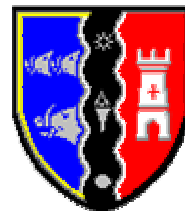


Recent developments in Diabetes

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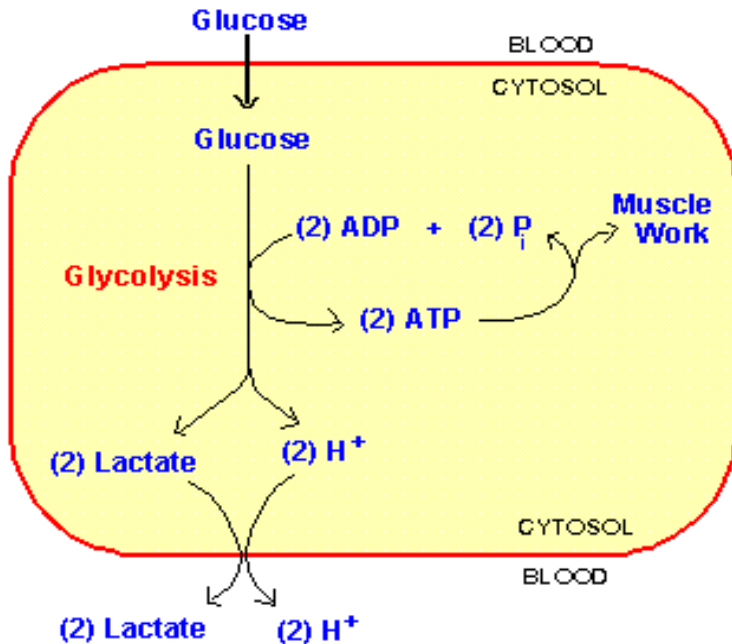


Summary

- Glucose –friend or foe?
- Diabetes – the global problem
- **Type 1 diabetes**
 - Characteristics
 - Treatment
 - Therapeutic targets
- **Type 2 diabetes**
 - Characteristics
 - Treatment
 - Therapeutic targets
- **Complications of diabetes**

Glucose - friend or foe?

- Essential nutrient
- Glucose metabolism generates ATP



- Homeostatic mechanisms fight to maintain physiological glucose concentrations ~5mmol/l

Diabetes

- Normal homeostatic mechanisms fail to regulate glucose concentration
- Incidence
 - UK 1998 – 1.4 million predicted to double by 2010
 - Reflects world wide changes
- Health impact?

Diabetes

- Normal homeostatic mechanisms fail to regulate glucose concentration
- Type 1 diabetes
 - pancreatic β cells fail to produce sufficient insulin
 - immune destruction of β cells
 - peak incidence 10 -14 years of age
 - ~15-20% of total diabetes cases

Diagnosis

PRELIMINARY DIAGNOSIS BY ONE OF:

- Random venous plasma glucose ≥ 11.1 mmol/L
- Fasting plasma glucose ≥ 7.00 mmol/L
- Plasma glucose ≥ 11.1 mmol/L 2hr after consumption of 75g in an oral glucose tolerance test (OGTT)

CONFIRMATION OF DIAGNOSIS

Impaired glucose tolerance test

Treatment of Type 1 diabetes

Insulin type

- analogue
- short-acting
- intermediate acting
- long acting



Prepared by

- genetic engineering
- human or animal

Delivery route

- **Usual route:** intra-muscular / sub-cutaneous
- Abdominal self-regulating infusion pumps
- Needle-less insulin: *oral route requires combination of insulin and carrier with polymers resistant to acid and enzyme hydrolysis*
 - *e.g. calcium phosphate nanoparticles*
BioSante - Pre-clinical testing.

Therapeutic targets for treatment of Type 1 diabetes

- Pancreas transplant
 - Rejection
 - Stem cell research
 - Sustainability
- Identification and destruction of autoimmune response to β cells
 - 10-20% antibody-negative - *idiopathic*
- Genetic identification of susceptible individuals
(HLA polymorphisms account for 30-60% of genetic susceptibility) **Germline therapy?**

Type 2 Diabetes

- Insulin resistance (genetic and environmental factors)
- >40 years
- 80-95% of total diabetes cases

- **Why is the incidence rising?**

- Ageing population?
- Dietary habits?
- Sedentary lifestyles?
- Genetic susceptibility is conserved?

