicarbonate. As a result, the respiratory quotient will increase

2. Accumulation of ammonia

3. Accumulation of heat, leading to increased sweat secretion. The loss of water may lead to dehydration

B. Exercise-related changes within muscle fibres

1. Accumulation of P_i (inorganic phosphate) in the sarcoplasm, causing a decrease in contractile force due to an inhibition of cross-bridge interactions

2. Accumulation of H^+ ions in the sarcoplasm, also causing a decrease in contractile force due to an inhibition of cross-bridge interactions. In addition, the accumulation of H^+ ions may cause a depression in calcium re-uptake in the sarcoplasmic reticulum. This might be the main cause for the lengthened relaxation time after fatiguing contractions

3. Accumulation of Mg^{2+} ions in the sarcoplasm. Mg^{2+} counteracts the Ca^{2+} release from the sarcoplasmic reticulum

4. Inhibition of the Ca^{2+} release of the sarcoplasmatic reticulum by accumulation of P_i (see point 1). The Ca^{2+} release is inhibited by precipitation of calcium phosphate within the lumen of the sarcoplasmatic reticulum and by phosphorylation of the Ca^{2+} release channels

5. Decline of glycogen stores and (in extreme cases) decline of blood glucose levels. Even a short-lasting decline of blood glucose might seriously interfere with CNS functions. A depletion of the glycogen stores leads, in a manner not well understood, to increased muscle fatigue

6. Decreased conduction velocity of action potentials along the sarcolemma, probably as a result of exercise-associated biochemical changes in and around the muscle fibres. The drop in conduction velocity is reflected in the EMG (change of frequency content) but has no known immediate effect on the muscular force production

7. Increased efflux of potassium ions (K^+) from muscle fibres. The increase in potassium in the lumen of the t-tubuli may lead to a block of the tubular action potential and, hence, less force due to a depression of excitation-contraction coupling

8. Neuromuscular synaptic transmission may become blocked; however, this seems to be a factor mainly of importance in disease (myasthenia gravis)

II. Central fatigue

1. The conduction of axonal action potentials may become blocked at axonal branching sites, leading to a loss of muscle fibre activation. The relative importance of this factor is unknown

2. The motor neuronal drive might be influenced by reflex effects from muscle afferents. Thus, central fatigue effects might, to some extent, be compensated for by mechanoreceptor reflexes (types IA and II from muscle spindles; type IB from Golgi tendon organs)

3. Stimulation of type III and IV nerves (chemo- and nociceptive afferents) induces a decrease in motor neuron firing rate and an inhibition of the motor cortex output

4. The excitability of cells within the cerebral motor cortex might change during the course of maintained motor tasks, as suggested by measurements using transcranial magnetic stimulation

5. The synaptic effects of serotoninergic neurons might become enhanced, causing an increased sense of tiredness and 'fatigue'. This may occur as a result of an increased influx into the brain of the serotonin precursor tryptophan. During prolonged exercise, such an increased influx of tryptophan may result from an exercise-evoked decrease in the blood concentration of BCAAs

6. Exercise-induced release of cytokines. IL-6 induces sensations of fatigue and IL-1 induces sickness behaviour in animals. In many diseases the production of these cytokines is enhanced

BCAAS = branched-chain amino acids; **EMG** = electromyograph; **IL** = interleukin; **OBLA** = onset of blood lactate accumulation; $\mathbf{P_i}$ = inorganic phosphate.

3. A slower but very effective production of ATP using aerobic pathways for glycolysis and fat metabolism by the mitochondria.

Independent of which pathway is dominating, muscle contractions will always be associated with an increase in adenosine diphosphate (ADP) and inorganic phosphate (P_i) production (e.g. from the cross-bridge cycle itself). During intense contractions, the accumulation of P_i can even be measured *in vivo* using nuclear magnetic resonance (NMR) spectroscopy.[7-10] In addition, anaerobic glycolysis leads to an increased production of hydrogen ions (H^+) and a measurable decrease of intra- and extracellular pH. The concentration of these three metabolites (ADP, P_i and H^+) will be particularly increased in

contractions of high force and power, and they all have direct effects on the efficiency of the cross-bridge interactions. The efficiency of the cross-bridge interaction is estimated by two factors: (i) the duration of attachment and detachment of the actin and myosin filaments during the cross-bridge cycle; and (ii) the speed of the cross-bridge cycle (see figure 1). The rate-limiting step in the cross-bridge cycle is the release of P_i, which is the step from A-M-ADP~P_i to A-M-ADP.[12] An increase in [H+] reduces isometric contraction force[13] and decreases the period of filament attachment.[14] Perhaps, an increase in [H+] enhances the binding of ATP to the actin-myosin complex during the attachment phase of the cross-bridge cycle, which in turn speeds up the uncoupling of the actin and myosin filaments.[15] Cooke et al.[16] found a decrease in contraction velocity during increasing concentrations of [H+]. In her review, Myburgh[17] debates to what extent this decrease in contraction velocity is caused by the low temperature (10°C) in which these experiments were performed. Westerblad et al.[18] found no decrease in contraction velocity at temperatures of 30°C. Normally, skeletal muscle temperature is above 30°C. Therefore, a drop in intramuscular pH during exercise has most likely no effect on contraction velocity under normal physiological circumstances. An increase in [ADP] slows down the period of attachment, but increases the isometric tension.[19,20] Accumulation of inorganic phosphate depresses isometric contraction force[21,22] and decreases myofilament ATPase turnover.[23] During isokinetic contraction experiments, an increase in [P_i] also induces a decrease in the myofilament ATPase turnover.[24] Figure 1 provides a schematic outline of the cross-bridge cycle. In fact, the increase in concentrations of P_i and H+ gives a reduction of the force-producing capability of the filaments. In turn, the increase in ADP concentration increases force production and also reduces cross-bridge cycle velocity.

1.1.2 Depletion of Glycogen Stores in Muscles

Exercise intensities below the point of onset of blood lactate accumulation (OBLA) can be maintained for long periods (see section 1.2). The

limiting factor for these endurance exercises is the availability of glucose.[25,26] The concentration of blood glucose is maintained at constant levels and is regulated by the interaction of many hormones.[27] Glucose uptake by exercising muscles is mediated by glucose transporters.[28] Nitric oxide (NO) plays a role in the uptake of glucose by exercising muscles. Muscle cells contain NO-synthetase.[29] Most likely, NO-synthetase is
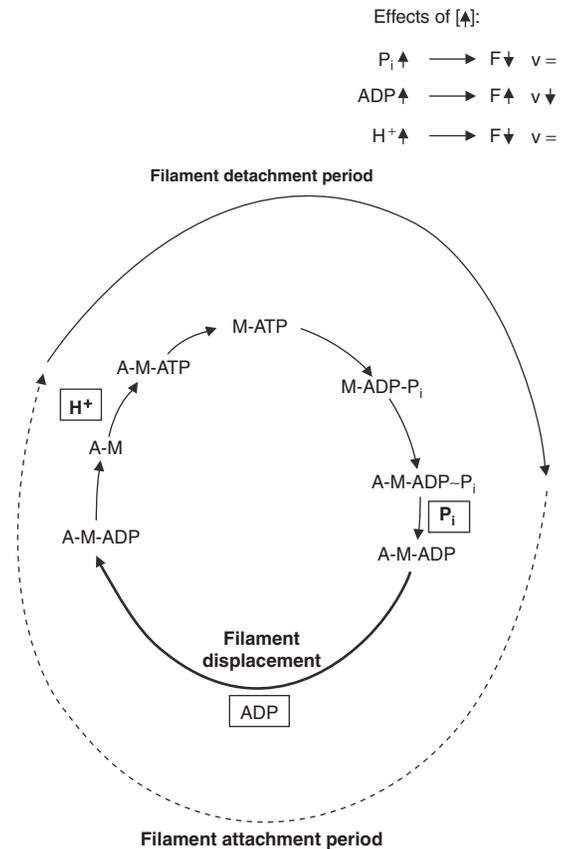
Fig. 1. Model of the cross-bridge cycle according to Cooke.[11] The effect changes in concentration of H+, adenosine diphosphate (ADP) and P_i during the cross-bridge cycle is shown schematically. The box at the right side of the figure shows the effects of these changes in concentration. **A** = actin; **A-M** = the actin-myosin complex; **A-M-ADP** = the actin-myosin-ADP complex; **A-M-ADP**~**Pi** = actin-myosin-ADP~P_i complex (~P_i is the energy rich chemical bonding used during the filament displacement); **A-M-ATP** = the actin-myosin-ATP complex; **F** = force generated by the filaments; **M** = myosin; **M-ADP-Pi** = myosin-ADP-P_i complex after ATP hydrolysis; **M-ATP** = myosin-ATP complex; **P**$_i$ = inorganic phosphate; **v** = cross-bridge cycle velocity; ↑/↓ indicates increase/decrease in concentration. The fat arrow indicates the displacement of the actin-myosin filaments, which is the power-generating period of the cross-bridge.

activated by the calcium increase in the sarco-plasm during muscle contraction. The effect is that the contracting muscle releases NO, which increases the activity of the glucose transporter, resulting in an increase in glucose uptake. It has been demonstrated that administration of local NO synthetase blockers decreases glucose uptake by the exercising muscles.[30]

During endurance exercise, the intracellular glycogen stores decrease little by little and the muscle tissue gradually increases its consumption of blood glucose. Finally, the availability of glucose is smaller than the glucose consumption and the concentration of blood glucose may even decrease.[27] This usually occurs at 1–2 hours after the onset of exercise: in marathon running this occurs after about 30 km, and the athlete experiences this as 'the hitting of a wall'. The trigger for these sensations may be a direct reaction of the brain to the decreased concentration of blood glucose; brain tissue needs a minimum amount of continuous glucose supply for normal function.[31] Athletes try to avoid the decrease in blood glucose by consuming glucose-containing drinks during the race.[32]

1.1.3 The Effect of Exercise on Muscle Membrane Structures: Excitation-Contraction Coupling

Cross-bridge interactions and force production are started as a result of a sequence of events leading to the release of calcium ions from the sarcoplasmic reticulum (SR). This sequence of events is referred to as the 'excitation-contraction coupling' (EC-coupling). A decreased efficiency or block of EC-coupling will lead to a decrease or disappearance of contractile force. Such changes play an important role in muscle fibre fatigue and associated phenomena.

The sarcolemmal action potentials of many simultaneously active muscle fibres can be recorded with extracellular electrodes on or in a muscle, i.e. using electromyographic (EMG) techniques. The amplitude of sarcolemmal action potentials (and of the EMG) may decrease during prolonged activation,[33-35] perhaps partly as a result of changes in the transmembrane electrolyte concentrations (efflux of potassium, influx of sodium).[36] Another commonly seen effect of

intense activity is a decrease in the propagation velocity of the action potentials along the sarcolemmae.[37,38] As a result, the frequency spectrum of the EMG shifts to lower frequencies, a change that has often been interpreted as a sign of muscle fatigue.[39] Our investigations support this opinion. During a treadmill exercise load of 18 W/kg bodyweight and an endurance time ranging from 31 to 162 seconds (far above the maximum oxygen uptake [$\dot{V}O_{2max}$], see also figure 4) we found a decrease in the EMG frequency spectrum.[40] However, at a workload of 12.4 W/kg bodyweight and during a cycle ergometer exercise above the lactate threshold we found no change.[41,42] These findings suggest that during dynamic exercise, local changes within the muscle cell occur only at supramaximal workloads far above the $\dot{V}O_{2max}$. At these supramaximal workloads, ATP turnover might be so intense that accumulation of muscle metabolites within the cell could occur during the exercise. The frequency content of the EMG also depends on other factors, such as the degree of synchronization of the various muscle fibre action potentials.[43,44] The EMG, especially the integrated EMG, might increase during sustained intermittent exercise at submaximal isometric contraction force.[45-47] Two mechanisms could contribute to this increase in the EMG: (i) an increase in the motor neuron discharge frequency;[46,47] and (ii) the increase in the pool of recruited motor neurons.[47]

Changes in transmembrane electrolyte concentration are particularly prone to appear along the very thin t-tubuli and, as a result, action potential propagation along these tubuli seems to become gradually more blocked during intense activity,[48,49] leading to an inhibition of muscle fibre activation. It is not known to what extent the accumulation of muscle metabolites (ADP, P_i, H^+) affects the activity of the ion pumps of the sarcolemma, which in turn can affect action potential propagation alongside the sarcolemma.

In fatigued muscles, the speed of force relaxation at the end of a contraction is typically slowed down (increased relaxation time[50]), probably largely as a result of a decreased rate of Ca^{2+} transport back into the SR. Such an inhibition of the SR Ca^{2+} pump might be caused by the

increased concentration of H^+ ions (decreased pH) that occurs during intense muscle activity. Subjects with a myophosphorylase deficiency (McArdle's disease) are unable to break down muscle glycogen and they hardly develop any decrease in pH during muscle activity.[51-53] Cady et al.[54] demonstrated that their relaxation time was also less affected than that of normal subjects.

Mg^{2+} ions play an important role in the functioning of the SR. During muscle activation, an increased Mg^{2+} concentration in the sarcoplasm reduces the Ca^{2+} fluxes across the membrane of the SR.[55,56] Westerblad and Allen[57] demonstrated increased intracellular Mg^{2+} concentrations during exercise and concluded that this might cause a decrease in muscle force. During activity, the concentration of free Mg^{2+} in the sarcoplasm increases, partly because Mg^{2+} ions are bound to the ATP molecules and to voltage sensors of the SR. Activation of these voltage sensors removes the Mg^{2+} ion and opens the Ca^{2+} channel.[55,56]

During repeated tetanic stimulation, sarcoplasmatic (or myoplasm) Ca^{2+} concentration in the active skeletal muscle fibres increases within the first and decreases in the last period of stimulation. The maximum obtained Ca^{2+} concentrations are 1–2 μmol/L.[45,58] In fast-twitch (type II) muscle fibres this mechanism evolves faster than in slow-twitch (type I) fibres. The contraction force of these stimulated fibres shows a small decrease within the first period of tetanic stimulation,[45] which is caused by the increase of the sarcoplasmatic P_i concentration, which directly affects the cross-bridge interaction of the myofilaments (see section 1.1.1). Sarcoplasmatic P_i concentrations can increase from 1–5 mmol/L during rest conditions to 30–40 mmol/L during intense contraction.[58] The drop of muscle fibre contraction force at the end stage of the stimulation period is caused by an impaired Ca^{2+} release by the SR. One reason for this impaired Ca^{2+} release is the decline of the amplitude of the action potential across the sarcolemma. Another reason could be the effect of the relatively high sarcoplasmatic P_i concentration, which has two effects at the SR Ca^{2+} release. The first effect is

precipitation of calcium phosphate in the lumen of the SR. Through high sarcoplasmatic concentrations, P_i enters the lumen of the SR by a passive process via the chloride channels.[58] The Ca^{2+} concentration within the lumen of the SR is estimated at 1 mmol/L.[58] The solubility product of $Ca(HPO_4)$ is about $10^{-7}-10^{-6}$, and the solubility of $Ca(H_2PO_4)_2$ is a larger by a factor of 60.[59] So most likely $Ca(HPO_4)$ precipitates inside the lumen of the sarcoplasmatic reticulum, reducing the concentration of free Ca^{2+}, which in turn reduces the Ca^{2+} concentration gradient between the lumen of the SR and the sarcoplasm. The other effect of the high sarcoplasmatic P_i concentration is phosphorylation of the Ca^{2+} release channels of the SR. These Ca^{2+} release channels are very large and complex polypeptide structures containing four tetramers, each of about 565 kDa.[60] The phosphorylation of these Ca^{2+} channels inhibits the SR Ca^{2+} release.[45,61] The increase of sarcoplasmatic Mg^{2+} during exercise[57] enhances the effect of P_i inhibition.[45] The final effect of the sarcoplasmatic increase of P_i concentration during persistent contraction is a drop in Ca^{2+} efflux by the SR. *In vitro* experiments suggest that caffeine releases this inhibition.[58]

The ion shifts across the sarcolemma during exercise have consequences for the internal environment.[62] Action potentials (APs) are associated with the efflux of potassium and the influx of sodium. Sjøgaard et al.[63] found a net loss of 20 mmol potassium from maximally exercising muscles during a one-leg knee extension exercise. They estimated the mass of the contracting muscle at about 2.5 kg. After the exercise, they measured potassium concentrations up to 6.0–6.5 mmol/L in the femoral vein and up to 5.0–5.5 mmol/L in the femoral artery (normal values at rest 3.6 up to 4.8 mmol/L). During graded treadmill exercise until exhaustion, Busse and Maassen[64] found final arterial potassium levels of 5.5–6.0 mmol/L. After 1 minute of running at a maximal speed, Medbo and Sejersted[65] observed potassium concentrations exceeding 7 mmol/L in the femoral artery.

