Sugar — the bitter truth

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Division of Endocrinology
Department of Pediatrics
UCSF

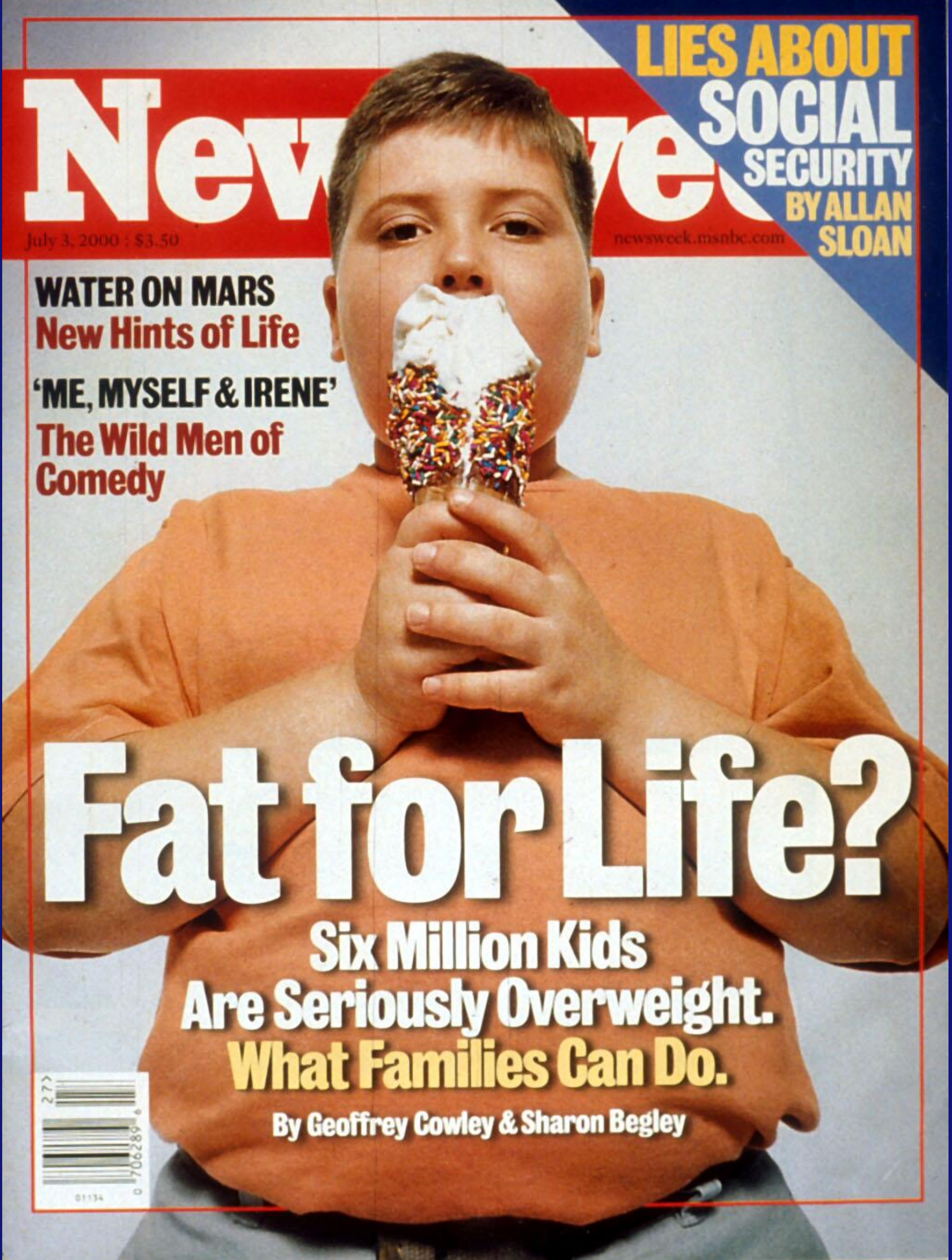
Nutrition nd Health Conference, San Francisco, CA May 9, 2011

- No disclosures

Venus von Willendorf, Vienna Museum of Natural History
Dated to 22,000 BCE, unearthed in 1908

Obesity has been part of the human condition since there were humans

But something's happened—
How did the world get so obese?
And how so fast?


Newsweek
July 3, 2000 : $3.50
newsweek.msnbc.com
LIES ABOUT SOCIAL SECURITY
BY ALLAN SLOAN
WATER ON MARS
New Hints of Life
'ME, MYSELF & IRENE'
The Wild Men of Comedy
Fat for Life?
Six Million Kids Are Seriously Overweight.
What Families Can Do.
By Geoffrey Cowley & Sharon Begley

The First Law of Thermodynamics

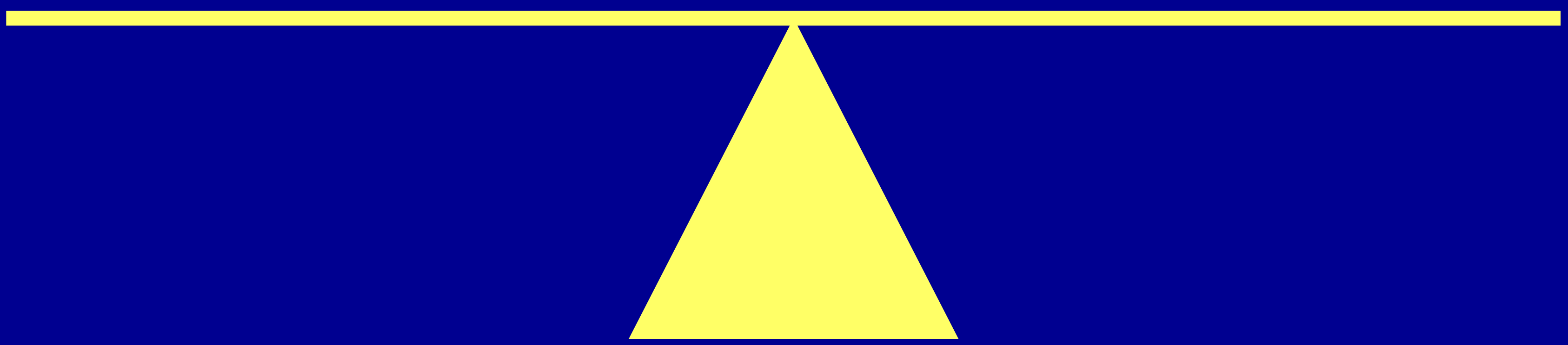
The total energy inside a closed system remains constant.

The First Law of Thermodynamics

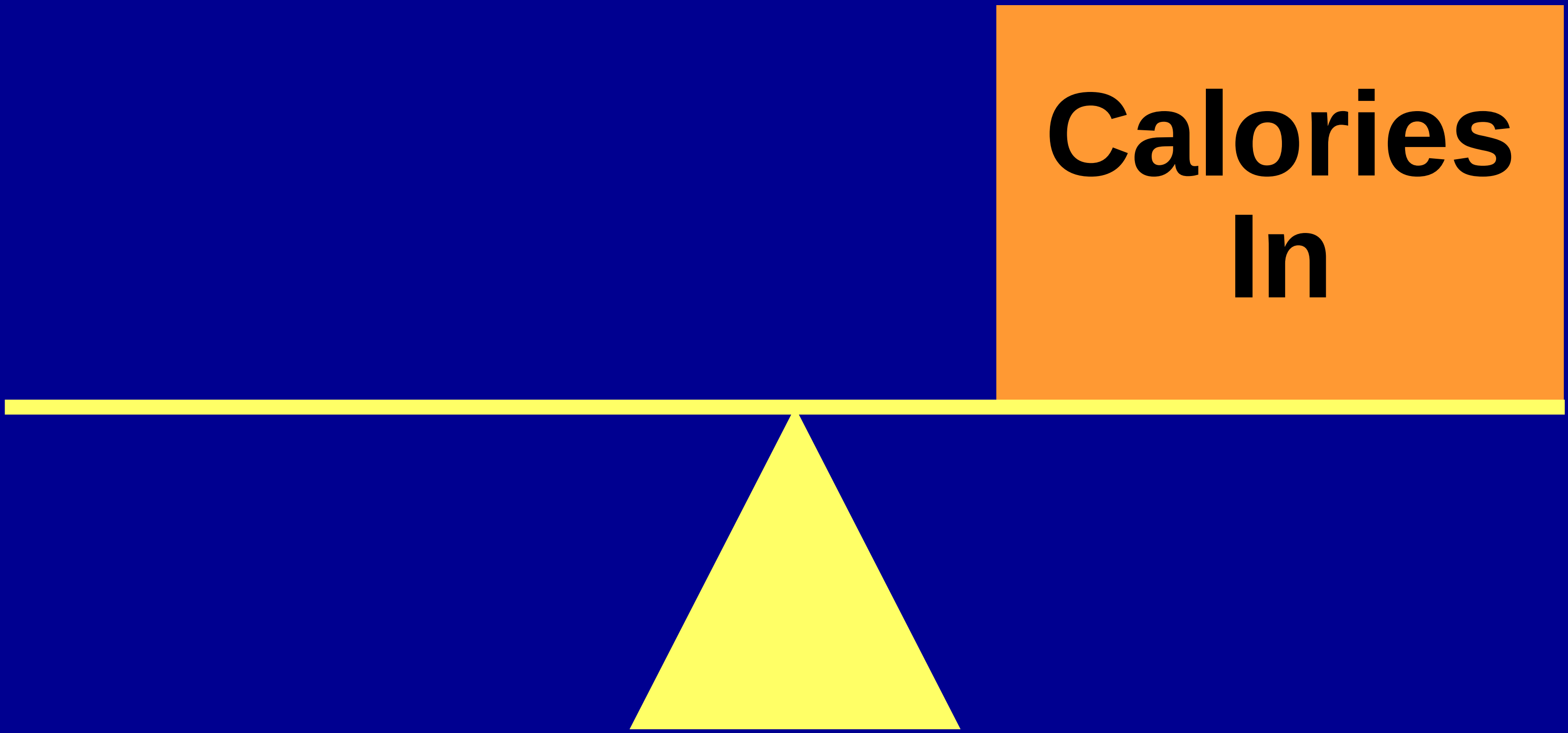
The total energy inside a closed system remains constant.

Two interpretations:

