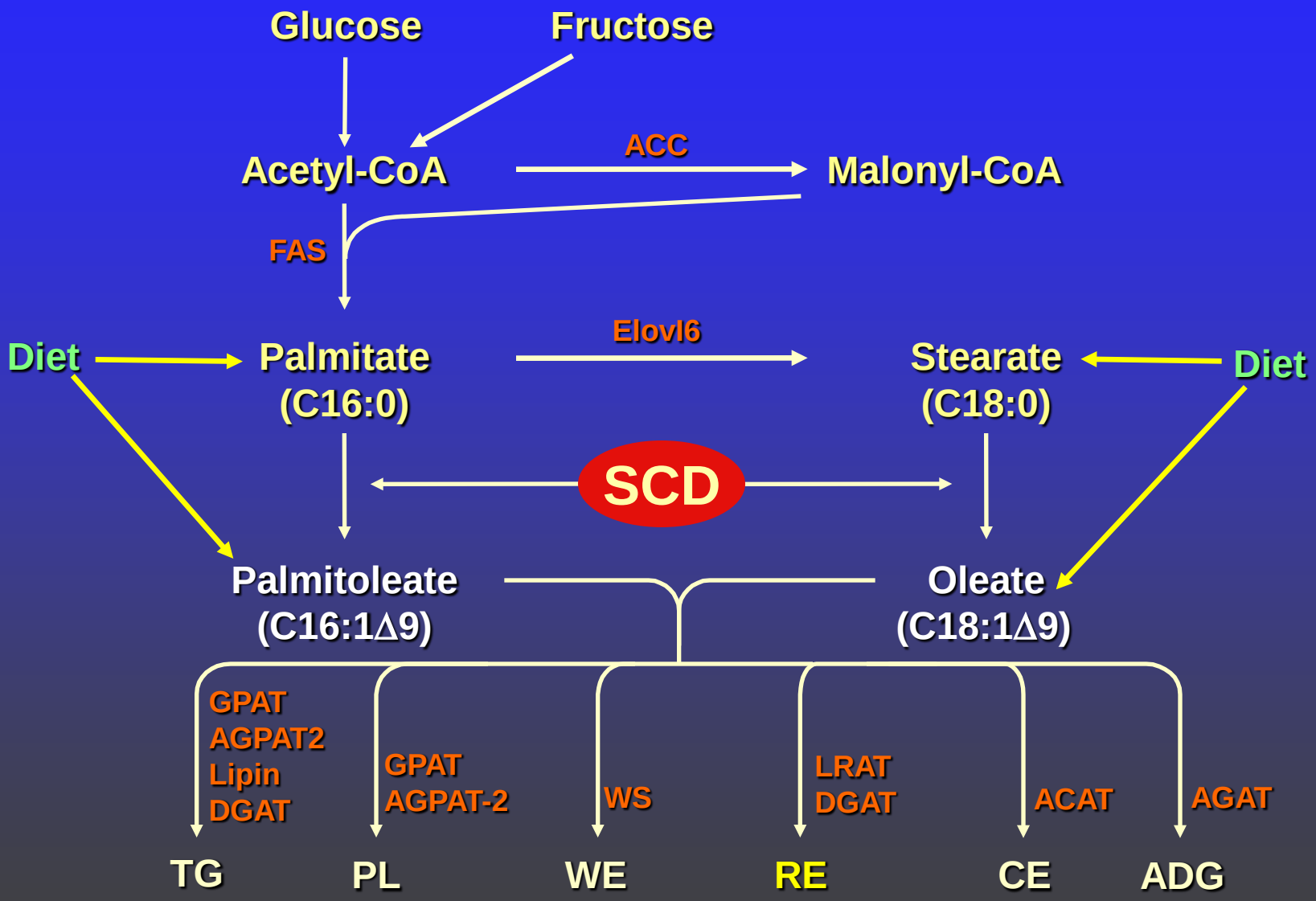
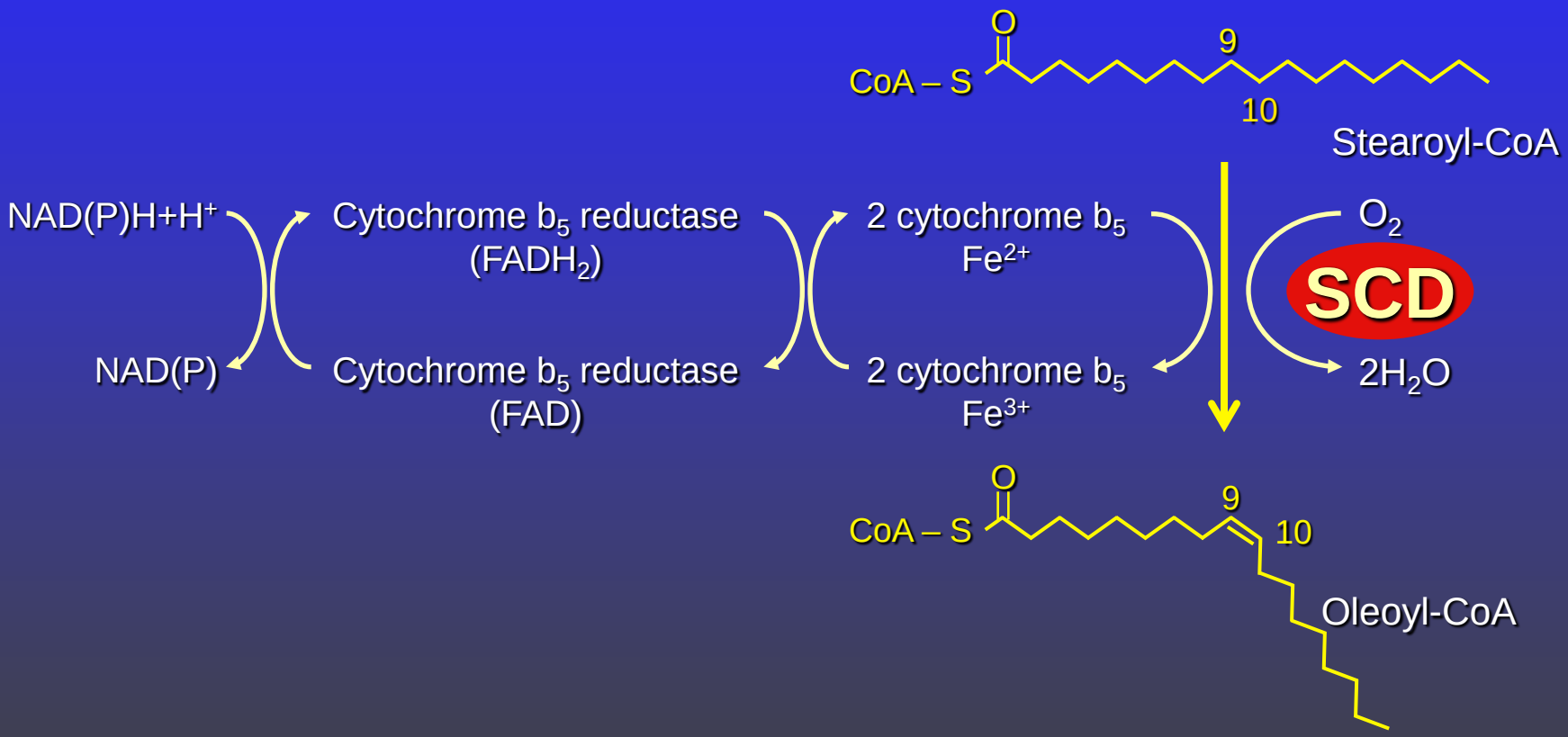
Gene Polymorphisms and Carbohydrate Diets

James M. Ntambi Ph.D

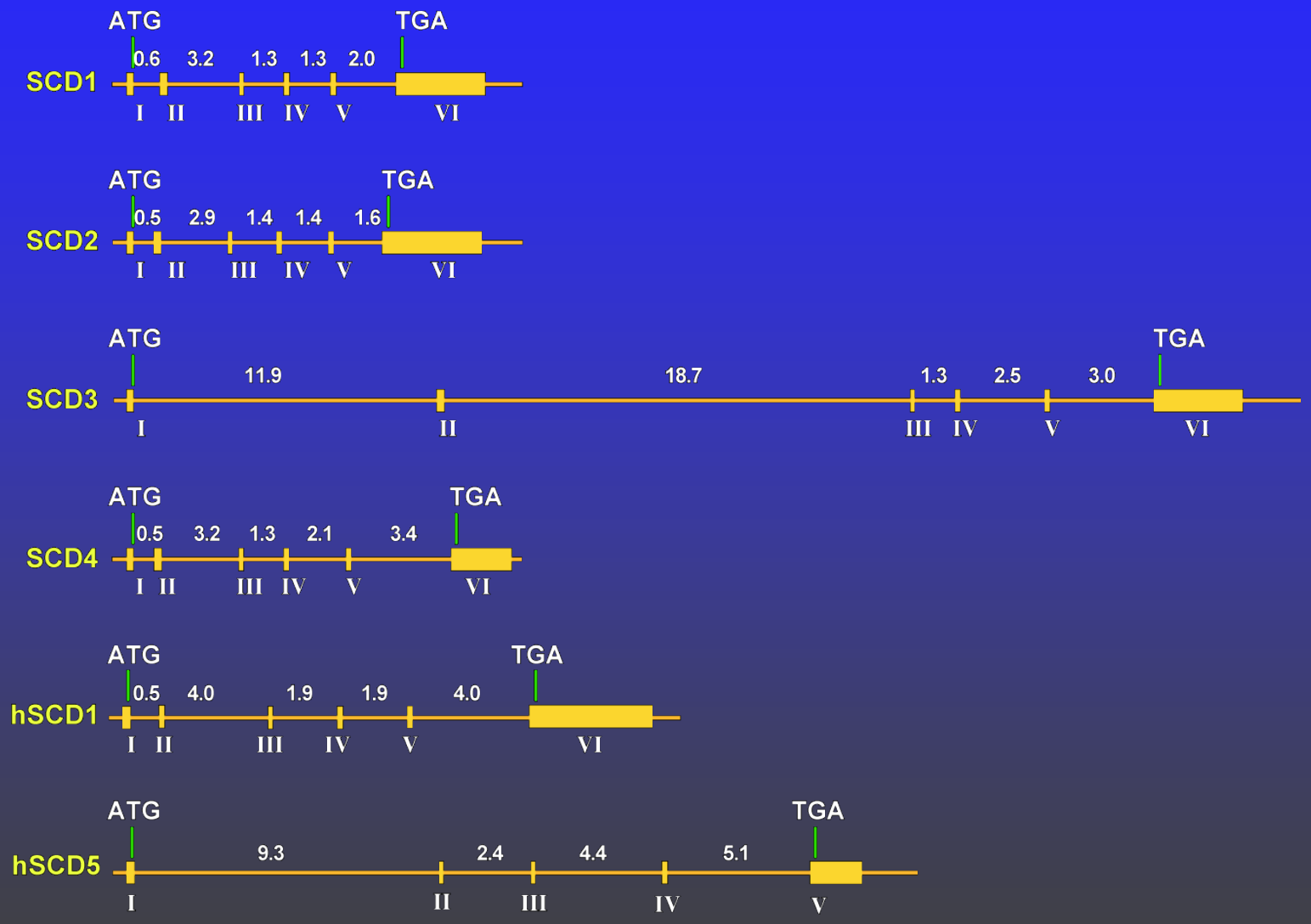
Fatty Acids that Flux into Tissue Lipids are from Dietary Sources or are Made De novo from Glucose or Fructose



