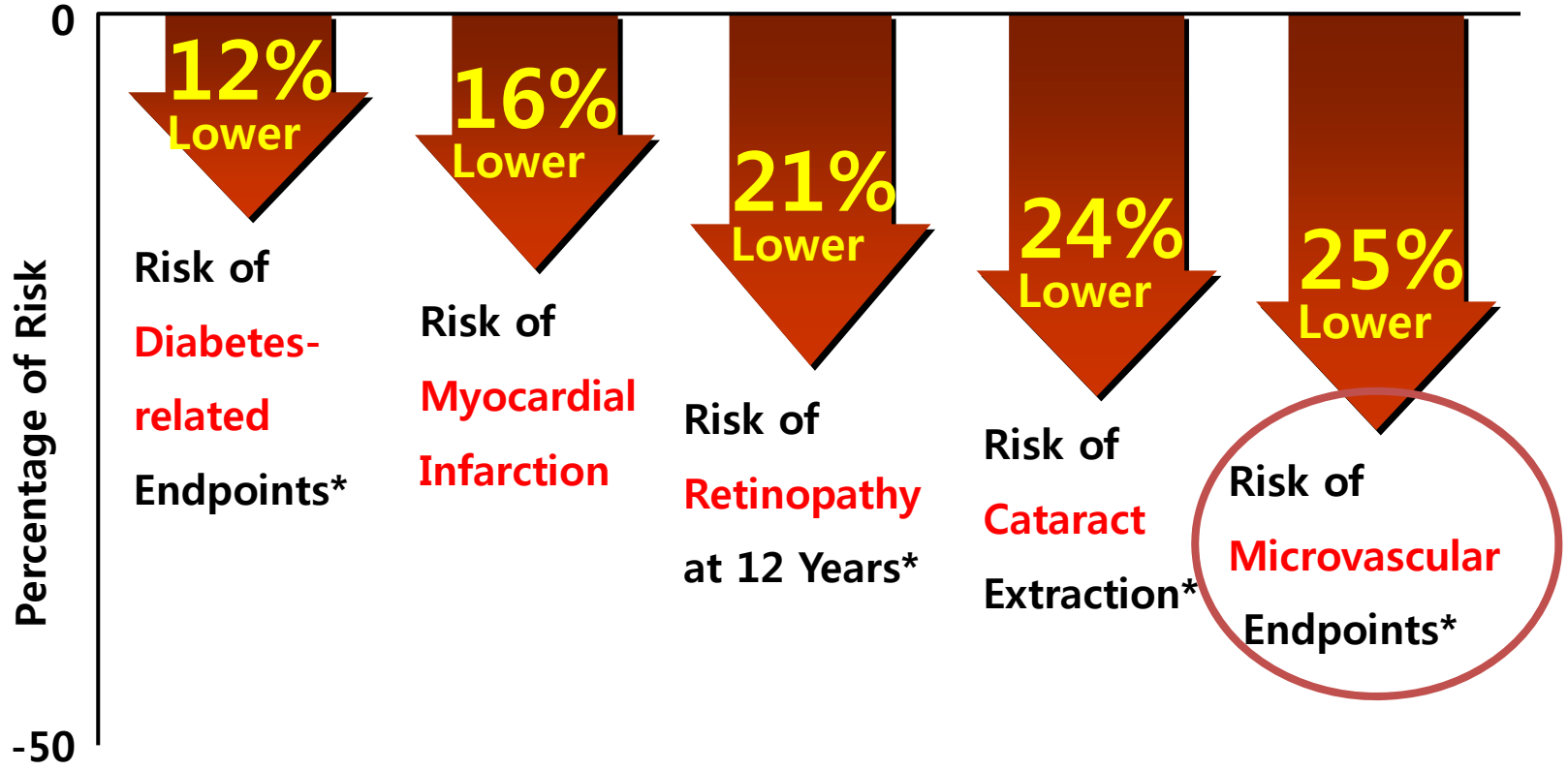
How to prevent vascular complication in DM?

Diabetic microangiopathy: Pathophysiological, clinical and therapeutic aspects

울산의대
서울아산병원
박 중 열

Glycemic Control and Complications

- Intensive glucose control in UKPDS 33 results in:



*Decreases were statistically significant.

UKPDS 33. *Lancet*. 1998

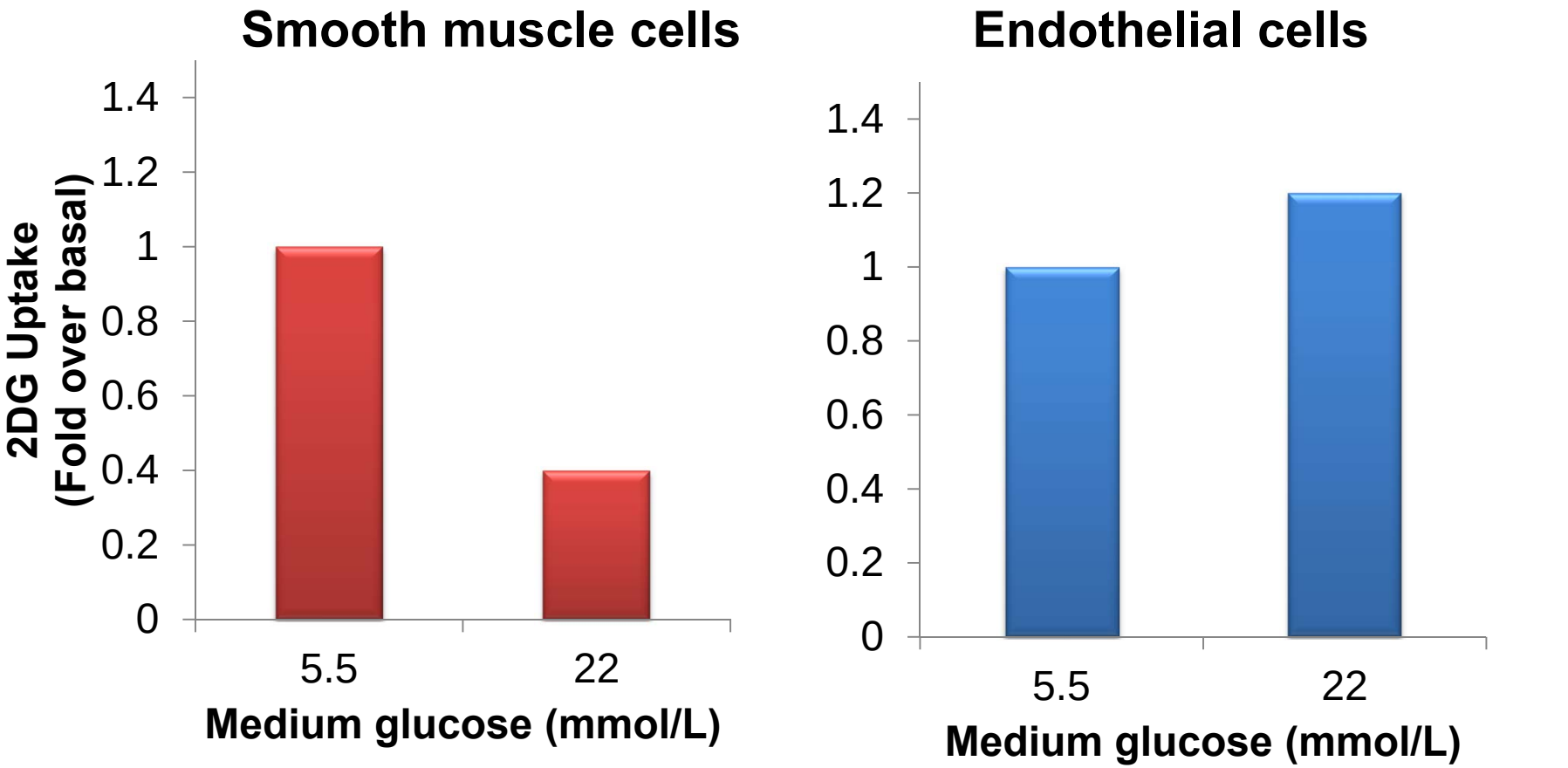
HbA1c and Microvascular Complications

	UKPDS	Kumamoto	ADVANCE
HbA1c	7.9 → 7%	9 → 7%	7.3 → 6.5%
Retinopathy	17-21%	69%	5%
Nephropathy	24-33%	70%	21%
Neuropathy	–	–	–

당화혈색소가 **1%** 감소하면 미세혈관합병증의
상대 위험도가 약 **20%–30%** 감소함.

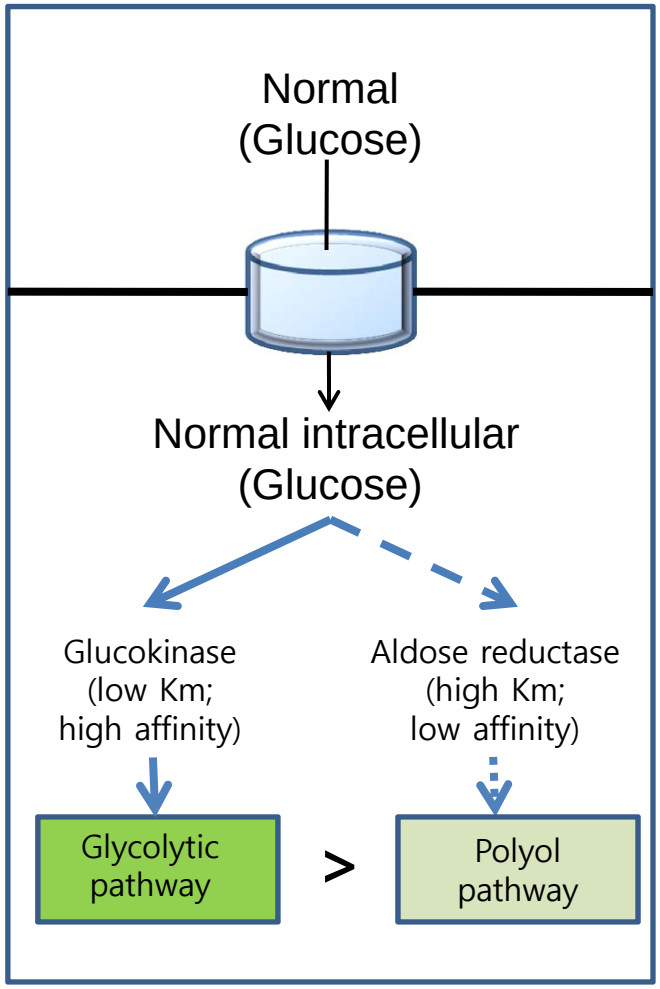
Ohkubo Y. *Diabetes Res Clin Pract*. 1995
UKPDS 33. *Lancet*. 1998
The ADVANCE Collaborative Group. *NEJM*. 2008

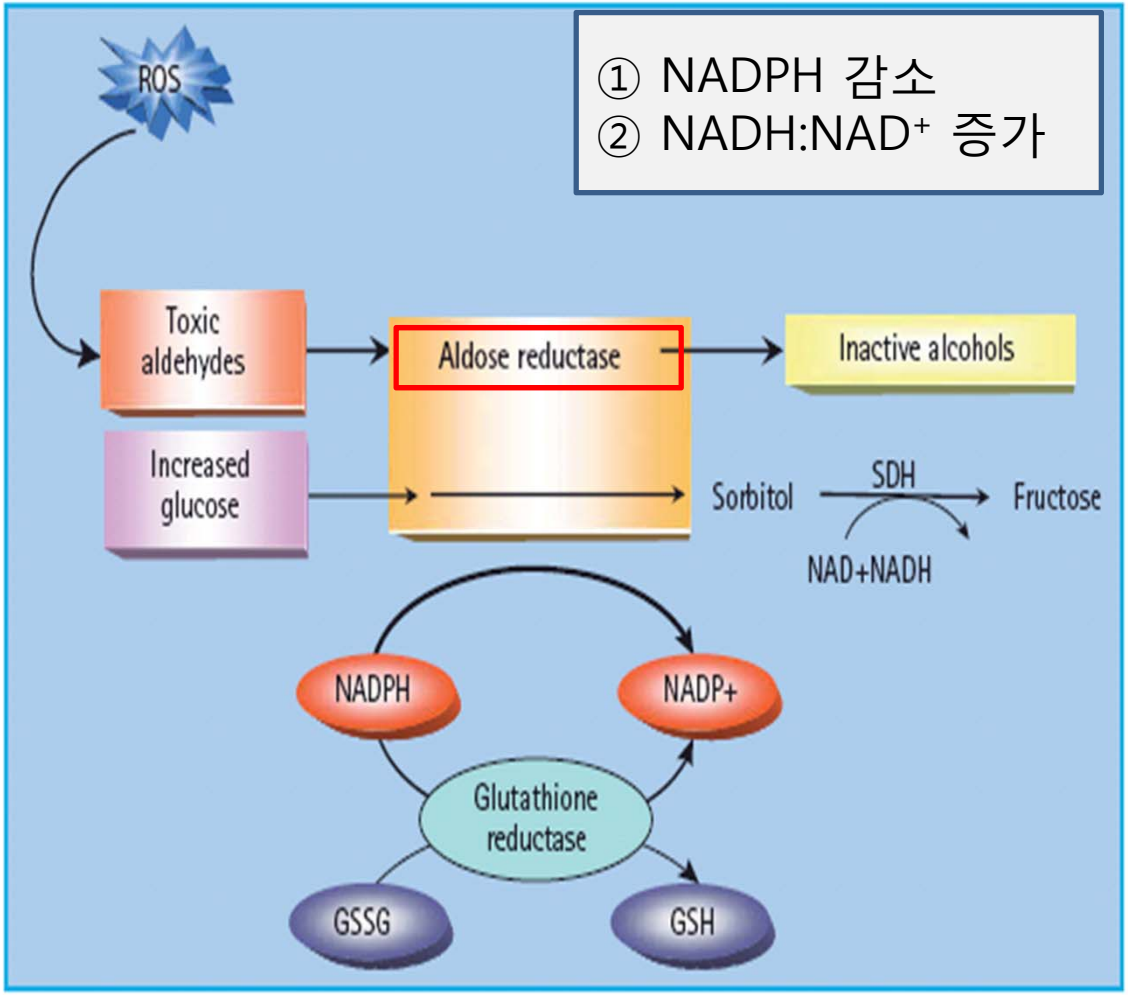
Why vascular complications?



