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Endothelium as a gatekeeper of fatty acid transport

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Abstract

The endothelium transcends all clinical disciplines and is key to the function of every organ system. A crucial, but poorly understood role of the endothelium is its ability to control the transport of energy supply according to organ needs. Fatty acids (FAs) in particular represent a key energy source that is utilized by a number of tissues, but whose utilization must be tightly regulated to avoid potentially deleterious consequences of excess accumulation, including insulin resistance. Recent studies have identified key endothelial signaling mechanisms involving vascular endothelial growth factor B, peroxisome proliferator-activated receptor- γ , and the peptide ligand apelin, that are critical to endothelial regulation of FA transport. Here we discuss the mechanisms by which these signaling pathways regulate this key endothelial function.

Keywords

VEGF-B; PPAR- γ ; Apelin; Endothelium; Fatty acid transport

Endothelium as a key energy barrier

Our understanding of the endothelial layer has progressed significantly since its historical view as an inert layer of cells that serve as the inner lining of “plumbing” for the circulatory system [1]. Now more than ever, the endothelium is implicated in regulation of both physiologic and pathologic processes via its signals and cues to the encasing organs in the context of development and function. The heterogeneity of the endothelial layer is also remarkable, from differences that exist based on the location of the conduit vessels (arteries vs. veins) to the functional heterogeneity in the context of specific organs, such as the heart, liver, and adipose tissue. Such diversity of the endothelium is key to specialized roles of its function, including permeability, leukocyte trafficking, and ability to achieve hemostasis marking some key aspects of endothelial function that varies depending on the location and the type of blood vessel. The dense network of endothelial capillaries is especially important for function of multiple organ systems, and indispensable for regulating transport of fluid and nutrient from the circulation to the target tissues. Endothelial cells (ECs) outnumber the tissue specific cells in the majority of the cases, with minimal distances (as close as 15 μ m) in organs such as the heart [2]. Such architecture provides optimal context for the diffusion and transport of nutrients and oxygen to the target tissues, including the heart and the

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skeletal muscles. The vascular network needs to readily adapt to significant fluctuations in metabolic changes. Periods of fasting are associated with increased release of FAs from the white adipose tissue (WAT) into the circulation, to be utilized by highly metabolic tissues such as the heart and skeletal muscles. This release, as well as the endothelial mediated uptake, needs to be closely regulated. The concept of endothelial mediated FA transport has existed for many years, but has transitioned from a viewpoint of passive, diffusive transfer to a highly regulated, active process that involves multiple, complex signaling pathways [3]. This metabolic function of the endothelium, which likely has adapted evolutionarily to accommodate periods of fasting and regular diet, has been challenged by the emergence of obesity as a worldwide public health problem. Deleterious consequences of excess FA uptake in tissues including the skeletal muscle and the heart, and the resulting metabolic derangements such as impaired glucose uptake and insulin resistance [4, 5], continue to exponentially rise.

Obesity, metabolic syndrome, and endothelial dysfunction

Global changes, including trade liberalization, economic growth, and urbanization, have promoted lifestyle changes that have resulted in a net positive energy balance, with greater sedentary lifestyles and transitions to increased consumption of animal products, refined grains and sugar [6]. The worldwide obesity pandemic associated with these changes has brought to the forefront the need to better understand the endothelial mechanisms that can be targeted as novel therapeutic strategies to protect against the metabolic derangements in such context. These changes in metabolic state, in turn, have been widely associated with endothelial dysfunction. Endothelial dysfunction refers to the abnormal behavior of ECs under conditions that are associated with metabolic disturbances, including diabetes and insulin resistance. Signaling perturbations such as excess of pro-inflammatory cytokines (interleukin 6 (IL-6) [7, 8] and tumor necrosis factor α (TNF- α) [9] being two of those that are well-recognized) likely have a significant impact on promoting endothelial conversion from a quiescent phenotype towards an activated one. Signaling consequences include disruption of nitric oxide (NO) synthesis and its homeostatic effects [10], and exacerbation of reactive oxygen species (ROS) mediated effects [11]. These pro-inflammatory milieus likely place a significant burden on the endothelial signaling mechanisms that mediate the normal uptake of circulating FAs, leading to accumulation in non-adipose tissues such as the heart and skeletal muscles. Excess FAs in these organs are widely associated with impairment of glucose uptake and insulin signaling, leading to insulin resistance [4, 5]. What regulates the endothelial function as a regulator of FA transport and uptake by the target tissues have remained poorly defined until recently; emerging evidence make it evident that there is a clear orchestration of endothelial FA transport by molecules including vascular endothelial growth factor-B (VEGF-B), PPAR- γ , and apelin, that directly target the endothelium and determine its ability to maintain a balance of energy transfer and storage.