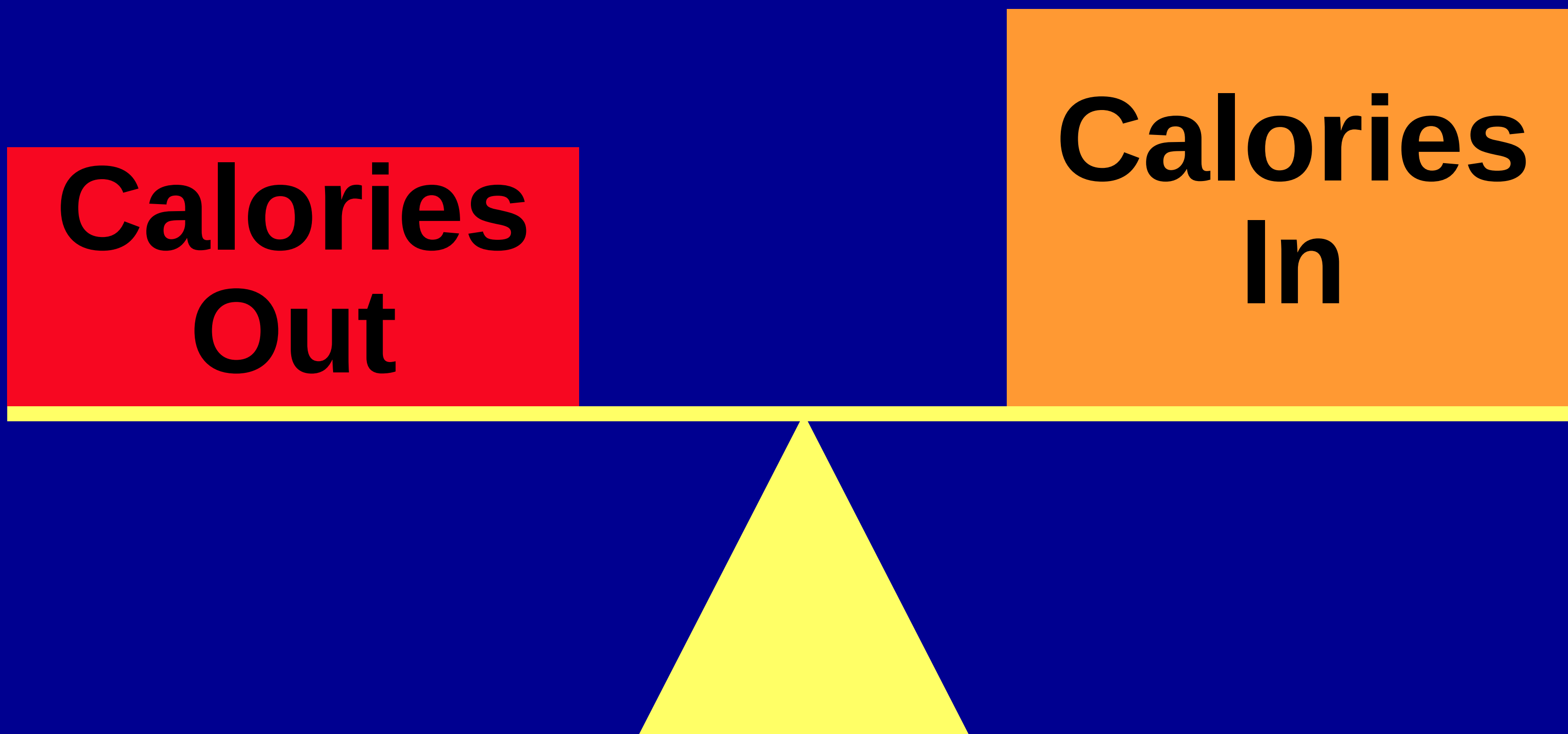
The First Law of Thermodynamics



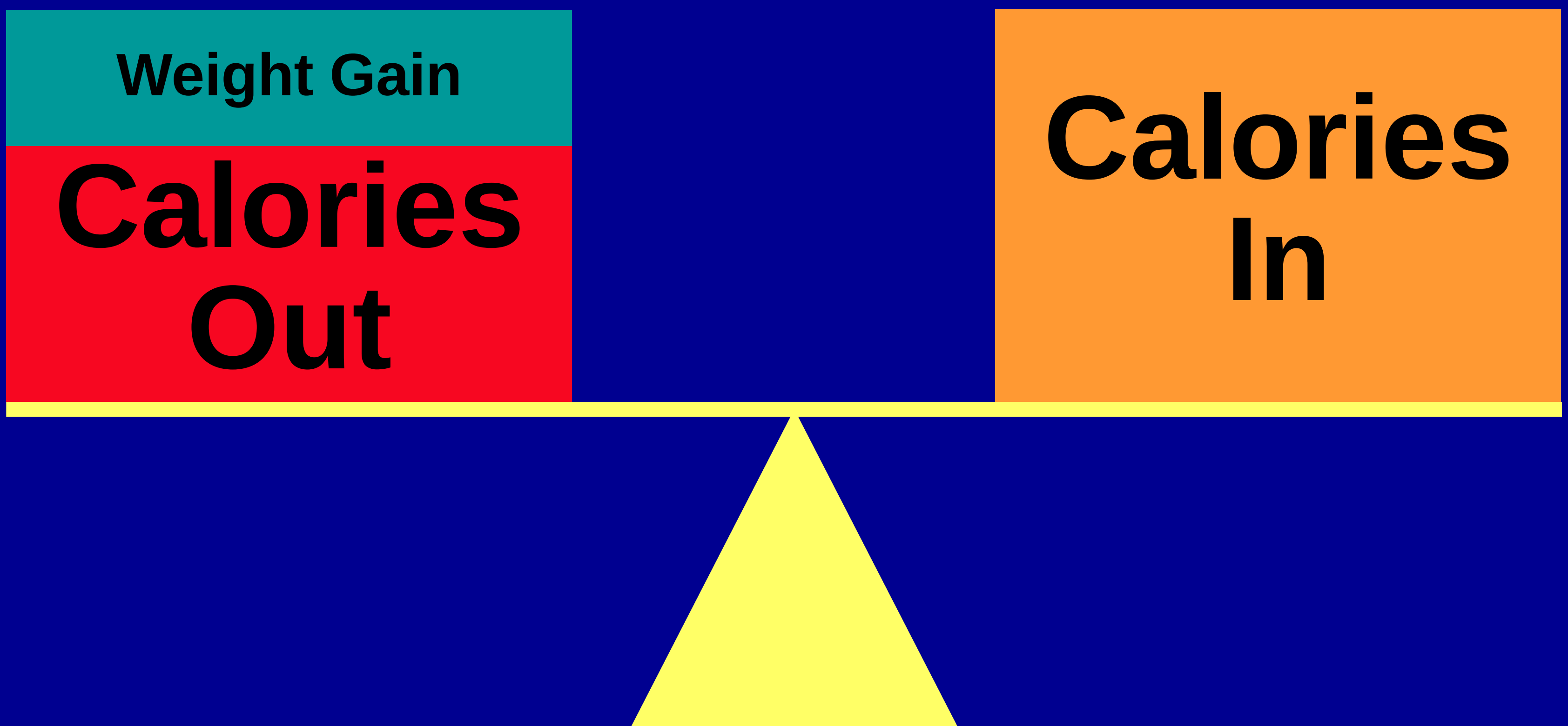
The First Law of Thermodynamics



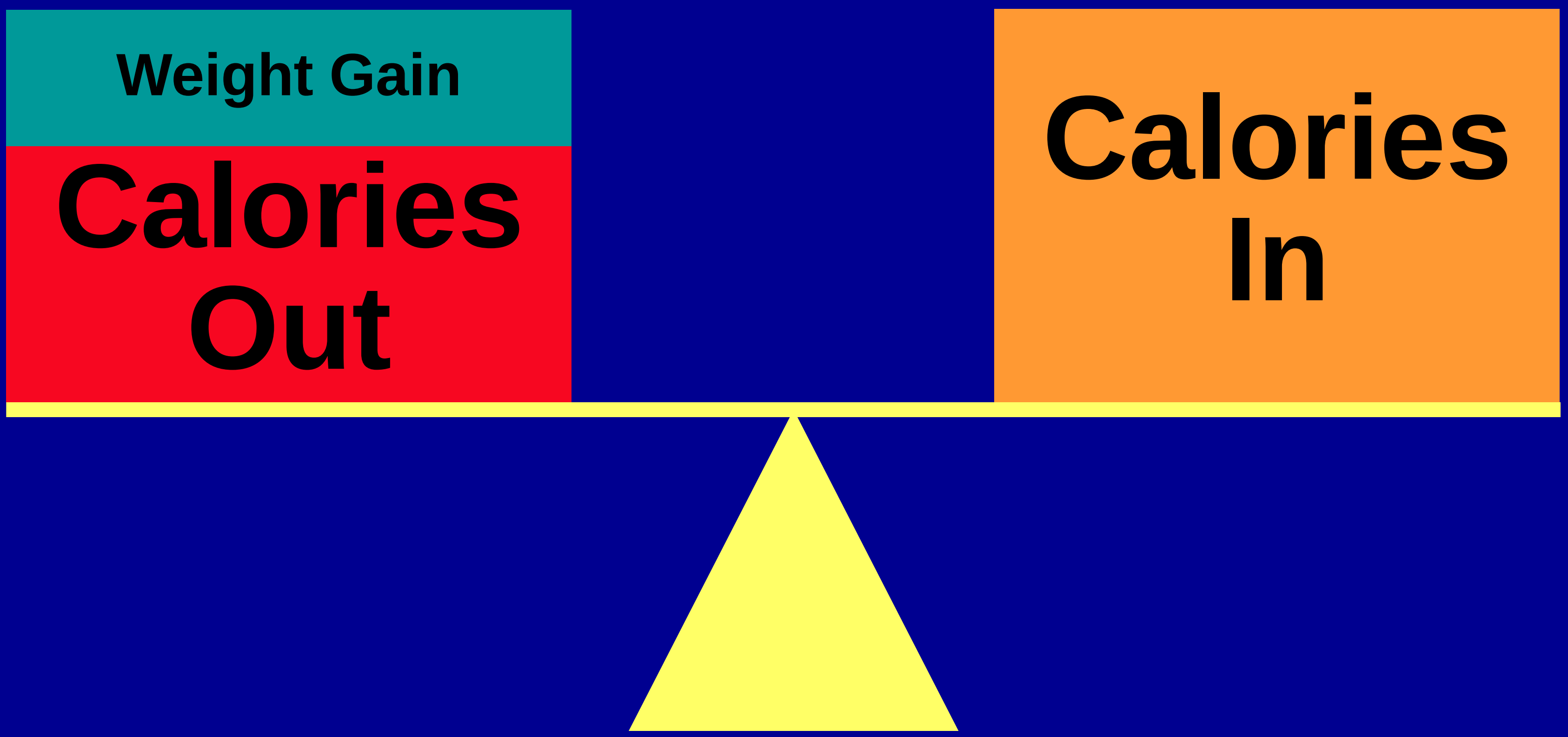
The First Law of Thermodynamics



The First Law of Thermodynamics

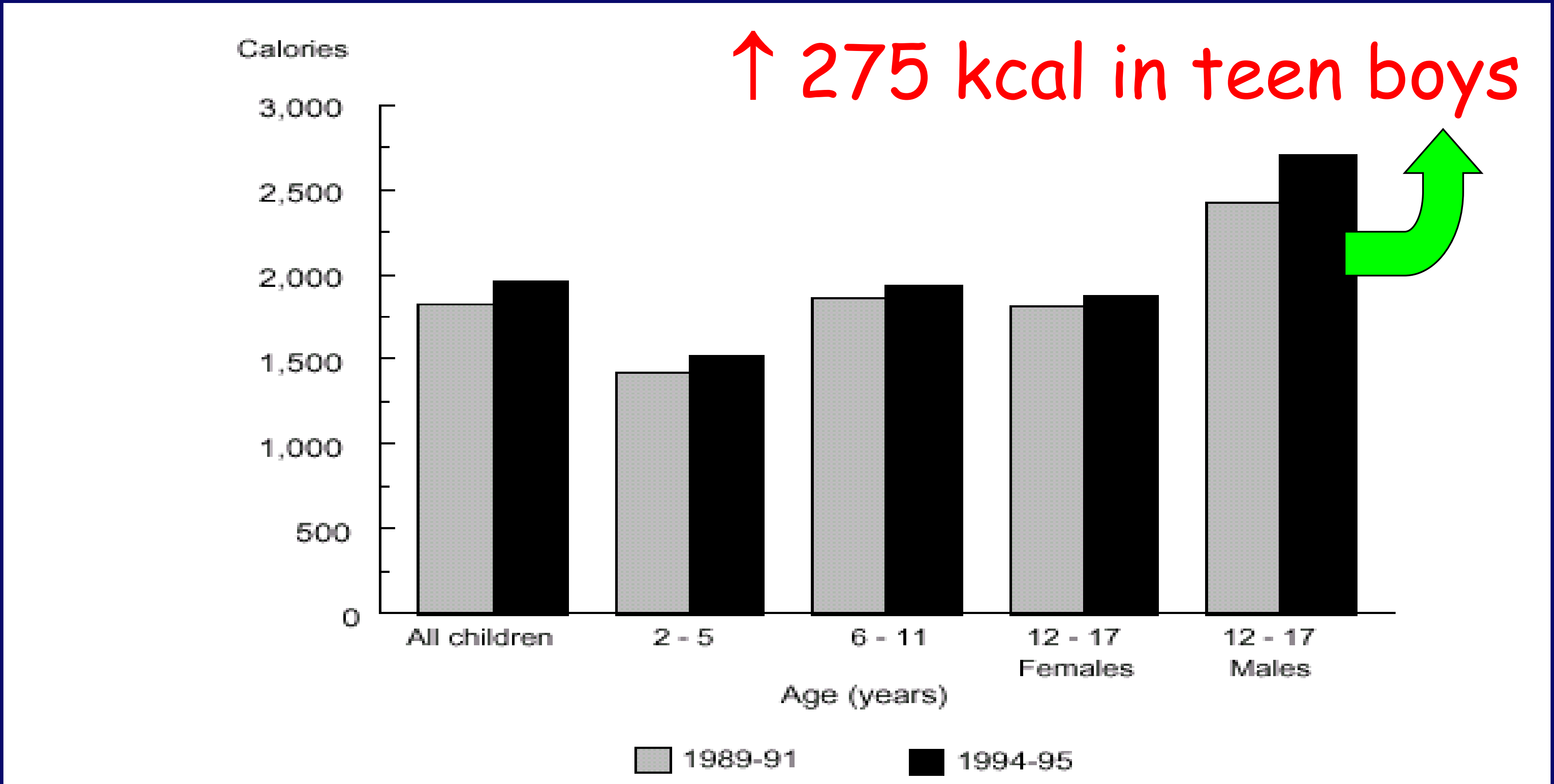


The First Law of Thermodynamics



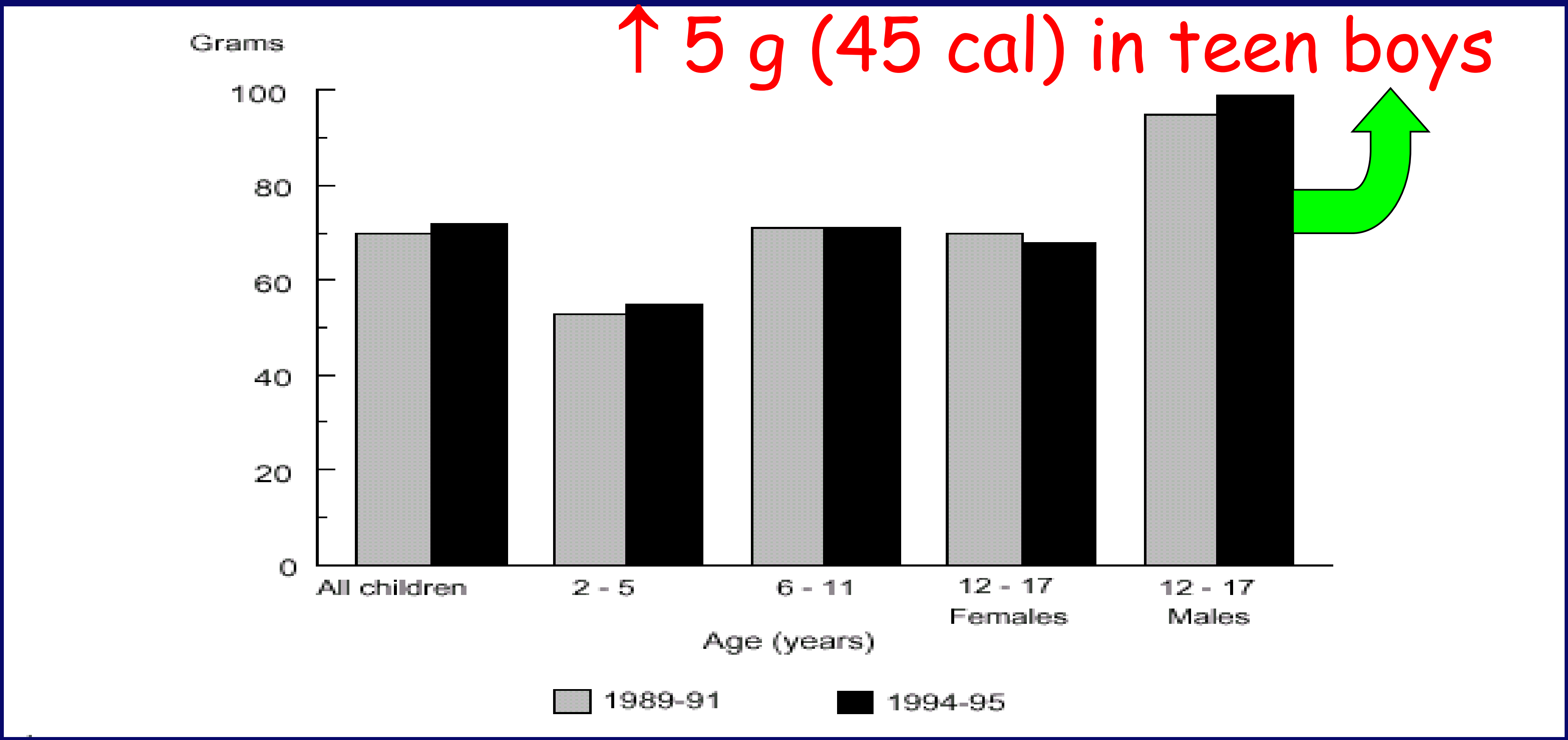
Obesity is the result of two aberrant behaviors

Total Caloric Intake



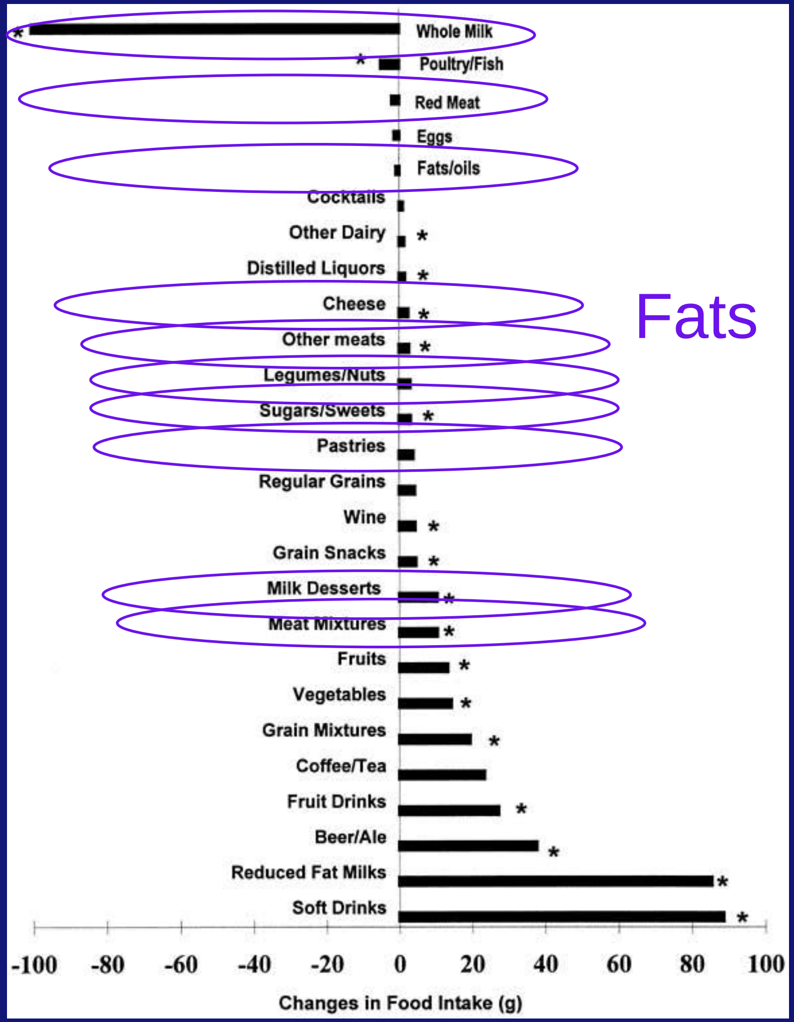
Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95
http://www.usda.gov/cnpp/FENR%20V11N3/fenrv11n3p44.PDF

Fat Intake: Grams



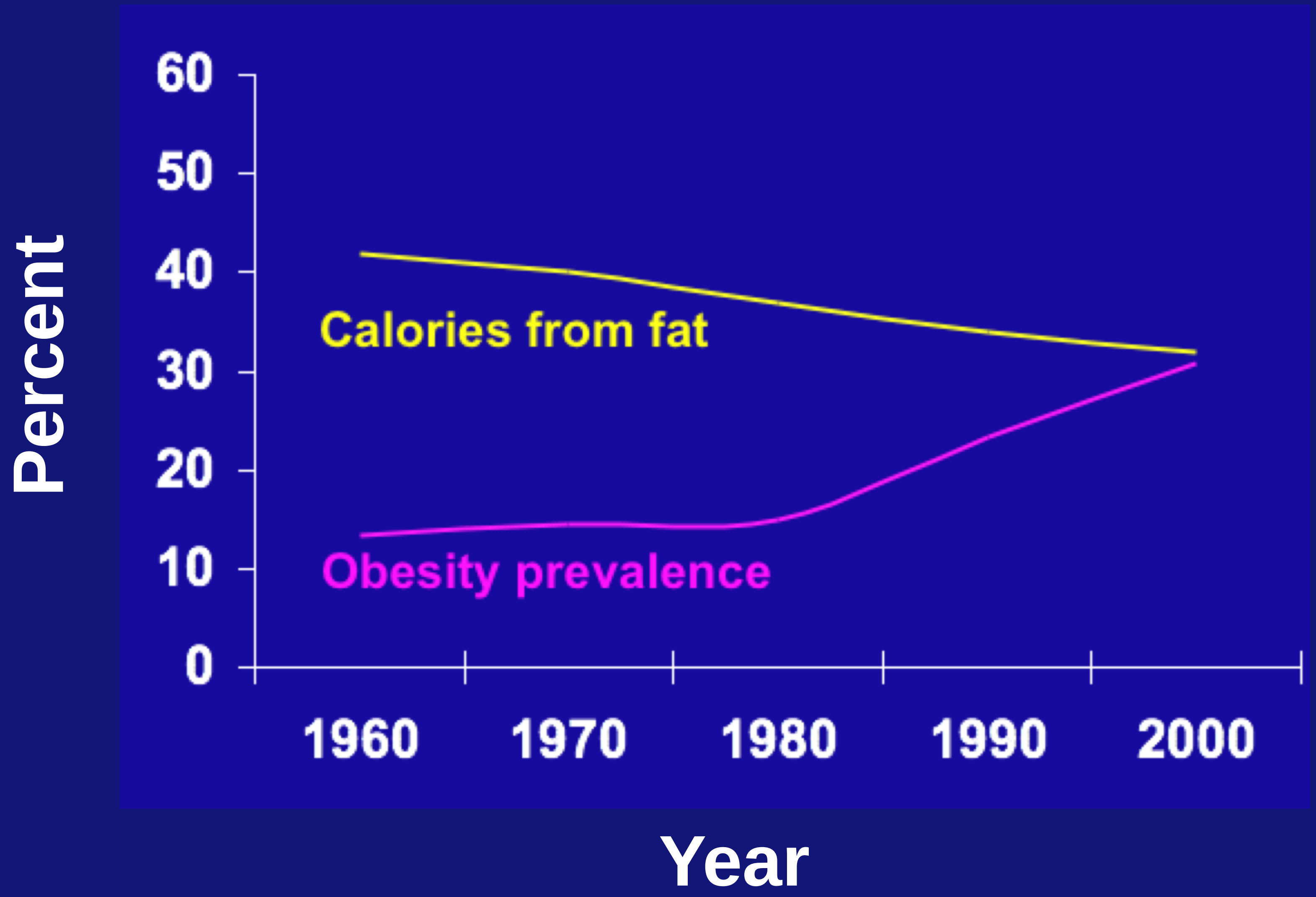
Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Secular trends in specific food intake 1989-1996

