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The Endothelium in Diabetes: its role in insulin access and diabetic complications

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Abstract

The vascular endothelium has been identified as an important component in diabetes-associated complications, which include many cardiovascular disorders such as atherosclerosis, hypertension and peripheral neuropathy. Additionally, insulin's actions on the endothelium are now seen as a major factor in the metabolic effects of the hormone by increasing access to insulin sensitive tissues. Endothelial function is impaired in diabetes, obesity, and the metabolic syndrome, which could reduce insulin access to the tissue, and thus reduce insulin sensitivity independently of direct effects at the muscle cell. As such, the endothelium is a valid target for treatment of both the impaired glucose metabolism in diabetes, as well as the vascular based complications of diabetes. Here we review the basics of the endothelium in insulin action, with a focus on the skeletal muscle as insulin's major metabolic organ, and how this is affected by diabetes. We will focus on the most recent developments in the field, including current treatment possibilities.

Keywords

diabetes; endothelium; insulin; interstitium; muscle; vascular

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, a figure almost double that of ten years previously[1]. In fact, 11.3% of the adult population was estimated to have diabetes, either diagnosed or undiagnosed. Currently the main treatment proposed for type 2 diabetes is lifestyle modification, including diet and exercise, though drugs are used when lifestyle changes are not sufficient.

Diabetes is often grouped with other diseases including dislipidemia, hypertension, cardiovascular disease and obesity. Together these conditions are termed the “metabolic syndrome” [2] or the “insulin resistance syndrome”, suggesting that insulin resistance *per se* may underlie the development of these conditions [3]. Common complications of diabetes include heart disease, blindness, kidney disease and peripheral neuropathy, often leading to amputation. Interestingly, many of these complications have a vascular basis.

INSULIN IN THE HEALTHY VASCULATURE

The primary effect of insulin is to appropriately store nutrients into suitable tissues. Insulin increases glucose uptake into skeletal muscle and suppresses endogenous glucose

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production by the liver, but also has effects regulating lipid and protein storage [4]. Aside from its primary effects on nutrient disposal and storage, insulin has hemodynamic effects.

Insulin at physiological concentrations causes the release of nitric oxide (NO), to vasodilate blood vessels [5], and endothelin (ET-1), a vasoconstrictor [6]. To initiate these divergent effects, binding to insulin receptors on the endothelial cells initiates two different insulin signaling pathways (Figure 1). The PI3K pathway leads to eNOS activation and NO release, which then causes vasodilation of the underlying vascular smooth muscle cell. A signaling cascade through the MAPK pathway leads to ET-1 release, which can cause vasodilation through ET_B receptors on the endothelial cell, but is more commonly associated with vasoconstriction by ET_A receptors on vascular smooth muscle cells. Since insulin causes a release of both ET-1 and NO, insulin-mediated vasodilation can often only be detected in the presence of ET-1 antagonism [7].

The combination of these vasodilation and vasoconstriction effects of insulin leads to the perfusion of a greater number of blood vessels throughout skeletal muscle in a process termed capillary recruitment [8]. This leads to an increased permeable surface area for diffusion to the interstitial space and thus an increased volume of distribution through the muscle [9], improving delivery of nutrients to the cell surface. Insulin is therefore able to manipulate the vasculature to improve insulin and nutrient delivery in skeletal muscle [10].

Consistent with the insulin-induced increase in perfusion, functional capillary density is directly correlated with insulin sensitivity in human skin microcirculation [11], reinforcing the idea that capillary recruitment is an important process in enhanced insulin-mediated glucose uptake. The increased microvascular blood volume observed with insulin is due to NO; blocking these vasodilation effects of insulin also diminished the metabolic effects [12]. We showed a strong correlation between insulin concentration at the cell surface and local glucose uptake [13], emphasizing the importance of insulin access to skeletal muscle, and thus insulin sensitivity. Thus, modification of skeletal muscle perfusion can have major effects on metabolism, as reviewed in Barrett et al [14], and thus insulin sensitivity.