Diabetes 1993;42:80-89

Mechanisms of hyperglycemia -induced damage (1)

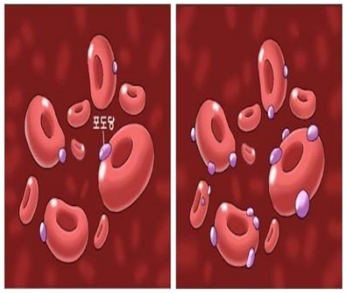




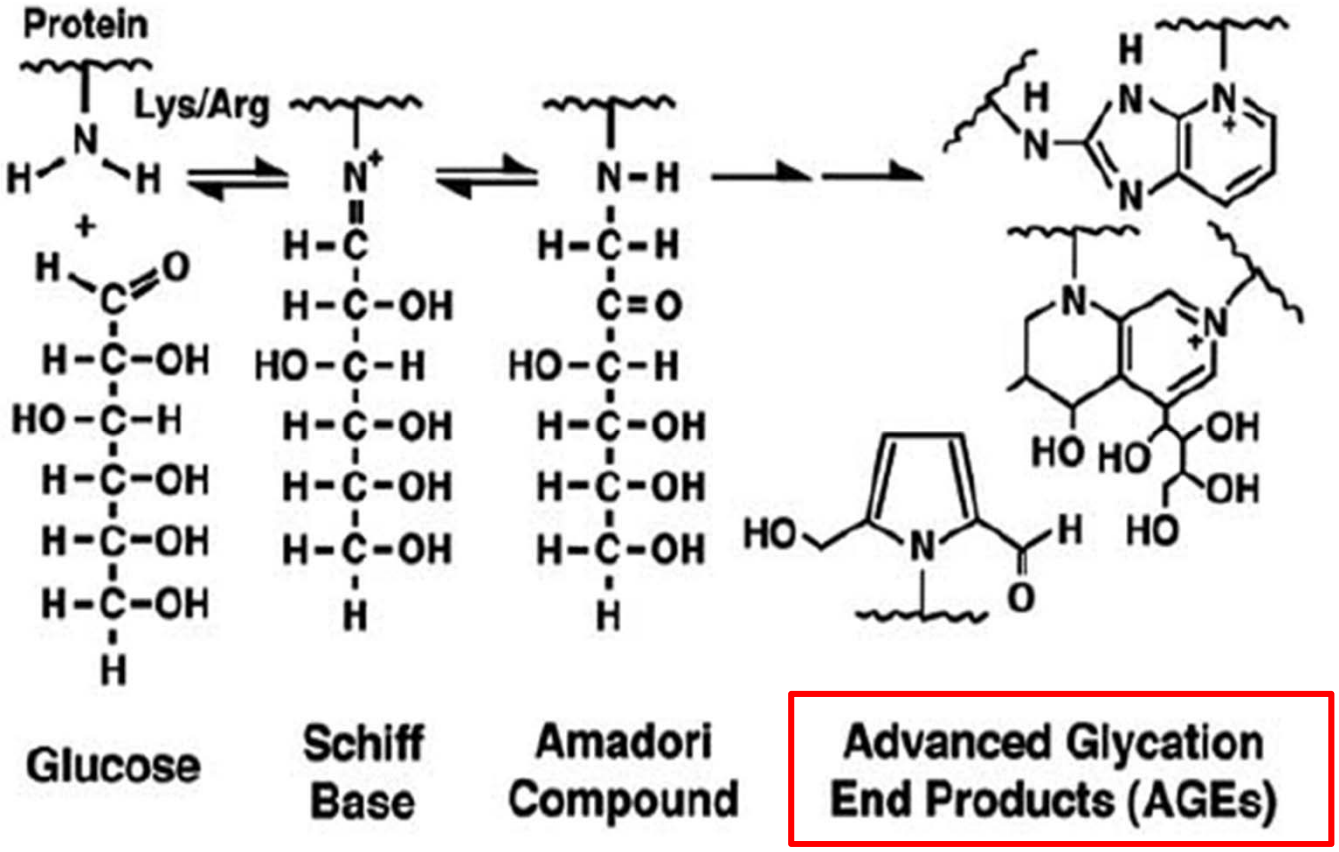
SDH: Sorbitol dehydrogenase

Nature 2001;414:813

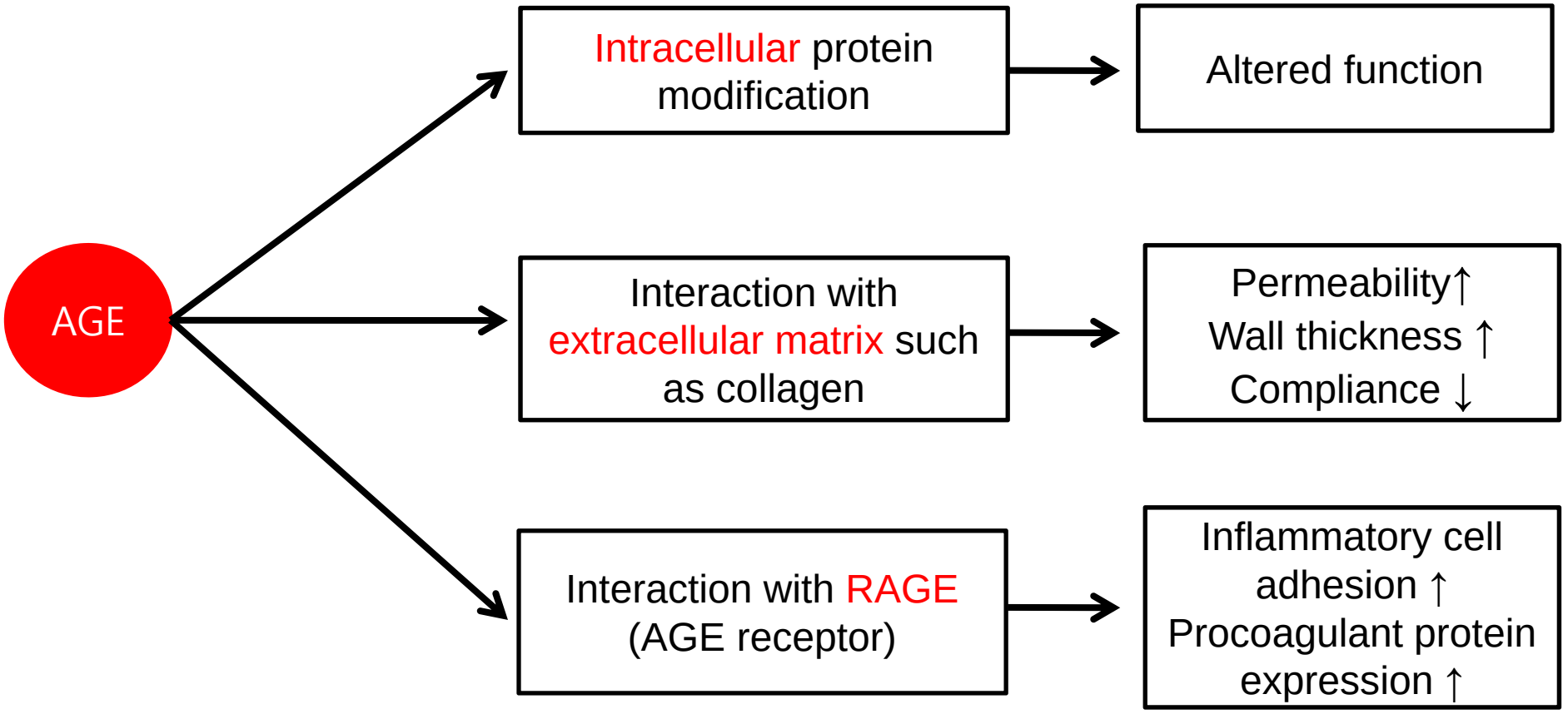
Mechanisms of hyperglycemia -induced damage (2)



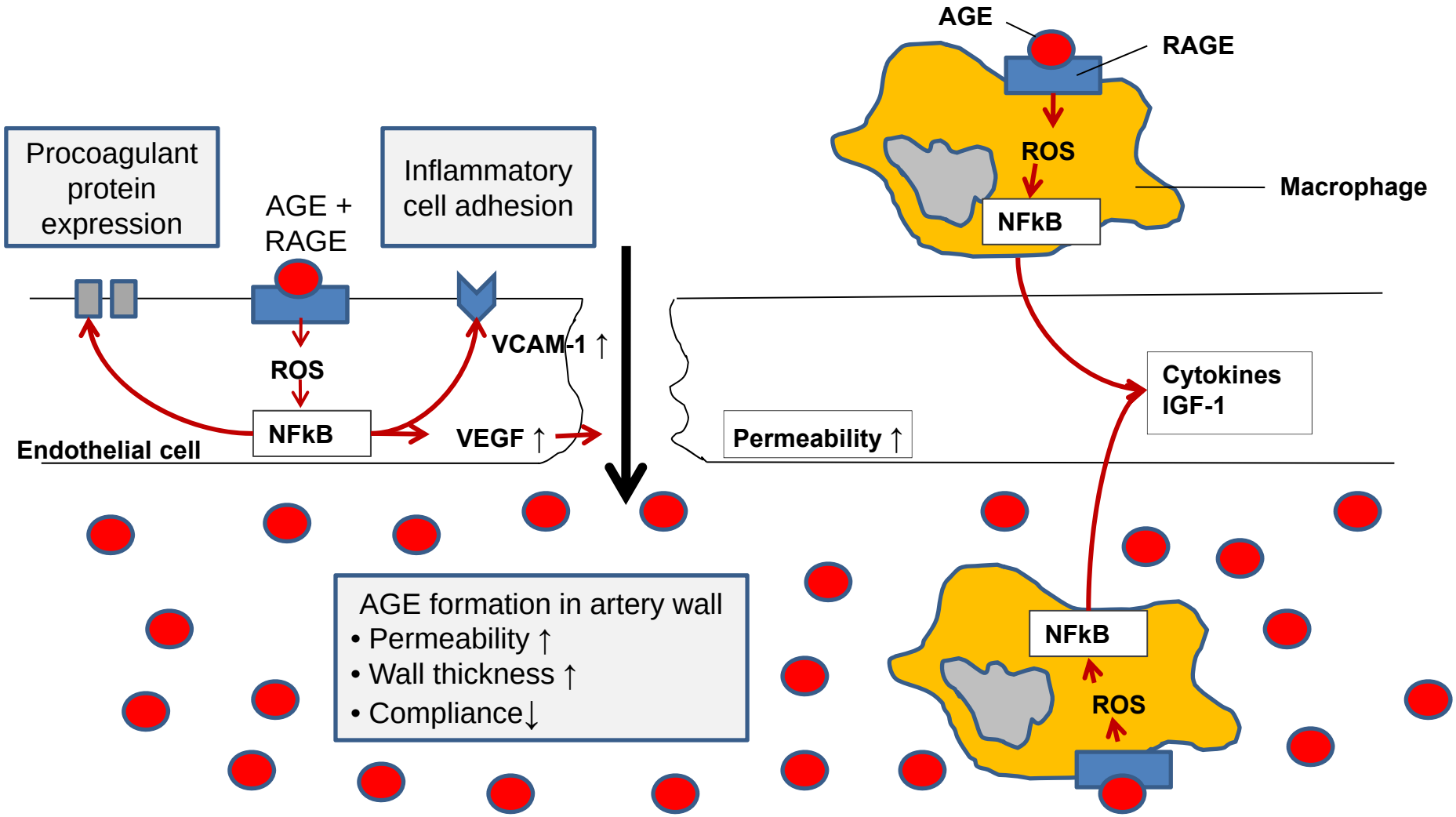
Glycated hemoglobin



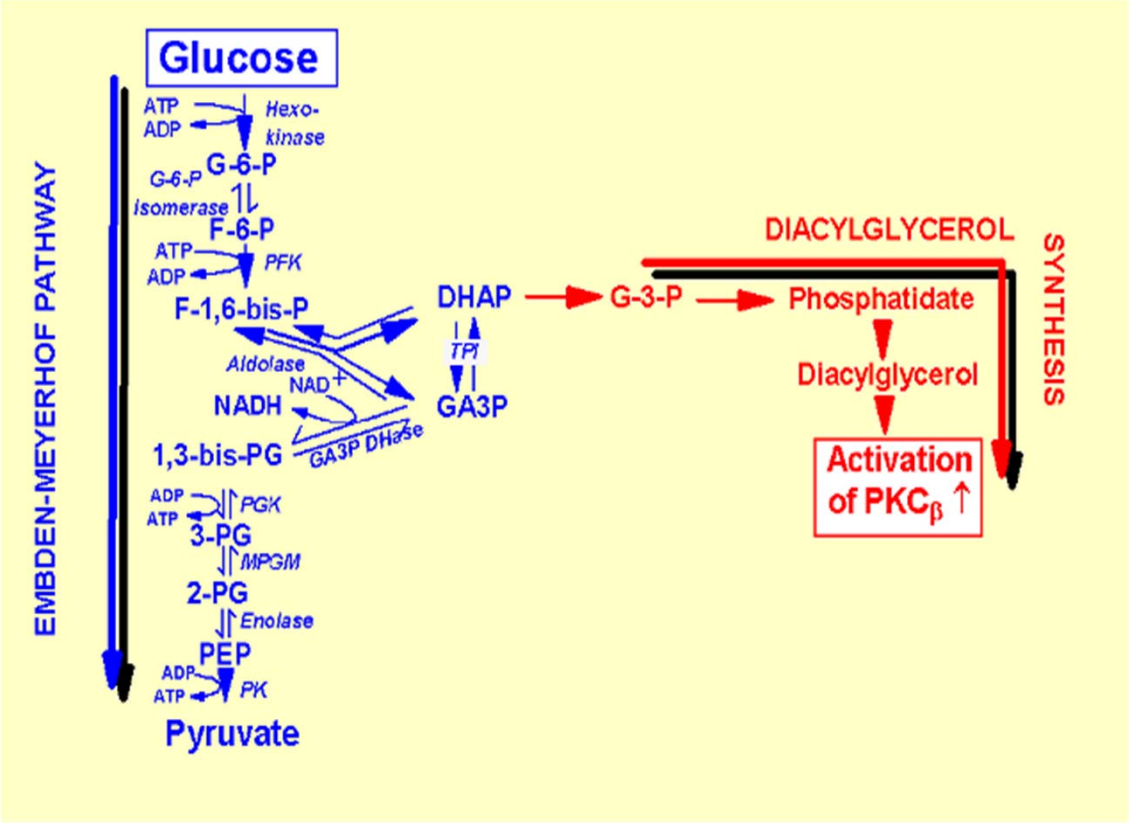
Mechanisms of hyperglycemia -induced damage (2)

