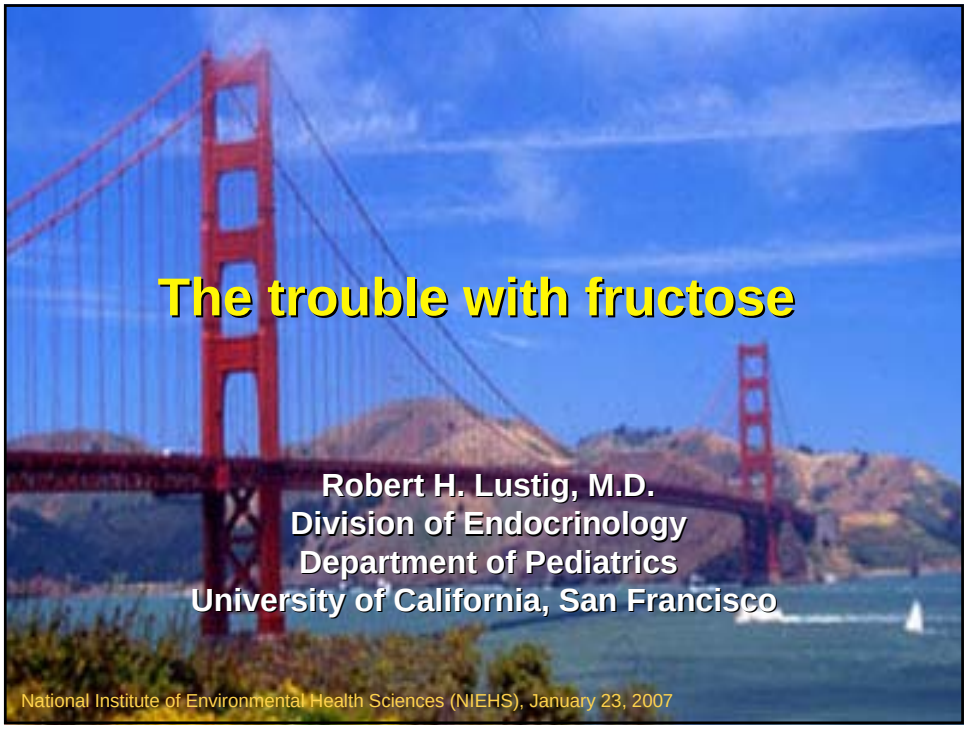
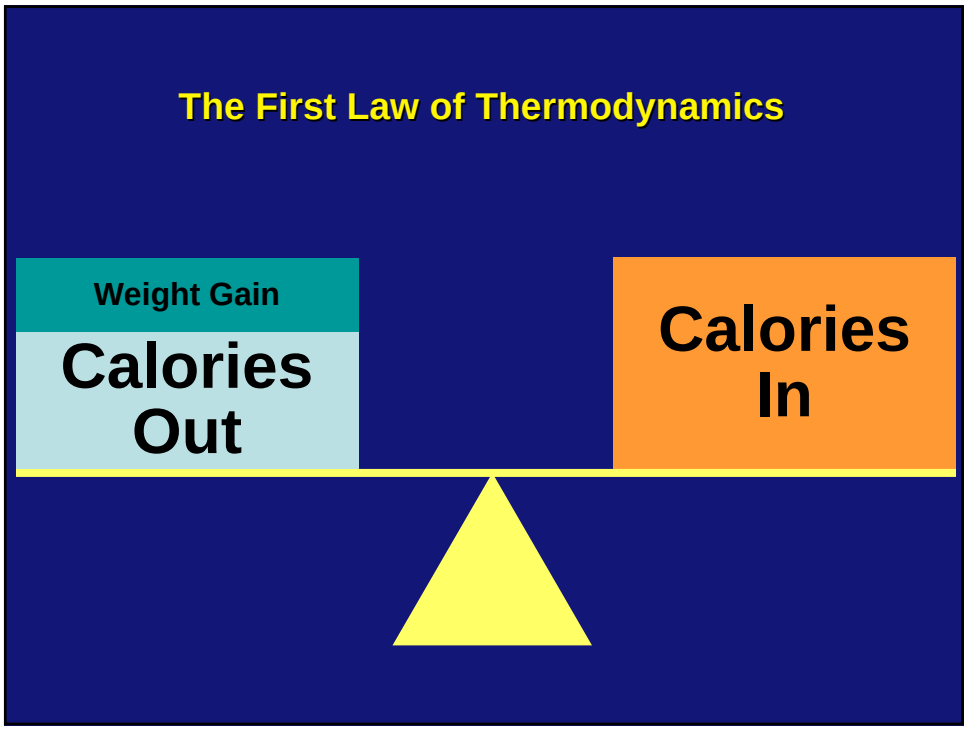
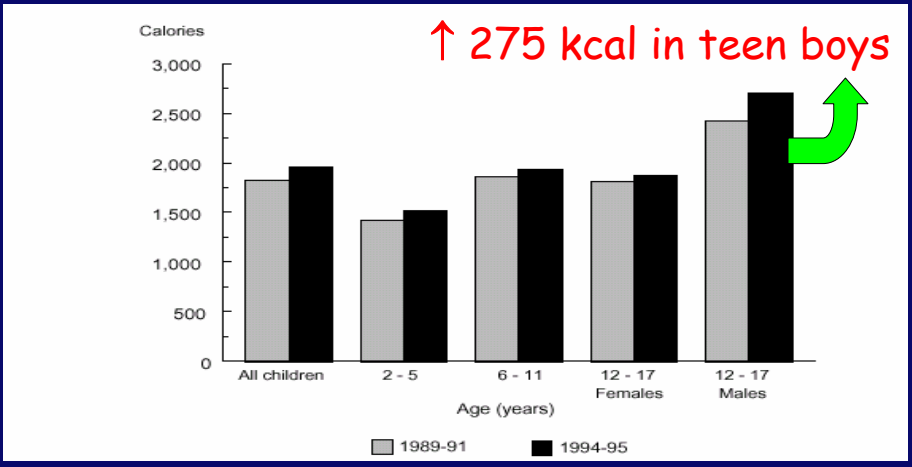

The trouble with fructose
Robert H. Lustig, M.D.
Division of Endocrinology
Department of Pediatrics
University of California, San Francisco
National Institute of Environmental Health Sciences (NIEHS), January 23, 2007


The First Law of Thermodynamics
Weight Gain
Calories Out
Calories In

What happened to willpower? I love fat people. Every fat person says it's not their fault, that they have gland trouble. You know which gland? The saliva gland. They can't push away from the table.

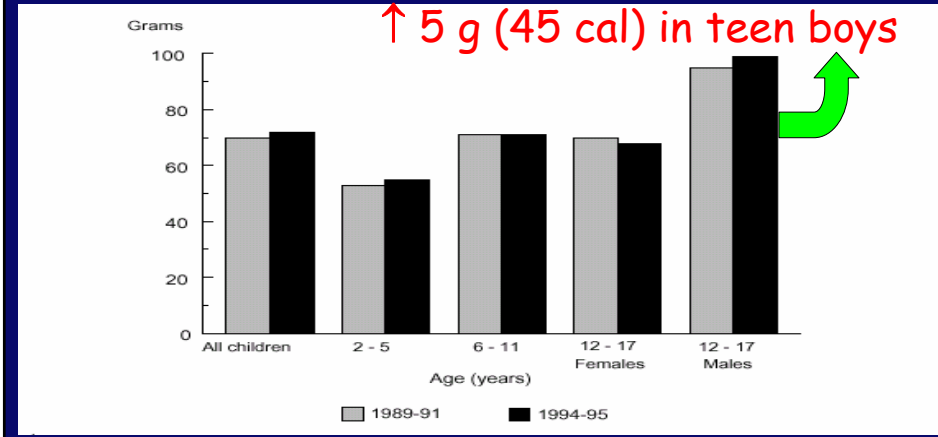
Jesse Ventura (I), Former Governor of Minnesota. *Playboy*, November 1999;46:55.

Total Caloric Intake



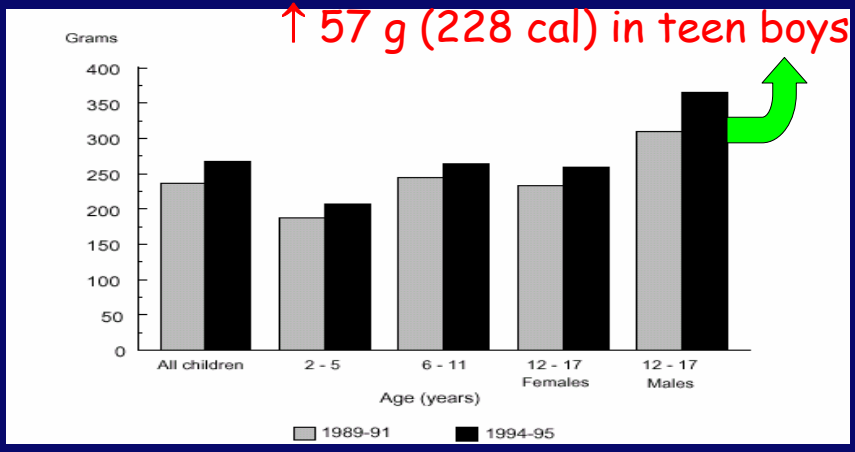
Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95
http://www.usda.gov/cnpp/FENR%20V11N3/fenrv11n3p44.PDF

Fat Intake: Grams



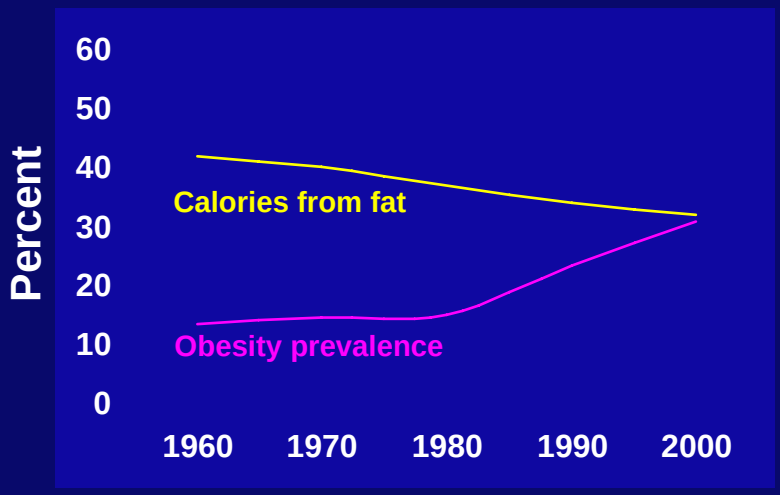
Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Carbohydrate Intake: Grams

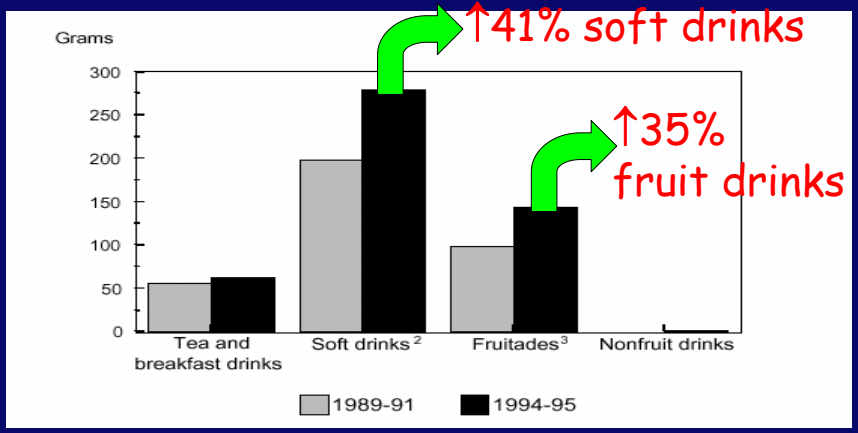


Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Prevalence of Obesity Compared to Percent Calories from Fat Among US Adults