The Stearoyl-CoA Desaturase (SCD) Reaction

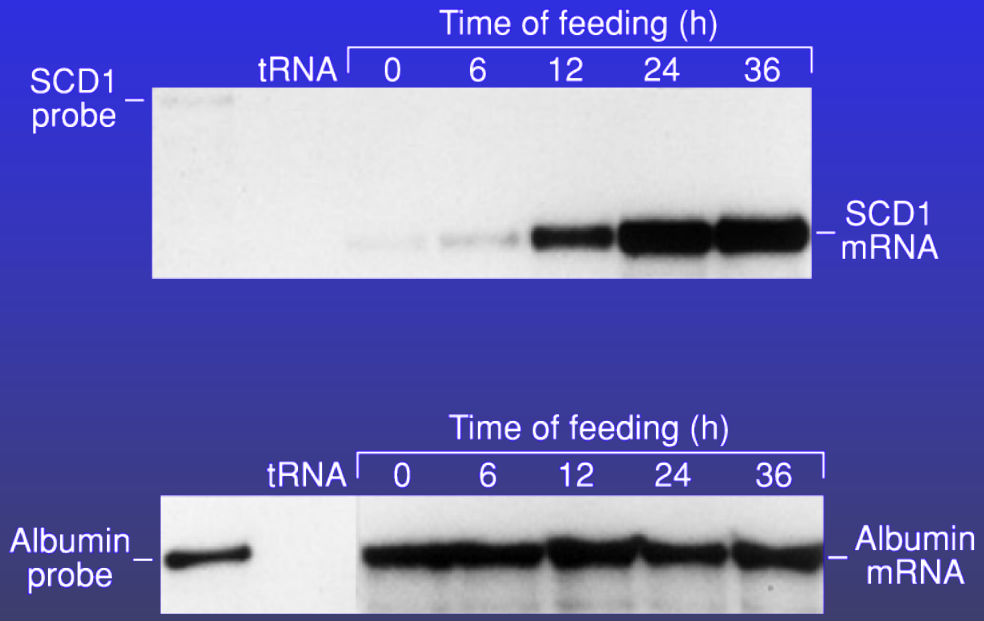


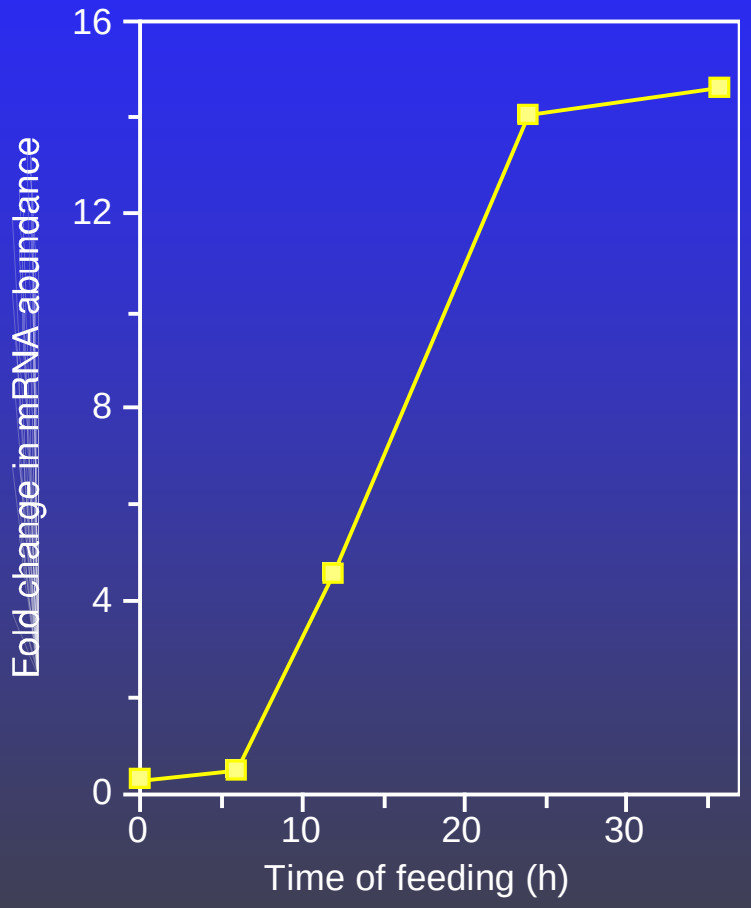
Mouse has 4 and Human has 2 SCD Gene Isoforms

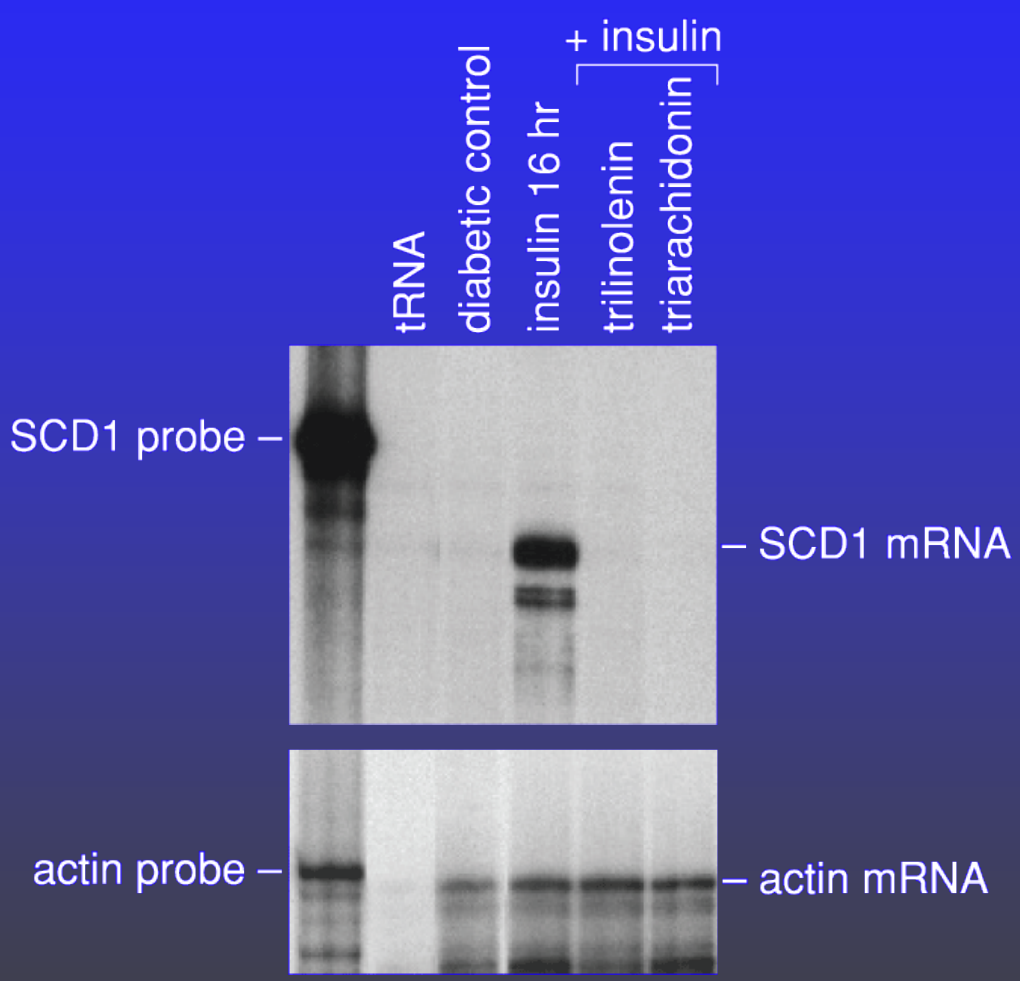


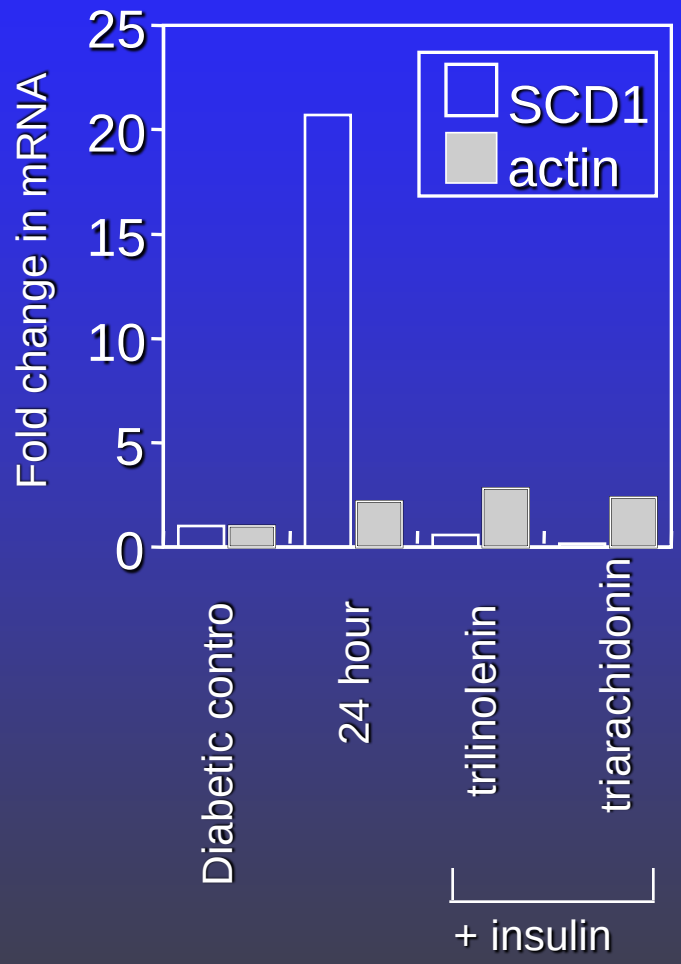
Inducers	Repressors
Glucose	**PUFA (w-3, w6)**
Fructose	**Leptin**
Insulin	**Thyroid Hormone**
Cholesterol	**Glucagon**
LXR Agonists	**TZDs**
Vitamin A	Dehydroepiandrosterone
Vitamin D	Cadmium
Growth hormone	TNF-α
Estrogen	
Androgen	
Peroxisome proliferators	
Low temperature	
Iron	
TGF-β	
KGF	
β-Amyloid	

???