Some viral infections are accompanied by myocarditis.[66,67] In most cases these viral forms of myocarditis are asymptomatic.[66] During the

influenza epidemic of 1957, Gibson et al.[68] showed that these infections can induce ECG changes. Of the 87 male students in the study who were infected by the influenza virus, five students showed ECG changes during illness and six during recovery. The ECGs of these infected students showed changes in T-wave and ST-segment elevations in the precordial leads. Based on these observations, one should take care with performing vigorous exercise during a common cold, because the sudden increases in plasma potassium during exercise might trigger unexpected cardiac pathology. In our exercise studies, volunteers who had symptoms of a common cold within 7 days prior to the study were excluded.

1.1.4 The Neuromuscular Junction and the Peripheral Nerve

The neuromuscular synapse has been the subject of many investigations in the context of peripheral fatigue (for a definition of peripheral fatigue, see section 1.3.2). The results of these investigations are somewhat inconsistent. Several authors found a decrease in the amount of released acetylcholine from the presynaptic nerve terminal during repetitive nerve stimulation.[69,70] Others observed signs of postsynaptic desensitization at the motor end-plate.[71] However, such changes do not mean that the transmission from nerve endings to muscle fibres becomes blocked; the respective postsynaptic potential (the end-plate potential) normally has an amplitude largely exceeding the amplitude needed for eliciting a postsynaptic action potential. Bigland-Ritchie et al.[72] concluded that despite intense voluntary activation, the propagation of the action potential across the motor end-plate (from nerve terminal to muscle) remained unaffected. During voluntary activity, the only well described failures of transmission across the neuromuscular junction are seen during curarization and in the disease myasthenia gravis.

In adult muscles, each skeletal muscle fibre receives innervation from only one α motor neuron, whereas each motor neuron makes contact with several muscle fibres. The mean number of muscle fibres per motor neuron (the 'innervation ratio') is about 10 for the small extraocular

muscles, about 100 for intrinsic muscles of the hand, and up to about 2000 for large leg muscles like gastrocnemius.[73] The higher the innervation ratio, the greater the number of axonal branch points of a motor unit. The axonal branch points are thought to be particularly susceptible to propagation failure of the axonal action potential.[74,75] However, the role of axonal propagation failure in muscle fatigue is still unclear.

1.1.5 Differentiation of Muscle Fibre and Motor Unit Properties

Practically all muscles contain fibres and motor units of widely varying biochemical and physiological properties.[76,77] Physiological studies of motor units have shown that, within a single muscle, they typically vary greatly in their contractile speed, maximum force and resistance to fatigue. Furthermore, these various properties are co-varying, such that the slowest units tend to be fatigue resistant (type I fibres) and weak and the strongest ones are fast but relatively sensitive to fatigue (type II fibres). The differences in fatigue resistance are partly associated with differences in the 'vulnerability' of the EC-coupling.

The biochemical properties of the myofilament ATPase activity are different between type I and II fibres. Several myosin subtypes can be distinguished.[78] The head of the myosin filament shows ATPase activity during the cross-bridge cycle.[11] The different myosin subtypes show different rates of ATPase activity and biomechanical properties. The cross-bridge cycle rate is slower in type I than type II fibres and therefore the ATPase turnover is lower in type I fibres. The cross-bridge cycle rates can differ up to 30 times between the different subtypes of type I and II fibres.[21] The consequence of these different subtypes of myofilaments is that one muscle can contain many subtypes of muscle fibres. Furthermore, fatigue-resistant fibres tend to have a higher activity of enzymes engaged in oxidative metabolism than the more fatigue-sensitive fibres.

Isometric force generation of type II fibres decreases more than type I fibres during P_i accumulation at 30 mmol/L.[21,23] This effect is more evident at low temperatures.[79] In contrast, contraction speed of type I fibres is more susceptible

to P_i accumulation than type II fibres.[80] These effects are also more pronounced at low temperatures.[81] One should realise that the temperature of human skeletal muscle *in vivo* is about 32°C at rest conditions and can rise to >39°C during exercise.[82] Therefore, the effects of P_i accumulation on the biomechanical properties of myofilaments may be more pronounced in the *in vitro* experiments at low temperatures than during *in vivo* circumstances of exercise.

The distribution of the different fibre types varies greatly between different muscles and across homologous muscles in different animal species.[83] Type I fibres tend to be relatively more frequent in muscles with a crucial role in posture (e.g. in antigravity muscles needed for standing). Compared with commonly studied laboratory animals (mice, rats, cats), human muscles have a very high percentage of type I fibres; in many human muscles, type I fibres ('slow') constitute about 50% of all fibres.[84]

The firing frequency of the motor neuron declines during sustained isometric contractions.[85,86] The reason for this firing frequency decline is most likely an afferent feedback loop.[87] Fuglevand and Keen[88] have shown that a decrease in motor unit discharge rate may contribute to a decrease in muscular output during sustained isometric contractions. As mentioned above, the speed of the cross-bridge interaction of the muscle cell decreases due to accumulation of intracellular ADP (see figure 1).[19,20] This means that the firing frequency can slow down to maintain a fully fused muscle cell contraction. The reduction of the motor neuron firing frequency in combination with the decreased speed of the cross-bridge interaction enables the contracting muscle cell to maintain its mechanical output at a lower cost of energy. Some researchers hypothesize that a special mechanism exists for the optimal motor neuron firing frequency according to the change in biomechanical properties in the muscle fibres during sustained isometric contractions.[2,86] This phenomenon is known as 'muscle wisdom'. Others debate this theory,[89] because the muscle relaxation after isometric contraction has not been thoroughly investigated yet. They argue

that, in order to study muscle wisdom properly, patients suffering from muscle disease with abnormal slow relaxation time, as in myotonia (affected sarcolemma) or Brody's disease (affected sarcoplasmatic reticulum), should be investigated.

1.2 Effects of Exercise on the Internal Environment

In sudden muscle activation, the change from rest to intense activity is too rapid for an immediate external supply of the required energy substrates, so internal energy stores are used. The energy for muscle contraction has to be supplied as ATP. At very short notice, ATP can be generated from internal stores of creatine phosphate. Furthermore, ATP can be generated relatively rapidly by anaerobic glycolysis, using intracellular stores of glycogen as fuel and producing lactic acid as one of the metabolites. Only after some time can the increased metabolic requirements of an activated muscle be balanced, partly or completely, by increasing the level of functioning of the cardiovascular and respiratory systems. More oxygen and fuel (glucose, fatty acids) need to be supplied and more CO_2 and other waste products (e.g. lactic acid) need to be removed.

The intensity of the workload, the amount of muscle tissue involved and the type and duration of exercise all influence the impact of the active muscles on the internal environment. After the sudden onset of a steady level of exercise, it typically takes several minutes before heart rate and oxygen uptake have reached a new, higher, steady state. Under anaerobic conditions, the breakdown of glucose (glycogen) generates lactic acid as one of the end-products. Under aerobic conditions, lactic acid can be further processed, generating more ATP, CO_2 and water. The performance of a matching rate of aerobic glycolysis becomes increasingly difficult at increasingly higher general workloads. The increase of lactate concentration in blood and extracellular fluids shows a marked acceleration above a certain workload, i.e. the 'lactate threshold' or OBLA (see also later, figure 4). The lactate threshold can be defined as the workload at which tissue

lactate production is exactly in equilibrium with the tissue lactate consumption. Above this workload the blood lactate concentration starts to increase.[90] Others define the lactate threshold as the workload at which blood lactate concentration exceeds 1 mmol/L above baseline.[26,91] OBLA is defined as the workload at which the blood lactate concentration exceeds 4 mmol/L.[92] An increased concentration of acid means an increased concentration of hydrogen ions, i.e. a lowering of pH. This increased proton load is partly buffered according to the reaction:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

This reaction is associated with the generation of extra CO_2, which is exhaled. As a result, there will be an increase in the respiratory quotient during the last stages of heavy exercise. For untrained subjects this occurs at about 50–60% $\dot{V}O_{2max}$, and for trained subjects at about 70–80% $\dot{V}O_{2max}$ (figure 4).[26,27]

In muscle tissue, the metabolism of the anaerobic glycolysis and purine nucleotide breakdown are linked to each other.[93,94] Ammonia emerges as adenosine 5'-monophosphate and is broken down to inosine monophosphate. Lactate is the end-product of the anaerobic glycolysis. As a consequence, the blood concentrations of both ammonia and lactate will increase during graded exercise.

It is well known that workloads above the OBLA can be maintained for only a limited period of time before subjects get seriously fatigued and are forced to stop their exercise due to exhaustion (figure 4).[25-27] Hence, exercise-associated fatigue sensations tend to increase in parallel with the accumulation of exercise-associated metabolites (e.g. lactate). It is still unknown to what extent this parallel accumulation reflects a direct causal relationship.

During graded exercise, only about 20–25% of all the consumed metabolic energy is converted into mechanical work, while the rest emerges as heat.[5,95] Thus, exercise causes a 'heat load' in the internal environment (see also section 1.3.4).

Summarizing, the large number of effects of muscle exercise on the internal environment include:

1. An increased consumption and potential lack of oxygen and nutrients (glycogen, glucose, fatty acids);
2. An increased production and potential accumulation of CO_2, hydrogen ions ('proton loading'), lactate and ammonia;
3. An increased production and accumulation of heat ('heat loading').

The larger the workload, the larger the effects of these variables are on the internal environment. It is conceivable that such changes in the internal environment might affect the functioning of the CNS, directly by interoceptive afferents and indirectly to a deterioration of the performance of the exercise-associated muscles. Visceral afferents from some cranial nerves project to the solitary nucleus of the brain stem.[96] To maintain the steady-state of the internal environment, the brainstem and hypothalamus are crucial.[97] A deterioration of the steady-state of the internal environment by exercise can induce inconvenient sensations of fatigue and of exhaustion. These inconvenient sensations have a devastating effect on exercise performance.

1.3 Effects of Exercise on the CNS

The function of the CNS is complex. The CNS plays a crucial role in the maintenance of the steady state of the internal environment. The motor cortex of the brain is responsible for the generation of the motor drive during exercise. We are conscious of this motor drive, but we are unaware of the concomitant motor control of muscles regulating our posture during exercise. Furthermore, the brain is the centre of our cognition. Despite the complexity of all these functions, our mind can concentrate on only one issue at a time; this issue is the object of our consciousness. In fact, we have a very limited state of consciousness. Gradually we become aware of sensations of fatigue and exhaustion during exercise. From a physiological point of view the awareness of these sensations has a warning role.

Besides these sensations of fatigue, neurophysiological changes also occur in the CNS during exercise.

1.3.1 Afferents and Motor Control

The CNS controls motor behaviour using sensory signals of many modalities. In humans, vision is very important for motor control,[98] and skin sensitivity is essential for the guidance of movements in direct contact with the external world (e.g. for manipulating objects). In all movements, the many afferents coming from the muscles themselves also play an important role. Muscle afferents have widely varying diameters and their functions are related to axonal size and, therefore, to conduction speed.

All muscle afferents are connected to multiple different parts of the CNS, and their signals can be used in a multitude of ways. However, in all muscle contractions the muscle spindle afferents play a role because the afferents have a direct connection to motor neurons, producing mono-synaptic excitation. Activity of muscle spindle afferents is caused by activity in gamma motor neurons. Thus, in voluntary muscle activation, a (minor) part of the total excitatory input to the motor neurons arrives via the reflex circuit of the 'gamma loop': gamma motor neurons/muscle spindles/α motor neurons. The role of muscle afferent feedback mechanisms in exercise and fatigue has been the subject of various recent investigations.[99-101]

During sustained isometric contractions at maximum voluntary contraction (MVC) the EMG and the contraction force decrease synchronously. Bigland-Ritchie et al.[102] registered the firing rate of single motor units of the biceps brachii muscle during MVC by micro-electrodes under normal and ischaemic circumstances. During MVC, firing rates declined and recovered within 3 minutes after contraction. The recovery of the firing rate was absent if ischaemia was applied. The motor neurons are positioned in the spinal cord and show a decrease in the firing rate. These experiments suggest an afferent feedback loop between the muscle and its motor neuron in the spinal cord.

It is hypothesized that the small chemo- and nociceptive muscle afferents (thin myelinated [III] or unmyelinated [IV or C] fibres) are responsible for this feedback loop.[99,103] Martin et al.[103] evoked the biceps and triceps brachii muscles, the elbow flexor and its extensor, at two different levels in the neuromuscular tract by electrical stimuli. The corticospinal and reticulospinal tracts were stimulated via the mastoid processes at the cervicomedullary level. The response to this stimulus was an evoked twitch contraction of both muscles, which are each other's antagonists. These experiments were applied with and without muscle ischaemia produced with an inflated cuff. The results of this study suggest that there is a feedback loop of III and IV nerve fibres in the extensor muscles. A response to this stimulus of fatigue in the extensor muscle was found. Surprisingly, the feedback loop of the extensor muscle also facilitates the contraction properties of the flexor antagonist. The feedback loop of the III and IV nerve fibres of the flexor muscles showed a response in the extensor antagonist, but no response in the flexor itself.

It is hypothesized that the afferents that were triggered in the experiments of Martin et al.[103] and Bigland-Ritchie et al.[102] are type III and IV nerve fibres. Bigland-Ritchie et al.[102] measured the rate frequency of the single motor units, and Martin et al.[103] tested the excitability of the corticospinal tract. These observations suggest two different feedback systems. Recent research of Martin et al.[104] showed that stimulating type III and IV nerve fibres by saline infusions (triggering pain sensations by these nerves) reduced the motor-evoked potential (MEP) response to electromagnetic motor cortex stimulation (for an explanation of MEPs see section 1.3.3.[106,110]). The corticospinal tract has no presynaptic inhibition.[105] This suggests that the corticospinal tract is inhibited at the cortical level by the type III and IV nerve fibres. In summary, muscle afferents of type III and IV nerves have three effects:

- a decrease of the firing frequency of the motor neuron;[102]
- an inhibition or facilitation of the motor neuron;[103]
- an inhibition of the motor cortex neuron.[104]

1.3.2 Central and Peripheral Fatigue

Two types of fatigue can be distinguished: central versus peripheral fatigue. In peripheral fatigue, the origin of fatigue is outside the CNS. In all other cases the fatigue is generated somewhere in the CNS. However, these terms can be defined more precisely. Peripheral fatigue is defined as the loss of contraction force or power caused by processes distal to the neuromuscular junction, and central fatigue is a similar loss proximal to the neuromuscular junction.[106,107]

During muscle exercise, an increased sense of effort probably means that, for some reason, the exercise or contraction can only be continued at the expense of an increased intensity of cortical commands. The reasons for such changed command requirements are often peripheral (drop of force-producing capability in muscles) but may also be situated within the CNS (e.g. changes in neuronal and/or synaptic properties). The degree of fatigue in the muscles themselves may be estimated using, for instance, electrical stimulation for assessing whether their maximum force has decreased. Under some experimental conditions, the component of 'central fatigue' can be estimated by comparing the maximum force obtained voluntarily versus the force resulting from maximum voluntary plus electrical stimulation (e.g. the 'twitch interpolation technique').[108,109] The superimposed electrical stimulation adds more force at high than at low levels of central fatigue. In 'the superimposed electrical stimulation or twitch interpolation technique' the muscles are activated by applied electrodes. These electrodes are attached at the skin surface. During sustained isometric contractions the muscles are activated electrically. This activation creates a superimposed contraction. By means of this technique one can distinguish between fatigue components in the contracting muscle (peripheral fatigue) and components within the CNS (central fatigue).

In addition to central changes causing a less efficient central drive of the motor neurons, prolonged and intense bouts of motor exercise may also cause qualitative changes in the CNS control of movement, e.g. loss of coordination and increased correction-errors. Such aspects of 'central control fatigue' have been the subject of little experimental investigation to date.

