Integration of the metabolic and cardiovascular effects of exercise

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

*Exercise Metabolism and Biochemistry Group, School of Sport and Exercise Sciences, University of Birmingham, U.K., †Eindhoven Systems Biology Group, Eindhoven University of Technology, The Netherlands, ‡Department of Cardiovascular Medicine, Medical School, University of Birmingham, U.K., and §Department of Medicine, Medical School, University of Birmingham, U.K.

Abstract

Most of the essays in this volume have adopted a reductionist approach and have focused on the biochemistry either in skeletal muscle or in the vascular wall. There is however a complex interaction between the biochemistry in the endothelium of the microvascular wall, the vascular smooth muscle and the skeletal muscle fibres involving signalling pathways in the three tissues and an intense exchange of signal molecules between them. In the present essay an integrative overview is given of this complex metabolic interaction and the impairments in it that lead to type 2 diabetes and cardiovascular disease. A reduced nitric oxide production by the (micro)vascular endothelium is identified as the key event and is reversible by regular exercise and a reduced

†To whom correspondence should be addressed (email a.wagenmakers@bham.ac.uk).
calorie intake. The chapter also contains a description of the complex metabolic network controlled by the inducible transcription factor nuclear factor-κB, that is activated in more advanced stages of the chronic diseases, and either leads to repair of the microvascular wall or to irreversible damage and the severe complications of end stage cardiovascular disease and type 2 diabetes.

**Introduction**

We will first summarize the wide variety of metabolic and functional benefits of regular exercise that occur at the level of the muscle and the (micro)vascular endothelium. Together they lead to maintenance of optimal health in trained individuals, who regularly perform a combination of endurance and resistance exercise. This will be followed by a discussion of the mal-adaptations in lean and obese sedentary subjects taking healthy, active man as the norm for reasons explained by Chakravarthy and Booth [1]. These impairments progress with ageing and are rapidly accelerated by obesity. Endothelial impairments seem to lead to a chronic underperfusion of skeletal muscle, resulting in suboptimal exposure of the muscle to nutrients, oxygen and hormones. In the period following meal ingestion this leads to disturbances in the distribution of nutrients between skeletal muscle, liver and adipose tissue, and large transient increases in the concentration of blood nutrient and insulin concentrations (loss of homoeostasis). During exercise the underperfusion (potentially affecting both skeletal muscle and the heart) leads to exercise limitations. In combination with the reduced maximal cardiac output and a low oxidative capacity of skeletal muscle (low content of mitochondria) this does not make exercise training into an attractive treatment option for affected patients. Atherosclerosis develops in feed and resistance arteries, but potentially also deep down into the microvasculature and probably contributes to the metabolic barriers and dysfunction of the (micro)vasculature. As all tissues in the body seem to suffer from this microvascular pathology, eventually tissue degeneration and multiple organ failure occurs and results in the severe complications of end stage diabetes and cardiovascular disease. NADPH oxidase and the complex metabolic network controlled by NF-κB (nuclear factor-κB) play important roles in the underlying mechanisms and make the final choice between tissue repair or destruction.

**Biochemistry and function of the (micro)vasculature and skeletal muscle in healthy, physically active individuals**

The combined essays in this volume carry the message that only a physically active lifestyle combining regular periods of both endurance and resistance exercise leads to optimal human health. As explained by Chakravarthy and Booth [1] this is in line with the lifestyle of our ancestors who existed as hunter-gatherers in the 50000–10000 BC period. It was in this period that
evolution via the ‘survival of the fittest’ principal selected the genes that most of us still carry today [1]. Endurance exercise activates the signals that lead to a high oxidative capacity, that induce mitochondrial biogenesis and that lead to a dense capillary network around the muscle fibres (Chapters 1 and 2). Resistance exercise leads to muscle protein anabolism and maintenance of a large muscle mass and strength (Chapters 5 and 6). As the muscle is continuously in a post-exercise state in subjects performing moderate- to high-intensity exercise ≥3 times per week, the insulin signalling cascade remains activated (Chapters 3 and 6). Regular exercise also leads to activation of glycogen synthase because of a regular lowering of the muscle glycogen stores (Chapter 3) and, therefore, to an increased extraction rate of glucose from the blood following ingestion of carbohydrate-containing meals. Regular exercise in trained muscles also leads to lipolysis and oxidation of intramuscular triglycerides, which are stored as lipid droplets next to the mitochondria (Chapter 4). This increases the ability of the muscle to extract plasma fatty acids and lipids from the blood in the period following a meal and guarantees maintenance of a plasma lipid profile with a low cardiovascular and diabetes risk (Chapter 7). Also the concentration of long-chain fatty acyl-CoAs, diacylglycerols and ceramides (fatty acid metabolites suggested to lead to insulin resistance) is kept low (Chapter 4).