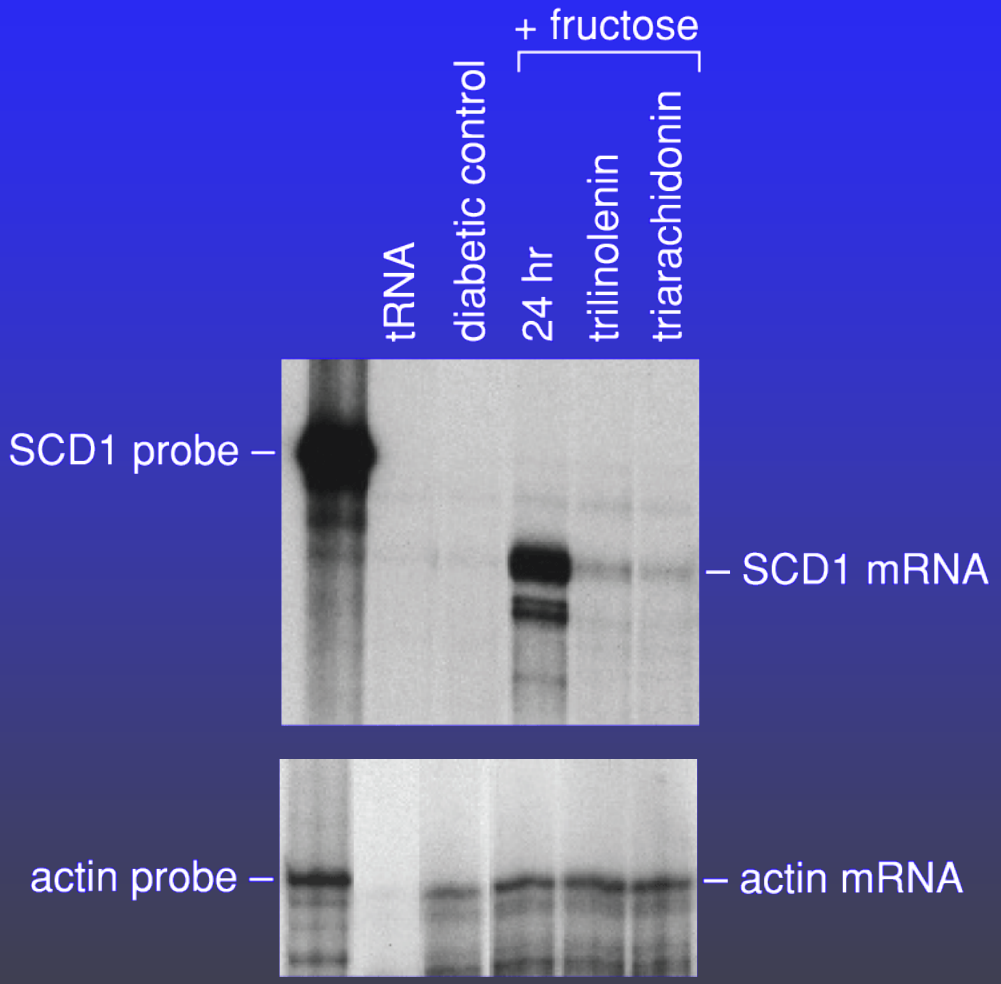

Time of feeding (h)
tRNA
0
6
12
24
36
SCD1 probe
SCD1 mRNA
Time of feeding (h)
tRNA
0
6
12
24
36
Albumin probe
Albumin mRNA

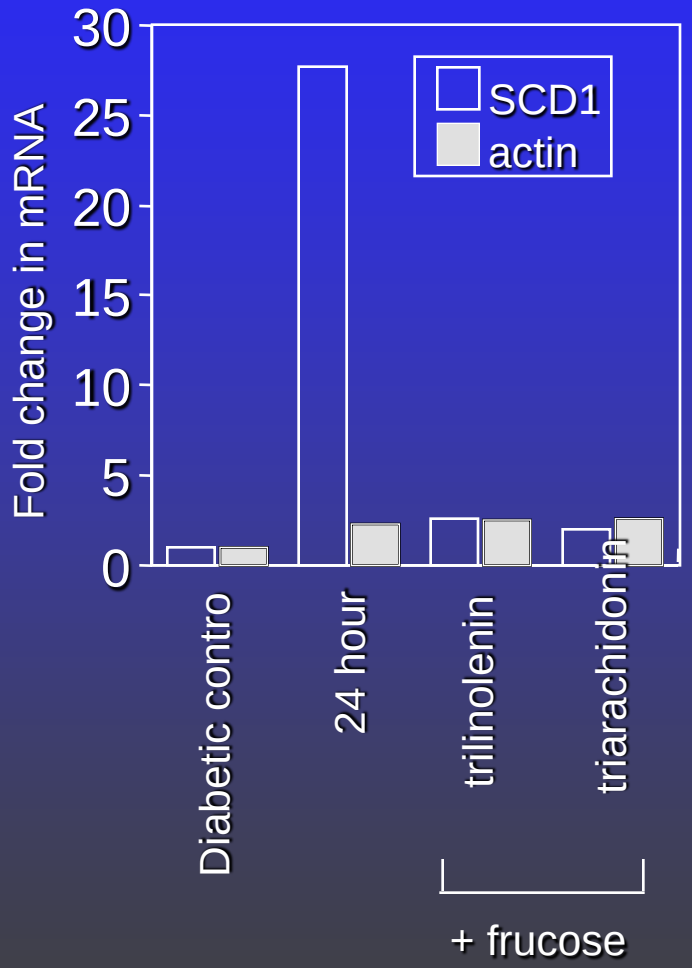

16
12
8
4
0
Fold change in mRNA abundance
0
10
20
30
Time of feeding (h)


tRNA
diabetic control
insulin 16 hr
+ insulin
trilinolenin
triarachidonin
SCD1 probe –
– SCD1 mRNA
actin probe –
– actin mRNA


Fold change in mRNA
25
20
15
10
5
0
SCD1
actin
Diabetic contro
24 hour
trilinolenin
triarachidonin
+ insulin

