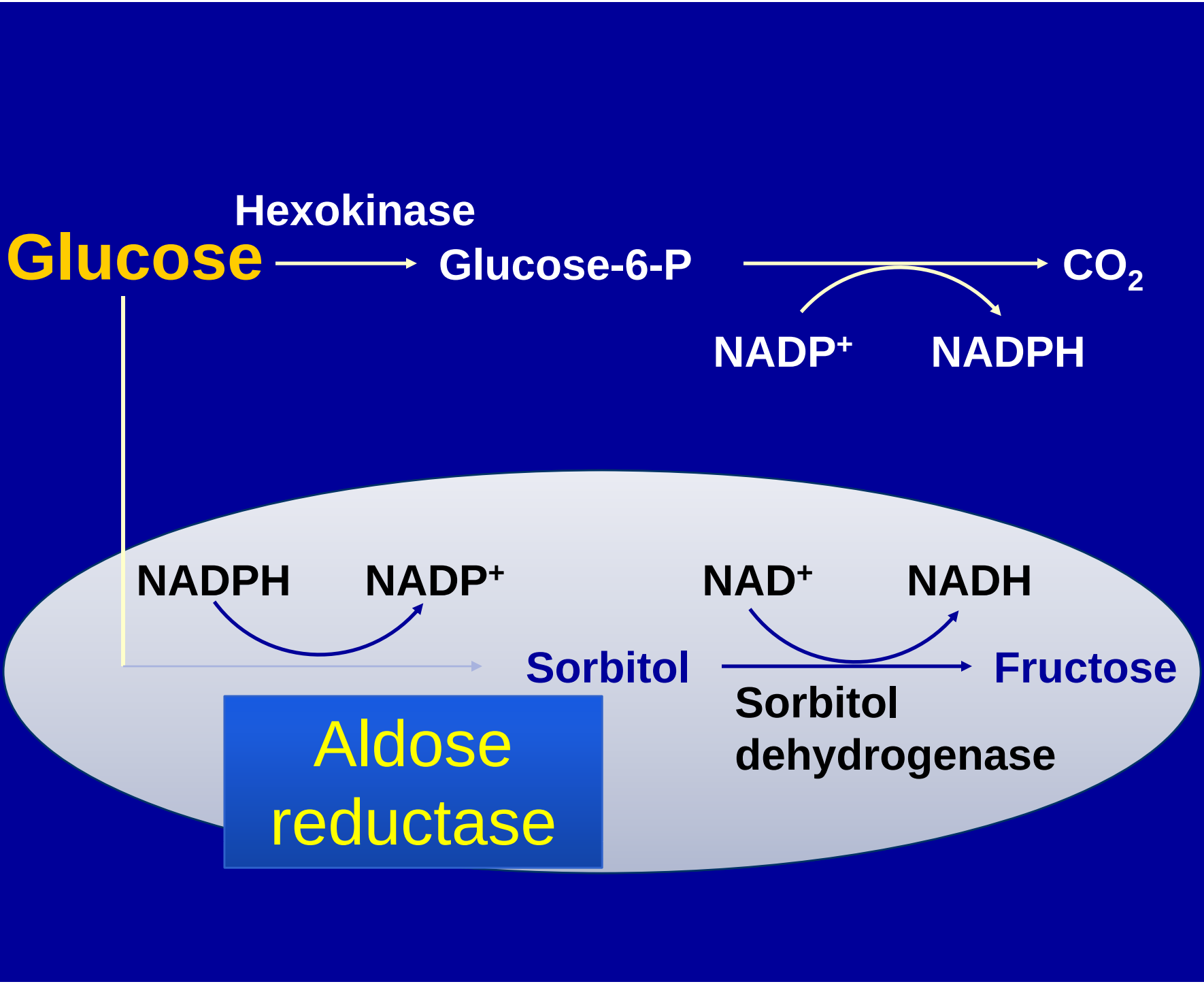
Aldose Reductase and Diabetic Atherosclerosis

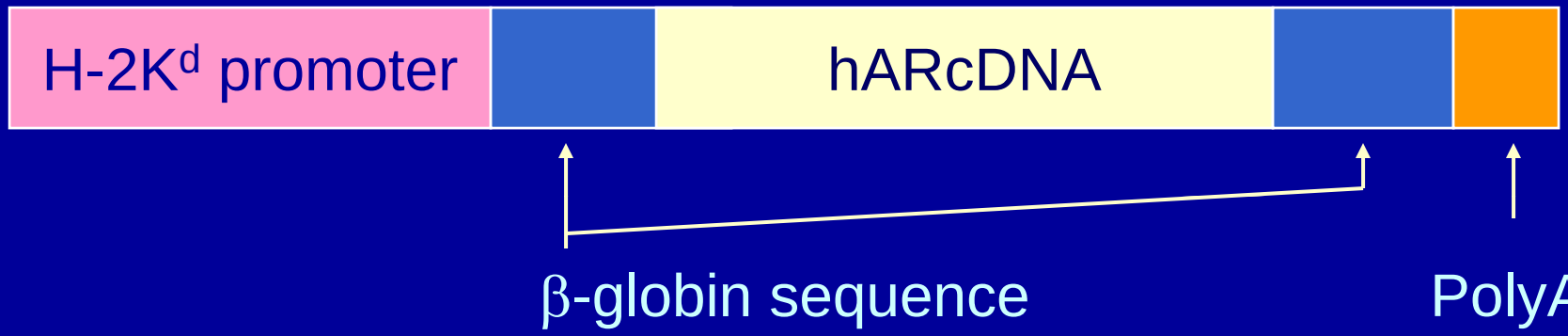
HyeLim Noh, Ph.D.

Columbia University, NY
Dr. Ira J Goldberg lab

Hypothesis: Diabetic mice are deficient in a gene required for toxic effects of glucose


Hexokinase
Glucose
Glucose-6-P
CO_2
$NADP^+$
NADPH
NADPH
$NADP^+$
NAD^+
NADH
Sorbitol
Fructose
Sorbitol dehydrogenase
Aldose reductase