In periods after meal consumption the blood insulin concentration rises and leads to recruitment of an increased number of muscle fibre capillaries (Chapter 10; Figure 1) and ensures high rates of glucose and triglyceride clearance by the muscle. A physically active lifestyle will therefore prevent large post-meal excursions in blood glucose and lipid concentrations as seen in sedentary subjects and patients with diabetes and insulin resistance. An increased buffering capacity of adipose tissue for the daily lipid flux also keeps plasma triglycerides low [2]. The responsiveness of the vascular endothelium to shear stress and other physiological stimuli is optimal too, leading to efficient opening of terminal arterioles, larger arterioles, resistance arteries and feed arteries during moderate- and high-intensity exercise (Chapter 9 and 11). The trained muscle, therefore, can increase blood flow 100-fold during high intensity aerobic exercise and can sustain exercise at high intensities for prolonged periods [3]. The trained individual also has high NOS (nitric oxide synthase) activities in the vascular endothelium and a high endothelial NO (nitric oxide) production in response to insulin and shear stress (Chapter 9). This will reduce vascular tone via its effect on the VSM (vascular smooth muscle) and prevent the development of high blood pressure. It has also been suggested that a high endothelial NO production prevents binding of leucocytes and reduces inflammation leading to atherosclerosis, and enhances training/shear stress induced angiogenesis (Chapters 9, 11 and 12) [4–6].

When master athletes (seniors) are compared with sedentary healthy elderly people then it is clear that the aforementioned benefits of regular exercise are maintained. However, ageing is inherently attended by a loss of
muscle oxidative capacity and a slow progressive loss of muscle mass (sarcopenia). Reductions in both can be kept to a minimum when the frequency and duration of the exercise is maintained at appropriate intensities. Continued exercise in elderly subjects greatly improves independence, mobility, strength, quality of life and wellbeing (Chapter 6). A continued mixed exercise programme will also keep shifts in the plasma lipid profile, increases in percentage body fat, loss of muscle fibre capillaries, endothelial (micro)vascular impairments, increases in blood pressure, atherosclerosis and increases in fasting blood insulin and glucose concentration to a minimum (Chapter 6). Rises in proinflammatory cytokines are also an important cause of insulin resistance in the elderly and will be reduced by exercise and potentially counteracted by the increased IL-6 (interleukin-6) production of the exercising muscles (Chapter 8).

The consequences of the switch to a sedentary lifestyle in the second half of the 20th century

As explained in the introduction, a major shift in physical activity has occurred in the second half of the 20th century with most adults and children today leading a sedentary lifestyle. A sedentary lifestyle seems to be compatible with an acceptable health in those individuals who manage to keep caloric intake low despite the challenges of today’s food quality and affluence. However, a major proportion of today’s world population combines the sedentary lifestyle with a positive energy balance, eating more calories than their energy expenditure, and consuming food with a high fat content. This abrupt change in lifestyle is regarded as the primary cause for the dramatic increase in obesity and chronic diseases in the last 20 years [7] (Chapters 8 and 13 for epidemiological evidence). The physiological consequences for human metabolism of being sedentary are the exact reverse of the benefits described for the physically active lean individuals with faster and bigger metabolic and functional changes occurring in obese than in lean subjects.