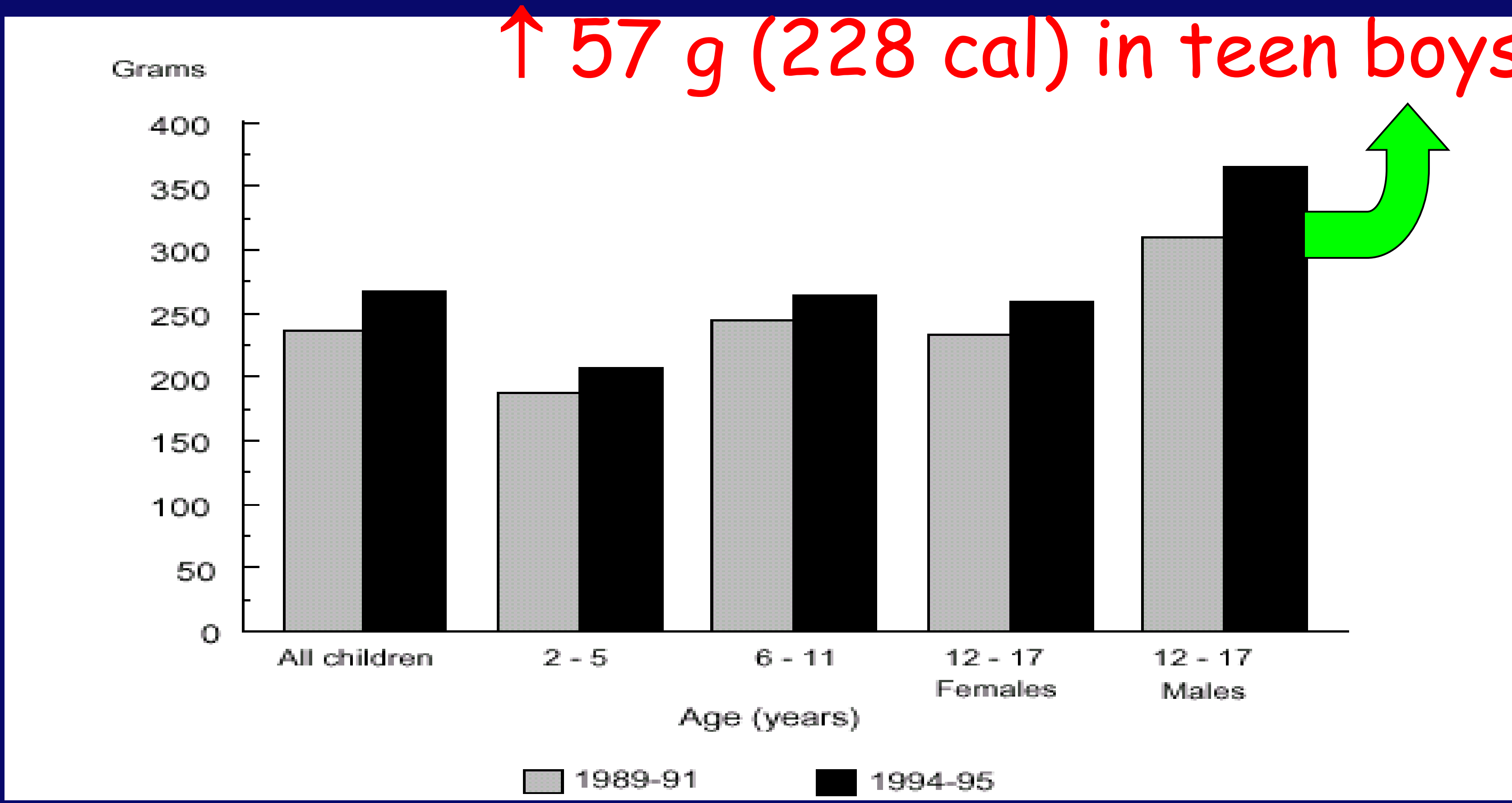


Chanmugam et al. J Am Diet Assoc 103:867, 2003

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

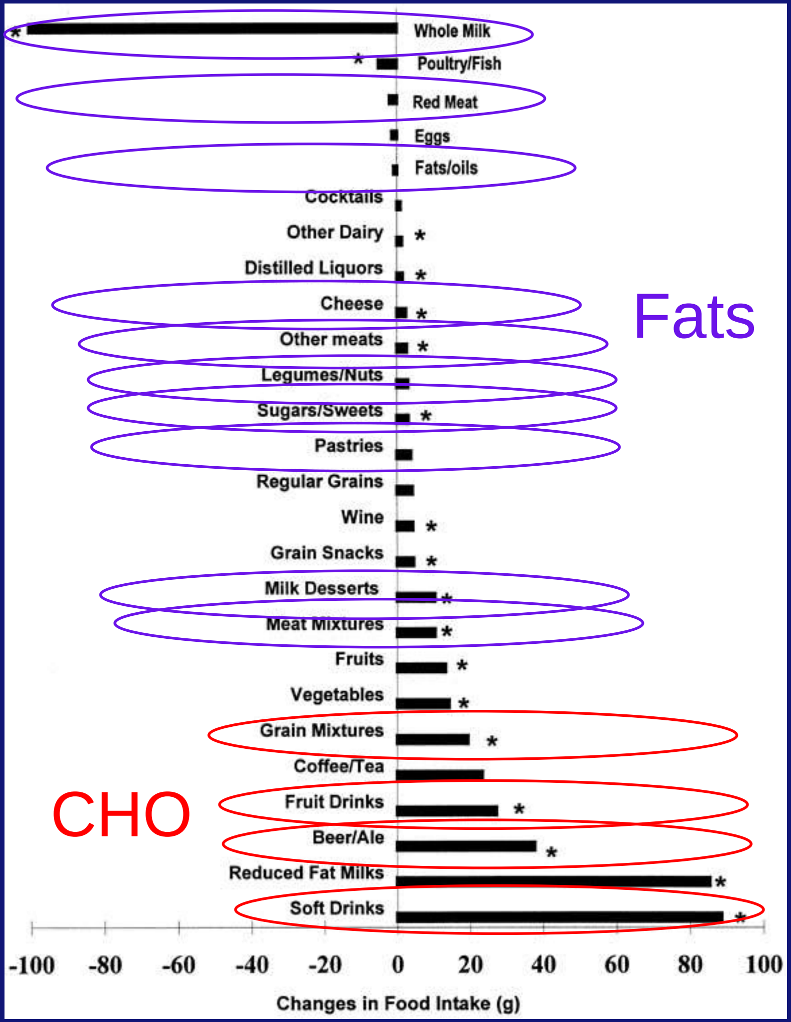


Carbohydrate Intake: Grams



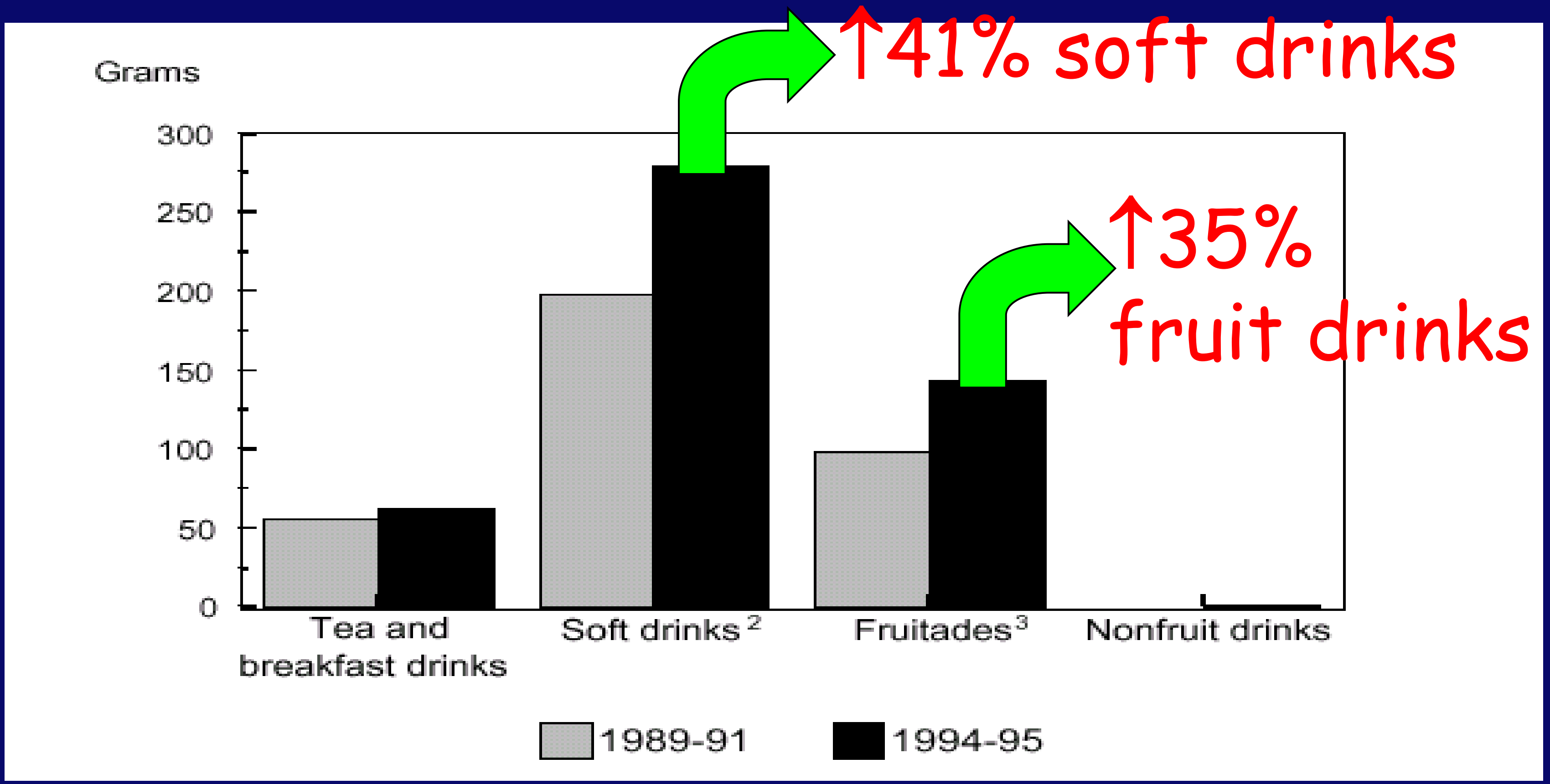
Children 2-17 yrs, CSFII (USDA) 1989-91 vs. 1994-95

Secular trends in specific food intake 1989-1996



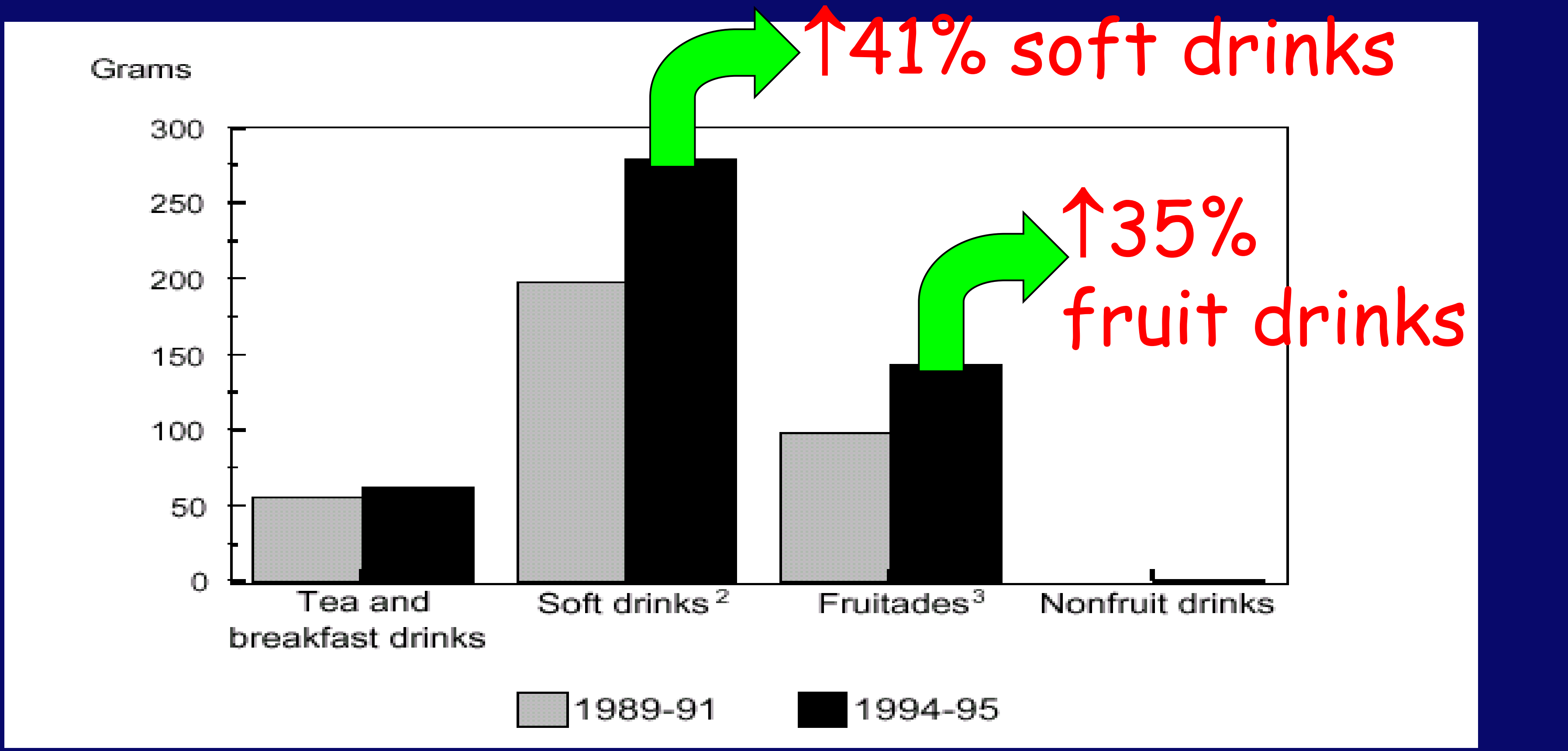
Chanmugam et al. J Am Diet Assoc 103:867, 2003

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

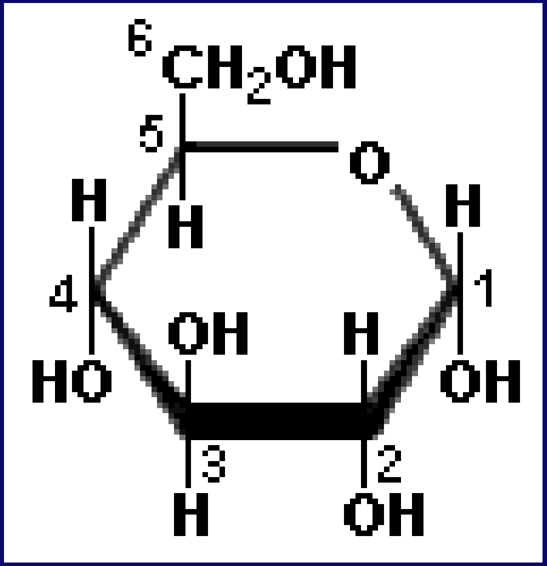
One can of soda/day = 150 cal x 365 d/yr ÷ 3500 cal/lb = 15.6 lbs/yr!

High Fructose Corn Syrup

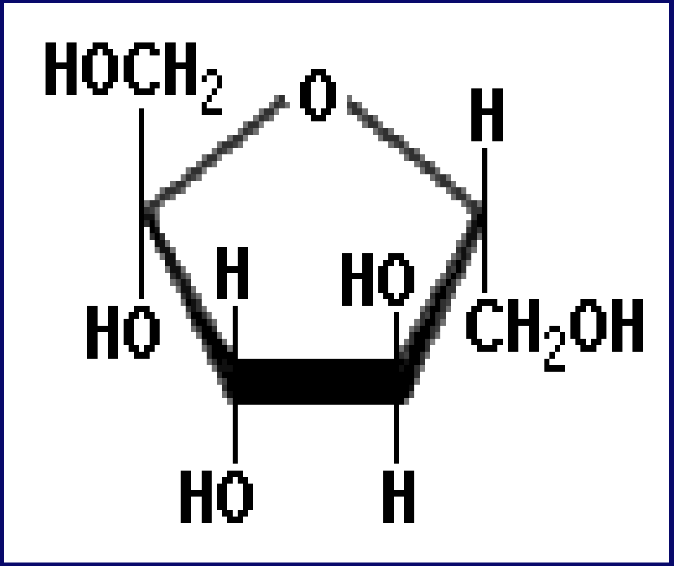
Current US annual consumption of HFCS

- **63 pounds per person**

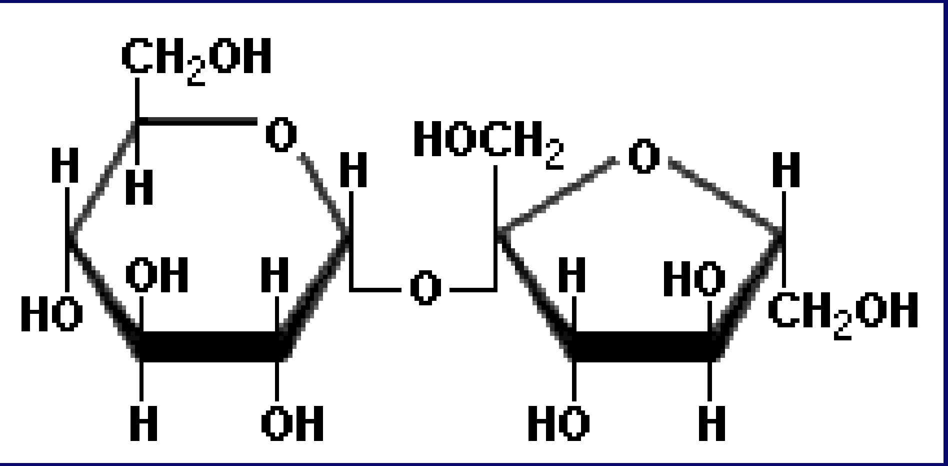
High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose



Glucose

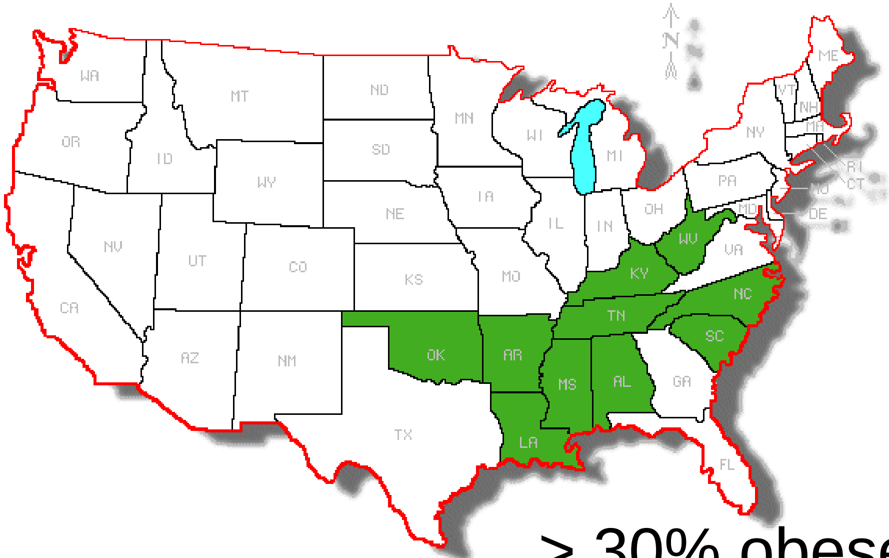


Fructose



Sucrose

10 Most Obese States



> 30% obese

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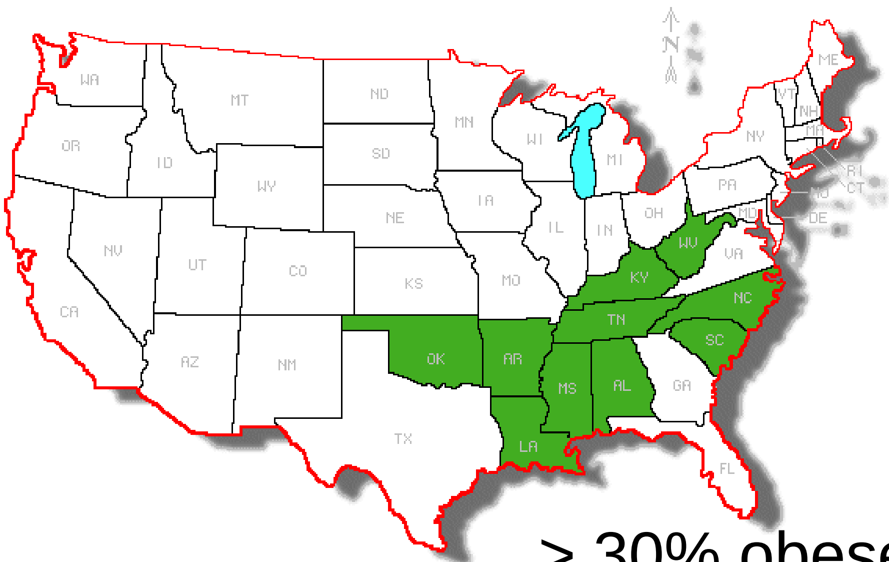
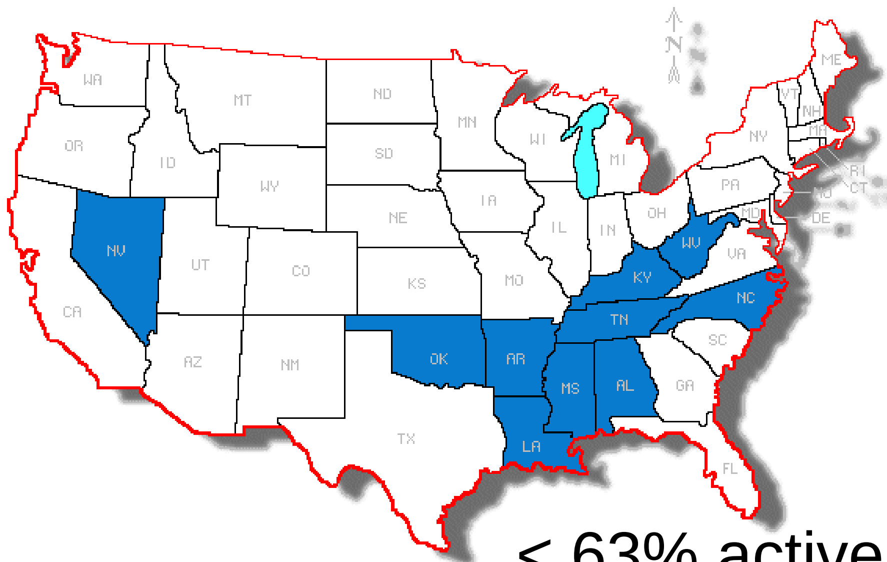


> 30% obese

10 Laziest States



< 63% active

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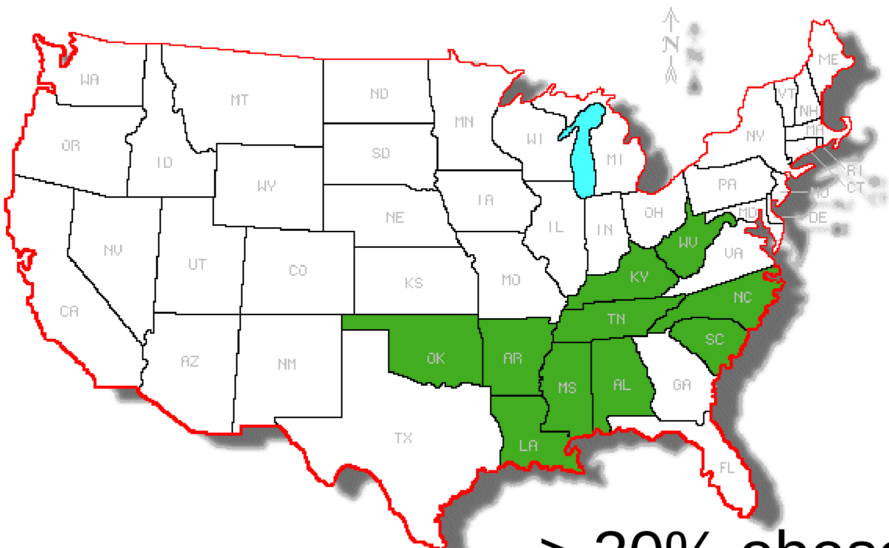

