Chapter 3

The Skeletal Muscle Microvasculature and Its Effects on Metabolism

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/63535

Abstract

Skeletal muscle is a major metabolic organ that plays a critical role in regulating glucose homeostasis and lipid utilization. Impaired muscle metabolic response is evident in diseases such as diabetes, obesity and cardiovascular diseases, and is also often associated with microvascular dysfunction. Here, we investigate the changes that can occur in the muscle microvasculature and the profound impact they can have on metabolism.

Under basal conditions, vasoactive compounds are able to affect metabolism in muscle by providing more glucose and oxygen to resting muscle. Insulin and exercise increase the perfusion of muscle, and thus provide more microvascular surface area, increasing the delivery of these metabolites to muscle. Endothelial dysfunction can therefore impair the delivery of oxygen, glucose and hormones to muscle, both through effects on blood flow distribution and the transport of these factors across the endothelium, leading to a decrease in oxygen consumption and glucose metabolism. Obesity and diabetes are associated with endothelial dysfunction and are accompanied by underlying changes in metabolism and reductions in insulin sensitivity.

The muscle is a highly metabolic organ, and the vasculature is essential to maintain appropriate metabolic response; therefore, the muscle microcirculation may be a target for treating metabolic disease.

Keywords: Skeletal muscle, blood flow, capillary, transendothelial transport, diabetes, endothelium, perfusion, exercise, insulin, vasodilation, vasoconstriction

1. Introduction

Skeletal muscle is normally thought of in the context of exercise or posture, and its ability to contract to generate force or motion is an essential part of mobility. It is a highly metabolic organ, responsible for breakdown and storage of glucose and fat in order to provide the energy required for these contractions. In addition, skeletal muscle is the primary tissue responsible for the increased glucose metabolism during hyperinsulinemia and exercise [1]. The vascular system in skeletal muscle is essential in metabolism and exercise, and can directly affect its ability to generate the energy needed for contraction and movement, and to appropriately dispose of glucose. Here, we will discuss the structure and function of the muscle microcirculatory system, and the role that microvascular function plays in muscle metabolism. We will discuss the effects of diet and obesity on vascular function, how these effects may translate to impaired muscle metabolism, and the possibility of targeting the microcirculatory system in order to treat both vascular and metabolic disease.

2. Muscle microcirculatory system

As is common in other tissues, the vascular network in skeletal muscle consists of arteries branching into smaller and smaller vessels. In skeletal muscle, a terminal arteriole gives rise to groups of capillaries that run parallel to muscle fibres, and each muscle fibre can be supplied by several different groups of capillaries from independent terminal arterioles [2]. Vascular casts of the rat hind limb have demonstrated that the muscle capillaries are long and tortuous [3], and thus have a lot of contact with myocytes (**Figure 1**). Original methods to assess the structure and location of the microcirculatory system in skeletal muscle used microscopy to gain 2D images from fixed or frozen tissues. However, the skeletal muscle is particularly sensitive to certain artefacts when freezing [4], and limitations to counting capillaries in 2D include lack of estimation of capillary length, tortuosity or fibre size [5]. More recent advances in 3D visualization *in vivo* supply more spatial information about the relationship between the microcirculation and the muscle tissue, as capillaries are found to be embedded in grooves in the sarcolemma of muscle fibres [6].

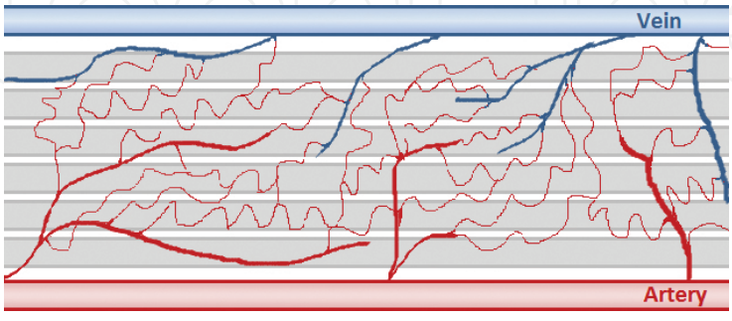

Figure 1. Muscle microcirculatory system. Arteries feed into the muscle, supplying arterioles, each of which controls a capillary network. Blood is then removed from the capillaries through venules and veins. (Grey: muscle fibres. Red: artery, arterioles and capillaries. Blue: venules and vein).

http://dx.doi.org/10.5772/63535

Blood flow through these capillaries can be controlled through dilation or constriction of the blood vessel network. Most of this regulation does not occur at the capillary level, as the capillaries are not associated with an underlying smooth muscle network required for dilation and constriction. While subject to changes in blood flow, as well as being in direct contact with factors in the blood, the capillary itself does not usually regulate blood flow. Instead, the vessels that have smooth muscle surrounding the endothelial wall, such as the arteries, precapillary arterioles, post-capillary venules and veins, are responsible for vasoconstriction and vasodilation. Factors that are vasoactive throughout the body also affect the muscle microvasculature. Nitric oxide (NO), endothelium-derived hyperpolarizing factor and prostacyclin are known vasodilators, and more recently carbon monoxide and hydrogen sulphide have been included in this list [7], and there are a range of hormones that can cause vasoconstriction, including endothelin, angiotensin, serotonin and others. The effects can vary depending on where the vasomotion is taking place. For example, vasoconstriction in the precapillary arteriole will induce low pressure in the capillaries, whereas venular constriction will increase blood pressure in the local capillary environment, and may increase shear stress.

