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A Critical Regulatory Site for Trans-capillary Insulin Delivery: Trans-endothelial Transport

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Introduction

In the process of insulin reaching its major extravascular sites of action such as skeletal muscle and adipose tissue that are lined by a continuous endothelium, it must first traverse the vascular endothelium. Previous *in vivo* studies have shown that trans-capillary insulin transport from the plasma to the interstitial fluid compartment of skeletal muscle is a rate-limiting step in insulin's peripheral action [1,2]. This process has been reported to be delayed in insulin-resistant, obese humans with a significantly lower interstitial insulin level in the early phase of insulin infusion compared to normal controls [3-5]. The question raised from these *in vivo* studies is: How is this process regulated? What are the major contributors for regulation of insulin trans-capillary transport? There are several components such as muscle blood flow [6], flow distribution [7] and capillary density [8] have been suggested by *in vivo* studies to contribute to regulate insulin trans-capillary delivery and could determine in part the biological activity of the hormone. However, the observation by an *in vivo* study [1] that the plasma insulin concentration at the steady-state during a three hour euglycemic insulin clamp is almost twice those in muscle interstitium strongly indicates that vascular endothelium constitutes a barrier for insulin's trans-endothelial transport and trans-endothelial insulin transport process per se is yet another potential site for regulation of insulin delivery. Since King and Johnson [9] published their pioneering work in 1985 in which they demonstrated that insulin trans-endothelial transport was mediated by its receptor and was a saturable process, later studies not only have confirmed this finding [10,11] but also have found at high insulin concentrations insulin trans-endothelial movement is mediated by both insulin receptor and IGF-1 receptor (IGF-1R) [11] that may offer a reasonable explanation for the lack of saturation of insulin trans-capillary transport in muscle at higher insulin doses in some *in vivo* studies [12]. Moreover, direct microscopic studies have shown that insulin's trans-endothelial transport follows a trans-cellular pathway during insulin clamp in animals [11]. Recent *in vitro* study has found that insulin's intracellular signaling regulates insulin uptake, the first step of insulin trans-endothelial transport. Inhibition of intracellular insulin signaling pathways either by PI3-kinase inhibitor wortmannin or MEK inhibitor PD 98059 or cSrc-family tyrosine kinase inhibitor PP1 or by pro-inflammatory cytokines TNFα or IL-6 treatment strikingly inhibits insulin uptake, whereas stimulating intracellular insulin signaling via inhibition of phosphotyrosine phosphatase 1B significantly enhances insulin uptake [13]. In addition, insulin transport has recently been shown to be mediated by transporting caveolae [13-16]. Down-regulation of the expression of caveolin-1, a constitutive protein of caveolae, by either specific siRNA against caveolin-1 or by pro-inflammatory cytokine TNFα or IL-6 treatment, almost completely eliminates insulin uptake, whereas over-expression of caveolin-1 significantly increases insulin uptake by aortic endothelial cells [16]. Taken together, all these experimental evidences indicate that not only the blood flow or the flow distribution can affect insulin's trans-capillary delivery as suggested by those *in vivo* studies but also the factors direct acting on vascular endothelial cells may modulate insulin's movement across the endothelial cell barrier.

Given that many vascular active drugs/bioactive reagents have pleiotropic effects and they may act not only on vascular smooth muscle cells to cause changes in blood flow or flow distribution via vasodilation but also on vascular endothelial cells to modulate endothelial function leading to changes in insulin's trans-endothelial transport (one example of such reagents is nitric oxide which has similar action on both vascular smooth muscle cells and vascular endothelial cells [17]), it is difficult to differentiate whether the change in trans-capillary insulin transport induced by such a particular vascular active reagent is due to a vasodilating response [5] or due to its action on trans-endothelial process [10,11,18] or both under an *in vivo* setting. To dissect such a reagent's effects on endothelial cells from its whole-vasculature effects that affects insulin trans-capillary transport, it is necessary to take an alternative *in vitro* experimental approach that allows to exclude its effects on other components in whole vesculature system except that on endothelial cells per se [9,13-16]. Thus, carefully identifying individual components of the endothelial machinery that controls insulin's trans-endothelial transport not only will allow us to better understand the cellular mechanism whereby insulin moves across the endothelial barrier but also may suggest new interventions for insulin resistance and type 2 diabetes.

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