Metabolic and functional abnormalities in obese sedentary subjects and the metabolic syndrome

Obese subjects with normal fasting plasma glucose, were recently shown to have a blunted insulin-mediated microvascular recruitment in muscle (Chapter 10). Infusion of intralipid plus heparin (leading to high plasma fatty acid concentrations) and of TNF-α (tumour necrosis factor-α), an inflammatory cytokine that is high in obese subjects, elderly people and patients with type 2 diabetes (Chapter 8), also leads to an acute blunting of the insulin-mediated microvascular recruitment (Chapter 10). In healthy individuals a 40–50% increase in the number of perfused or recruited muscle capillaries is seen in response to low physiological increases in insulin concentration (Chapter 10). This will lead to an increase in the capillary
permeability surface area, which is a prerequisite for an insulin-induced increase in the transport of both insulin and glucose from the capillary lumen into the interstitium of the muscle [8,9] and, therefore, for insulin induced increases in muscle glucose uptake.

The mechanism which has been proposed for the insulin induced recruitment of muscle capillaries is that insulin binds to the insulin receptor on the endothelial cells of terminal arterioles leading to activation of Akt (protein kinase B) and eNOS (endothelial NOS) and increased NO production. NO then diffuses to the VSM in the terminal arteriolar wall leading to opening of the terminal arterioles and recruitment of additional muscle capillaries further downstream in the vascular tree (Figures 1 and 2 in Chapter 10).

Failure of insulin to increase the number of perfused muscle capillaries has not only been observed in humans with uncomplicated obesity, but also in obese Zucker rats, an animal model of the metabolic syndrome. The metabolic syndrome is a transition state with a high risk for type 2 diabetes (see Chapter 11 for an exact definition). In type 2 diabetic patients insulin failed to increase glucose uptake and the capillary permeability surface area [10].

Failure of insulin to increase the number of perfused muscle capillaries reduces the total amount of insulin and glucose that enters the muscle capillaries, reduces transport through the endothelial cell layer covering the capillary wall, and thus limits uptake in the interstitial fluid that surrounds the skeletal muscle fibres (Figure 1). This then leads to a reduced insulin and glucose concentration in the external milieu of the muscle fibres and a reduced activation of the insulin signalling cascade in muscle fibres. These recent discoveries have important implications for our understanding of the mechanisms leading to insulin resistance as (i) insulin resistance may simultaneously occur at the level of the microvascular endothelium and in the muscle fibres; (ii) a defect in muscle capillary recruitment occurs in clinically uncomplicated obese subjects and thus seems to be an early event in the pathogenesis leading to insulin resistance and type 2 diabetes; and (iii) this defect reduces the insulin concentration seen by the insulin receptor in the muscle plasma membrane and thus prevents activation of the insulin signalling cascade in the skeletal muscle fibres.

