

## Role of equilibrative nucleoside transporters in endothelial dysfunction: adenosine/L-arginine/nitric oxide pathway

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Removal of extracellular adenosine is mediated via the human equilibrative nucleoside transporters 1 (hENT1) and hENT2 in human fetal endothelium, a phenomenon that is crucial for the modulation of adenosine vascular effects. Adenosine stimulates L-arginine transport and nitric oxide (NO) synthesis via activation of A2A adenosine receptors (ie. ALANO pathway) in human umbilical vein endothelial cells (HUVEC). This effect of adenosine requires increased expression and activity of the endothelial NO synthase (eNOS) as well as p42/44mapk. In HUVEC from gestational diabetes mellitus the effect of adenosine is due to increased extracellular adenosine level and reduced expression, activity and plasma membrane availability of hENT1. This effect of gestational diabetes results from lower SLC29A1 gene promoter activity due to increased NO levels and specific Sp1 binding to a consensus sequence of SLC29A1 promoter. Similar results have been found in HUVEC from normal pregnancies exposed to elevated extracellular D-glucose. Involve-

ment of hENT2 transporters seems to be less critical in response to D-glucose or in gestational diabetes mellitus, but changes in SLC29A2 expression and hENT2 activity, but not SLC29A1 and hENT1, could become a protective mechanism in response to insulin under these pathological conditions. We propose a crucial role for hENT1 and hENT2 in the modulation of ALANO pathway resulting from its capacity to remove extracellular adenosine in human fetal endothelium.

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