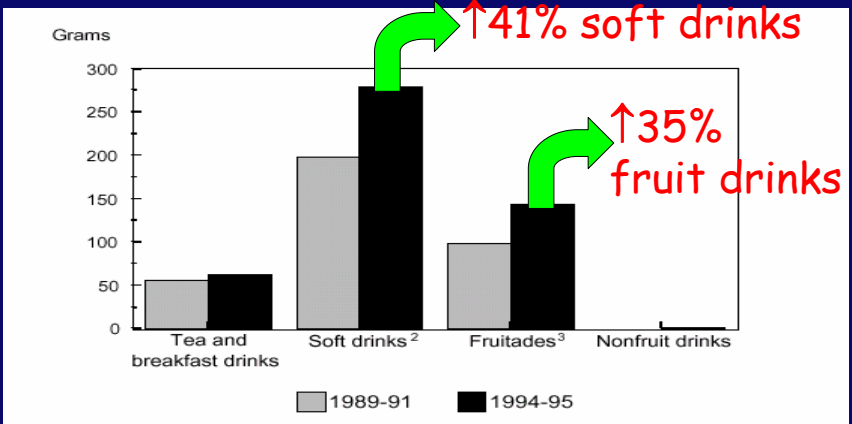


Beverage Intake



Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

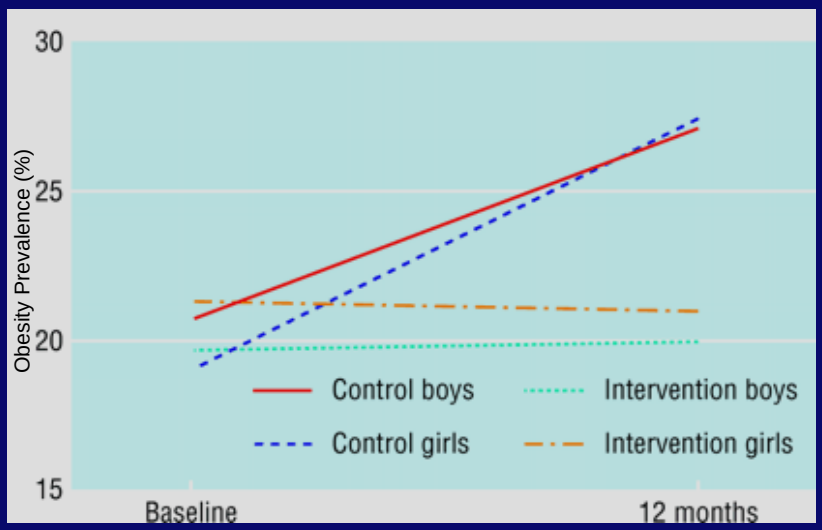
Beverage Intake



Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

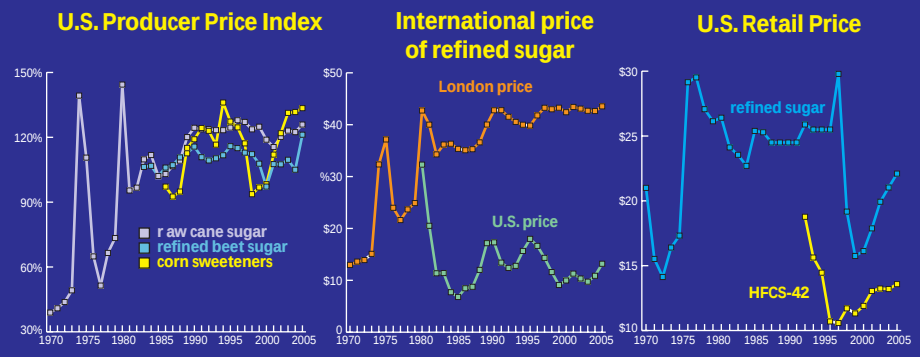
One can of soda/day = 150 cal x 365 d/yr ÷ 3500 cal/lb = 15.6 lbs/yr!

Curtailing soft drinks limits childhood obesity

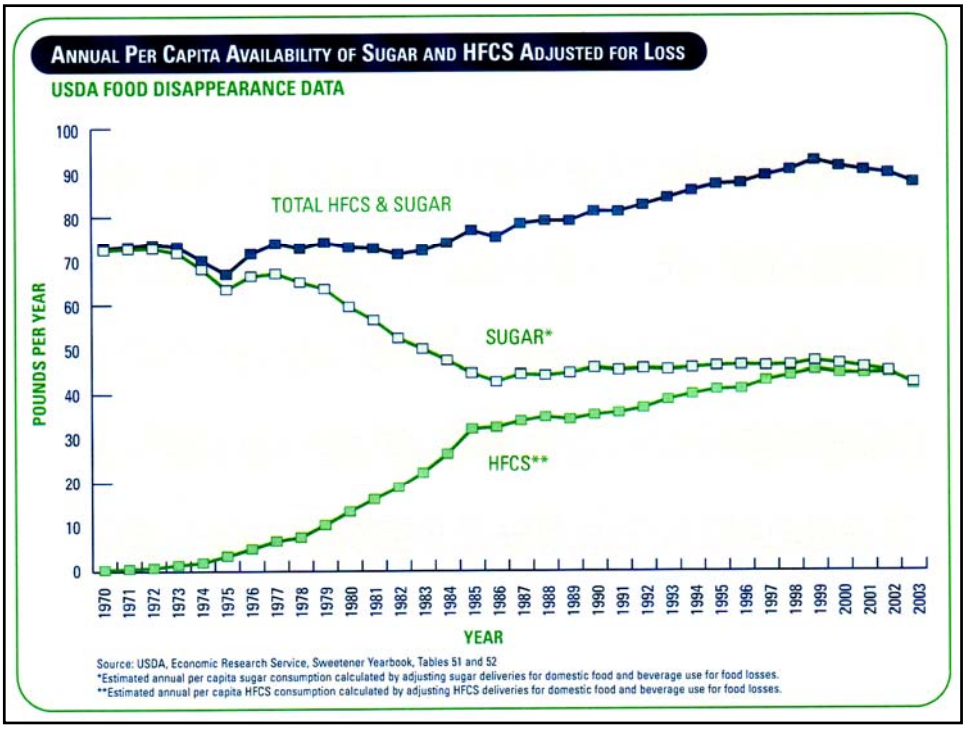


James et al. BMJ 328:1237, 2004

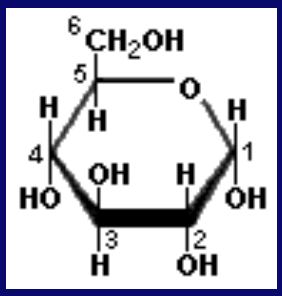
Influence of corn sweeteners on the price of sugar



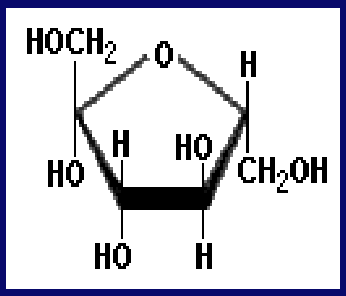
U.S. Department of Agriculture



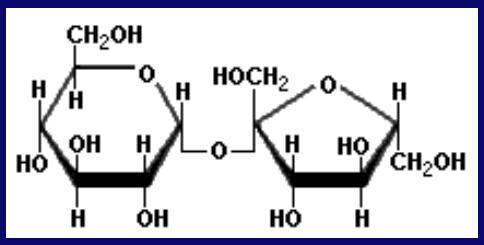
High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose



Glucose

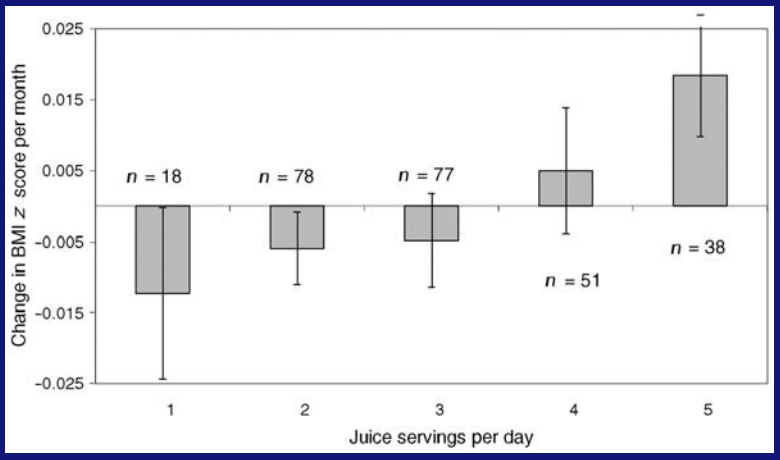


Fructose



Sucrose

Juice is sucrose: Change in BMI z-score in lower socioeconomic status children versus number of fruit juice servings per day



Faith MS et al. Pediatrics 118:2066, 2006

Fructose is not glucose

- Fructose is 7 times more likely than glucose to form Advanced Glycation End-Products (AGE's)
- Fructose does not suppress ghrelin
- Acute fructose does not stimulate insulin (or leptin)
- Hepatic fructose metabolism is different
- Chronic fructose exposure promotes the Metabolic Syndrome

Elliot et al. Am J Clin Nutr, 2002
Bray et al. Am J Clin Nutr, 2004
Teff et al. J Clin Endocrinol Metab, 2004
Gaby, Alt Med Rev, 2005
Le and Tappy, Curr Opin Clin Nutr Metab Care, 2006
Wei et al. J Nutr Biochem, 2006

Ethanol is a carbohydrate

Ethanol is a carbohydrate

CH_3-CH_2-OH

Ethanol is a carbohydrate

CH_3-CH_2-OH

But ethanol is also a toxin

Acute ethanol exposure

- CNS depression
- Vasodilatation, decreased BP
- Hypothermia
- Tachycardia
- Myocardial depression
- Variable pupillary responses
- Respiratory depression
- Diuresis
- Hypoglycemia
- Loss of fine motor control

Acute fructose exposure

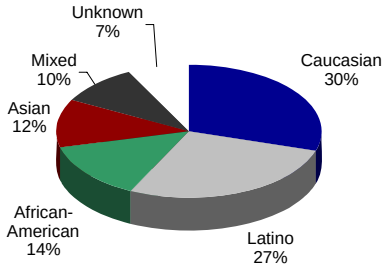
UCSF Weight Assessment for Teen and Child Health (WATCH) Clinic

294 patients 2003-2006

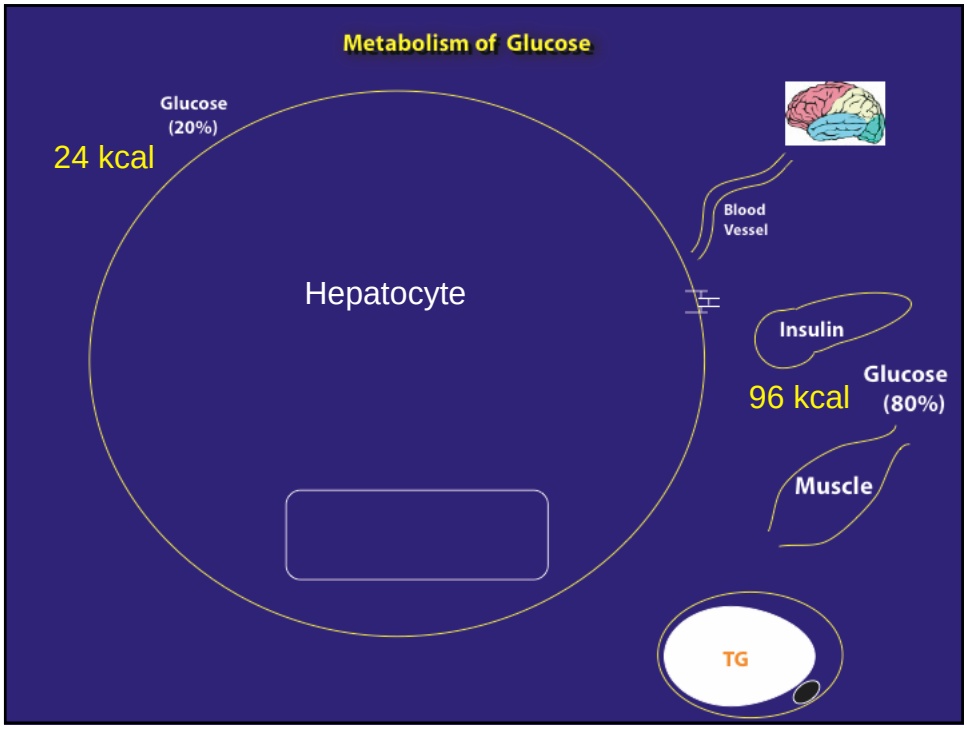
- Biochemistry

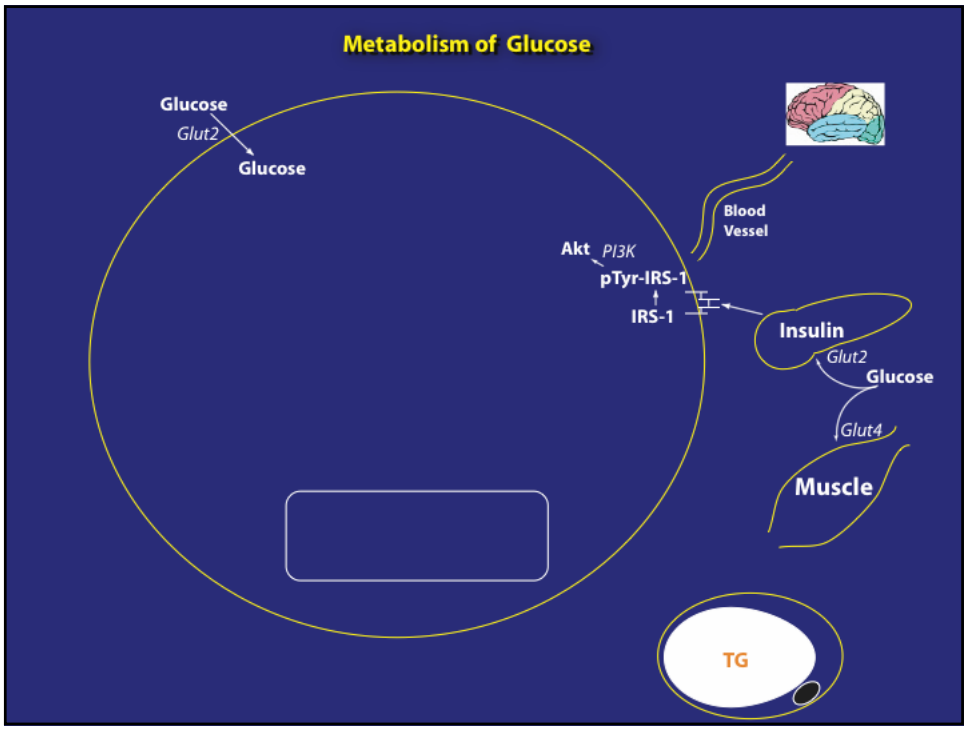
	Median	Min	Max	Normal
BMI	33.2	20.0	92.4	<25
BMI z-score	2.5	1.3	4.4	0
FBG	87	58	119	<100
Insulin	20.7	2	117.5	5-20
HOMA-IR	4.3	0.34	28.1	<4
Maternal BMI	28.9	17.7	58.6	<25
Paternal BMI	28.9	16.7	48.8	<25