**Further metabolic implications of impaired capillary recruitment by insulin**

The supply of amino acids, fatty acids and triglycerides (to be split by lipoprotein lipase present on the endothelium of the muscle capillary bed; Figure 1) are also reduced by impaired insulin induced capillary recruitment. Therefore hyperaminoacidaemia and hypertriglyceridaemia result because of a failure of muscle clearance of meal-derived amino acids and triglycerides from the circulation (Chapter 7). A muscle capillary recruitment defect may also explain the reduction of diet-induced thermogenesis in obese subjects and patients with type 2 diabetes and the reduced insulin-induced increase in
Figure 1. Insulin induced opening of terminal arterioles leads to recruitment of more muscle capillaries in the period following meal ingestion (top of Figure 1). As a consequence, more insulin, glucose, amino acids, and fatty acids (FA) will be transported over the endothelial layer of the muscle capillaries and penetrate into the interstitial fluid surrounding the muscle fibres. This then leads to increased uptake of these nutrients in the muscle. The higher concentration of insulin activates the insulin signalling cascade in muscle and leads to translocation of GLUT4 (Chapters 5 and 6) and FAT (fatty acid translocase; Chapter 4), and higher rates of amino acid uptake. The higher insulin concentration also leads to an increased stimulation of glycogen synthesis, protein synthesis, and triglyceride synthesis. Failure of this opening mechanism in insulin-resistant states (obesity, type 2 diabetes, and cardiovascular disease) leads to high blood concentrations of glucose, triglycerides, amino acids, and insulin in the postprandial period (following ingestion of mixed meals). Note that capillary recruitment increases the access of VLDL-TG (very low density lipoprotein-triglyceride) and CM-TG (chylomicron-TG) to muscle capillary LPL (lipoprotein lipase). Also note that insulin in contrast with exercise does not increase the rate at which red blood cells travel through individual capillaries and does not increase total muscle blood flow (see Chapter 10 for detailed explanation). The latter may increase 100-fold during high-intensity exercise [3].
muscle ATP turnover that has recently been observed in the offspring of type 2 diabetic parents [11,12]. Reduced recruitment of muscle capillaries will prevent insulin and other anabolic hormones and growth factors reaching the muscle plasma membrane and will reduce escape of locally produced hormones (e.g. cortisol and noradrenaline) into the circulation. This will acutely change muscle metabolism (e.g. reduced protein synthesis, increased protein degradation and increased lipolysis). A long-term change of the external milieu of the muscle fibres is likely to change the expression of genes and the protein profile and to contribute to the molecular adaptation and tissue degeneration that is observed in the chronic diseases.

**The metabolic network leading to insulin resistance in endothelial cells and skeletal muscle fibres**

The molecular mechanisms that have been proposed to lead to insulin resistance in the microvascular endothelium and in skeletal muscle fibres are initiated by the same signals and seem to involve the same pathways [13–16]. A high flux of fatty acids (Chapters 4 and 7) originating from enlarged adipose tissue stores is assumed to lead to increases in long-chain fatty acylCoA and diacylglycerol concentrations and to activate the PKC (protein kinase C) isomers β and θ (Figure 2). The PKC-isomers are serine kinases which are able to phosphorylate the insulin receptor and IRS-1 (insulin receptor substrate-1) on specific serine residues thus preventing insulin-induced tyrosine phosphorylation and activation of the insulin signalling cascade (Chapter 4). PKC-β is chronically activated in the muscle of obese subjects [13] and PKC-θ in patients with type 2 diabetes [14]. PKC-β can also be switched on in the muscle of healthy lean subjects by acute 5–6 h infusions of intralipid plus heparin [15]. In skeletal muscle PKC activation leads to reduced GLUT-4 (glucose transporter 4) translocation (Chapters 3 and 4). In the vascular endothelium it leads to attenuation of insulin induced NO production and reduced recruitment of muscle capillaries (Figure 2) [16].

Activation of the inducible transcription factor NF-κB (see below) has also been implicated in serine phosphorylation of IRS-1, again both in the microvascular endothelium and the muscle [15,17–19]. NF-κB is activated in cultured endothelial cells by high fatty acid levels [18], high glucose concentrations [19] and inflammatory cytokines of the TNF superfamily [20,21].

**Impairments in flow (shear stress)-mediated increases in muscle perfusion**

Vasodilation of feed and resistance arteries and of larger arterioles is essential for the massive increase in total muscle blood flow seen during exercise [3]. Vasodilation of these larger vessels is in part achieved by the effects of shear stress (physical interaction of the high blood flow with
Figure 2. The mechanisms leading to reduced NO production in the endothelium of the microvasculature