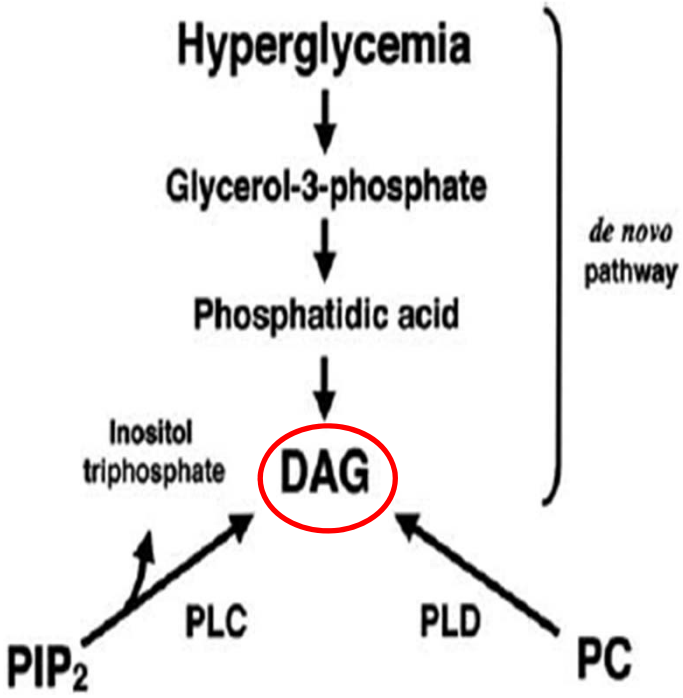


Mechanisms of hyperglycemia -induced damage (2)



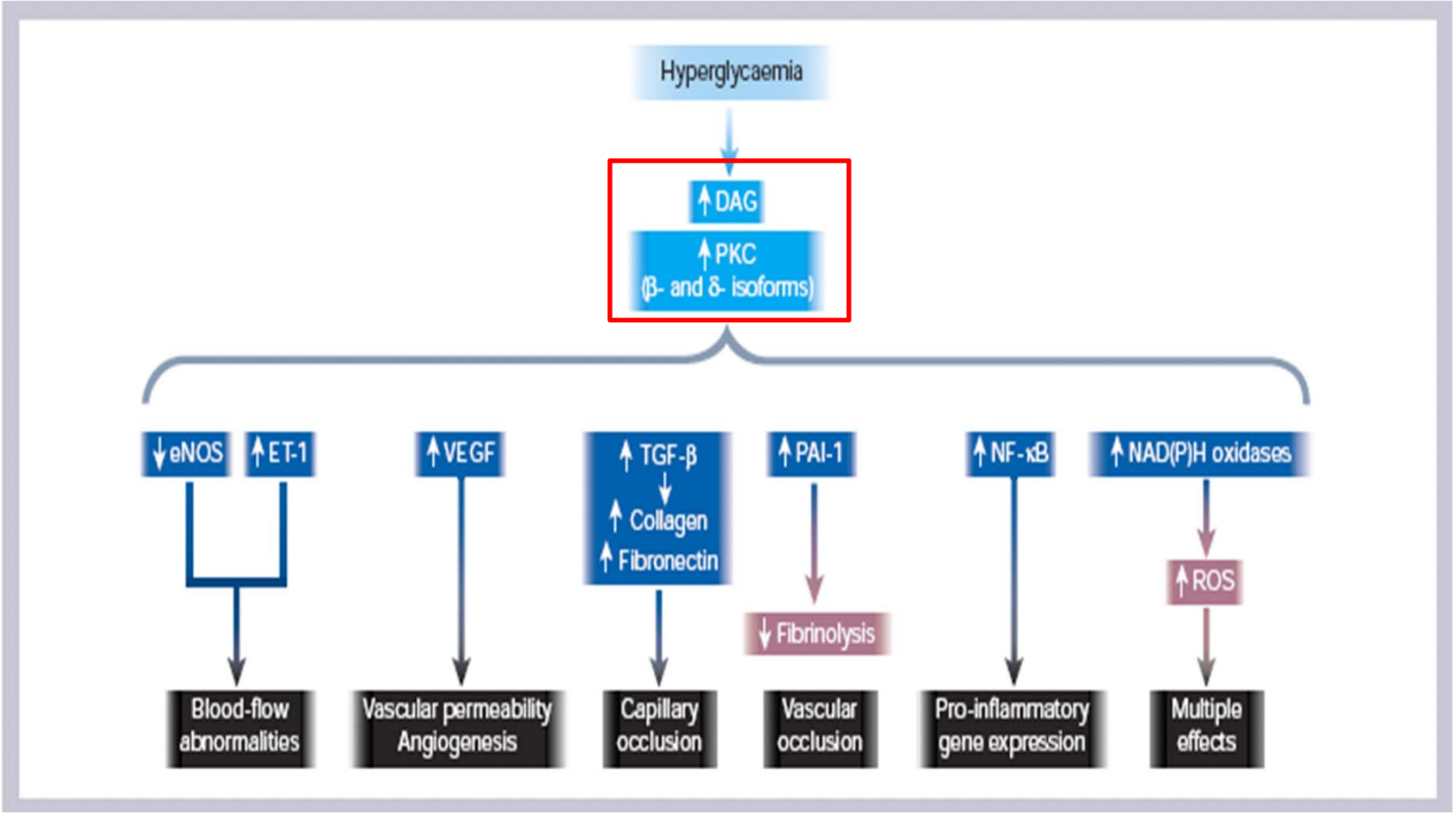
Mechanisms of hyperglycemia -induced damage (3)





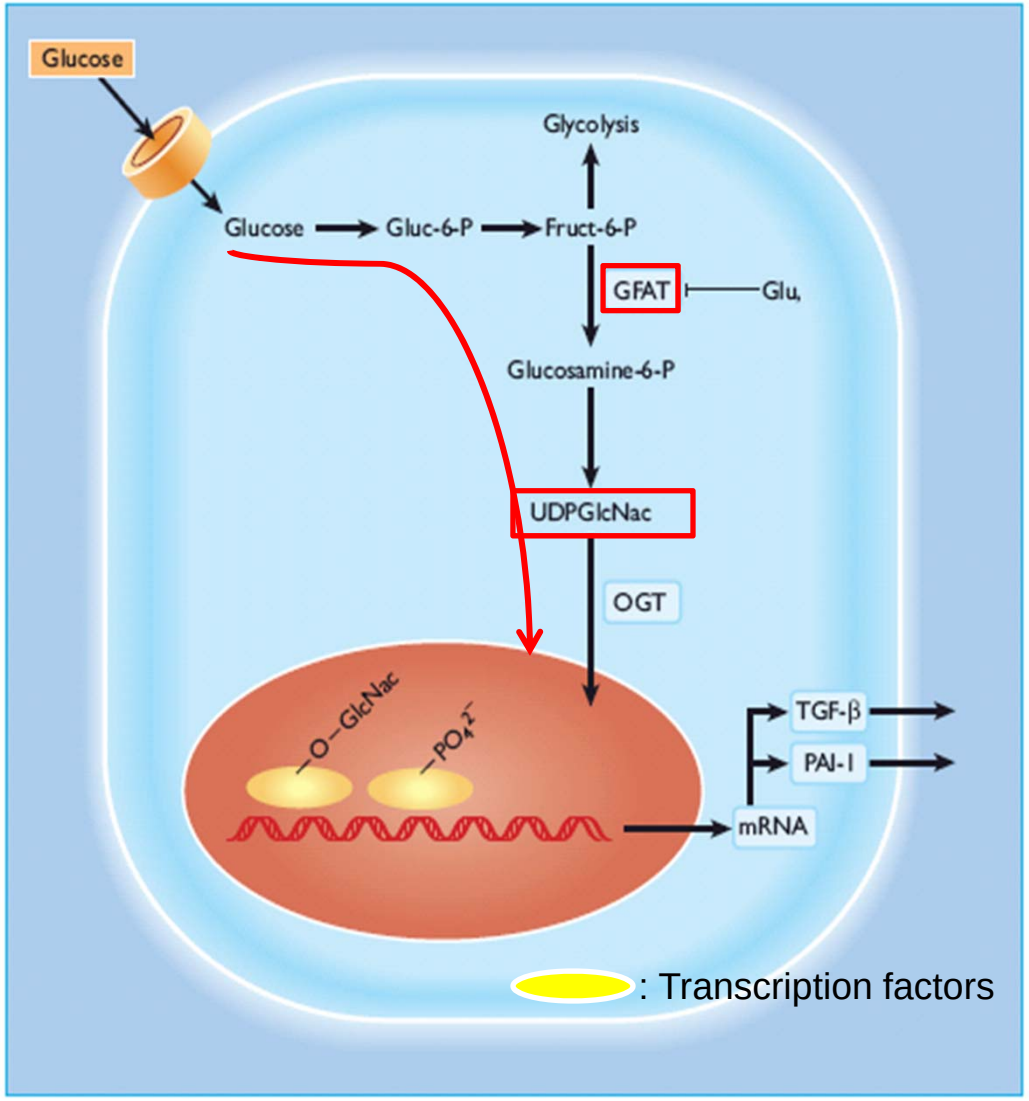
<De novo synthesis of DAG>

Mechanisms of hyperglycemia -induced damage (3)



Nature 2001;414:813

Mechanisms of hyperglycemia -induced damage (4)

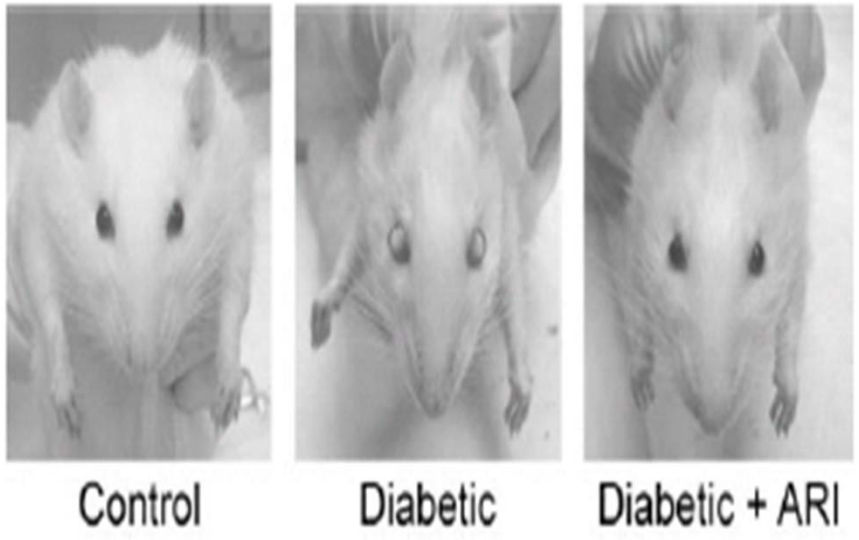


GFAT: glutamin,fructose-6-phosphate amidotransferase
UDPGlcNac: UDP-N-acetylglucosamine

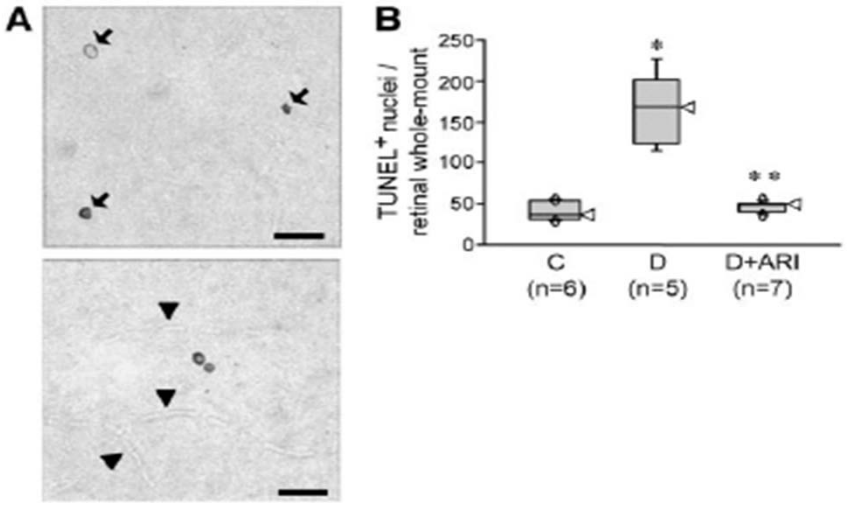
Nature 2001;414:813

Animal study
– Aldose Reductase inhibitors (ARI)