1.3.3 The Motor Cortex

Large parts of the brain are involved in the production and control of motor behaviour. Many of the final commands seem to be channelled via the primary motor cortex, which is also one of the best known portions of the motor system (partly due to its accessibility for experimental investigation).

In conscious and intact humans, strong magnetic pulses may be used for activating the motor cortex transcranially, causing contractions and EMG responses to be facilitated and/or occur in various muscles.[106] By using this technique one is able to investigate the corticospinal tract by triggering the motor cortex and measuring the EMG signal and the produced mechanical output. The transcranial induced electromagnetic pulse evokes an activation of the neurons of the motor cortex. Via their action potentials these cortical neurons activate the motor neurons in the spinal cord. The final effect is a twitch contraction of the motor units of these motor neurons. These twitch contractions, the MEPs, can be recorded by the EMG. There is some delay between the transcranial magnetic pulse and the MEP due to the propagation time of the afferent signal from motor cortex to muscle fibre.[110]

Applying such techniques, it has been shown that the excitability of the motor cortex changes during a fatiguing muscle contraction. After transcranial stimulation of the motor cortex during voluntary isometric contractions, the return of the continuous EMG signal of the isometric voluntary contraction showed a delay of about 200 ms.[111] This delay lengthens during a sustained contraction of 2 minutes at MVC. These transcranial stimulating tests suggest a change in the neuronal activity of the motor cortex and are considered to be a sign of central fatigue.

Various investigations of normal and diseased nervous systems have led to the conclusion that the 'sense of effort', as felt during muscle contractions and motor exercise, somehow reflects the intensity of 'commands' issued from the

motor cortex.[112] Thus, this sensed information concerns internal CNS processes, reported via 'corollary discharges', rather than messages received from the periphery via sensory afferents. It is still unknown in which cortical region the 'sensing' of effort exactly takes place. The 'sense of effort' should be distinguished from a perception of the force produced. Usually, the effort is more easily assessed than force. However, under some conditions, some subjects may distinguish between these two modalities.[113]

1.3.4 The Core Temperature

In order to maintain a steady body temperature, extra body heat has to be dissipated.[114,115] In the last years, researchers have shown a clear link between hyperthermia and motor drive. The CNS is vulnerable to hyperthermia. Special neurons in the pre-optic area of the hypothalamus are sensitive for temperature changes, and the hypothalamus plays an important role in core temperature regulation.[116] During exercise, the contracting muscles produce heat, which acts upon the core temperature. Gonzalez-Alonso et al.[117] measured a gradual increase of the core temperature up to 40°C during prolonged exercise. If it exceeded 40°C, the central drive of the subjects faded away and they were unable to maintain the workload. A similar observation was obtained by Nielsen et al.[118] They measured the EEG activity of seven endurance-trained subjects during a gradual increase of core temperature. The subjects stopped at an average core temperature of about 39.8°C. Probably, a core temperature of about 40°C is a critical temperature. Reaching this core temperature reduces the central motor drive. Most likely the brain temperature during these circumstances could be an important limiting factor.[119]

Todd et al.[120] investigated the effect of increased core temperature at the isometric MVC and during transcranial magnetic stimulation tests of the motor cortex at MVC. The motor cortex excitability remained unchanged at increased core temperature, but the silent period in the EMG after the superimposed stimulus increased under these circumstances. Reza et al.[121] investigated the relationship between trans-

cranial magnetic stimulation of the motor cortex during voluntary contraction at different forces and its evoked silent period at the cortex using EMG recording. This silent period increased when the applied voluntary contraction force or torque decreased. These observations of Todd et al. and Reza et al. suggest that the increased core temperature induces an unknown inhibiting mechanism at the motor cortex. It is supposed that the thermoregulatory centres of the hypothalamus play a central role in this process.[120] The level of inhibition could be acting directly on the motor cortex or acting at a level before the motor cortex. NO-synthetase blockers were administered in the lateral ventricle of the brain in rats.[122] The exercise performance of these rats on rodent treadmills was reduced and they demonstrated a faster increase of body temperature compared with controls. After the exercise, the heat dissipation of the treated rats was reduced. The same researchers discovered that cerebral NO-synthetase blocking causes a decrease in the mechanical efficiency during rodent treadmill exercise in rats.[123] The cost of energy during exercise is therefore increased under these circumstances. Cheung and Sleivert[124] describe two models showing how exercise-induced hyperthermia might affect the motor drive of the CNS during exercise. One model states that during exercise the progressive heat loading is stressing the cardiovascular system, which in turn could limit the blood flow to the brain. Besides providing nutrition, the brain blood flow also drains heat. Therefore, a reduced brain blood flow is accompanied by a reduced brain heat loss. The other model suggests that the increased brain temperature may introduce the sensations of fatigue and the sense of effort during exercise directly.

1.3.5 Branched Chain Amino Acids and the Serotoninergic System

Skeletal muscle tissue consumes branched-chain amino acids (BCAAs; i.e. leucine, isoleucine, valine). This consumption of BCAAs is increased during exercise, i.e. the BCAA concentration in blood will then tend to decrease. BCAAs enter the brain using the same carrier

as tryptophan. Thus, if BCAA concentration goes down without a corresponding change in tryptophan level, more tryptophan will enter the brain. Tryptophan is the precursor of serotonin (5-hydroxytryptamine; 5-HT), an important transmitter substance in the brain.

Prolonged exercise has two effects. Firstly, the concentration of BCAAs decreases, thereby altering the ratio of tryptophan-BCAA entering the brain in favour of tryptophan. Secondly, prolonged exercise leads to increased levels of fatty acids in the blood (see figure 2). The increase in free fatty acids causes an increase in the ratio of free versus bound plasma tryptophan, which in turn causes a further increase in the amount of tryptophan entering the brain. The increased levels of brain tryptophan lead to an increase in the effects of serotoninergic transmission. The final net effect seems to be an increased level of tiredness, such as the level that is associated with going to sleep.[125] Inspired by these findings, some athletes try to counteract sensations of fatigue by consuming BCAA-containing drinks during prolonged exercise. Blomstrand et al.[126] found a decreased tryptophan uptake by the brain during a prolonged exercise of 180 minutes with carbohydrate supplementation. However, oral supplementation of BCAA or omega-3 fatty acids had no effect on the endurance time of the exercise.[127] The results of Blomstrand et al.[126] suggest a decrease in tryptophan uptake by brain tissue during exercise with carbohydrate supplementation. However, investigations by Cheuvront et al.[127] raise some doubts about the effectiveness of this carbohydrate supplementation.

1.3.6 The Role of Cytokines

In the last decade the release of cytokines has been the focus of scientific interest. Fatigue is one of the major complaints in medical practice and is usually one of the symptoms of disease. In most cases the immune system is activated during illness. This activated immune system reacts in a cascade of response reactions. Cytokines play an important role in these response reactions. There is an increase in several types of cytokines during illness. The 'sensation of fatigue' during illness induces indolent and sluggish behaviour, an adaptive response to minimize metabolism. A reduced metabolism consumes less energy, saving the energy stock. It is hypothesized that cytokines induce this adaptive behaviour. Skeletal muscle exercise is accompanied by increased production of several cytokines. It is hypothesized that the same kind of cytokines that acts at the onset of illness introduces sensations of fatigue during and after exercise.[128,134]

Cytokines form a heterogeneous group of small intercellular signalling proteins. They are produced *de novo* and secreted by many different cells. The same cytokine can be produced by different types of cells. The production of cytokines is induced by specific stimuli, such as an infection, physical and chemical stress, or traumatic events. The release of some cytokines can also trigger the release of other cytokines. Therefore, the kinematics of cytokine release is rather complex. Cytokines act on their target cells by binding at a special membrane receptor. After binding, the receptor is selectively stimulated by the cytokine and induces gene expression in these target cells via a second messenger. The final effects of the cytokine depend on the properties of its target cells.
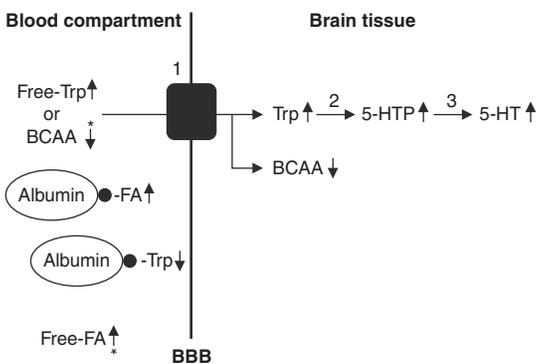
Fig. 2. Tryptophan brain uptake and synthesis of serotonin (5-hydroxytryptamine; 5HT) during prolonged exercise. **1** = the blood-brain barrier transporter; **2** = tryptophan hydroxylase; **3** = 5-hydroxy tryptophan decarboxylase; **BBB** = the blood-brain barrier; **BCAA** = branched chain amino acid; **FA** = fatty acid; **5-HTP** = 5-hydroxytryptophan; **Trp** = tryptophan. The vertical arrows indicate the increase or decrease of concentration, and the arrows with an asterisk (∗) are the effects introduced by the prolonged exercise.
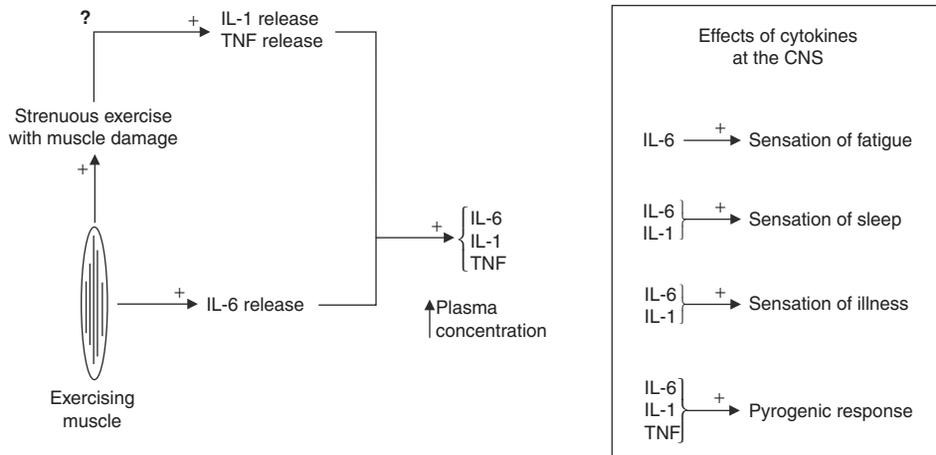
Fig. 3. Overview of the interaction between exercise and cytokines. During exercise muscle cells start to release an increasing amount of interleukin (IL)-6. During strenuous exercise, messenger RNA (mRNA) of IL-1 and tumour necrosis factor (TNF) is synthesized in the mechanically stressed muscle cells. It is likely that the transcription of these mRNAs is the source of elevated plasma concentrations of IL-1 and TNF. + indicates that the 'exercising' muscles release IL-6 and that the cytokines IL-6, IL-1 and TNF induce the described effects in the CNS; ? indicates that exercising muscles during strenuous exercise might release IL-1 and TNF; ↑ indicates increased.

Physical exercise is accompanied by increased blood plasma concentrations of interleukin-6 (IL-6).[128-131] It has been demonstrated that contracting muscles themselves are the source of the IL-6 that is produced during exercise.[131-133] The increase in IL-6 caused by physical exercise can be up to 50 times the baseline values during rest conditions.[134] Most likely, the recurrent calcium influx from the sarcoplasmatic reticulum to the sarcoplasm during muscle contraction is a major factor inducing IL-6 release from the muscles.[135] It is well known that strenuous muscle exercise, particularly eccentric exercise, is accompanied by muscle fibre damage introducing an inflammatory process post-exercise.[136] IL-6 is defined as a 'myokine', a cytokine that is released by exercising muscles.[137]

The final effect of the exercise-induced IL-6 release and perhaps of the inflammatory reaction of the 'post-exercising' muscle is an increase in many different cytokines[134,138] including IL-1 and tumour necrosis factor (TNF). The increase in IL-1 and TNF is probably induced by strenuous exercise.[139,140] This hypothetical mechanism is shown in figure 3. After intense endurance workloads of 2.5 hours' cycling[141] or 3 hours' running,[142] the amount of muscle cell messenger RNA (mRNA) for TNF and IL-1 was elevated. So probably, besides IL-6, the cytokines IL-1 and TNF are also produced by the active muscle cells. It is not known to what extent the myofibrillar damage caused by the mechanical stress of muscle cell contraction induces this synthesis of mRNA for IL-1 and TNF.[141,142]

The CNS is sensitive for some cytokines: IL-1 and IL-6 promote sleep,[143] and TNF, IL-6 and IL-1 have pyrogenic capabilities.[144] Administration of IL-6 in athletes introduced an increased sensation of fatigue and a reduced exercise performance.[145] Furthermore, IL-1 introduces sickness behaviour in animals.[146] The intensity of the sensations of illness in patients correlates with the levels of IL-1 and IL-6 spontaneously released from peripheral blood mononuclear cell cultures of these patients. There was no correlation between the sensations of illness and the plasma levels of IL-1 and IL-6.[147] These observations in animals and humans suggest that IL-1 and IL-6, among other factors, might introduce sensations of fatigue. Both interleukins are still increased post-exercise, thereby introducing exercise-avoiding behaviour because of
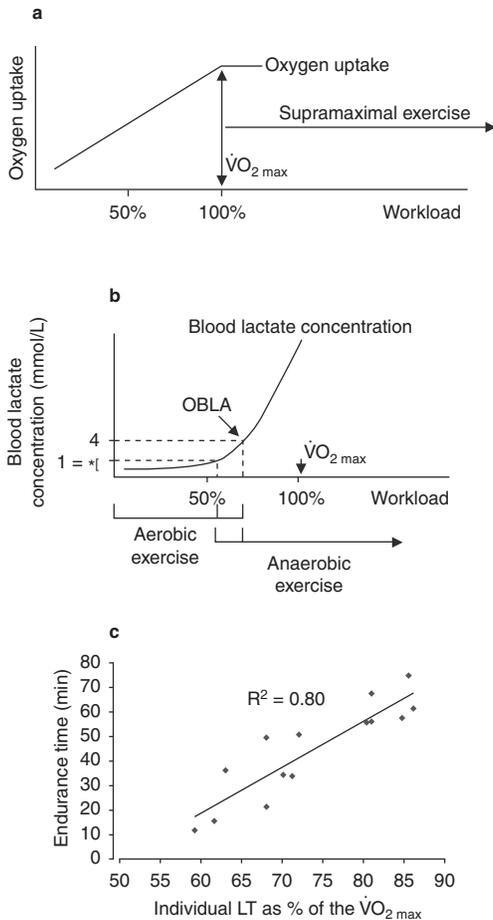
Fig. 4. Terminology used in exercise physiology and its physico-physiological meaning. (**a**) Relationship between workload and oxygen uptake. Workloads above maximal oxygen uptake ($\dot{V}O_{2max}$) are 'supramaximal workloads'. At these supramaximal workloads, most of the power is produced by type II muscle fibres, which generate their intracellular adenosine triphosphate (ATP; necessary for the cross-bridge interaction), by the glycolytic pathway and breakdown of creatine phosphate. (**b**) Relationship between workload and blood lactate concentration. The different definitions for the lactate threshold (LT; exceeding 1 mmol/L increase of the baseline) and the onset of blood lactate accumulation (OBLA; 4 mmol/L) are shown. In this graph, aerobic exercise is defined as the workload until the lactate threshold or OBLA has been reached. The anaerobic threshold is the workload beyond lactate threshold and OBLA. During aerobic exercise, muscle power is produced predominantly by type I muscle fibres, which generate most of their ATP via the aerobic pathway. The aerobic exercise ends at about 50% $\dot{V}O_{2max}$ in untrained subjects and at more than 80% $\dot{V}O_{2max}$ in very well trained subjects. (**c**) Relationship between LT and endurance time. The LT was defined as the workload at which the blood lactate concentration exceeded the 1 mmol/L of baseline. The endurance time was estimated during a workload at 88% $\dot{V}O_{2max}$ in 14 volunteers (data obtained from Coyle et al.[91]).

fatigue, which lasts for some period of time. It is not known whether the sense of effort (see section 2.1) is affected by these interleukins.