Increases in insulin, VEGF (vascular endothelial growth factor) and shear stress stimulate endothelial NO production via activation of the insulin signalling cascade. High fatty acid levels lead to high intracellular concentrations of long chain fatty acylCoA’s (FAcylCoA) and diacylglycerol. These fatty acid metabolites activate the protein kinase C isomers PKC-β or -θ, which then phosphorylate IRS-1 on specific serine residues preventing the normal activation of IRS-1 by tyrosine phosphorylation. This prevents eNOS phosphorylation by activated Akt and reduces NO production and smooth muscle cell relaxation. Activation of NADPH oxidase in the endothelium of patients with the chronic diseases leads to superoxide anion production which takes away NO via the formation of peroxynitrite. TNF-α and other members of the TNF superfamily activate NADPH oxidase via a direct mechanism involving activation of PKC-ζ and via a number of indirect mechanisms. TNF-α increases activity and nuclear translocation of NF-κB. This leads to the increased expression of cellular adhesion molecules (CAM) playing a role in the binding of leukocytes. Secondary cytokines produced by the leukocytes and macrophages lead to local inflammation processes in the (micro)vascular wall, attract platelets and destroy the normal endothelial barrier function among others leading to the uptake of oxLDL (oxidized low density lipoprotein), which contains lysophosphatidylcholine a known activator of NADPH oxidase. The platelets produce lysophosphatidic acid (LPA) another signal molecule that activates NADPH oxidase. Hypertension activates NADPH oxidase both via mechanisms involving increases in angiotensin II and increased strain. Finally the enzyme eNOS itself can produce oxygen free radicals via uncoupling due to a low availability of its cofactor tetrahydrobiopterin. IR, insulin receptor; TNFR, TNF-receptor; FAT, fatty acid translocase. Consulted sources [4,13–16,22,24]
the endothelium-mediated NO-dependent dilation (Chapters 9, 11 and 12). The mechanism is also assumed to involve eNOS activation and is mediated by the insulin-signalling cascade (Figure 2). This most likely implies that the same molecular mechanisms that impair insulin-induced NO-production in terminal arterioles also restrict shear stress-mediated dilation of feed and resistance arteries during exercise in obese subjects and patients with chronic diseases. This restriction is potentially present both in skeletal muscle and the heart and may contribute to the reduced work capacity of both tissues. In patients with hypertension there is also an increase in vasoconstrictor tone (Chapters 11 and 12) and a substantial decrease in muscle capillary density (also called rarefaction; Chapters 11 and 12), both of which restrict muscle perfusion during exercise. These mechanisms, in combination with other causes of cardiac failure, limitations in ventilation and a low oxidative capacity of skeletal muscle (reduced number of mitochondria) limit the exercise capacity of patients with type 2 diabetes and cardiovascular disease.

**Loss of functional NO by superoxide anion production**

The NADPH oxidases are an enzyme family activated in the vasculature in cardiovascular disease and are thought to play an important role in the initiation of microvascular impairments [22]. Many vascular stimuli, including all those known to lead to insulin resistance, activate NADPH oxidase via both increased gene expression and complex activation mechanisms [22]. NADPH oxidase activation, like IRS-1 serine phosphorylation, has been suggested to depend on prior PKC activation. NADPH oxidase leads to superoxide anion production ($\cdot O_2^-$). Superoxide reacts with NO resulting in the formation of peroxynitrite, reducing the bioactive NO needed to dilate terminal arterioles, feed arteries and resistance arteries. Superoxide anion, peroxynitrite and other ROS (reactive oxygen species) also lead to pathology via peroxidation of proteins and lipids and via activation of redox-sensitive [depending on the NAD(P)H/NAD(P) ratio] signalling cascades and protein nitrosylation.

Another potential source of superoxide anion production in the vascular endothelium is the enzyme eNOS itself. *In vitro*, in the presence of low concentrations of its substrate (arginine) and of its main cofactor (tetrahydrobiopterin), eNOS acts on molecular oxygen to form superoxide anion [23]. This process is called eNOS uncoupling and has been suggested to be a major cause of hypertension [23,24]. Addition of tetrahydrobiopterin to microvascular endothelial cells reduces eNOS uncoupling [24,25], whereas infusion of tetrahydrobiopterin in patients with type 2 diabetes and coronary heart disease improves insulin sensitivity [26].