Ex) Sorbinil
Tolrestat,
Ponalrestat and,
Epalrestat



The effect of ARI-809 on cataracts in diabetic rat



The effect of ARI-809 on neuronal apoptosis

Diabetes. 2006; 55(10):2757-62

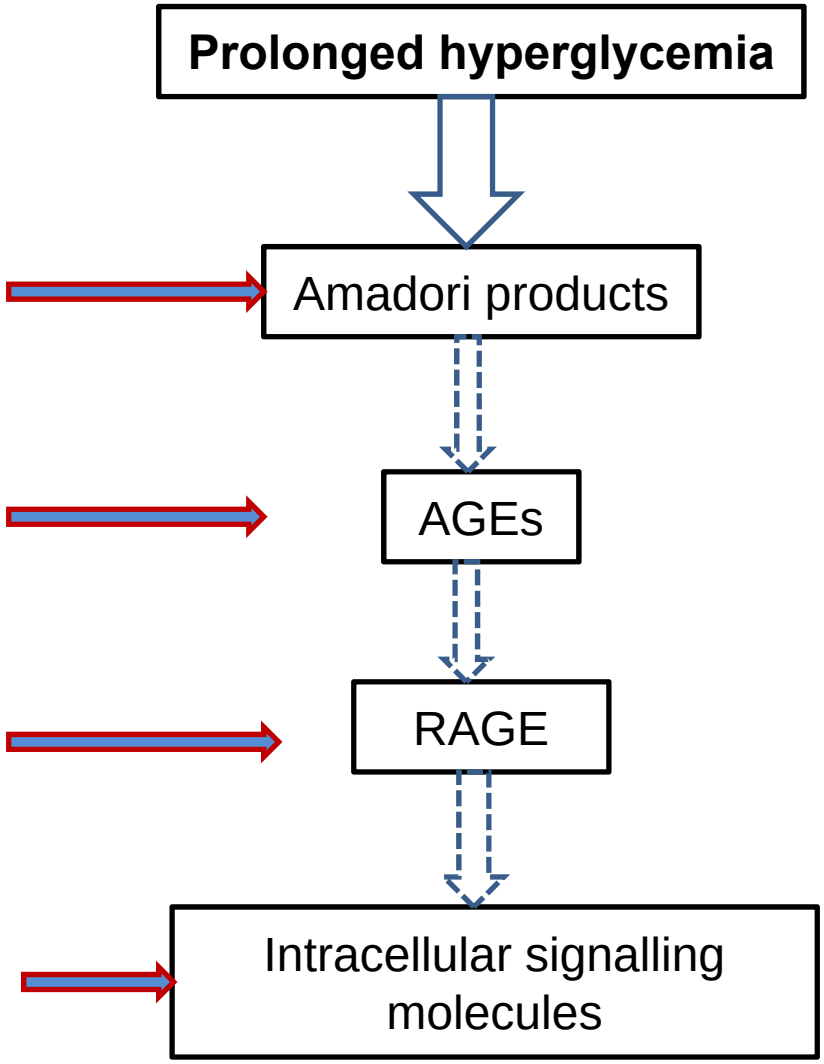
Clinical Trials
– Aldose Reductase inhibitors (ARI)

ARI	complication	N, f/up duration	Effect	Comments
Sorbinil	Retinopathy	497, 41 mo	NS	7 % 과민반응
Ponalrestat	Retinopathy	30, 12 mo	NS	
Tolrestat	Nephropathy	20, 6 mo	Beneficial	
		16, 12 mo	NS	
Epalrestat	Nephropathy	35, 5 yrs	Beneficial	Incipient stage 에서 효과
Ranirestat	Neuropathy	549, 52wk	NS	Motor N는 효과 보임.
Fidarestat	Neuropathy	279, 52wk	Beneficial	
Epalrestat	Neuropathy	289, 3 yrs	Beneficial	

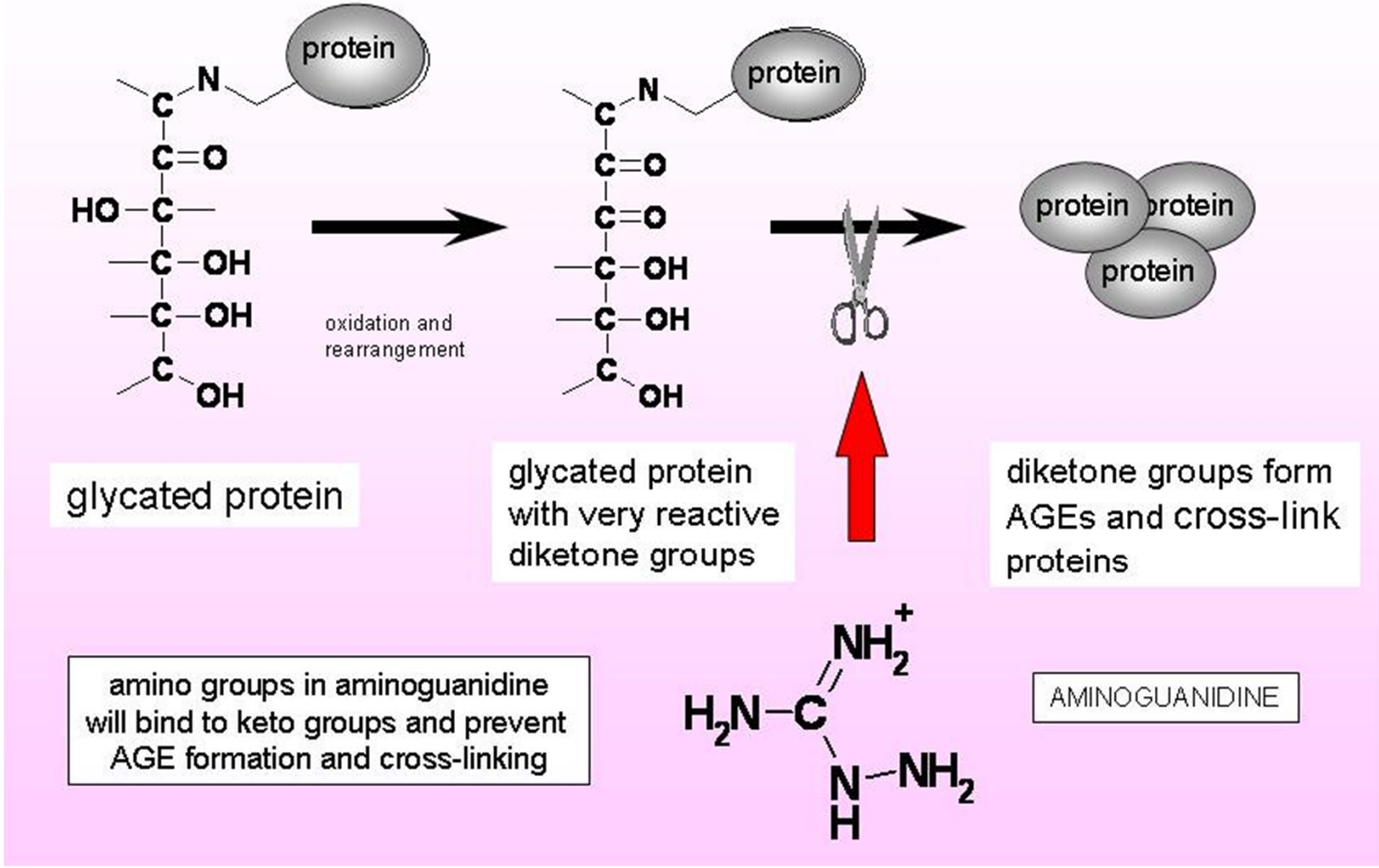
NS: not significant

AGE inhibitors

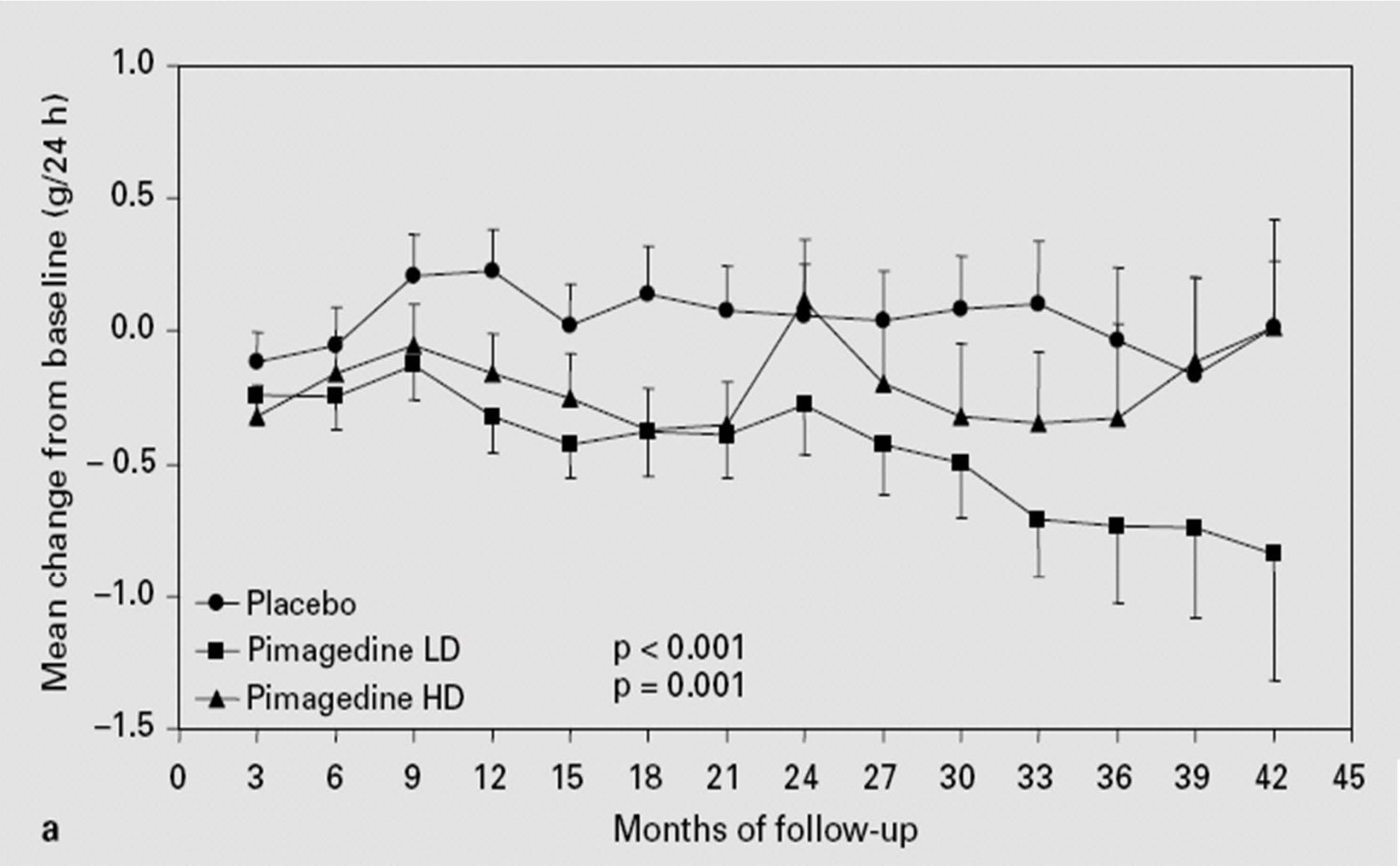
- **AGE formation inhibitors**
  Aminoguanidine, ALT-946,
  Pyridoxamine, OBP-9195
  LR-90, Benfothiamine
- **AGE crosslink breakers**
  PTB, ALT-711, C-36, TRC-4186
- **AGE receptor antagonists**
  sRAGE, RAGE antibody
- **Interventions targeting signal molecules**
  PKC inhibitors, TGF-b inhibitors
  Growth factor inhibitors



Aminoguanidine



Clinical Trials
– AGE inhibitors (aminoguanidine)



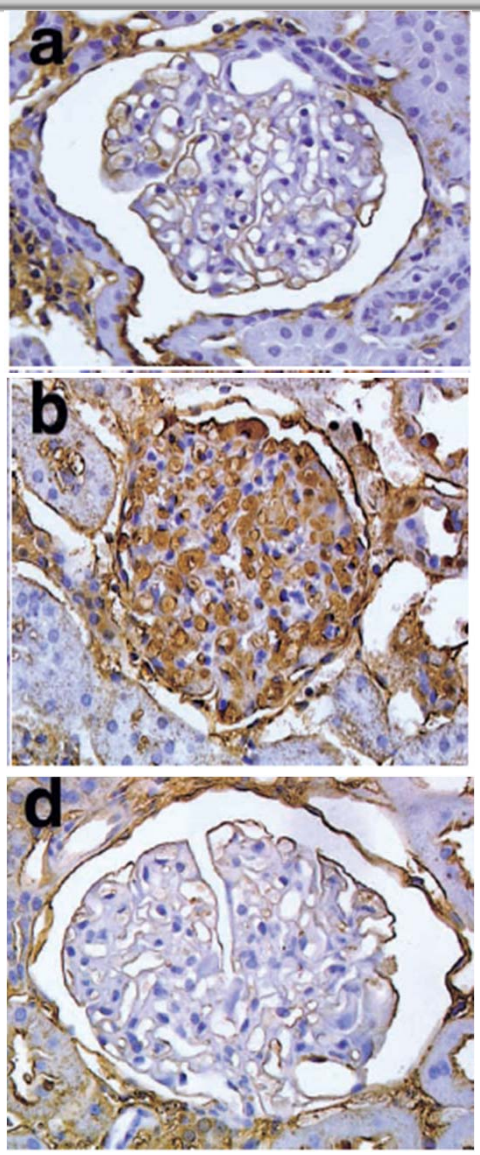
Am J Nephrol 2004;24:32-40

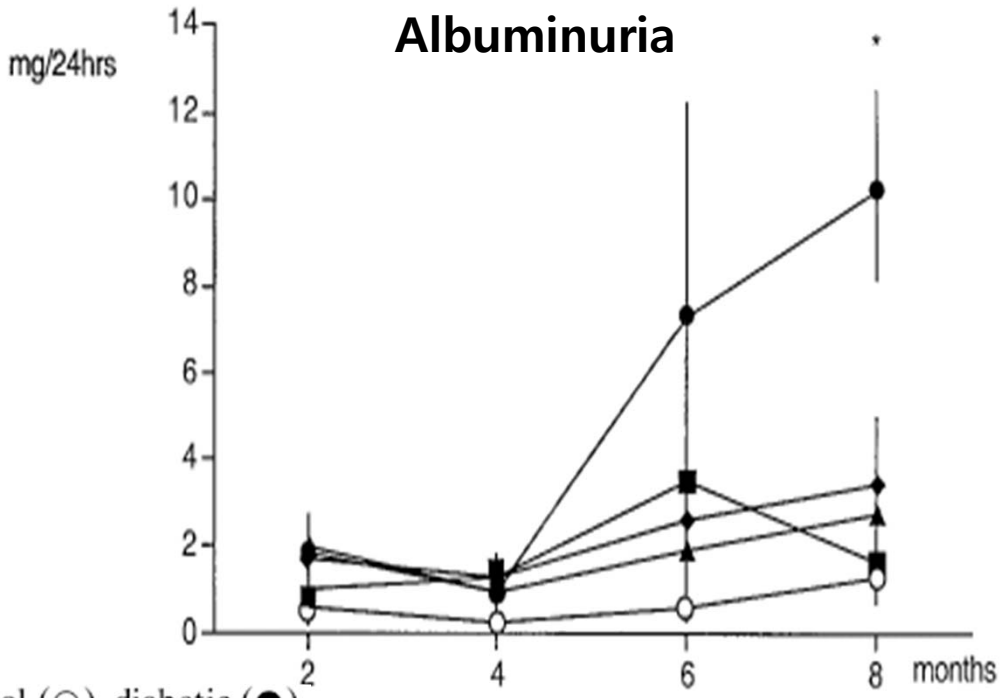
Animal study
– AGE inhibitors (ALT-946)

Control

Diabetes

Diabetes
+
ALT-946





control (○), diabetic (●),
Diabetic + aminoguanidine (◆),
diabetic + ALT-946 (▲)
diabetic + ALT-946INT (■).