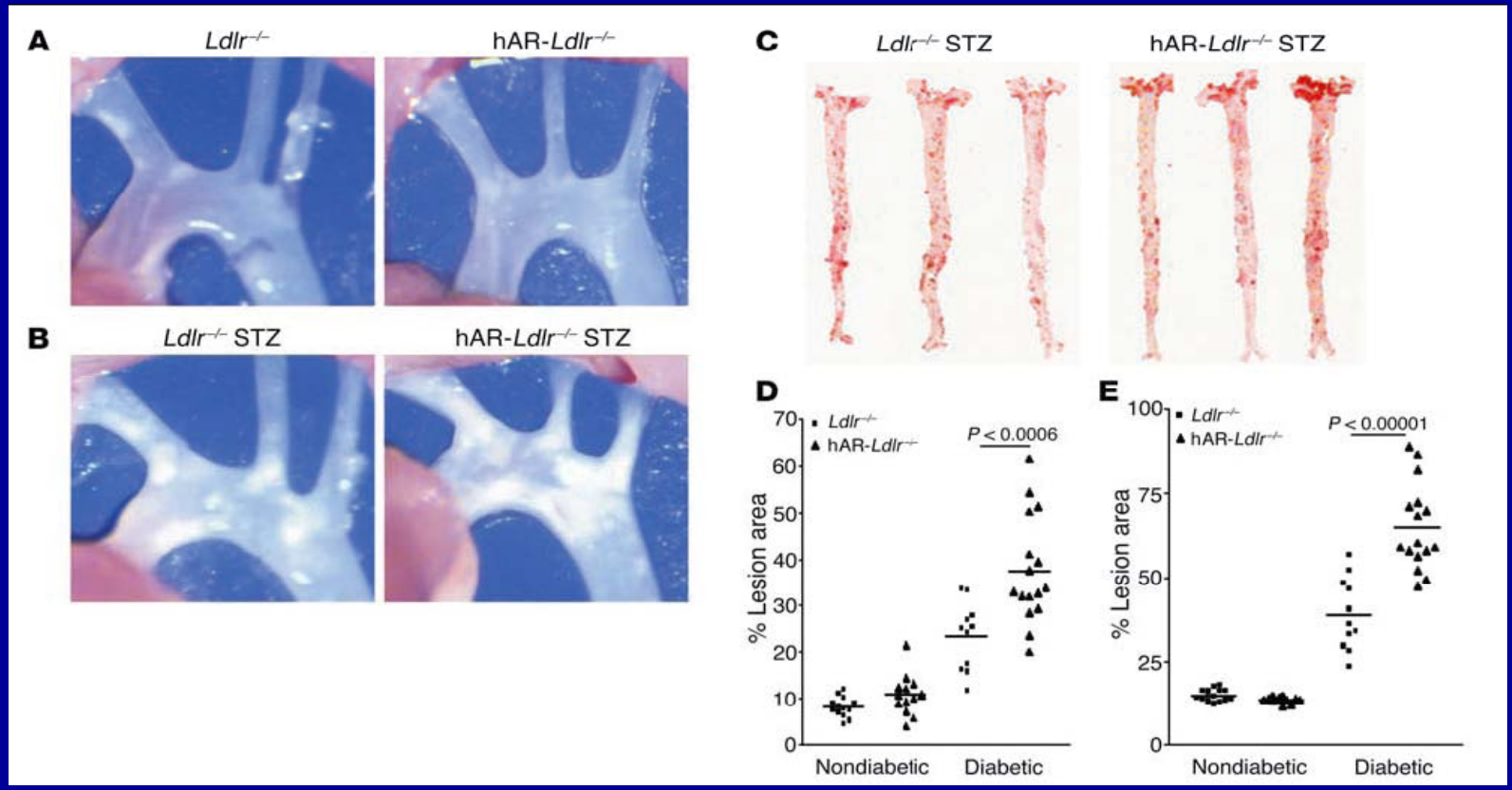
Aldose Reductase Transgenic Mouse



AR expressed ubiquitously

Yamaoka et al. Diabetologia 38: 255-261, 1995

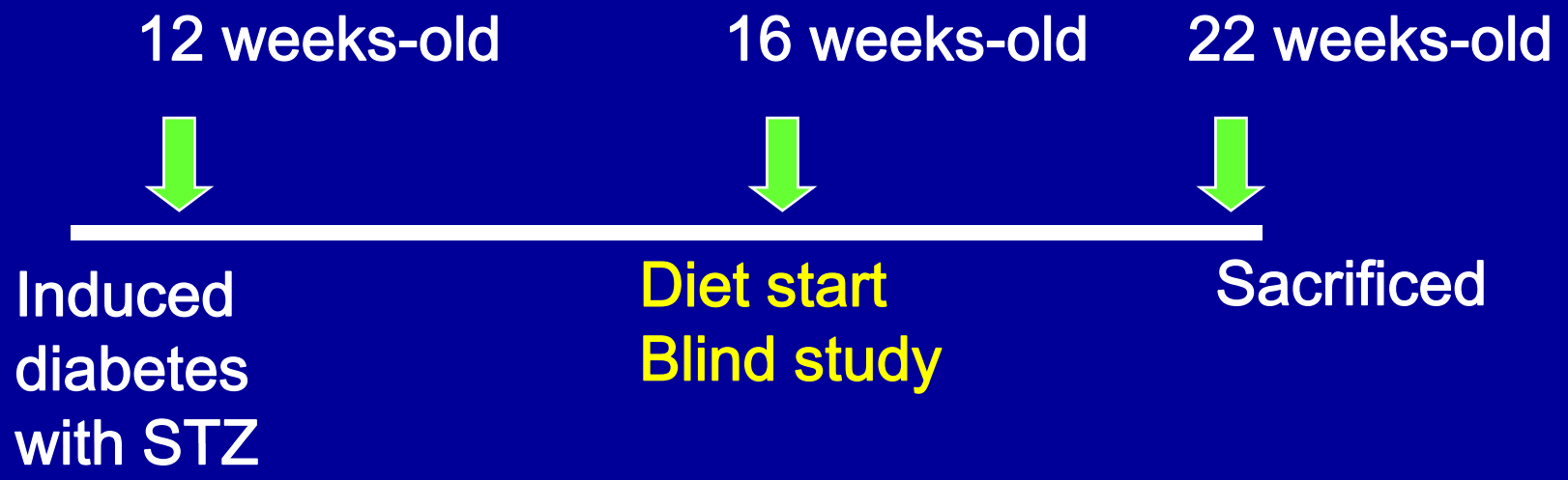
Human AR Increased Atherosclerosis in Diabetic Mice



