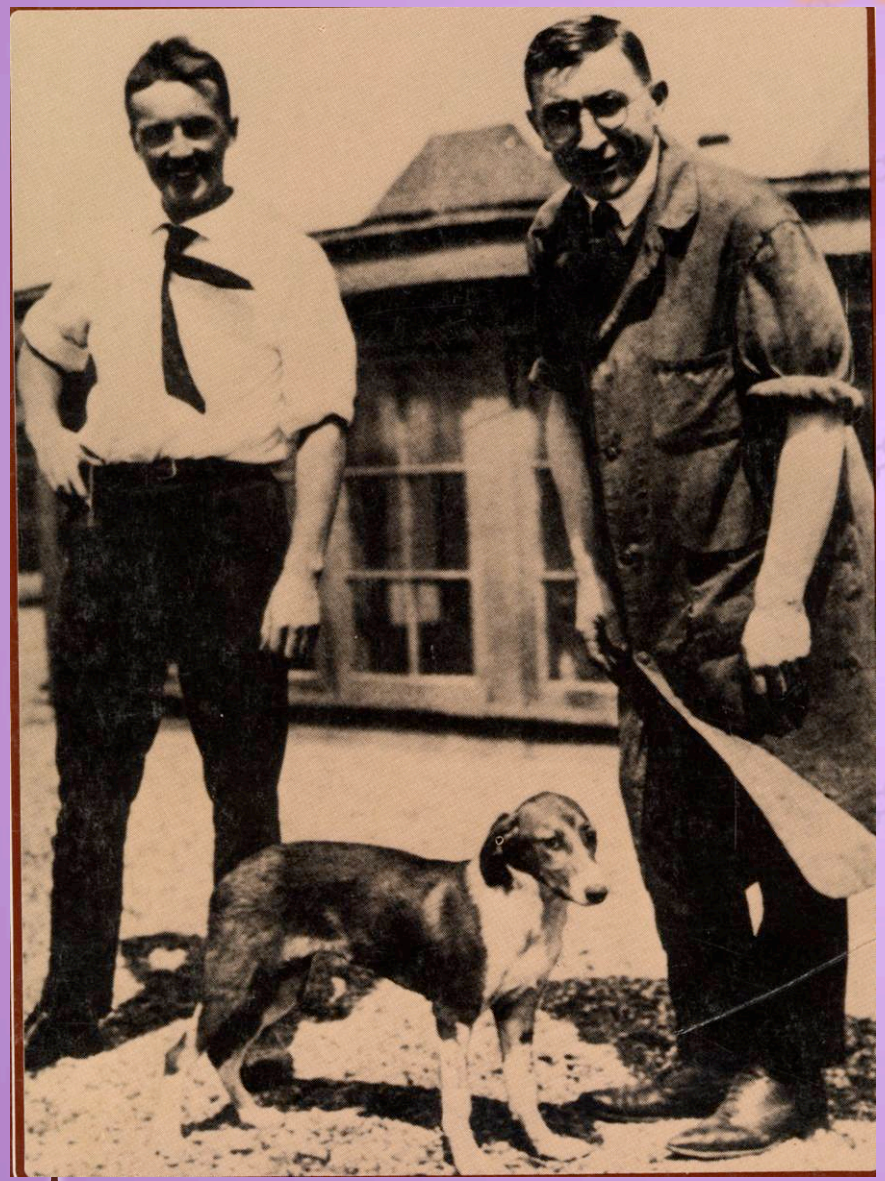
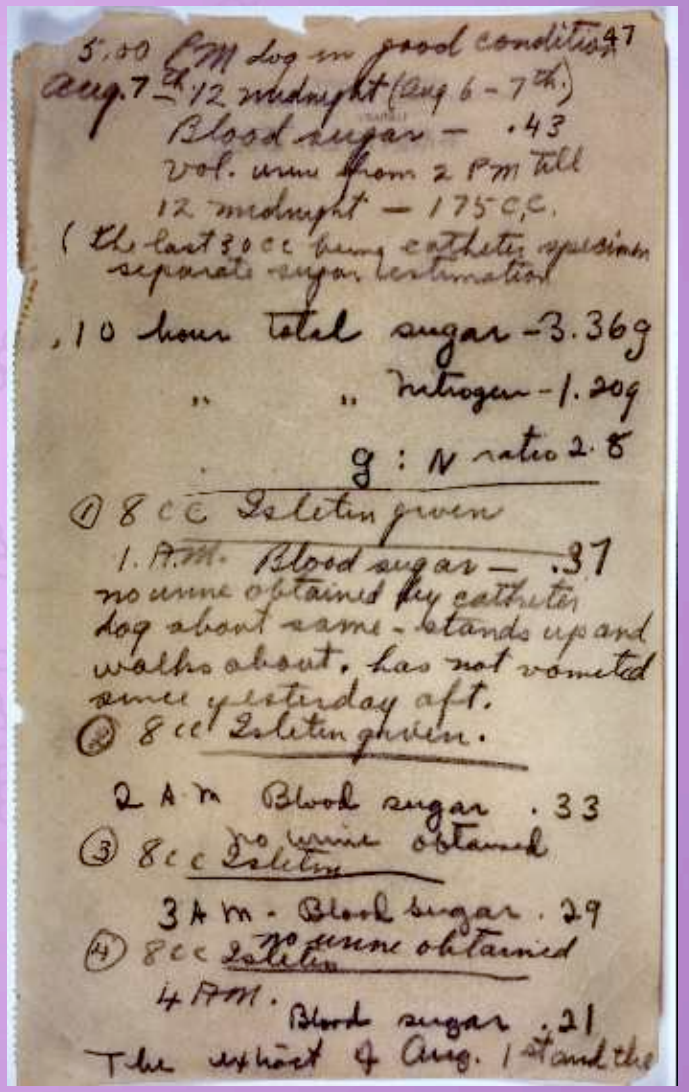
Biochemistry of Glucose Damage in Diabetes