VEGF-B targeting of endothelial fatty acid transport proteins in regulation of FA transport

The VEGF family of growth factors has been studied extensively as key regulators of angiogenesis [12]. There are at least five members in this family, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF (placental growth factor). All members of the VEGF family bind to the VEGF receptors (VEGFRs), which are tyrosine kinase receptors expressed by ECs and by some leukocytes [13]. Of these factors, VEGF-B has been found to be less potent than the other class members in promoting angiogenesis, but does promote coronary arterIALIZATION in rats [14], with both pro-angiogenic (in ocular angiogenesis [15]) and anti-angiogenic (in tumor angiogenesis [16]) effects. A transgenic mouse line with cardiomyocyte specific overexpression of VEGF-B was found to induce cardiac hypertrophy

with preservation of cardiac contractility, but also found to have evidence of mitochondrial lipotoxicity [17]. Based on the predominant expression of its receptors, namely VEGFR1 and neuropilin 1 (NRP1), being in the ECs, these observed changes in the cardiomyocytes are thought to be predominantly mediated via the endothelium.

Two recent studies shed further insights into the endothelial based mechanisms by which VEGF-B regulates endothelial metabolic control (Figure 1). Hagberg et.al. made the initial observation that VEGF-B expression was closely correlated to expression of nuclear-encoded mitochondrial genes, suggesting that VEGF-B may be important in metabolism [18]. Evaluation of *Vegfb*^{-/-} mice led to the observation that lipid uptake in the heart, skeletal muscle, and brown adipose tissue (BAT) was significantly decreased, while excess lipid uptake was observed in WAT. This was associated with a likely compensatory increase in glucose utilization and insulin sensitivity, which was in part attributed to increased expression of *Glut4*, a glucose transporter in heart and skeletal muscles.

The endothelial based metabolic effects of VEGF-B were linked to increased expression of fatty acid transport proteins 3 and 4 (FATP3 and FATP4). FATPs (solute carrier family 27) are a family of integral transmembrane proteins that enhance cellular long chain FA uptake [19–21]. The mechanism by which FATPs mediate long chain FA uptake remains poorly defined, and may involve cooperation with other transmembrane proteins such as Cluster of Differentiation 36 (CD36) [22, 23]. Of the FATPs evaluated in response to VEGF-B stimulation, only FATP3 and FATP4 were induced in ECs [18]. FATP3 and FATP4 were increased in mouse hearts that overexpress VEGF-B, and conversely were reduced in *Vegfb*^{-/-} mouse hearts. VEGF-B effect on FATP3 and FATP4 expression is mediated by the receptors VEGFR1 and NRP1, as their expression was significantly decreased in *Flt1-TK*^{-/-} mice [24], lacking the tyrosine kinase domain of VEGFR1, and *Nrp1-EC*^{-/-} mice [25], with EC specific deletion of the *Nrp1* gene. These initial findings were further extended to the context of rodent diabetic models in a follow up study [26]. Again, invoking the primary mechanism of VEGF-B mediated tissue lipid deposition, *Vegfb*^{-/-} mice on either high fat diet (HFD) or on the *db/db* diabetic background (carrying mutation in the leptin receptor [27]) were found to have normalization of glucose levels. This was in the context of comparable insulin levels with increased insulin sensitivity. Rather, the improved metabolic state was attributed to decreased lipid storage in the heart, skeletal muscle, and pancreas, rendering these tissues to be more efficient in their glucose uptake. Moreover, normalization of the high density lipoprotein-c (HDL-c) to low density lipoprotein-c (LDL-c) ratio, as well as decreased circulating levels of non-esterified fatty acids (NEFAs) and ketones were also seen in the *Vegfb*^{-/-} mice, although the mechanism of these serum metabolic improvements remain unclear.