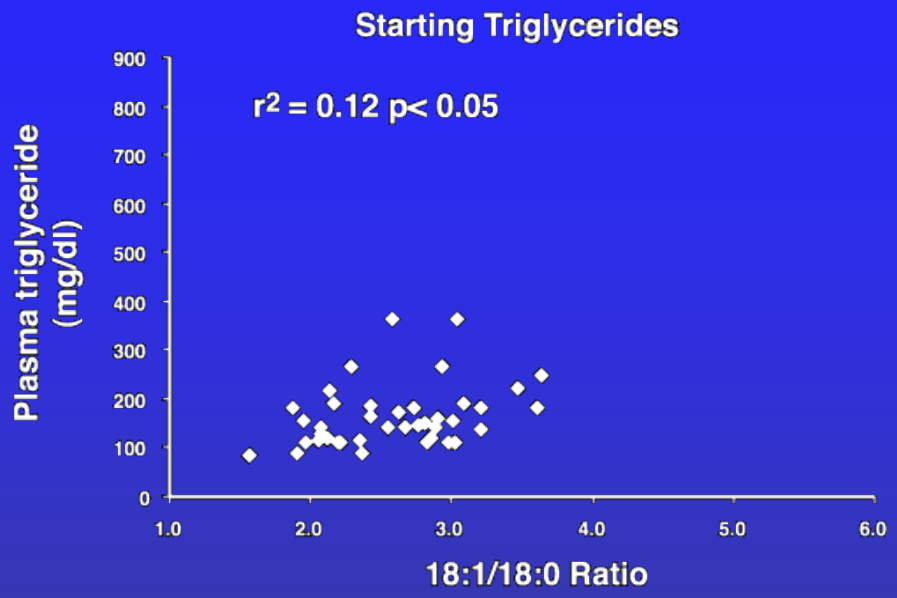
Fructose Induces SCD1: PUFAs Repress



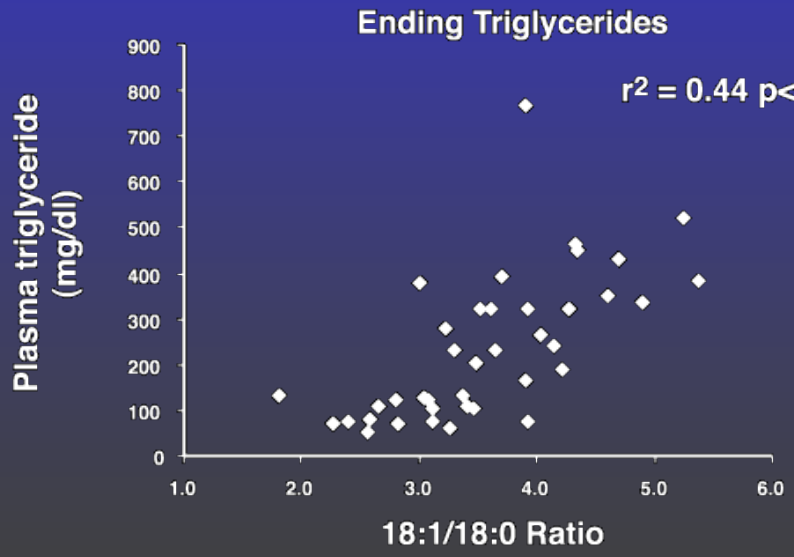


18:1/18:0 Ratio *vs.* Diet

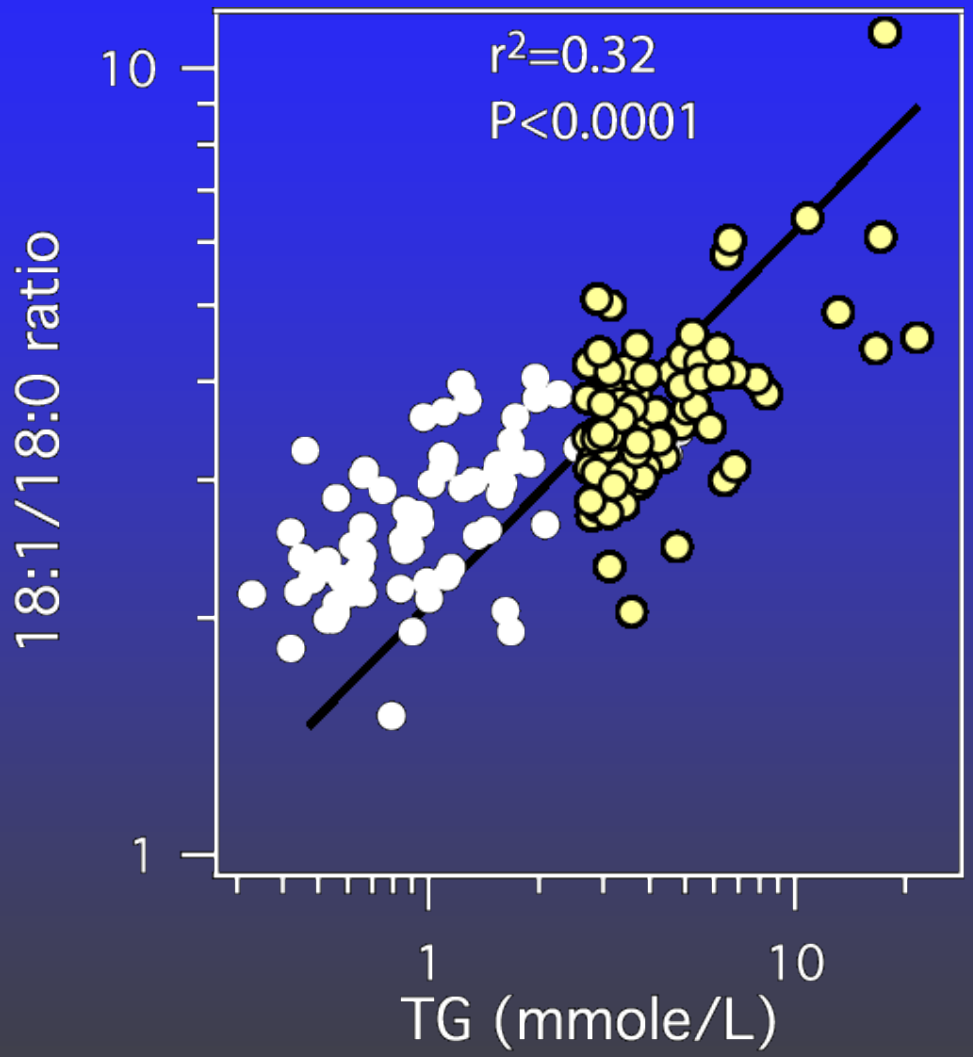
Low-carbohydrate diet



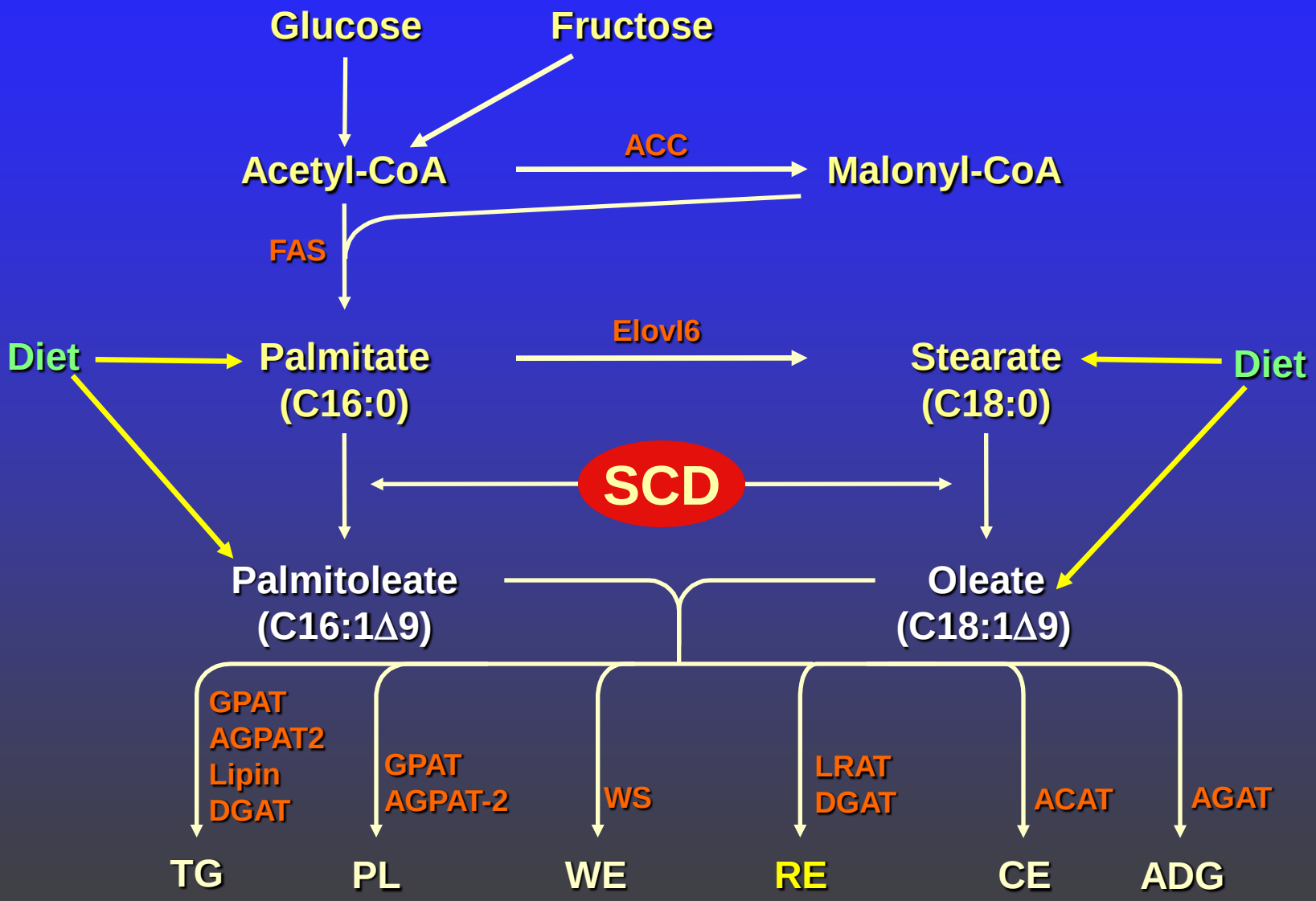
High-carbohydrate diet



Desaturation Ratio in FCHL Subjects

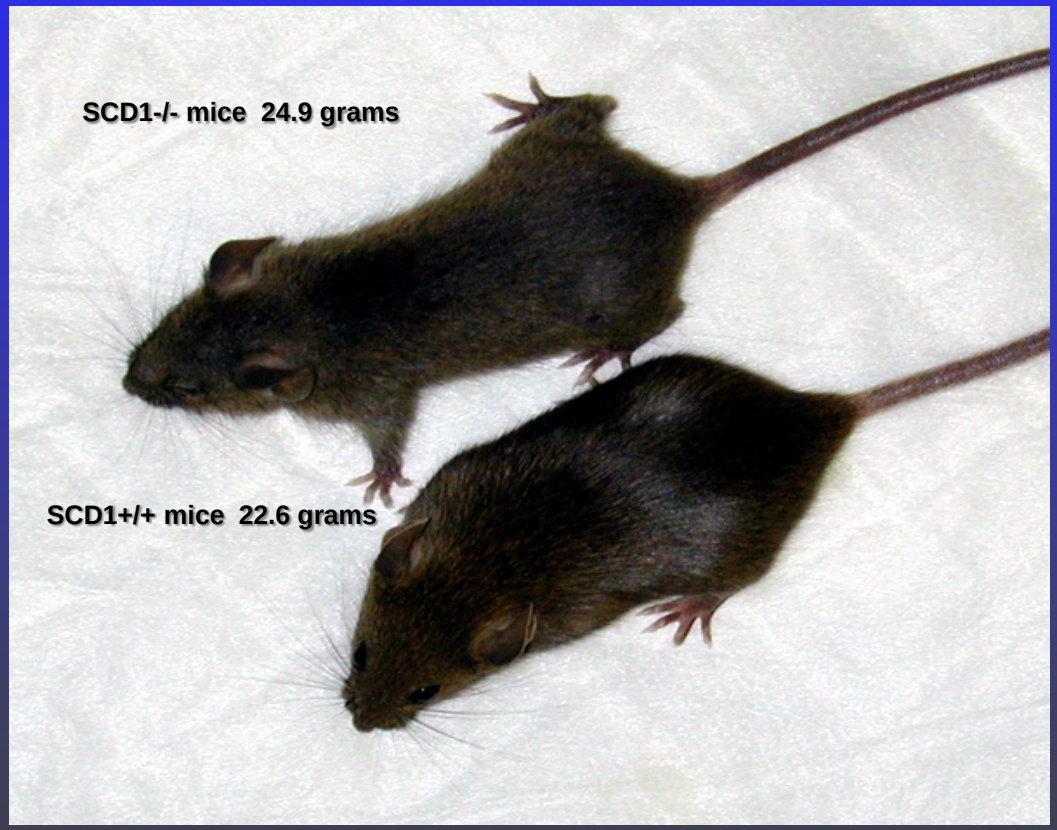


Fatty Acids that Flux into Tissue Lipids are from Dietary Sources or are Made De novo from Glucose or Fructose

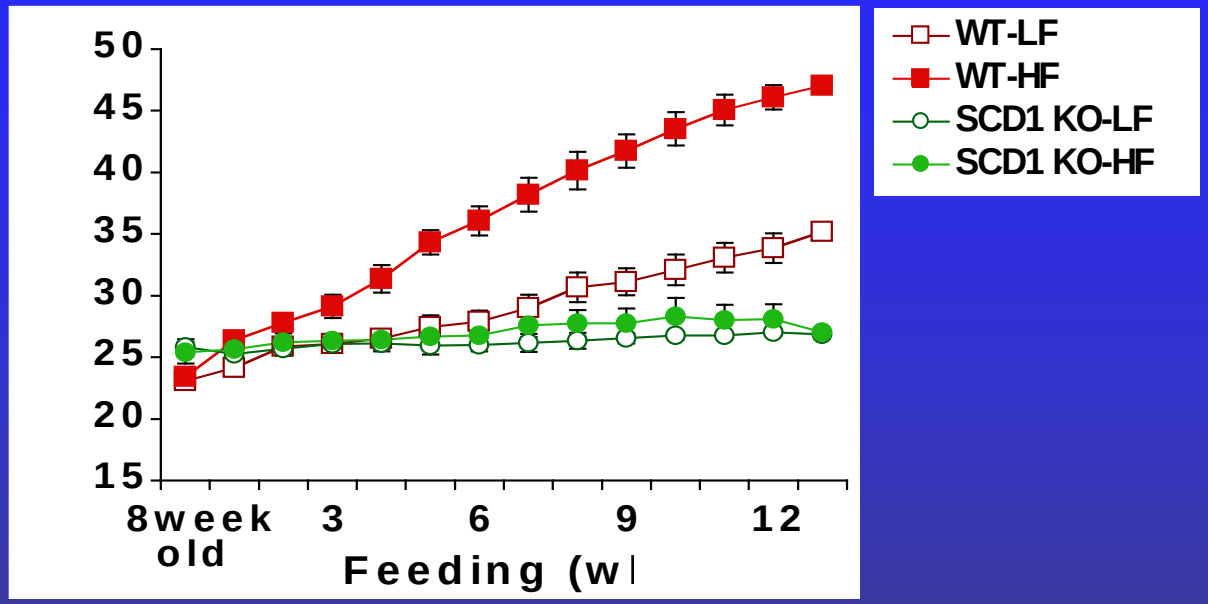


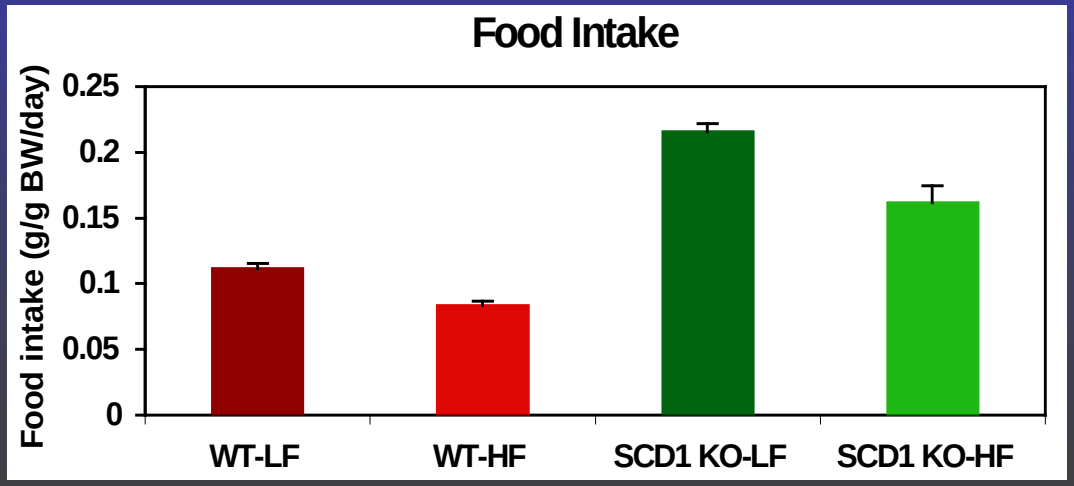
Gene Knockout Technology produced SCD1-/- mice which look leaner but weigh more than SCD1+/+ Mice

(At the University of Wisconsin-Madison)