5.00 PM Dog in good condition 47
Aug. 7th 12 midnight (Aug 6 - 7th)
Blood sugar — .43
Vol. urine from 2 PM till
12 midnight — 175 c.c.
(the last 30 cc being catheter specimen
separate sugar determination
10 hour total sugar - 3.36g
" " Nitrogen - 1.20g
g : N ratio 2.8
① 8 cc Isletin given
1. A.M. Blood sugar — .37
no urine obtained by catheter
Dog about same - stands up and
walks about. has not vomited
since yesterday aft.
② 8 cc Isletin given.
2 A.M Blood sugar .33
③ 8 cc Isletin no urine obtained
3 A.M. Blood sugar .29
④ 8 cc Isletin no urine obtained
4 A.M. Blood sugar .21
The subject 4 Aug. 1st and the

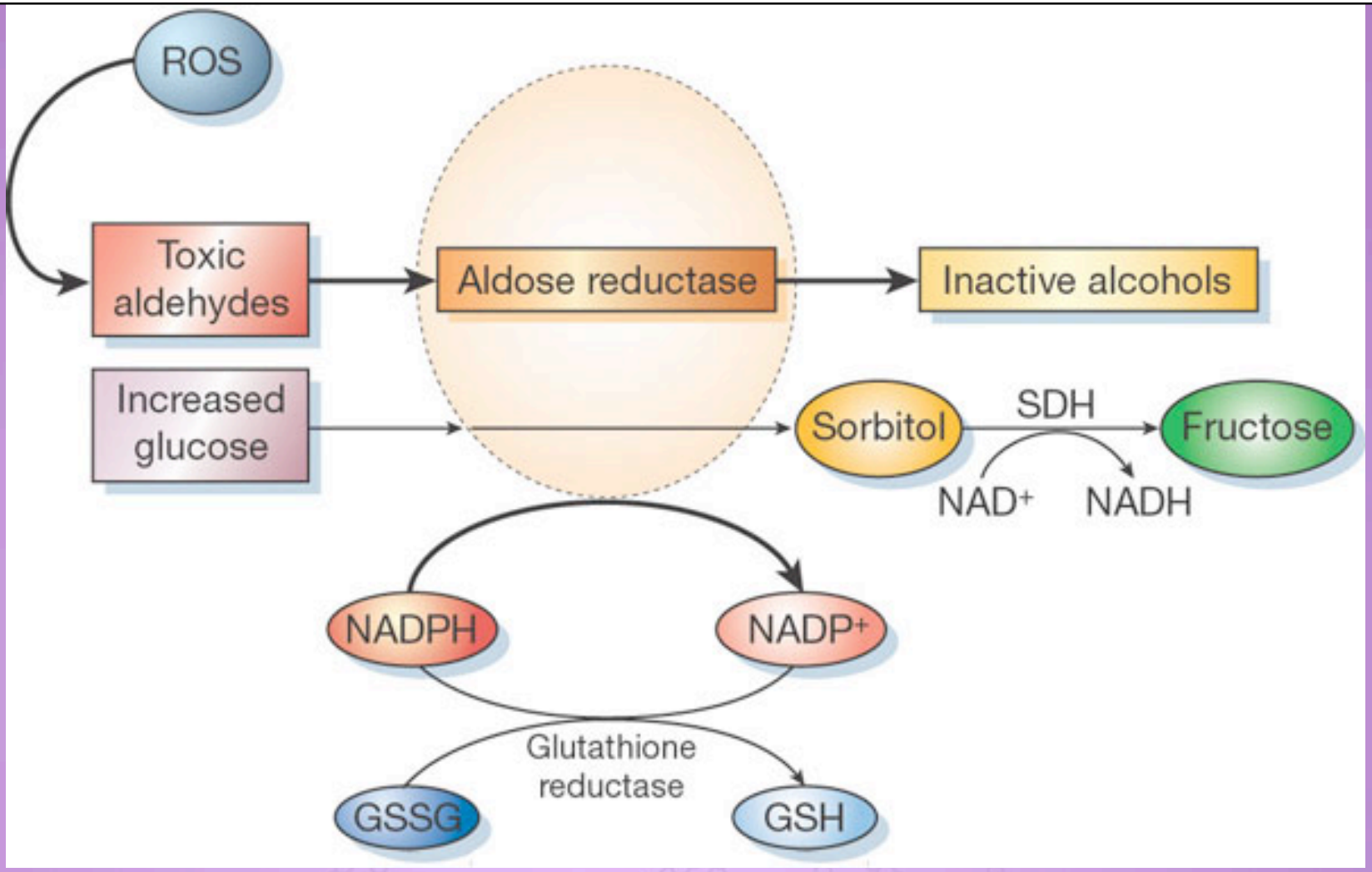


Figure 1 Aldose reductase and the polyol pathway. Aldose reductase reduces aldehydes generated by reactive oxygen species (ROS) to inactive alcohols, and glucose to sorbitol, using NADPH as a co-factor. In cells where aldose reductase activity is sufficient to deplete reduced glutathione (GSH), oxidative stress is augmented. Sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose using NAD+ as a co-factor.