Resting blood flow is low, approximately 5–10 ml/min/100 g [7], but increases rapidly by a factor of up to 20 (up to 80–100 ml/min/100 g) during exercise [8]; however, this can be highly variable depending on the muscle. In resting skeletal muscle, it is estimated that only about 25% of the capillaries are perfused at any time [9], but that this can increase to 100% with exercise; however, some recent publications suggest that no capillaries are unperfused at rest, and instead capillary surface area is recruited by exercise [10]. A coordinated response between the terminal arterioles has been shown, and capillary perfusion can increase through broad regions of a muscle [2]. Early studies by Lindbom and Arfors using intravital microscopy showed that oxygen partial pressure itself in the rabbit tennuisimus muscle could increase perfusion. This is likely mediated through the nervous system [11], which is thought to maintain a low-level vasoconstriction in muscle microvasculature. Thus, the sympathetic nervous system is likely to be important in blood flow regulation [12].

Measurement of functional capillary density in skeletal muscle has been made possible by advances in imaging techniques. Contrast-enhanced ultrasound (CEU) technology is used in perfusion studies in a variety of tissues, and showed that physiologic hyperinsulinemia can increase human skeletal muscle perfusion and microvascular volume [13]. This technique can also detect microvascular complications [14]. However, an *in vitro* study designed to more fully understand the data acquired from CEU has shown that while alterations in the filling rate of the microvascular volume can be detected, CEU cannot discriminate between different flow patterns that reflect changes in capillary perfusion *in vivo* [15]. This may be explained by new developments to the capillary recruitment theory, whereby instead of recruiting previously unperfused capillaries, capillary surface area is recruited by elevating capillary haematocrit and extending the length of the capillary available for exchange [10].

There are several other techniques that have been used to estimate functional capillary density or capillary recruitment. Earlier methods used laser Doppler fluxmetry (LDF) at the muscle surface, and showed effects of different vasoconstrictors to either increase or decrease the capillary surface area [16]. Further studies demonstrated an increase in LDF signal by insulin,

but not by adrenaline, which increases bulk flow without effect on capillary recruitment [17], suggesting that LDF does indeed reflect changes in capillary recruitment, and not bulk flow. Skeletal muscle perfusion can also be assessed by nuclear magnetic resonance (NMR) arterial spin labelling, which has been validated as a method with strong spatial and temporal resolution [18], and can be combined with assessments of muscle oxygenation and energy metabolism [8]. Positron emission tomography (PET) utilizes short-lived radioisotopes to measure blood flow and its distribution, and also offers the ability to measure oxygen consumption and extraction. This technique has been used to show that NO is involved in maintaining resting skeletal muscle blood flow [19]. In addition, the PET technique demonstrated that exercise can recruit capillaries [20]. Near-infra red spectroscopy (NIRS) is a non-invasive method that has been used in skeletal muscle to measure blood flow and oxygen consumption [21], and can be used to show differences in oxygen consumption in tissue, which may indicate the distribution of blood flow through skeletal muscle. NIRS has been used to link tissue oxygenation to blood flow in a range of conditions from critically ill patients to athletes [22, 23].

The microvascular endothelium functions as a barrier between the blood and the underlying tissue [24]. In skeletal muscle, there is a continuous endothelial barrier with tight junctions between the endothelial cells, and thus the molecule's ability to reach the muscle is restricted. In comparison, an organ with a discontinuous endothelium or one with large pores in the endothelial barrier, such as liver, has a greater direct contact with molecules in the blood. These differences make the muscle microvasculature highly regulated; thus, the constitution of the plasma is very different to the muscle interstitium. Our own results have shown very different concentrations of insulin and lipid in the muscle interstitium when compared to plasma [25], and the endothelial barrier may account for a lag time of 5 min between plasma and interstitial glucose levels [26], in spite of the fact that glucose is a small molecule thought to easily diffuse across the endothelium. Plasma is therefore substantially different from the interstitial fluid [27, 28]; and as the interstitial environment is largely modified by supply from the blood, or removal through the lymph, the endothelial barrier is an important component of regulating the muscle microenvironment.

In addition to the basic structure of the endothelium, the endothelial glycocalyx is an approximately 1 μm thick layer on the luminal side of the vascular endothelial cells, which consists of a mesh of polysaccharide structures, which provide a layer of protection for the endothelial cells, regulating access of molecules in the plasma based on molecular size, charge and structure [29]. The glycocalyx is a dynamic addition to the endothelial barrier [30–32] and, while perhaps not directly involved in regulating blood flow or metabolism, is a structural and functional barrier that may alter the composition of the muscle interstitium.

Sampling the interstitial environment is difficult, with many techniques inducing inflammation, allowing only small sample sizes, or being unable to provide a dynamic measure of changes in response to certain stimuli [28]. Our own studies use lymph sampling [25, 33–36], which does not induce inflammation at the sampling point, and allows studies of temporal changes. The lymph vessel is highly permeable and has a slow flow rate, allowing equilibration with the interstitial fluid. However, the volume sampled is quite small, restricting this

http://dx.doi.org/10.5772/63535

technique to larger animals. In addition, there may be some modification of the lymph fluid, which may alter results [37]. Other techniques can indirectly sample the interstitium, such as microdialysis. For larger molecules, this technique can have a low recovery, providing only a dilute sample, and the insertion of the probe may induce inflammation. However, this technique has been used in many human applications [38–44]. In general, the consensus is that the muscle interstitium is substantially different from plasma, and the muscle microvasculature is an important component of the regulation of the muscle microenvironment.