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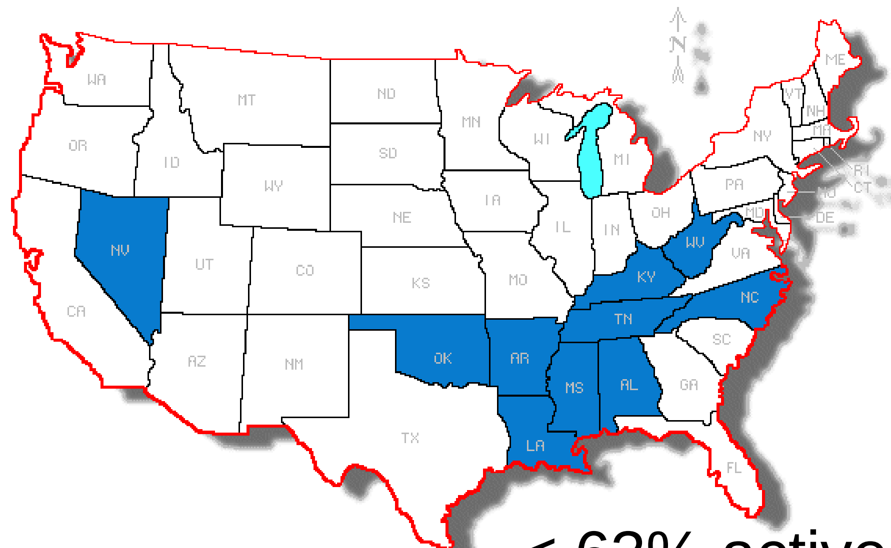
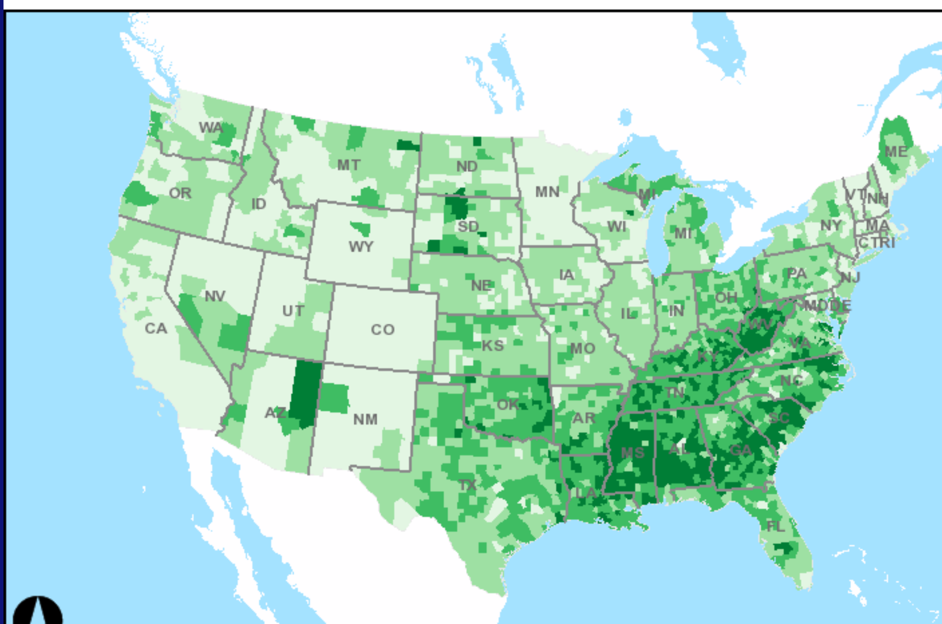


< 63% active

Adult Diabetes Rate



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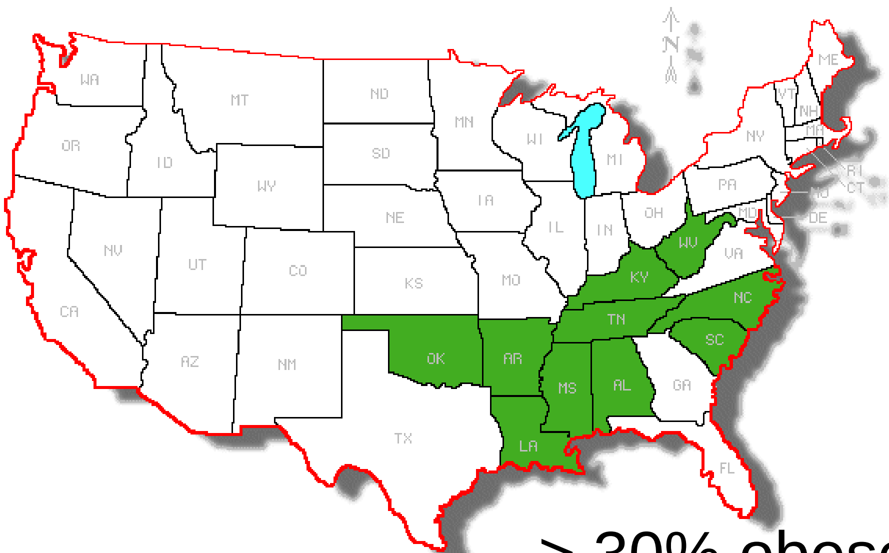

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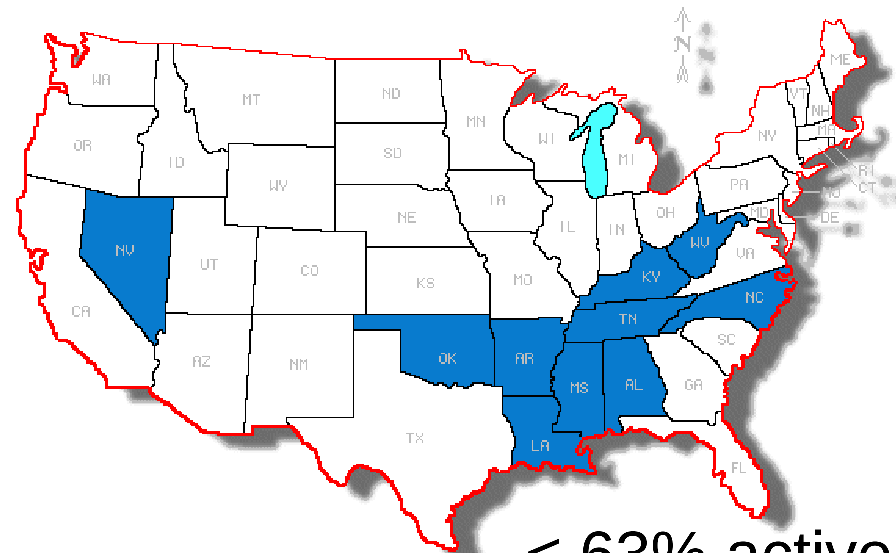

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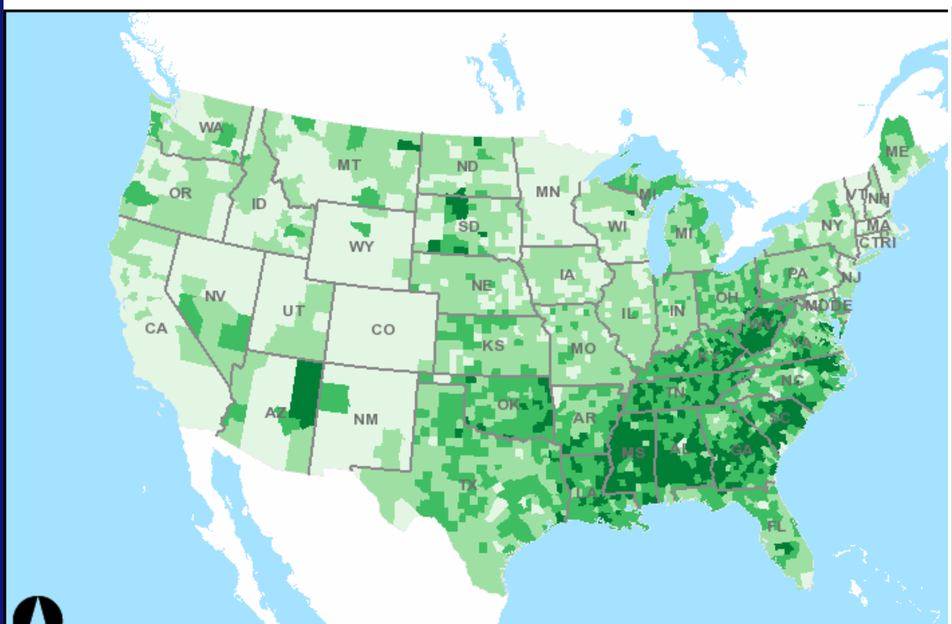
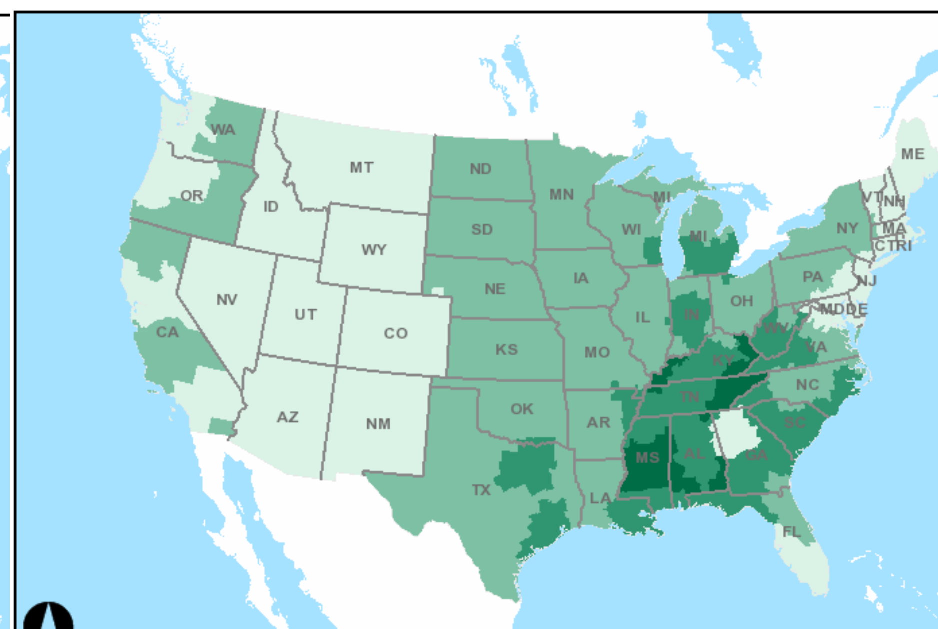
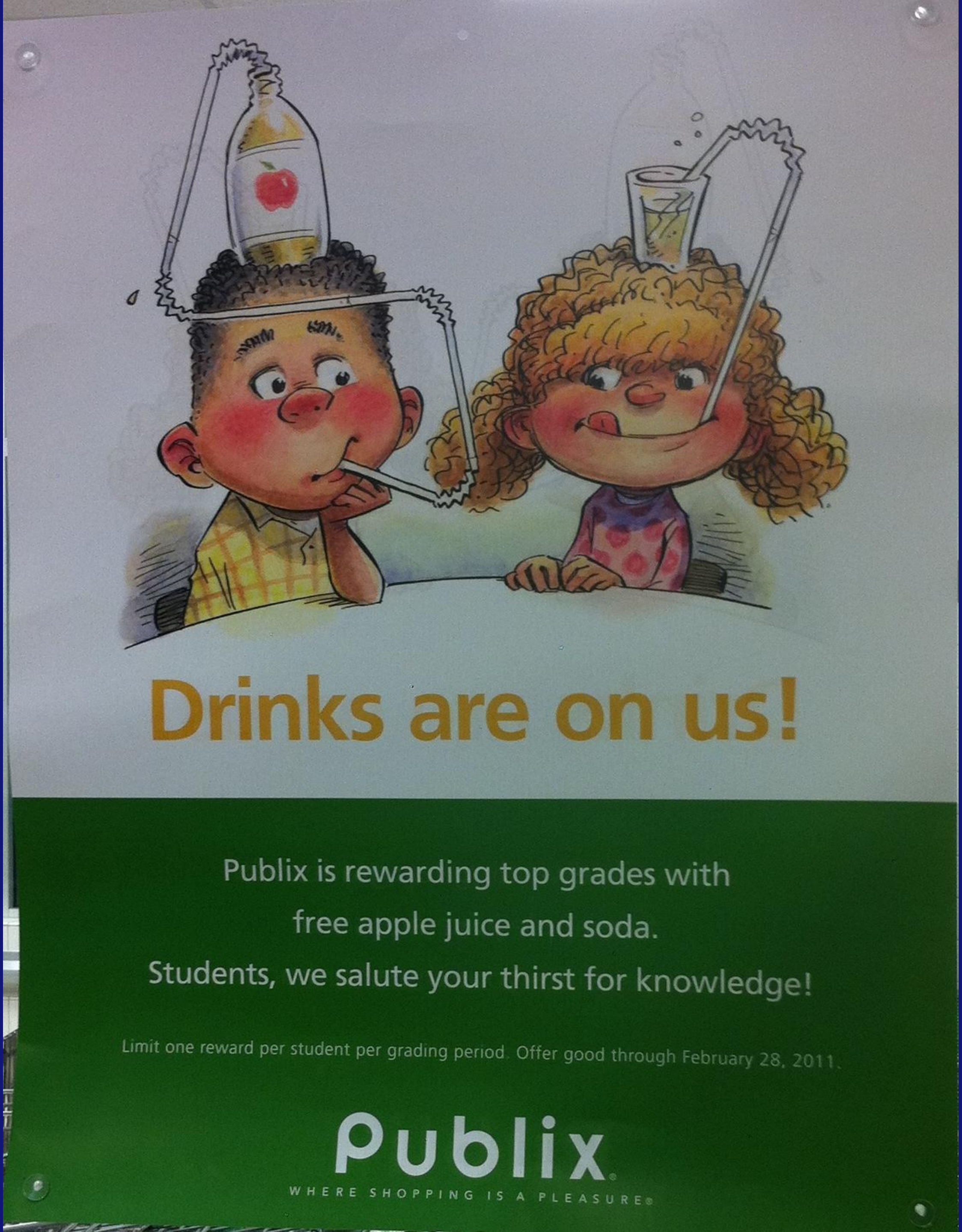


Soda Per Capita



The "birth" of the cola wars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Publix is rewarding top grades with
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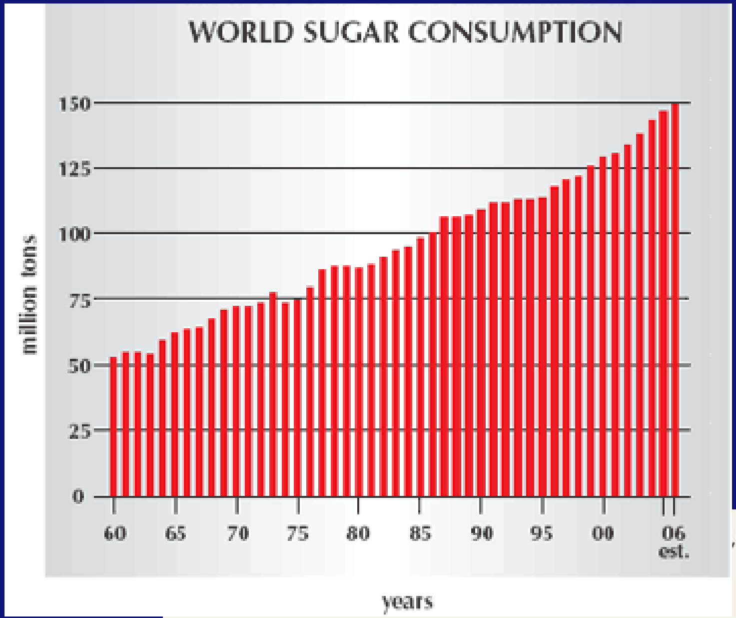
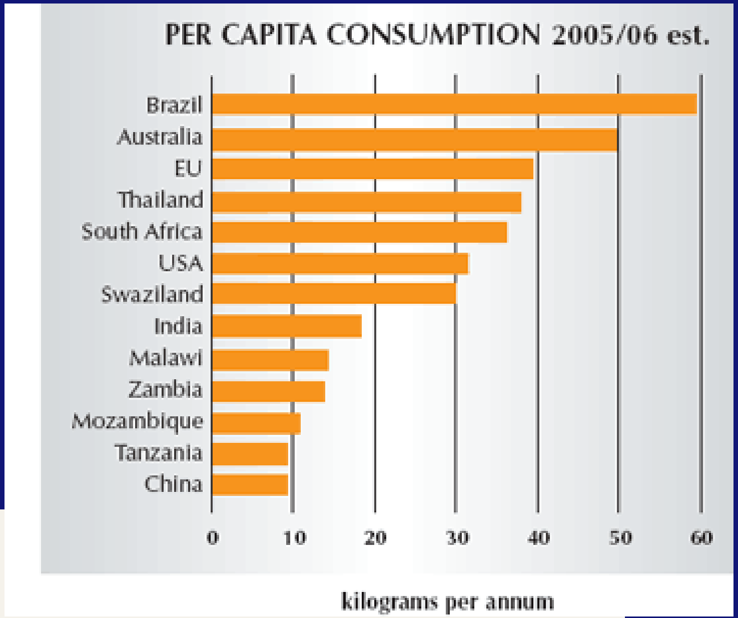
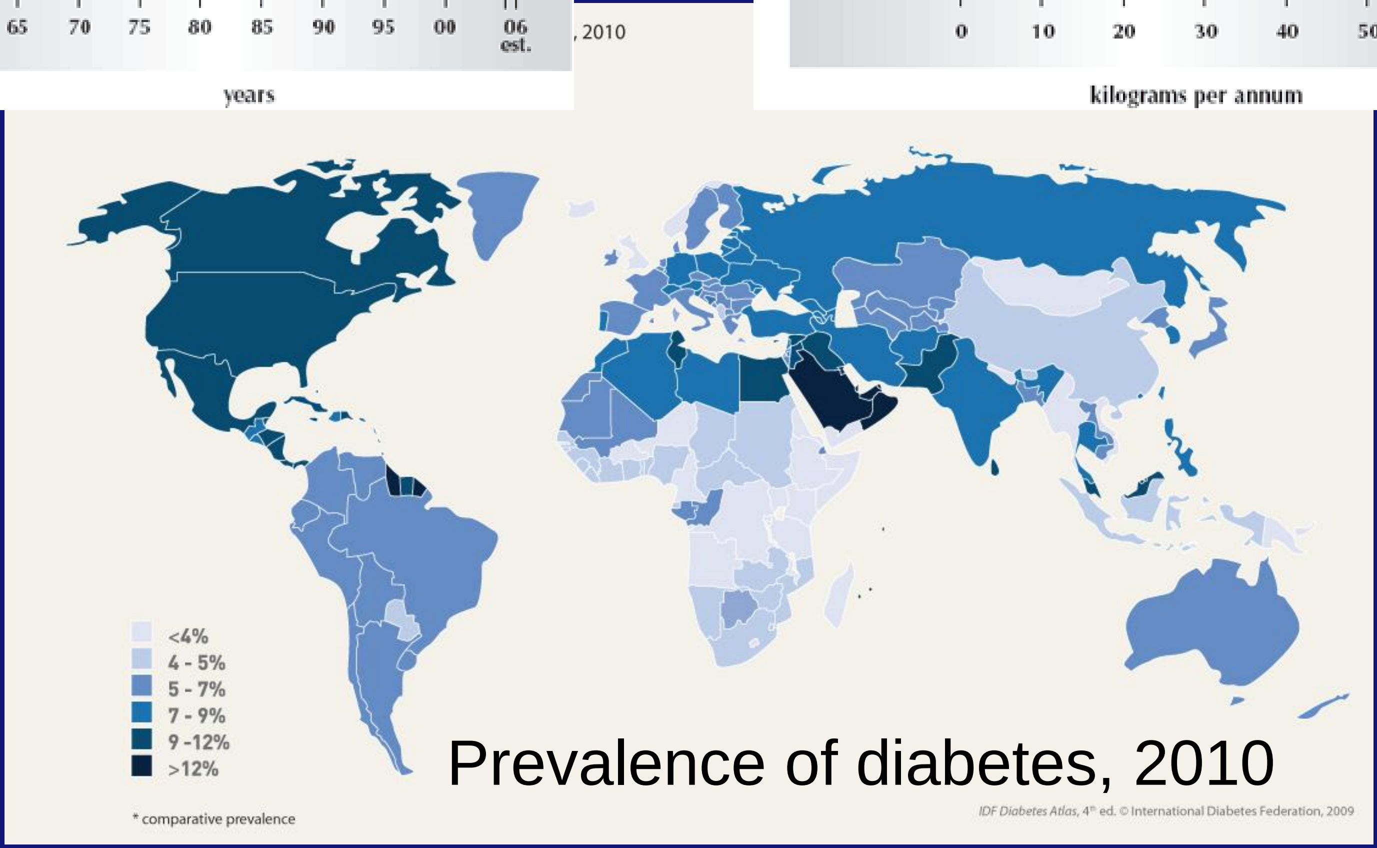
Students, we salute your thirst for knowledge!
Limit one reward per student per grading period. Offer good through February 28, 2011.
Publix
WHERE SHOPPING IS A PLEASURE