Advancing the potential therapeutic aspect of their mechanism, *db/db* mice were injected with an anti-VEGF-B antibody (2H10). Administration of 2H10 led to improved glucose levels, decreased lipid deposition in skeletal muscle and heart, and improved glucose tolerance. 2H10 administration also led to improved triglyceride levels, HDL-c to LDL-c ratio, NEFA and ketone levels.

Collectively, these observations demonstrate a promising role for antagonism of VEGF-B as a potential therapeutic target in type 2 diabetes (T2D). However, the path towards developing this as a clinically feasible anti-diabetic therapy would need to overcome a number of hurdles. First, although VEGF-B is not known as a crucial factor for normal angiogenesis, overexpression of VEGF-B in rats resulted in robust coronary arteriogenesis [14]. Abrogating such effect of endogenously expressed VEGF-B may be detrimental in patients with T2D, many of whom suffer from myocardial ischemia and coronary artery disease, and would potentially benefit from VEGF-B's coronary arteriogenic effects.

Moreover, prominent neuroprotective and neurogenic effects of VEGF-B have been described, which would be important considerations given the high prevalence of diabetic neuropathy [28, 29].

PPAR- γ as a key regulator of endothelial FA transport

PPAR- γ , also known as the glitazone receptor, represents a class of nuclear receptors that belong to the nuclear receptor superfamily of ligand-inducible transcription factors [30]. Three PPARs exist in mammals: PPAR- α (NR1C1), PPAR- β/δ (NR1C2), and PPAR- γ (NR1C3). The ligands of PPARs include common dietary fats such as oleic, linoleic and linolenic acids, as well as other diverse group of lipid metabolites [31–33]. PPARs bind to PPAR-responsive transcriptional regulatory elements (PPREs) as heterodimers with retinoid X receptor (RXR), and regulate transcription of key target genes involved in biological processes such as adipogenesis, lipid storage and transport, inflammation, and metabolic homeostasis [34, 35]. Of the PPARs, PPAR- γ has been studied extensively, and targeted therapeutically by the class of anti-diabetic drugs known as thiazolidinediones (TZDs). Although an endogenous ligand for PPAR- γ remains elusive [31, 33], TZDs provide potent activation of PPAR- γ with robust insulin-sensitizing activities [36]. Unfortunately, the initial enthusiasm for these agents have been hampered by recent meta-analyses of clinical trials that have demonstrated increased risk of cardiovascular morbidities such as congestive heart failure and myocardial infarction and all-cause mortality with one of these agents, rosiglitazone [37]. A second agent currently available, pioglitazone, has also been associated with increased risk of congestive heart failure and bladder cancer, and have been taken off the market in a number of European and Asian countries [38–40]. These findings demonstrate a clear need to reconsider and improve upon the use of PPAR- γ agonists as a mainstay therapy for T2D, to achieve better outcomes that can minimize the adverse effects while maintaining the insulin-sensitizing efficacy.

PPAR- γ in the endothelium

PPAR- γ is expressed in both WAT and BAT and with highest expression in WAT, where it serves as a key regulator of adipogenesis, lipid metabolism, and insulin sensitivity [30, 41]. In addition to its specific role in adipocytes [42], cell type specific deletion of PPAR- γ have shed insights into its role in neurons [43, 44], myocytes [45, 46], and hepatocytes [47]. Most pertinent to the present topic, the metabolic phenotypes of EC specific deletion of PPAR- γ have been recently described [48, 49]. Prior endothelial-based studies of PPAR- γ function have predominantly described an anti-inflammatory effects of PPAR- γ , with mechanisms including decreased endothelial expression of chemokines [50], inhibition of NF- κ B [50], and inhibition of pro-inflammatory adhesion molecules such as ICAM-1 and VCAM-1 [51, 52]. The key limitation of these findings is the reliance on cell culture systems and PPAR- γ agonists including TZDs and 15 deoxy- Δ -12,14-prostaglandin J2 (15-dPGJ2), providing a rather limited perspective of endothelial PPAR- γ function.