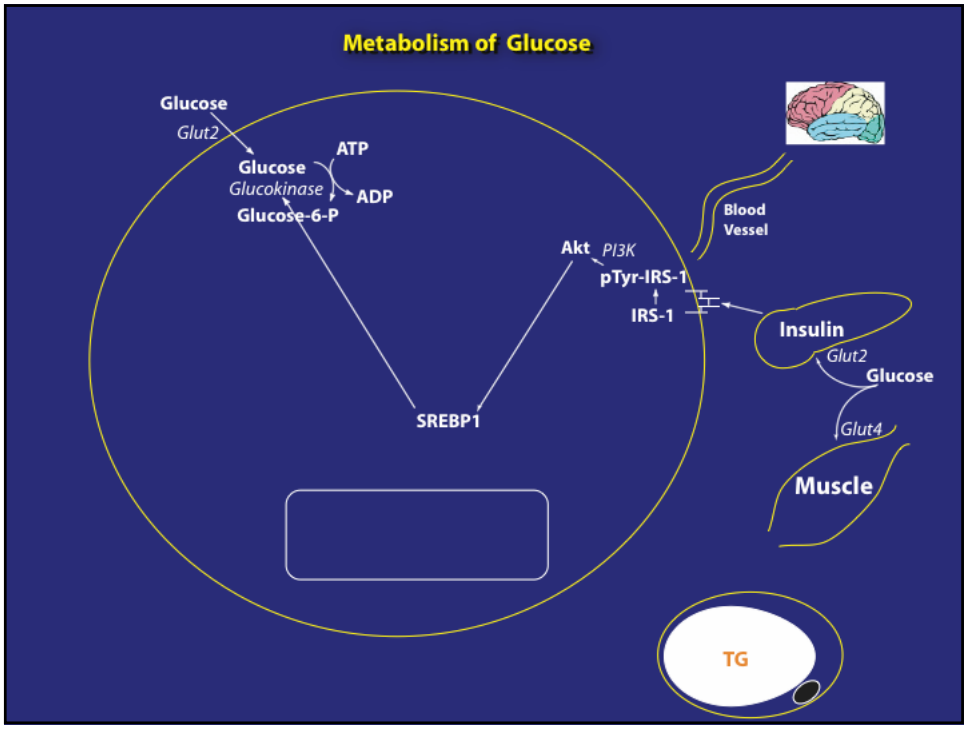
- Race/Ethnicity

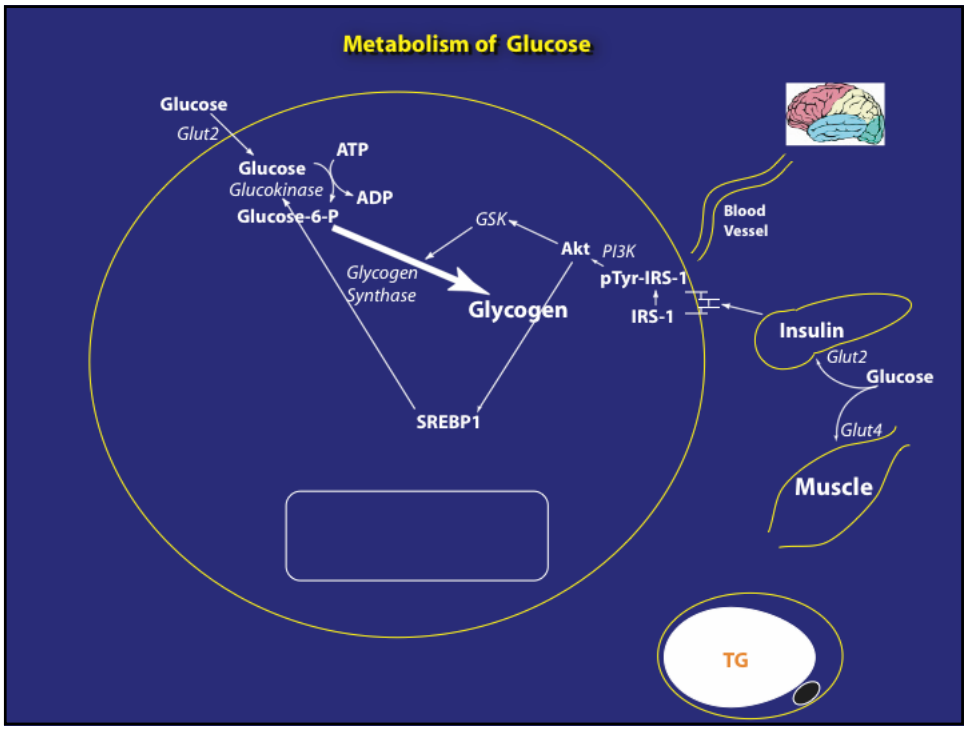


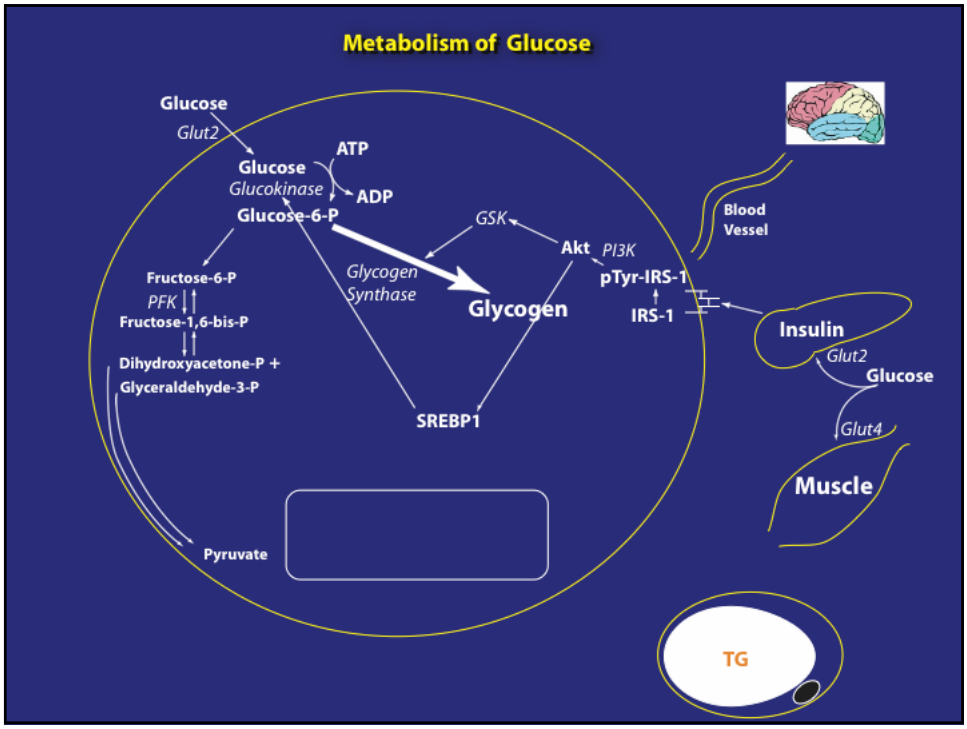
Mietus-Snyder et al. (submitted)

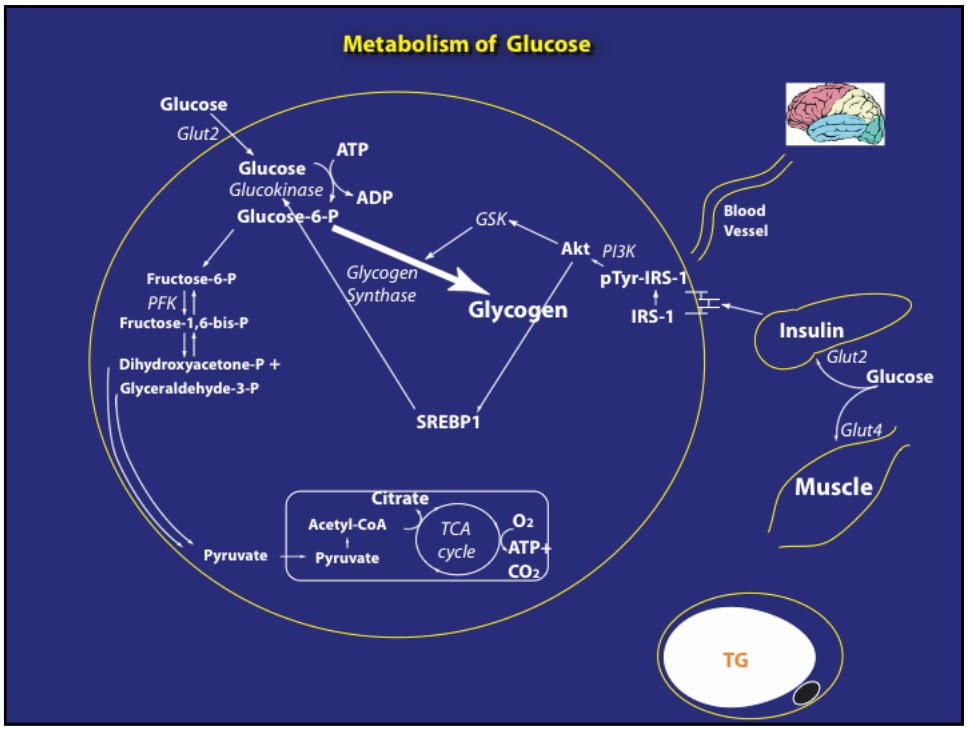

Metabolism of Glucose
Glucose
(20%)
24 kcal
Hepatocyte
Blood
Vessel
Insulin
96 kcal
Glucose
(80%)
Muscle
TG

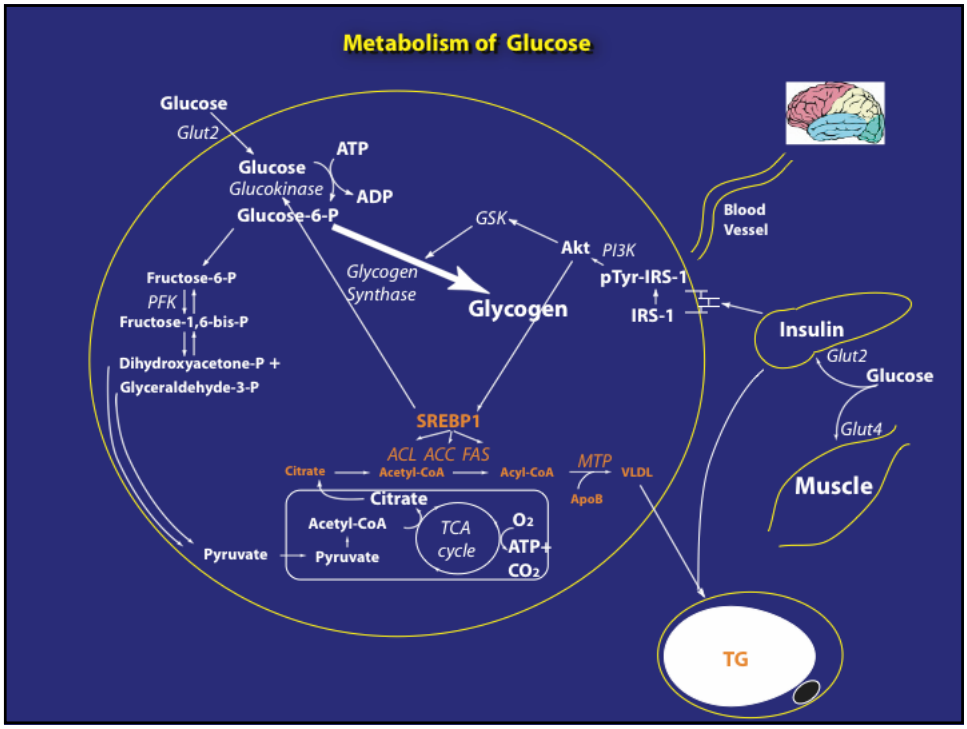

Metabolism of Glucose
Glucose
Glut2
Glucose
Blood
Vessel
Akt
PI3K
pTyr-IRS-1
IRS-1
Insulin
Glut2
Glucose
Glut4
Muscle
TG

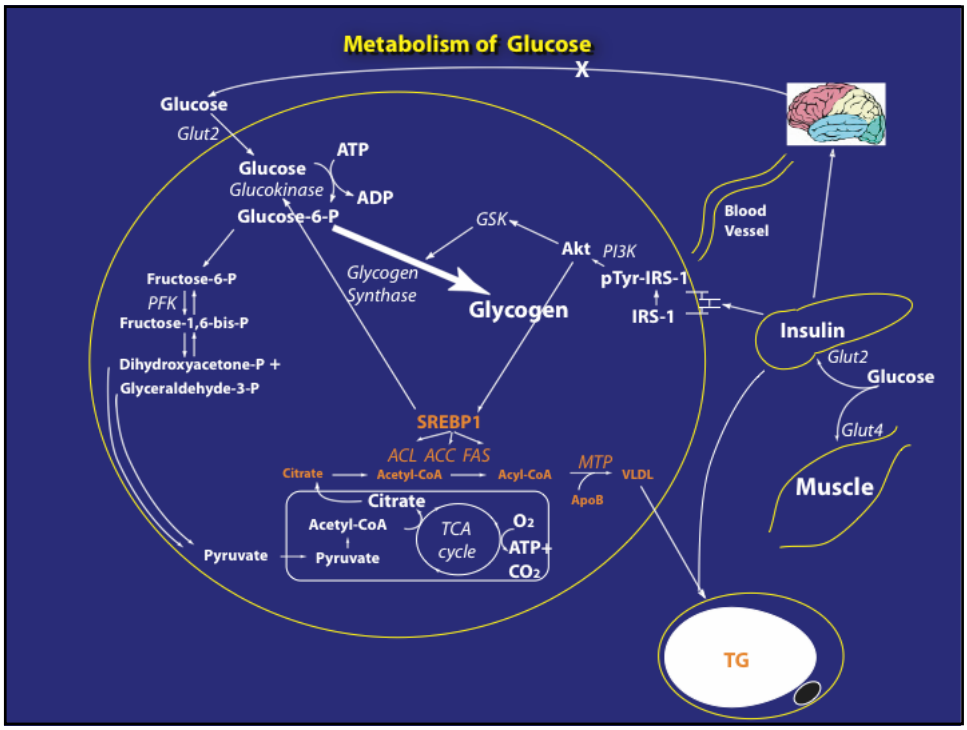

Metabolism of Glucose
Glucose
Glut2
ATP
Glucose
Glucokinase
ADP
Glucose-6-P
Akt
PI3K
pTyr-IRS-1
IRS-1
SREBP1
Blood
Vessel
Insulin
Glut2
Glucose
Glut4
Muscle
TG