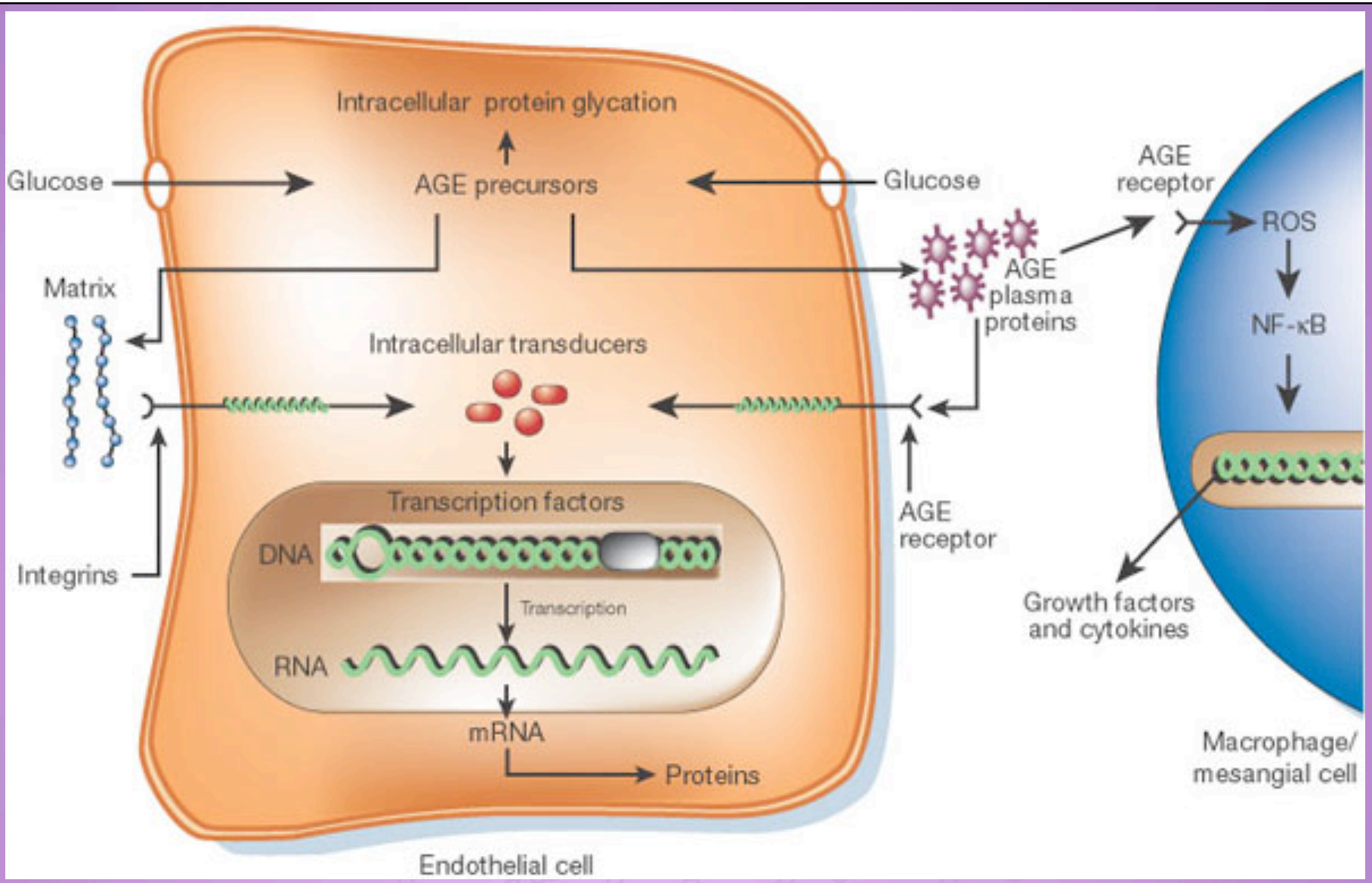


Figure 2 Mechanisms by which intracellular production of advanced glycation end-product (AGE) precursors damages vascular cells. Covalent modification of intracellular proteins by dicarbonyl AGE precursors alters several cellular functions. Modification of extracellular matrix proteins causes abnormal interactions with other matrix proteins and with integrins. Modification of plasma proteins by AGE precursors creates ligands that bind to AGE receptors, inducing changes in gene expression in endothelial cells, mesangial cells and macrophages.