Diabetologia 2001:33:108-114

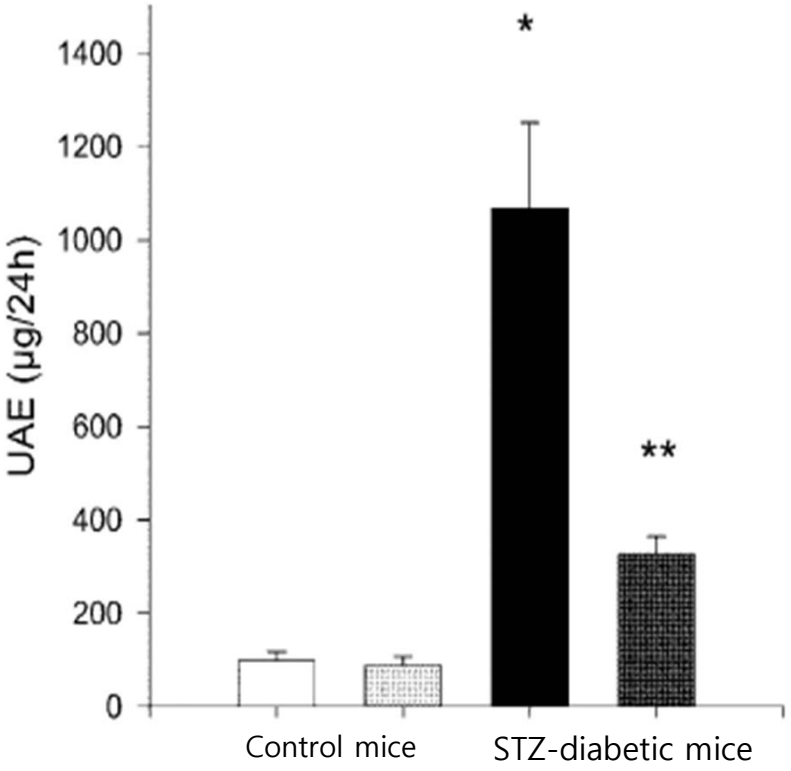
Ongoing Clinical Trials – AGE inhibitors

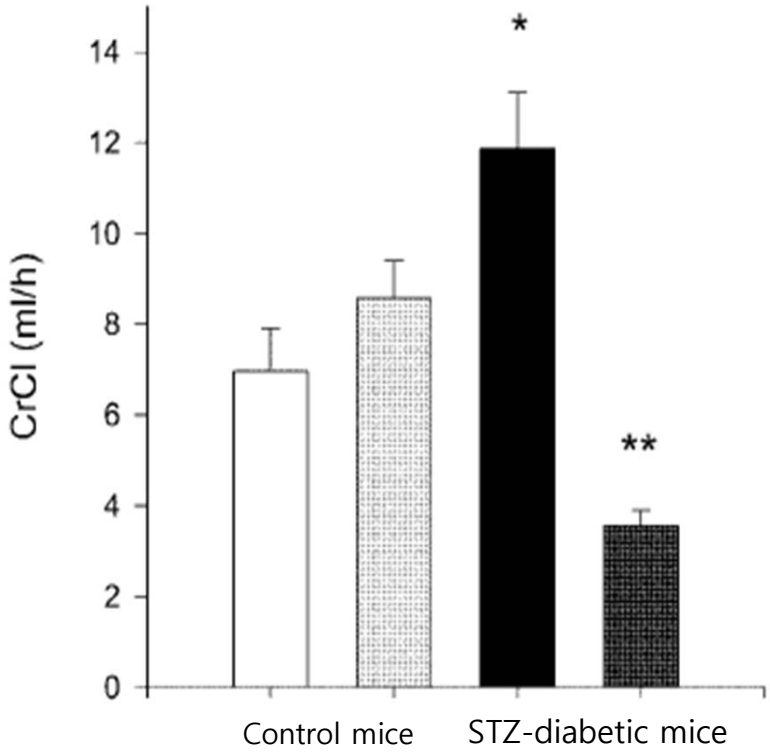
Table 2. Ongoing Clinical Trials of Potential New Therapeutic Agents for Diabetic Kidney Disease

Drug (registration no.)	Study Design	Estimated Enrollment	Treatment Plan	Primary End Point
Pyridorin (NCT00734253)	R, DB, PC	300	150 or 300 mg/d of pyridoxamine for 1 y	ΔSCr from baseline to end of study
Benfothiamine (NCT00565318)	R, DB, PC	86	900 mg/d of benfothiamine for 12 wk	Change in urinary excretion of kidney injury molecule 1 and albumin
FG-3019 (NCT00754143)	R, DB, PC	36	FG-3019, 5 or 10 mg /kg, for 34 wk	Safety and tolerability

Abbreviations: DB, double-blind; PC, placebo-controlled; R, randomized; SCr, serum creatinine.

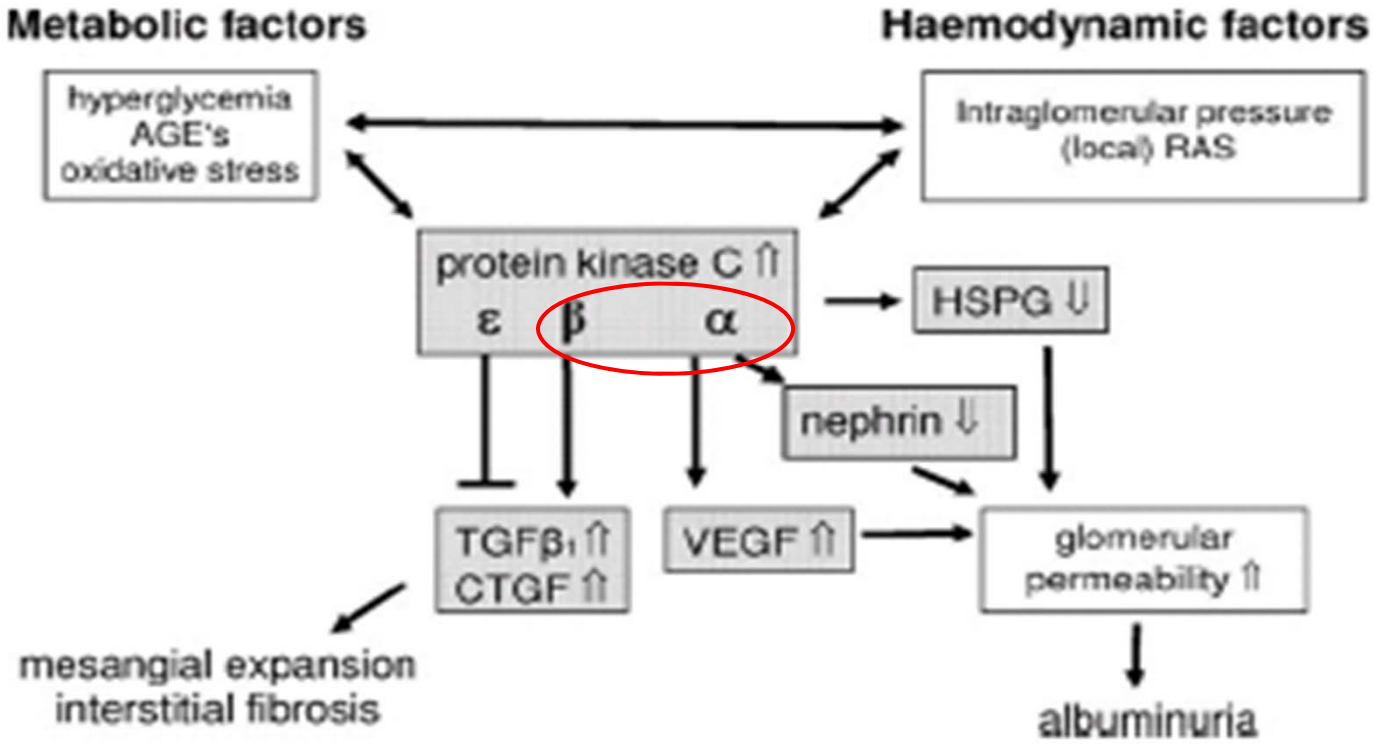
Animal study
– RAGE antagonists





J Endocrinol 2006;188:493-501

Animal study
– PKC inhibitors



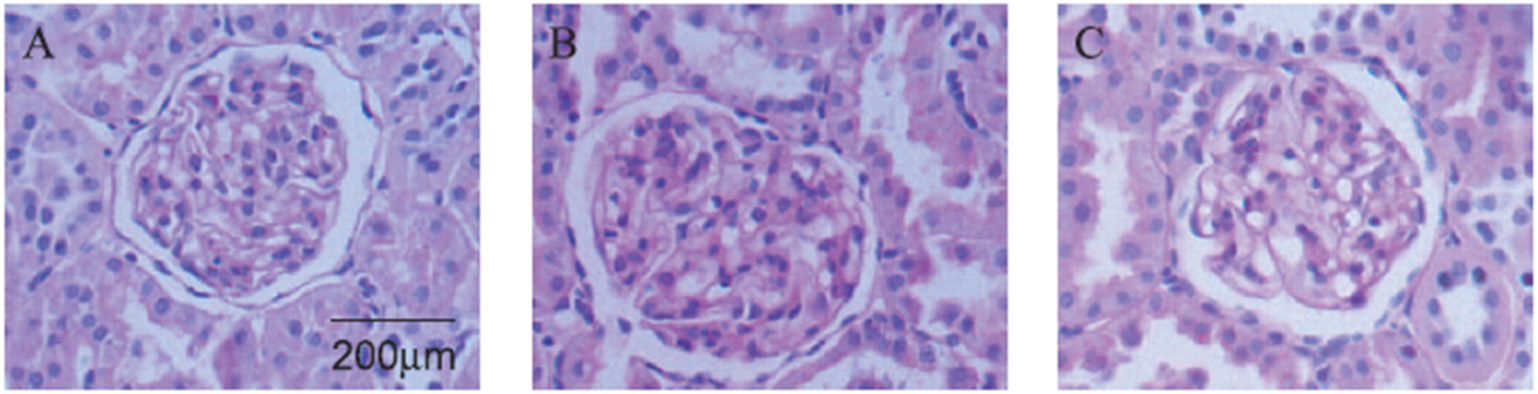
<Pathogenesis of diabetic nephropathy>

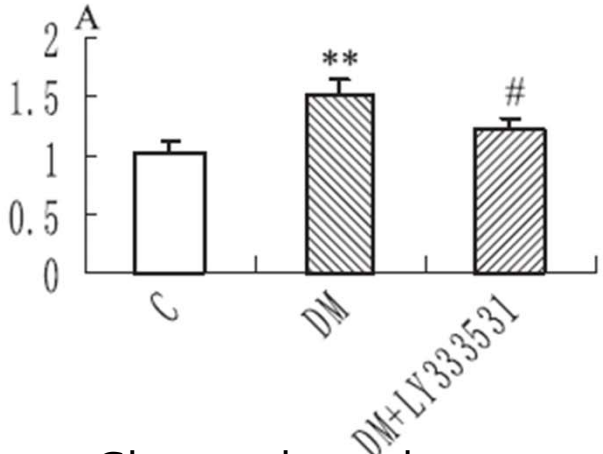
HSPG: heparin sulfate proteoglycan
VEGF: vascular endothelial growth factor
CTGF: connective tissue growth factor

Nephrol Dial Transplant 2009;24:2021

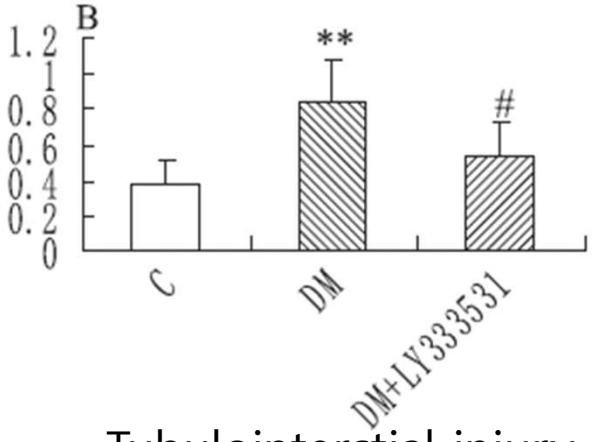
Animal study
– PKC β inhibitors

LY333531 = Ruboxistaurin
selective PKC β inhibitor





Glomerular volume



Tubulointerstial injury

J Pharmacol Sci 2006;101:335-343

Human studies – Ruboxistaurin

Emerging Treatments and Technologies

ORIGINAL ARTICLE

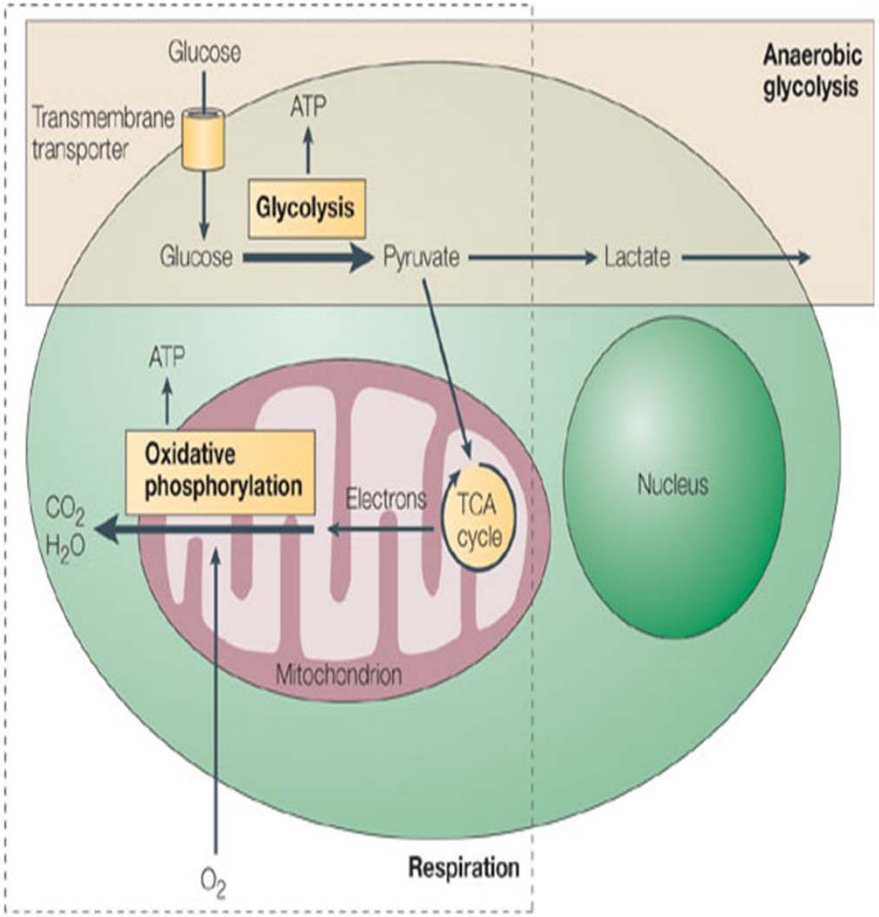
The Effect of Ruboxistaurin on Nephropathy in Type 2 Diabetes

