The significance of glucose transporters in abdominal aortic aneurysms

Nikesh Dattani BSc (Hon) MBBS MRCS, Department of Cardiovascular Sciences. Supervisors - Mr. Matthew Bown and Professor Rob Sayers.

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The problem

- Aneurysms are localised blood vessel swellings
- Abdominal aortic aneurysms (AAA) are common and mainly affect elderly males (~7000 deaths per year in UK)[1]
- Treatment involves an operation when AAA reaches 5.5 cm
- Aim of treatment is to prevent rupture
- Ruptured AAA has a high mortality rate (~50%)[2]
- No drug therapies for AAA currently exist
- National AAA Screening Programme will lead to detection of more small AAA not yet suitable for surgical repair[3]

Diabetes and AAA

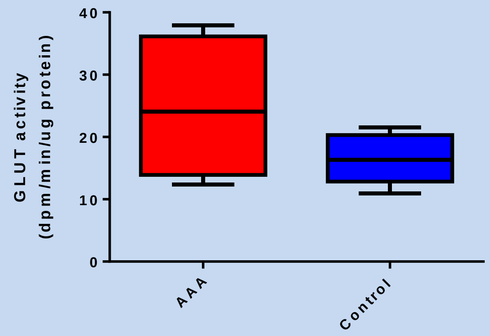
- Diabetes Mellitus (DM) is defined by high blood sugar levels (with or without high insulin levels)
- DM protects against AAA
  - Fewer AAA[4]
  - Slower growth[5]
- Mechanisms underlying protective effect poorly understood
- Potential for therapeutic use

Glucose transporters

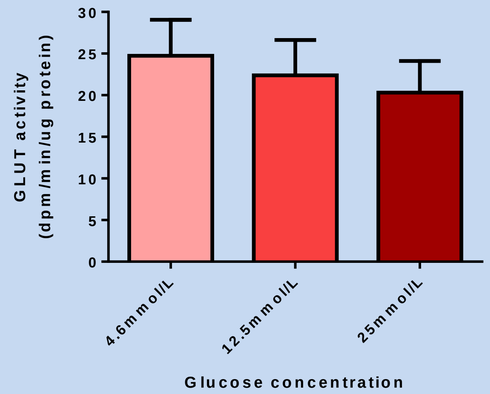
- Glucose is important for most cells in the body
- Enters cells via transmembrane proteins called glucose transporters (GLUTs)
- 14 different types, GLUT1 widely distributed
- GLUT abnormalities found in DM[6] and diabetic complications such as nephropathy[7] and retinopathy[8]

Preliminary data

- *Overall GLUT activity higher in aortic smooth muscle cells (AoSMCs) from AAA patients versus controls*



- *GLUT activity decreases with increasing ambient glucose concentrations in AoSMCs from AAA patients*

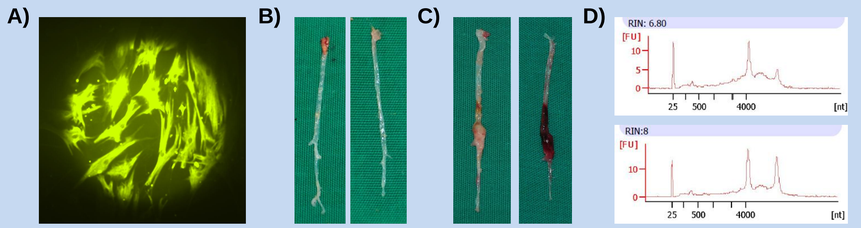


Hypothesis

1. **GLUT expression and/or activity is increased in AAA patients and reduced by diabetic environment**
2. **GLUT1 inhibition can reduce development and progression of AAA in an experimental mouse model**

Methods and Feasibility

- Phase I: Compare expression and activity of GLUTs in AAA and control patients (currently underway)
- Phase II: Examine the effect of DM (high glucose and/or high insulin) on AoSMC from AAA and control patients
  - GLUT expression and activity
  - Expression levels of AAA-associated growth factors and enzymes
- Phase III: Test the effect of partial GLUT1 inhibition using a drug (Fasentin) in the ApoE-deficient angiotensin II mouse model
  - AAA size and growth (small animal MRI)
  - RNA and protein expression levels of AAA-associated growth factors and enzymes (qRT-PCR and western blotting)
  - Assess aortic wall elastin, collagen and glycosylation levels to determine aortic wall composition and stiffness (immunostaining)



A) Successful AoSMC culture from AAA patients B) ApoE-deficient mouse aorta after saline infusion (no aneurysms)
C) ApoE-deficient mouse aorta after angiotensin II infusion (aneurysms evident)
D) Successful RNA extraction from mouse aorta with good RNA integrity

Expected value and future directions

- Identify a pathway by which DM protects against AAA
- Show that modulation of this pathway can reduce experimental AAA and thus potential for translation into a real-life therapy
- Test effect of genetic GLUT1 knockout in novel experimental models of AAA developed by our group (LRP1 knockdown AoSMC model and LRP1 -/- nicotine exposure mouse model)

References. 1. Office of National Statistics 2010. 2. Bown MJ et al. *Br J Surg* 2002. 3. Davis M et al. *J Vasc Surg* 2013. 4. Shantikumar S et al. *Eur J Vasc Endovasc Surg* 2010. 5. Sweeting MJ et al. *Br J Surg* 2012. 6. Kahn BB. *J Clin Invest* 1992. 7. Gnudi L et al. *Hypertension* 2003. 8. Badr GA et al. *Diabetes* 2000.

Other abbreviation definitions. ApoE (Apolipoprotein E), MRI (magnetic resonance imaging), RNA (ribonucleic acid), qRT-PCR (quantitative real-time reverse transcriptase polymerase chain reaction), LRP1 (low-density lipoprotein receptor-related protein 1).