What are AGES??-The Maillard Reaction

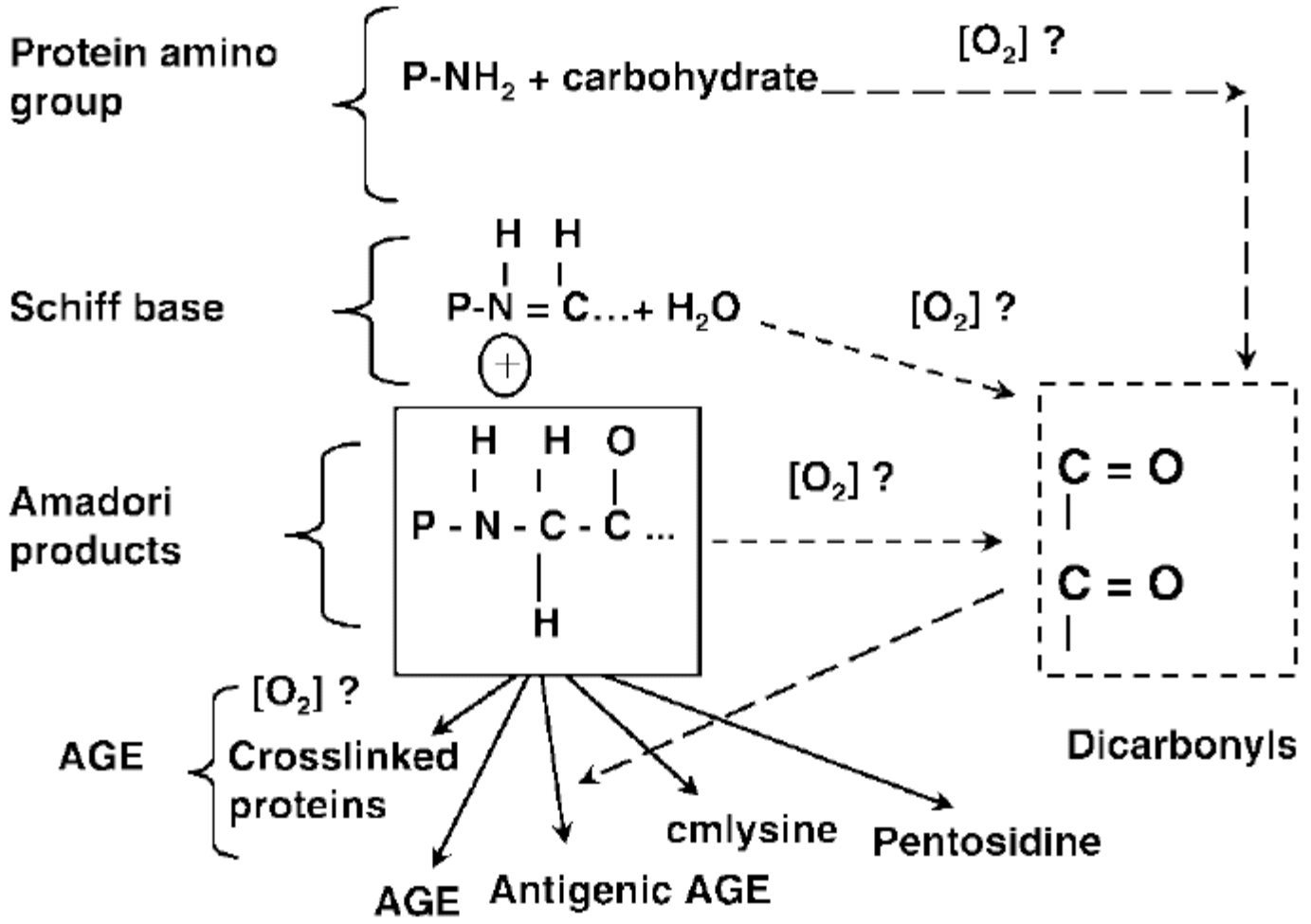


FIG. 1. *Reaction of Maillard (in vitro formation of antigenic AGEs).*

What are AGES??