**Consequences of reduced NO production**

In summary, NO production in the microvascular endothelium is reduced in patients with the metabolic syndrome, type 2 diabetes and cardiovascular
disease because of a reduced expression and activity of eNOS, reduced phosphorylation of eNOS via the insulin signalling cascade and removal of functional NO by superoxide anions produced by activation of NADPH oxidase and uncoupling of eNOS (Figure 2). This reduction in NO available for relaxation of the VSM cells also has been suggested to increase monocyte/macrophage adhesion to endothelial cells, to enhance platelet aggregation/thrombosis, to increase the degree of inflammation, atherosclerosis and VSM proliferation and hypertrophy throughout the circulation (Chapters 9, 11 and 12) [4]. The effect of chronic exercise on angiogenesis (an increase in capillary density with training) has been shown to depend on the original increase in shear stress-induced NO production in the pre-existent muscle capillaries, with less angiogenesis occurring when the NO production is reduced [6].

**The role of inflammation and atherogenesis in the communication between endothelium and VSM**

An important question when we consider the tissues and pathways activated by TNF-α and other members of the TNF superfamily (e.g. NADPH oxidase and the NF-κB network [21,22]) is whether the endothelial lining forms a barrier for these proinflammatory cytokines, other vascular metabolites and for monocytes and macrophages (Figure 3). If so, then the involved cytokines and immune cells could not exert direct effects on VSM and skeletal muscle fibres/cardiomycocytes. Suggestions have been made that TNF-α activates peripheral blood mononuclear cells to produce other cytokines that change the shape of endothelial cells and create large gaps between the cells [27]. Loss of the endothelial barrier function due to this local inflammatory process (Figure 3) will have large consequences for the interaction between the endothelium, the VSM and skeletal muscle fibres as the co-ordinated exchange of signal molecules will be lost. Loss of the endothelial barrier function probably also plays a role in the onset and progression of atherosclerosis and VSM hypertrophy.

Atherosclerosis is a slow progressive disease that may start in childhood and is dramatically accelerated by a sedentary lifestyle and obesity. The atherosclerotic process is still poorly understood but leads to a progressive deposition of fats, cholesterol, oxidized lipoproteins, platelets, macrophages, cellular debris, collagen and calcium in the wall of feed arteries and resistance arteries and is a major cause of arterial stiffness. The depositions are called atherosclerotic plaques. Eventually the diameter of the lumen of the artery will be reduced and less blood will flow to the downstream circulation and the oxygen supply to tissue beds will be reduced. Atherosclerotic plaques are present between the endothelial lining and the VSM cells and are a likely physical barrier for NO produced by the endothelium to reach the VSM and will thus further decrease NO availability.
Figure 3. The role of TNF-α and local inflammation in loss of the transendothelial barrier, atherosclerosis and muscle cell degeneration
In the healthy state (top of the figure) the endothelial cells form a closed barrier for TNF-α and members of the TNF family. VSM cells in arteries and arterioles and (cardio)myocytes will not be exposed to the cytokines and NF-κB will not be activated. In a state of chronic inflammation (bottom of Figure 3) the events described in Figure 2 lead to local inflammation and make the endothelial cells permeable for cytokines, while simultaneously widening the tight junctions and allowing leucocyte/macrophage penetration into deeper tissue layers. As a result, cytokines can reach VSM cells and (cardio)myocytes and activate NF-κB and NADPH oxidase. Loss of the endothelial barrier function also speeds up the atherosclerotic process.

Dual role of the NF-κB network in tissue repair and tissue damage
NF-κB is a transcription factor, inducible in most cells of our body. The activation signals and pathways and the effector pathways (enzyme pathways
expressed when NF-κB is activated) form an incredibly complex network with multiple overlapping processes and interaction/cross talk with many other signalling pathways [20,21,28,29]. Knowledge on gene expression and the signalling regulation network controlled by NF-κB is expanding rapidly (>5400 hits in PubMed in the last 18 months) but our understanding of its physiological role and the many regulatory mechanisms is still in a rudimentary state. NF-κB (among other factors) activates the expression of groups of genes promoting and regulating immune and inflammatory responses, cell survival and growth, cell cycles and also apoptosis and necrosis.