Two recent studies utilized the Cre recombinase driven by the Tie2 promoter to specifically delete PPAR- γ in the endothelial and hematopoietic cells (*Pparg-EC*^{-/-}) (Figure 2) [48, 49]. The earlier study by Kanda and colleagues found *Pparg-EC*^{-/-} mice to have significantly decreased adiposity, increased insulin sensitivity, and glucose tolerance when they were metabolically challenged with HFD [49]. These improved metabolic states were associated with significantly increased circulating free FA and triglyceride levels in the *Pparg-EC*^{-/-} mice compared to the control mice, which also inversely correlated with decreased triglyceride content and increased insulin sensitivity in the skeletal muscles. Moreover, administration of the PPAR- γ agonist rosiglitazone led to significant increase in adipose tissue weight in wildtype mice; however, *Pparg-EC*^{-/-} demonstrated an overall weaker response to rosiglitazone. Given that the Tie2 promoter can also lead to expression of the

Cre recombinase in the hematopoietic cell lineage, elegant bone marrow transplantation studies to reconstitute the hematopoietic PPAR- γ established that the metabolic effects observed in these mice were primarily due to the endothelial PPAR- γ function. Lastly, despite the metabolic improvements in *Pparg-EC*^{-/-} mice, these mice demonstrated impairment of vasodilation, suggesting distinct mechanisms that mediate the endothelial metabolic response from arterial vasoreactivity. The more recent study [48] also examined the role of endothelial PPAR- γ function using an independent line of *Pparg-EC*^{-/-} mice, focusing on fatty acid binding protein 4 (FABP4, also known as AP2), and CD36 (fatty acid translocase, FAT), which had been found to be decreased in *Pparg-EC*^{-/-} mice [49]. FABP4 is a member of the FABP family of proteins, which consist of at least 13 members that serve as intracellular lipid chaperones. These proteins reversibly bind hydrophobic ligands such as long chain FAs, eicosanoids and other lipids [53]. However, the exact biological function of these proteins remains poorly defined. FABPs vary in their expression profile; however, at least three FABPs, namely FABP3, FABP4, and FABP5 are known to be expressed in ECs [54–56]. CD36 is a membrane glycoprotein that is present on multiple cell types, including platelets, mononuclear phagocytes, adipocytes, myocytes, hepatocytes, and some epithelia [57]. In addition, CD36 is also expressed in microvascular ECs, where multiple studies have described its anti-angiogenic effects as a receptor for thrombospondin-1 [58, 59]. In the context of lipid metabolism, CD36 is a key membrane molecule involved in transport of long chain FA uptake [60, 61]. *Cd36*^{-/-} mice were found to have decreased FA uptake in the heart, skeletal muscle, and adipose tissue, associated with concomitant increase in insulin sensitivity and glucose uptake [22, 62]. In human microvascular ECs, induction of FABP4 and CD36 by pioglitazone was found to be important for enhanced FA uptake by the ECs, as knockdown of FABP4 or CD36 abrogated the effects of pioglitazone. Moreover, uptake of the FA analog 15-[piodophenyl]-3-[R,S]-methyl pentadecanoic acid (¹²⁵I-BMIPP) was significantly reduced in the heart, skeletal muscle, and adipose tissue of the *Pparg-EC*^{-/-} mice after olive oil gavage, although this decrease was not evident in two other nutritional states (HFD and standard chow diet) [48].

A number of key observations can be derived from these studies. First, it is clear that endothelial PPAR- γ is an important gatekeeper of FA transport, similar to the effects of VEGF-B. Second, FABP4 and CD36 are identified as important endothelial PPAR- γ transcriptional targets, although additional *in vivo* studies will be necessary to establish these molecules as the primary mediators of PPAR- γ effect in the endothelium. These findings also raise an intriguing question with respect to the ongoing debate on the use of TZDs to treat T2D. Despite multiple studies demonstrating significant improvement in both diabetic and cardiovascular parameters, recent studies have identified increased cardiovascular risk in some contexts [37]. One could hypothesize that such a difference in outcomes may in part be related to the cell types that may be preferentially targeted by specific TZDs, as a TZD that significantly activates endothelial PPAR- γ and increase FABP4 and CD36 expression may promote endothelial and cardiac dysfunction. Moreover, these findings support the potential therapeutic role of FABP4 or CD36 inhibition [63, 64], which could provide further protection against cardiovascular complications of T2D.