Treatment of Type 2 diabetes

- Biguanides e.g. metformin
 - increases glucose release from liver
- Sulphonylureas e.g. glicazide
 - encourages pancreas to produce insulin
- Alpha glucosidase inhibitors e.g. acarbose
 - slows CHO absorption in the gut
- *acarbose*
 - *can delay progression to Type 2 diabetes if given to patients with impaired glucose tolerance Lancet (2002) 359. P2072.*



Therapeutic targets

- Lifestyle
- Improved insulin sensitivity
- Improve insulin production
- Altered CHO absorption
- *Early diagnosis*
 - *e.g. acarbose*
 - *can delay progression to Type 2 diabetes if given to patients with impaired glucose tolerance Lancet (2002) 359. P2072.*

Glucose monitoring and control



Establishing a treatment regimen

- involves all of Health Care Team and the patient

Monitoring blood glucose

- Diabetes Clinic (HbA1c <7.2% good: 7.2 - 8.2. Borderline: >8.2 poor)
- Patient: Daily regimen using glucose sensors
 - *pin prick*
 - *generation of vacuum (reduced pain)*
 - *continuous monitoring through skin*

Complications of diabetes

- Affected areas
 - heart (atherosclerosis)
 - nerves (diabetic neuropathy)
 - kidney (diabetic nephropathy)
 - eye (diabetic retinopathy)
 - impaired wound healing
- Common link is vascular damage induced by high glucose concentrations

Clinical trials

- **DCCT: type 1 diabetes**
 - improved glucose control significantly reduced the incidence and the severity of diabetic complications e.g. 76% reduction in severity of diabetic retinopathy
- **UKPDS: type 2 diabetes**
 - improved glucose control significantly reduced the incidence and the severity of diabetic complications

Early tissue damage by high glucose concentration

- **Early target - endothelium**
 - is the damage generic?
 - is the same type of damage manifested differently in different tissues?
 - can we reverse the consequences of high glucose?

- **Systemic factors**

- serum von Willebrand Factor increased in circulation due to increased release from damaged endothelium
- adhesion molecules shed by endothelial cells can be detected in serum
- altered expression of leucocyte and endothelial adhesion molecules
- impaired wound healing
- gene expression altered in peripheral blood leucocytes

Knott et al, Metabolism 48, 1172-1178 (1999)

Is the damage to the endothelium
generic? **Yes**

Is the same type of damage manifested differently in different tissues? **Yes**

- **Tissue specific damage**
 - heart, kidney, eye, nerves, brain?
- **Why is manifestation different if the damage is generic?**
 - Glucose transport
 - Insulin sensitivity
 - Degree of dependence upon blood supply
 - Relationship to function

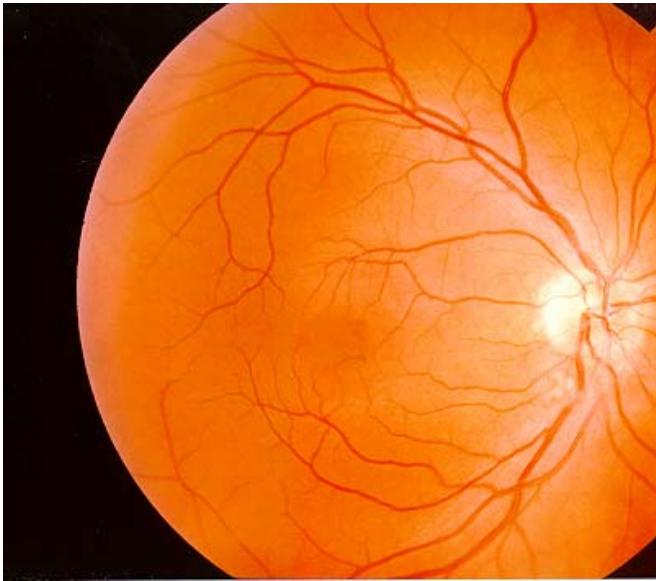
Can we reverse the consequences of high glucose?

- **Early stage of vascular disease**
 - improved glucose control can improve or prevent deterioration in most cases
- **Late stage of vascular disease**
 - primary role of glucose in mediating damage has passed. Tissue dysfunction has set in leading to specific pathological changes.