3. Skeletal muscle metabolism

Metabolism in muscle provides working muscle with energy, and metabolic processes are increased in times of need. Muscle can utilize both glucose and fat for energy, and typically relies on fat oxidation during both increased energy expenditure (exercise) and decreased energy intake (fasting) [45], but is also the primary tissue for insulin-mediated glucose uptake [1]. Plasma free fatty acids typically supply most of the fuel for skeletal muscle under low and moderate levels of exercise [46]; however, rates of glycogen utilization also increase with contraction [47]. The fuel selection is dependent on not only the intensity of exercise but also the type of muscle fibre recruited for exercise and the availability of fuels [48].

Metabolism of both fat and glucose requires mitochondria to generate energy through aerobic respiration. Within the mitochondria, glucose, fats and proteins are broken down through a series of enzymatic reactions, and the products feed into the electron transport chain, causing oxidative phosphorylation and the generation of ATP (energy) (**Figure 2**). Skeletal muscle is heterogenous, and the mitochondrial content of different muscle fibre types is a major component of the metabolic preference of each muscle fibre type. Red muscle contains a high number of mitochondria, thus providing a very high level of oxidative capacity. These red fibres (Type I) are useful in endurance type activities, and are served by an extensive vascular network in order to supply the oxygen required for oxidative phosphorylation and thus efficient production of ATP, which provides the energy for all forms of muscle work [49]. In contrast, Type II muscle fibres, known as white fibres, have lower levels of mitochondria and vessel density. This muscle is typically used for very short maximal intensity activities, such as sprints: it is more glycolytic, such that instead of undergoing full oxidation, glucose is broken down to lactate to give a quick release of energy (**Figure 2**). Recent studies have shown that red fibres have a larger capillary to fibre ratio, a greater capillary density and more tortuous capillary pathways than white [50]. Thus, vascularization is tightly tied to metabolism in skeletal muscle—vascularized muscle is more oxidative, and leads to more complete metabolism of glucose, and less vascularized muscle supplies less oxygen to the myocyte leading to anaerobic respiration and production of lactate [49]. However, studies have shown that capillary density in some muscles has a greater relativity to muscle fibre size, rather than the oxidative capacity of the muscle fibre [5]. Glancy et al. concluded that the embedding of the capillaries in the sarcolemma increased oxygen delivery to the myocyte. Interestingly, the mitochondrial pool was located close to embedded capillaries, though the authors believe that

while this increased oxygen delivery to the myocyte, it was not associated with mitochondrial oxygen access [6].

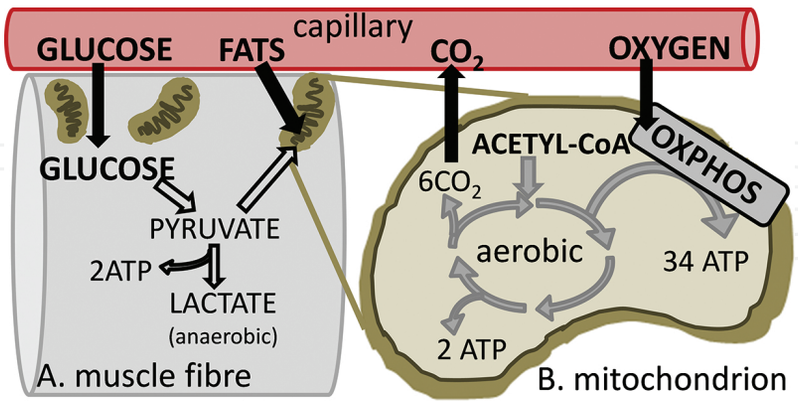

Figure 2. Role of microcirculation in muscle metabolism. Glucose and fats are the main source of energy for muscle fibres (A). Glucose is broken down to pyruvate, which can be metabolized without oxygen to lactate, producing 2ATP, a pathway used preferentially in white muscle fibres. Alternatively, pyruvate can be transported into the mitochondria of the muscle fibre (B), where both pyruvate and fats can be converted to acetyl-CoA. This enters the Krebs cycle and activates oxidative phosphorylation (OXPHOS), requiring the delivery of oxygen from the blood. This method is common in red muscle fibres: it produces much more ATP than anaerobic production of lactate, but also produces carbon dioxide, which must be removed by the blood. Thus, the microcirculation is essential for delivering glucose, fats and oxygen, and removing carbon dioxide from the muscle.

Exercise requires more ATP [49], which can be derived both anaerobically for short-term activity or aerobically using the electron transport chain in mitochondria (**Figure 2**). A model has been generated to predict this transition from rest to work, and has shown the importance of myoglobin in oxygen delivery to working muscle [51]. Exercise causes increases in blood flow primarily to red muscles [52]: muscles consisting of more red fibres showed a quicker increase in blood flow than white, and, interestingly, the red muscles also showed a quicker return to rested blood flow levels than the white [53]. The maximal metabolic rate is related to both mitochondrial size and number as well as capillary volume [54], emphasizing the importance of the microvasculature in metabolism.

Aerobic exercise training has been shown to double skeletal muscle mitochondrial content, yet maximal whole body oxygen uptake only increased approximately 15% [55]. As these effects of exercise on mitochondrial content and oxygen consumption are not proportional, some conclude that the ability to deliver oxygen to mitochondria is in fact limiting to aerobic respiration, rather than mitochondrial content [6, 56]. This contribution of the vasculature may include both the presence of blood vessels and also their function, specifically their ability to redirect blood flow through the muscle.