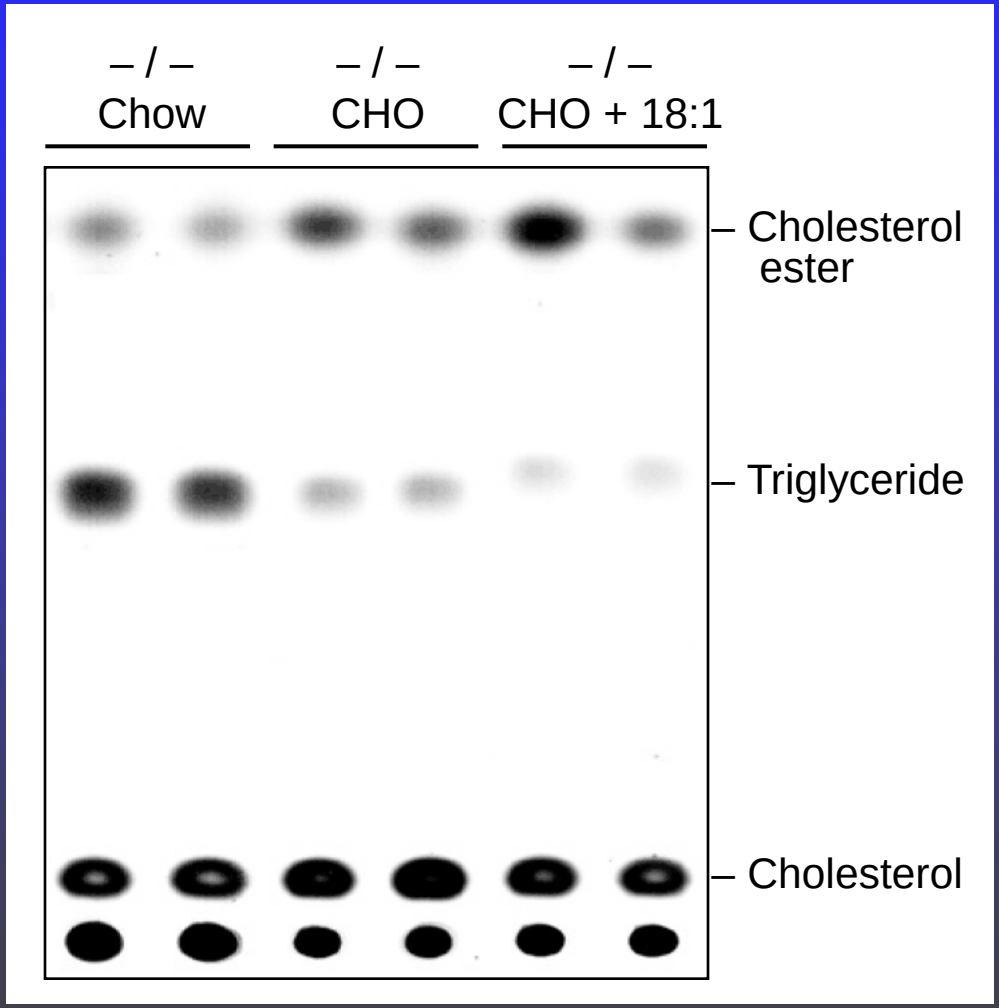


SCD1 Deletion Prevented HF and CHO-Induced Weight Gain: Mice Hyperphagic





Lipids from Liver of SCD1$^{-/-}$ Mice Fed CHO + Oleate



Mouse models of obesity

Ob/ob (B6)

Leptin deficient

Hyperphagic

Insulin resistant

Agouti obese (A^y/a) (B6)

Expresses leptin

Hyperphagic

Leptin and Insulin resistant

Diet-induced obesity (DIO) (B6)

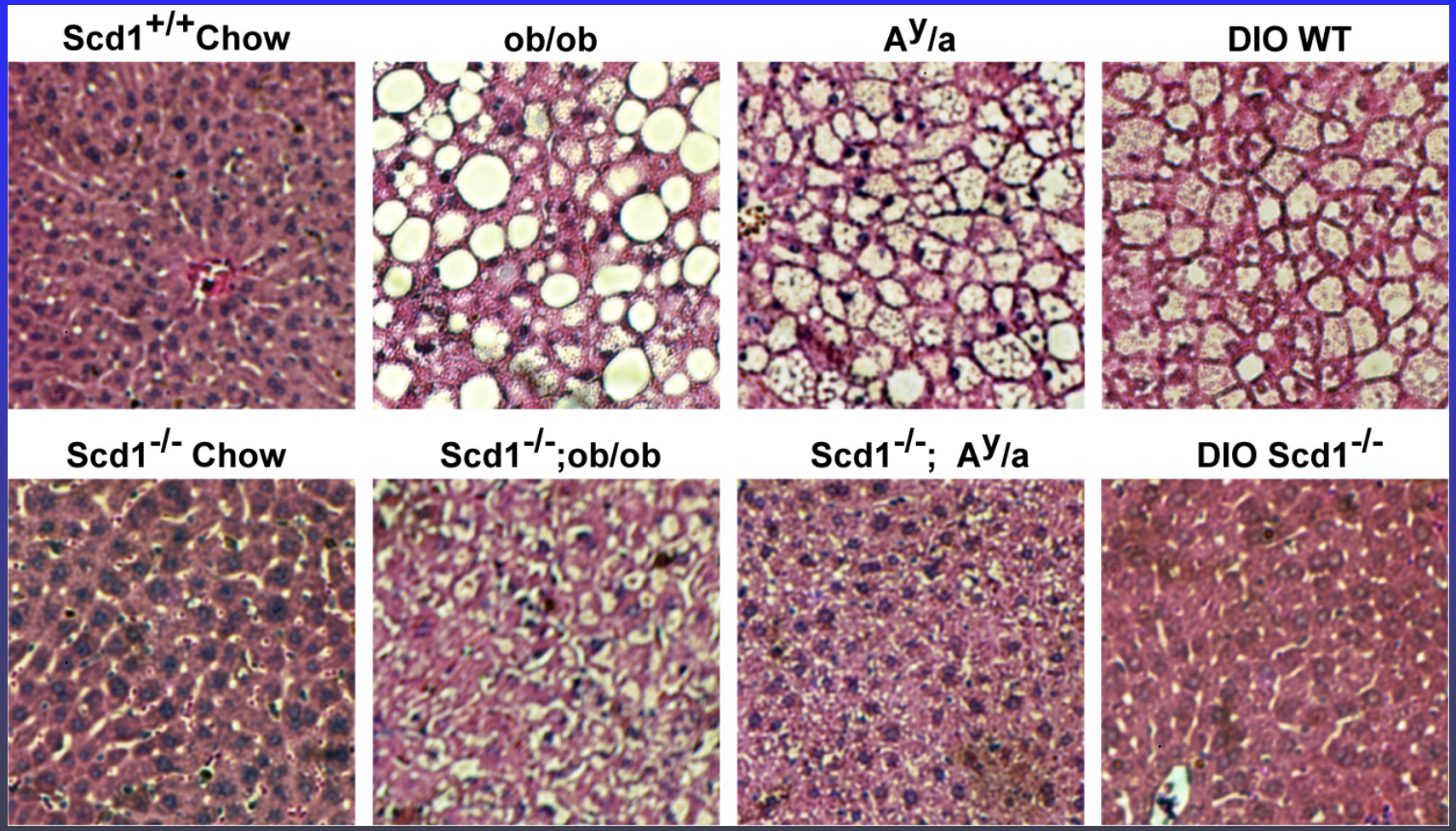
60% kcals from fat (32% by weight)

16 wk feeding

Leptin and Insulin

Sampath, Miyazaki & Ntambi et al., (unpublished)

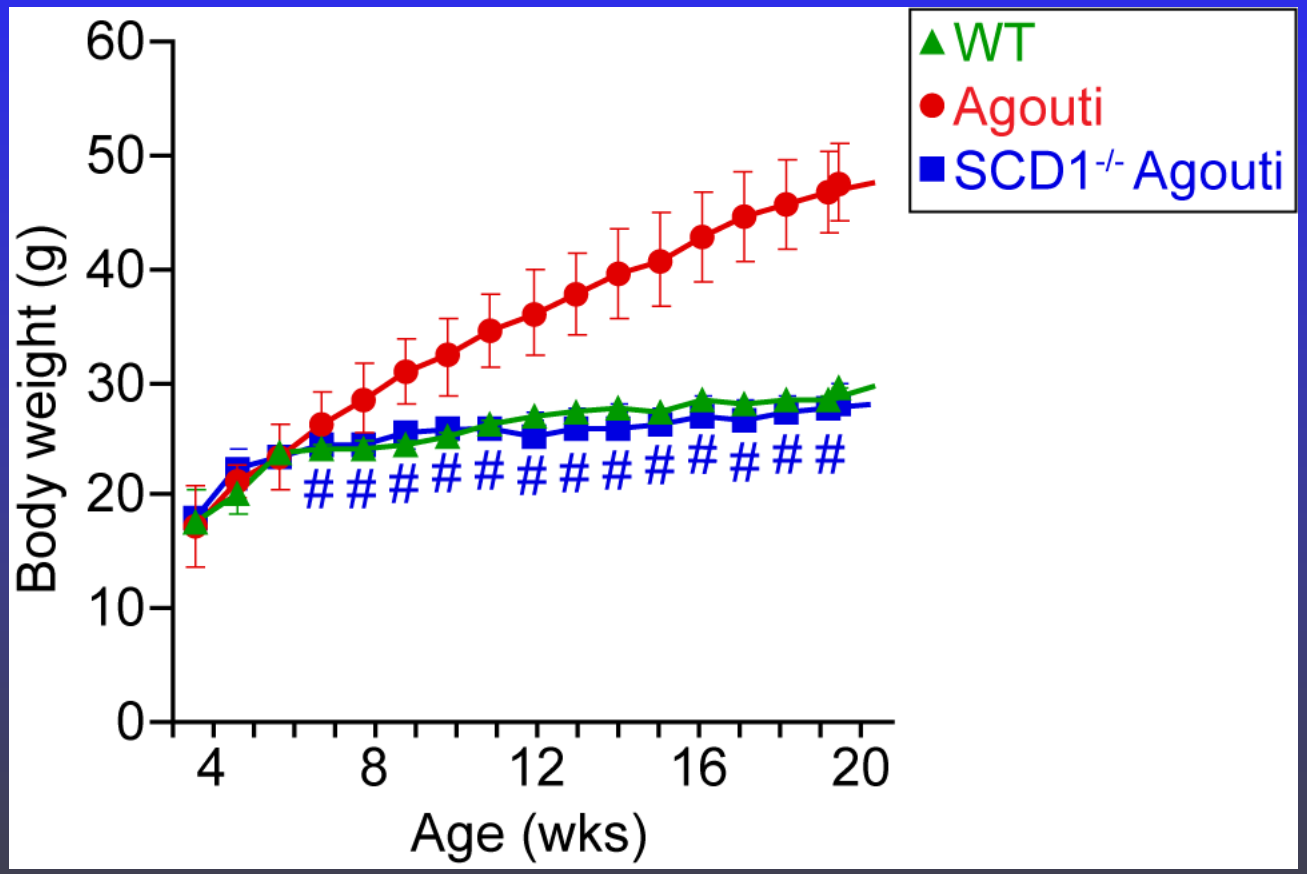
SCD1 Deficiency Prevents Liver Steatosis: Reduced VLDL Production



Sampath, Miyazaki & Ntambi et al.