1.3.7 Brain Metabolism during Exercise

Cerebral blood flow is impaired during exercise.[148,149] This has been demonstrated by different techniques. Herholz et al.[148] used ^{133}Xe and Ide et al.[149] used near-infrared spectroscopy. Ultrasound Doppler methods showed an increase in blood velocity in the medial cerebral artery.[105,119,141,142,149-154] Nybo and Nielsen[154] demonstrated that this blood flow decreased during hyperthermia, suggesting an impaired cerebral blood flow. These results are contradicted by the findings of Madsen et al.,[155] who showed an increased blood velocity in the medial cerebral artery during dynamic exercise, but no increase in cerebral blood flow measured by [133]Xe. Most likely, these investigations reflect an enhanced brain tissue blood flow during exercise.

Brain metabolism alters during exercise. Madsen et al.[155] did not find a clear increase in brain oxygen uptake during exercise at a workload of 50% of the maximum oxygen uptake. Compared with resting levels, Ide et al.[149] found a decreased difference between the oxygen content of arterial versus venous blood at a workload of 30% of the maximum oxygen uptake. However, at a workload of 60% of the maximum oxygen uptake, the decrease was reversed into an increase. The same observations were found by Dalsgaard et al.[150] If cerebral blood flow increases during exercise, these observations suggest that oxygen uptake by brain tissue is increased, especially during intensive workloads.

In resting conditions, brain metabolism relies almost completely on the oxidation of glucose for its ATP production.[150] This means that the ratio of brain tissue oxygen uptake to brain glucose uptake is 6 : 1. During starvation, the oxidation of ketone bodies contributes to a considerable proportion (up to 25–50%) of brain metabolism.[156] The ratio of the cerebral oxygen/glucose uptake decreases during an exercise workload of 60% of the maximum oxygen uptake (Ide et al.[149]). However, this ratio first decreases during an exercise protocol with a graded workload till

exhaustion and then increases to resting levels in the last part of the exercise (Ide et al.[157]). In both experiments an uptake of blood lactate was measured in brain tissue. During exercise, brain tissue shows a disproportionately higher uptake from glucose and lactate than from oxygen. These observations suggest that exercise might have an anabolic effect on brain tissue.

Kemppainen et al.[158] investigated brain metabolism during exercise with [18]fluoro-deoxy-glucose positron emission tomography (PET). They investigated two groups of subjects, an exercise-trained group and a less trained group. The subjects exercised at three different workloads (30%, 55% and 75% of their maximum oxygen uptake) for 30 minutes. In general, glucose uptake in the brain decreased and showed a negative correlation with the obtained blood lactate concentration. Furthermore, the reduction in brain glucose uptake was more pronounced in the frontal brain areas. Even though there were no changes in the blood lactate concentration in both groups, the effect on brain glucose uptake reduction was more pronounced in the well trained group. It was hypothesized that the brain glucose uptake was reduced due to an increased brain lactate uptake with increasing exercise loads and that brain tissue used lactate in favour of glucose for its oxidative energy production.

2. Psychological Aspects of Exercise

2.1 Sensations Related to Exercise

The sensations of fatigue that develop during a sustained isometric contraction are different from the sensations of fatigue that develop during running a 42 km marathon. In both situations the sense of effort increases but the two types of exercise differ in the associated physiological effects and in the associated experienced sensations of fatigue. The sustained contraction leads to a marked accumulation of muscle metabolites. When running a marathon, there is a prominent depletion of the muscle glycogen stores. The day after prolonged isometric contraction one may not notice any lasting sensations associated with the exercise, while after a marathon one is likely to experience tiredness for one or several days. Thus, an increase of sense of effort might be associated with different patterns of 'fatigue'. As a psychological quantity, the 'sense of effort' reflects one's exercise capacity. From the physiological point of view, the 'sense of effort' reflects more or less the quality of the motor drive from the cerebral cortex to the motor neurons of the spinal cord.

It is supposed that the centrally generated motor commands create the sense of effort by a corticofugal feedback system.[2,112,159] In rats, collaterals of the corticospinal tract terminate at the striatum.[160-162] Therefore, the striatum receives an exact copy of the motor cortex output to the spinal cord. Exercise might change the steady state of the internal environment. Interoceptive afferents send back the actual physiological status of the internal environment to the CNS. It is not known which neuro-anatomical structures in the CNS generate the sense of effort and the sensation of fatigue. A synopsis of possibilities is shown by St Clair Gibson et al.,[163] who suggest that 'the sensation of fatigue' is the conscious awareness of changes in subconscious homeostatic control systems. During exercise this means a gradual shift from a subconscious to a conscious awareness. The homeostatic control systems of the CNS are situated in the nuclei of the brainstem and hypothalamus. These nuclei integrate the physiological changes of the internal environment and most likely modulate the higher centres of the brain. Finally, the highest centres of the brain are reached by creating an awareness of sensation of fatigue and sensation of exhaustion. The PET images from Laureys et al.[164] of the brains of people in four different states of consciousness are interesting, but also very sad. These different states were healthy people, patients with a 'locked in syndrome', patients with a 'minimal consciousness state' and patients with a 'vegetative state'. In these subsequent PET images the brain tissue glucose uptake decreased, especially in the medial posterior cortex (the precuneus or lobus quadratus). The glucose uptake by the precuneal cortex in the vegetative patient was hardly measurable. These authors[164] hypothesized that this mid-brain area, which is

situated posterior of the sulcus centralis, plays an important role in the state of consciousness. It is well known that the sensory input to the brain cortex is projected to and processed by the cerebral cortex posterior to the sulcus centralis. Based on the observations of Laureys et al.[164] and Cavanna and Trimble,[165] it is conceivable that the precuneus plays an important role "in the creation of awareness." Perhaps, this part of the brain cortex also plays an important role in the creation of the 'awareness of the sensation of fatigue' or 'awareness of the sense of effort' during exercise.

The sense of effort can also be affected by a decrease in the motor output because of physiological changes within the muscle itself. The pool of recruited motor units has to be extended in order to maintain the same motor output under these circumstances. This produces an increase of the pool or a change in firing frequency of active neurons of the motor cortex, which in turn may create an increase in the sense of effort. In this case one might also experience sensations of fatigue. However, this form of fatigue is not produced by changes in homeostatic control systems of the CNS, but by changes within the muscle itself.

2.2 Rating Points of Exertion (Borg Scale)

In the beginning of the sixties, Borg developed a psychophysical scale (Borg scale) that linked the experienced sensations of exertion to the performed exercise intensity.[4,166] These scales contain two variables, a 'physical component' and the 'perceived magnitude'. The latter is a psychological component and it represents the intensity of the perceived sensations during the exercise performance. The psychophysical scale represents the relationship between these two variables.[167] Two parameters estimate the physical properties of exercise, the type of exercise performed and the endurance time. In dynamic exercise there is a linear relationship between workload,[11,27,119] represented as $\dot{V}O_{2max}$, and heart rate (see figure 4). Other parameters can also be used, such as the percentage of MVC during isometric contractions.[168,169] Therefore, exercise workload can be represented by one of these parameters. The Borg scale contains 15

rating points of exertion (RPE). As a physical parameter, Borg used the heart rate during exercise.[4] There is a high correlation between these two parameters.[166,170]

It is hypothesized that cardiopulmonary, metabolic and other local afferents within the body cause the changes in perceived exertion during exercise. However, it is not clear how the CNS integrates these signals to the overall sense of exercise exertion. The afferent input to the heart muscle was manipulated in volunteers by using atropine and β-receptor blockers.[171,172] Atropine inhibits its parasympathetic innervation by blocking the acetylcholine receptor, β-receptor blockers inhibit its sympathetic innervation. Eklblom and Goldbarg found a nonsignificant increase of RPE after administration of nonselective β-adrenoceptor blockers (β-blockers) and atropine.[172] A similar effect of nonselective β-blockers on RPE was also found by others.[173,174] The effects of the selective $β_1$-blockers are less pronounced than the those of the nonselective agents.[173] The observations during prolonged exercise on cycle ergometers of RPE during differences in cadence of cycling are interesting. At a cycling rate of 40 rpm the RPE was higher than at 60 or 80 rpm.[175] These observations correspond to the observations of the optimal pedalling rate of about 90 rpm during competitive cycling.[176] Baron[177] found an optimal power output at about 100 rpm. These observations suggest that the RPE represents the essential sensitive information. This sensitive information enables the CNS to estimate the optimal power output during exercise.

2.3 The Teleoanticipatory System and Other Concepts

2.3.1 The Teleoanticipatory System
Ulmer[178] created the concept that a control system should exist which estimates the optimal power output to perform the goal of the exercise. This system contains a 'finishing point or the goal of the performed exercise' and a 'programme'. This 'programme' is able to 'estimate' the optimal power output to reach the 'goal of the performed exercise'. Ulmer[178] describes this system as a

'teleoanticipatory system' (teleos = final or last). This system could be compared with one of the important tasks of former flight engineers in aviation. The flight engineers calculated before a flight how much fuel an aeroplane should use to reach the destination at an optimal flying speed. Saving fuel is an important cost-reducing factor for aviation companies. During the flight the engineers measured fuel consumption continuously and recalculated how the destination of the flight could be achieved optimally. Ulmer[178] suggests that a similar system should also exist in the execution of human exercise. This 'teleoanticipatory system' contains a feed-forward component, which estimates the metabolic rate of exercise per time unit. A feedback control loop compares the actual metabolic rate with the estimated metabolic rate. For "a precise feed-forward calculation" it is necessary to have "a template which contains existing data of exercise performance."

If this 'teleoanticipatory system' exists in humans, it is interesting to contemplate whether this template is acquired by previous exercises (training) or whether this template is inborn. An essential parameter for the functioning of this system is the 'measurement of the energy turnover during the exercise'. It has been the scope of recent research to study how the CNS is able to estimate this turnover and how this 'metabolic rate measurement' is linked to the RPE.[170,178-180]

2.3.2 The Central Governor Model

Noakes[151-153] expects there must be a 'central governor' that matches 'the sensatory information of exercise' (feedback information) with 'the aim of exercise' (feed-forward information) – a system similar to Ulmer's. As an example he uses the 42 km marathon. The marathon is an endurance race of a little more than 2 hours. Haile Gebrselassie ran the Berlin marathon of 2007 just within 2 hours and 5 minutes. According to Noakes, this is only possible if there is a match between 'estimated workload' and 'performed workload'. There must be a centre in the body that obtains information on the maximum workload and maintains homeostatic control at the same moment. This concept is the 'central governor model' (CGM). Is the 'capability of

feed-forward estimation or calculation' one of the most important capabilities of the CNS in humans? Humans are able to give a preview and to work out a plan; we can act in this way because of the calculating capacity of our telencephalon. In other words the feed-forward capability in humans is well developed and has even reached abstract forms. So 'human feed-forward calculation' can be used during endurance exercise. This means that Noakes' central governor could be identified as a function of the higher centres of the CNS. Noakes states that his CGM explains all forms of exhaustion during exercise, including those exercises with an intense workload.[153]

2.3.3 The Catastrophic Failure Model

The opposite of the CGM is the model of 'catastrophic failure'.[151,153] In this model, exercise stops if one or more of the bodily systems are stressed beyond their capacity. For example, the limited oxygen and nutrition supply to exercising muscles leads to local intramuscular hypoxia and anaerobiosis, which is the cause of exhaustion. Weir et al.[181] debate Noakes' statement that the CGM explains all forms of exhaustion during exercise. They discuss the effect of accumulation of metabolites at exercise of full power output. For example, the decline in running speed during a 400 m athletics race is used as an argument. During every 100 m the average speed of the athletes declines by about 0.5 m/s (1.8 km/h). Therefore, the speed has reduced by about 7 km/h after 400 m. They wonder how far athletes are using a pacing strategy during these 400 m races, and how far is this decline of speed due to processes within the exercising muscle itself?

2.3.4 Arguments against the Central Governor Model

The authors of this manuscript also have their doubt about Noakes' concept of exercise-induced exhaustion in every form of exercise. First of all, a skeletal muscle is composed of different types of muscle fibres, ranging from fatigue-resistant (type I) to fast-fatiguable (type II) fibre types. Muscle fibres are recruited according to the size principle.[73] This means that at low exercise workloads, mainly type I fibres are recruited. If

the exercise workload gradually increases, type II muscle fibres are also recruited. The effect is an increase in performed workload. Type I fibres have a 'dominant mitochondrial metabolism',[182] suggesting that type I fibres are able to produce mechanical power when there is sufficient oxygen supply. Type II fibres have a higher glycolytic activity, indicating that type II fibres are able to produce power in the absence of sufficient oxygen supply. Therefore, sooner or later, lactate and proton accumulation will occur in these fibres. Proton accumulation causes a decrease in contraction force (see section 1.1.5). A second indication is the skeletal muscle metabolism during resting conditions. In muscles that contain mostly type I fibres, oxygen consumption is the highest and blood supply is the lowest. This suggests that the metabolism of muscles that contain mostly type II fibres relies on a higher amount of anaerobic metabolism that exists during resting conditions.[183,184]

The third argument comes from vertebrate evolution. Vertebrates and cephalochordates belong to the phylum of the chordata and have the same ancestor. The amphioxus, also called a lancelet, belongs to the cephalochordata and this animal has no skeleton, but a notochord. The CNS of the amphioxus, a tube-like structure, is studied nowadays to understand the early development of the CNS of the vertebrates (see Butler and Hodos[185]). The myotomes of the amphioxus possess superficial and deep muscle fibres.[186] The deep muscle fibres have type II (white fibre) morphology and the superficial muscle fibres have type I (red fibre) morphology.[187] These deep white muscle fibres are used in escape behaviour from predators.[186] To escape from predators is an all-or-nothing situation. The superficial red muscle fibres are used during undulating swimming, when the animals have prolonged periods of swimming during vertical migration.[186] In the larvae of the amphioxus these two different muscle fibre types are linked to two different neuronal circuits.[188] Amphioxus shows escape behaviour after triggering skin surface mechanoreceptors.[186] Primitive lower vertebrates such as agnatha, teleost fishes and amphibians possess one pair of giant Mauthner

neurons. These two Mauthner neurons are bilaterally situated near the synapse of the vestibular branch of the VIII nerve in the medulla oblongata.[185] The axons of these two Mauthner cells give collateral branches to each segment of the spinal cord, which terminate at the motor neurons of the white muscle fibres. Furthermore, these collaterals also trigger the descending axons of higher centres of the CNS, which innervate the motor neurons in the spinal cord. The Mauthner cells get afferents from the lateral line system (mechanoreceptors), the vestibulocochlear nerve (N VIII) and perhaps the visual system.[185] In the amphioxus, the escape system is also triggered by one pair of giant cells, the large paired neuron number 3.[188] Amphioxus and vertebrates have a common extinct ancestor. How far are these neuromuscular systems of these lower vertebrates analogues or homologues of those neuromuscular systems of the amphioxus larvae? In amphioxus larvae and in lower vertebrates, escape behaviour is mediated by a special neuronal locomotor system, which triggers the fast-fatigable type II muscle fibres. Because of the special properties of the type II muscle fibres, an instant high mechanical output, the animals are able to escape from predators in life-and-death situations. Accumulation of metabolites inside the type II muscle fibres, which affect the fibre contraction properties, is the concomitant consequence of the high power output by the type II muscles during escape. Therefore, the high muscular power output of these type II muscle fibres can be produced for only a short time. Muscular fatigue will decrease the power output. However, these fibres recover after the lifesaving escape. If fatigue develops in the muscle fibres during escape, the destiny for the animal is to be eaten.

To what extent can this escape be compared with the recruitment of type II muscle fibres during intense exercise? In higher vertebrates, including humans, the type I and II motor neurons of the spinal cord are to a large extent controlled by the neurons of the cerebral cortex via the corticospinal tract. So in higher vertebrates the dominant centres for motor control have shifted from hindbrain structures to forebrain structures. Humans are able to recruit the type I

and II motor neurons of the spinal cord gradually until MVC or intense workloads are reached during dynamic exercise (the size principle[73]). In fact, we are able to smoothly activate two evolutionary different muscle fibre systems. Despite this smooth gradual activation of the motor neurons, we notice to some extent how intensely and for how long we are able to sustain the produced power or contraction force. The higher the workload, the shorter the endurance time. If we choose exercise of high intensity, we accept that the endurance time is limited to a short period. In our opinion, it is better to distinguish between 'muscle fibre type I and type II exercise', which is based on the origin of the different tasks of motor output of the two muscle fibre types. The observation from one of the volunteers in our extremely exhausting treadmill experiments[40] (range of the endurance time was 30–160 seconds) is very interesting. During these intense exercises this volunteer said, "I wanted to maintain the running speed, but I noticed that my muscle power was fading away despite my motivated drive." He also said that this fading away of muscle power was a very unpleasant sensation for him. This volunteer was a well trained endurance time cyclist. How far did he show 'fibre type II exercise-avoiding behaviour'?