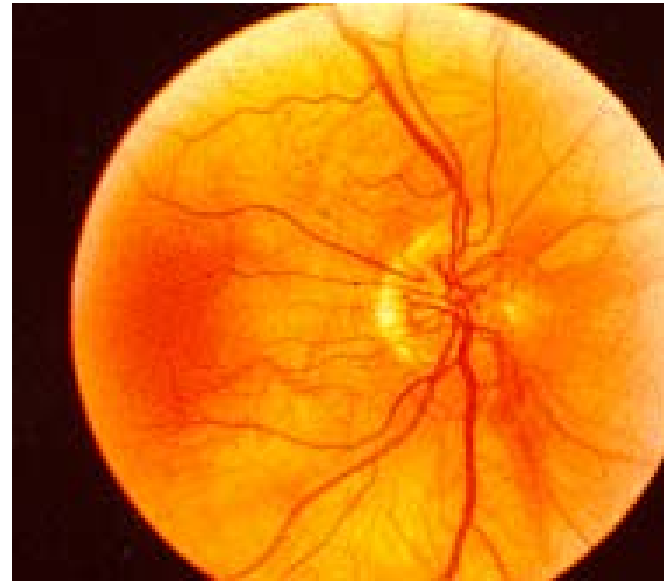
Where is the evidence?

