

Vascular Endothelial Nitric Oxide, Insulin Signaling and Insulin Transport: A Delicate Balance

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Vascular 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]. 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 [2]. 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 caveolae that provides a relatively tight diffusional barrier. This is in stark contrast to the discontinuous endothelium with gaps between ECs in liver. 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 [2]. Most importantly, this rate-limiting step for peripheral insulin action is delayed in insulin-resistant obese subjects [3-5]. Current evidence indicates that insulin trans-endothelial transport (TET) is mediated by the molecular transcytotic machinery that contains or associates with multiple structural and signaling molecules including insulin receptor (IR), IGF-1R, caveolin-1, dynamin 2, actin filaments and eNOS [6-14]. Insulin TET is a receptor-mediated saturable process [6,14] and is facilitated by its own intracellular signaling [10,11]. Insulin activates eNOS at physiologic concentrations [15] to produce NO. Knock-out of eNOS produces metabolic insulin resistance [16]. Inhibiting EC insulin signaling by endothelium-specific knockout of IRS-2 leads to a reduction of eNOS activity in the ECs and produces metabolic insulin resistance. In addition, endothelial specific knockout of IRS-2 inhibits insulin-induced microvascular recruitment and reduces insulin trans-capillary delivery to muscle interstitium [17]. Exogenous delivery of nitric oxide has recently been found to directly promote insulin transendothelial transport [12]. Interestingly, the NO's effect on insulin transport appears to be biphasic: in the range of low doses, it promotes insulin uptake, but beyond that it had no effects [12]. The dose response range over which the stimulatory effect of NO on insulin transport is observed appears to be in a more physiologic range as it corresponds well to that over which NO causes relaxation of aortic rings [12,18]. On the other hand, insulin transport is impaired under the condition of experimental insulin resistance induced by either chemical inhibitors of insulin signaling pathways or the pro-inflammatory cytokine TNF α in cultured vascular ECs or in vivo in the high fat fed rats [10-12,17,19]. Interestingly, the impaired insulin transport can be reversed by the low dose of NO [12]. Of note, under the condition of insulin resistance induced by either pro-inflammatory cytokine TNF α or the metabolic inflammation induced by high fat feeding, inducible nitric oxide synthase (iNOS) expression is increased leading to the production of large amounts of NO [20] suggesting that the deficiency of bioavailable NO may not be the trigger of insulin resistance seen under the metabolic inflammation.

In vascular ECs, exogenously delivering NO does not affect the classical NO signaling via cGMP-PKGs [12]; instead NO-induced protein S-nitrosylation is a common mechanism mediating intracellular NO signaling transduction [12,21]. Intracellular insulin

signaling is balanced by protein tyrosine kinase-catalyzed tyrosine phosphorylation and protein tyrosine phosphatase (PTP)-catalyzed dephosphorylation of the insulin receptor and insulin receptor substrate (IRS). PTP1B (a major PTP) activity under normal metabolic condition is tightly regulated by oxidation/reduction reactions including S-nitrosylation/denitrosylation involving the cysteine thiol moiety required for catalysis [22]. The low dose of NO causes PTP1B S-nitrosylation leading to the inhibition of its enzymatic activity that contributes to enhancing intracellular insulin signaling in both physiological and pathophysiological settings [12]. In contrast, the high concentration of NO generated by either activated iNOS or NO donor (e.g. ≥ 10 mmol/L S-nitrosoglutathione) has been found to increase protein denitrosylation through inhibition of Txnip (an endogenous inhibitor of denitrosylase) expression [23,24] that may contribute to activation of the inflammatory kinase IKK β and PTP1B leading to the impairments in EC insulin signaling and insulin transport [12,21]. In addition, saturated fatty acids (SFAs) stimulate vascular endothelial NADPH oxidase-dependent reactive oxygen species (ROS) production via activation of Toll-Like receptor-4 (TLR4) [25] and the increased ROS can interact with NO to form peroxynitrite, a highly reactive radical species with numerous detrimental effects in vascular ECs accompanied with reduced NO bioavailability [26].

Thus, current evidence indicates that maintaining intracellular NO homeostasis plays a critical role in maintaining EC insulin sensitivity and normal function and restoring the NO homeostasis under pathological conditions such as insulin resistance and metabolic inflammation may be an effective remedy for devastating metabolic diseases such as metabolic syndrome and type 2 diabetes.

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