4. Blood flow distribution affects muscle metabolism

As already discussed, there can be changes in the distribution of blood flow through muscle by altering functional capillary density. This redistribution of flow can directly alter metabo-

http://dx.doi.org/10.5772/63535

lism: some vasoconstrictors and vasodilators can alter oxygen consumption and glucose uptake independently of any direct effects on muscle metabolism [16, 57]. This was demonstrated by showing that the effects of vasoactive substances on metabolism in perfused skeletal muscle were not replicated in incubated skeletal muscle, implicating the essential role of the microvasculature in mediating those changes in metabolism [58, 59]. Vessel surface area, the distance for the factor to travel, and the concentration gradient can all alter the rate of diffusion according to Fick's equation. Vasodilation allows a greater surface area for exchange, and conversely vasoconstriction reduces the surface area for diffusion. However, as discussed above, the areas of the blood vessel responsible for exchange are typically the capillaries, which themselves do not undergo vasomotion, but are controlled by the larger surrounding vessels. Thus, a larger effect on diffusion of oxygen and other metabolites can be induced by vasomotion that alters the distribution of flow through muscle, which will decrease the distance for the factor to travel from the blood vessel to all areas of the muscle, as shown in Fick's equation [60]. When a greater number of capillaries are perfused, as occurs with capillary recruitment, each myocyte is supplied with a great amount of oxygen and glucose, and metabolism is increased. This is independent of extra work being performed by the muscle (such as during exercise), and demonstrates that changes in blood flow even during resting conditions may influence metabolism [60].

4.1. Factors that can induce capillary recruitment

There are several known factors that can increase the number of perfused capillaries. From a physiological perspective, exercise and reactive hyperaemia are both associated with a substantial increase in perfusion. Exercise also induces a major increase in blood flow: while muscle only uses approximately 15% of the cardiac output at rest, this increases to 88% during maximum exercise [49], mainly to muscles consisting predominantly of red fibres [53]. There is also an increase in capillary recruitment with exercise [61–64], and this was associated with an increased perfused capillary density of 1.5- to 3-fold [65]. It is possible that both exercise and reactive hyperaemia induce their blood flow effects through the sympathetic nervous system [11]; however, alternative models of local blood flow regulation have also been postulated [66]. NO does not appear to be involved in exercise-induced capillary recruitment [67], and in fact inhibiting NO during exercise can increase local muscle oxygen uptake, but seems to decrease glucose uptake [19, 67]. As discussed, NO is considered a vasodilator; however, there are some inconsistencies with regards to its effects on metabolism. In resting muscle, inhibition of NO synthesis causes free fatty acid uptake, increased oxygen uptake, but not glucose uptake [68], and the authors proposed a possible contribution of an inhibitory effect of NO on mitochondrial respiration to explain their data; thus, the contribution of NO to basal metabolism may be slight. PET has been used to show that NO is involved in maintaining resting skeletal muscle blood flow, and suppresses resting muscle oxygen uptake, likely because NO competes with oxygen and inhibits mitochondrial respiration [19]; further studies demonstrated that NO may contribute to the regulation of free fatty acid metabolism at rest [68]. Thus, while NO is a known vasodilator, its role in metabolism is unclear. These divergent results may reflect differences depending on the dose of NO inhibitor used, but also may

indicate a role of NO in the mitochondrial function of working muscle, as it can inhibit oxidative phosphorylation [69].

While many hormones are themselves vasoactive, including serotonin, epinephrine, norepinephrine and angiotensin, many do not appear to change muscle perfusion. GLP-1 (Glucagon-like peptide-1) increases capillary perfusion, though the involvement of NO in this process is so far controversial [70–73]. GLP-1 receptor agonists have beneficial effects on the vasculature [74–78] and metabolism of glucose [70, 71, 79–81]; though whether this reflects a direct effect on glucose metabolism, an indirect effect through blood flow changes, or a combination of these is not clear. GLP-1 induces angiogenesis, consistent with increasing functional capillary density, though this is a long-term adaptation rather than an acute increase in the perfusion of skeletal muscle [74]. This effect of angiogenesis, or increasing the size and number of capillaries, has been shown to protect against metabolic disease [82].

There are two classes of vasoconstrictors determined based on their general effects on metabolism. Type A vasoconstrictors, including angiotensin, vasopressin, and low doses of norepinephrine and endothelin increase oxygen consumption and perfusion pressure in the constant-flow pump-perfused hindlimb [3, 83, 84]. Type B vasoconstrictors reduce muscle metabolism, such as serotonin (5-hydroxytryptophan) [3, 85]. Studies have shown that vasoconstrictors from these different groups may control different areas of vascular flow in the muscle, as evidenced by both washout of red blood cells that had been trapped in the muscle, and by corrosion casting of the arterial tree [3], a technique which uses a polymer to fill the perfused vascular area, the tissue is then corroded away to form a 3D model. Serotonin was shown to reduce the available capillary surface area, and is associated with a reduction in metabolism measured by oxygen uptake [85].

Angiotensin II (Ang) is often associated with hypertension, and is a vasoconstrictor that can have different effects on metabolism depending on which receptor type it engages. Ang receptor 1 is associated with reduced metabolism, while Ang receptor 2 can recruit the microvasculature [86], and similar effects have been detected in cardiac muscle [87]. In addition, Ang may have effects on blood vessel permeability, which may separately alter the metabolism through increased delivery of oxygen and nutrients [88]. Ang II increases blood flow, but appears to impair insulin-mediated glucose metabolism, without altering the access of insulin to the muscle interstitium [89]. These data on insulin access are not consistent with other published data, indicating that Ang II can reduce the number of insulin receptors on endothelial cells, which may lead to a reduction in receptor-mediated transcytosis [90], if insulin transport is indeed receptor-mediated. Some of these inconsistences may be due to the time of exposure to the vasoconstrictor: one study has shown that short-term Ang II can increase NO production, but long-term can reduce NO bioavailability [91]. Acute Ang receptor blockade has been shown to improve microvascular responses in hypertensive individuals [92], who may have elevated levels of Ang: Ang receptors are therefore considered to be involved in both metabolic and microvascular actions *in vivo* [93].