SCD1 Deficiency Completely Prevents Leptin Resistance-induced Adiposity and Liver Enlargement

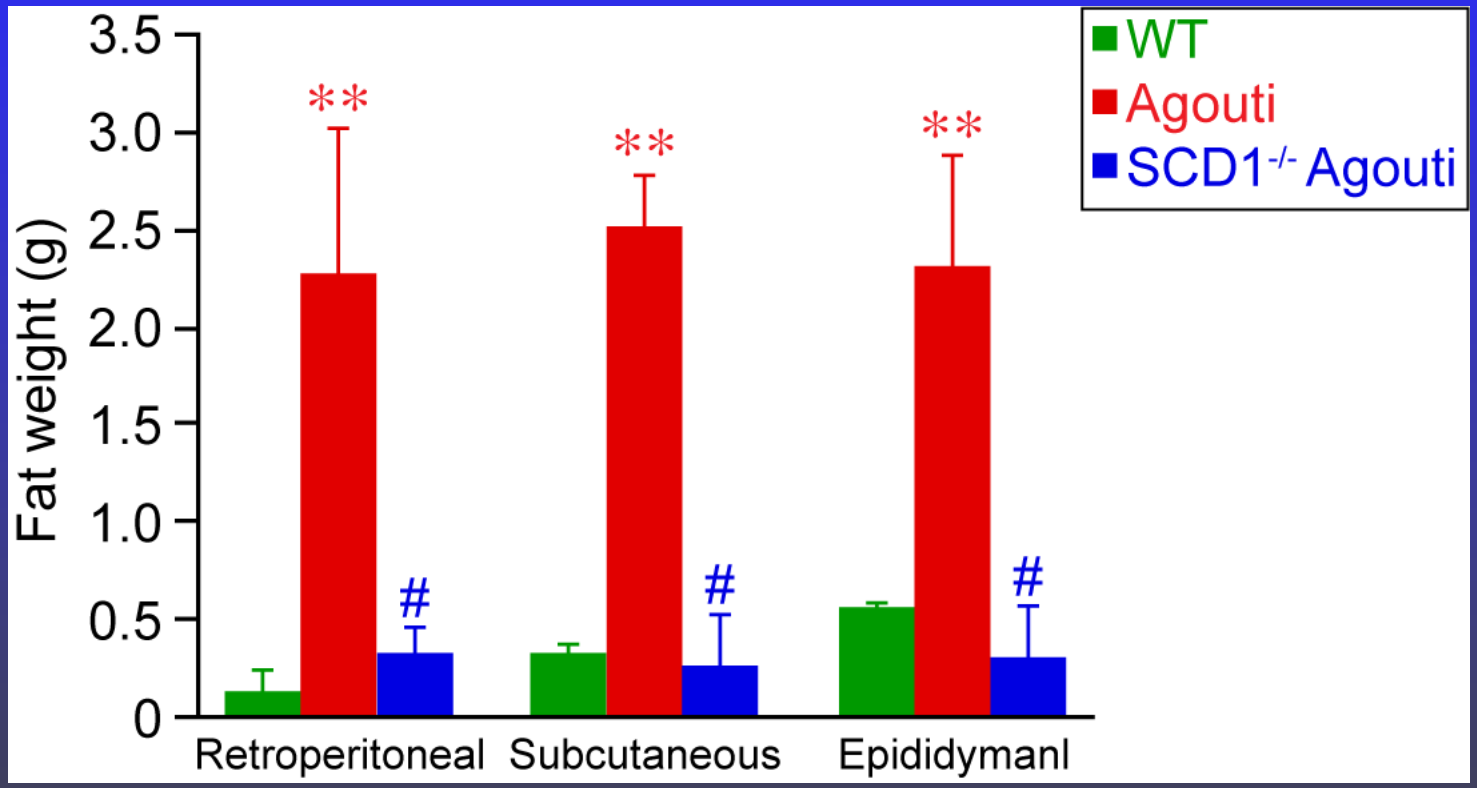
Growth curve



(n=12~18) **p<0.001 vs WT, #p<0.005 vs Agouti

SCD1 Deficiency Completely Prevents Leptin Resistance-induced Adiposity

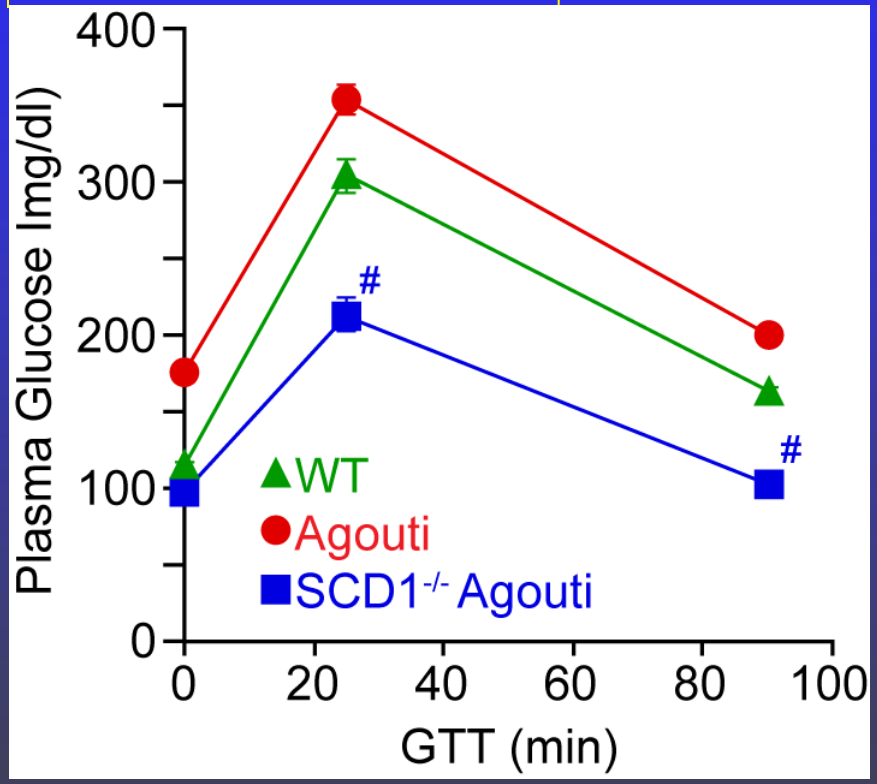
Weight of adipose tissue



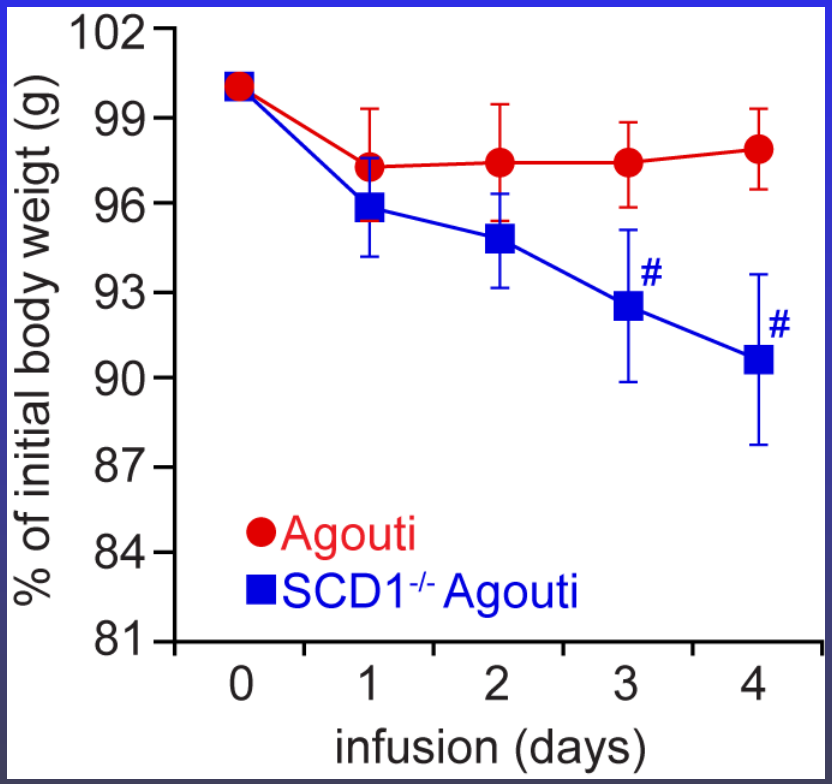
(n=12~18) **p<0.001 vs WT, #p<0.005 vs Agouti