The metabolic effects of VEGF-B and endothelial PPAR- γ function also suggest key differences. Both VEGF-B and PPAR- γ seem to promote endothelial mediated FA transport into the encasing tissue. However, VEGF-B effects are predominantly restricted to those tissues that highly express the ligand—namely the skeletal muscle, heart, and BAT, with its inhibition leading to shunting of FA to the WAT; endothelial PPAR- γ , on the other hand, has a broader effect on enhancing FA tissue uptake, including its key role in uptake by the WAT promoting insulin sensitivity. These findings raise the possibility that the PPAR- γ regulated increase of endothelial FABP4 and CD36 may have secondary effects in heart and

the ECs themselves, which may be contributing to the emerging cardiovascular adverse effects of TZDs.

Apelin and regulation of endothelial permeability: role in its effect as insulin sensitizer?

Emerging studies of apelin/APLNR signaling have identified a key role in insulin sensitivity. Since its original description as a peptide that binds to the orphan receptor APLNR (also known as APJ or AGTRL1), apelin has been studied extensively in the context of cardiac and vascular function [65]. Apelin can augment cardiac contractility, and induce vasorelaxation at least in part via NO dependent manner. These effects of apelin are attributed to its binding of the APLNR receptor, a seven transmembrane G protein coupled receptor that is thus far the only known receptor of the apelin ligand. Apelin and APLNR expression have been studied in many contexts. The most reliable expression data of apelin is from the apelin-lacZ reporter mouse, demonstrating that it is predominantly expressed in the microvascular ECs [66]. Adipocyte expression has also been demonstrated [67, 68], but whether its main cellular source of expression is from the adipocytes themselves or the encasing ECs remains to be determined. With respect to the APLNR receptor, the lack of a robust antibody has clouded determination of its tissue expression pattern. Existing studies suggest that it is expressed in ECs, cardiomyocytes, and vascular smooth muscle cells. In situ hybridizations, including our unpublished data, have demonstrated predominant endothelial expression in the developing cardiovascular system [69].

Apelin in diabetes

Emerging body of work has evaluated the role of apelin signaling as an insulin sensitizer [70, 71]. In obese, insulin-resistant, HFD fed mice, injection of apelin-13 (a cleaved product of apelin with highest affinity for the receptor) led to improved glucose tolerance via increased glucose uptake in skeletal muscle [70]. This effect of apelin was associated with increased endothelial nitric oxide synthase (eNOS) phosphorylation, as well as increased phosphorylation of AMPK and Akt in isolated soleus muscle. Providing perhaps even stronger genetic evidence, separate studies evaluated the metabolic phenotype of *Apln*^{-/-} null mice [71, 72]. These mice on normal chow diet exhibited significantly increased insulin levels and developed glucose intolerance, associated with weight gain and increased abdominal fat. Subjecting *Apln*^{-/-} mice to HFD and high sucrose water resulted in further exacerbation of the insulin resistant, glucose intolerant phenotype [71]. Overall, this line of evidence demonstrates an insulin sensitizing effect of apelin that can be explored as another strategy to improve metabolic and cardiovascular outcomes in T2D.

Apelin's role in maintenance of vascular integrity: indirect effect of FA uptake inhibition leading to improved insulin sensitivity?