It is clear today that damage and repair of the endothelial lining in the blood vessels of our body plays a crucial role in the long-term pathogenesis of type 2 diabetes and cardiovascular disease. It also is clear that the network controlled by NF-κB plays a key role in this process [20,21,28,29]. NF-κB activation leads to the expression of proteins involved in the binding of leukocytes, required to assist in these repair processes, but simultaneously able to produce severe damage among others by uncontrolled free radical production [28]. Once the endothelial barrier function is lost the NF-κB network seems to be able to extend its action to the VSM cells, (cardio)myocytes and most other tissues of our body (Figure 3). When the NF-κB network, with the help of the immune system, does not succeed in repairing these tissues, severe diabetic and cardiovascular complications will follow such as left ventricular hypertrophy [30,31], claudication, lower leg denervation [32], neurodegenerative diseases [33], retinopathy [34] and kidney disease [35]. However, we are a long way from understanding the exact regulatory mechanisms that lead to repair, and that decide on the balance between repair, apoptosis and necrosis.

**Complexity of the networks involved: added value of systems biology**

The picture that emerges above, shows a complex, intertwined network of many signalling pathways and metabolic networks in different cell types and tissues, operating at multiple scales in space and time (Figure 4). How these systems are interconnected and the sequence of events leading to metabolic dysregulation and pathology are largely unknown. A systems approach that combines comprehensive and accurate quantitative experimental work with a high temporal resolution and mechanism-based computational model is necessary to make progress in the understanding of these highly complex pathways and involves a rapidly growing body of literature comprising many thousands of publications per year. It is time to realize that the traditional integrative physiology/biochemistry approach is not enough in order to enhance our understanding of the biochemical and biological mechanisms leading to the chronic diseases and the effect of exercise upon it. We depend on the development of a new discipline called systems biology, which combines the expertise of molecular biologists and biochemists, integrative physiologists, computational biologists and control systems engineers with an interest in the...
A multi-scale problem requires a multi-scale approach, both in space and time. Mathematics can be used to form integrative (across scales) models of human physiology and disease. However, different processes that operate on time and spatial scales that are 14 respectively 9 orders of magnitude apart can never be combined in full detail in a single simulation model. From an experimental point of view, it is a huge challenge to accurately measure a multitude of system components in time and space in response to well-defined physiological or pharmaceutical perturbations.

chronic diseases. Systems biology aims to understand physiology and disease from the level of molecular pathways, regulatory networks, cells, tissues, and organs upwards, ultimately, to the level of the whole organism (Figure 4). To understand complex, multi-factorial diseases the system cannot be restricted to intracellular pathways (which currently dominate the literature). It also needs to include larger-scale systems physiology to identify the important control points that are determinants of disturbed metabolism [36]. Mathematical models can be used to identify the most important components and interactions in a complex system using high-throughput genomic, proteomic and metabolomic data complemented with quantitative data obtained in functional assays providing information on changes in time and space in response to well-defined physiological and/or pharmaceutical perturbations [37]. Models provide a platform for hypothesis-driven research and can assist in the optimization of new experiments and therapies. A continuous iterative cycle of prediction and experimental validation progressively strengthens the predictive power of the model and ultimately will lead to a full comprehension of the disease mechanism (Figure 5).

**Does underperfusion of skeletal muscle and the heart lead to an energy deficit?**

We have seen in this essay that there are many processes that might limit the supply of blood and the transport of fuels and oxygen from capillary blood
to the (cardio)myocytes. Therefore it might well be possible that a chronic energy deficit develops in skeletal muscle and the heart especially in the final stages of the chronic disease process. In line with this hypothesis, significantly lower PCr/ATP rates were indeed observed in the heart of patients with type 2 diabetes in the resting state [38]. This ratio was normal in skeletal muscle at rest, but the loss of PCr during exercise was faster in the type 2 diabetic individuals and the PCr recovery following exercise was slower. Lower ATP turnover rates have also been found in the offspring of parents with type 2 diabetes both in the fasted state and during a hyperinsulinaemic euglycaemic clamp all in line with a relative underperfusion [11,12]. Indications of a reduced skeletal muscle perfusion during exercise were also observed in obese Zucker rats in Chapter 10. A suboptimal perfusion of heart and skeletal muscle leading to an energy deficit or reduced ATP turnover rates is likely to contribute to a reduced contractility of these tissues or failure of other ATP requiring metabolic processes (maintenance of the Na\(^+\)/K\(^+\) gradient or protein synthesis rates etc.).