Aside from blood flow effects, insulin must cross the endothelium to reach its target tissue. Historically, the method by which insulin crossed the endothelium in muscle was quite controversial: some studies showed that the transport of insulin was not saturable, suggesting that receptors were not needed for transendothelial transport of insulin [15,16]. But recent results support saturable transport [17]. Wang et al [18] have shown that insulin does indeed co-localize with the insulin receptor in endothelial cells, then demonstrated the involvement of caveolin in the internalization of insulin into these cells [19] (Figure 1). This would be an essential step for the transport of insulin across the cell, but further studies are required to ensure that colocalization occurs in an *in vivo* situation, and that it is in fact linked to release to the interstitium, necessary for transendothelial transport *in vivo*. It is not yet known whether this is a bi-directional effect, allowing export from the interstitial space to the plasma. A concentration gradient has been detected between plasma and the interstitium of skeletal muscle [20,21], with a much higher level of insulin in the plasma, though the mechanisms involved in regulating transport and maintaining the lower interstitial level are not clear as yet. Further work is therefore required to more fully understand the role of the insulin receptor in the transendothelial transport of insulin.

The specific role of insulin signaling in the endothelium has been examined using mouse models. Mice with a specific endothelial cell knock out of IRS-2, which specifically inhibits the PI3K pathway (Figure 1), exhibit a reduced ability of insulin to increase capillary blood volume and impaired insulin-mediated glucose uptake, most likely due to a reduced interstitial insulin level [22]. This latter study did not report whether the reduced insulin

levels in the interstitium are due to the reduction in insulin-mediated capillary recruitment, impaired transport across the endothelium, or a combination. The finding of reduced interstitial insulin [22] is at odds with previous data showing insulin receptor knockout in the endothelial cell had no effect to limit access of insulin[23], but showed a reduction in both NO and ET-1 mRNA, as well as mild insulin resistance. One important aspect to note is that complete knockout of endothelial insulin signaling blocks direct vascular effects of insulin, whereas IRS-2 knockout in endothelial cells offers a more specific inhibition to just one branch of the insulin-signaling cascade[22]. While it is difficult to determine whether endothelial insulin signaling is necessary for receptor-mediated transport across the endothelium, insulin signaling in endothelial cells is required for an insulin-mediated increase in capillary volume, and possibly increased interstitial levels. Thus, it can be concluded that insulin signaling in endothelial cells is important in insulin action, possibly due to access of insulin to the muscle (reviewed in [10]).

The Endothelium in Diabetes

The insulin resistance associated with diabetes is usually considered a cellular inability of insulin to increase glucose disposal or suppress glucose production, leading to hyperglycemia. However, insulin resistance manifests itself in many tissues and cell types including the endothelium. Endothelial dysfunction often coincides with the development of insulin resistance, which has implications for insulin and nutrient access to muscle and other tissues.

Our recent studies have emphasized the importance of insulin access to skeletal muscle, with a strong correlation between insulin concentration at the cell surface and local glucose uptake [13], and an impairment of insulin access in cases of insulin resistance [24,25]. Impaired insulin-mediated capillary recruitment would reduce distribution of flow through muscle, and thus delivery of insulin to the interstitial space [10] (Figure 2). A detailed study in mice by Kubota et al demonstrated that endothelial insulin signaling is significantly impaired after a high fat diet, coinciding with a reduction in insulin-induced capillary recruitment and reduced interstitial insulin [22]. Thus the endothelial insulin signaling required for delivery of insulin to the interstitial space can be inhibited physiologically by diet. A recent study in obese women with postprandial hyperglycemia used a microdialysis technique to demonstrate that a higher circulating level of insulin was required to obtain similar interstitial insulin concentrations to lean controls [26]. This altered insulin gradient was shown in both skeletal muscle and adipose tissue; interestingly, interstitial insulin in the adipose tissue was much closer to the plasma concentration in healthy women, and showed a more substantial impairment in obese women. Thus impaired delivery of insulin in obesity may contribute to metabolic insulin resistance and diabetes.