Table 3—*Change from baseline in urinary ACR and eGFR, blood pressure, and A1C at follow-up visits*

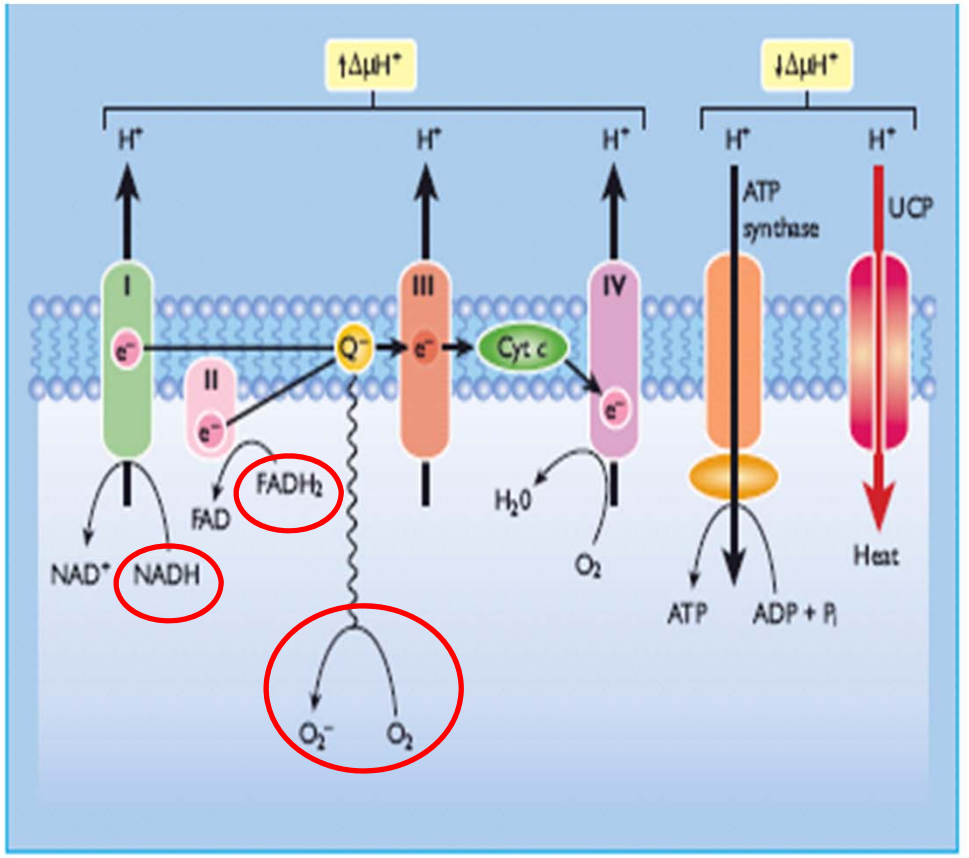
Treatment	*n*	1 month	3 months	6 months	12 months
Urinary ACR change (%)*					
Placebo	62	−16 ± 7†	−9 ± 8	−9 ± 10	−9 ± 11
RBX	59	−24 ± 7†	−28 ± 6†	−29 ± 8†	−24 ± 9†
Urinary ACR change (mg/g)‡					
Placebo	62	17 (424)	−37 (413)†	21 (661)	26 (896)†
RBX	59	−60 (363)†§	−139 (417)†§	−136 (598)	−121 (481)
eGFR change (ml/min per 1.73 m^2)					
Placebo	62	—	—	−2.7 ± 1.8	−4.8 ± 1.8†
RBX	57	—	—	−0.2 ± 1.9	−2.5 ± 1.9

Diabetes Care 2005;28:2686-80

Unifying pathogenic mechanism: Mitochondiral superoxide production

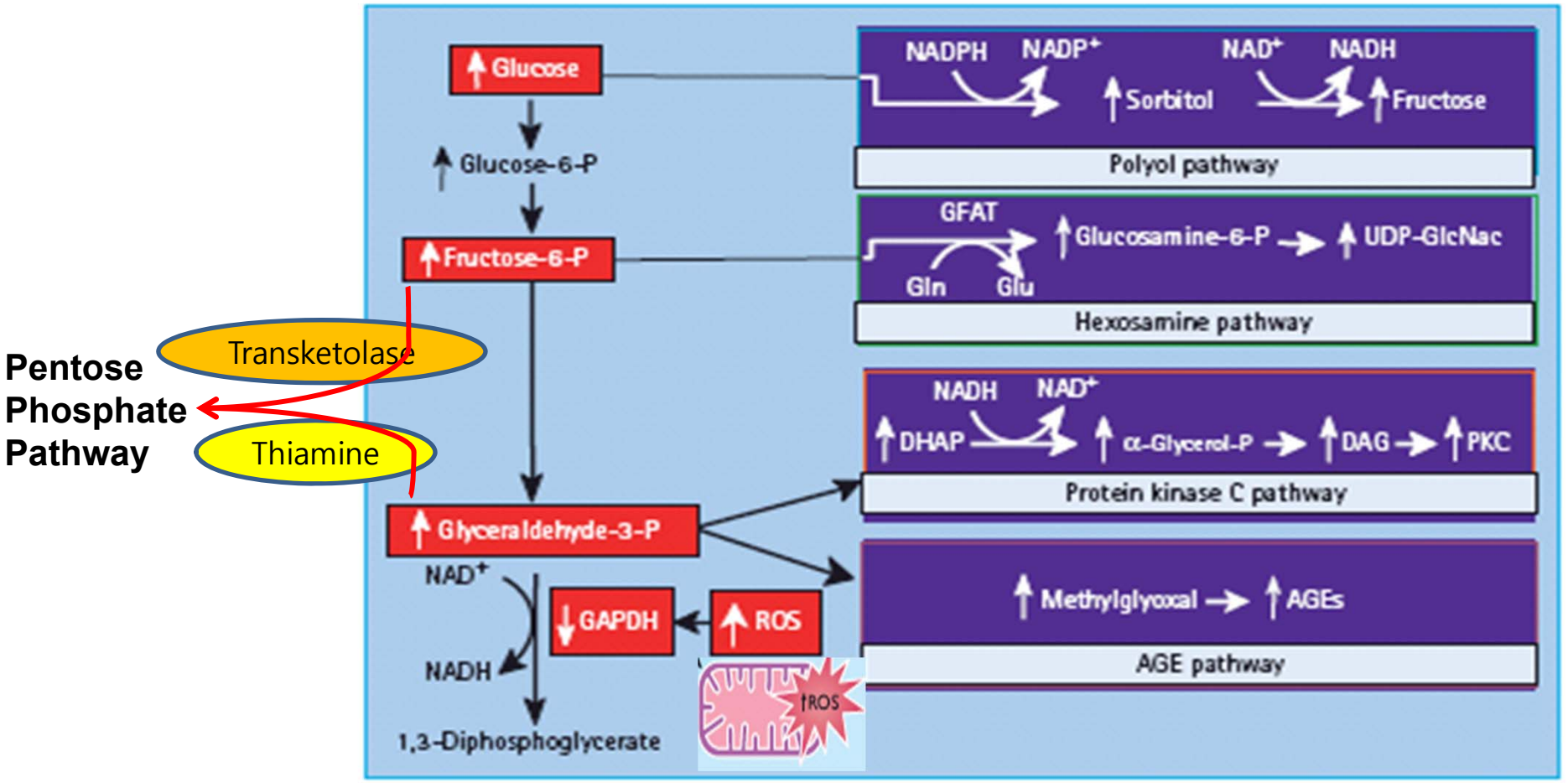


Glycolysis and TCA cycle



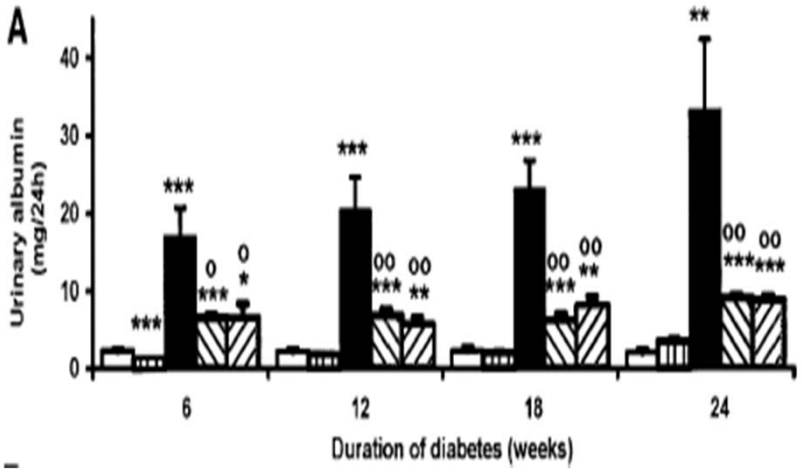
Mitochondrial oxidative phosphorylation

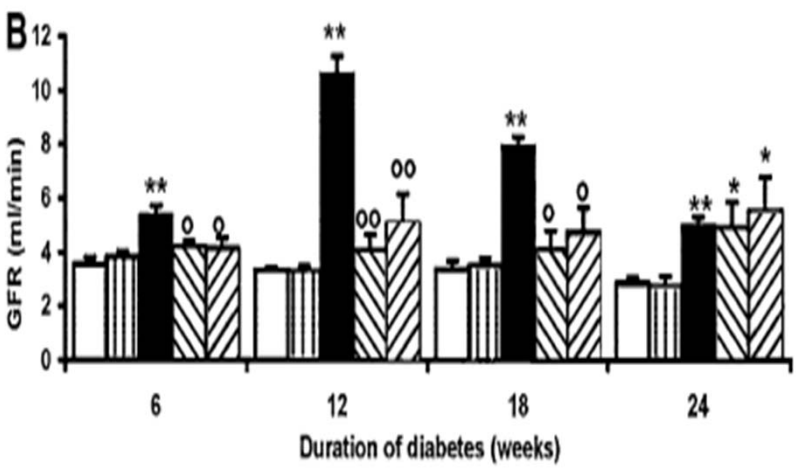
Unifying pathogenic mechanism: Mitochondiral superoxide production