The recent data demonstrating a role for apelin signaling as an insulin sensitizer begs the question: what are the cells that are targeted by apelin? The short term, acute effects of apelin were tested in isolated skeletal muscles, which may suggest that this is a direct targeting of APLNR on the skeletal myocytes. Moreover, increased muscle FA oxidation in response to apelin stimulation has been described [73]. However, no definitive evidence of APLNR expression in skeletal myocytes currently exists. Moreover, as described above in cases of VEGF-B and PPAR- γ , endothelial-based metabolic regulation may also be a significant factor in apelin mediated metabolic response. Vascular effects of apelin on the mature endothelium include antagonism of angiotensin II induced atherosclerosis and aneurysm [74], inhibition of vascular permeability [75], and promotion of pleiotropic effects of statin agents (HMG-CoA reductase inhibitors) in ECs [76]. Moreover, roles in lymphatic vascular function and pulmonary vascular disease have also been described [77–80]. Recent

work by Sawane and colleagues highlights how the role of apelin as a regulator of transendothelial FA transport may be involved in its metabolic effects (Figure 3) [77]. These authors suggest that the metabolic changes in *Apln*^{-/-} mice, including weight gain and increased adipocyte mass, are related to increased vascular permeability that allows for greater FA uptake in the adipose tissue. Their hypothesis was further supported by demonstration that apelin transgenic mice are protected against obesity and decreased vascular permeability. Assuming that apelin's effects on regulation of vascular permeability and FA uptake into adipose tissue also functions in a similar manner in other organs such as heart and skeletal muscles, one could postulate that inhibition of FA transport to these organs may be a key mechanism of apelin mediated increase in insulin sensitivity. Such possibility remains to be tested. Moreover, further analysis of intrinsic endothelial transcriptional targets regulated by apelin/APLNR [81] may lead to identification of other mechanisms by which apelin affects endothelial FA transport, glucose utilization, and insulin sensitivity. Additional in vivo studies using conditional, tissue specific *Aplnr* null mice will provide further insights into the metabolic effects of apelin signaling.

Concluding Remarks and Future Perspectives

The signaling paradigms discussed here demonstrate the complexity of the endothelial layer as a key regulator of metabolic homeostasis. It is most likely that rather than working independently from one another, the mechanisms described here are integrated in ways yet to be fully understood. A recent study demonstrating regulation of apelin expression by PPAR- γ in pulmonary artery ECs is an example of such possibility [82]. In addition to apelin and VEGF-B, other adipokines and endothelial targeting growth factors also will likely have roles in regulation of endothelial regulation of FA transport. Moreover, recent studies on the role of glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1) have shed light on the role of this molecule in the hydrolysis of triglycerides to generate FAs (Box 1). Ultimately, combinatorial approaches targeting specific aspects of endothelial signaling may lead to more robust strategies to counter the metabolic imbalances caused by increasing prevalence of obesity and associated metabolic disorders.

From a clinical perspective, the roles VEGF-B and apelin in the clinical context of FA uptake regulation remain to be evaluated. With respect to PPAR- γ , although the use of TZDs in the clinical setting consistently enhance FA uptake in multiple tissues, their endothelial specific effects remain to be determined. Further translational studies to determine the clinical relevance of the endothelial signaling components discussed here will provide greater insights that may ultimately lead to therapeutic advances against the increasing burden of the obesity pandemic and associated metabolic derangements.

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Box 1. Role of GPIHBP1 in regulation of lipolysis