- Clinical trials
- Basic science

E.g. *DIABETIC RETINOPATHY*

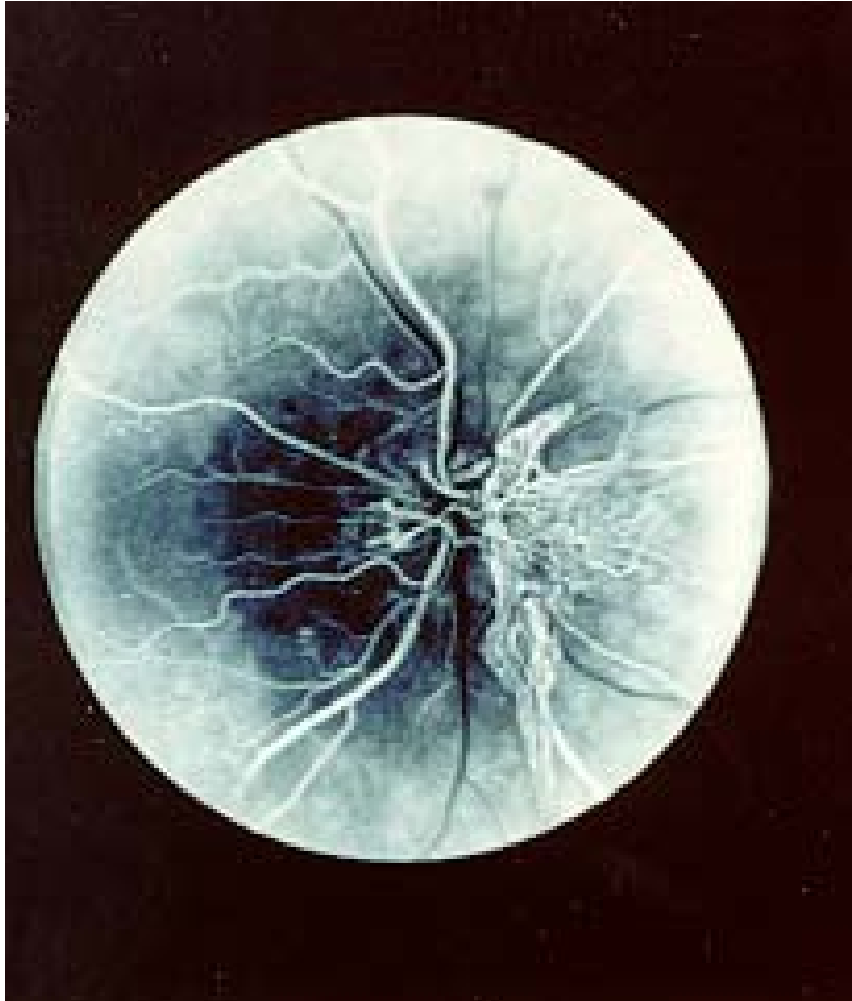


- Normal fundus



- Proliferative retinopathy

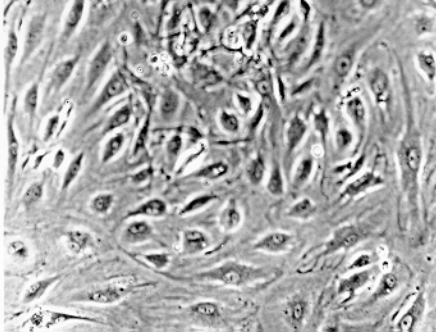
Proliferative diabetic retinopathy



- Fluorescein angiogram

Protein expression

Glucose transport



Retinal endothelial cells

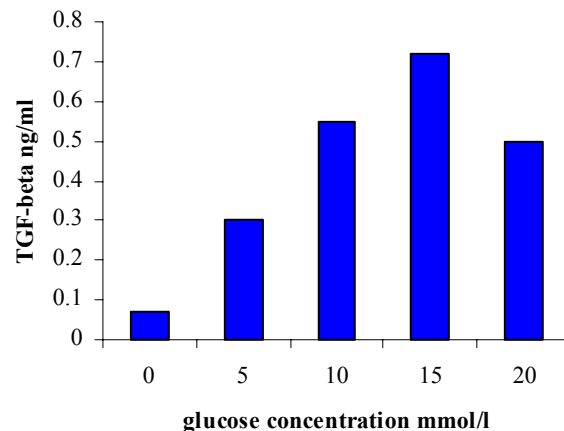
- Glucose transporters



- Immunohistochemistry
 - tissue specificity
 - GLUT-1, GLUT-3
 - low K_m
 - retina is highly metabolically active

GLUT-1 mediated regulation of REC growth

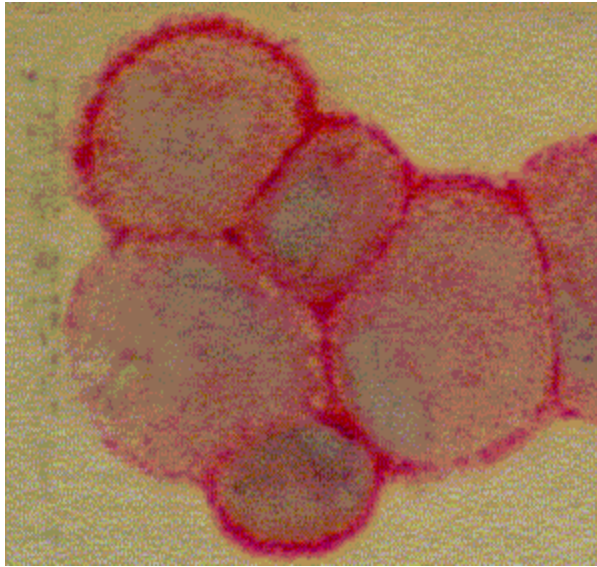
- High [glucose] reduces endothelial cell growth
- GLUT-1 antibody restored growth of REC in high glucose concentrations.
- TGF- β antibody restored growth in high glucose concentrations



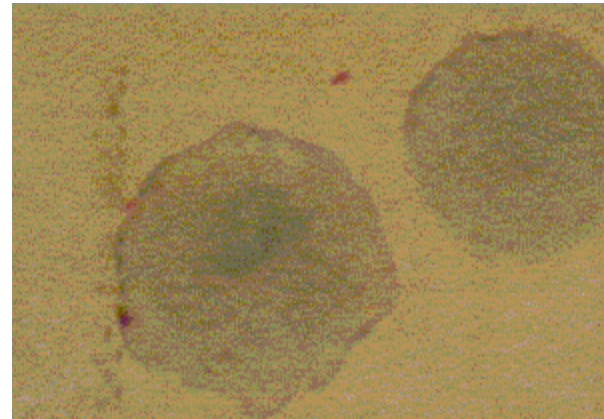
**High glucose concentration
increased expression of
TGF- β**