Modest fasting hyperglycemia is a hallmark of pre-diabetes, and recent studies have observed that hyperglycemia caused mitochondrial fragmentation and altered mitochondrial dynamics, associated with increased mitochondrial reactive oxygen species (ROS) production [27]. This increased oxidative state can cause a rapid breakdown in NO, thus impairing vasodilation[28]. This impairment could be responsible for the endothelial dysfunction observed in diabetes when hyperglycemia is established; however endothelial dysfunction is often evident prior to a significant elevation in plasma glucose levels, and can be induced by factors other than hyperglycemia. In fact, a family history of diabetes is associated with reduced endothelial function absent diagnosis of type 2 diabetes [29]. Therefore mitochondrial dysfunction due to hyperglycemia may contribute to impaired endothelial function, but is unlikely to be the primary cause.

Since poor diet has often been considered a contributor to diabetes, dietary aspects other than hyperglycemia (discussed above) on the microcirculation have recently been studied.

When poor diet leads to obesity, impaired endothelium-dependent vasodilation has been detected in the visceral fat as compared to subcutaneous adipose tissue [30]. Excess lipid induces insulin resistance in the microvasculature of skeletal muscle and cardiac muscle in humans [31] by reducing insulin's effects on both microvascular blood flow and volume. In one study, adipocytes from mice fed a high fat diet were shown to alter vascular smooth muscle proliferation and cell mortality [32], this may be particularly important when perivascular fat is considered [33]. Various trans fatty acids have been shown to increase superoxide production and induced inflammation [34], as well as impairment of endothelial insulin signaling and NO production in human endothelial cells. While *in vitro* results have not yet been translated into a physiological situation, diet may have both direct effects on vascular function [34], as well as indirect effects through adjacent tissues such as adipocytes [32].

We have cited studies showing impaired endothelial function in cardiac muscle, [31], skeletal muscle [31], and visceral fat[30]. Loss of endothelial insulin signaling accelerates atherosclerosis in an animal model [35], and reduced microvascular function is implicated in the development of diabetic complications, including nephropathy[36], retinopathy[37], neuropathy, and more recently Alzheimer's disease [38], suggesting effects on the kidney, retina, and central nervous system. Thus, endothelial function is impaired in many tissues in diabetes, contributing to reduced insulin metabolic action as well as diabetic complications, and presents the endothelium as a potential target of therapy in diabetes.

The Endothelium as a target in Diabetes treatment

Since up to 50% of the metabolic deficit observed in diabetes can be attributed to impairments in the vascular effects of insulin, improving endothelial function is a viable target for treatment of diabetes. We recently reviewed the role of the endothelium in the function of a variety of hormones, and noted that treatment of endothelial function may also improve hypertension and other cardiovascular disorders associated with the metabolic syndrome [39], including cardiomyopathy, retinopathy, neuropathy, nephropathy and atherosclerosis. Improving vascular endothelial function at an earlier disease stage can improve insulin resistance and reduce the development of cardiovascular risk factors, but may also improve life expectancy of patients suffering from peripheral artery disease [3]. A recent review focused on the benefits of developing new compounds that upregulate NO synthesis, target ROS-producing enzymes or mimic endogenous antioxidants, concluding that this strategy could help prevent diabetes and its associated vascular complications [28].

The role of the endothelium in diabetes depends upon the structure of the endothelium in each tissue [40]. The retina, peripheral nerves and kidney are particularly susceptible to defects in vascular function associated with diabetes, and lead to diabetic complications. Often, capillary rarefaction is observed, which can be either a functional or structural reduction in perfused capillaries[41]. Since blood supply is essential for nerve function, decreased microvascular effectiveness could contribute to diabetic neuropathy. In proliferative diabetic retinopathy, a reduction in perfusion is followed by angiogenesis, though new vessels often have abnormal structure and function [37]. A recent review discusses the role of endothelium in diabetic nephropathy [36], emphasizing that endothelial dysfunction may be the link between kidney disease and systemic vascular disease. Therefore, the endothelium is a potential target for treatment in diabetic complications, independent of any effects to improve metabolic function.