The benefits of acute and regular exercise for patients

Acute exercise will open the muscle capillaries among others via adenosine and K\(^+\)-induced opening of the terminal arterioles [3]. As these metabolites are released by the contracting muscle fibres, this is an opening mechanism that does not depend on endothelial function or integrity. Obese subjects and
patients with insulin resistance and other microvascular impairments may, therefore, experience acute benefits of exercise when they perform walking or resistance exercise in the period following meal ingestion. Exercise will help to recruit more muscle capillaries and will thus direct more insulin and meal-derived nutrients towards the muscle fibres, simulating the effect that insulin has in healthy individuals. Most of the benefits of regular exercise (≥3 times per week) that are seen in trained subjects do also occur in patients with the metabolic syndrome and advanced stages of type 2 diabetes and cardiovascular disease. However, due to the inherent lower exercise intensity, the effects will be smaller and it will take longer after the start of a physical activity increase before the benefits become significant and noticeable to the patient. This in part is due to the structural changes in the microvasculature, which prevent rapid improvement of the endothelial function and transendothelial oxygen and nutrient transport. An exhaustive description of all the benefits of regular exercise in healthy subjects and patients with chronic disease is given in previous chapters in this volume.

Recent studies in rats chronically increasing the coronary blood flow in hypertrophied hearts [5] and aortic blood flow [39] reveal large increases in expression of eNOS and the enzymes leading to the expression of its cofactor tetrahydrobiopterin. Brown et al. [5] also noted a marked increase in the density of the coronary capillary bed in hypertrophied hearts due to high rates of angiogenesis. These data suggest that the microvasculature in patients with left ventricular hypertrophy might benefit from regular bouts of exercise.

Conclusions

In recent years a major research effort worldwide has generated a massive amount of new information on the metabolic and vascular defects that lead to insulin resistance, type 2 diabetes and cardiovascular disease. In all these conditions, parallel biochemical pathways and mechanisms seem to be activated in many tissues, not only skeletal and cardiac muscle but also the central nervous system, peripheral nerves, the gut and the kidney. The comprehensive picture is far from complete though and therefore we cannot say at this moment in time what the primary event leading to tissue energy depletion and degeneration is. The working hypothesis of this and other essays in this volume is that people who avoid exercise in day-to-day life and eat too much fatty foods and calories, first develop an unresponsiveness of the vascular endothelium to insulin (in terminal arterioles) and shear stress (arteries and larger arterioles) and that changes in metabolism and function of skeletal muscle, heart and other tissues are secondary. The combined essays in this volume provide hard evidence that both the (micro)vascular wall defects and the impairment at the (cardio)myocyte level can be prevented by lifestyle changes involving regular exercise and a more balanced nutrition.
Summary

• In order to maintain optimal health, man should be physically active from birth to death.
• A sedentary lifestyle increases the risk for development of type 2 diabetes and cardiovascular disease, especially when combined with a high caloric intake.
• A reduction in vascular NO production is the key event leading to unresponsiveness of the vascular wall to insulin and shear stress.
• A reduced expression of eNOS, reduced activation of eNOS and increased superoxide anion production by NADPH oxidase and eNOS uncoupling all reduce the endothelial NO production.
• The reduction in NO production has a negative impact on atherosclerosis and angiogenesis.
• Changes in muscle metabolism and tissue degeneration are secondary to the changes in the microvascular wall.
• Activation of the metabolic network controlled by the transcription factor NF-κB originally seems to function to repair the endothelial lining and underlying tissues, but eventually leads to tissue destruction.
• The benefits of acute and regular exercise in patients are numerous and large and every GP should encourage patients to be as physically active as possible.
• More research is needed to investigate whether lifetime exercise interventions started in children prevent insulin resistance and the chronic diseases in adulthood.

References


© 2006 The Biochemical Society