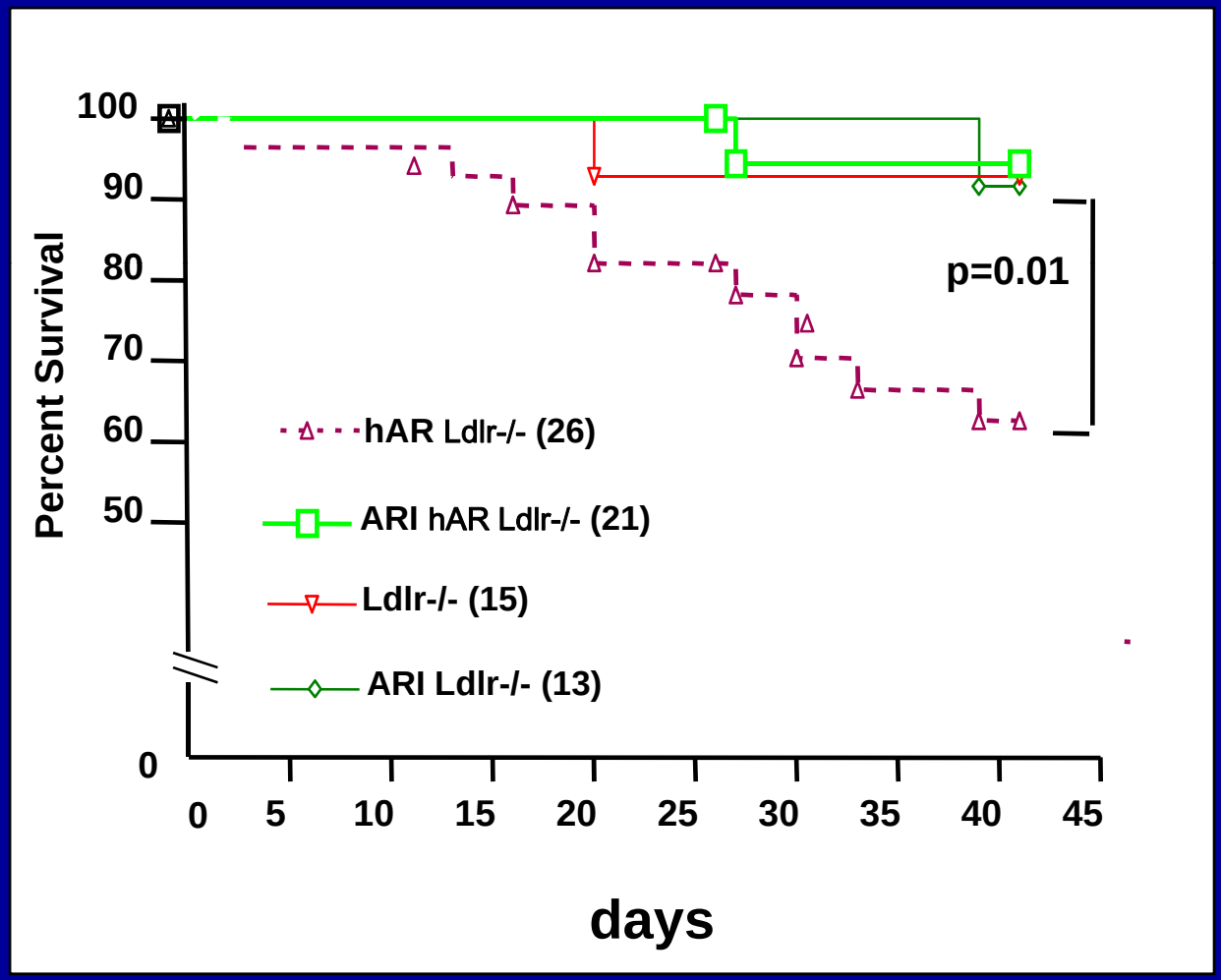
Vikramadithyan, R. K. et al. J. Clin. Invest. 2005;115:2434-2443

Treatment with Aldose reductase inhibitor (ARI) -whether ARI can reduce atherosclerosis

Mice: STZ- hAR/Ldlr-/-, Ldlr-/-
Diet : 0.15% cholesterol with Lidorestat(ARI), or placebo



ARI improved survival of diabetic hAR/Ldlr-/- mice, but did not alter atherosclerosis



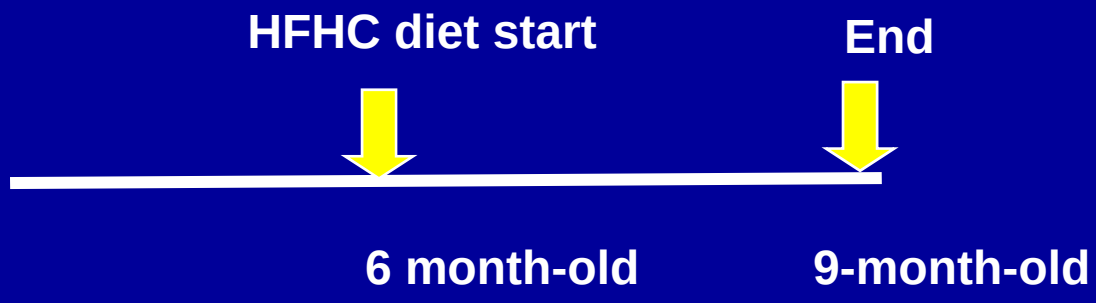
Aging and aldose reductase in atherosclerosis:

Older mice are more sensitive to diabetes and diet (per Dr. Hsueh)

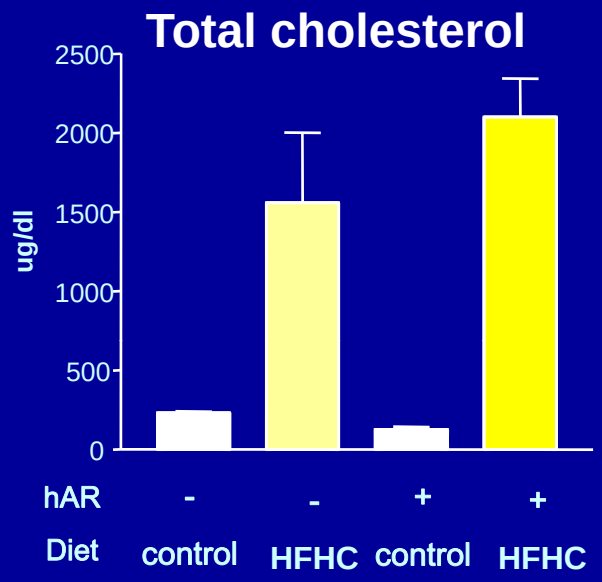
Preliminary study

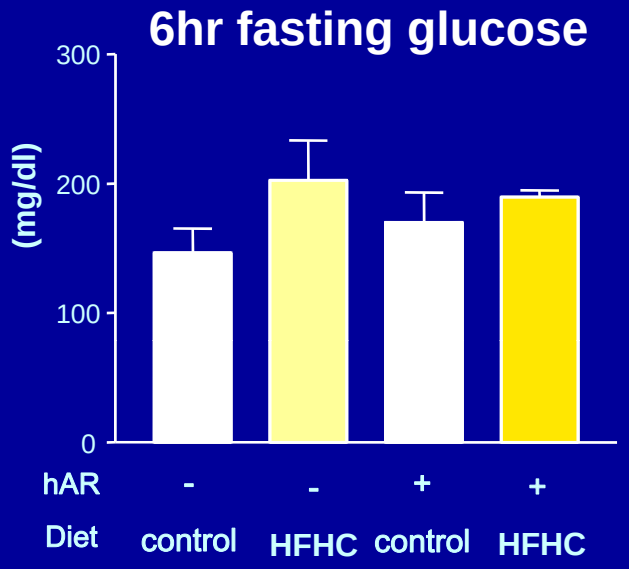
HFHC- western type diet
(fat 41% *kcal*, 0.15% cholesterol)
Ldlr-/- (4)
hAR *Ldlr-/-* (5)