Prevalence of diabetes, 2010

Secular trend in fructose consumption

Natural consumption of fruits and vegetables
- 15 gm/day

Prior to WWII (estimated):
- 16-24 gm/day

1977-1978 (USDA Nationwide Food Consumption Survey):
- 37 gm/day (8% of total caloric intake)

1994 (NHANES III):
- 54.7 gm/day (10.2% of total caloric intake)

Adolescents:
- 72.8 gm/day (12.1% of total caloric intake)
- 25% consumed at least 15% of calories from fructose

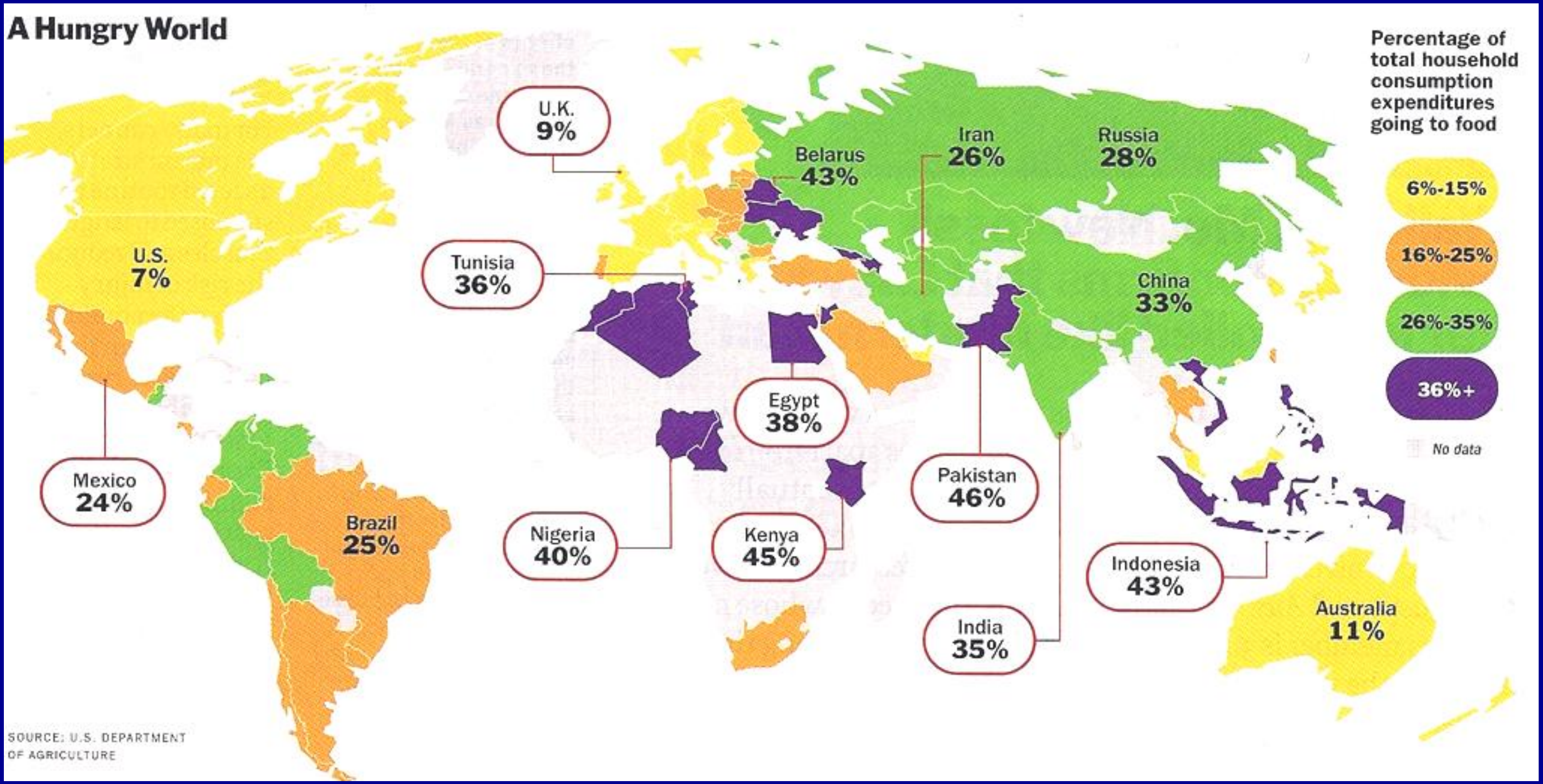
Bray, Am J Clin Nutr 86:895, 2007; Vos et al. Medscape Med J 10:160, 2008

The perfect storm from three political winds

The perfect storm from three political winds

1. Richard Nixon and USDA Secretary Earl Butz (1973)
   - food should never be an issue in a presidential election

Percent of Gross National Product spent on food, by country



Time Magazine, Feb 28, 2011

The perfect storm from three political winds

1. Richard Nixon and USDA Secretary Earl Butz (1973)
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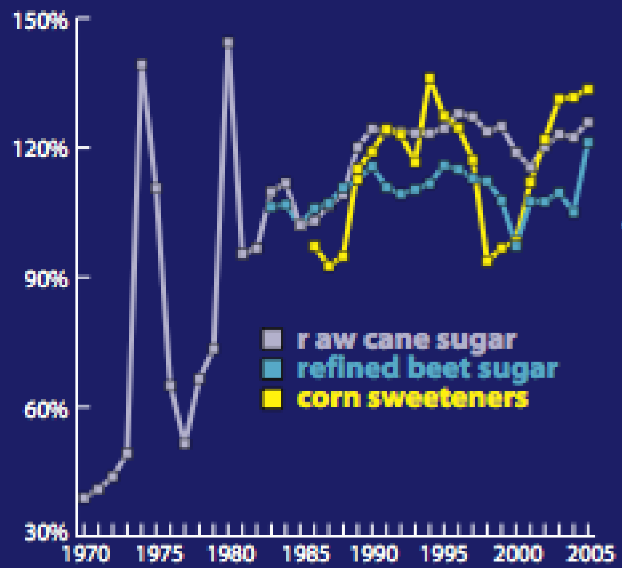
2. The advent of High Fructose Corn Syrup
   - invented in 1966 in Japan
   - introduced to the American market in 1975

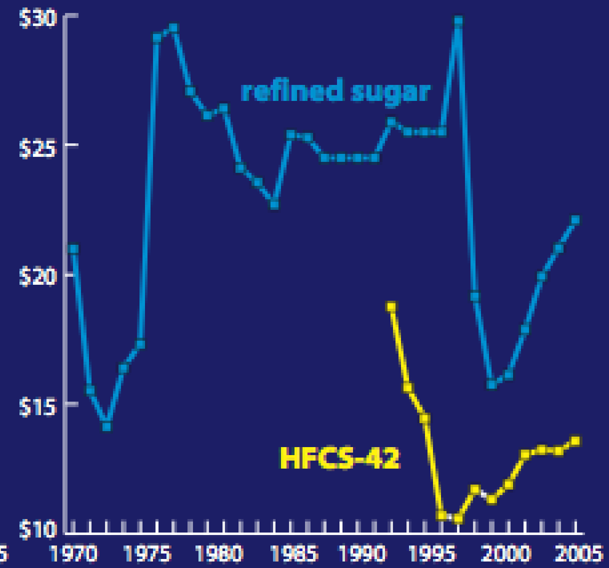
Influence of corn sweeteners on the price of sugar

U.S. Producer Price Index



International price of refined sugar

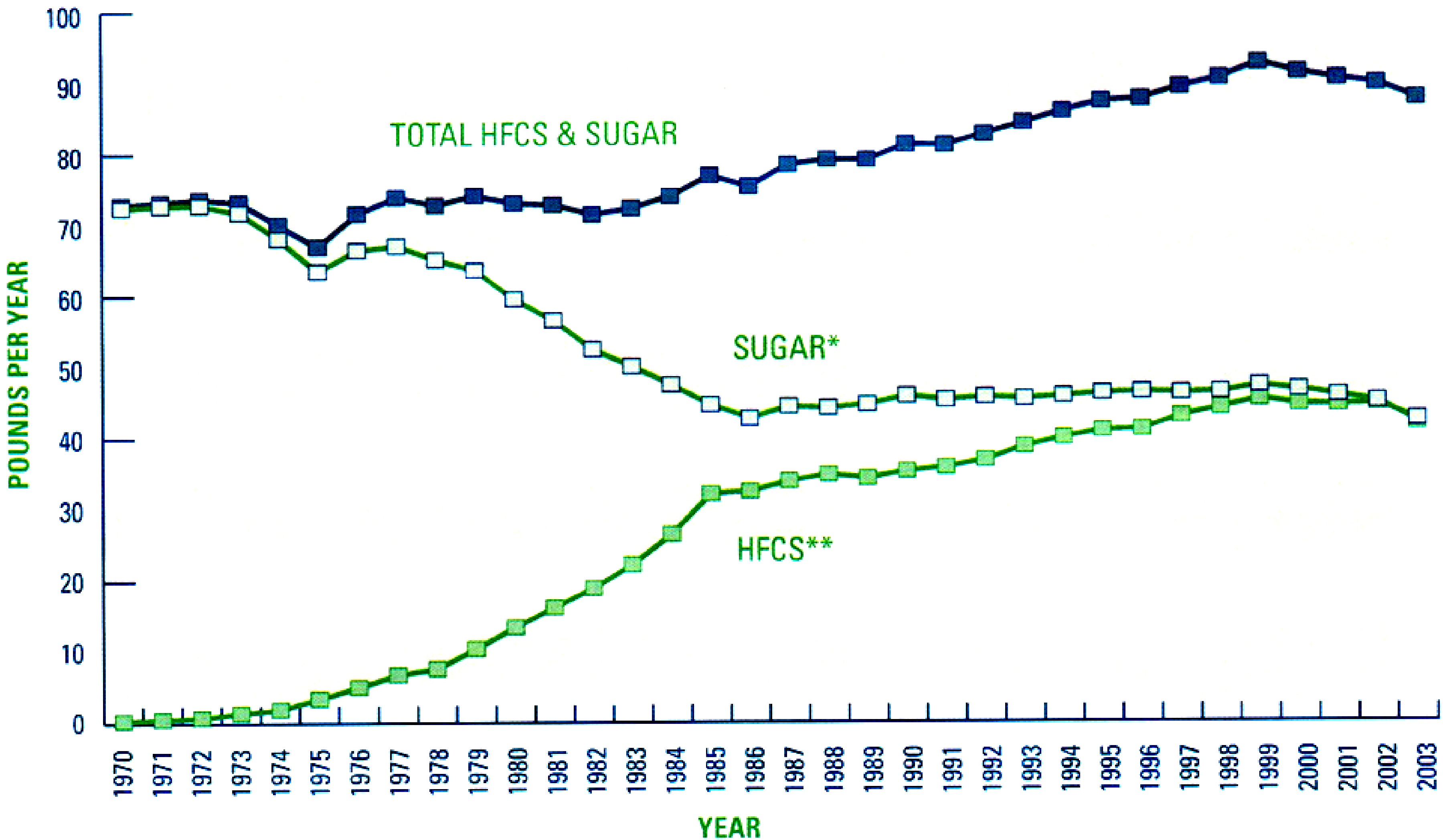
U.S. Retail Price



U.S. Department of Agriculture

Annual Per Capita Availability of Sugar and HFCS Adjusted for Loss

USDA FOOD DISAPPEARANCE DATA

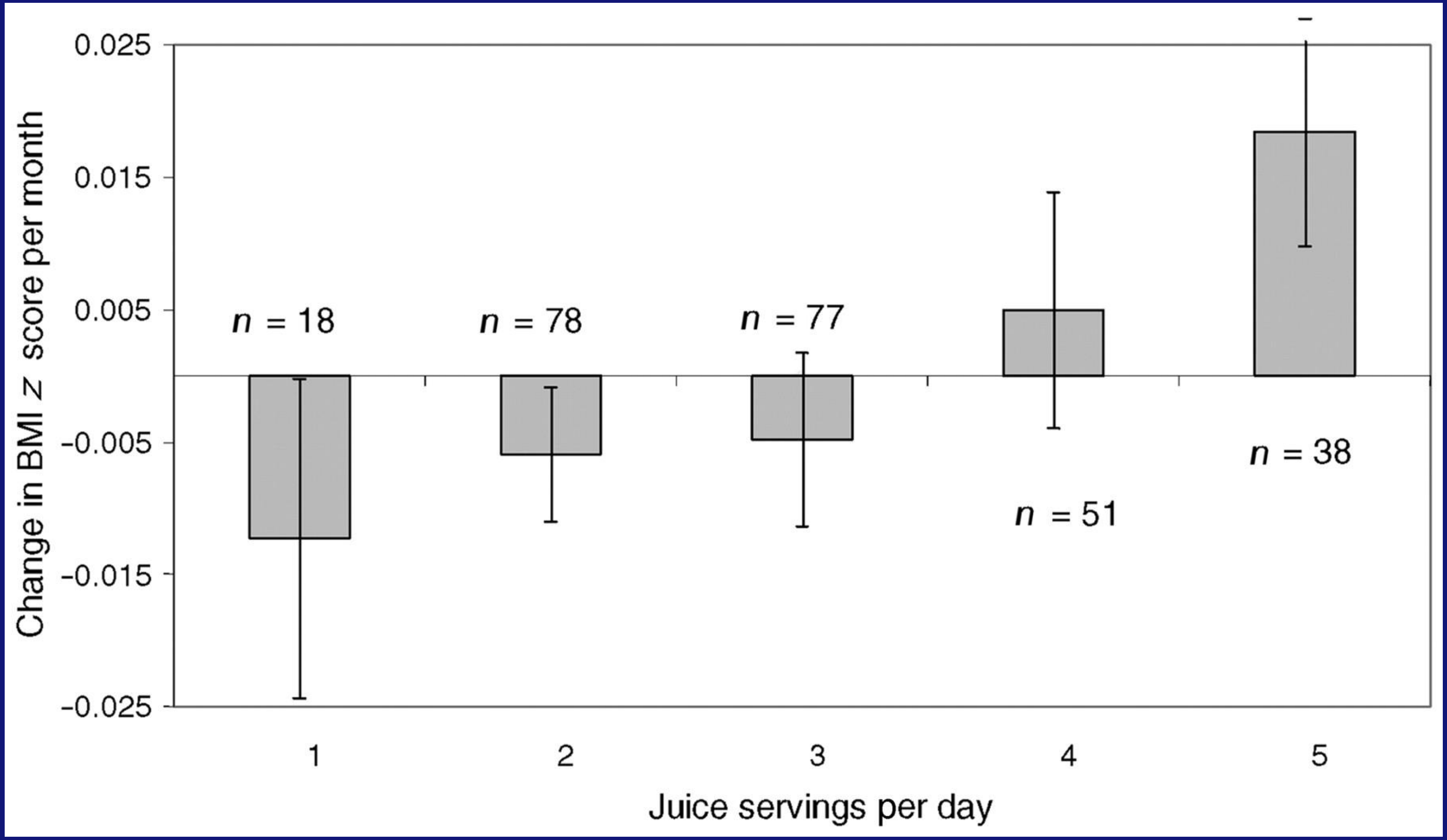


Source: USDA, Economic Research Service, Sweetener Yearbook, Tables 51 and 52

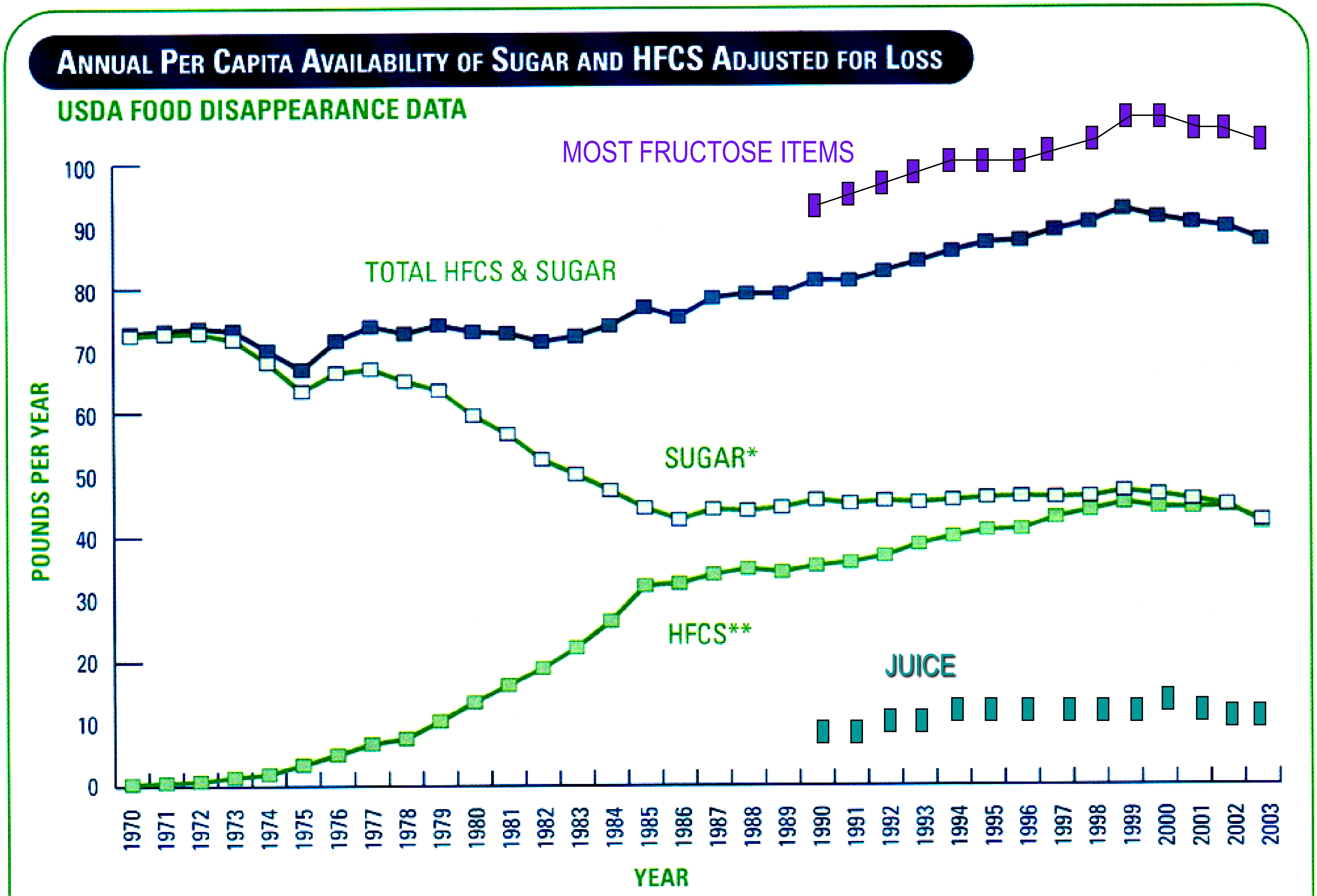
*Estimated annual per capita sugar consumption calculated by adjusting sugar deliveries for domestic food and beverage use for food losses.

**Estimated annual per capita HFCS consumption calculated by adjusting HFCS deliveries for domestic food and beverage use for food losses.