***Pascal, Forrester and Knott (1999)
Current Eye Research 19 162 -170***

Antisense technology



**GLUT-1
antisense**



Effect on

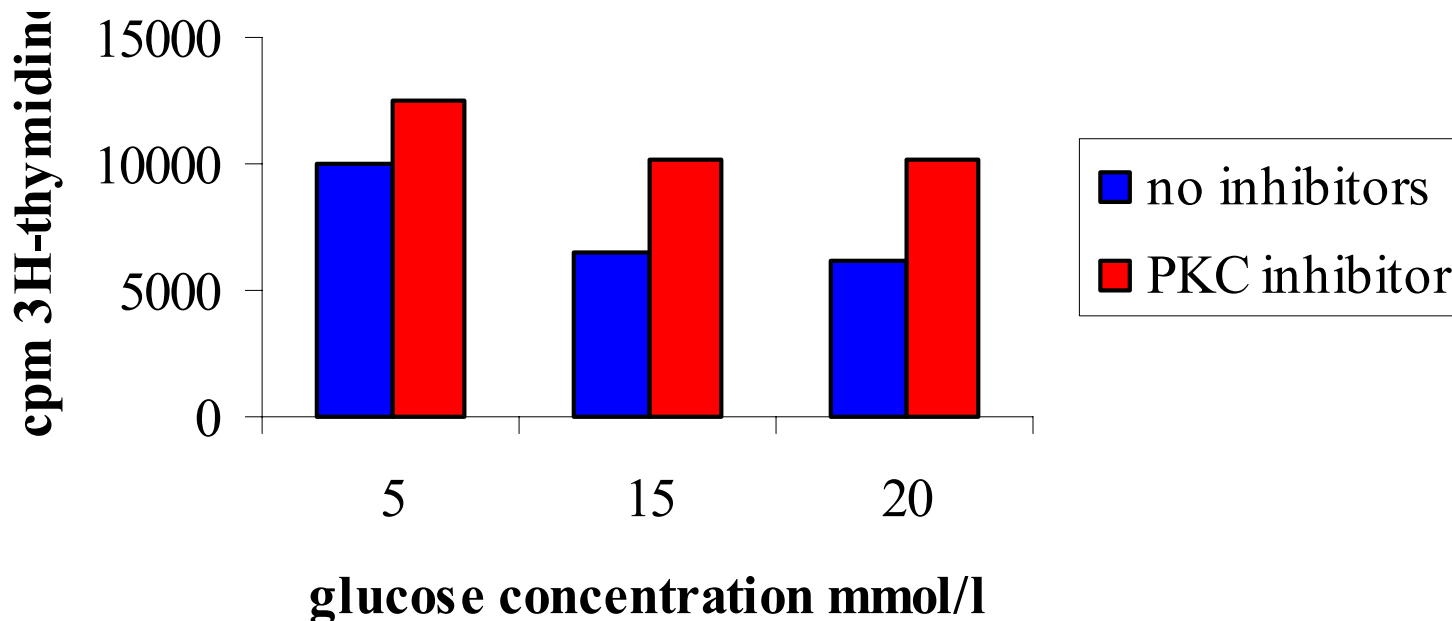
- cell growth
- cell response

**What is happening
inside the cell?**

Intra-cellular signalling