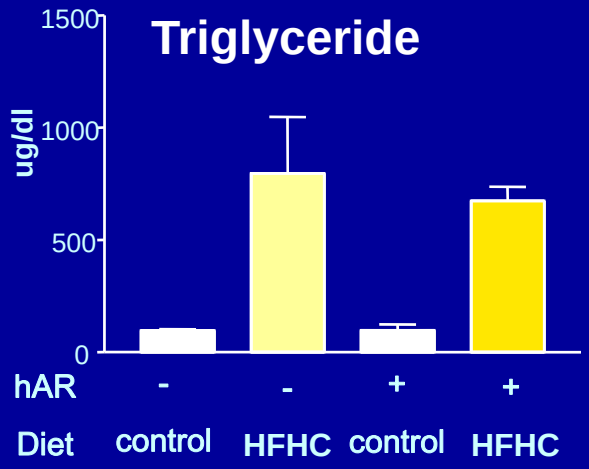
Control chow
(fat 11% *kcal*, 0.02% cholesterol)
Ldlr-/- (3)
hAR *Ldlr-/-* (3)

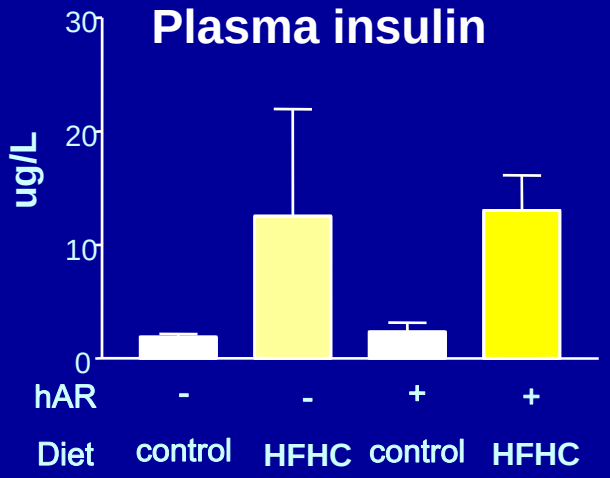


hAR does not make any difference in the mice plasma lipids and glucose