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



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The perfect storm from three political winds

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   - food should never be an issue in a presidential election

2. The advent of High Fructose Corn Syrup
   - invented in 1966 in Japan
   - introduced to the American market in 1975

3. The USDA, AMA, and AHA call for dietary fat reduction
   - Early 1970's: discovery of LDL
   - Mid 1970's: Dietary fat raises LDL (A ➔ B)
   - Late 1970's: LDL correlated with CVD (B ➔ C)
   - 1982: If A ➔ B, and B ➔ C, then A ➔ C, therefore no A, no C

The macronutrient wars 1970-1980

SEVEN COUNTRIES

Ancel Keys

A Multivariate Analysis of Death and Coronary Heart Disease

with
Christ Aravanis
Henry Blackburn
Ratko Buzina
B. S. Djordjević
A. S. Dontas
Flaminio Fidanza
Martti J. Karvonen
Noboru Kimura
Alessandro Menotti
Ivan Mohaček
S. Nedeljković
Vittorio Puddu
Sven Punsar
Henry L. Taylor
F. S. P. van Buchem

A Commonwealth Fund Book

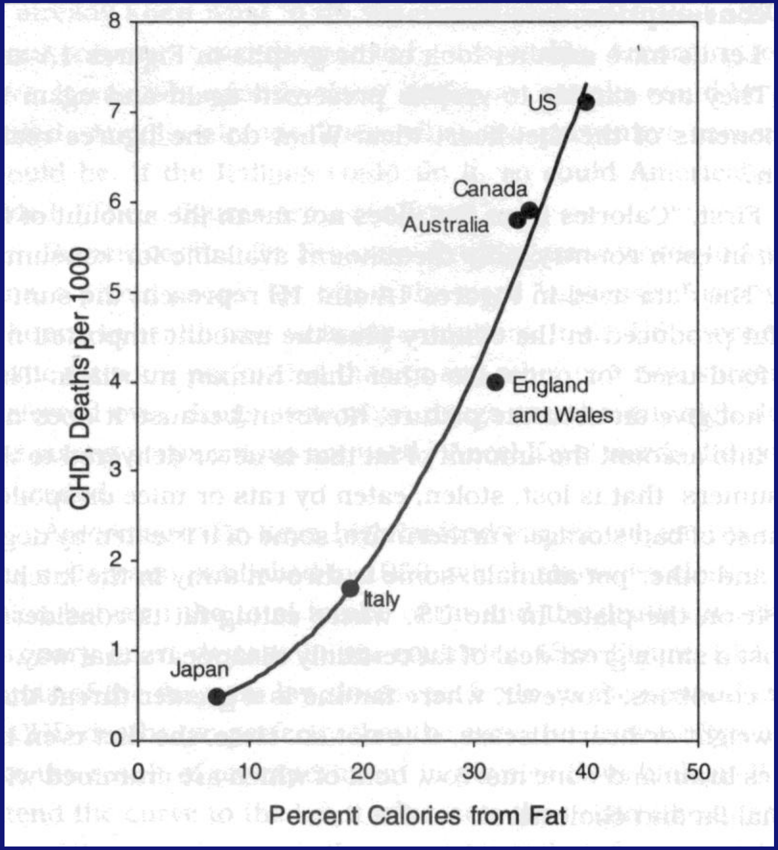
Harvard University Press
Cambridge, Massachusetts
and London, England
1980

John Yudkin

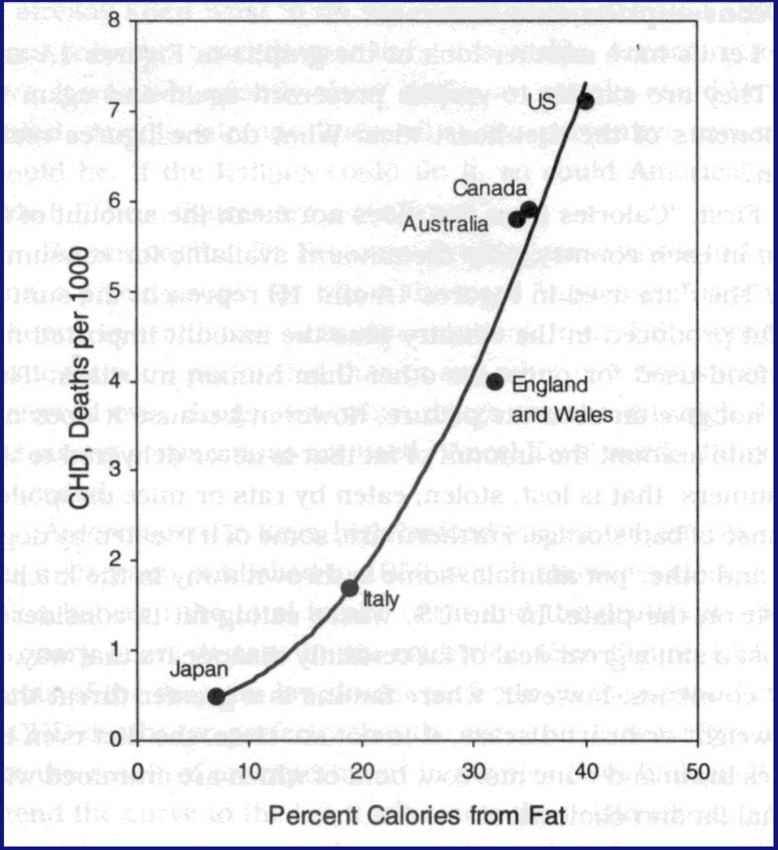
Pure, White and Deadly

Viking
1972, 1986

Seven Countries
Correlation of CHD with dietary fat



Seven Countries
Correlation of CHD with dietary fat

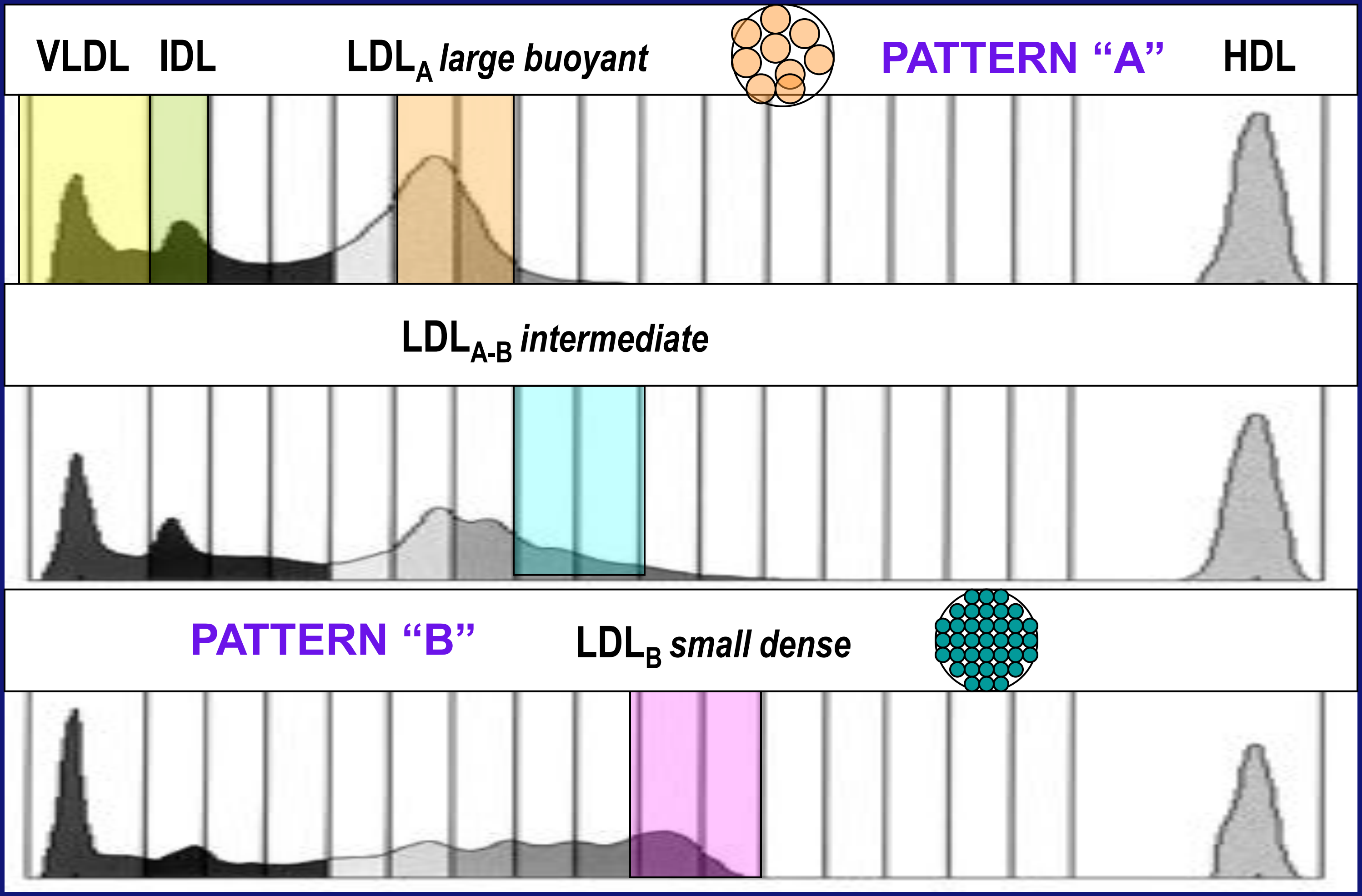


Page 262: Diet

The fact that the incidence rate of coronary heart disease was significantly correlated with the average percentage of calories from sucrose in the diets is explained by the intercorrelation of sucrose with saturated fat. Partial correlation analysis shows that with saturated fat constant there was no significant correlation between dietary sucrose and the incidence of coronary heart

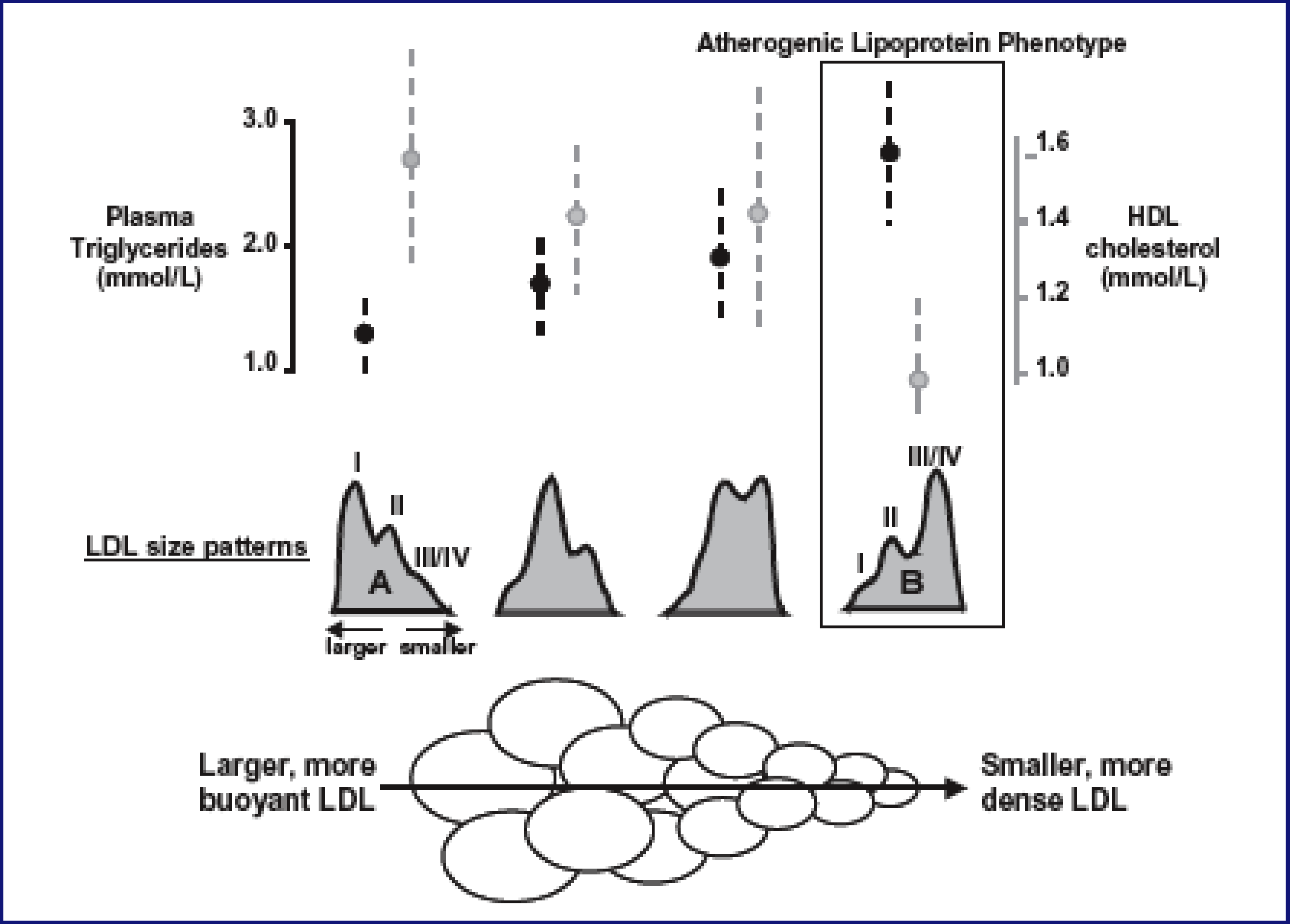
Comparisons of coronary death rates with estimates of national diets in in-

The lipoprotein continuum



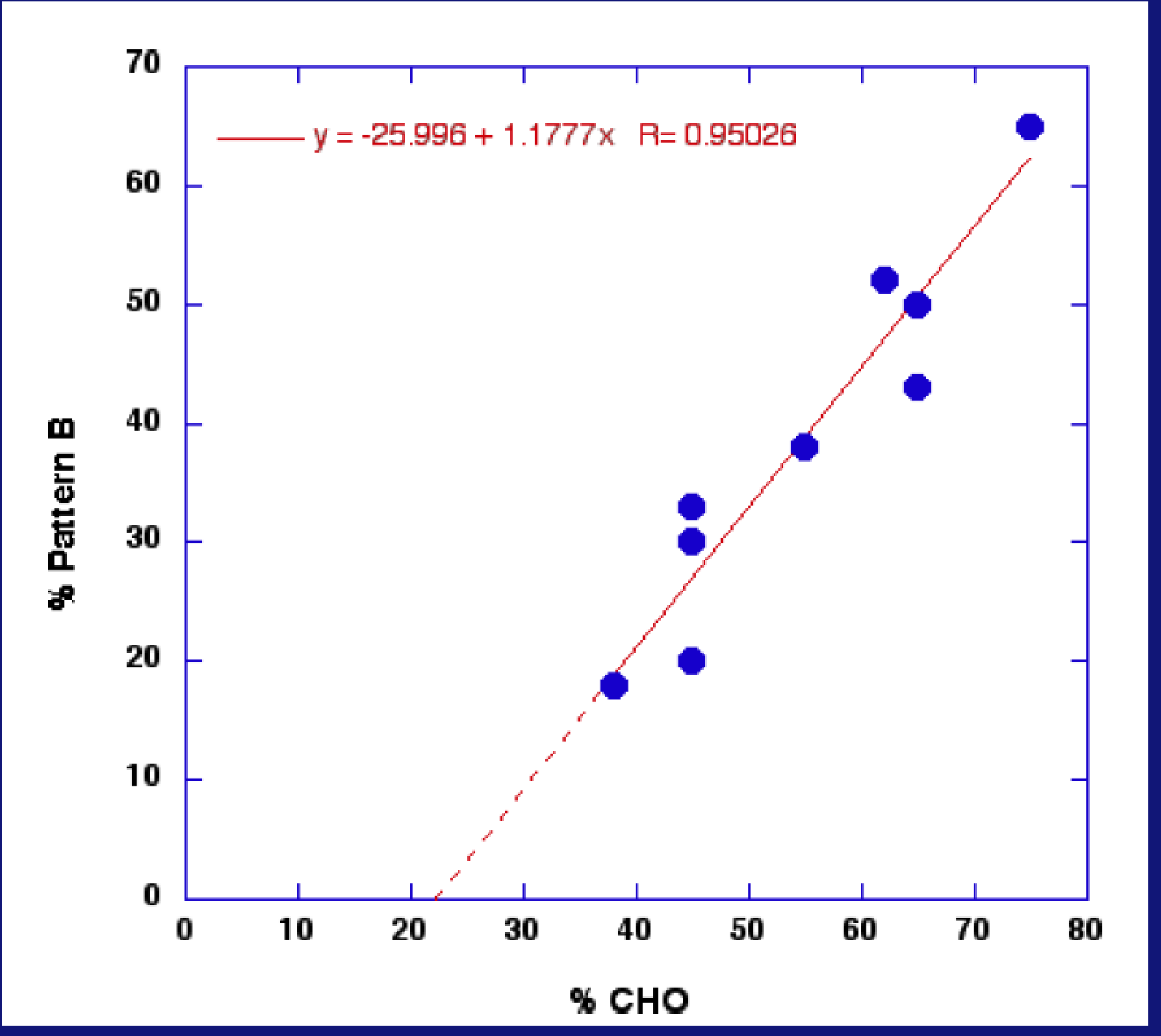
"Total LDL" won't tell you particle number -
There's more LDL_B than LDL_A at the same total concentration

TG and HDL change with LDL sizing



Rizzo and Berneis, Quart J Med 99:1, 2006

LDL particle size is responsive to dietary CHO



Krauss, J Nutr 131:340S, 2001

The low-fat craze

The content of low-fat home-cooked food can be controlled

But low-fat processed food means substitution with carbohydrate

Which carbohydrate?