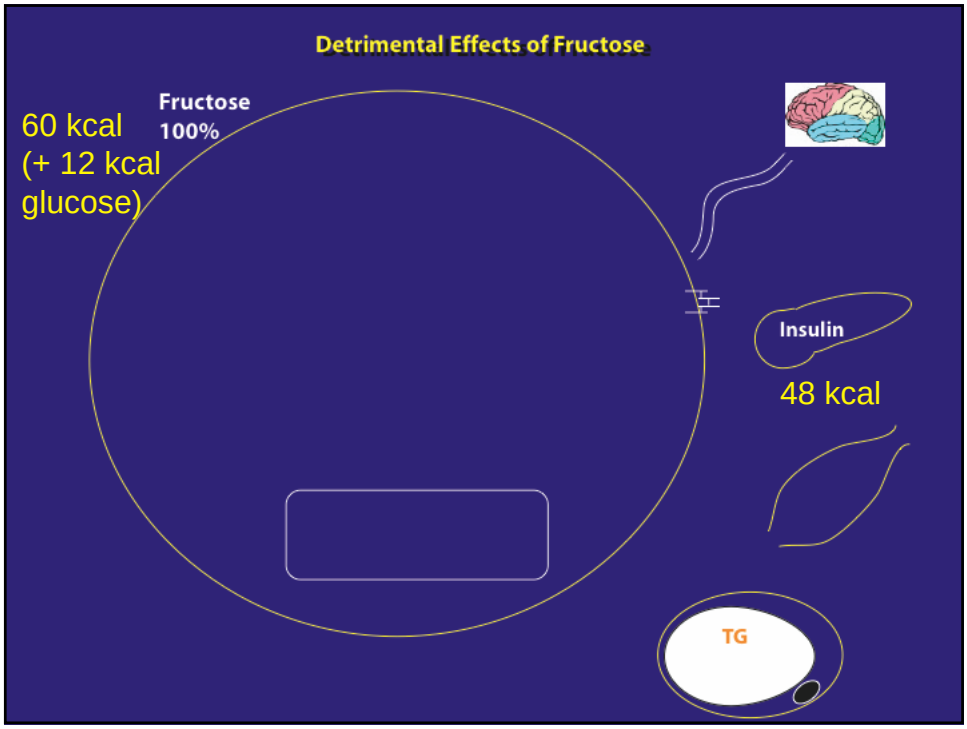

Metabolism of Glucose
Glucose
Glut2
ATP
Glucose
Glucokinase
ADP
Glucose-6-P
GSK
Akt
PI3K
Glycogen
Synthase
Glycogen
pTyr-IRS-1
IRS-1
SREBP1
Blood
Vessel
Insulin
Glut2
Glucose
Glut4
Muscle
TG

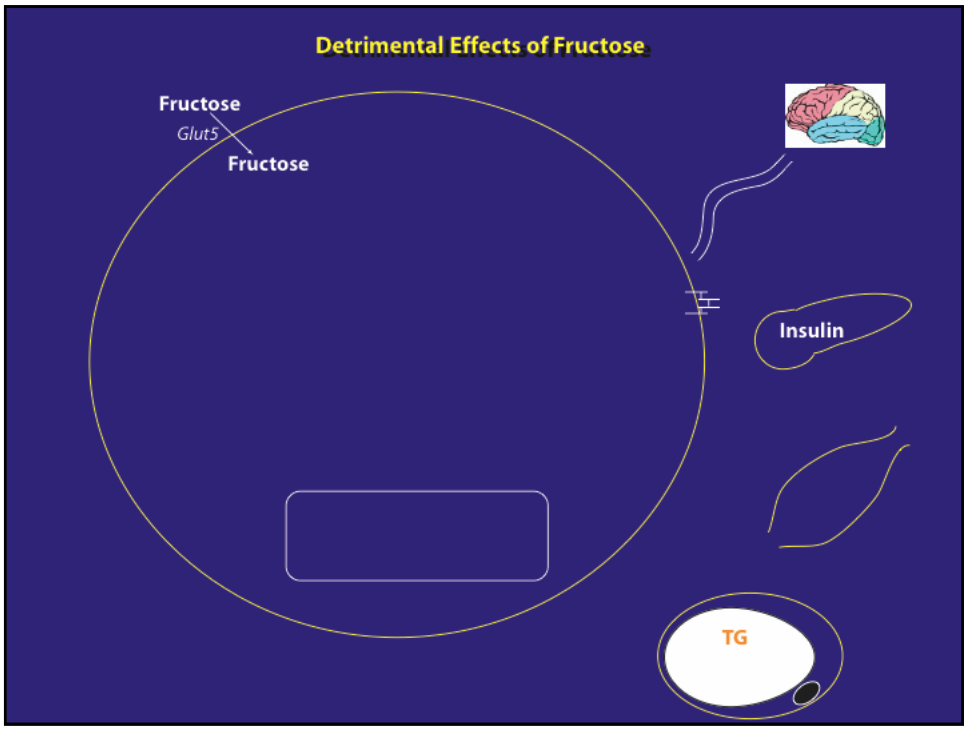

Metabolism of Glucose
Glucose
Glut2
ATP
Glucose
Glucokinase
ADP
Glucose-6-P
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Blood
Vessel
Fructose-6-P
PFK
Fructose-1,6-bis-P
Glycogen
Synthase
Glycogen
Dihydroxyacetone-P +
Glyceraldehyde-3-P
SREBP1
Insulin
Glut2
Glucose
Glut4
Muscle
Pyruvate
TG

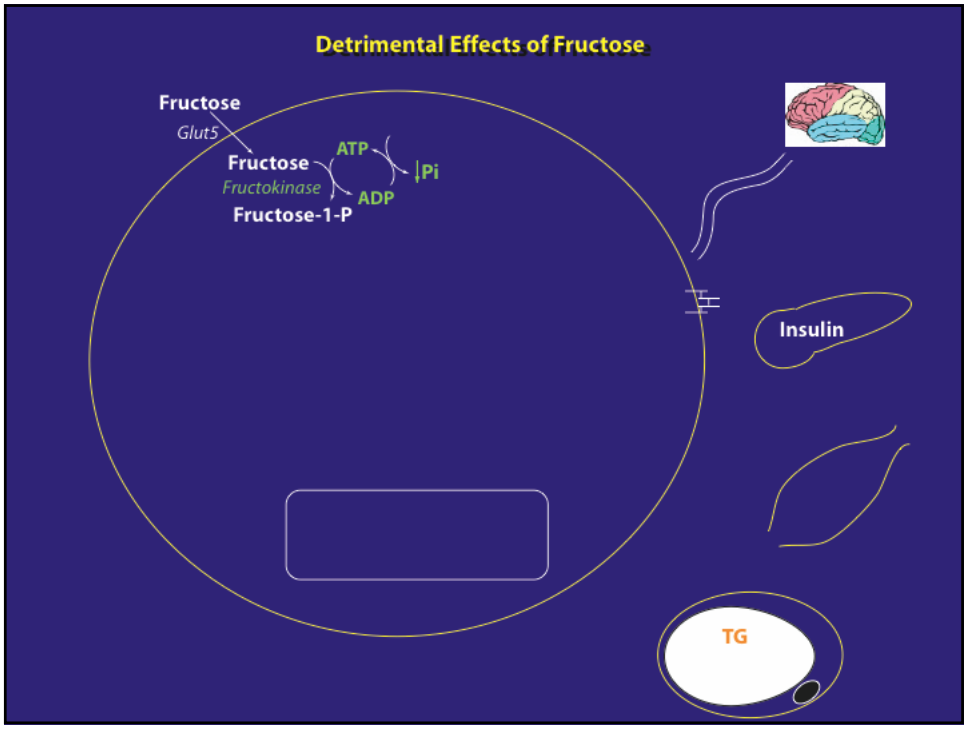

Metabolism of Glucose
Glucose
Glut2
ATP
Glucose
Glucokinase
ADP
Glucose-6-P
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Blood
Vessel
Fructose-6-P
PFK
Fructose-1,6-bis-P
Glycogen
Synthase
Glycogen
Dihydroxyacetone-P +
Glyceraldehyde-3-P
SREBP1
Insulin
Glut2
Glucose
Glut4
Muscle
Citrate
Acetyl-CoA
TCA
cycle
O2
ATP+
CO2
Pyruvate
Pyruvate
TG

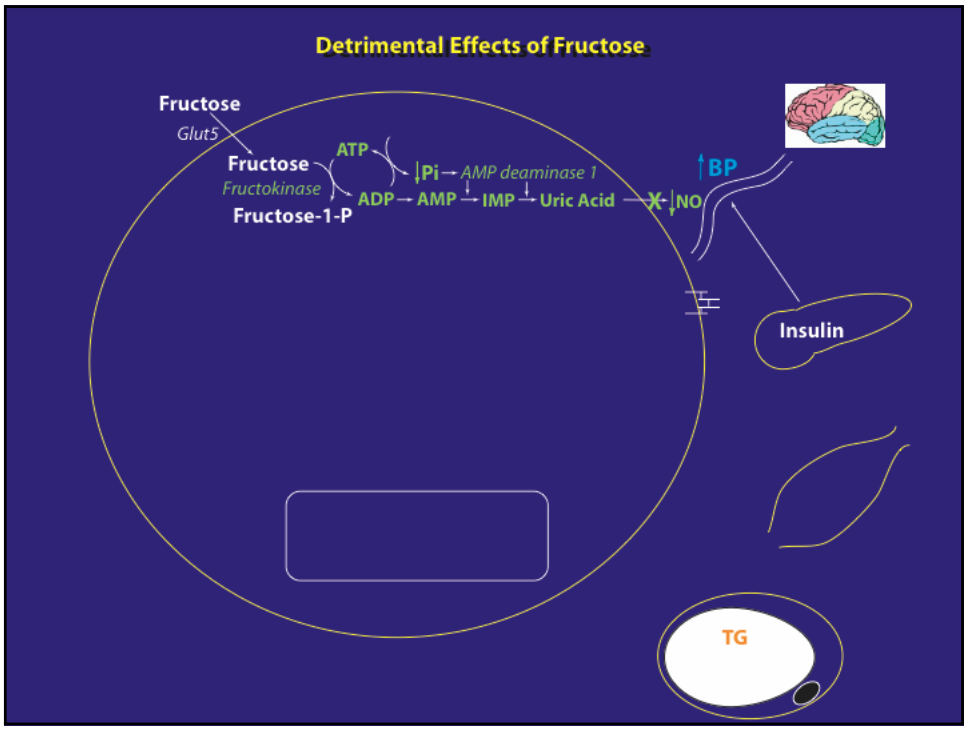

Metabolism of Glucose
Glucose
Glut2
Glucose
Glucokinase
ATP
ADP
Glucose-6-P
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Blood Vessel
Fructose-6-P
PFK
Fructose-1,6-bis-P
Dihydroxyacetone-P +
Glyceraldehyde-3-P
Glycogen Synthase
Glycogen
Insulin
Glut2
Glucose
Glut4
Muscle
SREBP1
ACL ACC FAS
Citrate
Acetyl-CoA
Acyl-CoA
MTP
VLDL
ApoB
Citrate
Acetyl-CoA
TCA cycle
O2
ATP+
CO2
Pyruvate
Pyruvate
TG


Metabolism of Glucose
X
Glucose
Glut2
Glucose
Glucokinase
ATP
ADP
Glucose-6-P
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Blood Vessel
Fructose-6-P
PFK
Fructose-1,6-bis-P
Dihydroxyacetone-P +
Glyceraldehyde-3-P
Glycogen Synthase
Glycogen
Insulin
Glut2
Glucose
Glut4
Muscle
SREBP1
ACL ACC FAS
Citrate
Acetyl-CoA
Acyl-CoA
MTP
VLDL
ApoB
Citrate
Acetyl-CoA
TCA cycle
O2
ATP+
CO2
Pyruvate
Pyruvate
TG

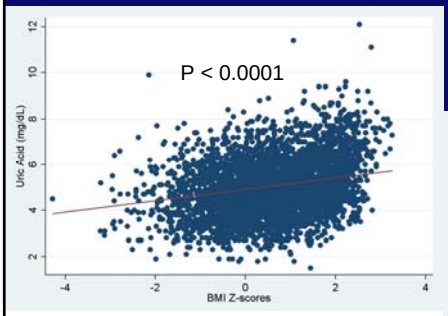

Detrimental Effects of Fructose
Fructose
100%
60 kcal
(+ 12 kcal
glucose)
Insulin
48 kcal
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Insulin
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
Pi
ADP
Insulin
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
Pi
AMP deaminase 1
ADP
AMP
IMP
Uric Acid
NO
BP
Insulin
TG