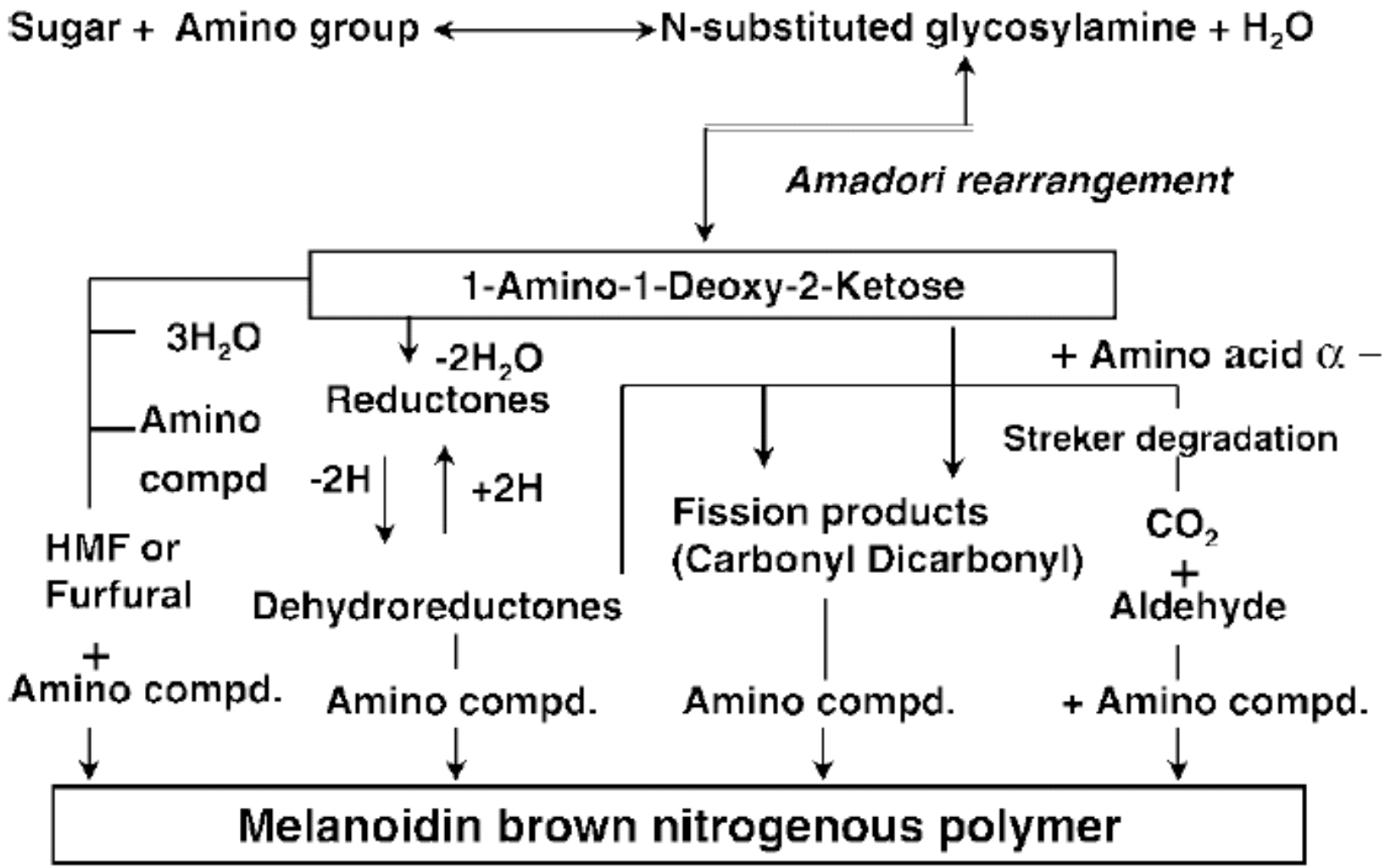


FIG. 2. *Initial steps of glycation.*

Where are AGES??

TABLE I. *Exogenous AGEs [11-13].*

Food	AGE content u/100 g
Cereal	193,400
Pastry	425,740
Cake	838,400
Duck skin	6 259,000

Condiments	AGE u/15 ml
Maple sirup	795
Brown rice vinegar	2,100
Soy sauce	8,700

Beverage	AGE u/250 ml	Sugar g/25 cl
Soda	475	26
Orange juice	600	23
Tea	2,025	0
Coffee	2,200	0
Classic coca-cola	8,500	27
Diet coke	9,500	0