While there are many diabetes treatments currently available, here we review those with a focus on the vasculature. Angiotensin receptor blockers, as well as incretins and thiazolidinediones have been major foci of much of the recent research in the area.

Angiotensin Receptor Blockers—Angiotensin receptor blockers are used to treat hypertension, but also show improvements in microvascular function [42]. While Jonk et al showed no effect on insulin-mediated glucose uptake, other studies have demonstrated improvements in insulin sensitivity as well as reductions in blood pressure [43]. Angiotensin receptor subtypes include Angiotensin II type 1 receptors, which signal for vasoconstriction, and type 2 receptors, which can cause vasodilation (reviewed in [44]). Interestingly, a new study shows that AT2R-mediated vasodilation is elevated in diabetic mice compared to controls, with a higher NO production [45]. This mechanism may assist with the anti-hypertensive effects of AT1R blockade, as blocking the vasoconstriction of AngII may lead to a net vasodilation through AT2R. The involvement of AngII in insulin resistance is reviewed by Muniyappa and Yavuz[44], and the effects of AT1R blockade in diabetes have been investigated for several years. The most recent results to emerge from these studies show that while AT2R blockade reduced insulin-mediated glucose uptake and prevented insulin-mediated increases in capillary recruitment, AT1r blockade with losartan increases insulin-mediated skeletal perfusion [46]. Losartan did not increase insulin-mediated glucose uptake in healthy rats, [46], yet angiotensin receptor blockers can increase glucose uptake in individuals with impaired glucose metabolism[47,48], suggesting that improvements may only be detectable in an already impaired state. Therefore, further investigation is required on AT1R blockers due to their beneficial effects on microvascular function and insulin resistance.

Statins have been shown to improve endothelial function and reduce oxidative stress, possibly independent of their LDL-lowering abilities. While different statin treatments exhibited the same improvement in endothelial function, atorvastatin caused a greater effect to reduce oxidative stress compared to pravastatin [49]. Tian et al [50] showed that rosuvastatin reduced oxidative stress in db/db mice possibly through inhibition of Angiotensin II type 1 receptor, again without altering lipid profiles. The authors suggested that statins could have renovascular protective effects in diabetic nephropathy, though these protective effects could potentially extend to other vascular pathologies associated with diabetes. Augmented Ang-II mediated contraction is noted in db/db mice, and rosuvastatin treatment normalized the upregulation of Ang-II type 1 receptor [50]. This latter result may not therefore have much physiological relevance when compared to a clinical situation, however it provides an interesting link between statin treatment and Ang-II receptor activity.

Thiazolidinediones—Recent efforts have focussed on the microvascular effects of thiazolidinediones. By stimulation of peroxisome proliferator-activated receptor (PPAR)- γ , this class of drugs has been shown to have anti-inflammatory, anti-atherogenic, and anti-oxidative effects. While prescription of rosiglitazone is limited due to reported increased risk for myocardial infarction and heart failure, its molecular mechanisms of action are still being studied [51]. A recent study of rosiglitazone detected increases in capillary density and angiogenic potential in adipose tissue, as well as reduced adipocyte size and increased serum adiponectin [52]. Six weeks of rosiglitazone treatment was sufficient to improve adipose tissue vascularization, which as discussed above may improve nutrient delivery, though effects in other tissues are yet to be investigated. Pioglitazone has also recently been shown to have vascular effects in retinal arterioles, improving both endothelium-dependent and -independent vasodilation [53]. Taken together, these positive effects of thiazolidinediones on the vasculature in different tissue beds provide encouragement for further investigation into their use to improve vascularization, endothelial function, and thus insulin sensitivity.