Relations between uric acid, hypertension, obesity, and fructose in NHANES IV children



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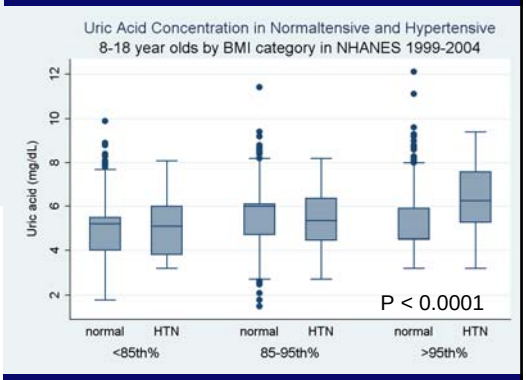
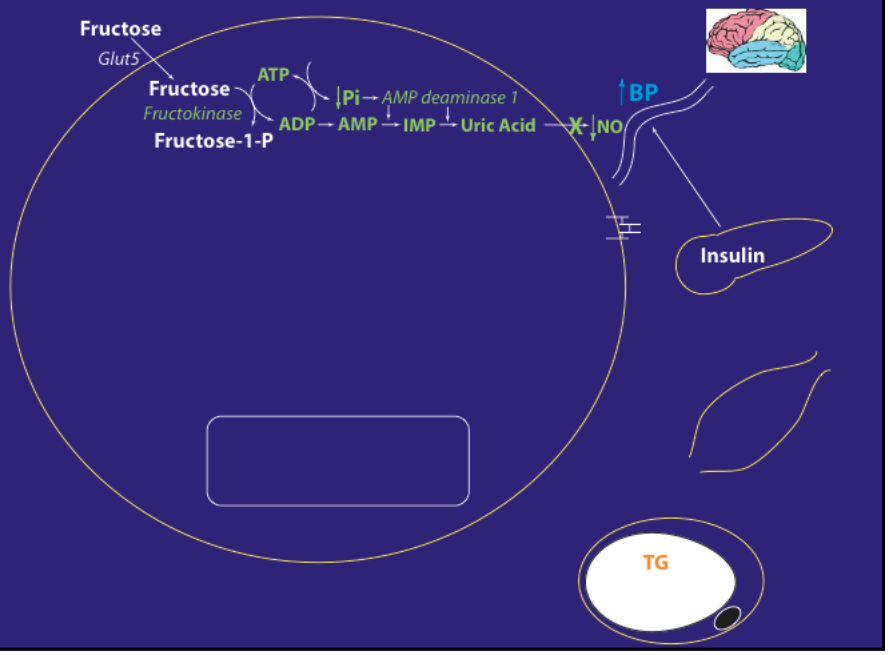
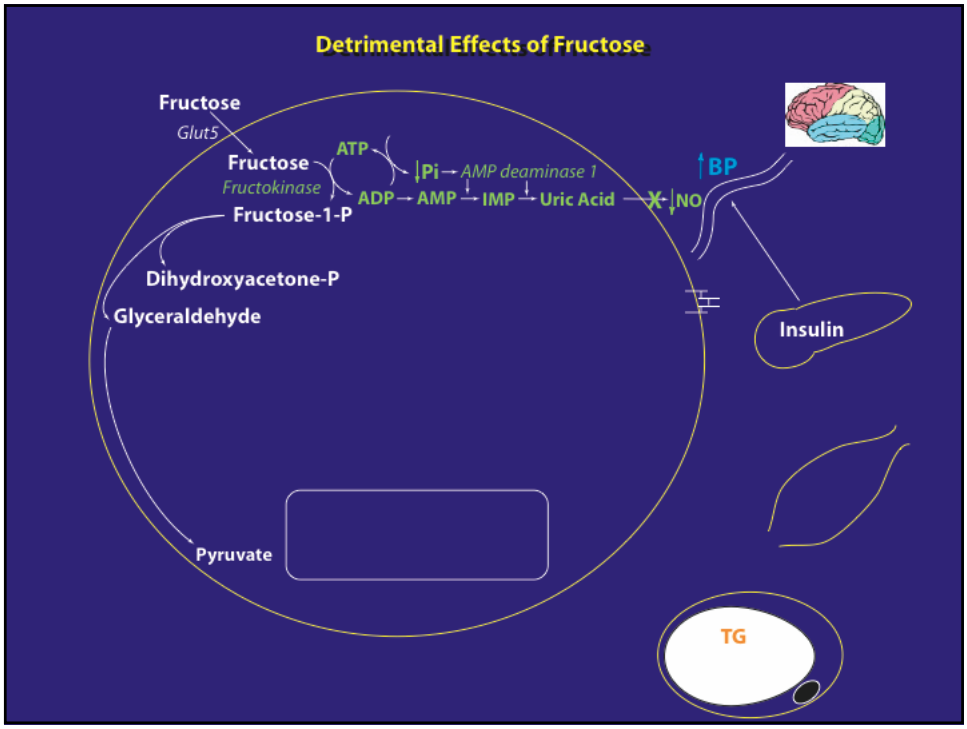
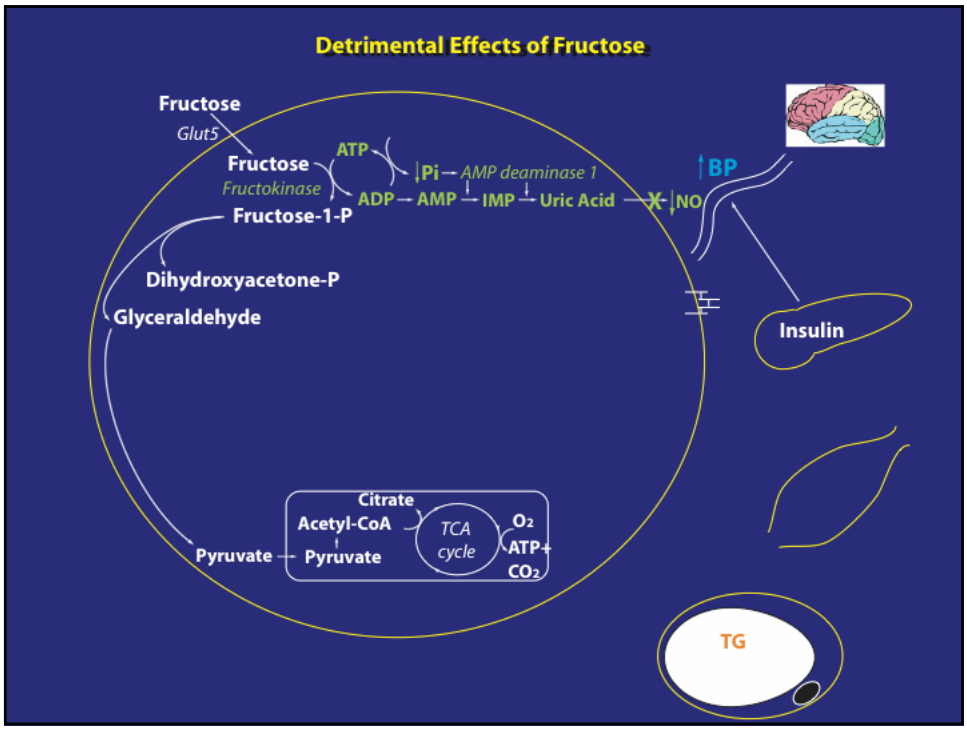


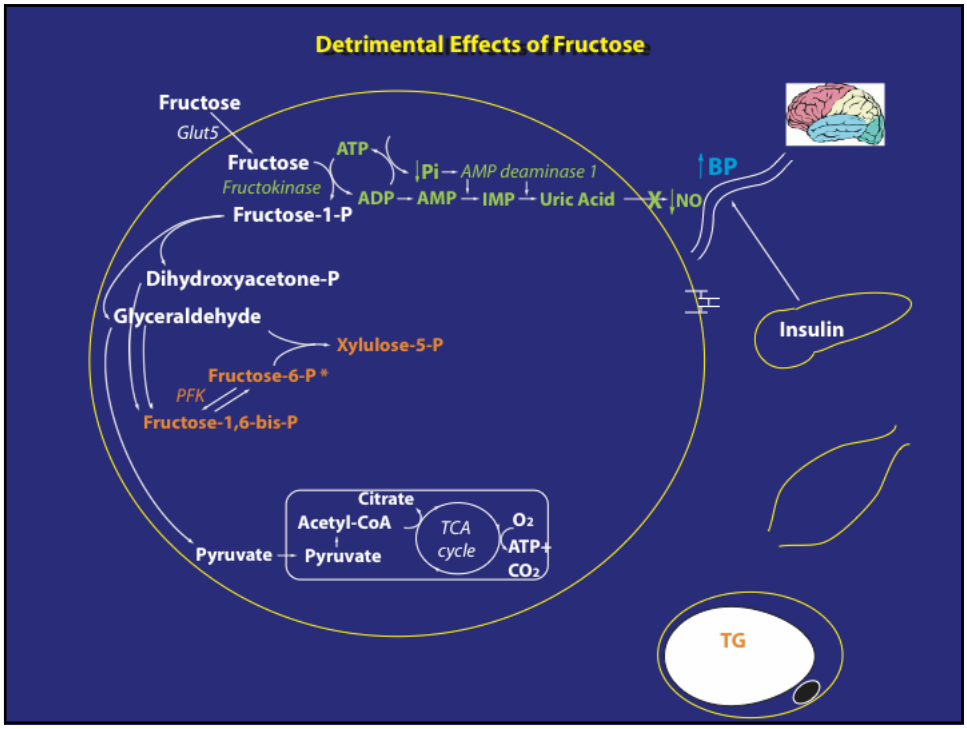
S Nguyen et al. (in preparation)

Detrimental Effects of Fructose

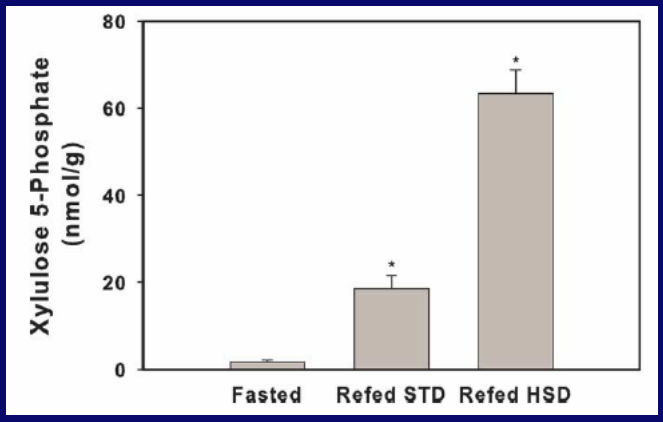



Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Fructose-1-P
Dihydroxyacetone-P
Glyceraldehyde
Insulin
Pyruvate
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Fructose-1-P
Dihydroxyacetone-P
Glyceraldehyde
Insulin
Citrate
Acetyl-CoA
Pyruvate
TCA cycle
O2
ATP
CO2
Pyruvate
TG