Skin SCD1 deficiency protects agouti mice against insulin and leptin resistances

A Gluocse tolerance test

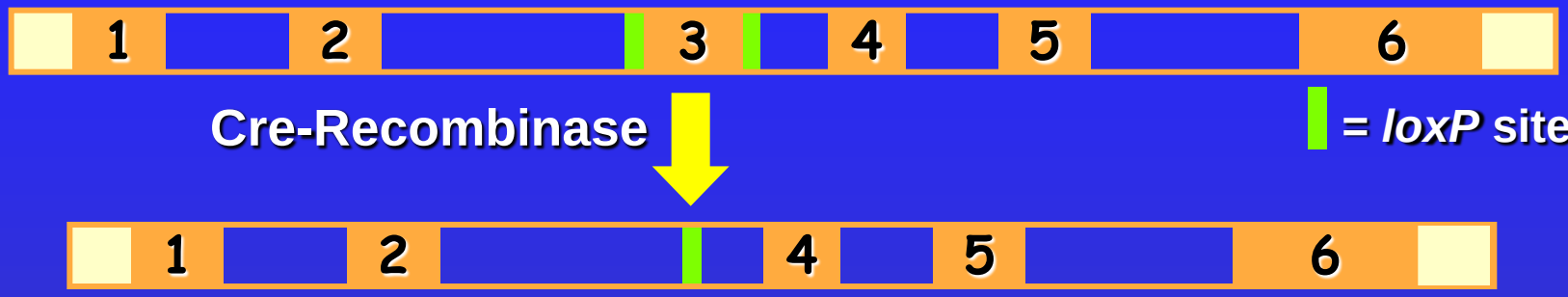


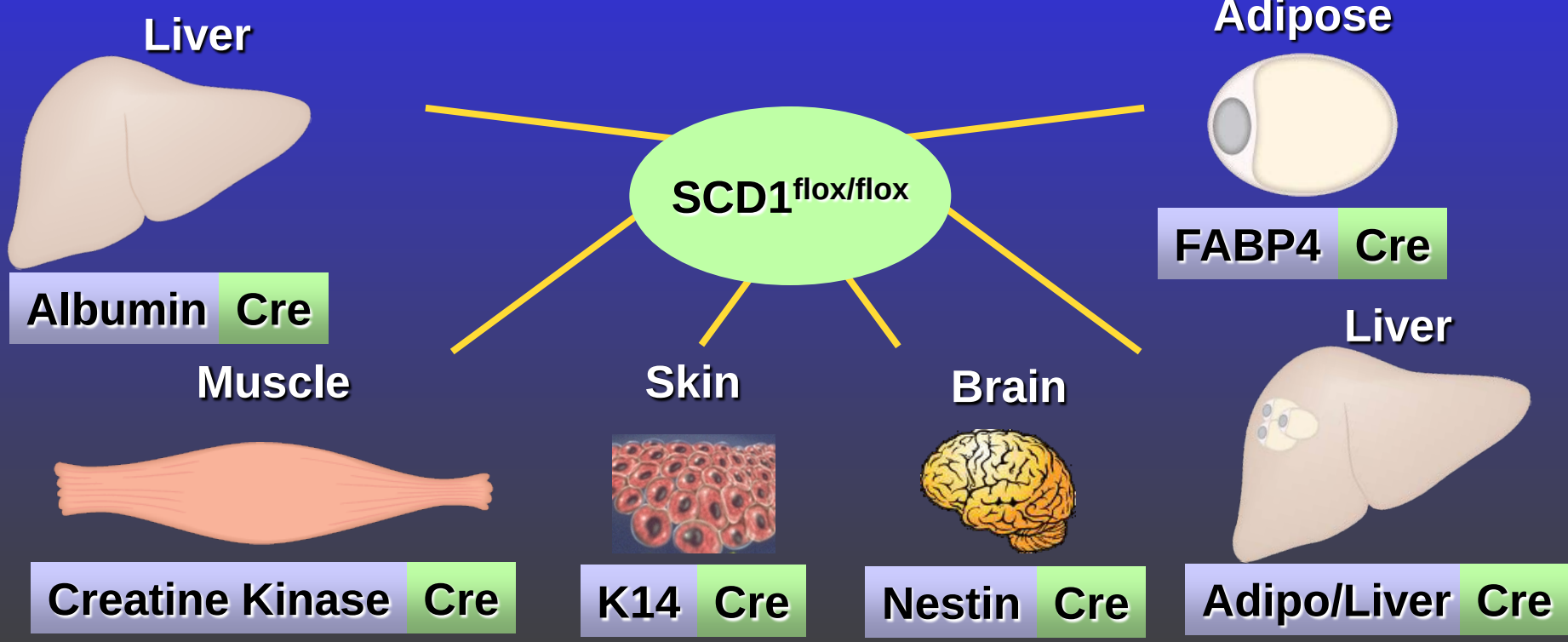
B Leptin tolerance test



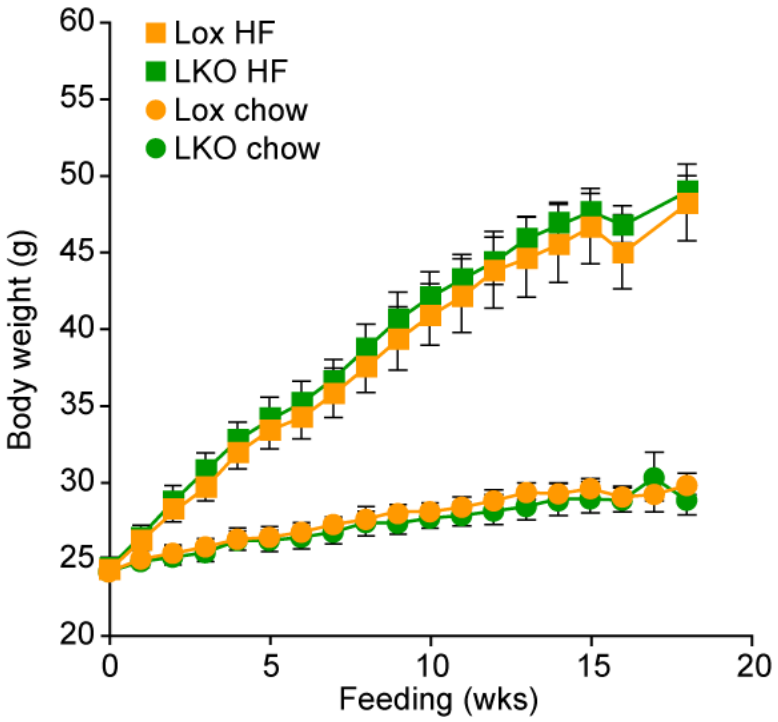
(n=5~7) #p<0.01 vs Agouti mice

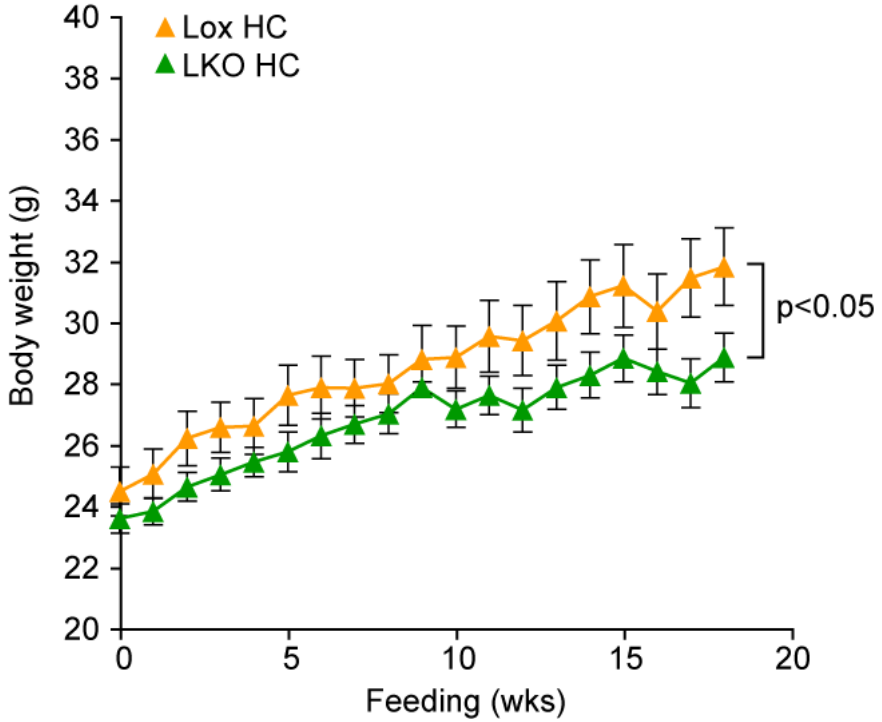
SCD1 Conditional Knockout



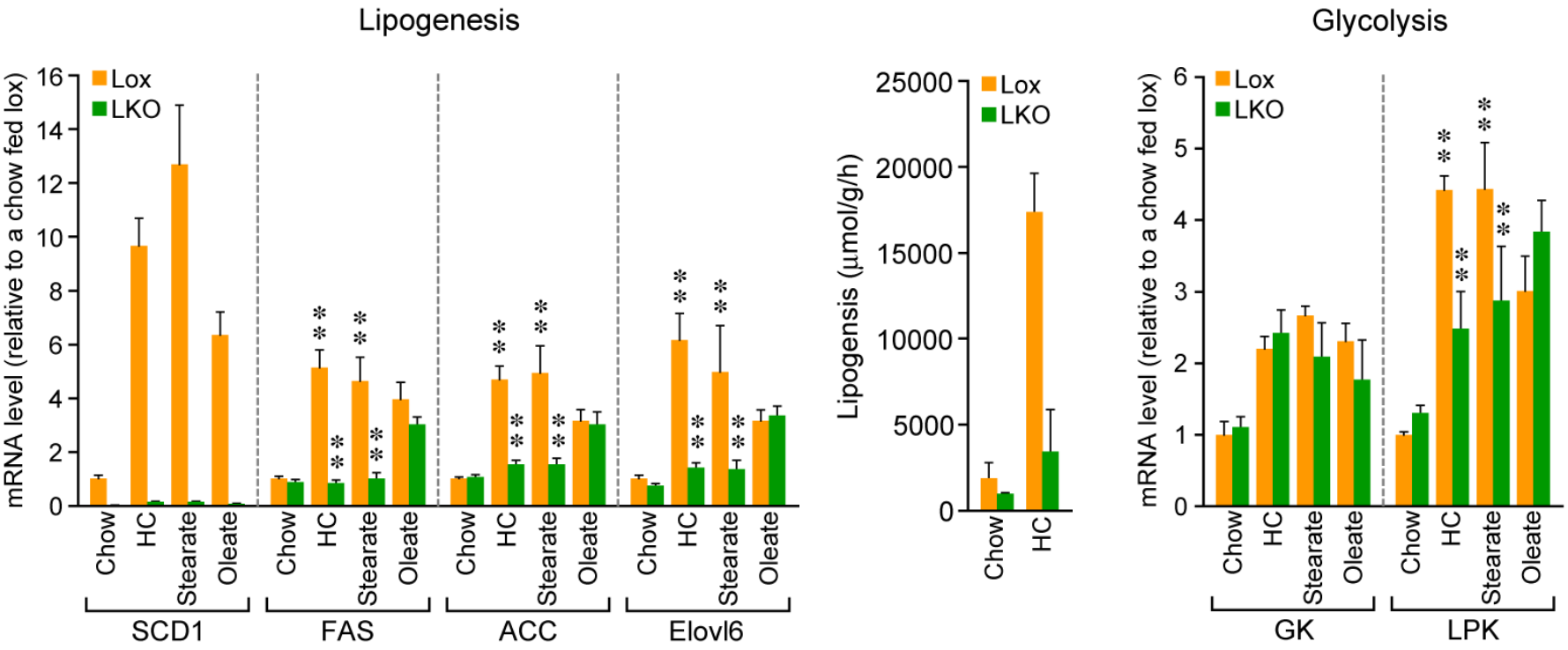


Challenge Lox and LKO with Lard and High Carbohydrate Diets

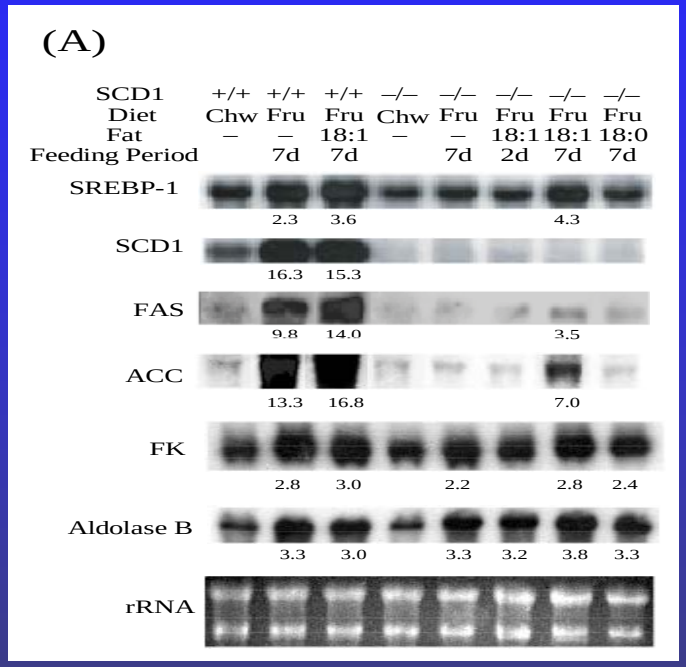


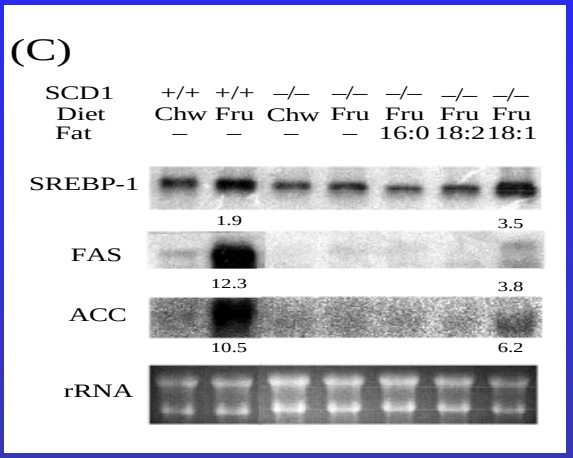


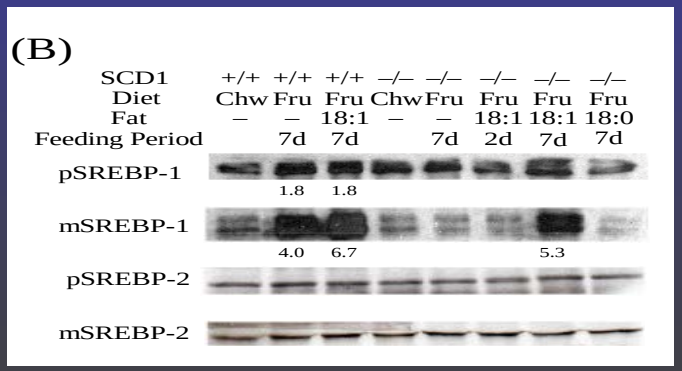
LKO Blocked CHO-induced Lipogenesis: Rescued by Oleate not Saturated Fat

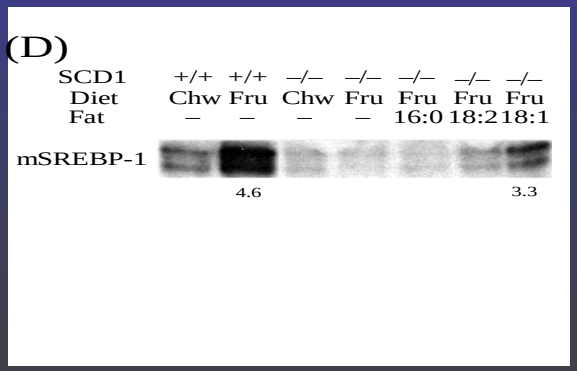


SREBP and Lipogenic Enzymes in Liver of SCD1$^{-/-}$ Mice Fed a High Fructose Diet