2.4 The Effect of the Intensity of the Workload

In the sixties, Rohmert[189] investigated the relationship between endurance time and isometric contraction. He found an inverse exponential relationship between applied isometric force and endurance time. One should realise that muscle blood flow is affected by contraction forces. An impaired blood flow reduces the endurance time of the contracting muscle. If skeletal muscle cells perform isometric contractions at high contraction forces, muscle blood perfusion is occluded by the high pressures inside the muscle compartment. Barcroft and Millen[190] found a complete occlusion of blood flow in calf muscles at 30% MVC. Lind et al.[191] demonstrated complete occlusion in the muscles of the forearm at 70% MVC. So, isometric contractions between 30% and 70% of MVC will lead to occlusion of muscle blood flow.

In dynamic exercise, endurance time is related to a subject's $\dot{V}O_{2max}$. The OBLA of a subject is somewhere between 50% and 80% of the $\dot{V}O_{2max}$ (figure 4). The OBLA of top athletes performing endurance sports like cycling, running or skating ranges between 70% and 80% of the $\dot{V}O_{2max}$. Exercises at workloads below OBLA can be maintained for very long times (figure 4), and they rely predominantly on the recruitment of type I muscle fibres. During these workloads, exhaustion is caused by emptying of the energy stock. The energy stock consists of glycogen stocks in muscle and liver tissue and of the stock formed by the fat tissue. Athletes need to eat and drink during the exercise in order to maintain their workload as long as possible. Cytokines probably play an important role in the release of glucose from intracellular glycogen and redistribution of glucose over the different types of cells. In isolated hepatocytes of rats it has been demonstrated that IL-6 reduces the intracellular glycogen stock.[192] One of the effects of IL-6 is the release of glucose by hepatocytes to maintain sufficient blood glucose concentrations during exercise.[193] Abdelmalki et al.[194] made some interesting observations. One hour prior to a prolonged treadmill run until exhaustion, rats received baclofen, a $GABA_B$ agonist. Control rats did not receive any drug. GABA is an inhibitory neurotransmitter. The endurance time of rats that had received baclofen was longer than the endurance time of control animals that had received placebo. The glycogen stock in liver and muscle tissue was more depleted in the baclofen-treated animals compared with the controls. It can therefore be concluded that baclofen boosts the glycogenolytic effect of IL-6 release of the exercising muscle.

At workloads above OBLA, the steady state of the internal environment cannot be maintained, because type II muscle fibres are also recruited. Under these circumstances, the homeostasis of the internal environment is affected by accumulation of lactate, ammonia, acid (proton loading) and body heat. Sooner or later the athlete has to stop or reduce the workload. To estimate a subject's OBLA, the blood lactate concentration is regularly

measured during a graded exercise with increasing workloads.[26,27]

It is possible to apply workloads above $\dot{V}O_{2max}$: the supramaximal workloads. Under these circumstances, a large part of the generated workload is produced by type II muscle fibres. During exercise loads far beyond the $\dot{V}O_{2max}$, the steady state within the muscle cell is the bottle neck. When exposed to these supramaximal workloads, the muscle cell ATP production has to rely on its cellular energy stock, creatine phosphate and glycogen. Glycogen and/or glucose are broken down to lactate and creatine phosphate to creatine and inorganic phosphate. These metabolites accumulate within the muscle cell itself, affecting the steady state. Most likely the endangerment of the intracellular steady state causes the EMG frequency spectrum to change to lower frequencies.[39,40]

3. Disease and Fatigue during Exercise

3.1 Diseases in General

3.1.1 General Aspects of Disease

Fatigue is one of the most often reported complaints during illness, and usually also the first symptom. Of the total number of people who died in the Netherlands in 2006, about 30% of deaths were caused by malignancies, and about the same percentage were caused by cardiovascular diseases. Lung diseases caused 10% of the total deaths (source: Statistics Netherlands; see www.cbs.nl). It is not known whether the Dutch data are comparable to the data of other countries. These diseases usually involve a long time (months to years) of deteriorating illness, which can affect a patient's exercise capacity tremendously. Especially in malignancies, the foremost complaints a long time before the disease is finally detected are often only malaise and fatigue, which affect the patient's exercise performance. It is of medical interest to know how pathological processes inside the body generate these sensations of fatigue and malaise, but the current knowledge is only fragmentary. In many cardiovascular diseases, cardiac output is often reduced, which has a direct effect on exercise capacity. In lung diseases, oxygen uptake and
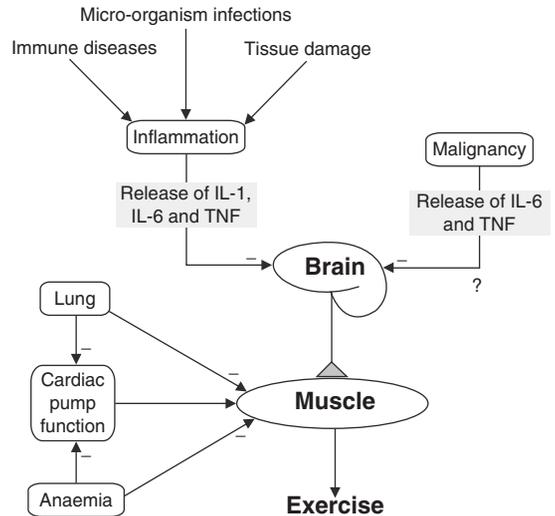
Fig. 5. Schematic view of how different kinds of diseases might influence exercise performance. Some links are not shown in this figure to keep this schematic view simple. Usually, malignancies induce inflammation reactions. Bone marrow malignancies can be accompanied by anaemia. Lung diseases such as chronic obstructive pulmonary disease are often accompanied with chronic inflammation. These links between the different diseases are not shown, but they enhance the symptoms of exercise-induced fatigue and malaise. **IL** = interleukin; **TNF** = tumour necrosis factor; – indicates the inhibiting effect on brain and muscle performance of the different cytokines and organ systems.

carbon dioxide output might be reduced. Diseases of the intestines affect the steady state of the internal environment, causing onset of fatigue symptoms at an earlier stage of exercise and a more prolonged recovery after exercise. In many illnesses more than one organ is affected. For example, malignancies, especially of bone marrow origin, are often accompanied by anaemia. Therefore, fatigue and exercise performance can be harmed by several mechanisms. Figure 5 shows how these different mechanisms can influence exercise performance.

3.1.2 Cytokines and Illness

Sick individuals experience malaise accompanied by fatigue and disinterest for daily activities. Animals also show 'sickness behaviour'. One of the important effects of sickness behaviour is a reduction in daily activities, which in turn lowers the daily energy expenditure. The 'sickness

behaviour of humans and animals' is an efficient strategy to reduce energy consumption during illness. The energy-saving strategy during such a period is to reduce muscular activity by a change in behaviour.

In many diseases the immune system is activated. The reason for this activation is usually an infection by micro-organisms (viruses or/and bacteria) or tissue damage by trauma.[195] The penetration of micro-organisms into the internal environment causes cell and tissue damage, which in turn may activate the immune system. Macrophages and mast cells are the first cells of the immune system to be activated. Activated macrophages release, amongst other cytokines, IL-1, IL-6 and TNFα.[128,136,146,196,197] During illness, the same cytokines are released as those causing fatigue sensations during exercise. Cytokines and other substances activate leukocytes during inflammation.

In one study, intraperitoneal administration of IL-1[198] in rats caused reduced social activities and feeding behaviour. Many researchers have observed a pyrogenic effect of IL-1 and IL-6, but most likely this was caused by the use of heterologous cytokines. Wang et al.[199] demonstrated that homologous IL-1 and IL-6 have no pyrogenic effect in animals when they are administered intraperitoneally. Recently, Blatteis[200] argued that cytokines possess no pyrogenic capacity themselves, but mediate the pyrogenic response. It is not known whether his observation regarding heterologous and homologous cytokines will affect the observations of many researchers in relation to sickness behaviour and other effects of cytokines. The current opinion is that the cytokines IL-1, IL-6 and TNFα play an important role in the pathogenesis of sensations of sickness and its accompanying behaviour in humans. During illness, humans show lethargic behaviour accompanied with sensations of fatigue and malaise (see figure 5).

3.1.3 Some Effects of Anti-Inflammatory Drugs

Autoimmune diseases often need prolonged medication. Usually the aim of the medication is to suppress the chronic inflammation, which can cause irreversible tissue damage. NSAIDs and corticosteroids have a potent anti-inflammatory effect. Corticosteroids induce catabolism, which can induce loss of skeletal muscle mass. This loss of muscle mass directly reduces exercise capacity. In animal studies, subcutaneous injections with dexamethasone for 3 weeks caused a decrease in the diameter of type I and II muscle fibres. The contraction properties of the muscles of these animals were also investigated *in vitro*. The diaphragm muscles of the dexamethasone-treated animals were less fatigue resistant than those of controls.[201] To the best of our knowledge, there is only one report about the effect of corticosteroids on the composition of muscle fibre types in humans.[202] In this study, transplanted kidney patients were observed, where one group received prednisolone and the other group was treated with an IL-2 receptor inhibitor. A shift in the type I/type II muscle fibre ratio towards more type II fibres was found in the prednisolone-treated patients. Based on these observations, it can be concluded that corticosteroids, especially when used chronically, can induce muscle fibre atrophy. This will in turn cause a reduction in total muscle mass, which negatively affects muscle contraction properties.

Contracting muscles adapt to the applied exercise workload by fibre proliferation after several weeks. This is a normal effect of training.[182,203] NSAIDs negatively affect these training effects in animals.[204] Therefore, care needs to be taken when using NSAIDs in sports injuries. Treatment of pain after sports injuries with NSAIDs relieves the pain in the first days, but can induce other sports injuries at a later time because of a decreased muscle fibre adaptation. Therefore, prolonged use of NSAIDs and corticosteroids during chronic illnesses induces muscle fibre atrophy and reduces muscle adaptations to exercise training. However, the first aim in these diseases is to reduce the intensity of the inflammation. Most likely this effect of reduced intensity in inflammation counterbalances its negative effect on the skeletal muscle properties, which overall might create better exercise performance and exercise-induced fatigue resistance. [See discussion between physicians ('*in vivo* research') and researchers ('clinical experience') in the *Journal of Bone Joint and Surgery*.[205]]

3.1.4 Vascular and Heart Diseases

One of the major effects of vascular and heart disease is a decrease in cardiac output and/or decrease in blood supply to organs and muscles. The amount of oxygen that can be transported per unit time from the lungs to the muscles depends on several factors. In healthy subjects these factors are the haemoglobin concentration and the cardiac output. In these healthy subjects the maximum cardiac output determines the $\dot{V}O_{2max}$ (see figure 4). Reduced cardiac output can have a dramatic effect on muscle oxygen uptake and muscle lactate formation. Usually during these diseases a reduction of the $\dot{V}O_{2max}$ is observed, which decreases one's exercise capacity.[206-208] Wasserman[208] showed that the ratio of oxygen uptake/performed workload remained normal in coronary artery patients, despite the reduced oxygen uptake. This decrease in oxygen uptake may be caused by a decrease in cardiac output due to myocardial ischaemia. Occlusion of the main arteries supplying muscle tissue can reduce exercise performance. An example of this is intermittent claudication. The predominant cause of cardiac pump malfunction and vascular occlusion is the occurrence of lesions in the arterial wall by arteriosclerosis. These lesions finally narrow the lumen of the artery. Arteriosclerotic lesions show IL-6[209] and TNF gene expression.[210] In arteriosclerosis, IL-6 levels are increased.[211] Ridker et al.[211] showed that there was a positive correlation between a higher baseline IL-6 blood concentration and myocardial infarction. Therefore, besides the negative impact of reduced cardiac output due to the myocardial ischaemia, the increased levels of IL-6 and TNF produced by the arteriosclerotic plaques can also cause prodromal symptoms of exercise-induced fatigue and symptoms of malaise (see sections 1.3.6 and 3.1.2). It is not known how the decreased muscle blood supply changes the exercise-induced IL-6 release of the contracting muscles. Is the proportion of IL-6 release the same as in contracting muscles with sufficient blood supply or is this muscle IL-6 release enhanced by the reduced blood supply?

In sports and rehabilitation, weight-lifting training programmes are used. The aim of these programmes is to improve total muscle mass and muscle strength.[182,203] Intense muscle contractions cause compression of the muscular vessels and capillaries. This vascular compression increases total peripheral resistance, creating an increase in arterial blood pressure.[212] An increase in arterial pressure elevates the systolic pressure in the left ventricle and increases the intramural pressure of the left ventricular wall during the systolic phase. The increase in intramural pressure reduces the coronary blood flow, but the higher arterial pressure during diastole increases this coronary flow.[213] It is not known whether increased systolic intramural pressure has an effect on myocardial perfusion during intense muscle contractions. How far do situations of intense isometric contraction force, like weight-lifting, impede myocardial perfusion? This could be clarified through research, if technically possible. Dynamic exercise training increases muscle blood flow and induces blood volume workload for the heart muscle.

Thus, isometric contractions cause pressure loading and dynamic exercises cause volume loading of the left ventricle. These two different haemodynamic effects of exercise need to be distinguished.

3.1.5 Malignancies

One of the first signs of malignancy is complaints of fatigue symptoms and complaints of malaise. Sometimes they are accompanied by a reduced capacity of exercise performance. Every physician becomes alert if a 50- to 60-year-old patient starts to show these symptoms. "Could these symptoms be caused by a malignancy?" is one of the thoughts in the physician's mind.

These prodromal complaints usually manifest months before the malignancy is finally diagnosed. What or which substances could cause these prodromal symptoms to occur? Every malignancy shows expansion of tumour mass and dissemination of its tumour cells. There are signs that an intact immune system is able to eliminate developing malignancies – an indication that there must be a system of immunosurveillance.[214,215] Thus there is an interaction between the immune system and the developing malignancy.[216]

Immunosuppressed transplant patients show a higher incidence of malignancies. In some cases of malignancy the immune system can promote tumour growth.[217] It has been demonstrated that TNF is capable of inducing a tumour-promoting inflammation in CT-26 colon cancer cells.[218,219] Therefore in some cases of malignancy these research observations suggest that the exercise-induced TNF release could stimulate tumour growth. In these circumstances the symptom of fatigue could have a protective role. Langowski et al.[220] discovered in several human tumours a significant RNA up regulation of IL-23. The same authors have demonstrated in mice that IL-12 might have a protective role in papillomas. Peake et al.[221] demonstrated an increase of IL-12 (subtype 40) after prolonged exercise (45–60 minutes) at moderate to intense workloads. Might exercise therefore play a protective role in some types of malignancy? Kim et al.[222] screened 242 colorectal adenoma cases and 631 controls for the prevalence of increased levels of IL-6 and TNFα. They found evidence of higher levels of IL-6 and TNFα in the patients with colorectal carcinoma. If we know that increased levels of IL-6 and TNF are linked with sensations of fatigue in humans and exercise-avoiding behaviour in animals (see section 1.3.6), this study suggests that the release of cytokines by malignant proliferation could play an important role in complaints of fatigue.

In summary, it is hypothesized that exercise could have different effects in malignancy. It might protect via exercise-induced IL-12 release in some malignancies and it might enhance some tumour types by exercise-induced TNF release. Are the prodromal symptoms of fatigue and malaise at the onset of the malignancy caused by tumour-induced release by cytokines? IL-1, IL-6 and TNF are the first candidates for further research.

3.1.6 Pulmonary Diseases

Pulmonary diseases can have a tremendous effect on exercise capacity. The lungs are the organs that exchange oxygen and carbon dioxide with the environment. The gas exchange relies on three important factors: (i) the diffusion of oxygen and carbon dioxide via the alveolar-capillary membrane; (ii) the alveolar blood supply; and (iii) the ventilation of the alveolar space. The amount of gases crossing the alveolar-capillary membrane by diffusion depends on the total surface area of alveolar-capillary membrane, the thickness of the membrane and the gas pressure difference on both sides of the membrane (Fick's Law[224]). The intercostal muscles and the diaphragm are responsible for adequate ventilation of the alveoli. These 'respiration' muscles are especially active during inspiration. During inspiration the elastine fibres of the sustaining tissues of the alveoli are stretched and a certain amount of the generated workload during inspiration is stored as potential energy in the stretched elastine fibres. The energy necessary for expiration is generated to a large extent by these stretched elastine fibres and a small proportion of the expiration energy is produced by the intercostal muscles and diaphragm. So the total cost of muscle energy during lung ventilation in normal people is minimized very efficiently.