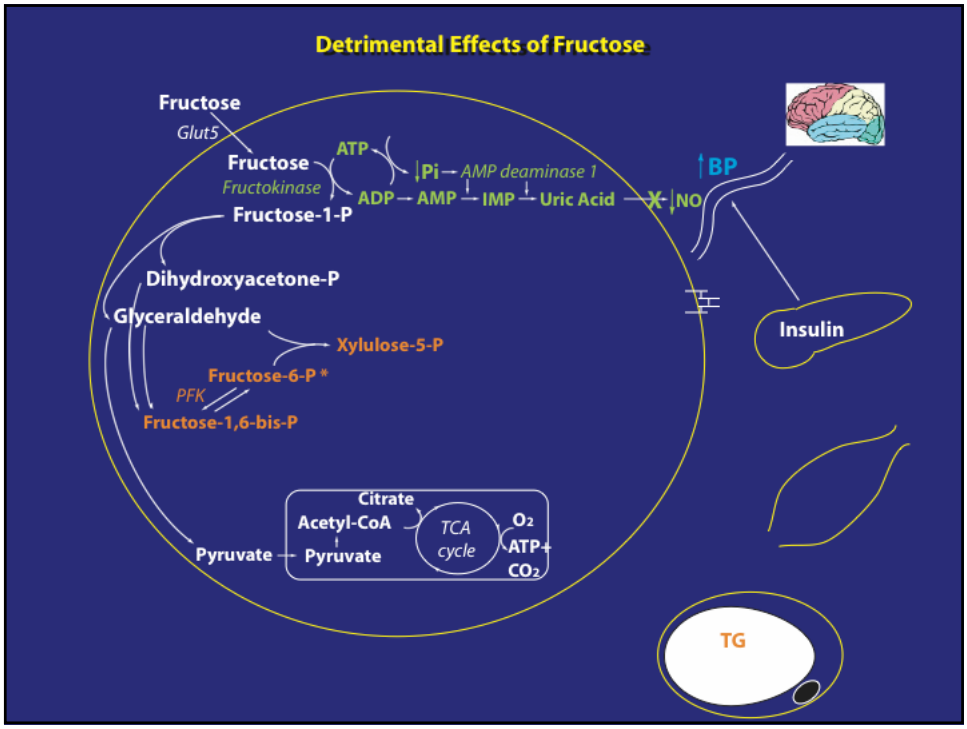


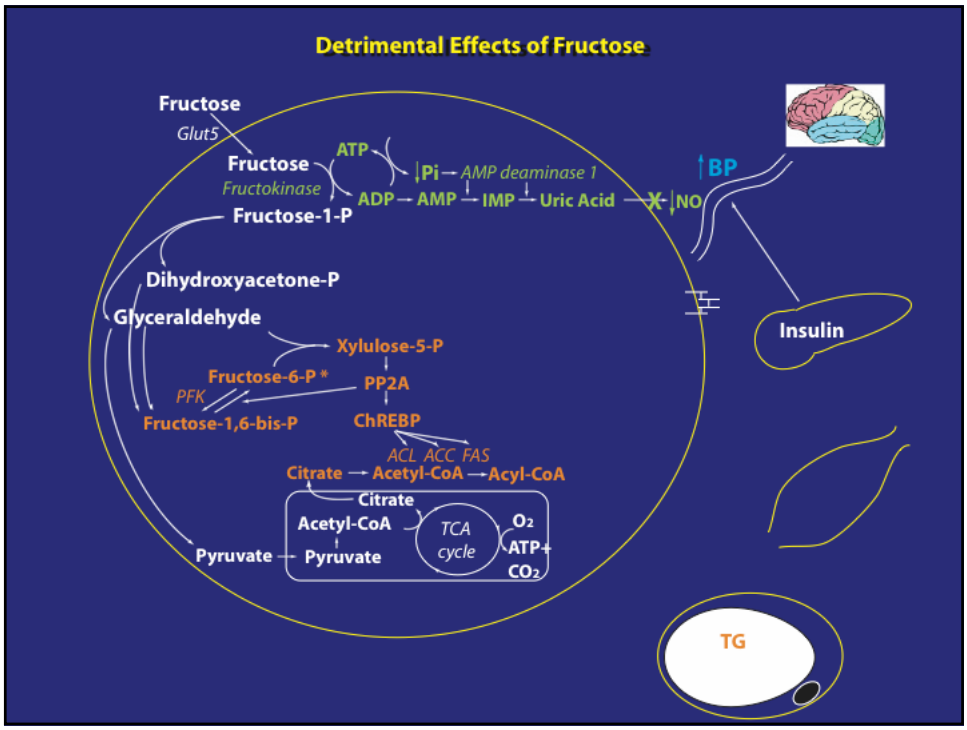
Xylulose-5-phosphate increases after sucrose refeeding in rats

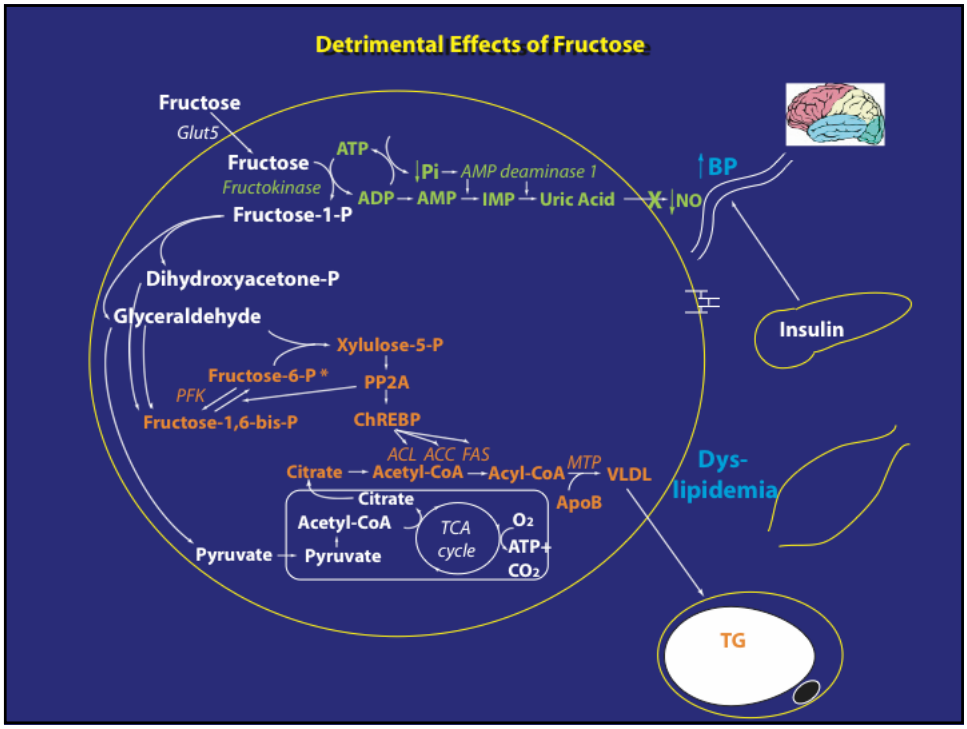


starch sucrose

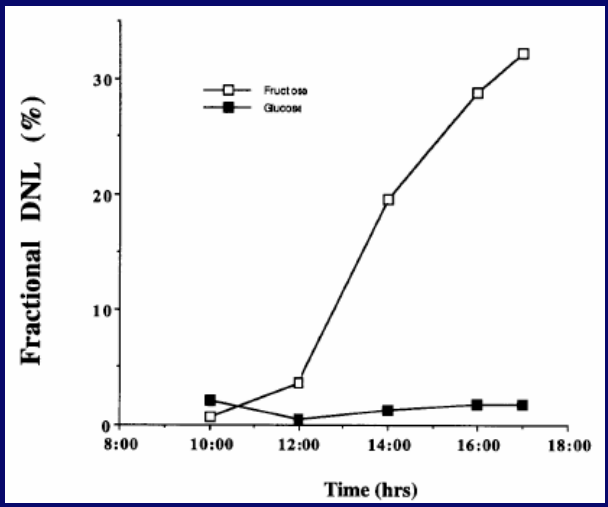
Wei et al. J Nutr Biochem epub, 2006


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Fructose-1-P
Dihydroxyacetone-P
Glyceraldehyde
Xylulose-5-P
Fructose-6-P *
PFK
Fructose-1,6-bis-P
Insulin
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Fructose-1-P
Dihydroxyacetone-P
Glyceraldehyde
Xylulose-5-P
Fructose-6-P *
PP2A
PFK
Fructose-1,6-bis-P
ChREBP
ACL ACC FAS
Citrate
Acetyl-CoA
Acyl-CoA
Insulin
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
TG



Fructose increases de novo lipogenesis in normal adults



Hellerstein et al. Ann Rev Nutr 16:523, 1996

Fructose increases de novo lipogenesis, triglycerides and free fatty acids in normal adults

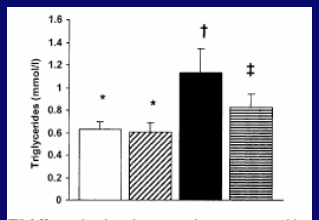


FIG. 3. Mean fasting triglyceride concentration after control condition (□), after 28 days of fish oil supplementation (▨), after 6 days of high-fructose diet (■), and after 28 days of fish oil supplementation plus high-fructose diet (▩) in seven men. Values are means ± SE represented by vertical bars. Values not sharing the same superscripts are significantly different ($P < 0.05$).

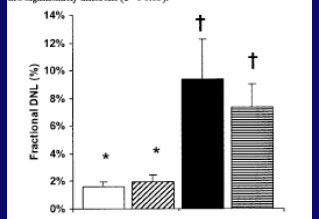


FIG. 4. Mean baseline fractional hepatic DNL after control condition (□), after 28 days of fish oil supplementation (▨), after 6 days of high-fructose diet (■), and after 28 days of fish oil supplementation plus high-fructose diet (▩) in seven men. Values are means ± SE represented by vertical bars. Values not sharing the same superscripts are significantly different ($P < 0.05$).

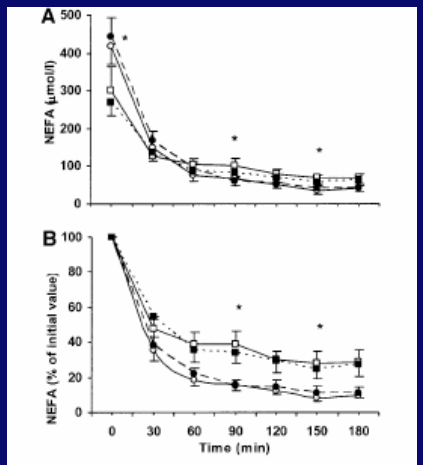
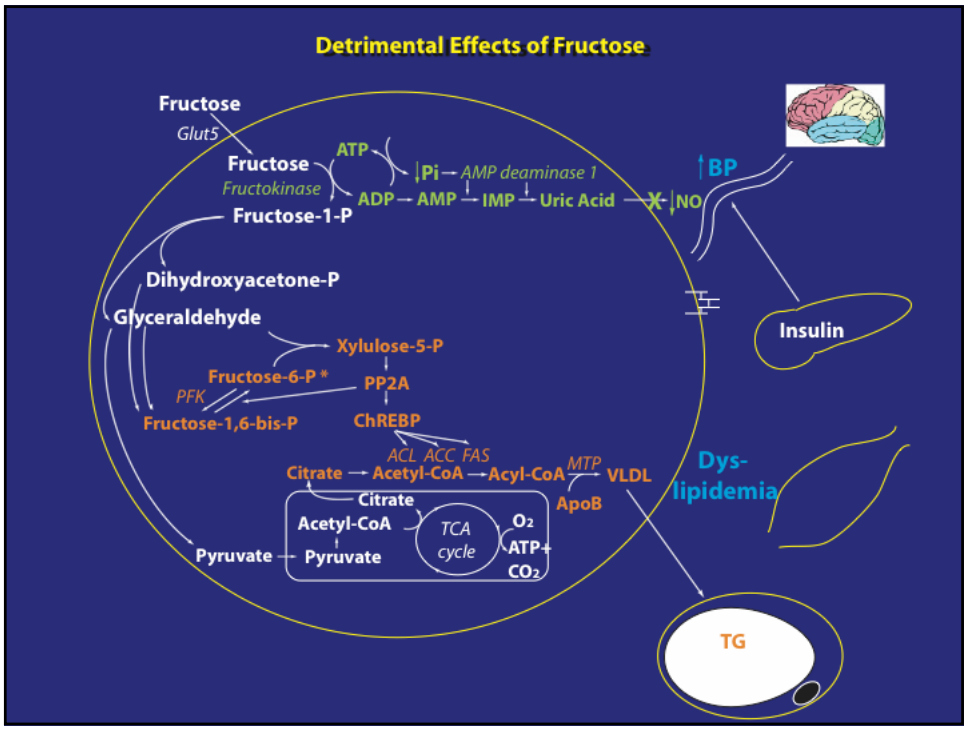
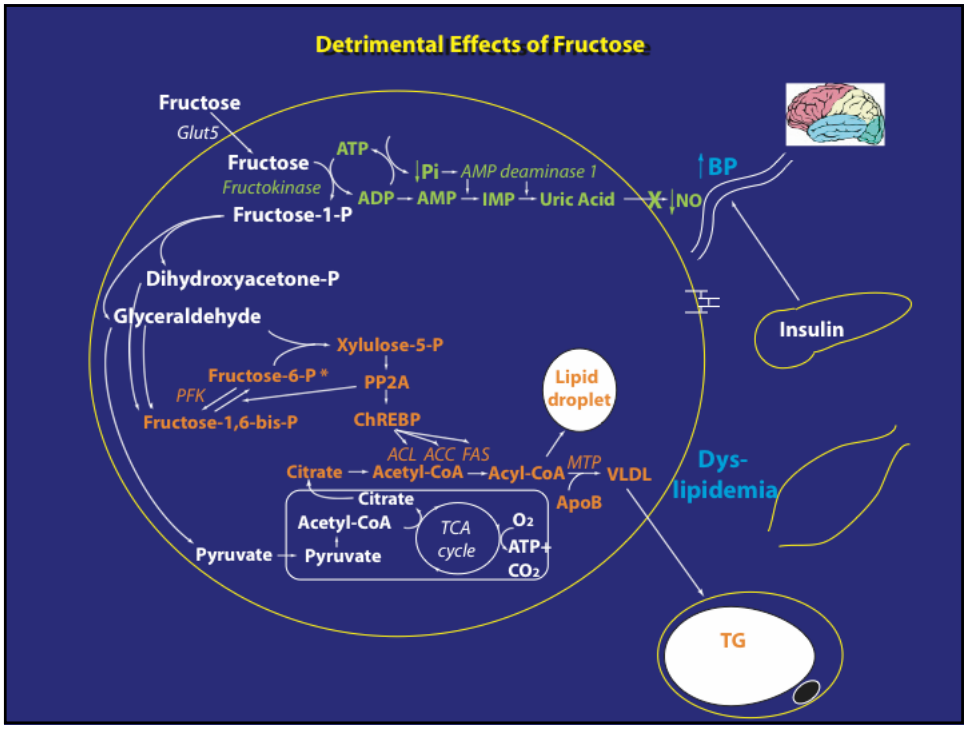


FIG. 7. NEFAs expressed as absolute values (*A*) and in percentage of the baseline value (*B*) during euglycemic-hyperinsulinemic clamping after control condition (○), after 28 days of fish oil supplementation (●), after 6 days of high-fructose diet (□), and after fish oil supplementation plus high-fructose diet (■) in seven men. Values are means ± SE represented by vertical bars. *$P < 0.05$ high-fructose diet versus control.

