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Fat, obesity, and the endothelium

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Endothelial cells line all blood vessels in vertebrates. These cells contribute to whole-body nutrient distribution in a variety of ways, including regulation of local blood flow, regulation of *trans*-endothelial nutrient transport, and paracrine effects. Obesity elicits dramatic whole-body nutrient redistribution, in particular of fat. We briefly review here recent progress on understanding endothelial fat transport; the impact of obesity on the endothelium; and, conversely, how endothelial function can modulate obesity.

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Introduction

Endothelial cells (ECs) comprise the largest proportion of non-blood cells in the body [1]. ECs form the endothelium, a thin layer of simple squamous cells that lines both circulatory and lymphatic networks, carriers of blood and lymph, respectively. The endothelium can be leaky to nutrients, by either being discontinuous, as found in liver sinusoids, or by containing fenestrae, large channels that permit bulk *trans*-endothelial transport of solutes, as typically found in endocrine organs. In most tissues, however, the endothelium forms a continuous barrier, separating circulating nutrients from the underlying parenchyma. Transport of nutrients, and in particular of fat, across that barrier remains poorly understood. Obesity is marked by dramatic accumulation of fat stores. This process has profound effects on endothelial function, both in adipose tissue and systemically. Conversely, endothelial dysfunction can, surprisingly, contribute to obesity. Here, we provide a brief review of recent progress in our understanding of *trans*-endothelial fat transport and of the reciprocal relationship between endothelial cell function and obesity.

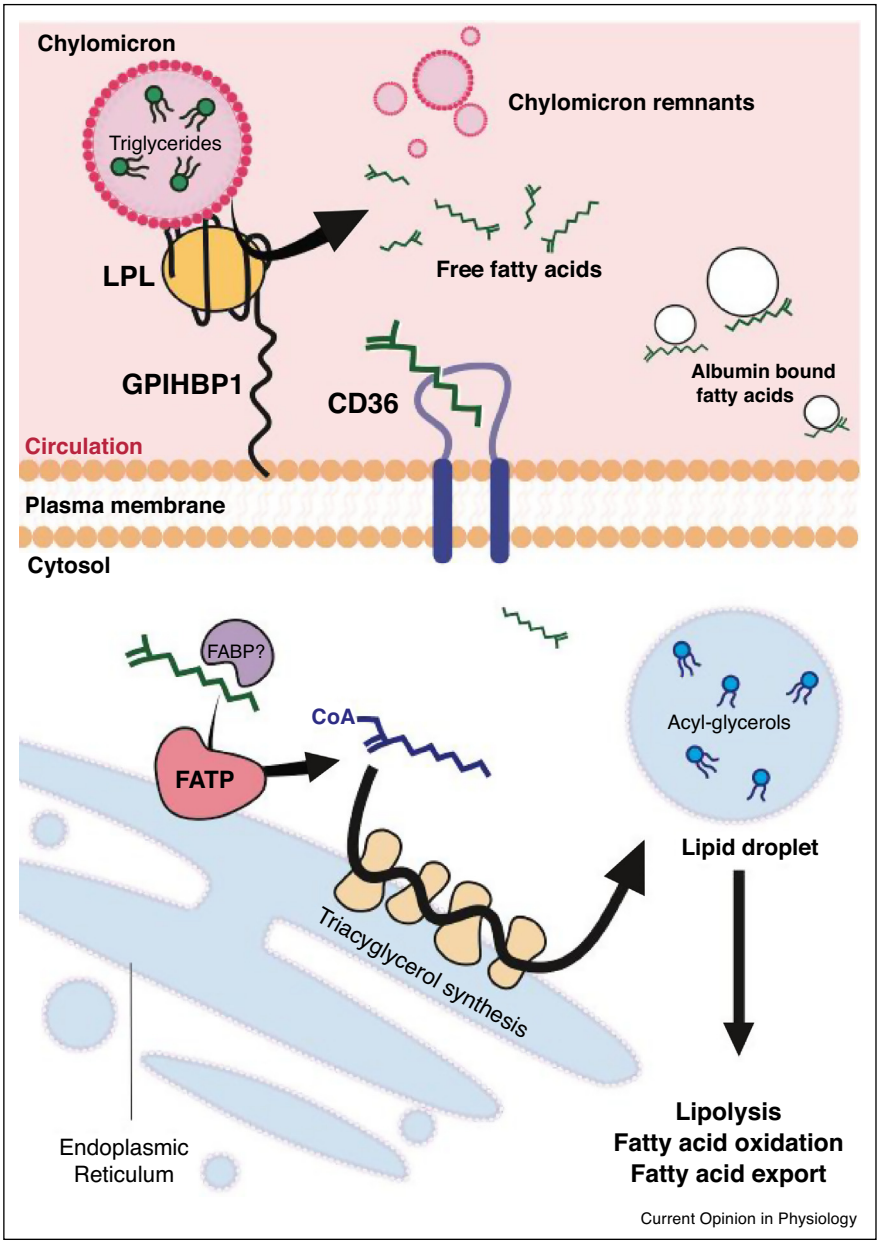
Endothelium and the physiology of fat intake