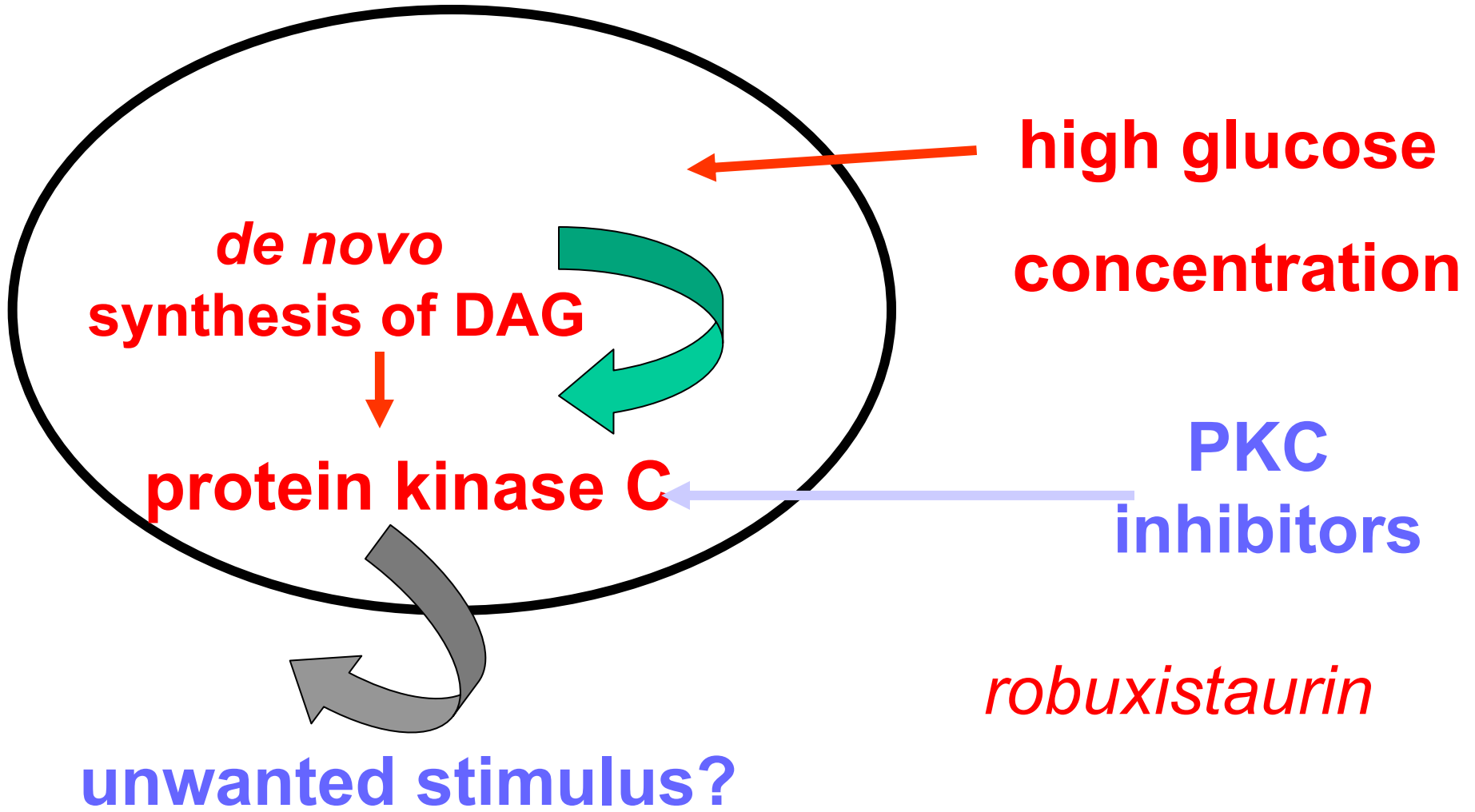
Protein Kinase C

- Implicated in cell proliferation, differentiation and apoptosis.
- Many different PKC isoforms
- PKC inhibitors restored cell growth



Knott et al., (1998) Curr Eye Res. 17.1-8

Microdermal endothelial cells (Kamal et al., 1998)