Faeh and Schwarz, Diabetes 54:1907, 2005





Relation between ALT and liquid calorie consumption

UCSF WATCH Clinic

210 observations

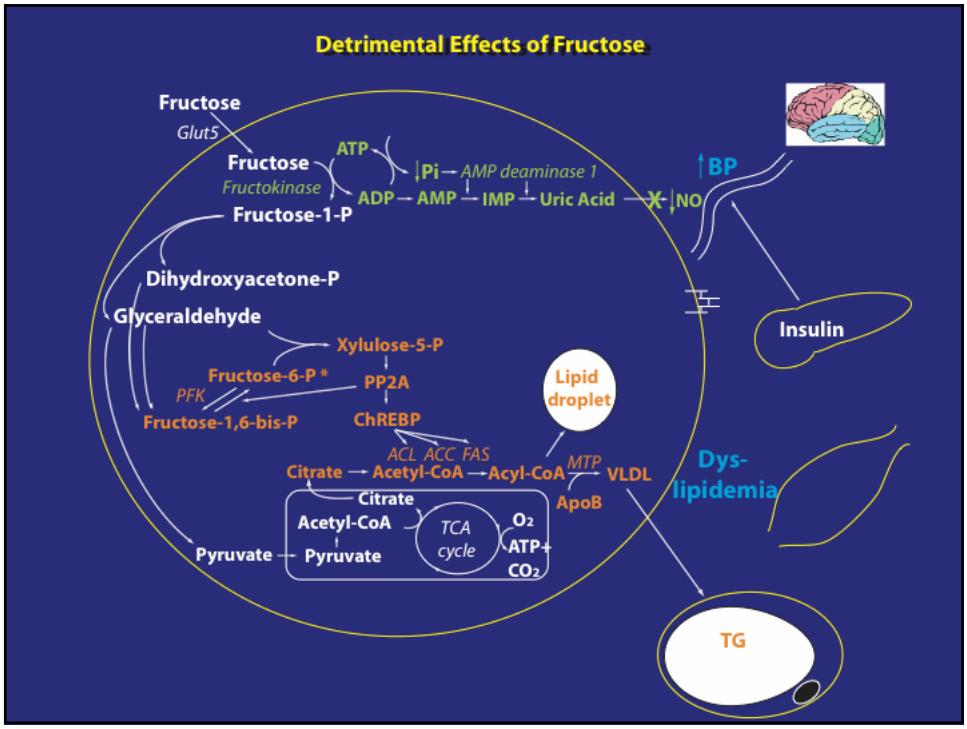
Univariate regression:

- Every 120 kcal/d increases ALT by 1 point (p = 0.013)

Multivariate regression:

- HOMA-IR (insulin resistance) predicts ALT (p = 0.048)
- liquid calories correlates with ALT less well (p = 0.1)

Mietus-Snyder et al. (in preparation)


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Fructose-1-P
Dihydroxyacetone-P
Glyceraldehyde
Xylulose-5-P
Fructose-6-P *
PFK
PP2A
Fructose-1,6-bis-P
ChREBP
ACL ACC FAS
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Acyl-CoA
MTP
VLDL
ApoB
Lipid droplet
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O2
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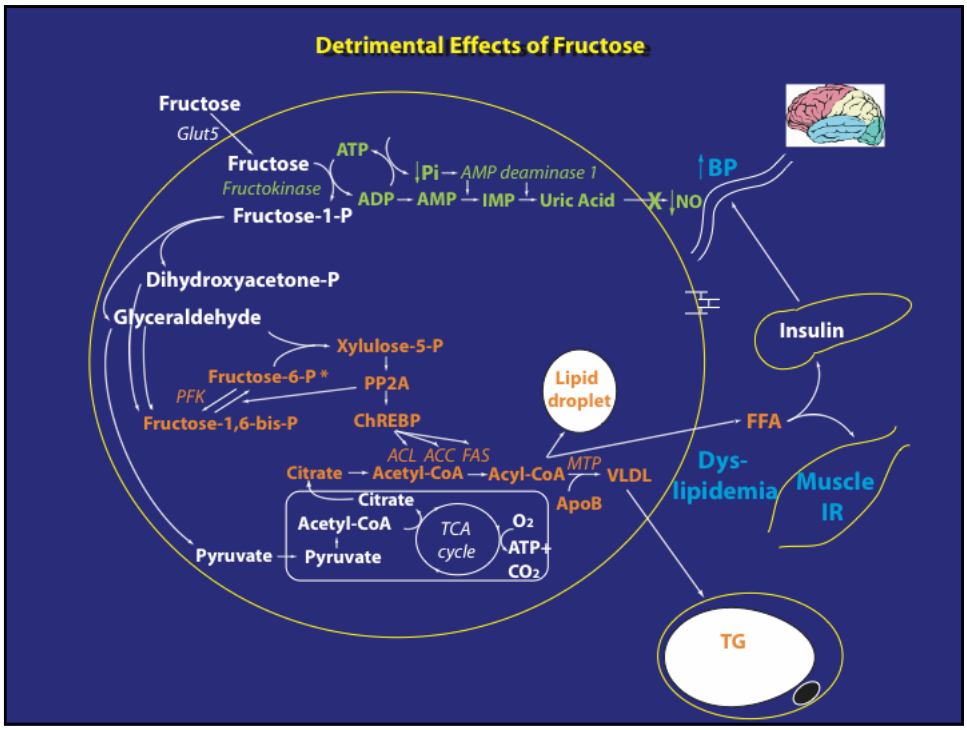
CO2
Pyruvate
Pyruvate
Insulin
Dys-lipidemia
TG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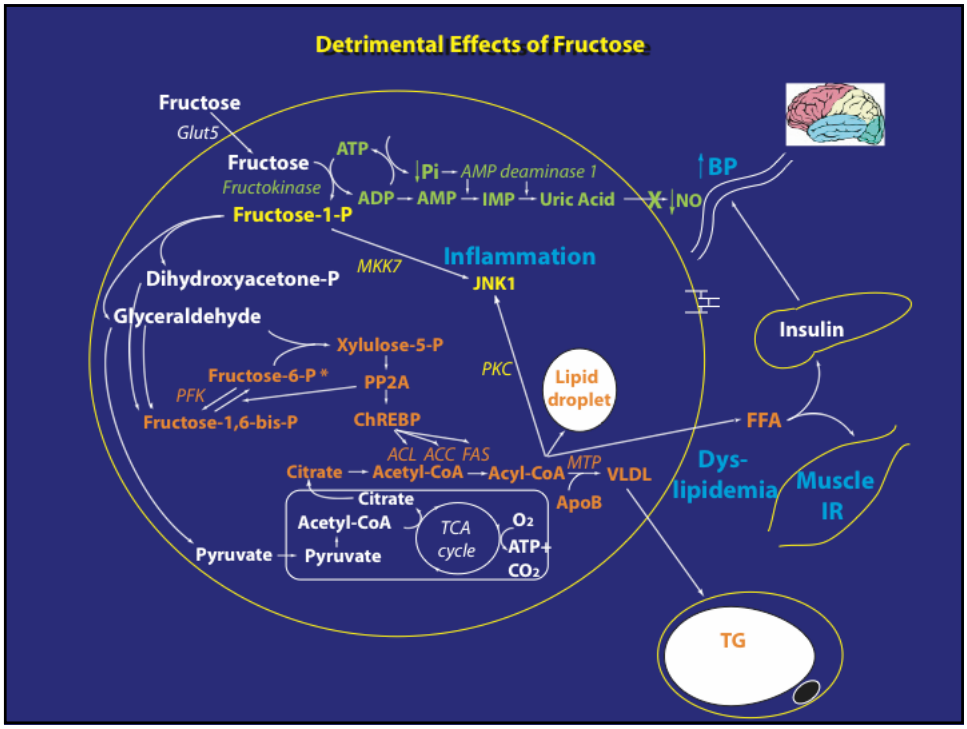
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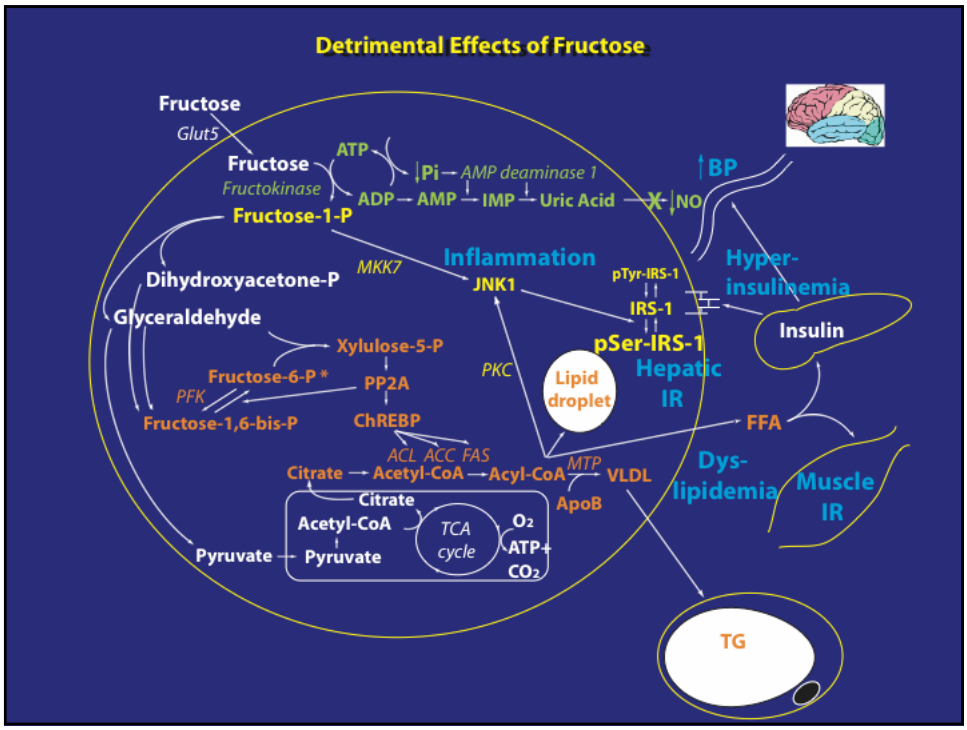
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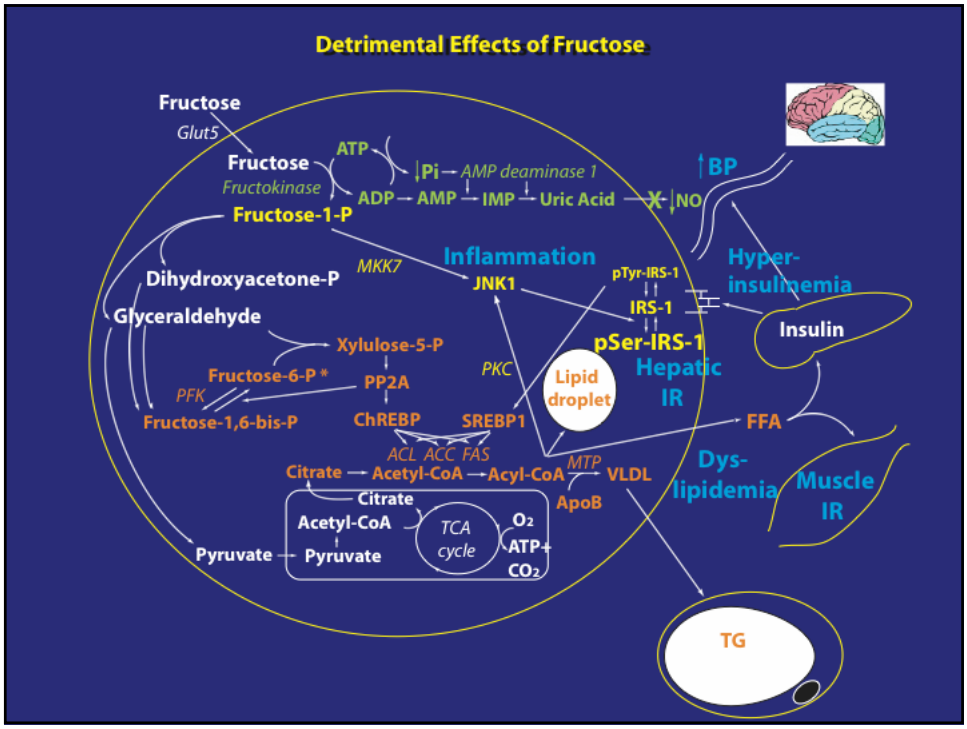
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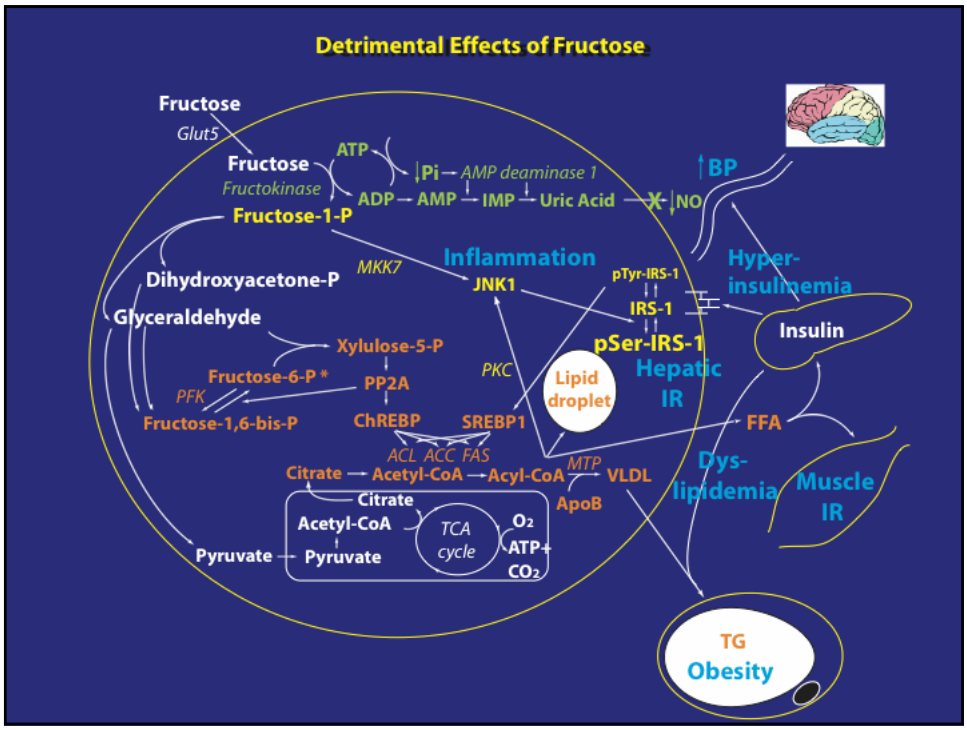
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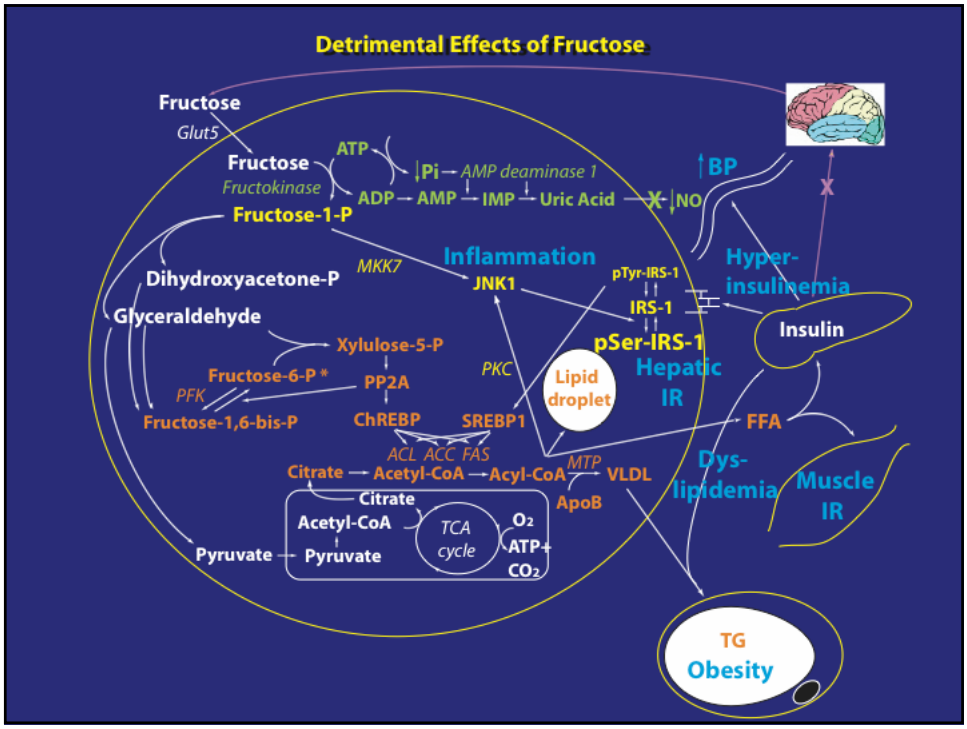
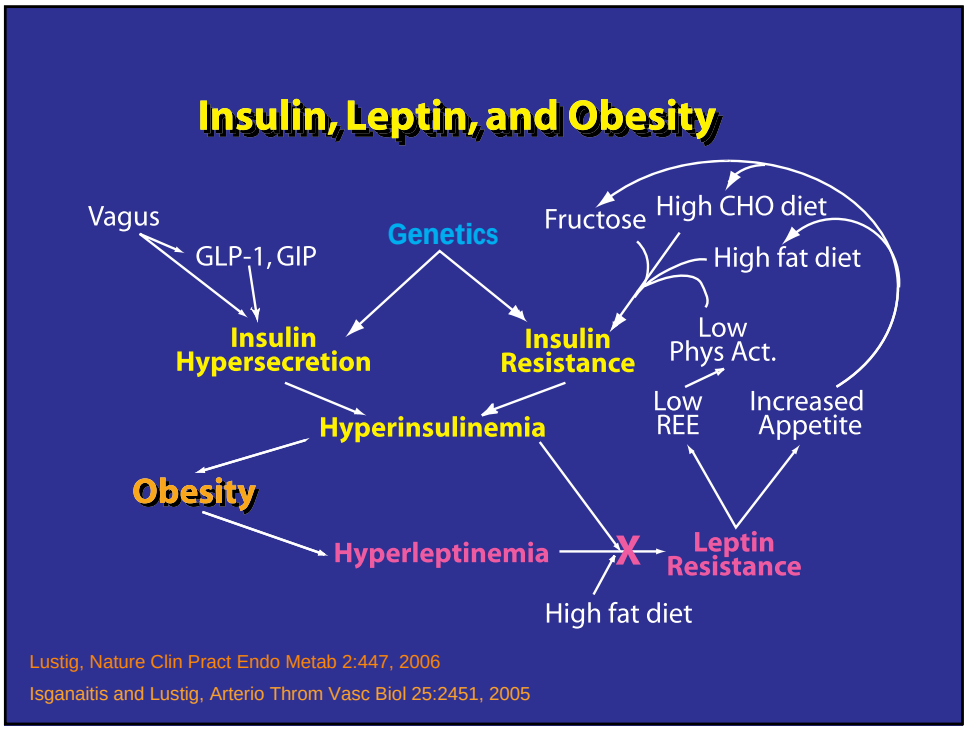
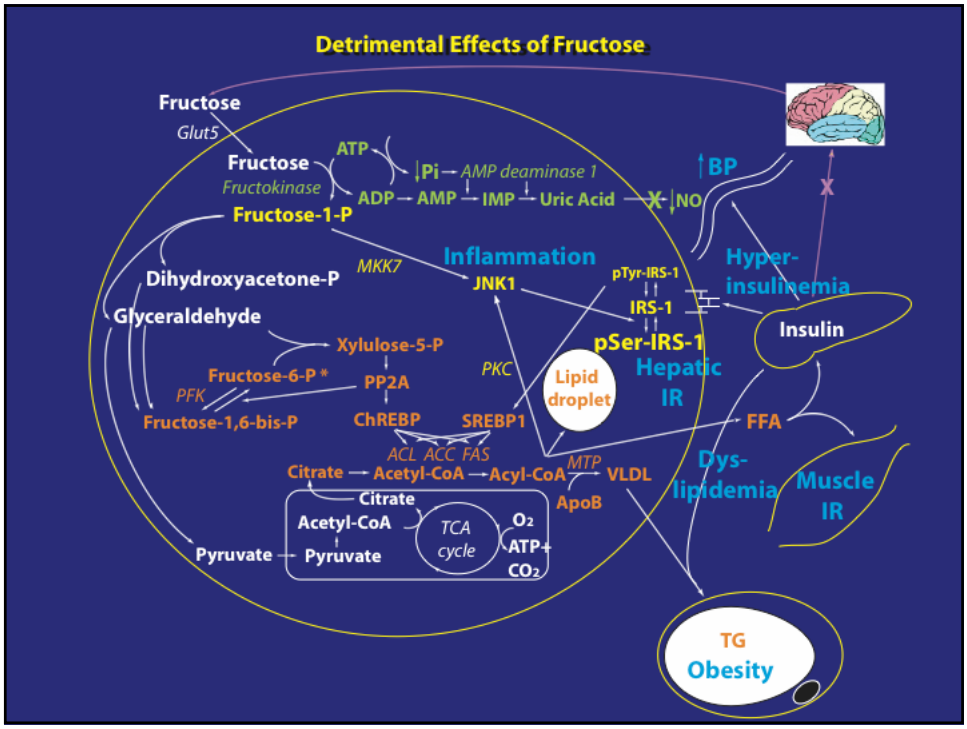
Obesity