The endothelial response to food intake is carefully regulated to meet the energetic demands of the digestive system, deliver necessary nutrients to tissues, and prevent the accumulation of toxic metabolites. After food intake, blood flow increases to digestive organs within 5 min [2,3], and within 10–15 min insulin secretion increases capillary blood flow [4]. This increase in blood flow, and consequently shear stress, results in vasodilation, which is regulated by increased levels of endothelial-specific nitric oxide (NO). Endothelial NO, first identified as 'endothelium derived relaxing factor' [5,6], is synthesized by endothelial-specific nitric oxide synthase (eNOS) and signals to the surrounding smooth muscle cells to elicit relaxation. Vasodilatation increases blood flow and increases the surface-area available for nutrients to be transported in and out of the vasculature.

Dietary fats are first processed in the intestinal lumen by lipases and bile acids secreted from the pancreas and liver, respectively. Free fatty acids are then esterified by intestinal epithelia, and packaged into lipoprotein particles called chylomicrons. Chylomicrons enter circulation through specialized intestinal lymphatic vessels called lacteals, which transport chylomicrons through the lymphatic system and into circulation [7]. Fatty acids are then once again liberated from chylomicrons by the action of lipoprotein lipase (LPL) in target tissues (Figure 1). Even though LPL is synthesized by underlying parenchyma, it acts on the luminal side of the endothelium. Endothelial GPIHBP1 transports and anchors lipoprotein lipase to the luminal membrane [8], facilitating hydrolysis of triacylglycerides (TAGs) and release of free fatty acids [9,10].

While the process described above has been characterized for some time, the mechanisms surrounding the subsequent transport of free fatty acids across the endothelium are less well understood. Unlike hydrophilic molecules like sugars and amino acids, fatty acids are unlikely to be transported through canonical solute transporters. Early debates that focused on whether fatty acids were transported via paracellular or transcellular routes, or whether the import of fats is regulated or diffusion limited [11] have not been entirely resolved. However, the discovery over the past 25 years of a number of proteins that can modulate FFA transport has proven that FFA transport can be transcellular, and can be regulated. Transport is in part mediated by the fatty acid translocase CD36 [12••], which binds to long chain fatty acids and transfers them to the plasma membrane. EC-specific deletion of CD36 blunts delivery of fatty acids to tissues with continuous endothelium, such as the heart [12••]. The nuclear receptor peroxisome

Figure 1



Transport of fatty acids across the endothelium. Free Fatty acids (FFAs) packaged as triglycerides in lipoprotein particles are liberated via lipoprotein lipase (LPL) on the luminal side of the endothelium, anchored by the protein GPIHBP1. FFAs uptake into endothelium is facilitated by fatty acid translocase CD36, on the endoplasmic reticulum, and fatty acid binding proteins (FABPs). Fatty acid transport proteins (FATPs) catalyze formation of Acyl-CoAs, which are further processed into the triglyceride pool of lipid droplets. Lipolysis once again liberates FFAs, to be used for fatty acid oxidation or transported to the underlying parenchyma.

proliferator activated receptor gamma (PPARg) regulates the expression of CD36, as well as the most abundant fatty acid binding protein in ECs, fatty-acid binding protein (FABP4) [13], which has been shown to deliver ligands from the cytosol to PPARg in the nucleus, enhancing fatty acid uptake. Conversely, knockout of endothelial PPARg results in decreased fatty acid uptake into underlying tissue, as well as decreased adipocyte size. Interestingly, endothelial cells have recently been suggested to also produce PPARg ligands to the underlying adipose tissue, although the exact nature of these ligands remains unresolved [14]. The transcription factor Notch, induced in quiescent cells and a well-established inhibitor of migration and angiogenesis [15] also positively regulates CD36, endothelial LPL, and fatty acid binding protein (FABP4) expression [16••].