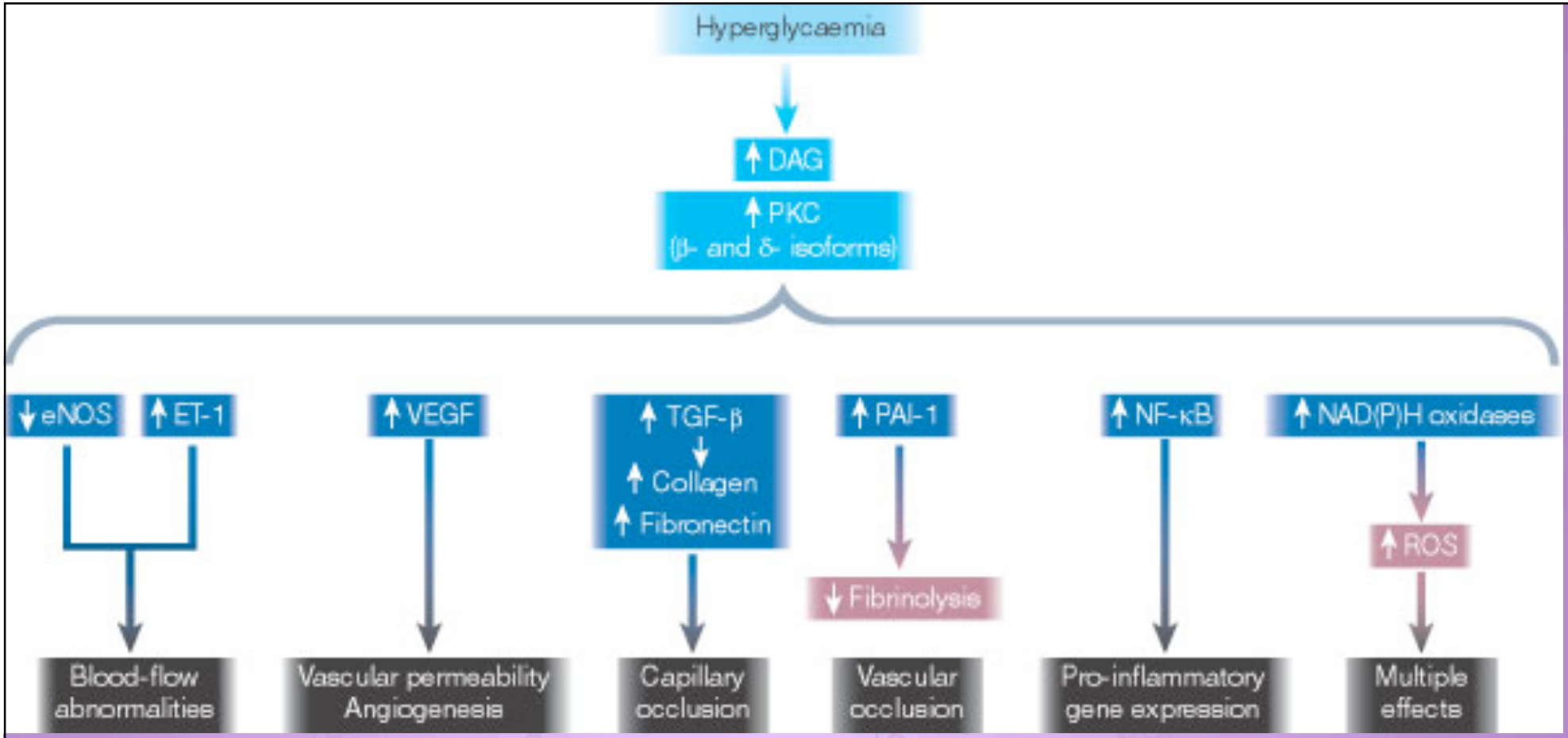


Figure 3 Consequences of hyperglycaemia-induced activation of protein kinase C (PKC). Hyperglycaemia increases diacylglycerol (DAG) content, which activates PKC, primarily the - and -isoforms. Activation of PKC has a number of pathogenic consequences by affecting expression of endothelial nitric oxide synthetase (eNOS), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), transforming growth factor- (TGF-) and plasminogen activator inhibitor-1 (PAI-1), and by activating NF-B and NAD(P)H oxidases.