Triglyceride hydrolysis is an important aspect of lipid metabolism, providing fuel to myocytes and delivering lipids to adipocytes for storage. Lipoprotein lipase (LPL), that catalyses the hydrolysis, generates the fatty acids (FA) in the endothelial capillaries of skeletal muscle, heart and adipose tissue [83]. It is synthesized and secreted by the parenchymal cells, myocytes and adipocytes[84] and contains positively charged heparin-binding sequences essential for anchoring on EC heparan sulfate proteoglycans (HSPGs) [85]. However, LPL depends on glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) for its transportation in the endothelial lumens, where lipolysis takes place[83]. GPIHBP1 is a lymphocyte antigen 6 (Ly6) protein expressed by capillary ECs[83, 86]. Recent electron microscopy studies have shown that both proteins localize in plasma membrane invaginations and transcytotic vesicles, while their trafficking is bidirectional, thus allowing GPIHBP1 recycling to the basolateral face of the cells[84]. In mice deficient for *Gpihbp1*, LPL mis-localizes in the interstitial spaces around parenchymal cells[83], resulting in severe hypertriglyceridemia even on low fat diet[86], phenocopying human mutations. To date one G56R substitution mutation[87] and seven missense mutations have been identified in patients with chylomicronemia[88–91]. Mutations in LPL that abolish binding to GPIHBP1 have also been identified in patients with chylomicronemia[92], underscoring the importance of LPL-GPIHBP1 interplay in lipid metabolism. This interaction is regulated on multiple levels, including LPL expression, GPIHBP1-controlled transport, recycling as well as the number of LPL binding sites within the endothelial capillaries. LPL requires apolipoprotein CII (apo-CII) to become catalytically active[93] while it is inhibited by angiopoietin-related protein 4 (ANGPTL4)[94]. Peroxisome proliferator-activated receptors (PPARs) are involved in the regulation of both LPL and GPIHBP1 expression. PPAR α and PPAR γ are known to increase *Lpl* expression in the liver and adipose tissue respectively[95]. PPAR γ but not PPAR α or PPAR δ agonists increase *Gpihbp1* transcripts in all expressing tissues apart from the liver[96]. Moreover, PPAR γ deficient mice present with significantly lower levels of *Gpihbp1* transcript in adipose tissue compared to littermate controls[96]. It was recently demonstrated that hypoxia could decrease *Lpl* and PPAR γ transcription but not *Gpihbp1*, *Cd36* or *Angptl4* in adipose tissue[97]. Last, dietary elements present an additional level of control. Correlating with tissue requirements for fuel, fasting results in downregulation of *Lpl* in white adipose tissue and upregulation in skeletal muscle and heart, which is reversed after feeding[98]. Conversely, *Gpihbp1* expression levels practically double during fasting in heart, brown and white adipose tissues, but return to normal after feeding[96]. Taken together, these results demonstrate that to ensure homeostasis, lipid metabolism in the endothelium must be tightly regulated on several levels and by different signaling pathways.

Box 2. Outstanding Questions

- How does a strategy to inhibit VEGF-B in diabetes affect its function in other processes such as arteriogenesis and neurogenesis?
- Can inhibition of endothelial PPAR- γ targets such as FABP4 or CD36 minimize the adverse effects of TZDs?
- What are the key cells that respond to apelin to mediate its insulin sensitizing effects?
- Does apelin regulate FA uptake in hearts and skeletal muscles?

Highlights

- Endothelium is a key regulator of fatty acid transport
- Endothelial fatty acid transport is regulated by a complex integration of signaling paradigms, including VEGF-B, PPAR- γ , and apelin
- These molecules can potentially be targeted as adjunct therapies to treat diabetes

Figure 1. Mechanism of VEGF-B mediated FA uptake

Vascular endothelial growth factor B (VEGF-B) expressed in skeletal muscle, heart, and brown adipose tissue (BAT) binds to VEGF receptor-1 (VEGFR1) and neuropillin 1 (NRP1) on the endothelial cells to induce expression of fatty acid transport proteins 3 and 4 (FATP3/FATP4). Increased fatty acid (FA) uptake in these tissues in diabetic mice result in insulin resistance and increased blood glucose. WAT: white adipose tissue.

Figure 2. Endothelial PPAR- γ regulates fatty acid transport

PPAR- γ in endothelial cells regulates the transcription of fatty acid binding protein 4 (FABP4) and fatty acid translocase CD36, which increases endothelial transport of FAs to the surrounding tissues, including heart, skeletal muscle, and white adipose tissue (WAT). Disruption of endothelial PPAR- γ results in improved insulin sensitivity and glucose tolerance. PPRE: PPAR responsive element.

Figure 3. Apelin regulates vascular permeability and fatty acid accumulation

Apelin regulates endothelial permeability/integrity via stabilization of VE-cadherin, which inhibits fatty acid (FA) uptake into white adipose tissue (WAT). Unresolved questions are whether apelin acts directly on the skeletal myocytes to improve insulin sensitivity, and whether the apelin's effect on vascular integrity affects FA uptake in other tissues such as the heart and skeletal muscles.