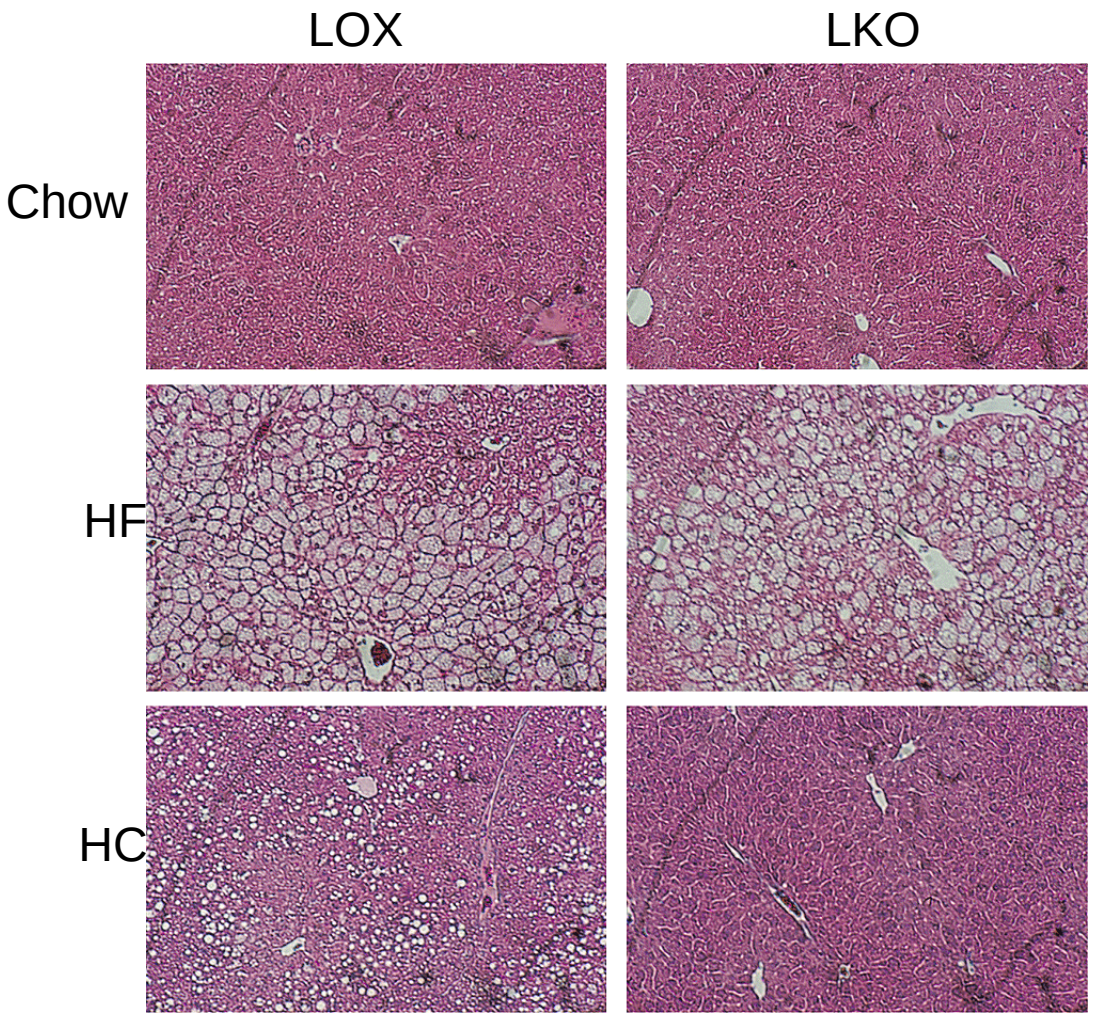




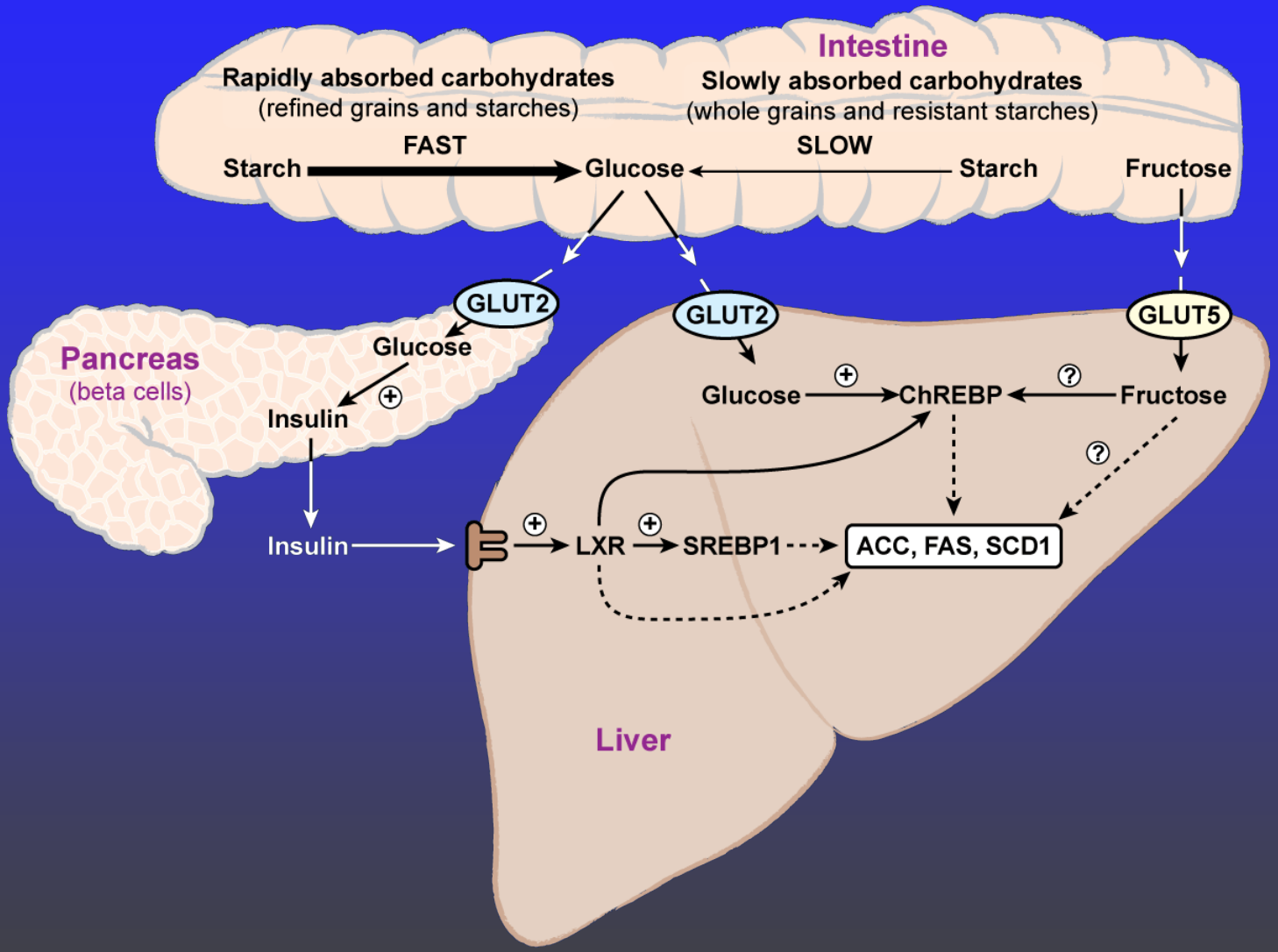




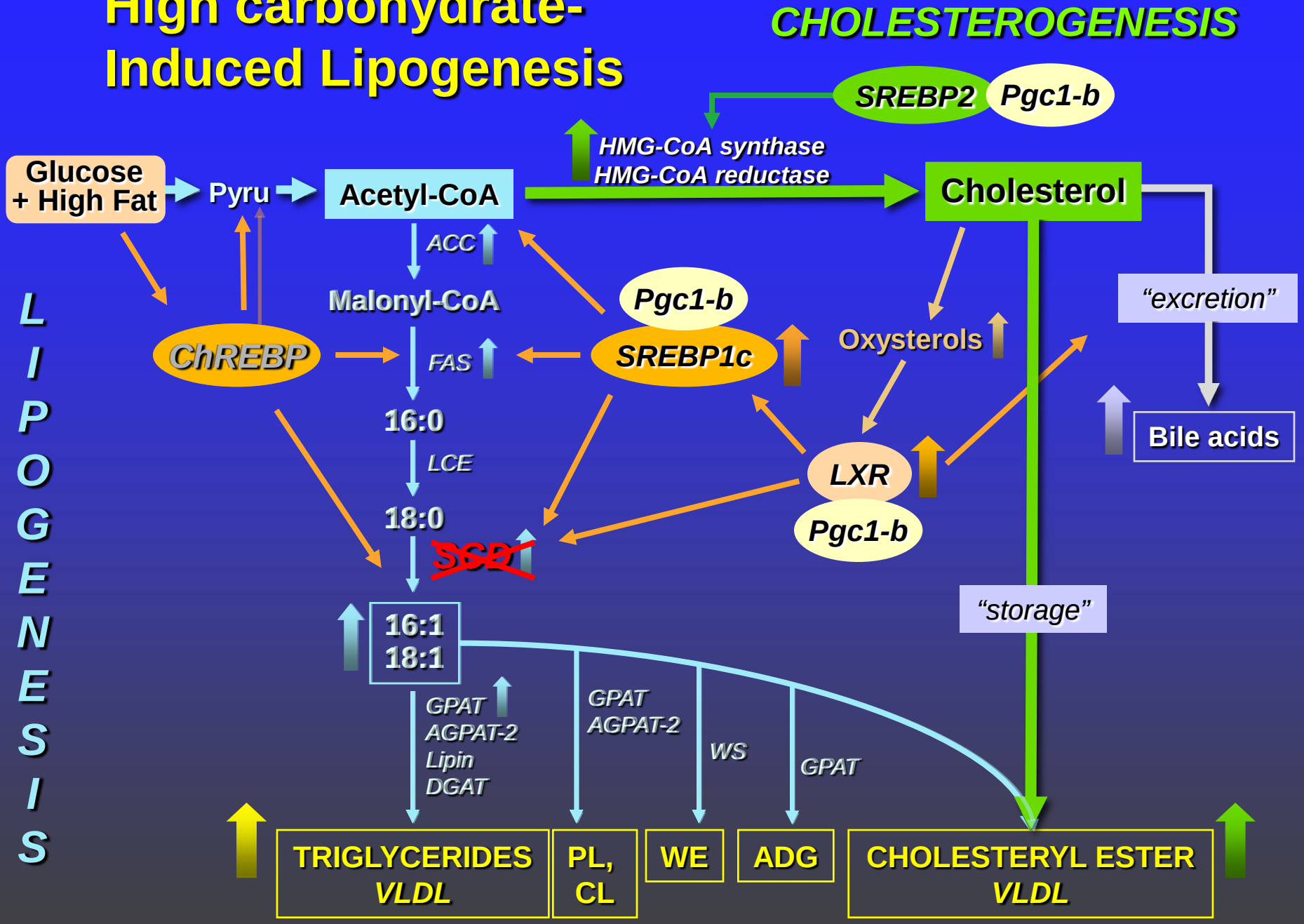
Liver steatosis is Reduced on HCHO, but not on Lard Diet



Carbohydrate-Induced Lipogenesis



High carbohydrate-Induced Lipogenesis



FUNDING SOURCES

NATIONAL INSTITUTES OF HEALTH (NIDDK)

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STEENBOCK ENDOWED PROFESSORSHIP