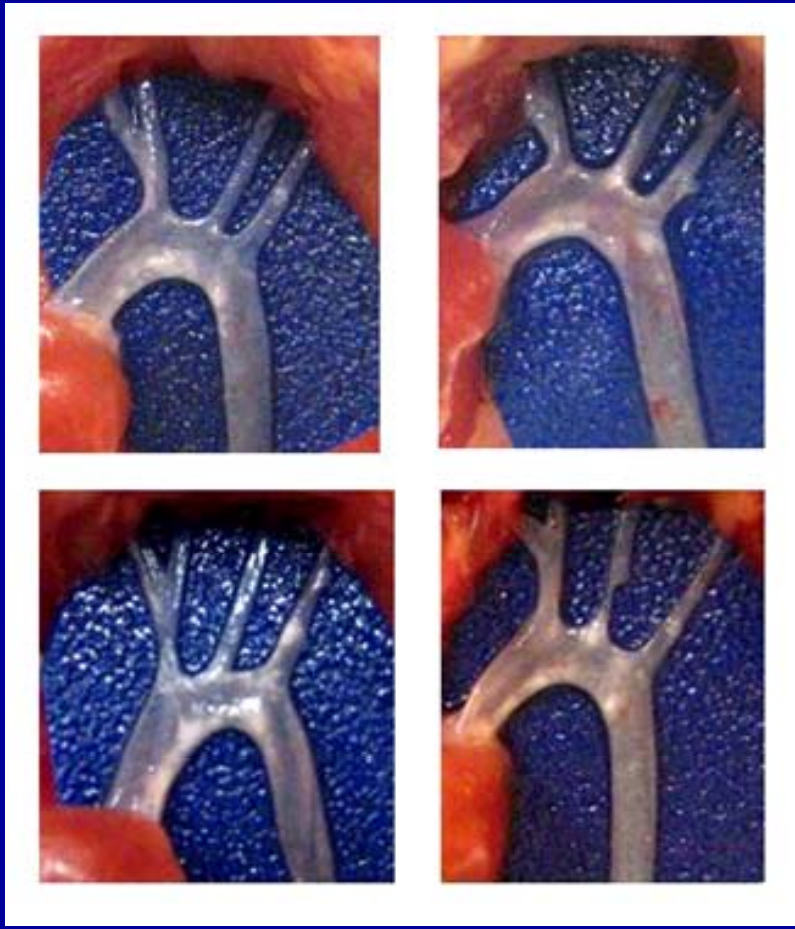




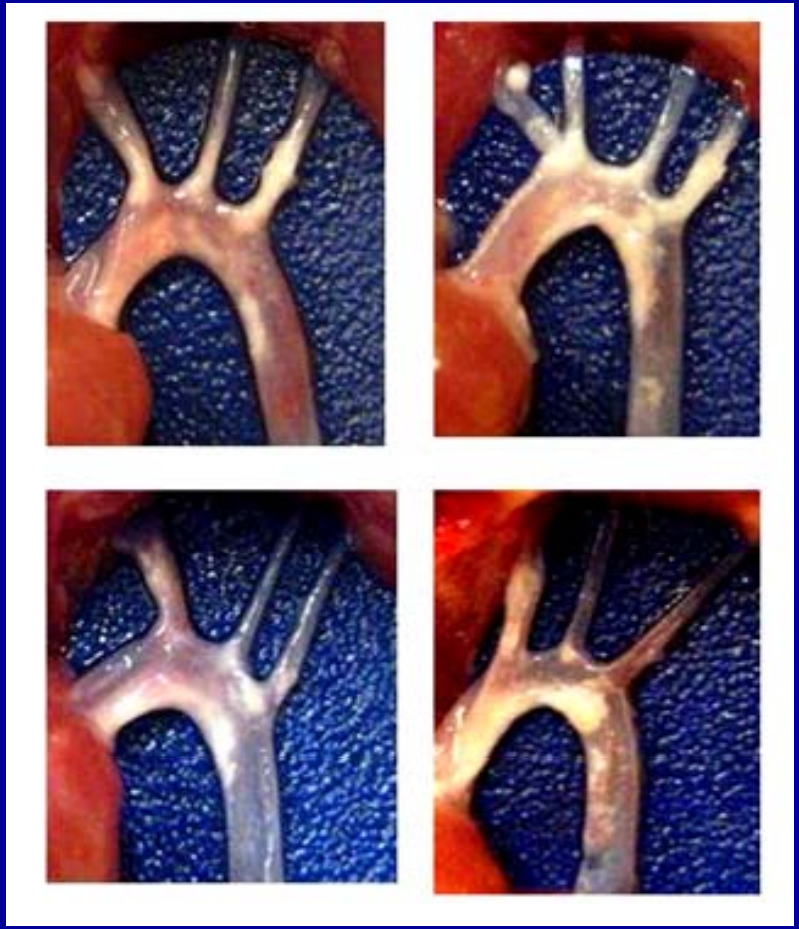


Aortic arch lesions:
HFHC diet for 12 weeks at 6 months-old

Ldlr-/-

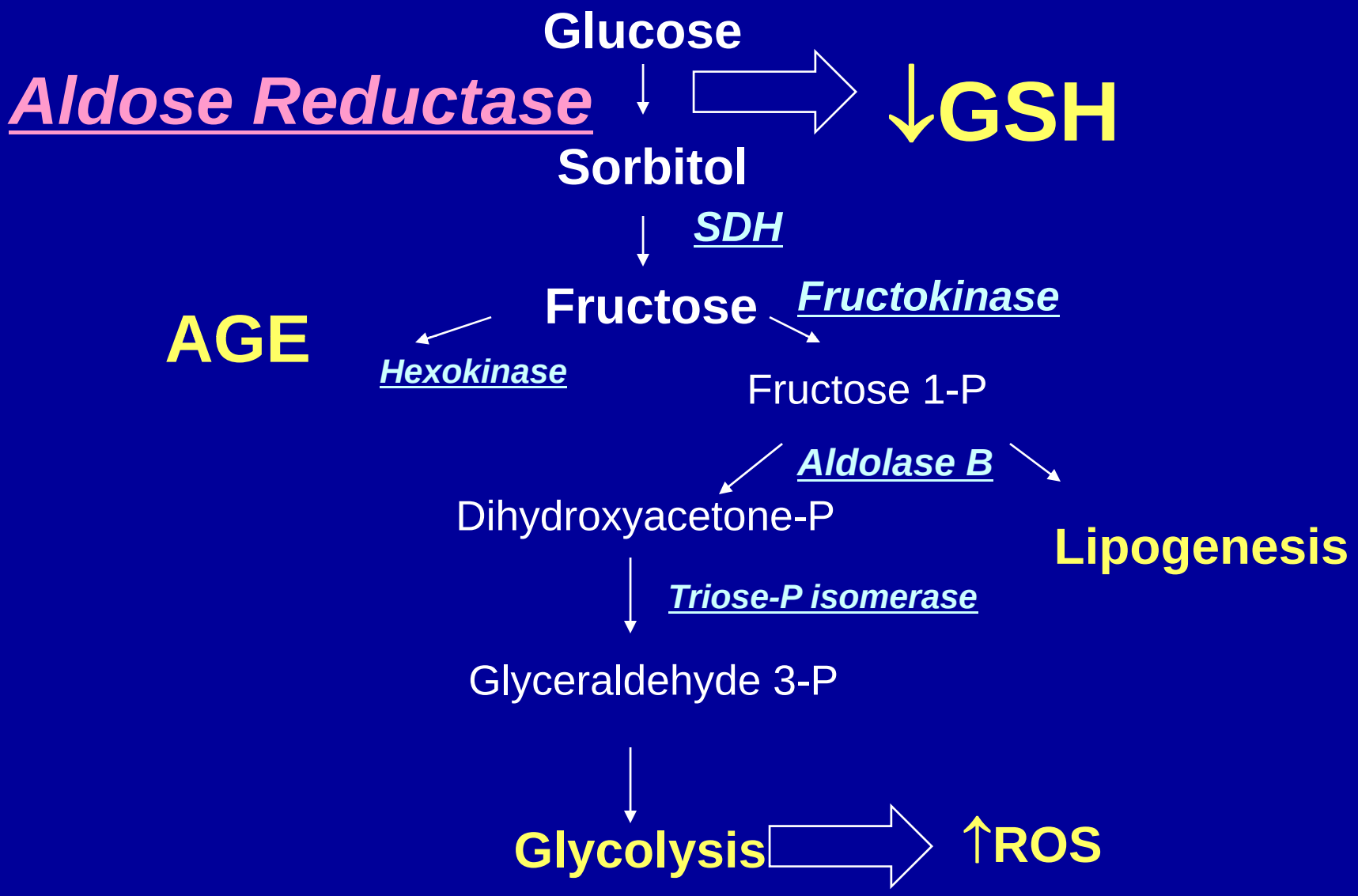


hAR/ *Ldlr-/-*



Question :
Why dose hAR more atherogenic ?