Endothelin is a vasoconstrictor released in response to insulin [94, 95], and at low doses behaves as a type A vasoconstrictor; increases in glucose uptake and oxygen consumption indicate augmented metabolism in the muscle. However, at high concentrations, this vasoconstriction

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continues to lead to high blood pressure, and also reduces oxygen consumption and glucose uptake by the muscle [83]. Thus, the concentrations of vasoconstrictors in the system are an important component of their effects on metabolism. However, it is important to realize that, *in vivo*, the plasma does not contain just one vasoconstrictor, but a mix of several vasoactive compounds, and the interactions among these molecules may be complex. Data have shown that adiponectin [96] and insulin [83] can prevent the vasoconstriction induced by endothelin. These results appear to depend on a prior vasodilation before endothelin-mediated vasoconstriction, and yet NO itself is able to prevent the increased pressure after exposure to endothelin [96]. This may perhaps be due to the systemic introduction of NO-donors to the system in comparison to the local action of insulin or adiponectin. The ability of insulin to dilate against endothelin-mediated constriction, and limit effects on pressure and oxygen consumption, has not been observed against any other vasoconstrictor. Thus, there is a very complex balance between a number of hormones and vasoactive molecules that act together to regulate metabolism.

4.2. Insulin's hemodynamic effects also alter metabolism

Insulin is known as a metabolic endocrine hormone; however, amongst its varied effects on nutrient disposal and storage, insulin also has hemodynamic effects and was first noted to increase blood flow at supraphysiological concentrations [97]. Later, physiological concentrations of insulin were found to induce vasodilation of blood vessels [98], and the release of the vasoconstrictor endothelin [94]. It is thought that the combination of the vasodilation by NO and the low dose of endothelin may combine to cause capillary recruitment [94, 95], as many studies have indicated that insulin is capable of inducing capillary recruitment in healthy individuals in skeletal muscle [13, 17, 99–102] and in skin, which is used as a surrogate measure of muscle [103]. Capillary density is directly correlated with insulin sensitivity in human skin [103], reinforcing the idea that capillary recruitment is an important process in insulin-mediated glucose uptake [13, 17, 99–103].

As we show above, altering muscle perfusion is sufficient to change basal metabolism without a direct effect on the myocyte; however, the increased perfusion induced by insulin-mediated capillary recruitment is also hypothesized to assist in the delivery of insulin to the myocyte, thus augmenting insulin's metabolic response. In a study by Miles et al. [104], the half time to maximum response for glucose disposal in dogs exposed to insulin infusion was not significantly different to that of interstitial insulin, yet the effects on arterial insulin were much quicker. This temporal relationship confirms that the time required for insulin to reach the interstitial space is the limiting factor for insulin-mediated glucose uptake, which agrees with results suggesting that insulin rapidly causes glucose uptake in cell culture [105]. Only once insulin is present at the cell surface can it bind to receptors to cause glucose uptake. In fact, the correlation between insulin levels and glucose uptake is strongest when using lymph insulin concentrations to represent the interstitium than the vein or arterial concentrations [33]. The study by Chiu et al. differs from that of Miles et al. because the focus is specifically on the muscle—local glucose uptake across the leg correlates with muscle lymph insulin concentrations, while Miles et al. used thoracic lymph, which is likely to be representative of the whole

body, and corresponds well with the whole body glucose disposal rate [104]. Therefore, the concentration of insulin at the cell surface, rather than in the blood, is a better predictor for the rate of insulin-mediated glucose uptake, thus increasing insulin delivery to the muscle is shown to improve insulin's metabolic effects.

As mentioned, insulin can increase the available surface area to augment its access to muscle, but it is possible that there may be other delays in the access of insulin to the interstitial space that are also altered by the microcirculatory system. The effects on metabolism occur during passive diffusion of oxygen, and probably glucose, in muscle. However, there can be regulated steps in transendothelial transport. Transport of insulin across the endothelial barrier is controversial: some studies have shown that transport is saturable, and as such must be receptor-mediated, yet others have shown no saturation, even at high concentrations, claiming that there is no evidence for receptor-mediated transport. The insulin receptors present on endothelial cells are suggested to be an important part of the trafficking of insulin across the endothelial barrier [106, 107]. However, these studies may be of limited relevance as they use a macrovascular cell type rather than a representative cell of a capillary. A knockout mouse model of endothelial IRS-2 is insulin-resistant and showed decreased access of insulin from the blood to the interstitium [108], implicating insulin signalling in transendothelial insulin transport. However, studies of microvascular cells demonstrated that fatty acids impair insulin transcytosis, and interestingly the insulin receptor and insulin signalling pathways did not appear to be involved [109]. There have also been studies showing that insulin itself can increase the accessibility of the glycocalyx in muscle, consistent with reports of insulin effects to increase blood volume [30], and the authors posit that structures within the glycocalyx are involved in insulin transport through the glycocalyx towards the endothelium for subsequent transport to the muscle interstitium. Thus, any defect in endothelial function may have severe implications for metabolism, particularly in the case of insulin and metabolic disease.