Either

- High fructose corn syrup (55% fructose)
- Sucrose (50% fructose)

e.g. Nabisco Snackwells® Oreos

(—2g fat, +13g CHO (+4g sugars))

Adulteration of our food supply

Addition of fructose

- palatability (esp. with decreased fat)
- browning agent

Removal of fiber

- shelf life
- freezing

Substitution of trans-fats

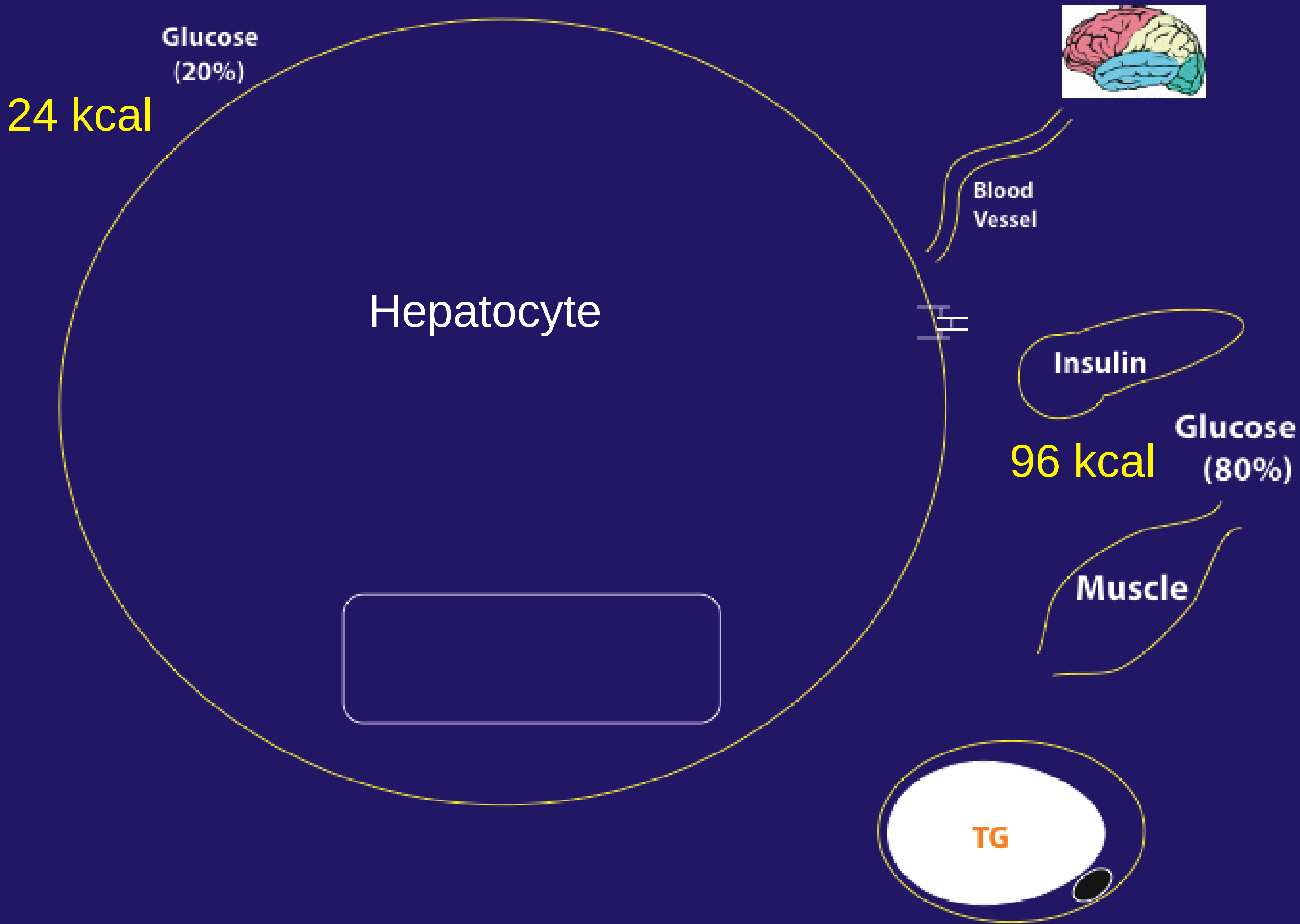
- hardening agent, shelf life
- now being removed due to CVD risk

Fructose is not glucose

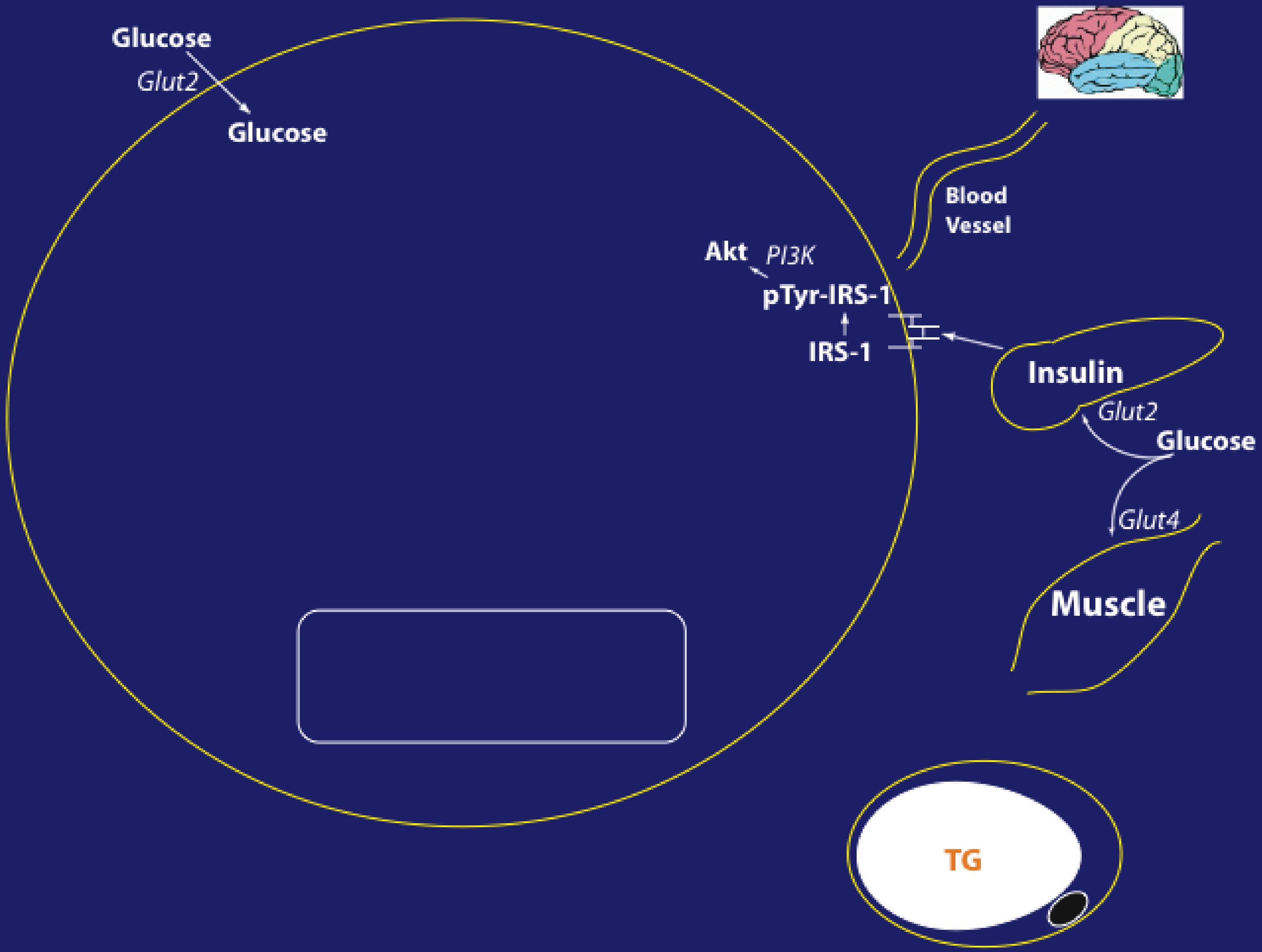
- Fructose is 7 times more likely than glucose to form Advanced Glycation End-Products (AGE’s)
- Fructose does not suppress ghrelin
- Acute fructose does not stimulate insulin (or leptin)
- Hepatic fructose metabolism is different
- **Chronic fructose exposure promotes the Metabolic Syndrome**

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
Johnson et al. Am J Clin Nutr 2007
Rutledge and Adeli, Nutr Rev, 2007
Brown et al. Int. J. Obes, 2008

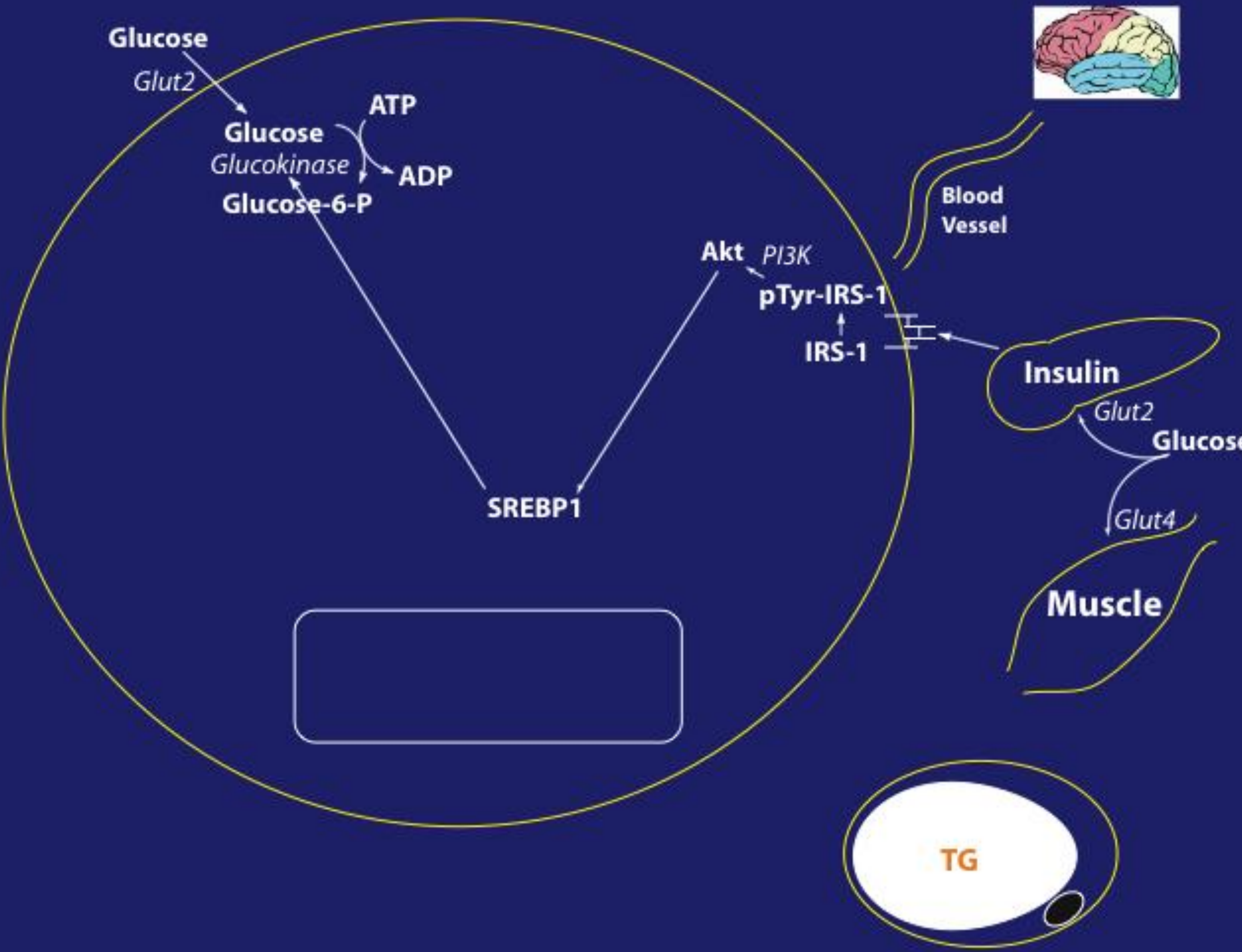
Metabolism of Glucose



Metabolism of Glucose



Metabolism of Glucose



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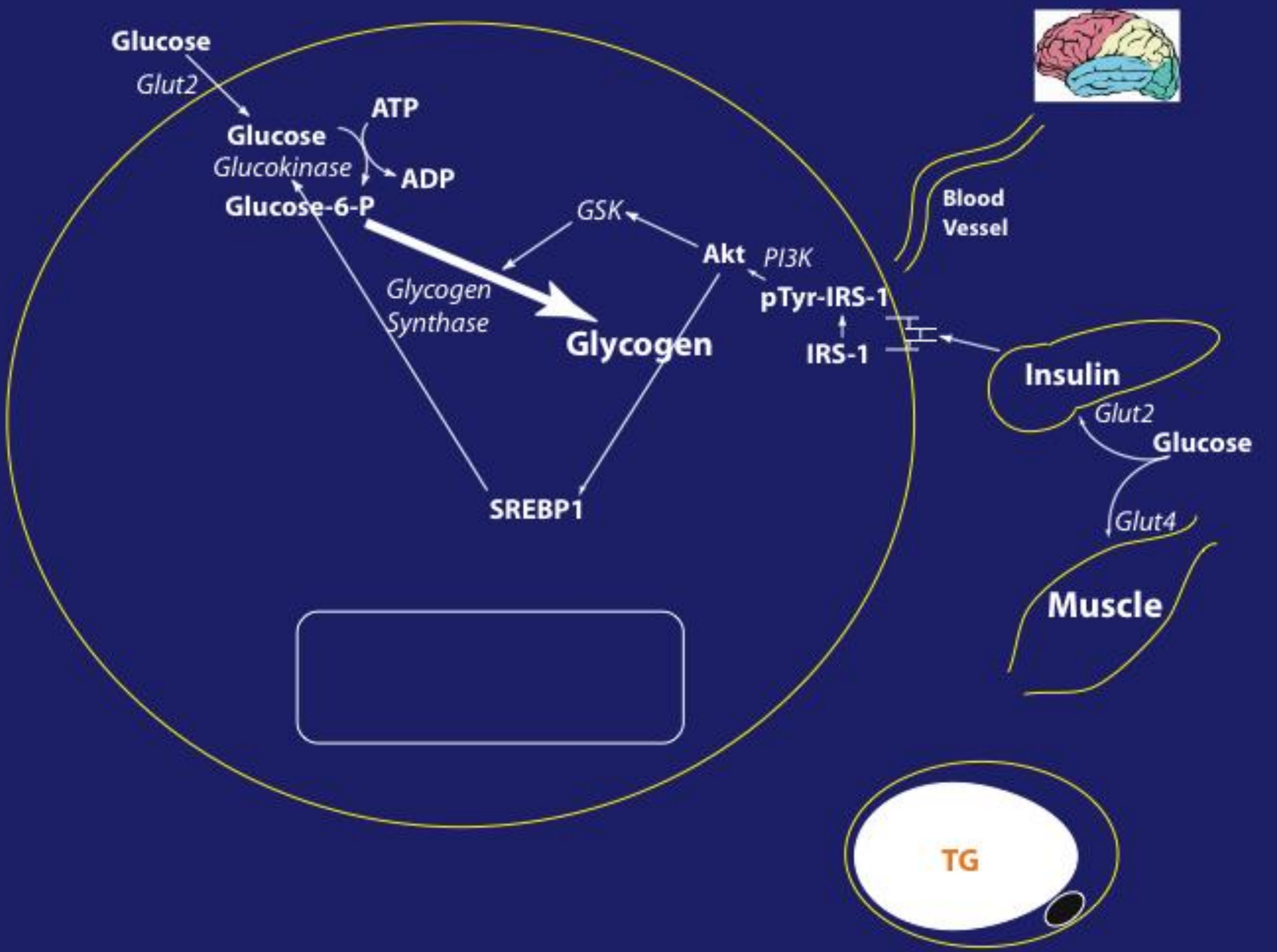

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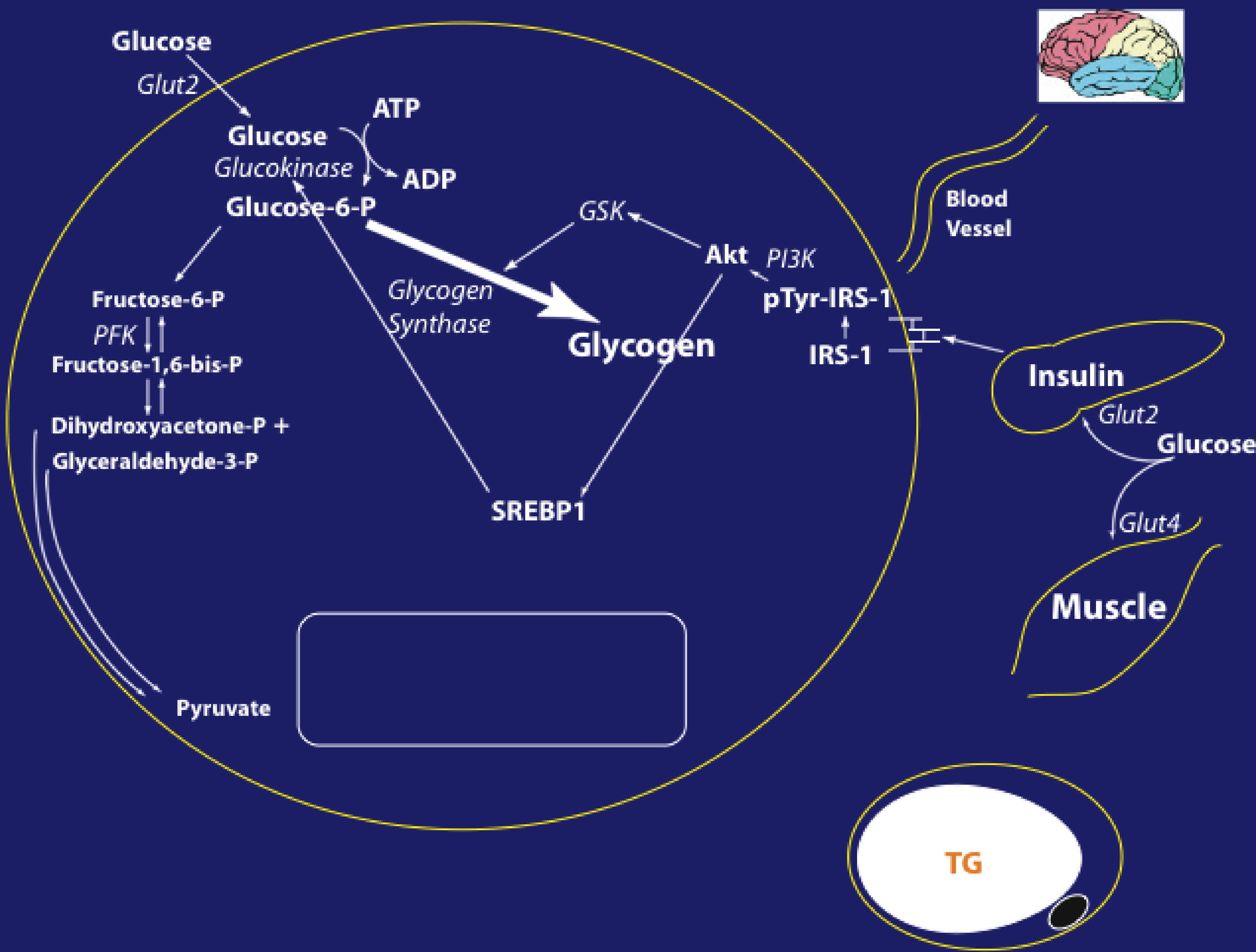