Polyol Pathway



Deficiency of GSH Production accelerates the progression of atherosclerosis

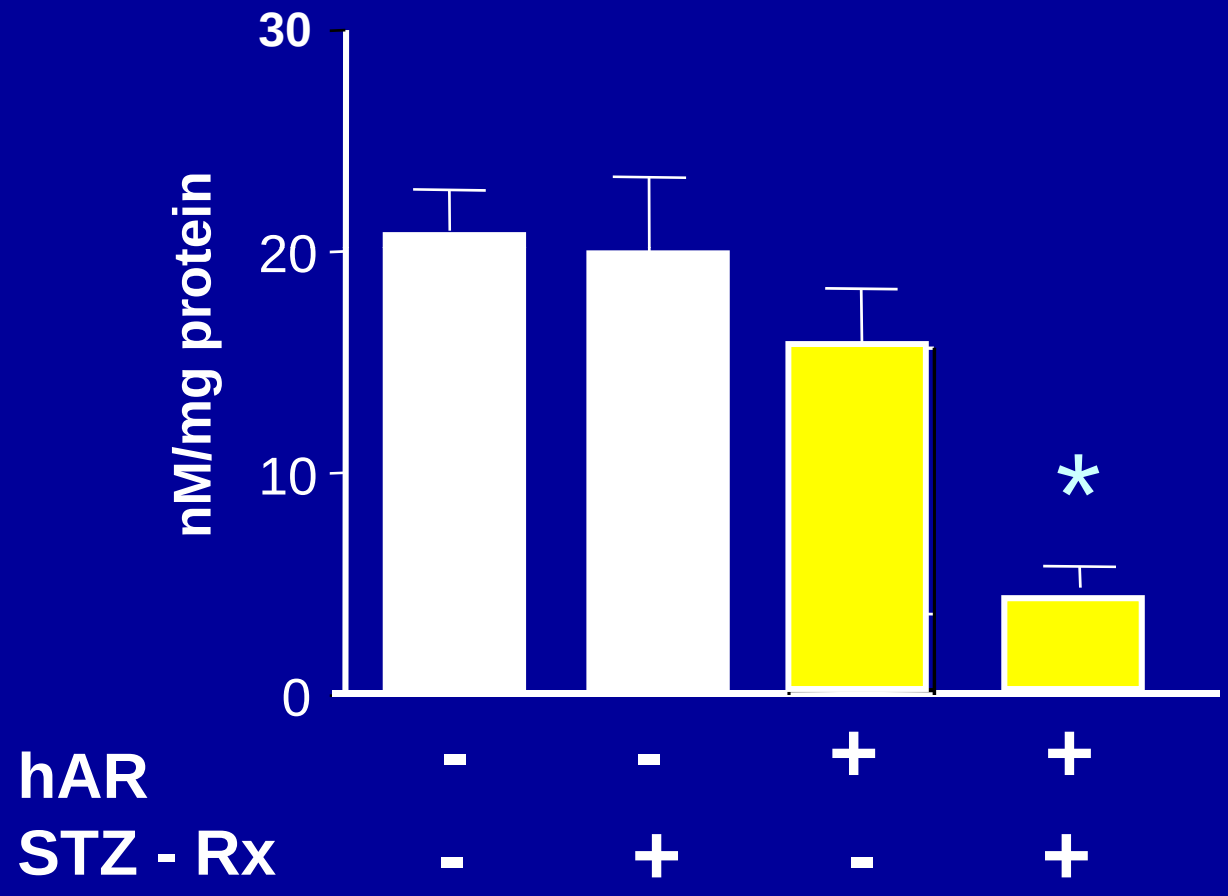
- Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E-deficient mice.

  Lewis et al. ***Circ. 115, 2178, 2007***

- Deficiency of glutathione peroxidase-1 accelerates the progression of atherosclerosis in apolipoprotein E deficient mice.

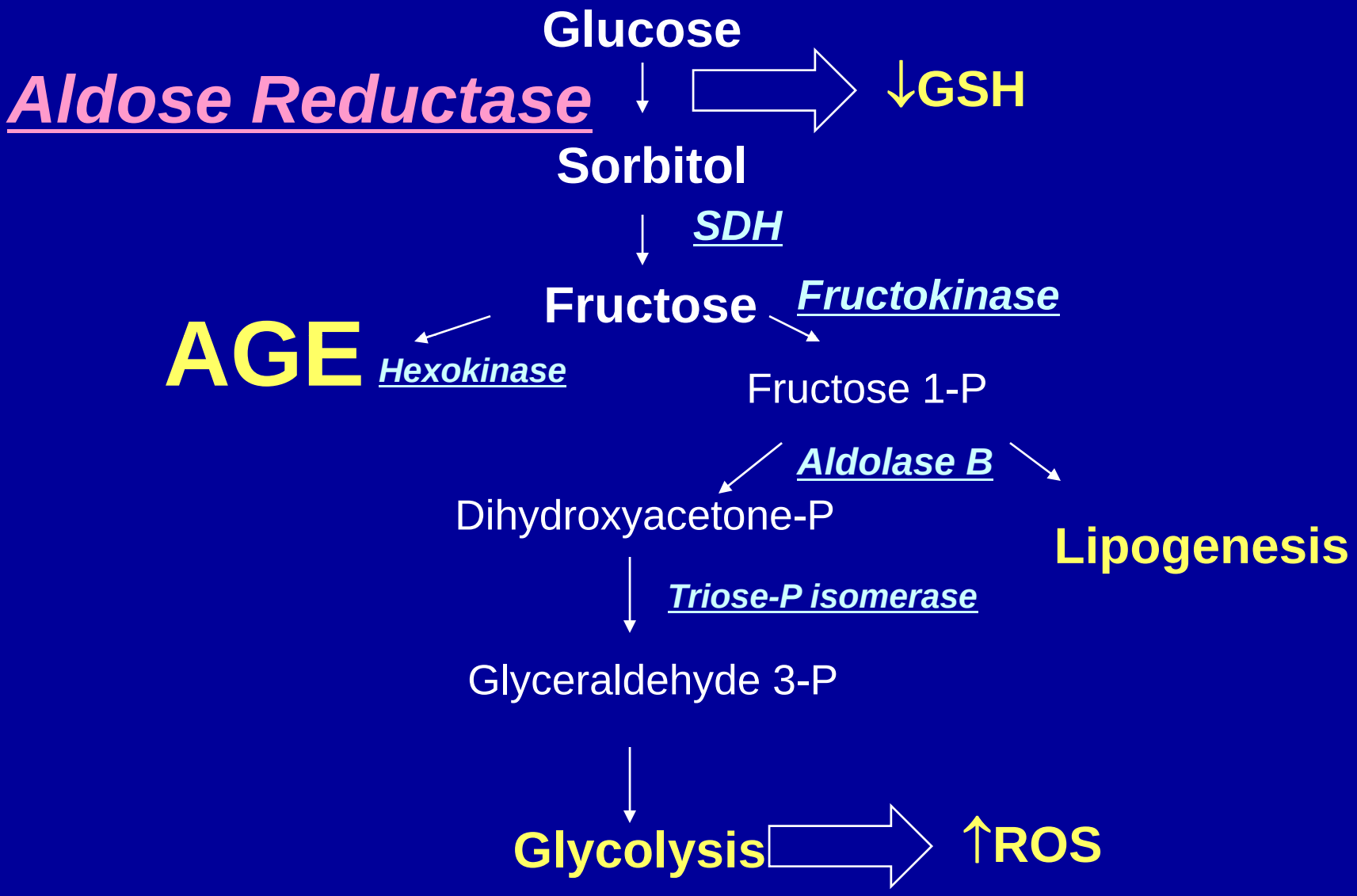
  Torzewski, et al. ***ATVB 27:850, 2007***

hAR decreased aortic glutathione levels in Ldlr-/- mice with 0.15% cholesterol diet



*p<0.05

Polyol Pathway



High fructose diet leads to more atherosclerosis than Western diet with same plasma cholesterol levels

Western-Type Diets Induce Insulin Resistance and Hyperinsulinemia in LDL Receptor-Deficient Mice But Do Not Increase Aortic Atherosclerosis Compared With Normoinsulinemic Mice in Which Similar Plasma Cholesterol Levels Are Achieved by a Fructose-Rich Diet

***ATVB. 1999;19:1223-1230*.**

Peter D. Reaven

Troglitazone Inhibits Formation of Early Atherosclerotic Lesions in Diabetic and Nondiabetic Low Density Lipoprotein Receptor–Deficient Mice