5. Vascular dysfunction in metabolic disease

The prevalence of diabetes has been increasing steadily in the United States and in many parts of the world. In 2010, 25.8 million individuals in the United States were diagnosed with diabetes, almost double the rate of ten years earlier [110]. In fact, 11.3% of the adult population was estimated to have diabetes, either diagnosed or undiagnosed. Diabetes is one of the leading causes of death and disease in the world currently, and is linked with a variety of cardiovascular diseases, including heart disease, stroke and hypertension [110]. The links between a metabolic disease such as diabetes and cardiovascular disease are not always readily apparent; however, as we have discussed here, the microcirculation is intrinsically tied to metabolism. Below, we will investigate various aspects of the metabolic syndrome, and how the muscle microvasculature may be affected.

http://dx.doi.org/10.5772/63535

5.1. Hypertension

Hypertension is often characterized by excessive vasoconstriction, which may be driven by dysregulation of the Ang system, excess amounts of endothelin, or changes in the autonomic nervous system. Microvascular dysfunction can occur due to functional issues as discussed here, but also structural impairments of the arterioles or capillaries, which may lead to capillary drop-out: this combined with arteriolar constriction increases peripheral resistance and thus blood pressure [111]. In addition, some forms of hypertension show a decreased capillary permeability, preventing hormone and nutrient access to the underlying tissue [112]. Excessive vasoconstriction by endothelin in hypertension and the metabolic syndrome may prevent appropriate insulin-mediated haemodynamics and also impair basal metabolism [83]. Further, we have shown that high levels of endothelin-1 can also reduce exercise capacity in muscle, likely due to the fact that oxygen and fuel access to the muscle is impaired with excessive vasoconstriction [113].

Some treatments for hypertension also have effects on metabolism. A recent study investigating the use of renal denervation to treat resistant hypertension has demonstrated a simultaneous improvement in metabolic parameters [114]. Recent studies showing negative results of renal denervation on metabolism also did not confirm effects on blood pressure [115, 116], which bring into question the technique of catheter-based renal ablation [117]. Some claim that renal denervation may have beneficial effects on the microvasculature [118], and the original findings posited that the skeletal muscle may be a primary site of improved metabolism [114], but have not yet been confirmed. Further, other studies have found no improvement in endothelial function as measured by peripheral arterial tone (PAT) using Endo-PAT [119], though these studies acknowledge that many of the patients did not have impaired endothelial function initially, thus no improvement may be detectable.

Regardless of the suitability of renal denervation in restoring endothelial function, other hypertensive treatments are known to restore microvascular function, including acute Ang receptor blockade [92]. Hypertension may therefore be linked to metabolic disease, including muscle metabolism, through effects on the microvasculature [111].

5.2. Obesity

Obesity is typically associated with excess caloric intake, or decreased energy expenditure. Our own studies have indicated that a high fat diet can increase both visceral and subcutaneous fat depots and also impair muscle metabolism [120]. Elevated levels of fat can induce inflammation [121] typically through Toll-like receptor 4. This inflammation has been detected in a number of tissues, including the muscle and the vasculature [122], and the type of fats are likely to affect the level of inflammation. Trans fats have been found to be particularly pro-inflammatory [123]. Saturated fatty acids, such as palmitate, activate an inflammatory response in microvascular endothelial cells; however, the related mono-unsaturated fatty acid did not [109]. In one study that used palmitate to induce inflammatory pathways in microvascular endothelial cells, transcytosis of insulin was reduced, and there was increased monocyte migration into the tissue [109]. While these studies were carried out in microvascular endothelial cells from adipose tissue, it is possible that a similar effect occurs in muscle. These *in*

vitro studies used palmitate, as it is the most abundant saturated fatty acid in the western diet —whether these effects could also occur *in vivo* must be confirmed. In association with obesity, perivascular fat accumulation in obesity may prevent appropriate vascular function, either through mechanical impairment, vasocrine signalling or the associated inflammation [124, 125].

While there are many studies demonstrating inflammation due to lipid and high fat diet, some show that there may be gender differences, as women do not seem to experience changes in inflammation with lipid infusion, and also experience a lower impairment in insulin sensitivity [126]. Yet, it is still generally accepted that plasma lipid induces endothelial dysfunction [127], and as such, regardless of inflammation, fat may directly alter endothelial function [128] and thus metabolism. Generally, lipids are known to cause endothelial dysfunction [129] and to impair muscle microvascular responses [130], and obesity is associated with blunted microvascular responses in humans [131]. Further, both visceral and subcutaneous adipose tissue are associated with impaired capillary recruitment [132]. A number of adipokines have been associated with effects on muscle metabolism. Adiponectin and leptin improve skeletal muscle metabolism [133], yet perhaps counter-intuitively, levels of adiponectin are inversely related to fat volume. Interestingly, adiponectin can also have beneficial effects on endothelial cells [134]. Leptin can stimulate fatty acid oxidation, and thus protect against fat deposition [135]. However, high levels of leptin with high fat diet [136] can lead to leptin resistance, including in endothelial cells [137]. Proinflammatory cytokines such as TNF-α (tumour necrosis factor-alpha) [138] and C-reactive protein are secreted from adipocytes and may cause insulin resistance at high levels [139]. An effect of TNF-α on endothelial cells is also known [134]. Other proinflammatory cytokines such as interleukin-6 (IL-6) have variable effects on endothelial function and skeletal muscle metabolism [140], and thus overall effects on metabolism are unclear. Alterations in the secretion of adipokines and interleukins from fat depots have been implicated in the progression of both metabolic and vascular disturbances associated with obesity [124], and visceral fat depots have been linked to a pro-inflammatory state and impaired capillary recruitment in skin [132], which may reflect impaired perfusion in skeletal muscle. Thus, obesity is associated with impaired capillary recruitment, which puts endothelial function as a potential link between obesity and metabolic disease.