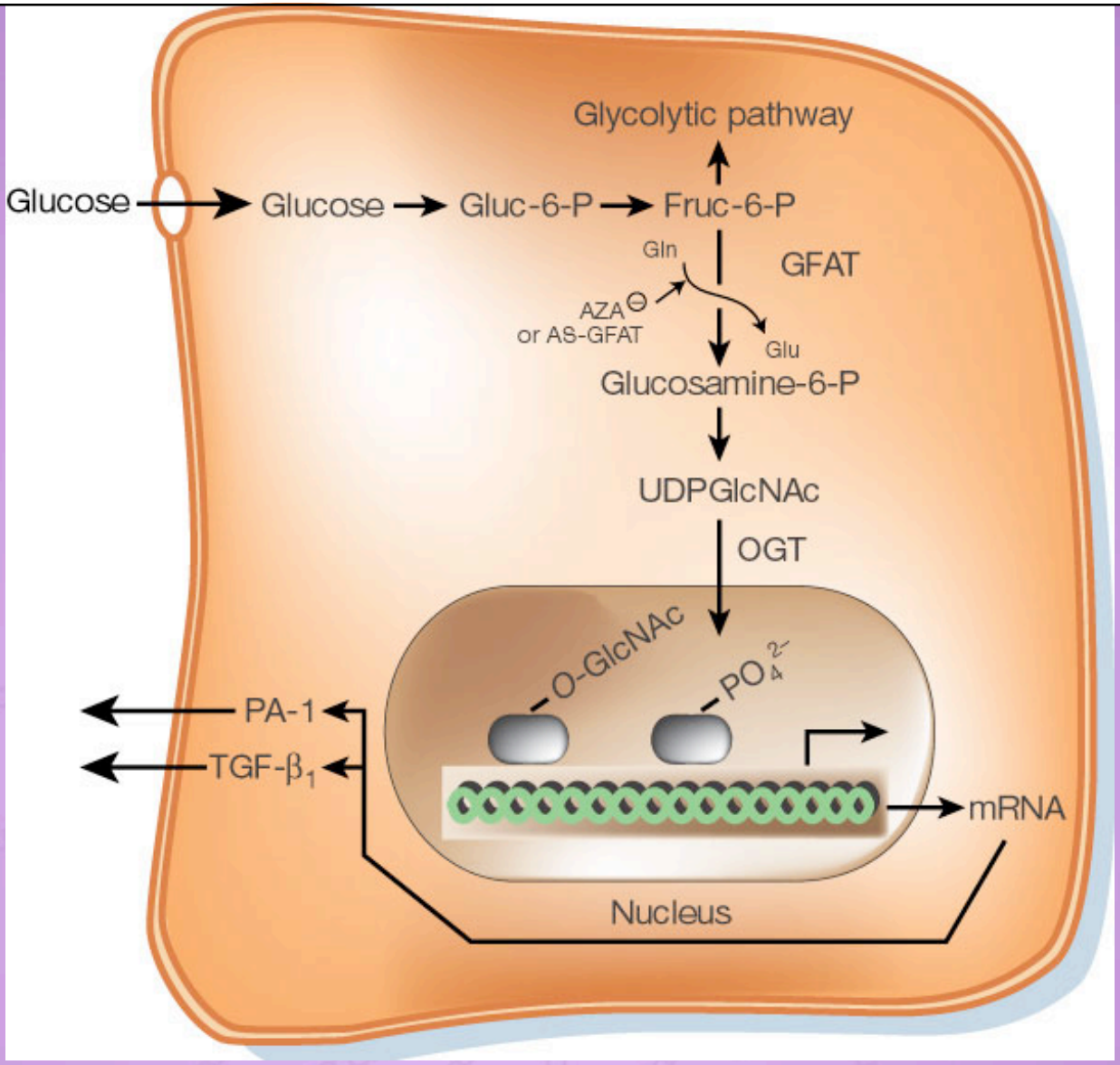


Figure 4 The hexosamine pathway. The glycolytic intermediate fructose-6-phosphate (Fruc-6-P) is converted to glucosamine-6-phosphate by the enzyme glutamine:fructose-6-phosphate amidotransferase (GFAT). Intracellular glycosylation by the addition of N-acetylglucosamine (GlcNAc) to serine and threonine is catalysed by the enzyme O-GlcNAc transferase (OGT). Increased donation of GlcNAc moieties to serine and threonine residues of transcription factors such as Sp1, often at phosphorylation sites, increases the production of factors as PAI-1 and TGF-1. AZA, azaserine; AS-GFAT, antisense to GFAT.

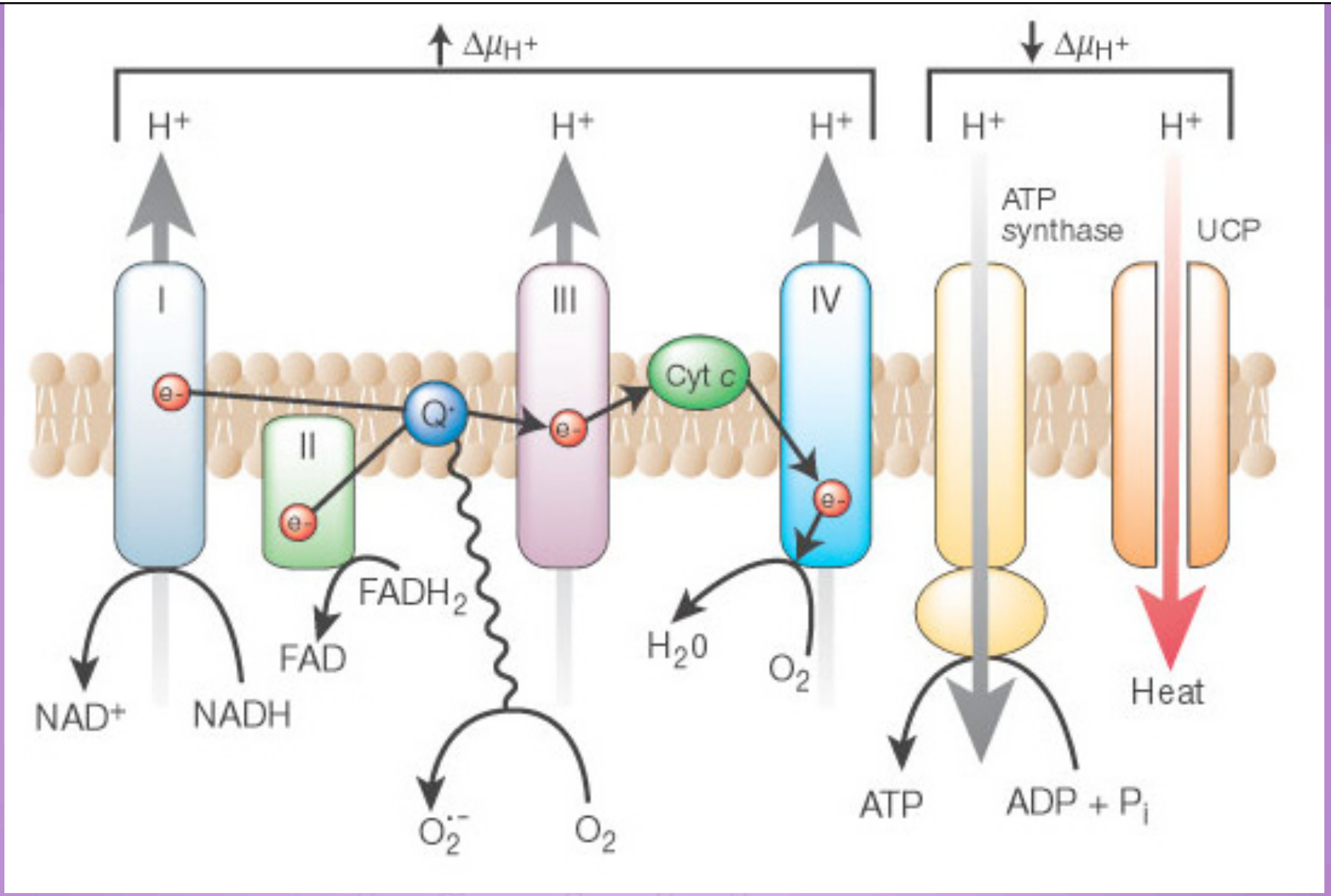


Figure 5 Production of superoxide by the mitochondrial electron-transport chain. Increased hyperglycaemia-derived electron donors from the TCA cycle (NADH and FADH2) generate a high mitochondrial membrane potential (H+) by pumping protons across the mitochondrial inner membrane. This inhibits electron transport at complex III, increasing the half-life of free-radical intermediates of coenzyme Q (ubiquinone), which reduce O2 to superoxide.