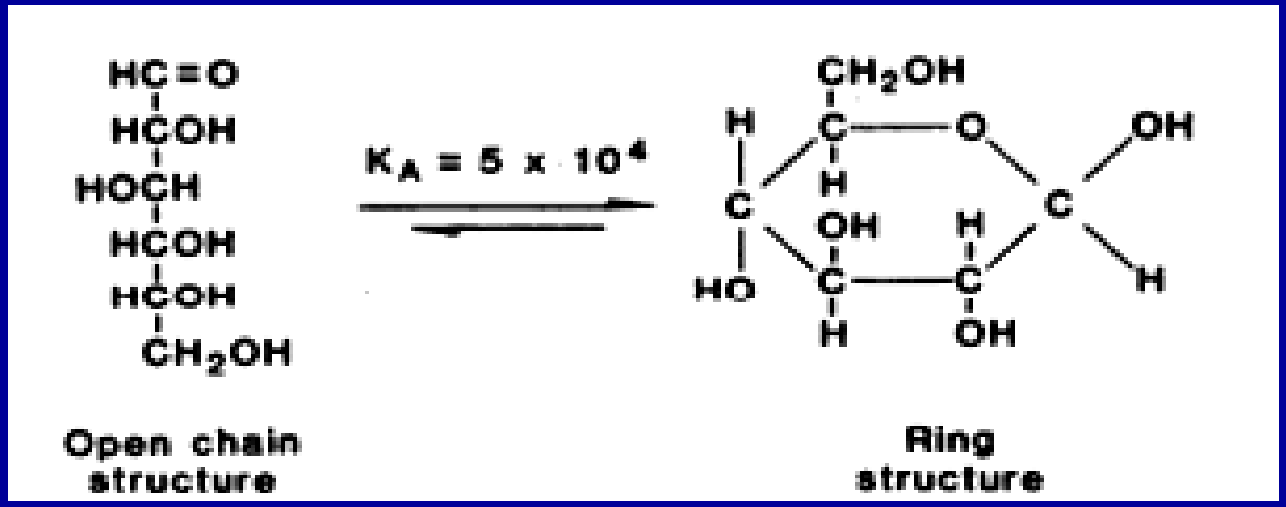
ATVB. 2001;21:365

Willa A. Hsueh; Ronald E. Law

Glycation

Depends on the percent of sugar in the open-chain form.

Fructose is more stable than glucose in the open-chain.