Incretins—Recently, interest has increased regarding demonstrated effects of certain incretins on the endothelium. GLP-1 is a gut hormone with a short half-life that has a spectrum of effects on insulin sensitivity, gastrointestinal function and the pancreatic islets.

The GLP-1 receptor on the endothelium is linked to eNOS activation through a PI3K dependent pathway, which causes proliferation of human coronary artery endothelial cells [54] and vasodilation, leading to an increase in the perfused microvasculature, and increased glucose uptake [55]. A GLP-1 agonist was found to have anti-inflammatory capabilities leading to reduced renal injury in type 1 diabetes [56], yet these protective effects were diminished in a model of type 2 diabetes [57]. GLP-1 has been shown to have effects on eNOS phosphorylation, leading to increased NO production and flow mediated vasodilation [58] [59]. Thus, GLP-1 agonists may have direct effects on the vasculature and NO production, or indirect beneficial effects through improved glucose homeostasis and therefore restored endothelial function.

Endothelial Progenitor Cells—Endothelial progenitor cells have been identified as both a biomarker for vascular dysfunction in diabetes, as well as potential treatment due to their ability to initiate vascularization [60]. The most recent studies have investigated the role of EPCs in diabetic wound healing [61] and stroke [62]. In particular, one study has blocked CXCR4 to increase progenitor cell recruitment, which reduces mortality after myocardial infarction [63]. Notably, recent investigations of EPCs focus on the improvement of major events resulting after diabetes and its comorbidities are established. The potential for EPCs to induce neovascularization and thus prevent the development of these cardiovascular outcomes should also be investigated. It was theorized that exogenous EPCs may only have beneficial effects in diabetic subjects that have a reduced level of EPCs, or compromised EPC function [60]. EPCs have reduced angiogenic potential in diabetic animals, suggesting that EPC function is already impaired, and as such their application to human disease requires further study, and may not be as beneficial as other options.

Conclusion

The endothelium plays a major role in diabetes and its associated cardiovascular disorders. Current research includes a focus on the effects of insulin directly on the endothelium, clarifying the purpose of the insulin signaling in the endothelial cell and the effect that disruptions in this cascade may have on insulin sensitivity. Vascular effects of insulin increase its delivery to tissues, and thus increase insulin action. Endothelial function is impaired in diabetes, obesity, and the metabolic syndrome, which could reduce insulin access to the tissue, and thus reduce insulin sensitivity independently of direct effects at the muscle cell. For this reason, much investigation into various molecules that can alter the endothelium in disease is underway, with great potential observed in the angiotensin receptor blockers, statins, and the thiazolidinediones.

Clearly, intense focus on insulin signaling and insulin resistance in myocytes and liver cells is being expanded to consider the *delivery* of important molecules to target tissues not just on their effects on said tissues demonstrated *in vivo*. Delivery of important molecules represents a new and exciting area for therapies in diabetes and related metabolic disorders, including cardiovascular disease.

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Figure 1.

Insulin receptors in endothelial cells co-localize with caveolae, and insulin signaling in endothelial cells leads to two downstream signaling pathways. Activation of the ERK pathway leads to ET-1 release, causing vasoconstriction in vascular smooth muscle cells, and the PI3K pathway leads to NO release and vasodilation. Studies have also shown that insulin binding to the insulin receptor is required for transcytosis of caveolae, possibly for translocation of insulin from the plasma to the interstitial space. (Image created in powerpoint)

Figure 2.

Blood is distributed throughout the tissue in capillaries. The number of perfused capillaries can be increased by exercise and insulin, leading to a situation depicted on the left.

However, in cases of insulin resistance, insulin is no longer able to recruit capillaries, and more of the tissue is left unperfused, as shown on the right. This reduced flow will reduce insulin delivery to tissues, but can also cause ischemia in the retina, kidney and peripheral nerves and muscle, leading to complications associated with diabetes. (Image created in paint)