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An Increase in Glucose Uptake per se is Insufficient to Induce Oxidative Stress and Vascular Endothelial Cell Dysfunction

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Abstract : Hyperglycemia is a hallmark of uncontrolled diabetes and causes vascular endothelial dysfunction. An increase in glucose uptake and metabolism by vascular endothelial cells is the presumed trigger for this hyperglycemia-induced dysfunction. Glucose uptake into vascular endothelial cells is mediated largely by Glut-1. Glut-1 is an equilibrative glucose transporter with a Km value of 2 mM. At physiologic glucose concentrations, Glut-1 is almost saturated and, therefore, increasing glucose concentration does not increase glucose uptake unless Glut-1 is upregulated. However, hyperglycemia downregulates Glut-1 and decreases rather than increases glucose uptake in vascular endothelial cells. This apparent discrepancy necessitates further study on the effect of increasing glucose uptake on the oxidative state and function of vascular endothelial cells. To test this, a Tet-on system was generated to conditionally regulate Glut-1 expression in endothelial cells by the addition and removal of doxycycline. Glut-1 overexpression was confirmed by Western blot and radiolabeled glucose uptake measurements. Upregulation of Glut-1 resulted in a 4-fold increase in glucose uptake into endothelial cells as determined by 3H deoxy-D-glucose uptake. Increased glucose uptake through Glut-1 did not induce an oxidative stress nor did it cause endothelial dysfunction in rat pulmonary microvascular endothelial cells determined by monolayer resistance, cell proliferation or advanced glycation end product formation. Increased glucose uptake through Glut-1did not lead to an increase in glucose metabolism, due in part to inhibition of hexokinase in Glut-1 overexpressing cells. In summary, this study demonstrates that increasing glucose uptake and intracellular glucose by overexpression of Glut-1 does not alter the oxidative state of rat pulmonary microvascular endothelial cells or cause endothelial cell dysfunction. These results conflict with the current paradigm that hyperglycemia leads to oxidative stress and endothelial dysfunction in vascular endothelial cells through an increase in glucose uptake.

Keywords : endothelial cells, glucose uptake, Glut1, hyperglycemia
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