high glucose concentration

PKC inhibitors

robuxistaurin

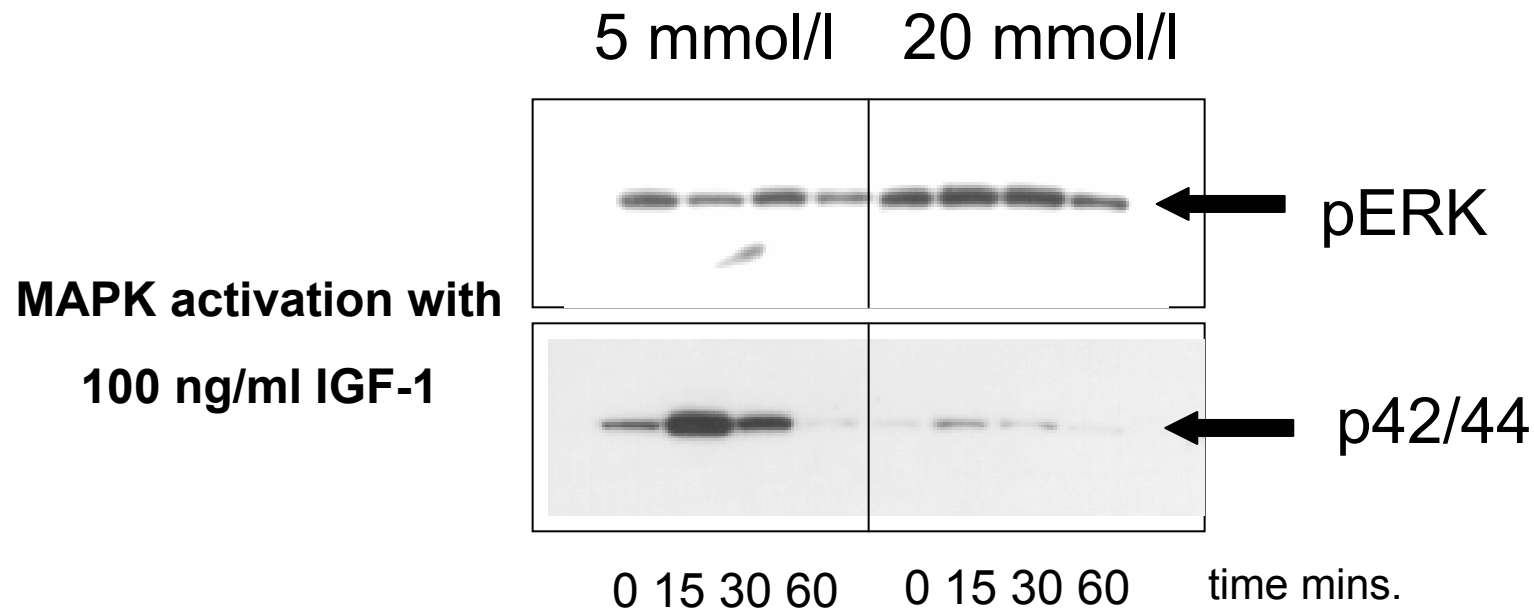
de novo synthesis of DAG

protein kinase C

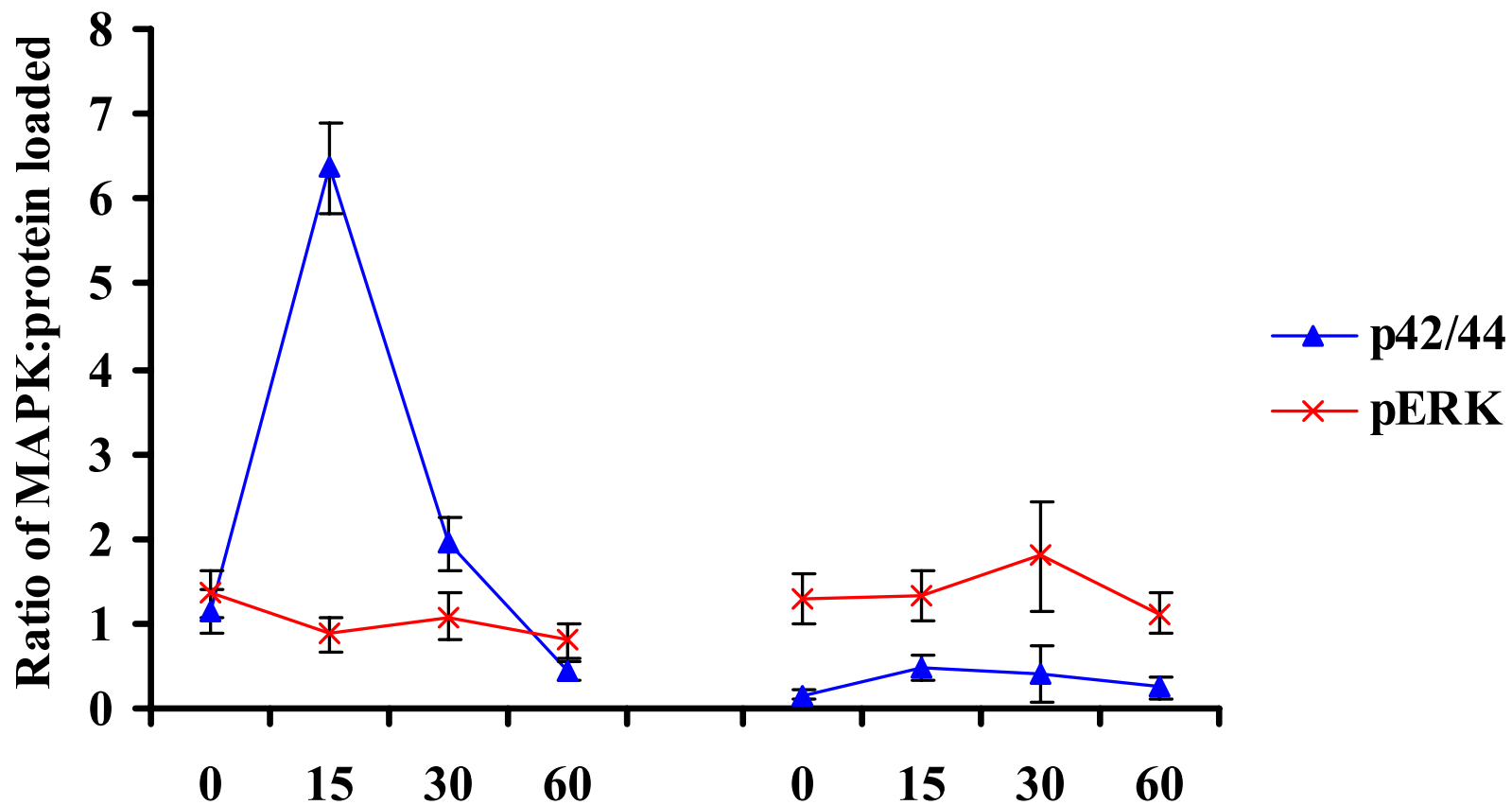
unwanted stimulus?

