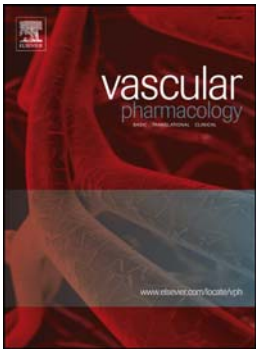

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PII: S1537-1891(16)30196-3
DOI: doi: 10.1016/j.vph.2016.11.001
Reference: VPH 6374

To appear in: *Vascular Pharmacology*

Received date: 27 June 2016
Revised date: 29 September 2016
Accepted date: 2 November 2016

Please cite this article as: Tumova, Sarka, Kerimi, Asimina, Porter, Karen E., Williamson, Gary, Transendothelial glucose transport is not restricted by extracellular hyperglycaemia, *Vascular Pharmacology* (2016), doi: 10.1016/j.vph.2016.11.001

Transendothelial glucose transport is not restricted by extracellular hyperglycaemia

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Keywords: endothelial cell, glucose transport, shear stress, hyperglycaemia, diabetes

ABSTRACT

Endothelial cells are routinely exposed to elevated glucose concentrations post-prandially in healthy individuals and permanently in patients with metabolic syndrome and diabetes, and so we assessed their sugar transport capabilities in response to high glucose. In human umbilical vein (HUVEC), saphenous vein, microdermal vessels and aorta, GLUT1 (SLC2A1), GLUT3 (SLC2A3), GLUT6 (SLC2A6), and in microdermal vessels also GLUT12 (SLC2A12), were the main glucose transporters as assessed by mRNA, with no fructose transporters nor SGLT1 (SLC5A1). Uptake of ^{14}C-fructose was negligible. GLUT1 and GLUT3 proteins were detected in all cell types and were responsible for ~60% glucose uptake in HUVECs, where both GLUT1 and GLUT3, but not GLUT6 siRNA knock-down, reduced the transport. Under shear conditions, GLUT1 protein decreased, GLUT3 increased, and ^{14}C-deoxy-glucose uptake was attenuated. In high glucose, lipid storage was increased, cell numbers were lower, ^{14}C-deoxy-glucose uptake decreased owing to attenuated GLUT3 protein and less surface GLUT1, and trans-endothelial transport of glucose increased due to cell layer permeability changes. We conclude that glucose transport by endothelial cells is relatively resistant to effects of elevated glucose. Cells would continue to supply it to the underlying tissues at a rate proportional to the blood glucose concentration, independent of insulin or fructose.

1. Introduction

The human endothelium is a large organ consisting of monolayers of endothelial cells lining all blood vessels in the body. Its many functions include regulating blood flow and maintaining normal vascular tone through production of NO, endothelin-1 and other factors [1-3], control of blood clotting and inflammation, and formation of a selective barrier between blood and tissues for distribution and exchange of nutrients, metabolites and gasses [4]. Endothelial cells in different vessels or organs are finely tuned to their specific functions [5-7]; for example, the permeability of the endothelial monolayer ranges from tightly controlled in blood brain barrier [8] to leaky in fenestrated endothelium of sinusoidal tissue in liver [9, 10]. One of the characteristic features of endothelial cells is their reliance on glycolysis for energy production [11-13], with sustained glucose consumption being critical for endothelial cell viability especially during angiogenesis [14, 15]. Thus glucose uptake and metabolism is critical for healthy endothelial physiology, and endothelial glucose transporters are especially important in the brain, where glucose can only cross the blood brain barrier via this mechanism [16]. On the other hand, dysregulated glucose transport and metabolism is linked to pathophysiological states [17-19]; increased GLUT expression is associated with carcinogenesis and tumour progression [20-22] and both hypo- and hyperglycaemia can lead to increased endothelial stress and inflammation, contributing to cardiovascular disease [23-25]. Despite the critical functional role of glucose in the endothelium, our understanding of its uptake and utilization by endothelial cells remains limited. As a hydrophilic molecule, glucose requires transporters in order to cross the plasma membrane. Glucose transporters (GLUTs) of the SLC2A family are transmembrane proteins classified in three groups (reviewed in [26-28]. Type I (GLUT1-4 and 14) and II (GLUT5, 7, 9 and 11) are largely present on the plasma membrane and typically enable glucose (Type I) or fructose (Type II and GLUT2) flux in/out of the cells. Type III (GLUT 6, 8, 10, and 12) have