Fatty acid transport into cells has also been proposed to occur by 'vectorial' transport (Figure 1), whereby fatty acids are 'trapped' in the cytosol by conversion to acyl-CoAs, a process akin to trapping glucose in cells by phosphorylation. This reaction is carried out by so-called fatty-acid transport proteins, of which FATP3 and FATP4 are expressed in ECs. These molecules are single-pass membrane proteins with cytoplasmic acyl-CoA synthetase activities [17–19]. Although frequently schematized as plasma membrane proteins, FATP3 and 4 are likely in fact localized to the endoplasmic reticulum (ER) [18,19]. siRNA-mediated suppression of FATP3 and four blocks fatty acid uptake and transport in ECs [17,20••]. How these molecules perform this task from the ER is not clear.

The observation that the formation of acyl-CoA in ECs may be required for fatty acid transport suggested the possibility that these species may in turn cycle through the triglyceride (TG) pool, which Kuo *et al.* recently demonstrated to be the case [21••]. After oil gavage, significant amounts of lipid droplets can transiently be seen in the endothelium of mice. Furthermore, cycling through the TG pool appears to require canonical pathways of TG formation and degradation, including DGAT and ATGL. The physiological consequence of this transient accumulation is not clear, but may serve to delay and buffer entry of potentially toxic fatty acid species into the underlying parenchyma [22]. Evidence of increased EC lipid droplets has also been found in obesity models [23,24], although again, the functional consequence of these droplets is not clear.

Finally, recent evidence has shown that the underlying parenchyma can signal to the endothelium to increase fatty acid transport. In skeletal muscle, expression of PPARg coactivator-1alpha (PGC-1alpha) promotes the secretion of the branched chain amino acid (BCAA) metabolite 3-hydroxyisobutyrate (3-HIB), which acts on endothelial cells to increase lipid transport [20••], thus mechanistically linking BCAA and fat catabolism. PGC-1alpha in myocytes also promotes the expression of VEGFB. Despite being a member of the VEGF family, VEGFB is poorly angiogenic; instead VEGFB, like 3HIB, appears to promote *trans*-endothelial fatty acid transport, in a manner dependent on FATP3 and 4 [25]. In contrast, adipose tissue can secrete the peptide Apelin to reduce fatty acid uptake, in large part via the endothelial apelin receptor (APLNR), leading to inactivating phosphorylation of the transcription factor FOXO1, and reduced expression of FABP4 [26•]. In summary, endothelial cells and the underlying tissues reciprocally interact to regulate and hone fatty acid processing and transport across the endothelium and delivery to the parenchyma. These recent observations are likely only beginning to uncover this complex regulatory system.

How obesity affects the endothelium

Many classic studies showed that fats acutely (but temporarily) induce endothelial dysfunction in healthy subjects. For example, a single high fat meal decreases flow-mediated vasodilation, inversely proportional to the levels of serum triglycerides [27]. Similar impairment of vasoreactivity follows infusion or oral administration of lipids in healthy subjects [28,29]. Saturated fatty acids also induce an acute inflammatory reaction [30,69,70,71], resulting in increased expression of the pro-inflammatory adhesion molecules ICAM1 and VCAM1. Furthermore, long-chain saturated fatty acids have been found to inhibit endothelial cell growth by inducing apoptosis and necrosis [30].

The chronic effects of obesity on the endothelium, on the other hand, are different. The marked increase in adipose tissue that accompanies obesity necessarily requires expansion of the adipose tissue vascular bed. Activation of angiogenesis, an otherwise relatively rare process in normal adult physiology, is thus a *sine qua non* for increased adiposity in obesity. Angiogenesis is likely triggered by hypoxia in the setting of expanding fat mass [31], resulting in decreased capillary density, local hypoxia, and activation of hypoxia-inducible factor 1 (Hif-1alpha) that drives expression of VEGF [32,33]. Hif-1alpha KO animals exposed to high fat diet have less fat mass and reduced adipocyte size in addition to lower expression of endothelial growth factors, consistent with insufficient vascular support for adipose tissue expansion [34]. Pathologically, this angiogenic expansion can often be insufficient to match the increasing size of adipose tissue, leading to local hypoxia and inflammation, and contributing to systemic metabolic disease [35]. Adipose tissue from obese subjects also show markers of senescence, also resulting in an increased inflammatory profile [36]. Short term weight loss ameliorates some endothelial dysfunction [37] suggesting that while chronic obesity alters homeostasis of the endothelium, changes are reversible.