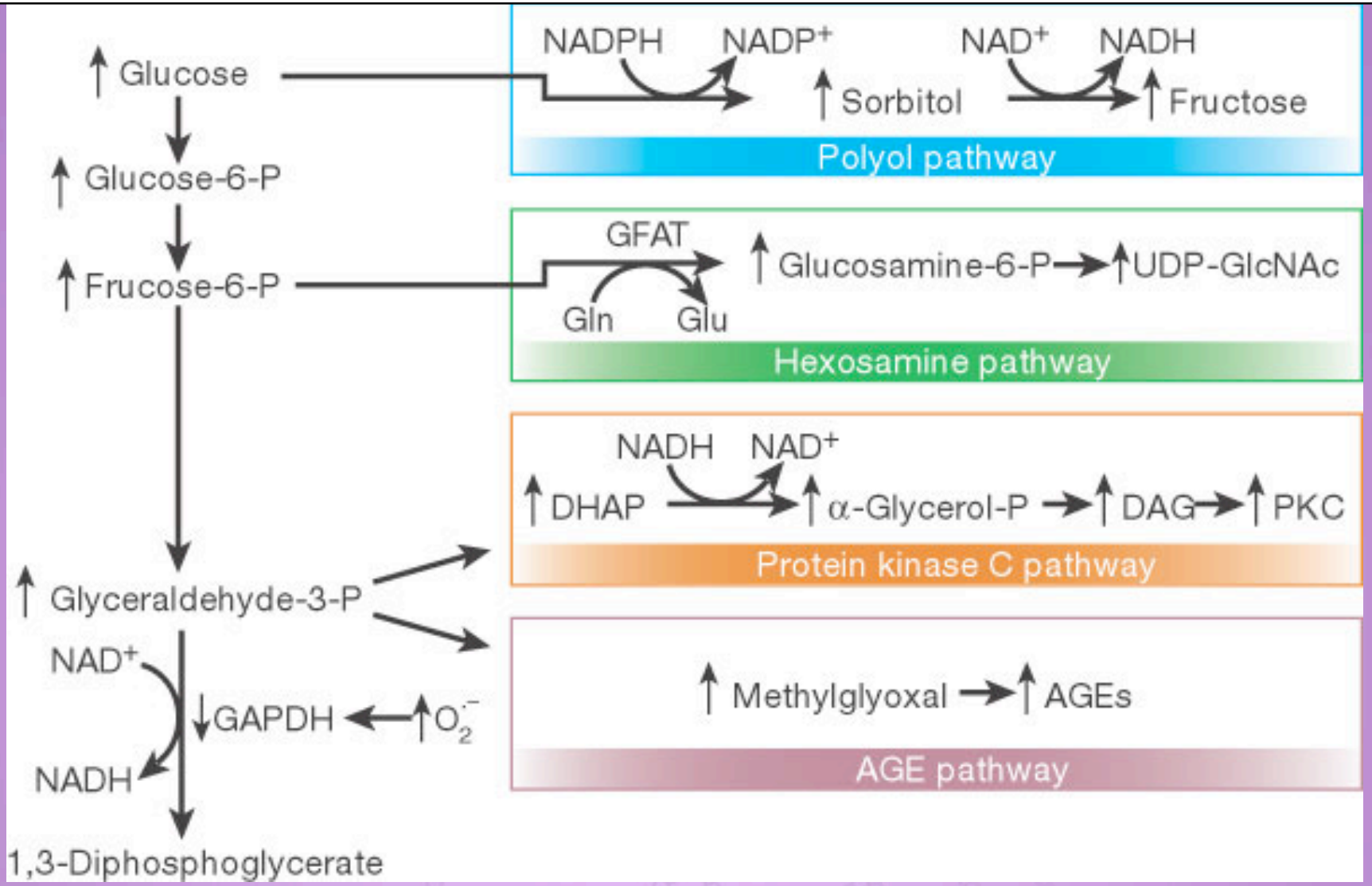


Figure 6 Potential mechanism by which hyperglycaemia-induced mitochondrial superoxide overproduction activates four pathways of hyperglycaemic damage. Excess superoxide partially inhibits the glycolytic enzyme GAPDH, thereby diverting upstream metabolites from glycolysis into pathways of glucose overutilization. This results in increased flux of dihydroxyacetone phosphate (DHAP) to DAG, an activator of PKC, and of triose phosphates to methylglyoxal, the main intracellular AGE precursor. Increased flux of fructose-6-phosphate to UDP-N-acetylglucosamine increases modification of proteins by O-linked N-acetylglucosamine (GlcNAc) and increased glucose flux through the polyol pathway consumes NADPH and depletes GSH.