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Short communication

GLUT1-deficient mice exhibit impaired endothelium-dependent vascular relaxation

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Abstract

We tested the hypothesis that decreased glucose transporter 1 (GLUT1) expression alters endothelial function. Nitric oxide-dependent endothelial relaxation, but not endothelium-independent relaxation, was significantly reduced in aortas from transgenic mice expressing GLUT1 antisense mRNA, compared to aortas from nontransgenic littermates. These data suggest that GLUT1-dependent glucose metabolism may play an important role in regulating endothelial function.
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Keywords: GLUT1 (glucose transporter1); Endothelium; Antisense

Glucose transporter 1 (GLUT1) is constitutively expressed in many cell types and plays a key role in maintaining basal glucose uptake (Mann et al., 2003), but the role of GLUT1-dependent glucose uptake in intracellular signaling is not well characterized. GLUT1 is expressed in endothelial and vascular smooth muscle cells in aorta, and appears to be the predominant transporter in endothelium (Mann et al., 2003). In this study, we hypothesized that decreased vascular GLUT1 expression alters endothelial function. The availability of a transgenic mouse expressing GLUT1 antisense mRNA (GLUT1AS) in which GLUT1 expression is reduced approximately 50% in tested organs (Heilig et al., 2003) allowed us to study the role of GLUT1-mediated glucose uptake on endothelial function.

Rings (2 mm) of thoracic aortas from GLUT1AS mice and control, nontransgenic littermates (22–24 weeks of age) were mounted in a myograph. Animal studies are in accordance with University of Michigan Committee on the use and care of animals guidelines and conforms to the standards in "The Guide for the Care and Use of Laboratory Animals", Department of Health, Education, and Welfare Publication No. (NIH) 86-23. A concentration response to prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$) was performed. The $PGF_{2\alpha}$ EC_{50} (5 μM) was used to contract a separate set of rings to assess endothelium-dependent and -independent relaxation, using acetylcholine and sodium nitroprusside, respectively. Relaxation to acetylcholine or sodium nitroprusside was expressed as a percent of the contraction mediated by 5 μM $PGF_{2\alpha}$. The acetylcholine-induced, endothelium-dependent relaxation in the C57Bl/6J mouse thoracic aorta is nitric oxide-dependent, as has been previous demonstrated (Jiang et al., 2001). Expression of endothelial nitric oxide synthase (eNOS) in aortas was measured by immunoblot.

$PGF_{2\alpha}$-mediated contractions in endothelium-intact rings from GLUT1AS and control mice were not different (data not shown). Acetylcholine-mediated relaxation was blunted significantly (~ 15%) in GLUT1AS aortas compared to control aortas (Fig. 1A). In contrast, no differences in sodium nitroprusside-induced relaxation (Fig. 1B) or eNOS expression (Fig. 1C) were observed.

GLUT1 and eNOS are localized to detergent-resistant membranes (DRM) of endothelium (Minshall et al., 2003; Rubin et al., 2003), which also include caveolae, invaginations in cellular membranes that concentrate many signaling molecules (Minshall et al., 2003). The proximity of GLUT1 and eNOS in DRM, or caveolae, suggests that GLUT1

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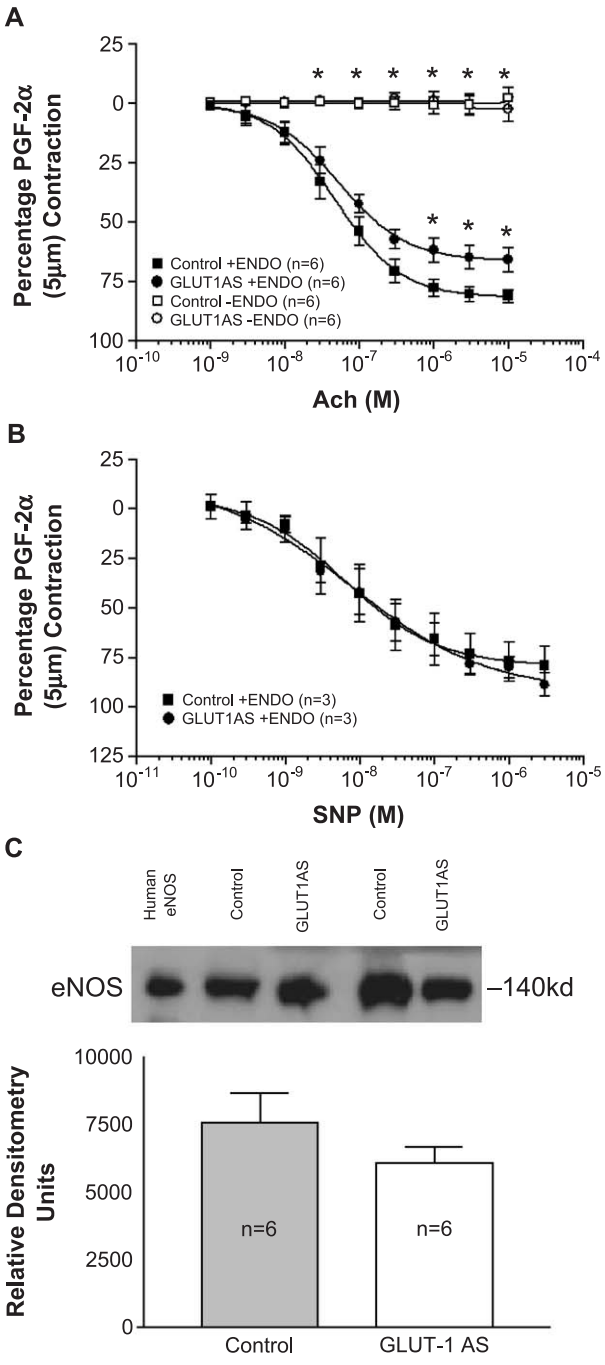

Fig. 1. Reactivity in mouse aorta from GLUT1AS or nontransgenic littermates (control). (A) Acetylcholine-dependent relaxation in GLUT1AS or control aortas. (B) Endothelium-independent relaxation to sodium nitroprusside in GLUT1AS or control aortas. (C) eNOS immunoblot of aortic homogenates from GLUT1AS or control mice. $*P < 0.05$ (analysis of variance followed by Bonferoni post hoc analysis).

contributes to localized glycolysis, thereby providing ATP for cell-signaling processes. A decrease in GLUT1 expression could disrupt signaling, including eNOS function associated with these DRM.

These results demonstrate that decreased GLUT1 expression attenuates endothelium-dependent relaxation without affecting vascular smooth muscle contraction, suggesting that GLUT1 may play a role in regulating normal endothelial function.

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