In addition to triggering angiogenesis in adipose tissue, obesity can impair the physiological and molecular function of the endothelium systemically. Obese but normotensive, normoglycemic human subjects show decreased endothelium-dependent vasodilation capacity [38] and increased aortic stiffness [39] compared to non-obese controls. Non-diabetic, obese subjects also have decreased vascular capillary density not only in adipose tissue [40] but also in skeletal muscle [41], and have decreased capillary recruitment following vascular occlusion in skin [37,42] and insulin-mediated capillary recruitment in skeletal muscle [43,44]. On a molecular level, these phenotypes have been generally attributed to decreased expression of eNOS [45–47], but how this occurs remains incompletely understood. One prominent mechanism is likely the impact of adipose-derived

hormones, including adiponectin and leptin. In obesity, adiponectin is decreased [48], while leptin is increased [49]. Adiponectin, which is negatively correlated with BMI and insulin levels, stimulates glucose utilization and fatty-acid oxidation, as well as NO production [50,51], and inhibits inflammatory gene expression response to TNFa in endothelial cells [72]. Conversely, adiponectin deficiency increases pro-inflammatory adhesion molecules, resulting in increased leukocyte-endothelium interaction [52]. In contrast, leptin is pro-inflammatory, and increases both vascular permeability and angiogenesis, resulting in increased delivery of nutrients to adipose tissue [53,54].

How the endothelium can affect obesity

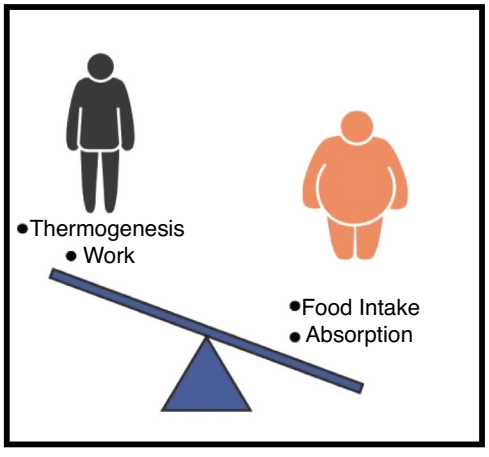
Thermodynamically, changes in body weight can only occur in one of two ways: [48] by altering intake of calories, either via modulating food intake or absorption of nutrients; or [55] by altering consumption of calories, either via thermogenesis or work (Figure 2). Surprisingly, recent research has indicated that the endothelium can impact these systemic processes in obesity.

Calorie consumption

The bulk of these studies have focused on the role of adipose tissue endothelial cells [56]. Enhanced angiogenesis in both brown or white fat can activate thermogenesis, leading to reduced body weight via increased energy expenditure [32,57,58•,59•,60–62]. These studies highlight the role of endothelial growth factors (VEGF's) and their receptors (VEGFR) in these processes. Secretion of VEGF-A by tissues, including adipose tissue, activates the endothelial cell VEGFR2 receptor to stimulate angiogenesis. A number of early studies demonstrated that promoting this process in adipose tissue was sufficient to activate a thermogenic program [57,60,62], although the precise details of how angiogenesis promotes mitochondrial uncoupling and thermogenesis remain unclear. More recent work has leveraged VEGFR1, which on ECs acts as a decoy receptor by binding to VEGFA and preventing it from signaling through VEGFR2 to promote angiogenesis. Overexpression of VEGF-B, which binds even more avidly to VEGFR1, displaces VEGFA, allowing it to signal through VEGFR2 and promote angiogenesis. Robciuc *et al.* recently demonstrated that overexpression of VEGFB augments angiogenesis and increases thermogenesis by enhancing activation of VEGFR2. Similarly, Seki *et al.* showed that genetic ablation or blockade of VEGFR1 increased adipose tissue angiogenesis and thermogenesis. These vascular effects of VEGFB versus VEGFA have also been demonstrated in other tissues, highlighting the complex regulation of angiogenesis. It is not clear, however, why thermogenesis and body weight are affected by manipulations of the VEGFB/VEGFR1 axis in these studies, while they were not in the studies by Hagberg *et al.* [25,63]. Recently, EC-specific knockout of FOXO1 was also shown to increase adipose vascular density and decrease adiposity, but in this case the thermogenesis was not activated, and the explanation for reduced body weight is not clear [64]. EC-specific overexpression of eNOS also reduces diet-induced obesity by increasing energy expenditure, likely via the adipose tissue [46].