Open chain structure

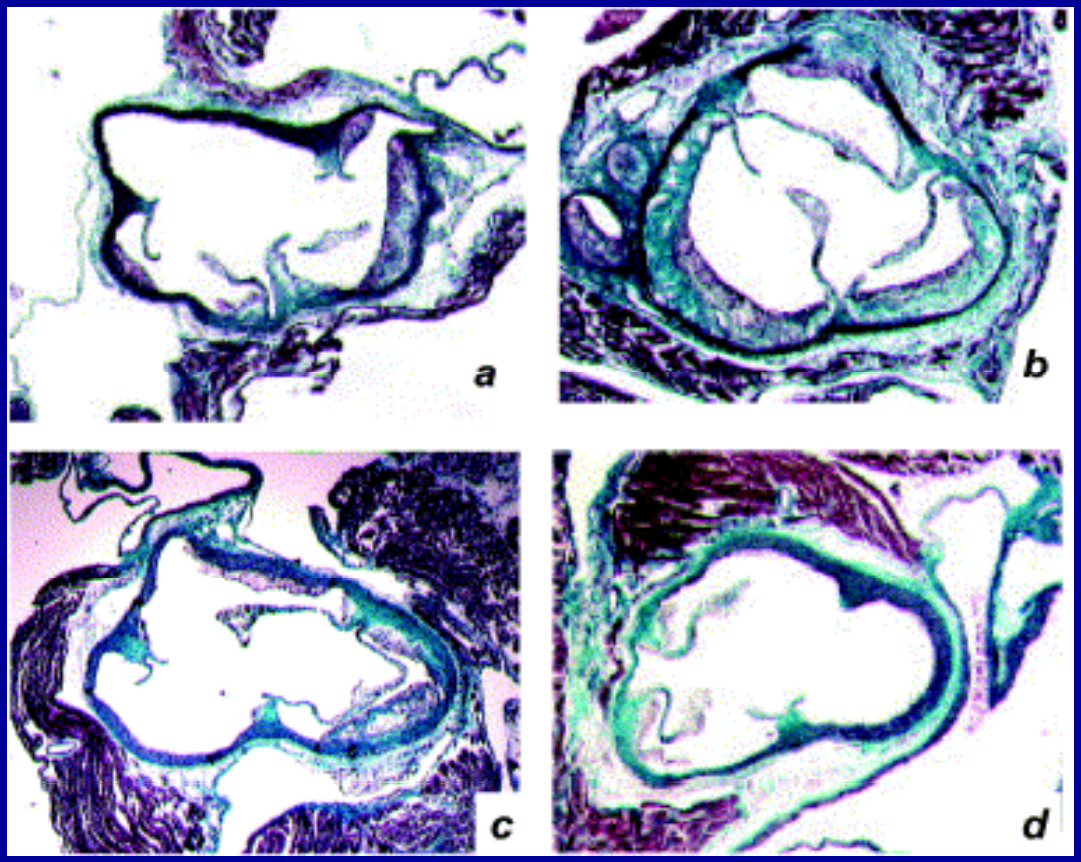
Ring chain structure

AGEs in the diet increases Atherosclerosis

L-AGE **H-AGE**

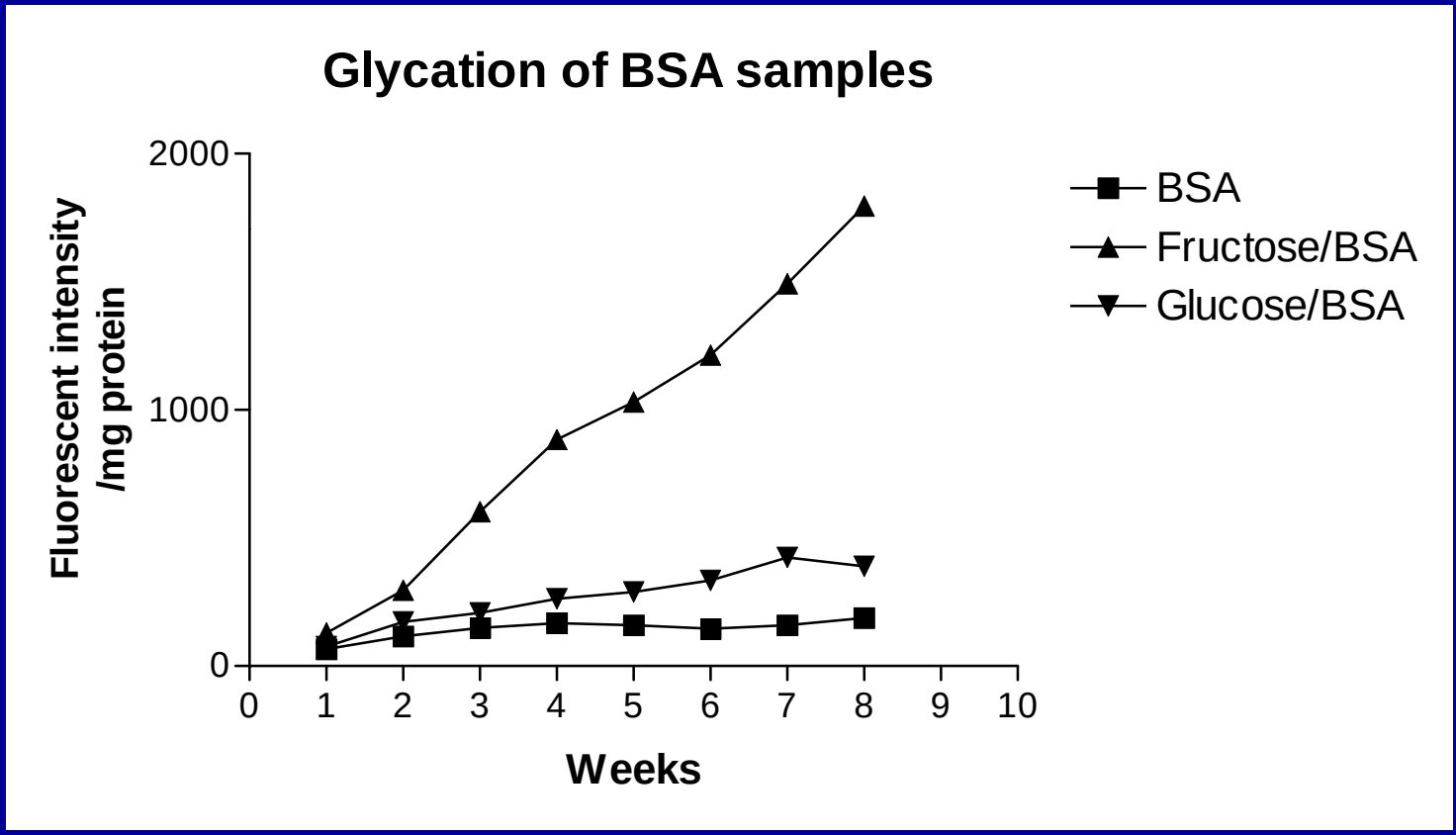
Diabetic ApoE-/-

ApoE-/-

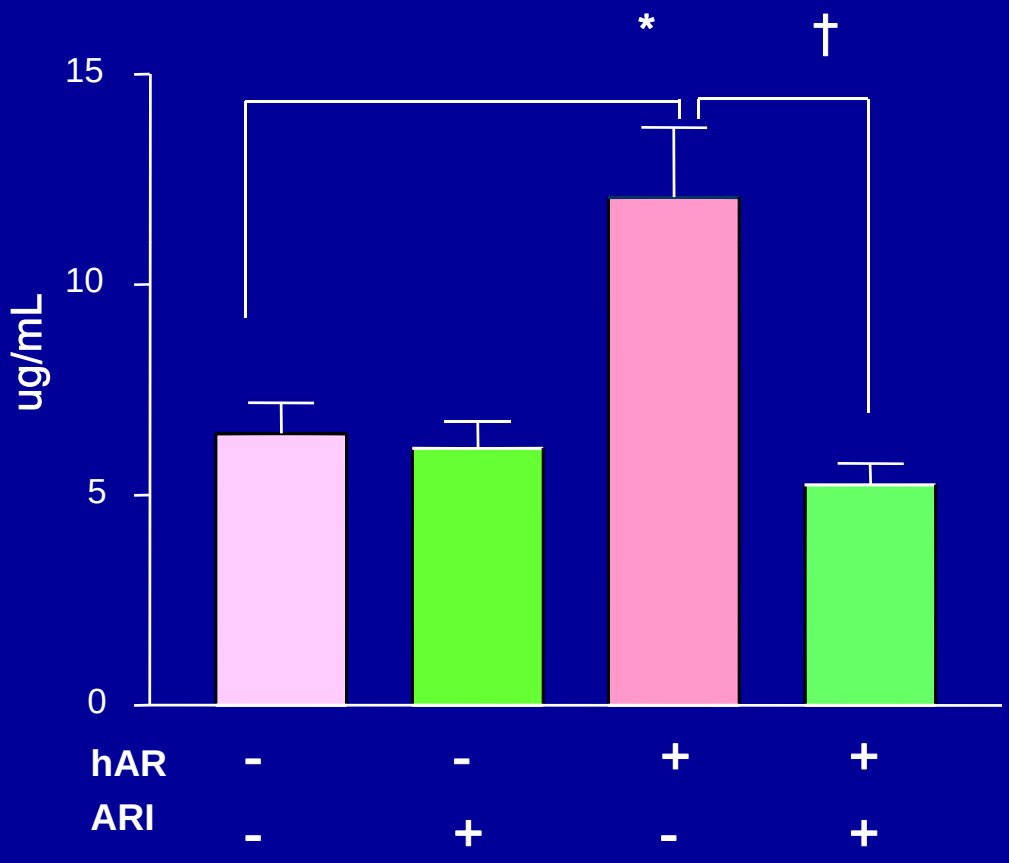


Lin et al. (including Fisher) Athero, 03

Fructose leads to more glycated albumin (AGEs) than glucose



hAR increased plasma fructose in STZ-treated Ldlr-/- mice



Data are means ± SD

* p<0.05 compare between hAR vs non-hAR

† p<0.05 compare between ARI vs placebo in the same genotype.

Summary

- hAR increased atherosclerosis in STZ diabetic mice.
- ARI treatment improved mortality in STZ treated hAR/Ldlr-/- mice.
- hAR MAY increase atherosclerosis in old high fat diet fed Ldlr-/- mice.
- Diabetes and hAR decrease glutathione
- Diabetes and hAR increase fructose, which may increase AGEs.

Models to study AR effects in vivo

- We have created two lines of Tie 2- hAR mice. we will study whether endothelial cell specific expression of hAR increases atherosclerosis.

- We have created two lines of MHC-hAR mice. We will test whether this transgene affects heart function with diabetes.

- We have made an hAR-expressing adenovirus for studies of cultured cells. We will test whether this virus will increase glucose to fructose conversion in vivo and affect atherosclerosis.