The workload and the $\dot{V}O_{2max}$ are often reduced in pulmonary patients.[223] The response of the oxygen uptake after the onset of exercise is reduced compared with controls.[223] This is caused by several factors, i.e. a slower rate of increase in skeletal muscle metabolism, a high pulmonary blood flow resistance, and the reduced ability of the pulmonary vascular bed to dilatate to the changed haemodynamics.[223] In chronic obstructive pulmonary disease (COPD) patients, Wasserman[208] showed that the ratio of oxygen uptake/performed workload remained normal compared with controls, but that this ratio was decreased in patients with pulmonary hypertension.

In many pulmonary diseases, due to loss of alveolar tissue caused by the process of chronic inflammation, the total alveolar surface area is dramatically reduced. The effect is an increase in dead space. Furthermore, the elastic properties of lung tissue slacken. These lung tissue changes can have dramatic physiological consequences. The diffusion of carbon dioxide is 20 times faster than the diffusion of oxygen.[224] A hampered oxygen diffusion creates in the milder forms of disease a lower arterial oxygen pressure and perhaps also a decrease in arterial haemoglobin saturation.

In severe forms of hampered diffusion capacity an increased arterial carbon dioxide pressure might occur. For adequate alveolar ventilation the workload of the 'respiration muscles' changes to a much more intense one. The respiration muscles are also very active during expiration, in contrast to normal circumstances. Due to the inefficient saturation of haemoglobin, the cardiac muscle has to transport more blood to the organs for an efficient oxygen supply, so cardiac output can be increased. The lung tissue damage can also cause an increase in the total resistance of the capillary bed of the lung, which might create in turn an increase in the blood pressure of the lung arteries. This is an extra workload for the right ventricle of the cardiac muscle. All these pathological changes can create, finally, COPD, the endstage of many prolonged lung diseases. In severe forms of COPD the exercise capacity is reduced dramatically, creating disability. Furthermore, many lung diseases are caused by chronic inflammation accompanied by long-term release of cytokine IL-1, IL-6 and TNF, which act directly on the brain (see figure 5).

Beside these changes caused by decreased lung ventilation, changes inside skeletal muscle also occur. [An extensive review of muscle dysfunction in pulmonary disease can be found elsewhere.[225]] Biopsies of the quadriceps muscle (lower limb) of patients with moderate COPD demonstrated atrophy of the type II fibres and a reduction of the type I fibres. It was hypothesized that the chronic hypoxia and the reduced daily activities cause these changes in the muscle cells. Biopsies of the biceps brachii (upper limb) of patients with COPD showed no change in the type I/type II muscle fibre ratio, but the diameter of these fibres was slightly reduced. These histological changes could also be induced by the chronic use of corticosteroids.[201] The final effect of muscle fibre atrophy is reduced muscle mass, which in turn reduces muscle strength. The oxygen content in muscle tissue can be measured with near infrared spectroscopy. Patients with COPD showed a steeper decrease in the muscle tissue oxygen content during exercise than controls. Also, the recovery rate after exercise was longer in COPD patients.[226] These observations suggest a faster and longer muscle tissue hypoxaemia during and after exercise in the COPD patients.

3.1.7 Anaemia

Several diseases cause anaemia, which reduces blood oxygen transport capacity. This reduction of oxygen capacity negatively affects the $\dot{V}O_{2max}$. The effect is that the blood supply to organs has to be increased to supply them with the same amount of oxygen. So at lower workloads cardiac output reaches maximum. Bone marrow malignancies are often accompanied by anaemia. In these circumstances, i.e. malignancy and anaemia, exercise performance could be reduced by several mechanisms (see figure 5).

3.2 Chronic Fatigue Syndrome and Overtraining Syndrome

3.2.1 Chronic Fatigue Syndrome

In patients with chronic fatigue syndrome (CFS) the sense of effort is increased. The exercise performance of these patients compared with controls is conflicting. Some investigators find reduced maximal workloads and maximal heart rates during incremental exercise tests in CFS patients.[227,228] However, during these incremental exercise tests there was no difference in physiological response of different variables like heart rate, maximum oxygen uptake and lactate metabolism with respect to workload.[227-230] So most likely the baseline of the sense of effort is changed in CFS patients, causing reduced maximal exercise performances under 'normal circumstances'.

Some researchers have stated that cytokines might play a role in the pathogenesis of CFS,[231] but others showed no change in the release of the cytokines IL-1 and IL-6 after exercise.[232,233] A systematic check-up by Di Giornio et al.[234] demonstrated a subtle alteration in the hypothalamic-pituitary-adrenal axis (HPA axis).

Recently, researchers of the Nijmegen Expert Centre of Chronic Fatigue discovered by MRI a reduced thickness of the cerebral cortex in female patients with CFS.[235] They found a relationship between the level of physical activity capacity and the reduction in grey matter. If their observation is correct, it is important to know which factor is responsible for this reduction. Is this caused by a

reduction in cortical neurons or by a reduction in the neuron-supporting cells, such as astrocytes? De Lange et al.[235] also suggest that the brain cortex is directly involved in the generation of the sensation of fatigue. It is likely that the fatigue symptoms in CFS patients have a neurological origin, changing the subjects' perception and changing the circadian rhythm of the HPA axis.

3.2.2 Overtraining Syndrome and the Neuroendocrine System

An example of hormonal effects that may be involved in (central) exercise-related fatigue is given by findings in relation to 'overtraining', i.e. a late stage of intense and prolonged training during which the exercise performance declines instead of becoming progressively better. It is hypothesized that, under these conditions, there is a disturbance in the feedback regulation of corticosteroids.

In healthy subjects the blood concentration of cortisol decreases in the early stages of a graded exercise and increases in the final stages when high workloads are being experienced.[27] During exercise levels at about 60% of $\dot{V}O_{2max}$, the concentration of cortisol starts to rise after about 1 hour.[236]

In the early stages of overtraining in athletes, the adrenal response to corticotropin (adrenocorticotropic hormone) is reduced and finally the HPA axis becomes deregulated, with seriously impaired corticotropin and concomitant cortisol responses.[237] Urhausen et al.[238] measured a higher plasma renin activity at unusually low workloads and a reduced endurance time (≈27%) in overtrained athletes during endurance stress tests (83% of $\dot{V}O_{2max}$). This suggests that there might be a link between the neuroendocrine system and higher CNS functions involved in exercise performance and perhaps the sense of effort.

Another hypothesis for the cause of overtraining is the chronic mechanical overload from the frequent training sessions, which induces microtrauma. These microtrauma in turn induce a chronic inflammation reaction accompanied by the activation of cytokines, especially IL-6, IL-1 and TNFα. This overtraining model is described by Smith.[239] Steinacker et al.[240] hypothesize

that the skeletal muscle itself produces unknown feedback signals that act at the HPA axis. The symptoms of the overtraining syndrome improve if the intensity of training is reduced or stopped.[241] This phenomenon – reducing or stopping training intensity for a period and the concomitant improvement in overtraining symptoms – is an indication of the protective role of the sensation of fatigue.

4. Conclusions

'Exercise-induced fatigue' is a poorly understood phenomenon that intrigues many researchers. Prolonged exercise is a very energy-consuming process, affecting fuel stocks in the long term. Exercise might also have deleterious effects on the homeostasis of the internal environment, causing accumulation of muscle metabolites and of muscle-produced heat. The sensation of fatigue is a psychophysical quantity that eventually will change the subject's behaviour 'for their own safety'. Decades ago, the scope of research was entirely just the contracting muscle itself. The mechanical output of the muscle could be reduced by factors within the muscle. Later it was discovered that exercise could introduce an intense shift in the homeostasis of the internal environment.

In the last two decades, the CNS has become the main focus of interest. It was shown that exercise induces signs of fatigue in the CNS. New techniques such as transcranial stimulation of the brain cortex by electromagnetic pulses and brain blood flow measurements by functional MRI and PET are important tools for studying the brain during exercise experiments.

However, many phenomena remain unclear. It is questionable whether the phenomenon of 'the sensation of exercise-induced fatigue' will be fully understood, because it is a conscious awareness. Which structures of our brain are involved in consciousness? The brain cortex plays a very important function in our cognitive skills and perhaps also in awareness of consciousness. However, lower centres of the CNS are necessary for proper functioning of the brain cortex. This means that consciousness, and most likely 'sense

of fatigue during exercise' and 'motor drive', are the result of the interaction between many brain centres. A defect in one of these centres might affect one's exercise properties. We have to realise that 'exercise-induced fatigue' and 'motor drive' are opposite entities within the scope of interest of both physiologists and psychologists.

In the last two decades the physiological effects of cytokines have been investigated. Exercising muscles release IL-6. Several researchers have demonstrated increased blood concentrations of IL-1 and TNF. In athletes, IL-6 causes increased sensations of fatigue during exercise. Many diseases are accompanied by increased levels of IL-1, IL-6 and TNF. IL-1 induces sickness behaviour in animals. Therefore, the effects of the different cytokines on exercise-induced fatigue need to be explored in more detail. Perhaps these cytokines are the key to elucidating the prodromal symptoms of fatigue and malaise during malignancy.

Acknowledgements

References

1. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001; 81: 1725-89
2. Enoka RM, Stuart DG. Neurobiology of muscle fatigue. J Appl Physiol 1992; 72: 1631-48
3. Human muscle fatigue: physiological mechanism. Ciba Foundation Symposium no. 82. London: Pitman Medical 1981
4. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Health 1990; 16 Suppl. 1: 55-8
5. Lehninger AL. Contraction and motion (chapter 11). In: Lehninger AL, editor. Bioenergetics: the molecular basis of biological energy transformations. 2nd ed. New York: WA Benjamin Inc., 1971: 211-24 (ISBN 0-8053-6103-0)
6. Murray RK. Muscle (chapter 58). In: Murray RK, Granner DK, Mayes PA, et al., editors. Harper's Biochemistry. 23rd ed. Norwalk (VA): Appleton & Lange, 1993: 647-64 (ISBN 0-8385-3658-1)
7. Chance B, Eleff S, Leigh Jr JS, et al. Mitochondrial regulation of phosphocreatine/inorganic phosphate ratios in exercising human muscle: a gated 31P NMR study. Proc Natl Acad Sci U S A 1981; 78: 6714-8
8. Minotti JR, Johnson EC, Hudson TL, et al. Forearm metabolic asymmetry detected by 31P-NMR during submaximal exercise. J Appl Physiol 1989; 67: 324-9
9. Molé PA, Coulson RL, Caton JR, et al. In vivo 31P-NMR in human muscle: transient patterns with exercise. J Appl Physiol 1985; 59: 101-4
10. Sapega AA, Sokolow DP, Graham TJ, et al. Phosphorus nuclear magnetic resonance: a non-invasive technique for the study of muscle bioenergetics during exercise. Med Sci Sports Exerc 1987; 19: 410-20
11. Cooke R. Actomyosin interaction in striated muscle. Physiol Rev 1997; 77: 671-9
12. Lionne C, Brune M, Webb MR, et al. Time resolved measurements show that phosphate release is the rate limiting step on myofibrillar ATPases. FEBS Lett 1995; 364: 59-62
13. Lamb GD, Stephenson DG. Effects of intracellular pH and [Mg^{2+}] on excitation-contraction coupling in skeletal muscle fibres of the rat. J Physiol 1994; 478: 331-9
14. Potma EJ, van Graas IA, Stienen GJM. Effects of pH on myofibrillar ATPase activity in fast and slow skeletal muscle fibres of the rabbit. Biophys J 1994; 67: 2404-10
15. Karatzaferi C, Myburgh KH, Chinn MK, et al. Effect of an ADP analog on isometric force and ATPase activity of active muscle fibers. Am J Physiol 2003; 284: C816-25
16. Cooke R, Franks K, Luciani GB, et al. The inhibition of rabbit skeletal muscle contraction by hydrogen ions and phosphate. J Physiol 1988; 395: 77-97
17. Myburgh KH. Can any metabolites partially alleviate fatigue manifestations at the cross-bridge? Med Sci Sports Exerc 2004; 36: 20-7
18. Westerblad H, Bruton JD, Lännergren J. The effect of intracellular pH on contractile function of intact, single fibres of mouse muscle declines with increasing temperature. J Physiol 1997; 500: 193-204
19. Cooke R, Pate E. The effects of ADP and phosphate on the contraction of muscle fibers. Biophys J 1985; 48: 789-98
20. Metzger JM. Effects of phosphate and ADP on shortening velocity during maximal and submaximal calcium activation of the thin filament in skeletal muscle fibers. Biophys J 1996; 70: 409-17
21. Millar NC, Homsher E. Kinetics of force generation and phosphate release in skinned rabbit soleus muscle fibers. Am J Physiol 1992; 262: C1239-45
22. Stienen GJ, Roosemalen MC, Wilson MG, et al. Depression of force by phosphate in skinned skeletal muscle fibers of the frog. Am J Physiol 1990; 259: C349-57
23. Potma EJ, van Graas IA, Stienen GJM. Influence of inorganic phosphate and pH on ATP utilization in fast and slow skeletal muscle fibres. Biophys J 1995; 67: 2580-9
24. Potma EJ, Stienen GJM. Increase in ATP consumption during shortening in skinned fibers from rabbit psoas muscle: effects of inorganic phosphate. J Physiol 1996; 496: 1-12
25. Coyle EF, Coggan AR, Hemmert MK, et al. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. J Appl Physiol 1986; 61: 165-72
26. McArdle WD, Katch FI, Katch VL, editors. Exercise physiology: energy III and human performance. 4th ed. Baltimore (MD): Williams & Wilkins, 1996 (ISBN 0-683-05731-6)

27. Powers SK, Howley ET, editors. Exercise physiology: theory and application to fitness and performance. 2nd ed. Madison (WI) and Dubuque (IA): WCB Brown & Benchmark Publishers, 1994 (ISBN 0-697-12657-9)

28. Hayashi T, Wojtaszewski JF, Goodyear LJ. Exercise regulation of glucose transport in skeletal muscle. Am J Physiol 1997; 273: E1039-51

29. Frandsen U, Lopez-Figueroa M, Hellsten Y. Localization of nitric oxide synthase in human skeletal muscle. Biochem Biophys Res Commun 1996; 227: 88-93

30. Bradley SJ, Kingwell BA, McConell GK. Nitric oxide synthase inhibition reduces leg glucose uptake but not blood flow during dynamic exercise in humans. Diabetes 1999; 48: 1815-21

31. Mayes PA. Integration of metabolism and the provision of tissue fuels (chapter 29). In: Murray RK, Granner DK, Mayes PA, Rodwell PA, editors. Harper's Biochemistry. 23rd ed. Norwalk (VA): Appleton & Lange, 1993: 279-92 (ISBN 0-8385-3658-1)

32. Jeukendrup AE. Carbohydrate intake during exercise and performance. Nutrition 2004; 20: 669-77

33. Balog EM, Thomson LV, Fitts RH. Role of sarcolemma action potentials and excitability in muscle fatigue. J Appl Physiol 1994; 76: 2157-62

34. Lännergren J, Westerblad H. Action potential fatigue in single skeletal muscle fibres of Xenopus. Acta Physiol Scand 1987; 129: 311-8

35. Metzger JM, Fitts RH. Fatigue from high- and low-frequency muscle stimulation: role of sarcolemma action potentials. Exp Neurol 1986; 93: 320-33

36. Juel C. Potassium and sodium shifts during in vitro isometric muscle contraction, and the time course of the ion-gradient recovery. Eur J Appl Physiol (Pflügers Arch) 1986; 406: 458-63

37. Juel C. Muscle action potential propagation velocity changes during activity. Muscle Nerve 1988; 11: 714-9

38. Lindström L, Kadefors R, Petersén I. An electromyographic index for localized muscle fatigue. J Appl Physiol 1977; 43: 750-4

39. de Luca CJ. Myoelectric manifestations of localized muscular fatigue in humans. Crit Rev Biomed Eng 1984; 11: 251-79