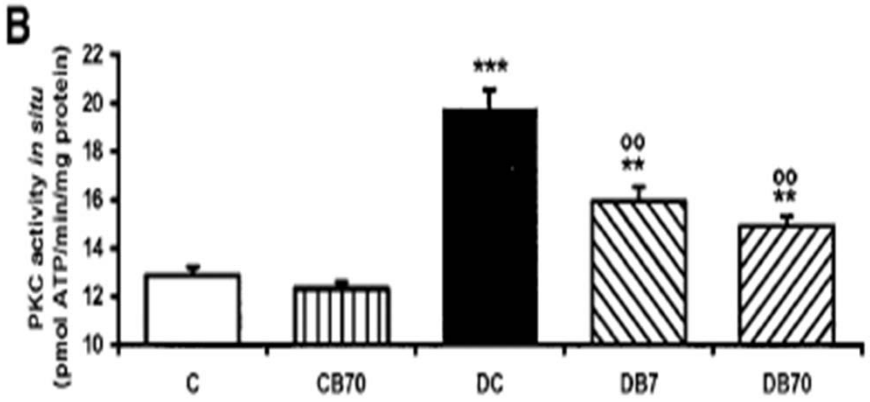


GAPDH: Glyceraldehyde-3-phosphate dehydrongenase

Animal study:
Activation of transketolase with thiamine







Diabetes 2003;52:2110-2120

Prevention of nephropathy by thiamine

Pathophysiology/Complications

BRIEF REPORT

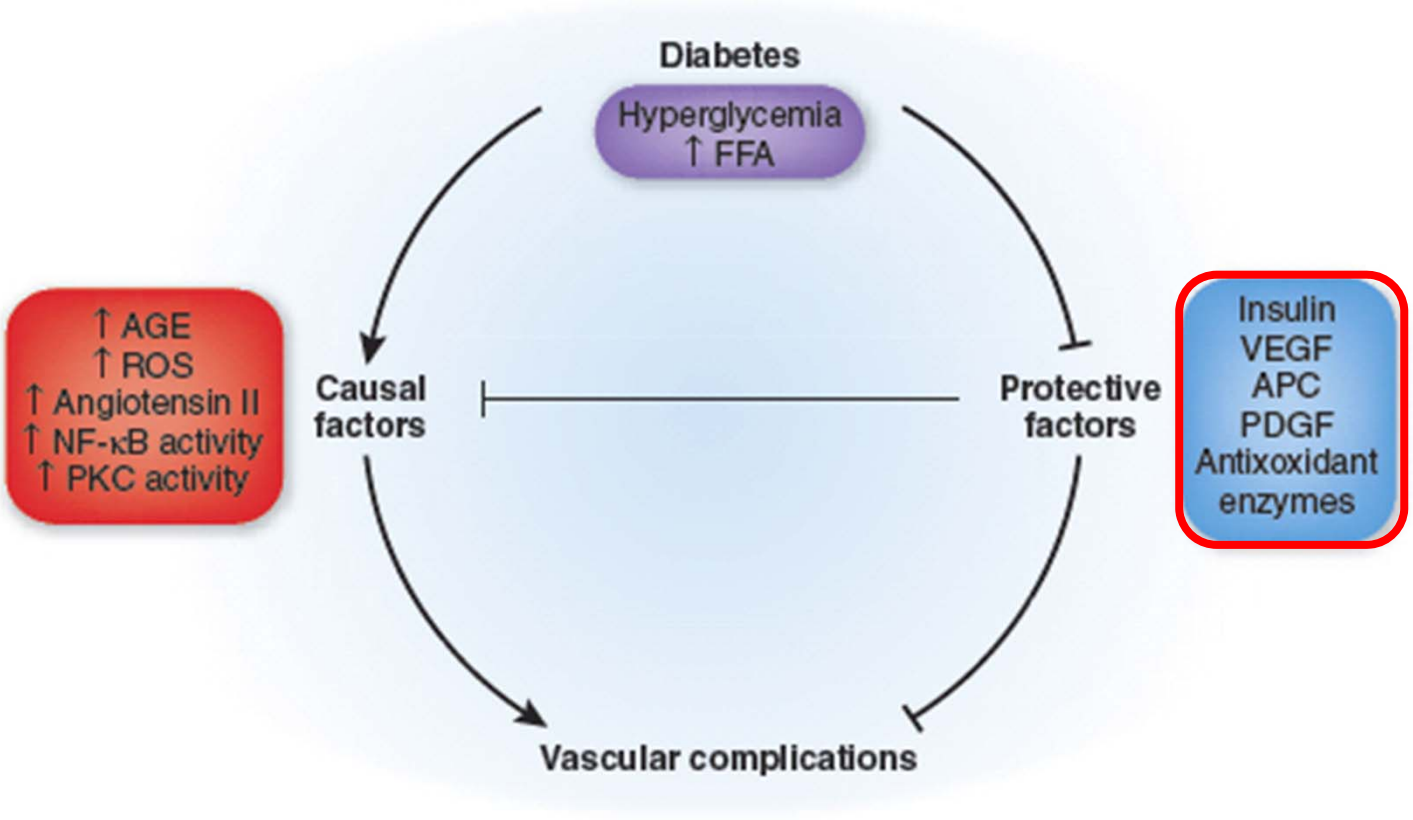
A Double-Blind, Randomized, Placebo-Controlled Clinical Trial on Benfotiamine Treatment in Patients With Diabetic Nephropathy

Benfothiamine (n=39, 900 mg/day)
Study duration: 12 weeks

Negative result.

