Vascular Changes in Diabetic Retinopathy

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Characteristics of the retinal microvasculature

How this microvasculature and the neuroglial network is altered in diabetes

Pathogenic mechanisms

Understanding pathogenesis can lead to better treatments

Type 2 Diabetic
9 years duration
Unique nature of the retinal vasculature

- Highly specialised end-artery system
- Autoregulation of blood flow in response to metabolic needs of neural retina
- Multi-cell capillary unit
- Inner retina blood barrier (analogous to Blood brain barrier)
Retinal blood vessels do not occur in isolation
Retinal Capillary Structure
Capillary pathology in human diabetic retinopathy: BM thickening
Progression of microvascular pathology in diabetic retinopathy
Vascular remodelling – not reperfusion in diabetic retina:

Gardiner et al. Microcirculation 2007 14: 1–14
Sight-threatening stages – only after extensive vasodegeneration
What causes vasogeneration?
AGE-inhibition prevents blood retinal barrier breakdown

AGE INHIBITION PREVENTS MICROGLIAL ACTIVATION IN DIABETIC RETINA

GCL
INL
ONL

Non-Diabetic
Diabetic
Diabetic (PM)

IL-1beta
TNF-alpha
IL-10

Relative expression versus β-actin

Expression ratio

control diabetic

0.0000
0.00005
0.00010
0.00015
AGE-inhibition prevents acellular capillary formation

**Figure A**

- Endothelial cell
- Acellular Capillary
- Pericyte

**Figure B**

- Average number of pericytes/field

**Graph**

- No. of acellular capillaries/field
- Control vs. Diabetic Control vs. Diabetic AGE-i

**Graph**

- Avg. number of pericytes/field
- Control vs. Diabetic Control vs. Diabetic AGE-i

References:

Neural & vascular dysfunction

Retinal capillaries Occlusion & death of

Neural abnormalities Neuroglial dysfunction

BRB breakdown

Retinal ischaemia & up-regulation of angiogenic GF's

Development of neovascularisation - onto retinal surface

Pan-retinal Laser photocoagul

Tractional detachment

Pre-retinal neovascularisation

Retinal Ischaemia

iBRB breakdown Oedema

Microaneurysms
• Tissue protective / anti-inflammatory in brain injury (stroke) models
• Non-erythropoietic
• 11 amino acid peptide – crosses blood brain (& retinal) barrier

Daily ip injections of pHBSP or scrambled peptide for 28 days

PNAS 2008 105:10925-30
An EPO analogue protects against capillary degeneration

• Diabetes is a vasodegenerative disease

• Diabetes impacts on all cells of the retina – not just the vasculature.

• Inflammation is now recognised as a key component of early-stage degenerative diabetic retinopathy

• Pathogenesis is complex and multi-factorial. Intervention could prevent progression to sight-threatening stages.
Hypoxia is increased in early diabetes

- Pimonidazole hydrochloride (2-nitroimidazole)
- Activated in cells at $pO_2<10\text{mmHg}$

Diabetes

Leukostasis

Inflammation

Endothelial cell death

Capillary dropout

BM thickening

Microaneurysms

Pericyte/Smooth Muscle Dropout

Hypoxia

Endothelial cell death

Capillary dropout

Hypoxia

Hyperpermeability

Neovascularisation

Early diabetes

Early and long-term diabetes

Long-term diabetes

Abnormal autoregulation

Retinal Hyperperfusion

Curtis et al. Eye 2009 Jul;23(7):1496-508
Static leukocytes are in flux, block capillary flow, and transmigrate.

Miyamoto K et al. PNAS 1999;96:10836-10841
Non-diabetic

Diabetic

Evans Blue Leakage

0
0.004
0.008
0.012

Non-diabetic

Diabetic
Glial – vascular abnormalities in early diabetes

Antonetti et al.
Diabetes 2006 55(9) 2401-2411
Pro-inflammatory processes in diabetic retina

- **IL-10**
  - Expression ratio
  - Control vs. diabetic

- **TNF-alpha**
  - Relative expression vs. β-actin
  - Control vs. diabetic

- **IL-1beta**
  - Relative expression vs. β-actin
  - Control vs. diabetic
Diabetic rodents show the early stages of retinopathy
Neural and glial abnormalities in early diabetes