40. Ament W, Bonga GJ, Hof AL, et al. Electromyogram median power frequency in exhausting exercise. J Electromyogr Kinesiol 1993; 3: 214-20

41. Ament W, Bonga GJ, Hof AL, et al. Electromyogram median power frequency in dynamic exercise at medium exercise intensities. Eur J Appl Physiol (Pflügers Arch) 1996; 74: 180-6

42. Jansen R, Ament W, Verkerke GJ, et al. Median power frequency of the surface electromyogram and blood lactate concentration in incremental cycle ergometry. Eur J Appl Physiol (Pflügers Arch) 1997; 75: 102-8

43. Buchthal F, Madsen A. Synchronous activity in normal and atrophic muscle. Electroencephalogr Clin Neurophysiol 1950; 2: 425-44

44. Datta AK, Stephens JA. Synchronization of motor units activity during voluntary contraction in man. J Physiol 1990; 442: 397-419

45. Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: cellular mechanisms. Physiol Rev 2008; 88: 287-332

46. Bigland-Ritchie B, Rice CL, Garland SJ, et al. Task-dependent factors in fatigue of human voluntary contractions (chapter 27). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms –advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 361-80 (ISBN 0-306-45139-5)

47. Garland SJ, Enoka RM, Serrano LP, et al. Behavior of motor units in human biceps brachii during a submaximal fatiguing contraction. J Appl Physiol 1994; 76: 2411-19

48. Fitts RH. Cellular mechanisms of muscle fatigue. Physiol Rev 1994; 74: 49-94

49. Lännergren J, Westerblad H. Force and membrane potential during and after fatiguing, continuous high-frequency stimulation of single Xenopus muscle fibres. Acta Physiol Scand 1986; 128: 359-68

50. Bergström M, Hultman E. Relaxation and force during fatigue and recovery of the human quadriceps muscle: relations to metabolite changes. Eur J Appl Physiol (Pflügers Arch) 1991; 418: 153-60

51. Pourmand R. Metabolic myopathies: a diagnostic evaluation. Neurol Clin 2000; 18: 1-13

52. Tsujino S, Nonaka I, DiMauro S. Glycogen storage myopathies. Neurol Clin 2000; 18: 125-50

53. Wolfe GI, Baker NS, Haller RG, et al. McArdle's disease presenting with asymmetric, late-onset arm weakness. Muscle Nerve 2000; 23: 641-5

54. Cady EB, Elshove H, Jones DA, et al. The metabolic causes of slow relaxation in fatigued human skeletal muscle. J Physiol 1989; 418: 327-37

55. Lamb GD, Stephenson DG, Stienen GJM. Effects of osmolality and ionic strength on the mechanism of Ca^{2+} release in skinned skeletal muscle fibres of the toad. J Physiol 1993; 464: 629-48

56. Meissner G. Ryanodine receptor/Ca^{2+} release channels and their regulation by endogenous effectors. Annu Rev Physiol 1994; 56: 485-508

57. Westerblad H, Allen DG. Myoplasmic free Mg^{2+} concentration during repetitive stimulation of single fibres from mouse skeletal muscle. J Physiol 1992; 453: 413-34

58. Allen DG, Westerblad H. Role of phosphate and calcium stores in muscle fatigue. J Physiol 2001; 536: 657-65

59. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. Am J Health Syst Pharm 2008; 65: 73-80

60. Marx SO, Reiken S, Hismatsu Y, et al. Phosphorylation-dependent regulation of ryanodine receptors: a novel role for leucine/isoleucine zippers. J Cell Biol 2001; 153: 699-708

61. Dulhunty AF, Laver D, Curtis SM, et al. Characteristics of irreversible ATP activation suggest that native skeletal ryanodine receptors can be phosphorylated via an endogenous CaMKII. Biophys J 2001; 81: 3240-52

62. Sjøgaard G, McComas AJ. Role of interstitial potassium (chapter 4). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 69-80 (ISBN 0-306-45139-5)

63. Sjøgaard G, Adams RP, Saltin B. Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. Am J Physiol 1985; 248: R190-6

64. Busse MW, Maassen N. Effect of consecutive exercise bouts on plasma potassium concentration during exercise and recovery. Med Sci Sports Exerc 1989; 21: 489-93

65. Medbo JI, Sejersted OM. Plasma K$^+$ changes during intense exercise in endurance-trained and sprint-trained subjects. Acta Physiol Scand 1994; 151: 363-71

66. Kearney MT, Cotton JM, Richardson PJ, et al. Viral myocarditis and dilated cardiomyopathy: mechanisms, manifestations, and management. Postgrad Med J 2001; 77: 4-10

67. Woodruff JF. Viral myocarditis: a review. Am J Pathol 1980; 101: 425-84

68. Gibson TC, Arnold J, Craige E, et al. Electrocardiographic studies in Asian influenza. Am Heart J 1959; 57: 661-8

69. del Castillo J, Katz B. The effect of magnesium on the activity of motor nerve endings. J Physiol 1954; 124: 553-9

70. Smith DO. Acetylcholine storage, release and leakage at the neuromuscular junction of mature and aged rats. J Physiol 1984; 347: 161-76

71. Feltz A, Trautmann A. Desensitization at the frog neuromuscular junction: a biphasic process. J Physiol 1982; 332: 257-72

72. Bigland-Ritchie B, Kukulka CG, Lippold OCJ, et al. The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. J Physiol 1982; 330: 165-78

73. Ghez C. Muscles: effectors of the motor systems (chapter 36). In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science (3rd ed). London: Prentice-Hall International, 1991: 548-63 (ISBN 0-8385-8068-8)

74. Sandercock TG, Faulkner JA, Albers W, et al. Single motor unit and fiber action potentials during fatigue. J Appl Physiol 1985; 58: 1073-9

75. Sieck GC, Fournier M. Changes in diaphragm motor unit EMG during fatigue. J Appl Physiol 1990; 68: 1917-26

76. Burke RE. Motor units: anatomy, physiology, and functional organisation (chapter 10). In: Brookhart JM, Mountcastle VB, Brooks VB, editors. Handbook of physiology, section 1: the nervous system (volume II, part I), motor control. New York: Oxford University Press, 1981: 345-442 (ISBN 0-683-01105-7)

77. Kernell D. Organized variability in the neuromuscular system: a survey of task-related adaptations. Arch Ital Biol 1992; 130: 19-66

78. Pette D, Staron RS. Transitions of muscle fiber phenotypic profiles. Histochem Cell Biol 2001; 115: 359-72

79. Coupland ME, Puchert E, Ranatunga KW. Temperature dependence of active tension in mammalian (rabbit psoas) muscle fibres: effect of inorganic phosphate. J Physiol 2001; 536: 879-91

80. Widrick JJ. Effect of P(i) on unloaded shortening velocity of slow and fast mammalian muscle fibers. Am J Physiol 2002; 282: C647-53

81. Lionikas A, Li M, Larsson L. Human skeletal muscle myosin function at physiological and non-physiological temperatures. Acta Physiol 2006; 186: 151-8

82. Saltin B, Gagge AP, Stolwijk JAJ. Muscle temperature during submaximal exercise in man. J Appl Physiol 1968; 25: 679-88

83. Ariano MA, Armstrong RB, Edgerton VR. Hindlimb muscle fiber populations of five mammals. J Histochem Cytochem 1973; 21: 51-5

84. Johnson MA, Polgar J, Weightman D, et al. Data on the distribution of fibre types in thirty-six human muscles: an autopsy study. J Neurol Sci 1973; 18: 111-29

85. Bigland-Ritchie B, Johansson R, Lippold OC, et al. Changes in single motor unit firing rates during sustained maximal voluntary contractions. J Physiol 1982; 328: 27P-8P

86. Bigland-Ritchie B, Johansson R, Lippold OC, et al. Changes in motoneuron firing rates during sustained maximal voluntary contractions. J Physiol 1983; 340: 335-46

87. Sacco P, Newberry R, McFadden L, et al. Depression of human electromyography activity by fatigue of a synergistic muscle. Muscle Nerve 1997; 20: 710-7

88. Fuglevand AJ, Keen DA. Re-evaluation of muscle wisdom in the human adductor pollicis using physiological rates of stimulation. J Physiol 2003; 549: 865-75

89. Kleine BU, Stegeman DF. Stimulating motor wisdom. J Appl Physiol 2007; 102: 1737-38

90. Brooks GA. Anaerobic threshold: review of the concept and directions for future research. Med Sci Sports Exerc 1985; 17: 22-34

91. Coyle EF, Coggan AR, Hopper MK, et al. Determinants of endurance in well-trained cyclists. J Appl Physiol 1988; 64: 2622-30

92. Heck H, Mader A, Hess G, et al. Justification of the 4 mmol/L lactate threshold. Int J Sports Med 1985; 6: 117-30

93. Goodman MN, Lowenstein JM. The purine nucleotide cycle. Studies of ammonia production by skeletal muscle in situ and in perfused preparations. J Biol Chem 1977; 252: 5054-60

94. Lowenstein JM. The purine nucleotide cycle revised. Int J Sports Med 1990; 11 Suppl. 2: S37-47

95. Di Prampero PE. Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 1981; 89: 143-222

96. Role LW, Kelly JP. The brain stem: cranial nerve nuclei and the monoaminergic systems (chapter 44). In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 3rd ed. Glenview (IL): Prentice-Hall International, 1991: 683-99 (ISBN 0-8385-8068-8)

97. Dodd J, Role LW. The autonomic nervous system (chapter 49). In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 3rd ed. Glenview (IL): Prentice-Hall International, 1991: 761-75 (ISBN 0-8385-8068-8)

98. Patla AE. Understanding the roles of vision in the control of human locomotion (review article). Gait Posture 1997; 5: 54-9

99. Garland SJ, Kaufman MP. Role of muscle afferents in the inhibition of motoneurons during fatigue (chapter 19). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 271-80 (ISBN 0-306-45139-5)

100. Hagbarth KE, Macefield VG. The fusimotor system: its role in fatigue (chapter 18). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 259-70 (ISBN 0-306-45139-5)

101. Windhorst U, Boorman G. Overview: potential role of segmental motor circuitry in muscle fatigue (chapter 17). In:

Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 241-58 (ISBN 0-306-45139-5)

102. Bigland-Ritchie BR, Dawson NJ, Johansson RS, et al. Reflex origin for the slowing of motoneurone firing rates in fatigue of human voluntary contractions. J Physiol 1986; 379: 451-9

103. Martin PG, Smith JL, Butler JE, et al. Fatigue-sensitive afferents inhibit extensor but not flexor motoneurons in humans. J Neurosci 2006; 26: 4796-802

104. Martin PG, Weerakkody N, Gandevia SC, et al. Group III and IV muscle afferents differentially affect the motor cortex and motoneurons in humans: afferents inhibit extensor but not flexor motoneurons in humans. J Physiol 2008; 586: 1277-89

105. Nielsen J, Petersen N. Is presynaptic inhibition distributed to corticospinal fibres in man? J Physiol 1994; 477: 47-58

106. Gandevia SC, Allen GM, Butler JE, et al. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. J Physiol 1996; 490: 529-36

107. Westerblad H, Lee JA, Lännergren J, et al. Cellular mechanisms of fatigue in skeletal muscle. Am J Physiol 1991; 261: C195-209

108. Gandevia SC, Allen GM, McKenzie DK. Central fatigue: critical issues and practical implications (chapter 20). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 281-94 (ISBN 0-306-45139-5)

109. Merton PA. Voluntary strength and fatigue. J Physiol 1954; 123: 553-64

110. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985; 325 (8437): 1106-7

111. Taylor JL, Butler JE, Allen GM, et al. Changes in motor cortical excitability during human muscle fatigue. J Physiol 1996; 490: 519-28

112. McCloskey DI. Corollary discharges: motor commands and perception. In: Brookhart JM, Mountcastle VB, Brooks VB, editors. Handbook of physiology, section 1: the nervous system (volume II, part II), Motor control. New York: Oxford University Press, 1981: 1415-48 (ISBN 0-683-01105-7)

113. Jones LA. The senses of effort and force during fatiguing contractions (chapter 22). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 305-13 (ISBN 0-306-45139-5)

114. Brengelmann GL. Body temperature regulation (chapter 80). In: Patton HD, Fuchs AF, Hille B, et al., editors. Textbook of physiology, volume II. 21st ed. Philadelphia (PA): W.B. Saunders Company, 1989: 1584-96 (ISBN 0-7216-2524-X)

115. Johnson JM, Brengelmann GL, Hales JRS, et al. Regulation of the cutaneous circulation. Fed Proc 1986; 45: 2841-50

116. Nagashima K, Nakai S, Tanaka M, et al. Neuronal circuits involved in thermoregulation. Auton Neurosci 2000; 85: 18-25

117. Gonzalez-Alonso J, Teller C, Andersen SL, et al. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol 1999; 86: 1032-9

118. Nielsen B, Hyldig T, Bidstrup F, et al. Brain activity and fatigue during prolonged exercise in the heat. Eur J Physiol (Pflügers Arch) 2001; 442: 41-8

119. Nielsen B, Nybo L. Cerebral changes during exercise in the heat. Sports Med 2003; 33: 1-11

120. Todd G, Butler JE, Taylor JL, et al. Hyperthermia: a failure of the motor cortex and the muscle. J Physiol 2005; 563: 621-31

121. Reza MF, Ikoma K, Chuma T, et al. Mechanomyographic response to transcranial magnetic stimulation from biceps brachii and during transcutaneous electrical nerve stimulation of extensor carpi radialis. J Neurosci Methods 2005; 49: 164-71

122. Lacerda AC, Marubayashi U, Coimbra CC. Nitric oxide pathway is an important modulator of heat loss in rats during exercise. Brain Res Bull 2005; 67: 110-6

123. Lacerda AC, Marubayashi U, Balthazar CH, et al. Evidence that brain nitric oxide inhibition increases metabolic cost of exercise, reducing running performance in rats. Neurosci Lett 2006; 393: 260-3

124. Cheung SS, Sleivert GG. Multiple triggers for hyperthermic fatigue and exhaustion. Exerc Sport Sci Rev 2004; 32: 100-6

125. Newsholme EA, Blomstrand E. Tryptophan 5-hydroxytryptamine and a possible explanation for central fatigue (chapter 23). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 315-20 (ISBN 0-306-45139-5)

126. Blomstrand E, Moller K, Secher NH, et al. Effect of carbohydrate ingestion on brain exchange of amino acids during sustained exercise in human subjects. Acta Physiol Scand 2005; 185: 203-9

127. Cheuvront SN, Carter 3rd R, Kolka MA, et al. Branched-chain amino acid supplementation and human performance when hypohydrated in the heat. J Appl Physiol 2004; 97: 1275-82

128. Ostrowski K, Hermann C, Bangash A, et al. A trauma-like elevation of plasma cytokines in humans in response to treadmill running. J Physiol 1998; 513: 889-94

129. Ostrowski K, Rohde T, Zacho M, et al. Evidence that interleukin-6 is produced by skeletal muscle during prolonged exercise. J Physiol 1998; 503: 949-53

130. Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans: effect of intensity of exercise. Eur J Appl Phsyiol (Pflügers Arch) 2000; 83: 512-5

131. Steensberg A, van Hall G, Osada T, et al. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. J Physiol 2000; 529: 237-42

132. Febbraio MA, Steensberg A, Keller C, et al. Glucose ingestion attenuates interleukin-6 release from contracting muscle in humans. J Physiol 2003; 549: 607-12

133. Helge JW, Stallknecht B, Pedersen BK, et al. The effect of graded exercise on IL-6 release and glucose uptake in human skeletal muscle. J Physiol 2003; 546: 299-305

134. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration and adaptation. Physiol Rev 2000; 80: 1055-81

135. Keller C, Steensberg A, Hansen AK, et al. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. J Appl Physiol 2005; 99: 2075-9

136. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil 2002; 81 Suppl. 11: S52-69

137. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005; 98: 1154-62

138. Pedersen BK. Exercise and cytokines. Immunol Cell Biol 2000; 78: 523-35

139. Ostrowski K, Rohde T, Asp S, et al. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol 1999; 515: 287-91

140. Tomiya A, Aizawa T, Nagatomi R, et al. Myofibers express IL-6 after eccentric exercise. Am J Sports Med 2004; 32: 503-8

141. Nieman DC, Davis JM, Henson DU, et al. Muscle cytokine mRNA changes after 2.5 h of cycling: influence of carbohydrate. Med Sci Sports Exerc 2005; 37: 1283-90