Lustig, Nature Clin Pract Endo Metab 2:447, 2006

Isganaitis and Lustig, Arterio Throm Vasc Biol 25:2451, 2005



Chronic ethanol exposure

- Hematologic disorders
- Electrolyte abnormalities
- Hypertension
- Cardiac dilatation
- Cardiomyopathy
- Dyslipidemia
- Pancreatitis
- Malnutrition
- Obesity
- Hepatic dysfunction (ASH)
- Fetal alcohol syndrome
- Addiction

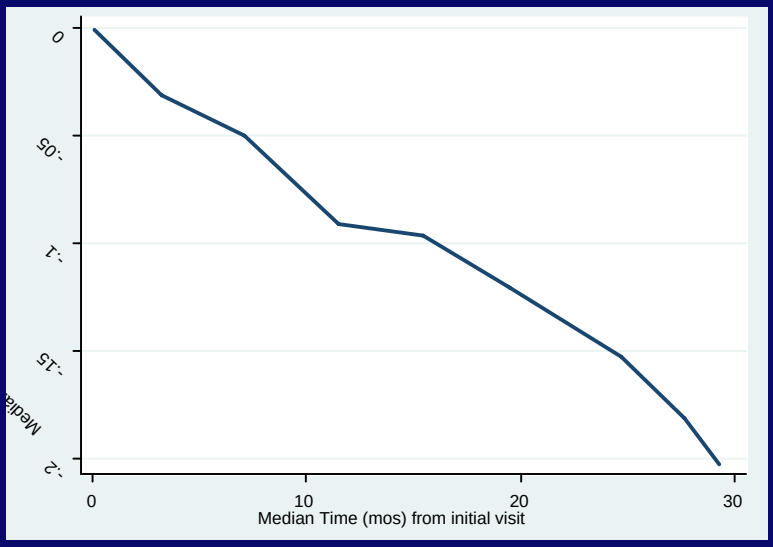
Chronic ethanol exposure	Chronic fructose exposure
• Hematologic disorders	
• Electrolyte abnormalities	
• Hypertension	• Hypertension
• Cardiac dilatation	
• Cardiomyopathy	• Myocardial infarction
• Dyslipidemia	• Dyslipidemia
• Pancreatitis	• Pancreatitis (2º dyslipidemia)
• Malnutrition	
• Obesity	• Obesity
• Hepatic dysfunction (ASH)	• Hepatic dysfunction (NASH)
• Fetal alcohol syndrome	• Fetal insulin resistance
• Addiction	• Habituation, if not addiction

UCSF WATCH Clinic
Associations with the Metabolic Syndrome

Baseline Characteristic (mean ± SD)	**HOMA-IR>5*** ***N=124***	**HOMA-IR≤5** ***N=147***	***P-value*****
BMI z-score	2.6, 2.3-2.8	2.5, 2.2-2.7	0.06
BP syst	125 ± 13	113 ± 15	<0.001
BP diast	68 ± 9	64 ± 8	<0.001
Triglyceride *(mU/dl)*	102, 69-138	83, 57-110	0.005
HDL-c *(mU/dl)*	41 ± 10	43 ± 10	0.04
Fasting Glc *(mg/dl)*	92 ± 9	85 ± 9	<0.001
Fasting Insulin *(mU/ml)*	33.7,28.6-47.1	15.2,11.2-19.8	<0.001
Creatinine *(mg/dl)*	0.64 ± 0.14	0.58 ± 0.15	0.003
ALT *(U/L)*	35, 23-50	23, 18-31	<0.001
MetS+	52%	29%	<0.001
Sugared Beverage Intake *(kcal/d)*	269, 100-423	129, 21-288	0.002
Breakfast *(days/wk)*	4, 0-7	7, 5-7	<0.001

Mietus-Snyder et al. (submitted)

UCSF WATCH Clinic Lifestyle Intervention: Median Change in BMI z-score from Baseline



Madsen et al. (submitted)

UCSF WATCH Clinic
Predictors of Lifestyle Intervention

- Forward selection model, 4 variables

```
      Source |       SS       df       MS              Number of obs =     130
-------------+------------------------------           F(  4,   125) =    6.49
       Model |  .169200646     4  .042300161           Prob > F      =  0.0001
    Residual |   .81467663   125  .006517413           R-squared     =  0.1720
-------------+------------------------------           Adj R-squared =  0.1455
       Total |  .983877276   129  .007626956           Root MSE      =  .08073

------------------------------------------------------------------------------
  Delta z/yr |      Coef.   Std. Err.      t    P>|t|                     Beta
-------------+----------------------------------------------------------------
  sugared bev|    .012786   .0048643     2.63   0.010                .2268616
        HOMA|   .0034239   .0018131     1.89   0.061                .1707474
Baseline BMIZ|   .0311507   .0199972     1.56   0.122                .1430862
Baseline Age |   .0027542   .0022543     1.22   0.224                .1055135
       _cons |  -.1475346   .0573037    -2.57   0.011                      .
------------------------------------------------------------------------------
```

Madsen et al. (submitted)

Fructose is a carbohydrate

Fructose is a carbohydrate

Fructose is metabolized like fat

Fructose is a carbohydrate

Fructose is metabolized like fat

Fructose is also a toxin

Summary

- Fructose (sucrose vs. HFCS) consumption has increased in the past 30 years, coinciding with the obesity epidemic
- Fructose is everywhere
- Fructose is not glucose
- Hepatic fructose metabolism leads to all the manifestations of the Metabolic Syndrome:
  - hypertension
  - de novo lipogenesis, dyslipidemia, and hepatic steatosis
  - inflammation
  - hepatic insulin resistance
  - obesity
  - CNS leptin resistance, promoting continuous consumption
- Fructose ingestion interferes with obesity intervention
- Fructose is a chronic toxin

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Sharon Fleming, Ph.D.
Lorene Ritchie, Ph.D.