Paradoxically, inhibition, rather than stimulation, of adipose tissue angiogenesis has also been suggested to decrease obesity. Pharmacological or genetic inhibition of angiogenesis has resulted in weight loss and reduced adiposity in both rodent [65,66,62] and non-human

Figure 2



Reference	Adipose angiogenesis	Energy expenditure	Fatty acid absorption	Food consumption	Mechanism
Elias, 2012 Sun, 2012 Sun, 2014 Robciuc, 2016 Seki, 2018	↑	↑	unchanged	unchanged	Multiple reports of increased angiogenesis inadipose tissue, via multiple means, results in increasedenergy expenditure due to increased thermogenesis.
Rudnicki, 2018	↑	↓	N/R	unchanged	EC-specific knockdown of FOXO1promotes angiogenesis infat and muscle, and mildly reduces body weight despite reduced MVO2and activity.
Sansbury, 2012	unchanged	↑	N/R	unchanged	Overexpression of endothelial eNOSincreases adipose tissue mitochondria and fatty acid oxidation, and whole body MVO_2.
Rupnick, 2002 Brakenhielm, 2004	↓	↑	N/R	↓	Systemic anti-angiogenic drug treatment results in decreased adipose tissue vascularity, increased total MVO2,and decreased food consumption
Barnhart, 2011	↓	N/R	N/R	↓	Primates treated with adipotide, an adipose-targeted anti-angiogenic peptide, reduce food consumption
Sung, 2013	↓	unchanged	N/R	unchanged	Adipose tissue VEGF-KOdecreases vascularization resulting in increased inflammation and worsening metabolic syndrome. Weight gain is reduced by unclear mechanism.
Zhang, 2018	N/R	unchanged	↓	unchanged	Disruption of endothelial Flt1/NRP1inhibits lacteal permeability to chylomicrons and leads to decreased absorption of dietary fats
Konishi, 2017	N/R	N/R	unchanged	↑	Knockout of endothelial insulin receptors results in increased food consumption due to decreased satiety signaling in the brain

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How the endothelium can affect obesity. Left, schematic of thermodynamic contributors to body weight regulation. Right, table outlining recent publications in which endothelial biology is altered, leading to changes in body weight. Effects on adipose tissue angiogenesis, energy expenditure (calories out), fatty acid absorption and food consumption (calories in) highlighted for each study.

primate [55] models. In many of these cases, however, the effect appears to be on food intake, rather than thermogenesis, via unclear mechanisms [55,65,66]. Loss of adipose vasculature in normal animals also results in increased inflammation due to hypoxia, and worsening metabolic defects despite reduced fat mass [62]. In contrast, blocking adipose tissue angiogenesis in a different model of obesity (ob/ob mice) appears to have beneficial effects on both body weight and metabolism, suggesting that the consequences of modulating adipose angiogenic activity are context dependent [60], which may explain some of the paradoxical observations made above.

Calorie intake

Can endothelial function also affect calorie intake? Recent studies have suggested that it can [67••]. Zhang *et al.* showed that ablation of VEGFR1 and its co-receptor, Neuropilin 1 (NRP1) renders mice resistant to obesity by decreasing chylomicron uptake. Reduced VEGFA activity during the formation of gut lacteals is critical to render them permeable to chylomicrons. Deletion of the decoy VEGFR1/NRP1 receptor in adjacent ECs results in high VEGFA activity, and these animals thus lose calories in their feces due to lipid malabsorption. Interestingly, in these studies, deletion of VEFGR1 had little impact on adipose thermogenesis, in contrast to the studies above. In addition to absorption, endothelial function may also affect food intake. As noted above, some anti-angiogenic agents may suppress food intake. Konishi *et al.* also recently showed that the insulin receptor (IR) on endothelial cells can affect food consumption [68•]. Endothelial IR is required for *trans*-endothelial transport of insulin, and thus affects the kinetics of insulin signaling to tissues with tight endothelial junctions, including the brain. Knockout of endothelial IR delayed insulin signaling in the brain, disrupting the satiety response and delaying reduction of food intake, leading to mild obesity. Overall, these studies show that endothelial cells can modulate obesity at multiple levels, including lipid storage in the white adipose tissue, energy expenditure, fat processing in the intestine, and food consumption.

Conclusion

The endothelium is intricately involved in whole-body nutrient transport and distribution. Obesity is a disease of nutrient excess, and in particular of excess fat distribution. It is thus not surprising that a reciprocal relationship exists between endothelial function and obesity. The details of that relationship are only beginning to emerge. The hope is that deeper understanding of that relationship may lead to novel approaches to treating obesity.

Conflict of interest statement

Nothing declared.

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