Obesity is associated with a muscle fibre type switch, promoting a more 'white' muscle [141]. The number of lipid droplets within muscle fibres was twice as abundant in obese compared to lean individuals [142], and intramyocellular lipid is associated with impaired metabolism *in vivo* [143]. This increased fat content may be associated with mitochondrial dysfunction [144]; however, lipid accumulation itself may not alter metabolism [145]. For example, endurance athletes typically have more red muscle fibres, associated with a high capillary density, but also high intramyocellular lipid content. Obese individuals also have high intramyocellular lipid, but less red muscle fibres and a lower capillary density, so it is likely that intramyocellular lipid is only associated with impaired metabolism when the lipid supply is in excess of need. While the energy and lipid oversupply in obesity may impair mitochondrial function [146], the possibility that appropriate blood supply is lacking may also drive the switch to a less efficient muscle fibre type. Obesity as measured by body mass index (BMI) is

associated with a reduced capillary density [147], and both capillary density and muscle fibre type are linked to metabolic disease in humans [148].

Therefore, the exact stimulus for the muscle fibre type switch in obesity is not clear—does a change in the metabolic requirements of white muscle cause capillary drop-out, or does the capillary rarefaction in fact decrease the transport of oxygen and nutrients to the muscle, and thus reduce metabolism? An interesting correlate exists in adipose tissue, where hypoxia due to a low level of blood vessel density was originally thought to be a method to limit adipose tissue expansion [149]. However, recent results have suggested that increased mitochondrial content and angiogenesis in fact alter adipose metabolism to be more energy-efficient [82]. A similar situation may exist in skeletal muscle, such that increased capillary density and function, as well as increases in mitochondria, may prevent an obesity-induced switch to white muscle fibres, and thus assist in preventing metabolic disease.

5.3. Insulin resistance and diabetes

A mixed meal increases flow to muscle capillaries in healthy lean people, and perhaps more importantly increases muscle perfusion, yet this effect is blunted in obese individuals [150]. As the degree of microvascular surface area is related to insulin sensitivity [103, 151], this impaired perfusion is likely to be responsible for impaired glucose disposal after the meal. In fact, in dogs fed a high fat diet, the ability of insulin to increase the dispersion area of insulin is impaired, and is associated with impaired glucose disposal [152]. Impaired insulin-mediated capillary recruitment has been detected in a range of disease models, including inflammation [138, 140], hypertension or excessive vasoconstriction [92, 153], dyslipidemia [129, 132, 154] and obesity in both rodents [138, 155, 156] and humans [147]. In a model of experimental insulin resistance achieved by pancreatic venous diversion in dogs, glucose disposal rate was suppressed, the time for insulin to move into the lymph was delayed and insulin receptor activity was impaired. The authors conclude that transendothelial transport was impaired, and was responsible for one third of the insulin resistance observed in these animals, cellular defects being responsible for the remaining insulin resistance [157].

In general, vascular dysfunction has been observed in prediabetes [158, 159], diabetes [99, 128, 160] and offspring from individuals with type 2 diabetes [161], which may have profound effects on metabolic responses to insulin, as discussed above.

5.4. Complications of diabetes

As mentioned above, many of the leading causes of death associated with diabetes are related to cardiovascular disease. While heart disease and stroke are major macrovascular complications of disease, diabetes has many microvascular co-morbidities, including diabetic retinopathy, peripheral neuropathy and nephropathy. The endothelium has been implicated in diabetic nephropathy [162], and the blood vessels formed in response to reduced perfusion in retinopathy show abnormal structure and function [163]. Because of this association, diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations and new cases of blindness in adults in the United States [110]. Around 60–70% of people with diabetes have

mild to severe nervous system damage, with 30% exhibiting impaired sensation in hands and feet, which can lead to non-traumatic amputation in extreme cases. Impaired blood flow may be one of the early signs of this diabetic neuropathy [164], and denervation of the skeletal muscle can cause muscle atrophy [165]. However, as the nervous system is partly involved in regulating microvascular function [12], through direct or hormonal means, neuropathic changes may also directly alter endothelial function, and therefore muscle metabolism [166]. Targeting endothelial dysfunction is therefore a viable treatment for preventing vascular complications associated with diabetes [167], and may help prevent muscle atrophy.

6. The vascular system as a target for treatment of metabolic disease

Since insulin resistance and its associated pathologies exhibit endothelial dysfunction; it follows that restoring blood flow patterns to normal would ameliorate at least some of the negative outcomes. For example, several studies have suggested that insulin's haemodynamic effects may account for a substantial amount of the metabolic outcome [168], and be impaired in disease and obesity, contributing to the metabolic deficit [97]; therefore, restoring endothelial function could help to improve insulin sensitivity.

Several drugs are also known to have effects on capillary recruitment. As discussed above, Ang can alter metabolism by vasoconstriction, and thus the disruption of the Renin-Angiotensin-Aldosterone system is likely to be a good target for treatment of any associated metabolic disease, whether by using angiotensin receptor blockers or through angiotensin converting enzyme inhibitors [169]. The differential expression of Ang receptors may provide local or tissue specific effects. Irbesartan, an Ang receptor blocker, improves microvascular responses to insulin in hypertensive individuals [92], however does not appear to induce capillary recruitment alone. While angiotensin receptor blockers also have effects in other tissues such as the pancreas [170], it is possible that their measured effects on insulin sensitivity may arise from effects on the muscle microvasculature, leading to alterations in metabolism. In support of this, studies have shown that Ang receptor blockade using losartan increases microvascular perfusion, leading to increased insulin delivery to muscle, and protecting against lipid-induced insulin resistance, thus protecting insulin's metabolic effects [171]. It is also important to note that these effects may not just be driven by plasma levels of vasoconstrictors, but also the receptor expression, as a change in expression of Ang receptor subtypes may alter endothelial function [86], and thus indirectly alter metabolism [93].