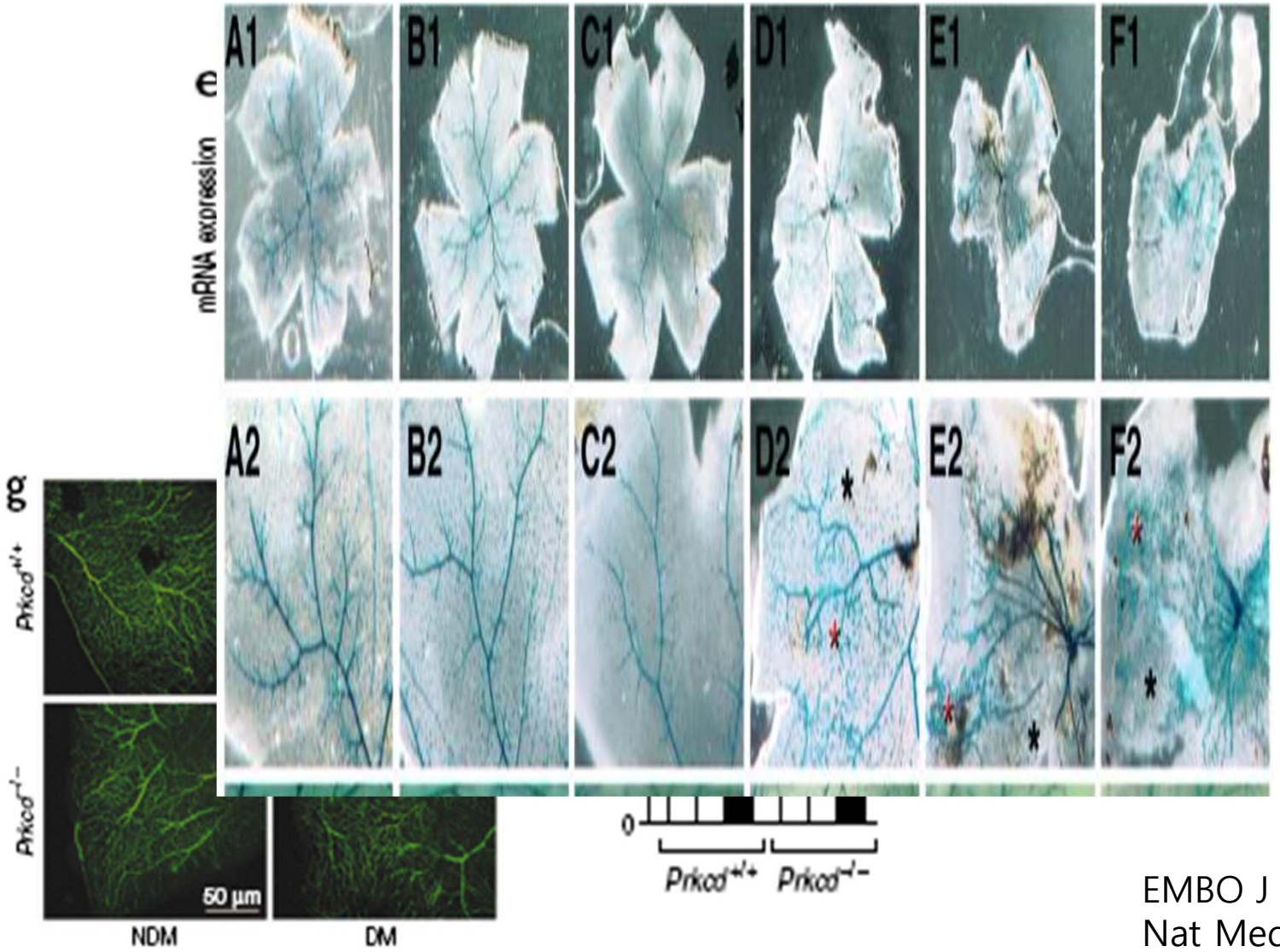
Diabetes Care 2010;33:1598

Recent perspectives:
Loss of Endogenous Protective Factors



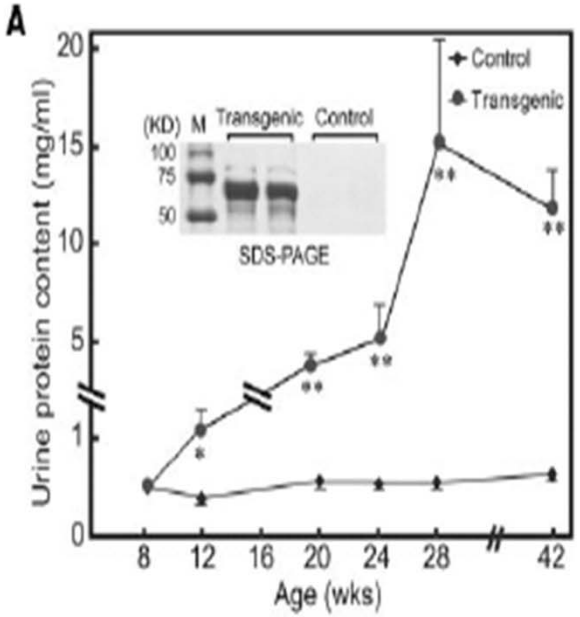
George L King. Nat Med 2010;16:40-41

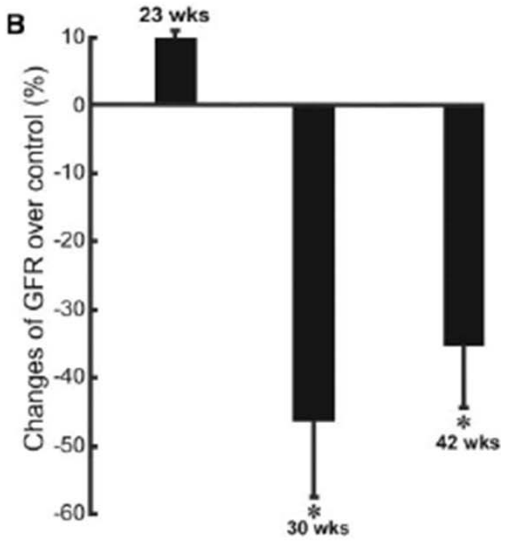
Endogenous Protective Factors: PDGF

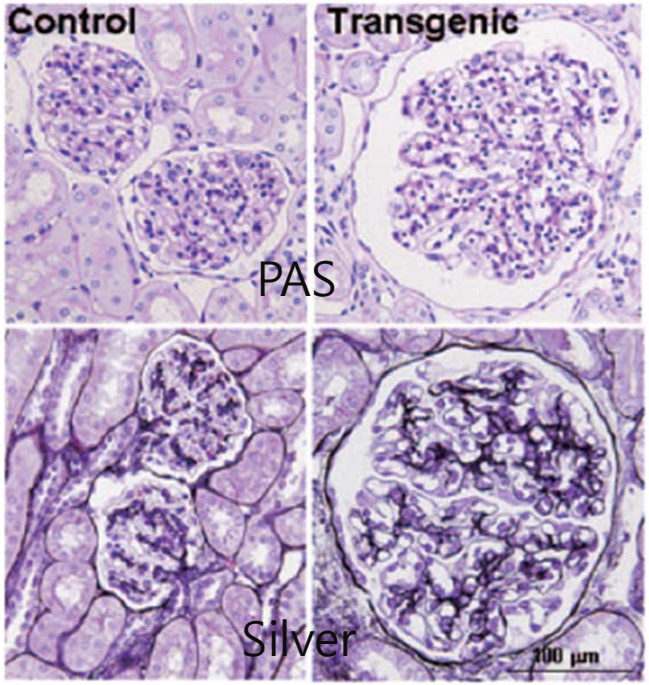


EMBO J 2002;21:4307
Nat Med 2009;15:1298

Protective or Causal Factor ? : VEGF

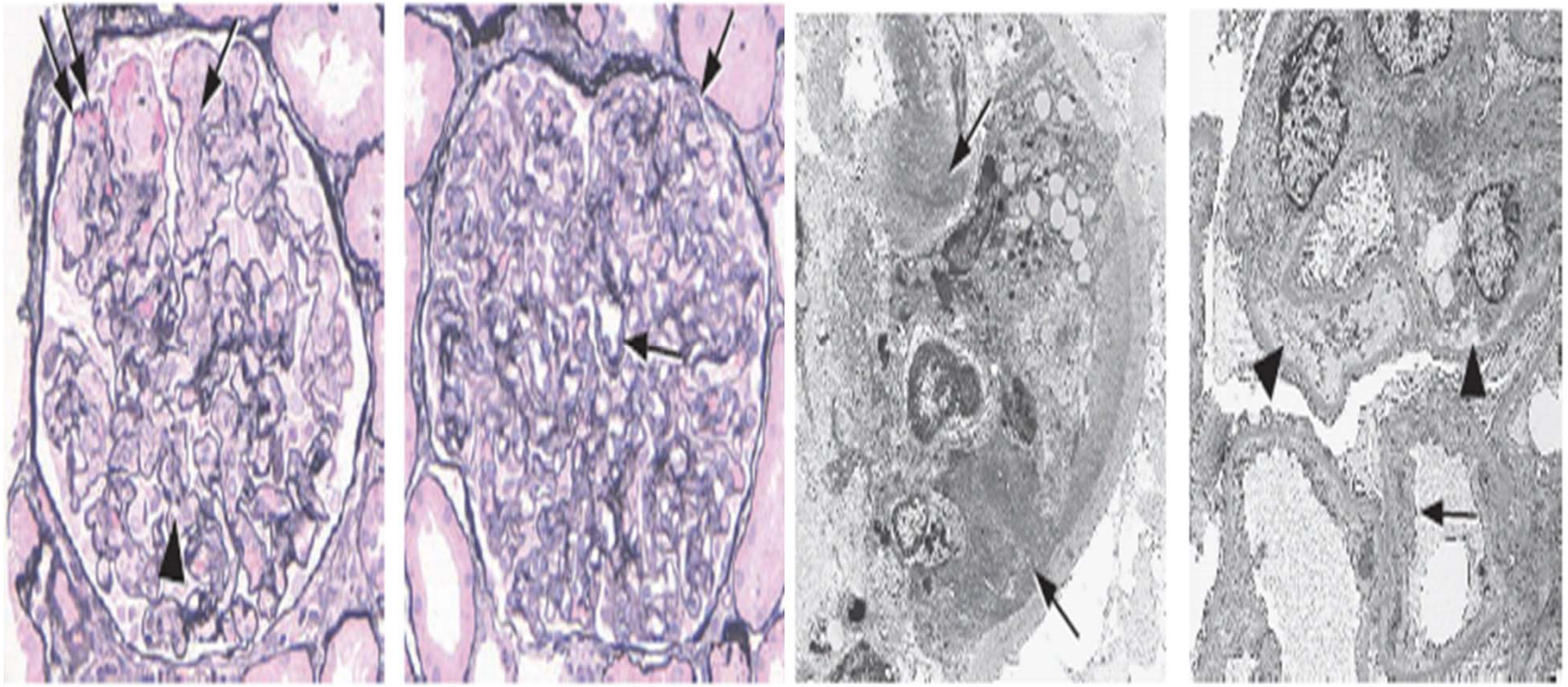






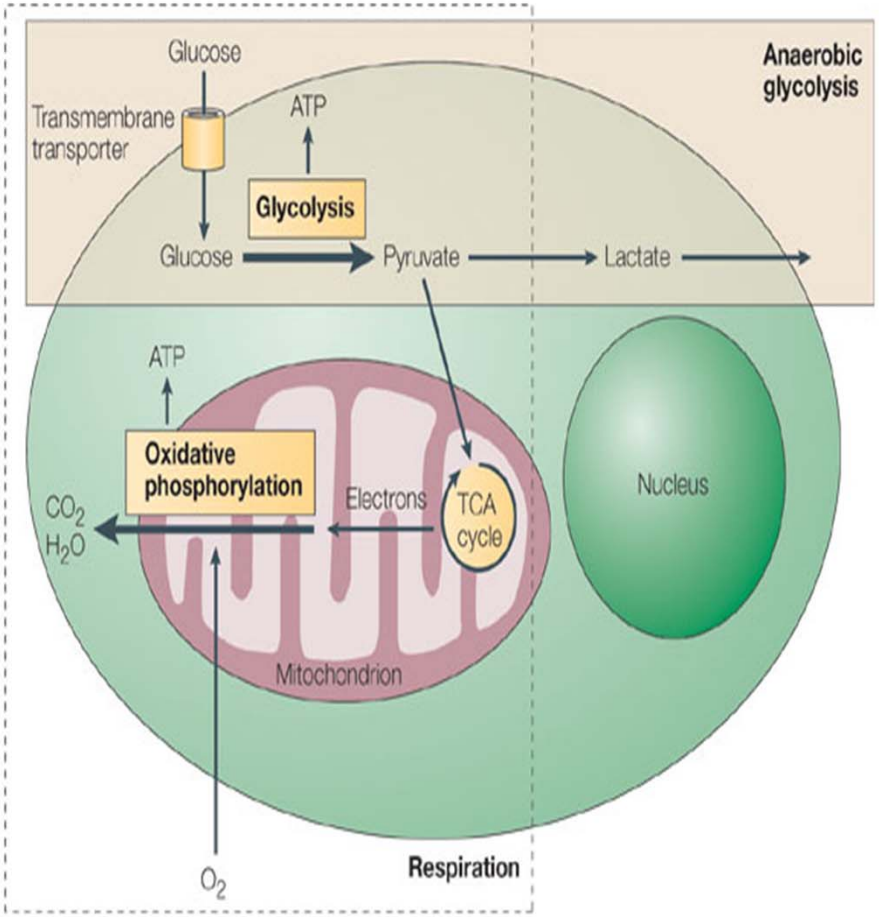
J Am Soc Nephrol 2007;18:2094-2104

Protective or Causal Factor ? : VEGF

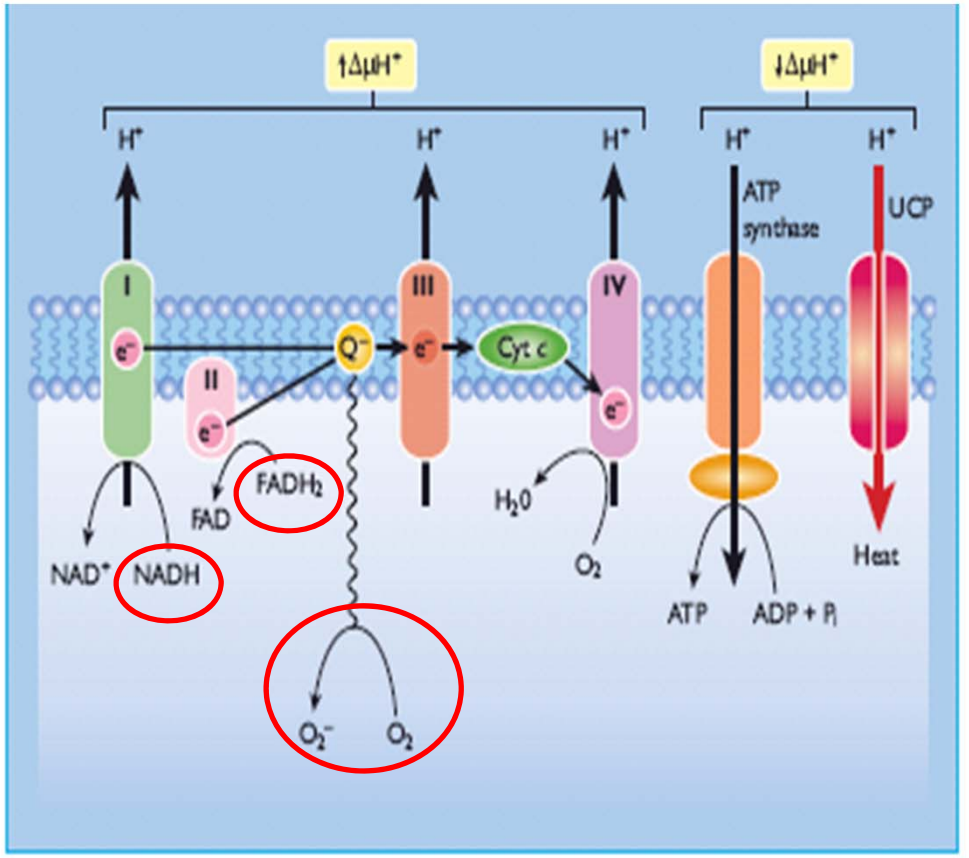


N Eng J Med 2008;358:1129

Unifying pathogenic mechanism: Mitochondiral superoxide production



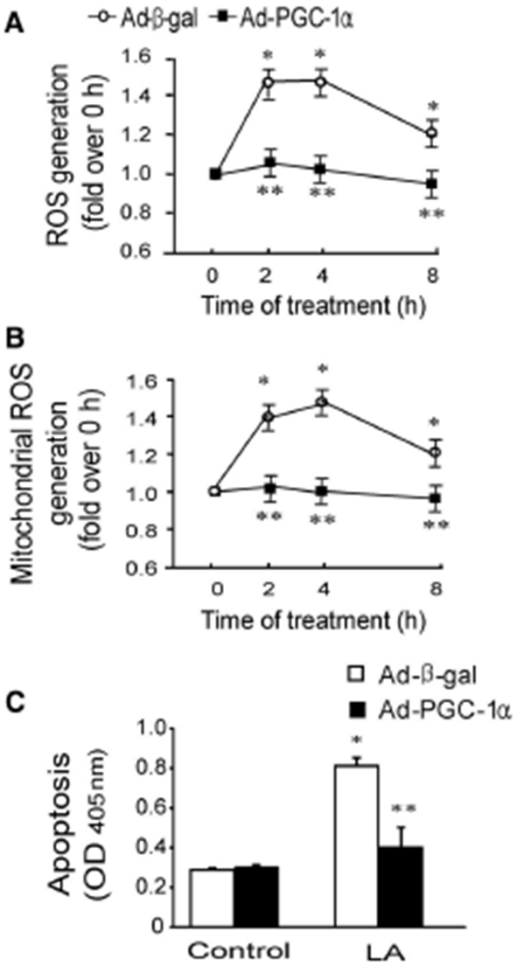
Glycolysis and TCA cycle

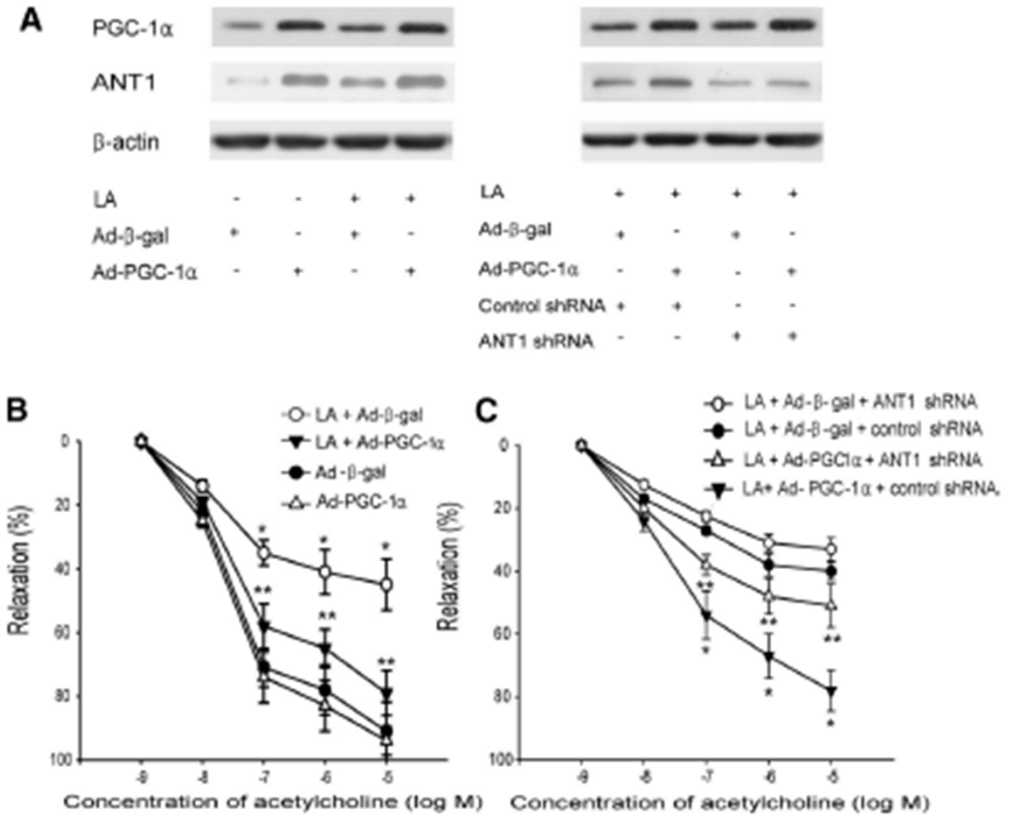


Mitochondrial oxidative phosphorylation

Peroxisome Proliferator-Activated Receptor-γ Coactivator 1-α Overexpression Prevents Endothelial Apoptosis by Increasing ATP/ADP Translocase Activity

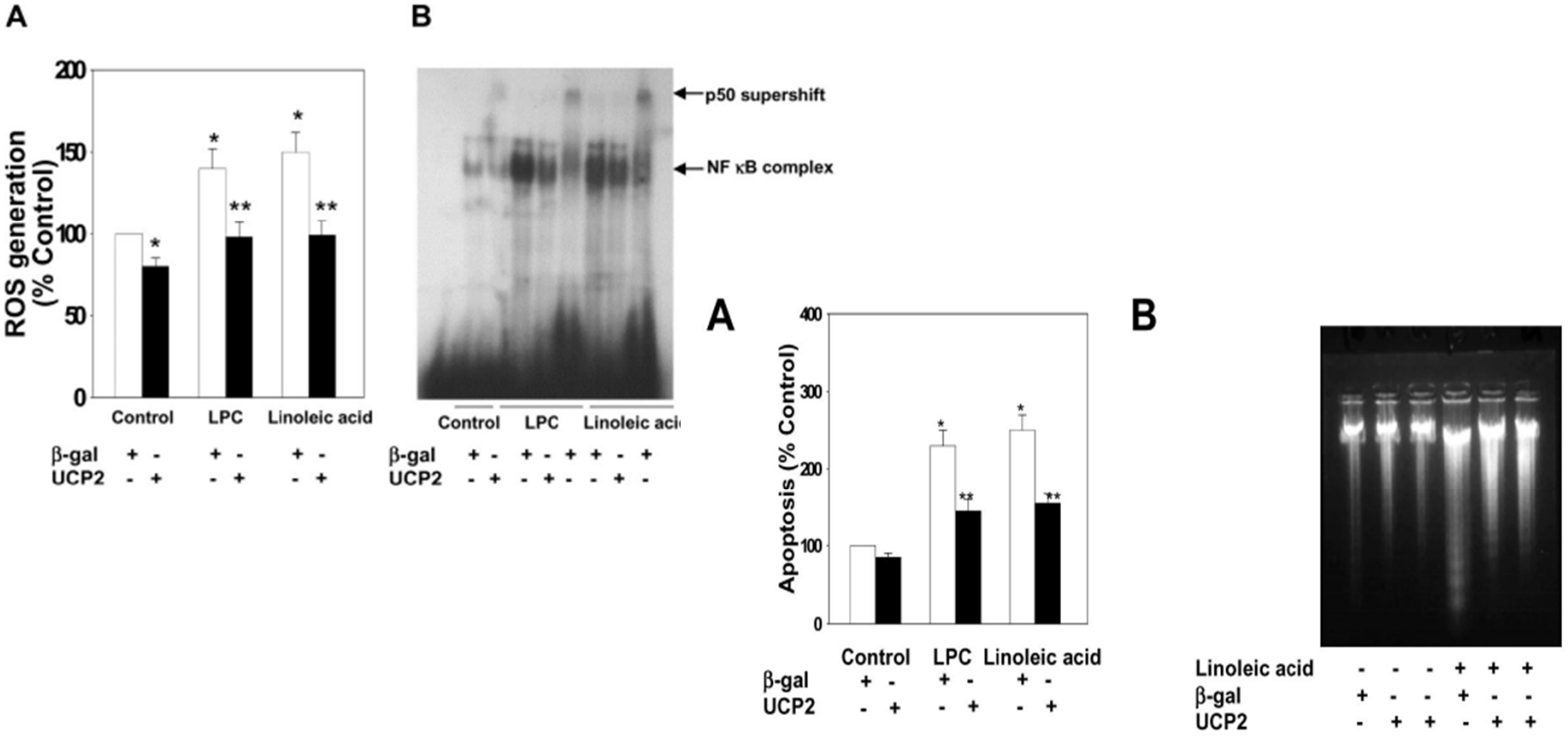
Arterioscler Thromb Vasc Biol. 2010;30:290-297.





Effects of Recombinant Adenovirus-Mediated Uncoupling Protein 2 Overexpression on Endothelial Function and Apoptosis

Circ Res. 2005; 96:1200-1207.



Summary (1)

- Chronic hyperglycemia causes diabetic microvascular complications through four main mechanisms, increased polyol pathway flux, increased AGE formation, activation of PKC and increased hexoamine pathway flux.

- Overproduction of superoxide by mitochondria has been known to be the unifying mechanism linking hyperglycemia and the four mechanisms mentioned above.

- The clinical efficacy of many potential therapeutic agents has been investigated so far, but the results are disappointing until now.

Summary (2)

- Many clinical trials are ongoing to investigate the efficacy and toxicity of the potential therapeutic agents.

- New therapeutic approaches for diabetic vascular complications need to focus on decreasing the toxic factors of diabetes, but also need to focus on increasing the action of protective factors.

Thank you for your attention !