Growth factor response of REC in high glucose

e.g. Insulin like-growth
factor type 1 (IGF-1)



Time course of MAPK activation in BRECs following IGF-1 treatment (100ng/ml)



5mmol/l

20mmol/l

Hypoxia

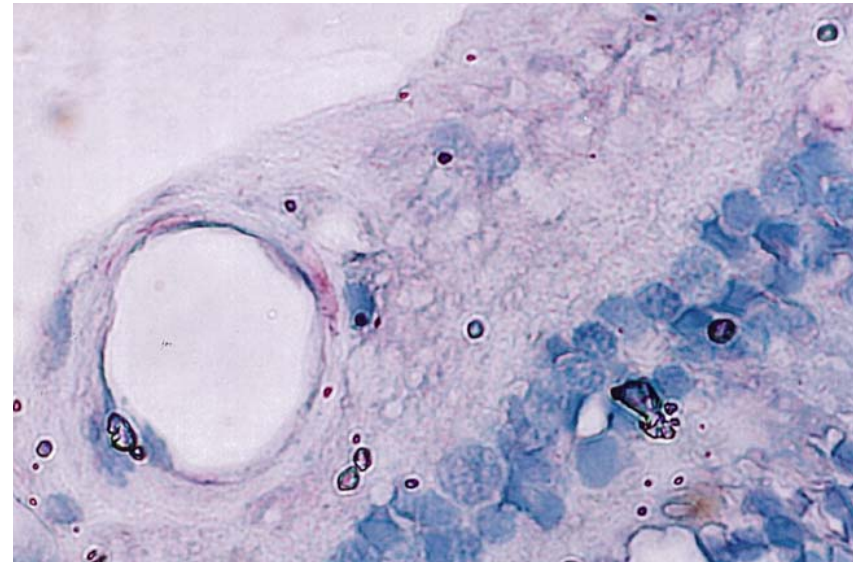
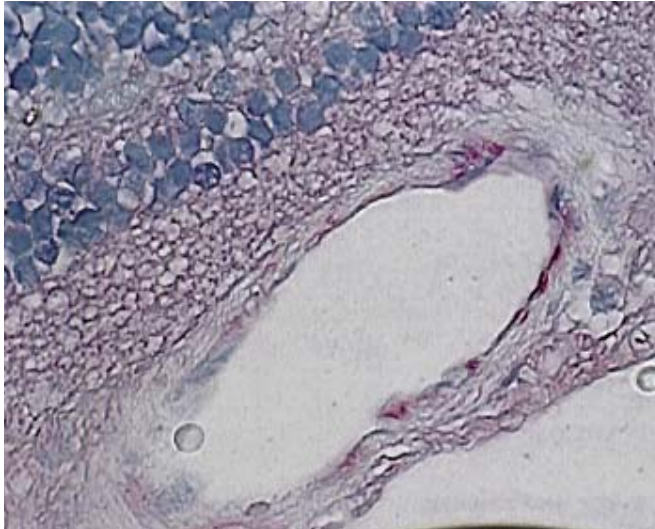
■ HIF-1 transcription factor

HIF1 α

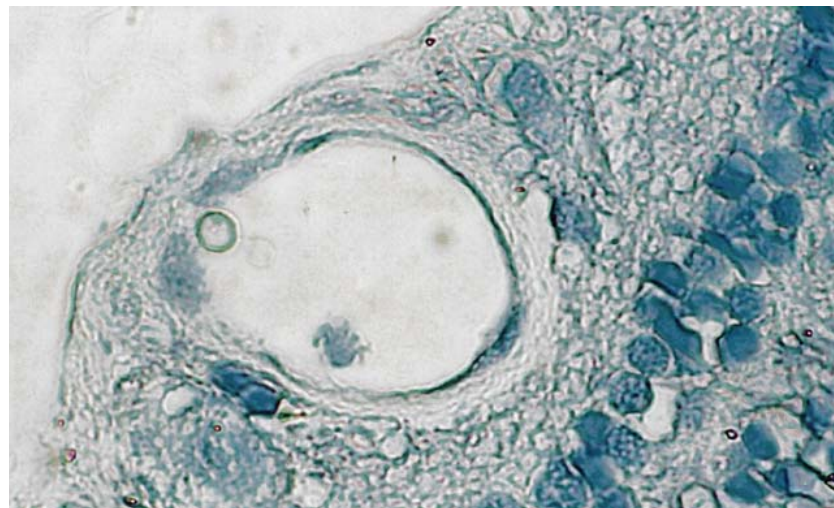
HIF1 β

- Regulated by glucose concentration?
 - High glucose plus low oxygen decrease HIF1 α mRNA and protein
 - Stability of HIF1 α mRNA (AUUUA rich 3'UTR)

HIF1 α in the human eye



HIF-1 α associated with vessels in proliferative diabetic retinopathy



Negative control

Where are we now?

- **Cure diabetes?**
 - potential
 - time
 - resources
 - money/economics
- **Management of diabetes**
 - improve glucose control
 - enhance therapeutic efficacy
 - early detection
 - Health Promotions
 - role for the Health Care Team

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