Phosphodiesterase (PDE) inhibitors were originally investigated as a possibly microvascular treatment that may increase metabolism. Studies on sildenafil have shown an effect to increase NO and induce arteriolar dilation [172], an effect that is now used in treatment of erectile dysfunction. Tadalafil, a PDE-5 inhibitor, increased capillary recruitment and also increased forearm glucose uptake in women with type 2 diabetes, possibly due to its effects on the microvasculature, though had no effect in healthy women [40]. These microvascular and metabolic effects have led to the proposal that tadalafil may be investigated as a treatment in insulin resistance [173], and this class of drugs have also been investigated in the setting of

http://dx.doi.org/10.5772/63535

muscular dystrophy; however, some have shown a direct effect on the myocyte to alter metabolism [174], so studies using this drug to link muscle microvascular function and metabolism are limited.

Some drugs, such as the thiazolidinediones, are known to have effects on blood flow and vasodilation [175, 176]. Some of this class of drugs can increase capillary density through angiogenesis [177], which may contribute to the beneficial metabolic effects of these drugs. However, while improvements in NO bioavailability are seen, this causes only minor effects on skeletal muscle blood flow [178]; and one review has indicated that while the effects of this class of drugs on macrovascular disease are well known, the microvascular effects, particularly to prevent the development of microvascular complications of diabetes, are less impressive [178]. While the thiazolidinediones may be protective in early cardiovascular disease, effects in end-stage atherosclerosis are deleterious [179] and so far data are lacking to indicate any substantial effects on the muscle microvascular to improve metabolism.

The glycocalyx may be considered another target for treatment. This dynamic structure is proposed to be involved in regulating metabolism [30–32], and is impaired by hyperglycemia, ischemia and other aspects of aging and type 2 diabetes [31, 32, 180, 181]. Thus, some have highlighted the glycocalyx as a potential therapeutic target for treatment in the acute care critical situation, long-term vascular health [182], as well as potentially in regulating metabolism; however, specific interventions are so far limited. Methods of protecting or restoring the damaged glycocalyx include synthesis of components or protection against enzymatic degradation, as well as blocking free radical production [182]. Some suggested pharmacological interventions have included infusion of albumin to maintain stability, inhibiting TNF-α, preventing enzymatic attack through use of anti-thrombin, or inhibition of mast-cell degranulation, though these strategies require further investigation [182].

A recent potential target for treatment of metabolic disease and energy excess is brown adipose tissue (BAT), which dissipates excess energy as heat from the body. BAT is scarce in humans, yet browning of white adipose tissue to form beige fat increases energy expenditure. Factors that affect brown adipose tissue, such as exercise, cold exposure and PGC1a (Peroxisome proliferator-activated receptor G coactivator-1 alpha), also can induce changes in skeletal muscle, and some studies have suggested that skeletal muscle may actually play a large role in these increases in energy expenditure [183]. There are several important components to increase the thermogenic capacity of a tissue: there must be an increase in mitochondria to metabolize glucose, uncoupling or proton leak to dissipate the energy, and an adequate supply of oxygen and glucose to cause this aerobic respiration. The angiogenesis that occurs during adipose tissue browning increases oxygen delivery, and we therefore hypothesize that blood vessels are an essential component of increased thermogenesis. This role of angiogenesis has not been completely studied; however, it has been shown that vascular endothelial growth factor-A (VEGF-A) overexpressing transgenic mice have increased vascularization and upregulated uncoupling protein-1 (UCP-1) and PGC-1a in BAT, and improves deleterious effects of high fat diet on metabolism [184]. From a metabolic perspective, overexpression of VEGF in adipose tissue protects against obesity and insulin resistance [82], even in the absence of changes in mitochondrial content and uncoupling, increased functional capillary density

by angiogenesis can increase metabolism. Skeletal muscle may undergo a process similar to browning of fat, leading to greater energy expenditure, and thus may be a target for treatment of obesity and its metabolic complications. In general, angiogenesis is likely to be a key player in increased oxidative capacity and energy expenditure in adipose tissue and muscle. If angiogenesis were also linked to increased mitochondrial content, causing a switch to a more 'red' muscle, and with potential effects on uncoupling in muscle, even greater energy consumption would occur.

Thus, there are many drugs and possibly other interventions that may target the muscle microvasculature, but simultaneously impact metabolism in muscle. In addition, factors that can change the basal or stimulated metabolic rate in muscle, by promoting angiogenesis or increased capillary density, may also have the potential for treating diseases associated with obesity and energy excess.

7. Conclusion

Metabolism in skeletal muscle, and in many other tissues, relies on appropriate delivery of oxygen and metabolites by the blood. The microvascular system is a major component in the delivery of any hormone, and should be considered in any endocrine disease. The muscle microvasculature is a dynamic system that can be altered by a wide range of factors, including vasoconstrictors and vasodilators, the nervous system, inflammation, obesity and other disease states. Thus, endothelial function is integral to regulating metabolism, in skeletal muscle and other tissues, and may be a target for treating not just diseases of the vascular system and cardiovascular disorders but also for treatment of metabolic diseases such as diabetes.

Acknowledgements

Many thanks to Dr Richard Bergman, Director of the Diabetes and Obesity Research Institute at Cedars-Sinai Medical Center.

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