Endothelial Metabolic Inflammation: A Link between High Fat Feeding, Insulin Resistance, and Impaired Trans-Endothelial Insulin Transport

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Obesity and its associated metabolic syndrome and type 2 diabetes are becoming epidemics in the United States. The most recent data show that nationwide incidence of obesity (BMI > 30 kg/m²) and type 2 diabetes has reached to 27.8% and 8.7%, respectively (CDC Behavioral Risk Factor Surveillance System 2012). Endothelial dysfunction, characterized by a deficiency of bio-available nitric oxide (NO), has been found to precede the development of type 2 diabetes and is significantly correlated with insulin resistance [1]. Early studies have shown that feeding rodent animals with a high fat diet (HFD) (~60% of calories) produces not only obesity [2] but also a state of insulin resistance [3]. These HFD-fed rodents develop striking hyperinsulinemia with significantly reduced whole body insulin sensitivity and glucose disposal rates, severe impairments in both muscle and adipose tissue insulin signaling and glucose uptake and an impairment of insulin-mediated suppression of hepatic glucose output [4-6]. Moreover, obesity has been shown to be a state of low-grade systemic inflammation known as the metabolic inflammation characterized by elevated levels of pro-inflammatory cytokines (such as TNFα, IL-6, IL-1β, CCL2 etc.), accumulation of leukocytes within adipose tissue and other organs, activation of macrophages in both liver and fat and activation of pro-inflammatory signaling pathways in multiple organs or tissues [7,8]. The mechanisms causing the metabolic inflammation are thought to be related to excess nutrient intake (metabolic stress) including HFD feeding [7,8]. Dietary fat intake not only significantly increases circulating free fatty acids (FFAs) concentration but also affects the composition of circulating FFAs [9]. Four-week HFD feeding has shown to cause metabolic endotheliaxia to the metabolic inflammation in mice [10]. The lipopolysaccharide (LPS) -induced inflammatory responses in macrophages have been shown to be mediated by Toll-Like Receptor-4 (TLR4) (pattern recognition receptors that sense lipopolysaccharides of bacterial walls) [11]. Interestingly, saturated fatty acids (SFAs), but not unsaturated fatty acids, can induce an inflammatory response like LPS through activation of TLR4 [12,13]. It has also been proposed that nutrients per se are naturally inflammatory [7]. While the flood of nutrients in a short period of time may induce a brief episode of stress signaling in the target cells, long-chain SFAs, particularly palmitate, have been shown to directly activate TLR4 that may require CD36 (a class B scavenger receptor) [14-16], leading to IKKβ/NFκB and c-Jun N-terminal kinase (JNK) pathway activation, increased production of pro-inflammatory cytokines TNFα, IL-1β and IL-6 [13,17-19] and significant insulin resistance as reflected by impairments in insulin-stimulated tyrosine phosphorylation of IRS-1, serine phosphorylation of Akt and eNOS, and NO production. Interestingly, recent studies have shown evidence that vascular endothelium that line up the inner wall of vasculature appear to be the first responder to the environmental insult, high fat feeding, leading to the vascular endothelial metabolic inflammation and insulin resistance.

Vascular endothelial cells (ECs) have pleiotropic functions and regulate a large variety of cellular processes including coagulation, fibrinolysis, angiogenesis, adhesion and transmigration of inflammatory cells and vasculature hemodynamics. Another very important vascular endothelial function is providing a barrier that regulates entry of nutrients and hormones into the interstitium of peripheral tissues and also signaling the vascular system's response to different stimuli [20,21]. This is particularly true for skeletal muscle, a major site of fuel use, where its continuous vascular endothelium has well-developed junctional structures and abundant caveolea that provides a relatively tight diffusional barrier. Muscle's tight endothelium has constituted the structural basis for a strong argument that the transit of insulin from the vascular to the interstitial compartment within skeletal muscle is rate limiting for insulin's metabolic action [21]. Most importantly, this rate-limiting step for peripheral insulin action is delayed in insulin-resistant obese subjects [22-24] and it has been estimated that slow trans-endothelial insulin transport may account for 30-40% of insulin resistance seen with human obesity or type 2 diabetes [22,23,25]. Current evidence indicates that insulin transendothelial transport (TET) is a saturable process being mediated by insulin receptor (IR) at a physiological concentration of insulin [26-28] and also involves IGF-1R (and IR/IGF-1R hybrid receptors) when a supraphysiological concentration of insulin is applied [28]. It has also been reported that insulin act on vascular ECs through its intracellular signaling to facilitate its own uptake and TET [29,30]. Inhibiting insulin signaling either by treatment of cultured vascular ECs with the specific inhibitor of insulin signaling pathways or by pro-inflammatory cytokines such as TNFα or IL-6 in vitro [30-32] or by HFD feeding [32] in vivo or by endothelium-specific knockout of IRS-2 in vivo [33] all severely impair insulin TET.

Several laboratories have also reported the increased expression of pro-inflammatory cytokines in the liver, skeletal muscle and adipose tissue which required between 8 and 16 weeks, respectively after starting HFD feeding [34-36]. The vascular EC appears particularly sensitive to HFD, for example, a single high-fat meal quickly provokes endothelial dysfunction in humans as measured by flow-mediated dilation and increases the plasma levels of TNFα, IL-6, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in healthy humans [37,38]. In a study, HFD induced defects in the insulin signaling and increased the inflammatory responses in thoracic aorta as early as one week after starting the HFD [35]. This suggests that the vasculature may be the “first responder” to the HFD insult.

The activation of TLR4/IKKβ/Jab1/NFκB pathway has been implicated to play a central role in the pathogenesis of both HFD-induced vascular inflammation in mice [18,35] and SFAs-induced endothelial inflammatory responses in cultured vascular ECs [19,39,40]. Inhibiting TLR4 signaling can effectively suppress palmitate-induced...
inflammation both in vivo and in cultured vascular ECs [13,18,19]. In addition, SFAs stimulate NADPH oxidase-dependent reactive oxygen species (ROS) production, and inhibition of TLR4 signaling inhibits both SFAs-stimulated ROS production and HFD-induced NOX4 expression [19].

Taken together, current data indicate that HFD feeding causes a chronic low-grade inflammatory state via activation of TLRs that occurs much earlier in vascular endothelial cells than that in multiple peripheral tissues or organs such as adipose tissue and liver. The HFD-induced metabolic inflammation mediates extensive cellular pathology, e.g., insulin resistance, leading to the impairment in insulin transendothelial transport. Thus, the vascular endothelial metabolic inflammation induced by high fat feeding clearly constitutes a critical link between high fat feeding, insulin resistance, and impaired trans-endothelial insulin transport.

References