142. Nieman DC, Davis JM, Walberg-Rankin J, et al. Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after 3-h run. J Appl Physiol 2003; 94: 1917-25

143. Kapsimalis F, Richardson G, Opp MR, et al. Cytokines and normal sleep. Curr Opin Pulm Med 2005; 11: 481-4

144. Blatteis CM, Li S, Li Z, et al. Cytokines, PGE2 and endotoxic fever a re-assessment (review). Prostaglandins Other Lipid Mediat 2005; 76: 1-8

145. Robson-Ansley PJ, de Milander L, Collins M, et al. Acute interleukin-6 administration impairs athletic performance in healthy, trained male runners. Can J Appl Physiol 2004; 29: 411-8

146. Dantzer R. Cytokine-induced sickness behaviour: a neuro-immune response to activation of innate immunity. Eur J Pharmacol 2004; 500: 399-411

147. Vollmer-Conna U, Fazou C, Cameron B, et al. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychol Med 2004; 34: 1289-97

148. Herholz K, Buskies W, Rist M, et al. Regional cerebral blood flow in man at rest and during exercise. J Neurol 1987; 234: 9-13

149. Ide K, Horn A, Secher NH. Cerebral metabolic response to submaximal exercise. J Appl Physiol 1999; 87: 1604-8

150. Dalsgaard MK, Ide K, Cai Y, et al. The intent to exercise influences the cerebral O_2/carbohydrate uptake ratio in humans. J Physiol 2002; 540: 681-9

151. Noakes TD. Maximal oxygen uptake: "classical" versus "contemporary" viewpoints: a rebuttal. Med Sci Sports Med 1998; 30: 1381-98

152. Noakes TD. The Central Governor Model of exercise regulation applied to the marathon. Sports Med 2007; 37: 374-7

153. Noakes TD, St Clair Gibson A. From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans: summary and conclusions. Br J Sports Med 2004; 38: 511-4

154. Nybo L, Nielsen B. Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. J Physiol 2001; 534: 279-86

155. Madsen PL, Sperling BK, Warming T, et al. Middle cerebral artery blood velocity and cerebral blood flow and O_2 uptake during dynamic exercise. J Appl Physiol 1993; 74: 245-50

156. Hasselbalch SG, Madsen PL, Hageman LP, et al. Changes in cerebral blood flow and carbohydrate metabolism during hyperketonemia. Am J Physiol 1996; 270: E746-51

157. Ide K, Schmalbruch IK, Quistorff B, et al. Lactate, glucose and O_2 uptake in human brain during recovery from maximal exercise. J Physiol 2000; 522: 159-64

158. Kemppainen J, Aalto S, Fujimoto T, et al. High intensity exercise decreases global brain glucose uptake in humans. J Physiol 2005; 568: 323-32

159. Kernell D. Neuromuscular frequency-coding and fatigue (chapter 9). In: Gandevia SC, Enoka RM, McComas AJ, et al., editors. Fatigue: neural and muscular mechanisms – advances in medicine and biology (volume 384). New York & London: Plenum Press, 1995: 135-45 (ISBN 0-306-45139-5)

160. Lévesque M, Charara A, Gagnon S, et al. Corticostriatal projections from layer V cells in rat are collaterals of long-range corticofugal axons. Brain Res 1996; 709: 311-5

161. Parent M, Parent A. Single-axon tracing study of corticostriatal projections arising from primary motor cortex in primates. J Comp Neurol 2006; 496: 202-13

162. Reiner A, Jiao Y, del Mar N, et al. Differential morphology of pyramidal tract-type and intratelencephalically projecting-type corticostriatal neurons and their intrastriatal terminals in rats. J Comp Neurol 2003; 457: 420-40

163. St Clair Gibson A, Baden DA, Lambert MI, et al. The conscious perception of the sensation of fatigue. Sports Med 2003; 33: 167-76

164. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004; 3: 537-46

165. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006; 129: 564-83

166. Borg GAV. Physical performance and perceived exertion. Dissertation Lund University (Sweden), 1962

167. Borg E, Borg G. A comparison of AME and CR 100 for scaling perceived exertion. Acta Psychol (Amst) 2002; 190: 157-75

168. Allman BL, Rice CL. Perceived exertion is elevated in old age during an isometric fatigue task. Eur J Appl Physiol 2003; 89: 191-7

169. Hummel A, Läubli T, Pozzo M, et al. Relationship between perceived exertion and mean power frequency of the EMG signal from the upper trapezius muscle during isometric shoulder elevation. Eur J Appl Physiol 2005; 95: 321-6

170. Hampson DB, St Clair Gibson A, Lambert MI, et al. The influence of sensory cues on the perception of exertion during exercise and central regulation of exercise performance. Sports Med 2001; 31: 935-52

171. Davies CT, Sargeant AJ. The effects of atropine and practolol on the perception of exertion during treadmill exercise. Ergonomics 1979; 22: 1141-6

172. Ekblom B, Goldbarg AN. The influence of physical training and other factors on the subjective rating of perceived exertion. Acta Physiol Scand 1971; 83: 399-406

173. Eston R, Connolly D. The use of ratings of perceived exertion for exercise prescription in patients receiving β-blocker therapy. Sports Med 1996; 21: 176-90

174. Tesch PA, Kaiser P. Effects of β-adrenergic blockade on O_2 uptake during submaximal and maximal exercise. J Appl Physiol 1983; 54: 901-5

175. Pandolf KB, Noble BJ. The effect of pedaling speed and resistance changes on perceived exertion for equivalent power outputs on the bicycle ergometer. Med Sci Sports 1973; 5: 132-6

176. Kohler G, Boutellier U. The generalized force-velocity relationship explains why the preferred pedalling rate of cyclists exceeds the most efficient one. Eur J Appl Physiol 2005; 94: 188-95

177. Baron R. Aerobic and anaerobic power characteristics of off-road cyclists. Med Sci Sports Exerc 2001; 33: 1387-93

178. Ulmer H-V. Concept of extracellular regulation of muscular metabolic rate during heavy exercise in humans by psychophysiological feedback. Experientia 1996; 52: 416-20

179. Eston R, Faulkner J, St Clair Gibson A, et al. The effect of antecedent fatiguing activity on the relationship between perceived exertion and physiological activity during a constant load exercise task. Psychophysiology 2007; 44: 779-86

180. Eston RG, Lamb KL, Parfitt G. The validity of predicting maximal oxygen uptake from a perceptually-regulated graded exercise test. Eur J Appl Physiol 2005; 94: 221-7

181. Weir JP, Beck TW, Cramer JT, et al. Is fatigue all in your head? A critical review of the central governor model. Br J Sports Med 2006; 40: 573-86

182. Jones DA, Round JM. Training for power (chapter 6) In: Jones DA, Round JM, editors. Skeletal muscle in health and disease. Manchester: Manchester University Press, 1990 (ISBN 0-719031648)

183. Ferreira LF, McDonough P, Behnke BJ, et al. Blood flow and O_2 extraction as a function of O_2 uptake in muscles composed of different fiber types. Respir Physiol Neurobiol 2006; 153: 237-49

184. Marsh RL, Ellerby DJ. Partitioning locomotor energy use among and within muscles: muscle blood flow as a measure of muscle oxygen consumption. J Exp Biol 2006; 209: 2385-94

185. Butler AB, Hodos W. Comparative vertebrate neuroanatomy. Butler AB, Hodos W, editors. 2nd ed. Hoboken (NY): John Wiley & Sons Inc., 2005: 139-55, 221-39

186. Lacalli TC. New perspectives on the evolution of protochordate sensory and locomotory systems, and the origin of brains and head. Phil Trans R Soc 2001; 356: 1565-73

187. Bone Q. Evolutionary patterns of axial muscle systems in some invertebrates and fish. Am Zoologist 1989; 29: 5-18

188. Wicht H, Lacalli TC. The nervous system of amphioxus: structure, development, and evolutionary significance. Can J Zool 2005; 83: 122-50

189. Rohmert W. Ermittlung von Erholungspause für statische Arbeit des Menschen. Int Z Angew Physiol 1960; 18: 123-64

190. Barcroft H, Millen JLE. The blood flow through muscle during sustained contraction. J Physiol 1939; 97: 17-31

191. Lind AR, Taylor SH, Humpreys PW, et al. The circulatory effects of sustained voluntary muscle contraction. Clin Sci 1964; 27: 229-44

192. Kanemaki T, Kitade H, Kaibori M, et al. Interleukin 1β and interleukin 6, but not tumor necrosis factor α, inhibit insulin-stimulated glycogen synthesis in rat hepatocytes. Hepatology 1998; 27: 1296-303

193. Febbraio MA, Hiscock N, Sacchetti M, et al. Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. Diabetes 2004; 53: 1643-8

194. Abdelmalki A, Merino D, Bonneau D, et al. Administration of a $GABA_B$ agonist baclofen before running to exhaustion in the rat: effects on performance and on some indicators of fatigue. Inter J Sports Med 1997; 18: 75-8

195. Nathan C. Points of control in inflammation. Nature 2002; 420: 846-52

196. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. New Engl J Med 1999; 340: 448-54

197. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood and cognition. Psychol Rev 1998; 105: 83-107

198. Kent S, Bluthe RM, Dantzer R, et al. Different receptor mechanisms mediate pyrogenic and behavioral effects of interleukin-1. Proc Natl Acad Sci U S A 1992; 89: 9117-20

199. Wang J, Ando T, Dunn AJ. Effect of homologous interleukin-1, interleukin-6 and tumor necrosis factor-alpha on the core body temperature of mice. Neuroimmunomodulation 1997; 4: 230-6

200. Blatteis CM. Endotoxic fever: new concepts of its regulation suggest new approaches to its management. Pharmacol Ther 2006; 111: 194-223

201. Lewis MI, Monn SA, Sieck GC. Effect of corticosteroids on diaphragm fatigue, SDH activity, and muscle fiber size. J Appl Physiol 1992; 72: 293-301

202. Topp KS, Painter PL, Walcott S, et al. Alterations in skeletal muscle structure are minimized with steroid withdrawal after renal transplantation. Transplantation 2003; 76: 667-73

203. Tarnopolsky MA, MacDougall JD, Atkinson SA. Influence of protein intake and training status on nitrogen balance and lean body mass. J Appl Physiol 1988; 64: 187-93

204. Mishra DK, Fridén J, Schmitz MC, et al. Anti-inflammatory medication after muscle injury: a treatment resulting in short-term improvement but subsequent loss of muscle function. J Bone Joint Surg Am 1995; 77: 1510-9

205. Discussion between Swaak (physician) and Mishra (et al.). J Bone Joint Surg (Am) 1997; 79: 1270-1

206. Belardinelli R, Barstow T, Nguyen P, et al. Skeletal muscle oxygenation and oxygen uptake kinetics following constant work rate exercise in chronic congestive heart failure. Am J Cardiol 1997; 80: 1319-25

207. Lele SS, Macfarlane D, Morrison S, et al. Determinants of exercise capacity in patients with coronary artery disease and mild to moderate systolic dysfunction. Eur Heart J 1996; 17: 204-12

208. Wasserman K. Diagnosing cardiovascular and lung pathophysiology from exercise gas exchange. Chest 1997; 112: 1091-101

209. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. Atherosclerosis 1996; 127: 263-71

210. Rus HG, Niculescu F, Vlaicu R. Tumor necrosis factor-alpha in human arterial wall with atherosclerosis. Atherosclerosis 1991; 89: 247-54

211. Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000; 101: 1767-72

212. Johnson JM. Circulation to skeletal muscle. In: Patton HD, Fuchs AF, Hille B, et al., editors. Textbook of physiology, vol. 2. 21st ed. Philadelphia (PA): W.B. Saunders Company, 1989: 87-889 (ISBN 0-7216-2524-X)

213. Pijls NHJ, de Bruyne B. The coronary circulation (chapter 2). In: Coronary pressure. 2nd ed. Boston (MA): Kluwer Academic Publishers, 2000 (ISBN 0-7923 6170 9)

214. Shankaran V, Ikeda H, Bruce AT, et al. IFNγ and lymphocytes prevent primary tumour development and shape tumor immunogenicity. Nature 2001; 410: 1107-11

215. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006; 90: 1-50

216. Bui JD, Schreiber RD. Cancer immunosurveillance, immunoediting and inflammation: independent or interdependent processes? Curr Opin Immunol 2007; 19: 203-8

217. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004; 22: 329-60

218. Luo JL, Kamata H, Karin M. IKK/ NK-κB signaling: balancing life and death – a new approach to cancer therapy. J Clin Invest 2005; 115: 2625-32

219. Luo JL, Maeda S, Hus LC, et al. Inhibition of NK-κB in cancer cells converts inflammation-induced tumor growth mediated by TNFα to TRIAL-mediated tumor regression. Cancer Cell 2004; 6: 297-305

220. Langowski JL, Zhang X, Wu L, et al. IL-23 promotes tumour incidence and growth. Nature 2006 Jul 27; 442 (7101): 461-5

221. Peake JM, Suzuki K, Hordern M, et al. Plasma cytokine changes in relation to exercise intensity and muscle damage. Eur J Appl Physiol 2005; 95: 514-21

222. Kim S, Keku TO, Martin C, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer Res 2008; 68: 323-8

223. Nery LE, Wasserman K, Andrews JD, et al. Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. J Appl Physiol 1982; 53: 1594-602

224. Hlastala MP. Gas transport and exchange (chapter 53). In: Patton HD, Fuchs AF, Hille B, et al., editors. Textbook of physiology, volume II. 21st ed. Philadelphia (PA): W.B. Saunders Company, 1989: 1012-25 (ISBN 0-7216-2524-X)

225. American Thoracic Society and European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Med 1999; 159: S1-40

226. Hamaoka T, McCully KK, Quaresima V, et al. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation in healthy and diseased humans. J Biomedical Optics 2007; 12: 062105

227. Bazelmans E, Bleijenberg G, Van Der Meer JW, et al. Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity. Psychol Med 2001; 31: 107-14

228. Jammes Y, Steinberg JG, Mambrini O, et al. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. J Intern Med 2005; 257: 299-310

229. Sargent C, Scroop GC, Nemeth PM, et al. Maximal oxygen uptake and lactate metabolism are normal in chronic fatigue syndrome. Med Sci Sports Exerc 2002; 34: 51-6

230. Wallman KE, Morton AR, Goodman C, et al. Physiological responses during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports Exerc 2004; 36: 1682-8

231. Cannon JG, Angel JB, Ball RW, et al. Acute phase responses and cytokine secretion in chronic fatigue syndrome. J Clin Immunol 1999; 19: 414-21

232. Peterson PK, Sirr SA, Grammith FC, et al. Effects of mild exercise on cytokines and cerebral blood flow in chronic fatigue syndrome. Clin Diagn Lab Immunol 1994; 1: 222-6

233. Tomoda A, Joudoi T, Rabab E-M, et al. Cytokine production and modulation: comparison of patients with chronic fatigue syndrome and normal controls. Psychiatry Res 2005; 134: 101-4

234. Di Giorgio A, Hudson M, Jerjes W, et al. 24-Hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. Psychosom Med 2005; 67: 433-40

235. de Lange FP, Kalkman JS, Bleijenberg G, et al. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage 2005; 26: 777-81

236. Schwarz L, Kindermann W. β-Endomorphin, catecholamines, and cortisol during exhaustive endurance exercise. Int J Sports Med 1989; 10: 324-8

237. Lehmann M, Foster C, Dickhuth H-H. Gastmann. Autonomic imbalance hypothesis and overtraining syndrome. Med Sci Sports Exerc 1998; 30: 1140-5

238. Urhausen A, Gabriel HHW, Kindermann W. Impaired pituitary hormonal response to exhaustive exercise in overtrained endurance athletes. Med Sci Sports Exerc 1998; 30: 407-14

239. Smith LL. Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress? Med Sci Sports Exerc 2000; 32: 317-31

240. Steinacker JM, Lormes W, Reissnecker S, et al. New aspects of the hormone and cytokine response to training. Eur J Appl Physiol 2004; 91: 382-91

241. Kuipers H, Keizer HA. Overtraining in elite athletes: review and directions for the future. Sports Med 1988; 6: 79-92

Correspondence: *Wim Ament*, c/o Xendo BV, P.O. Box 137, 9700 AC Groningen, the Netherlands.
E-mail: wim.ament@xendo.com