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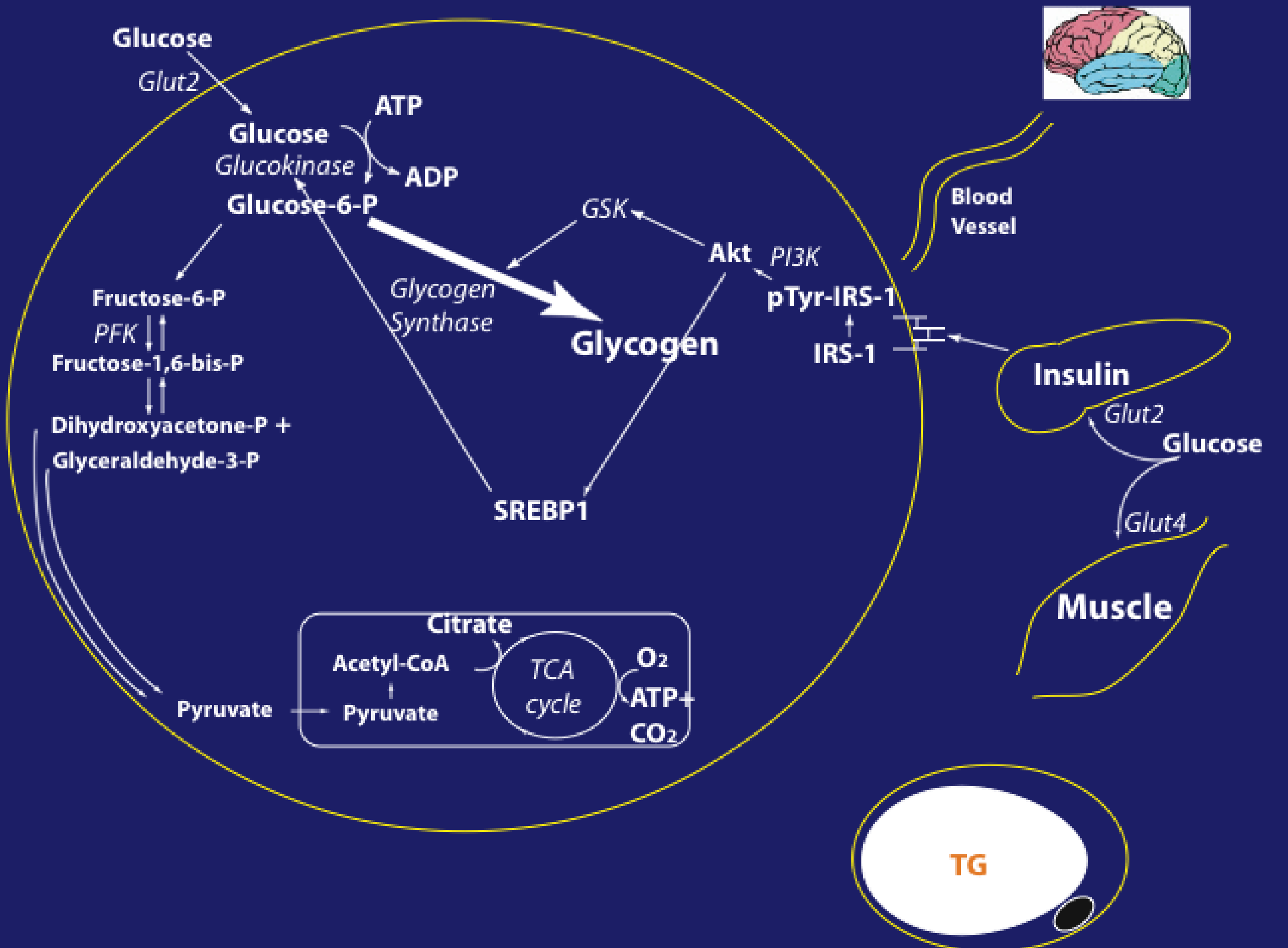
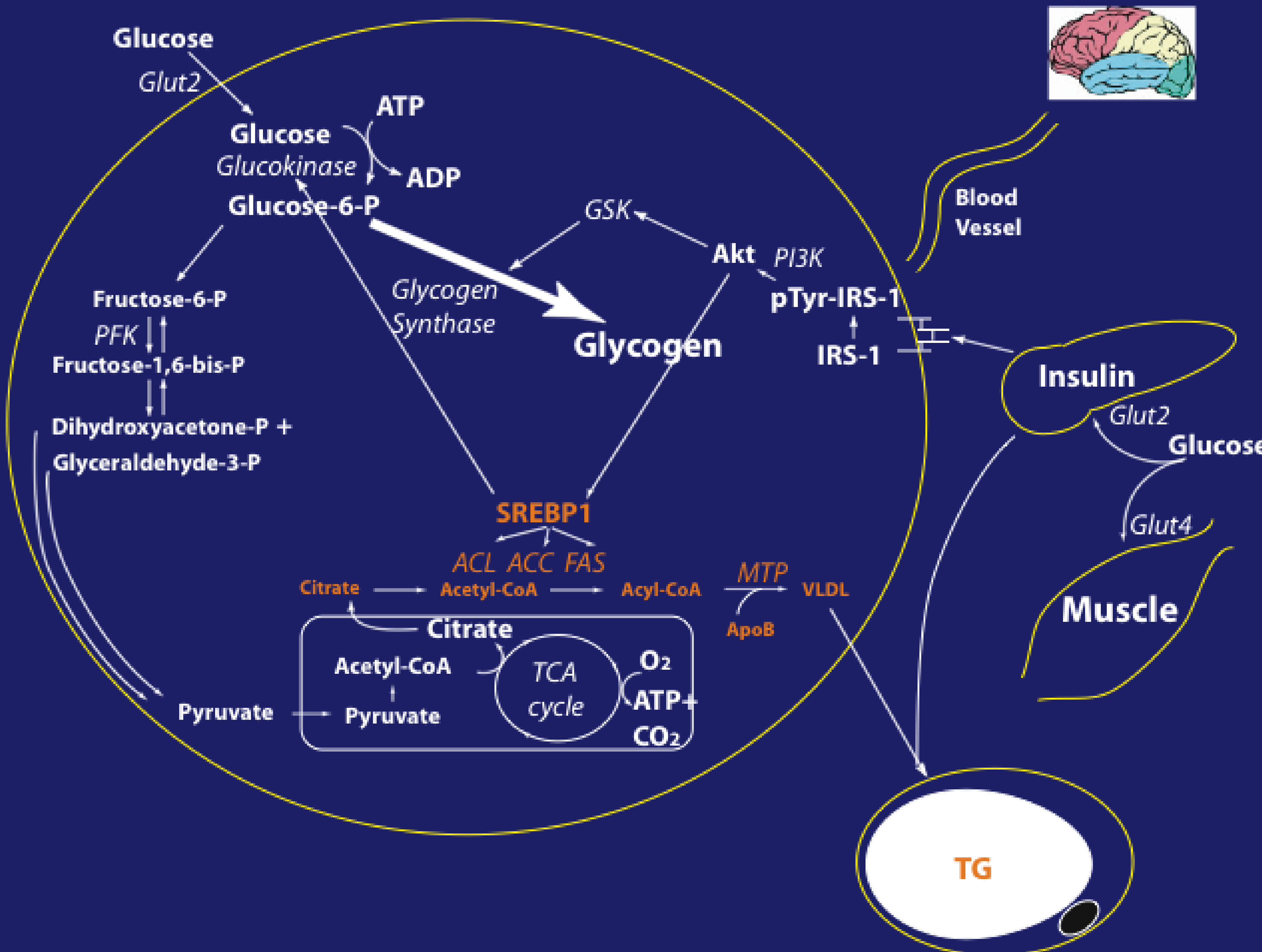
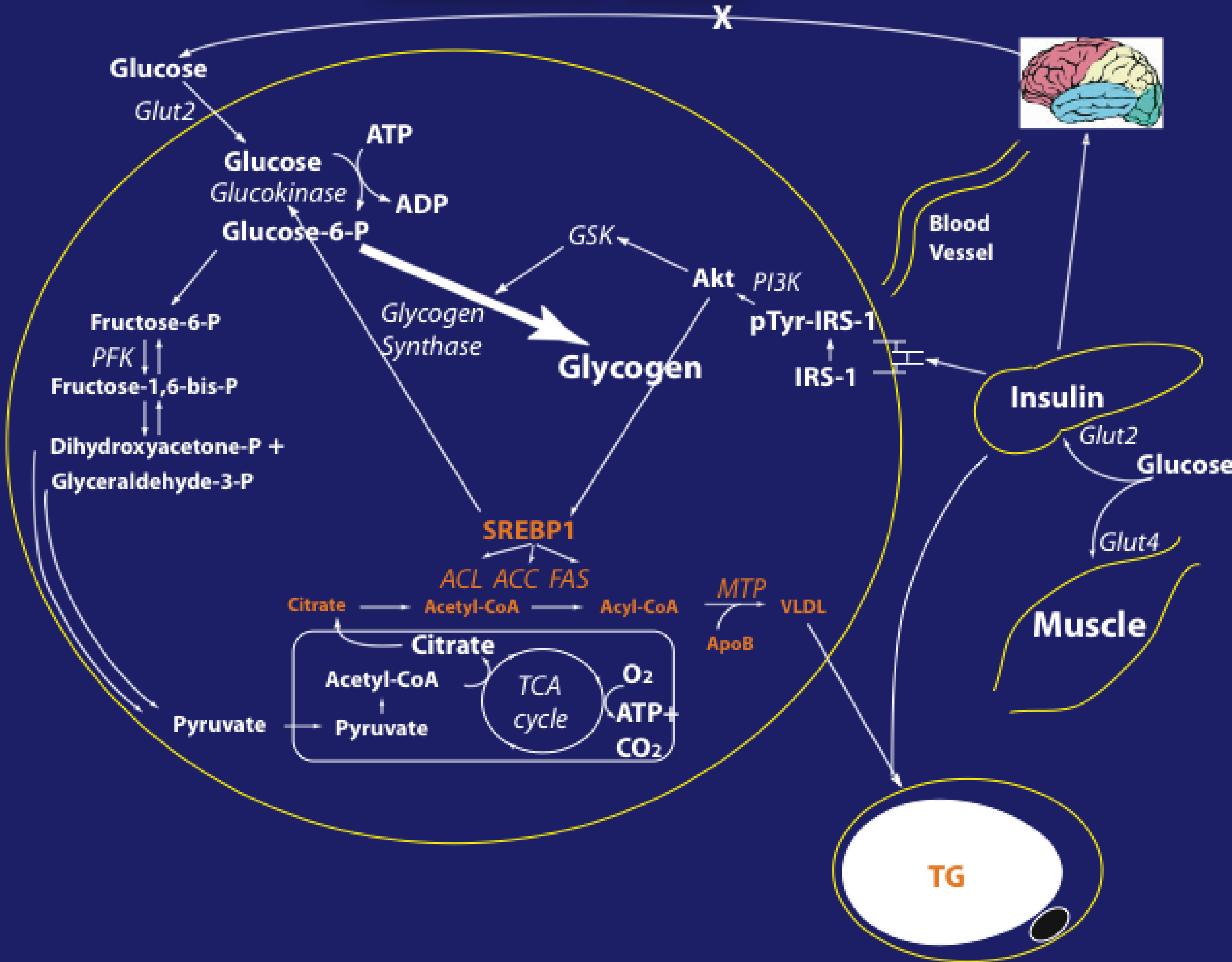


Metabolism of Glucose



Metabolism of Glucose



Ethanol is a carbohydrate

Ethanol is a carbohydrate

CH_3-CH_2-OH

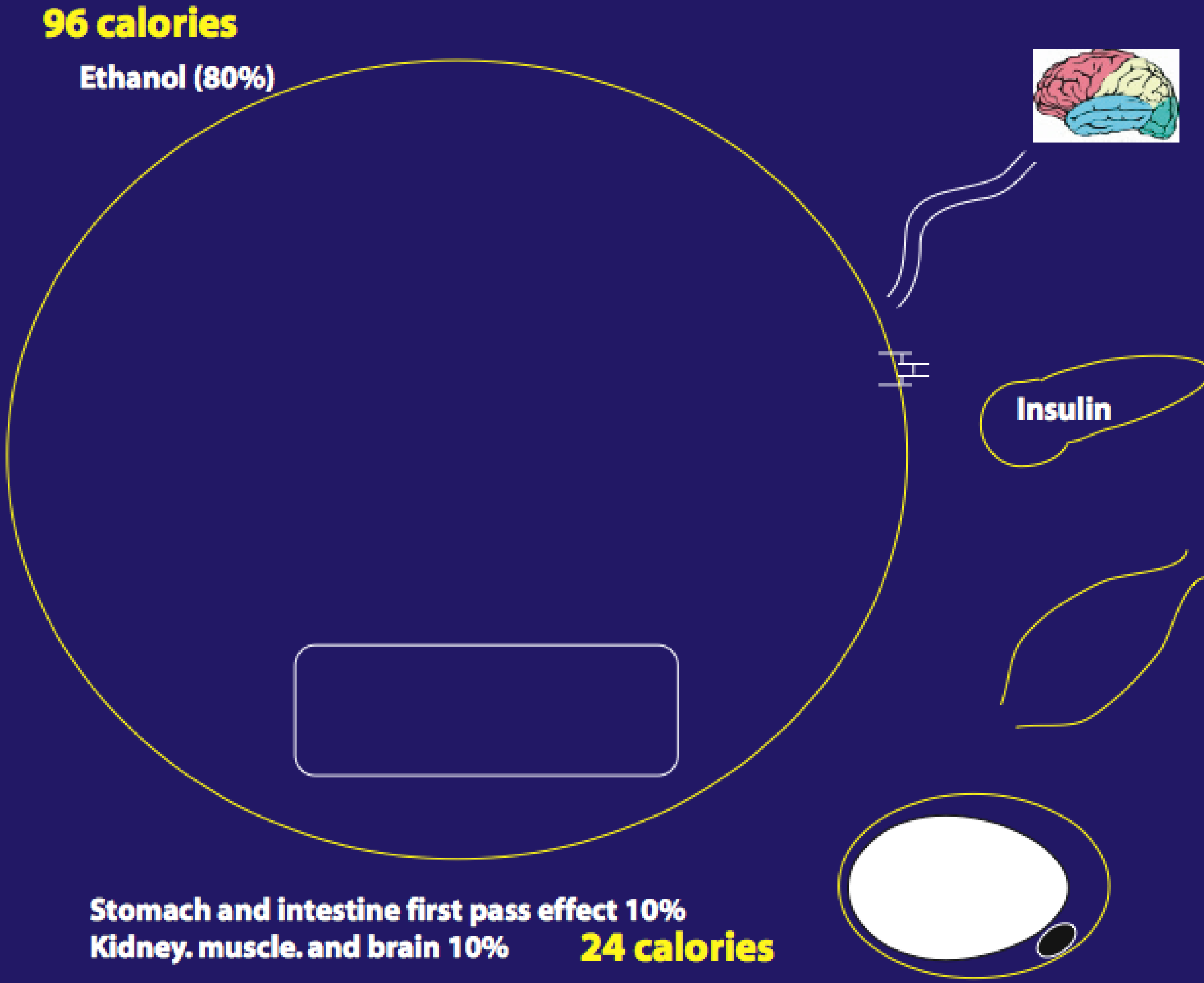
Ethanol is a carbohydrate

CH_3-CH_2-OH

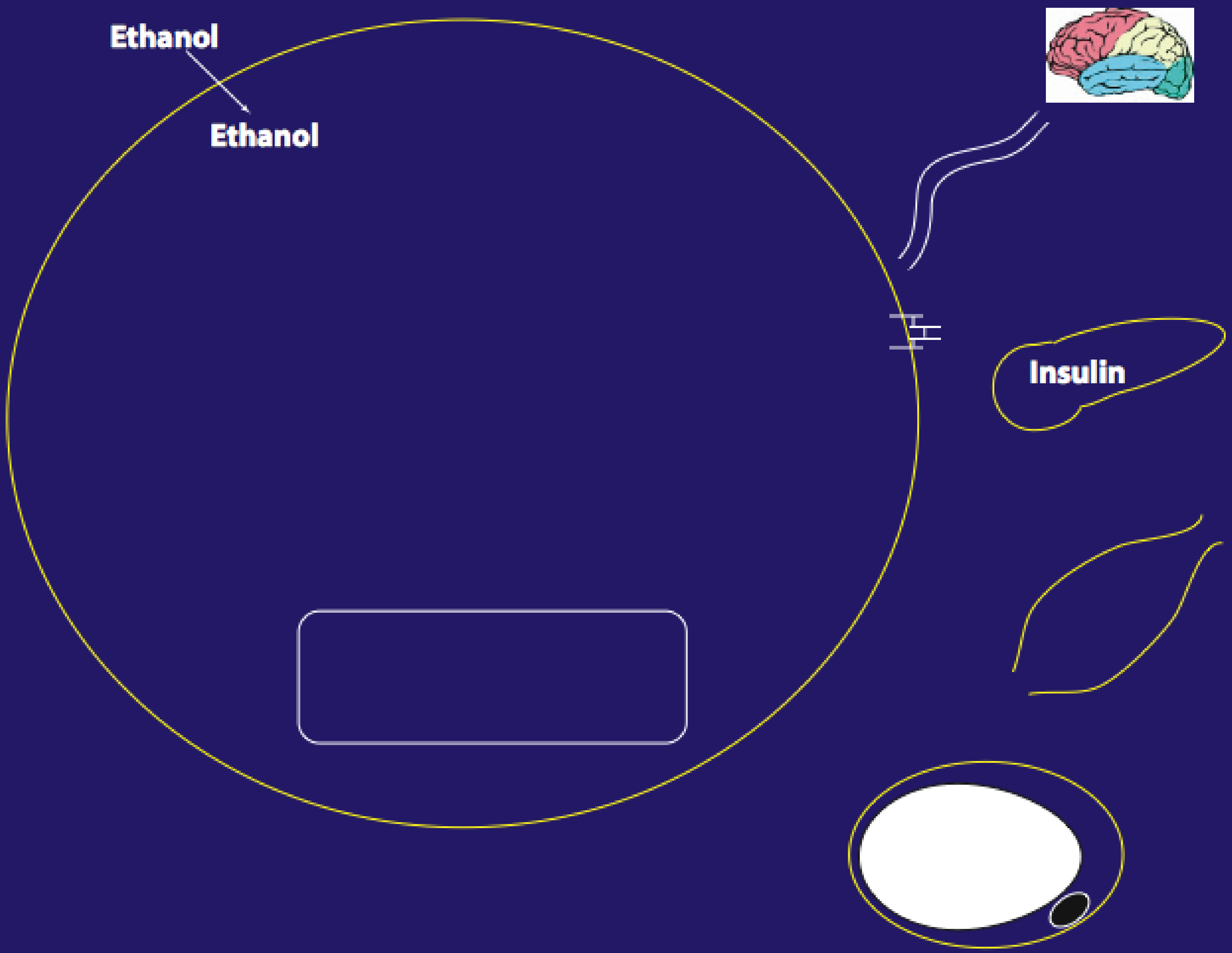
But ethanol is also a toxin

Acute ethanol exposure	Acute fructose exposure
• CNS depression	
• Vasodilatation, decreased BP	
• Hypothermia	
• Tachycardia	
• Myocardial depression	
• Variable pupillary responses	
• Respiratory depression	
• Diuresis	
• Hypoglycemia	
• Loss of fine motor control	

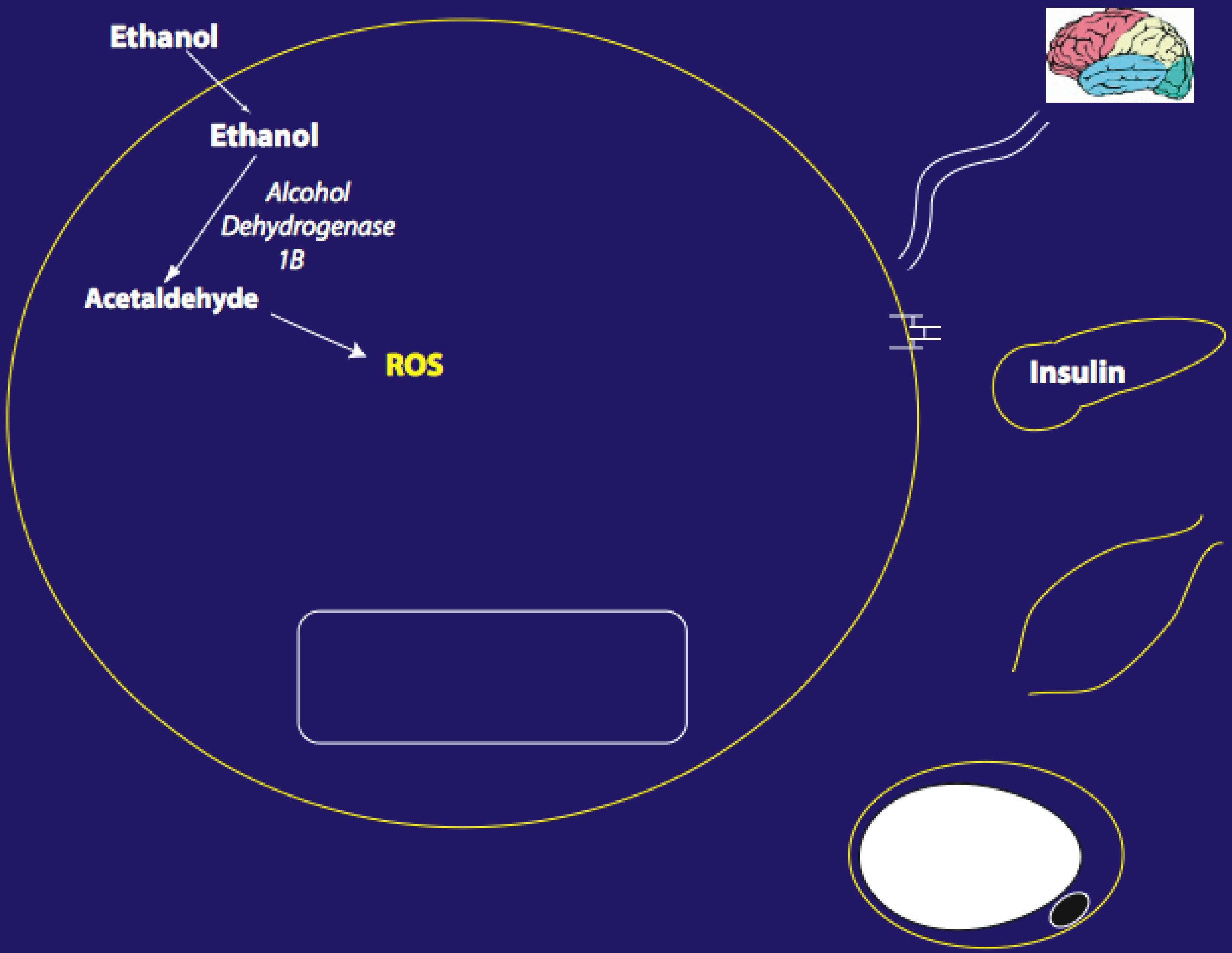
Metabolism of Ethanol



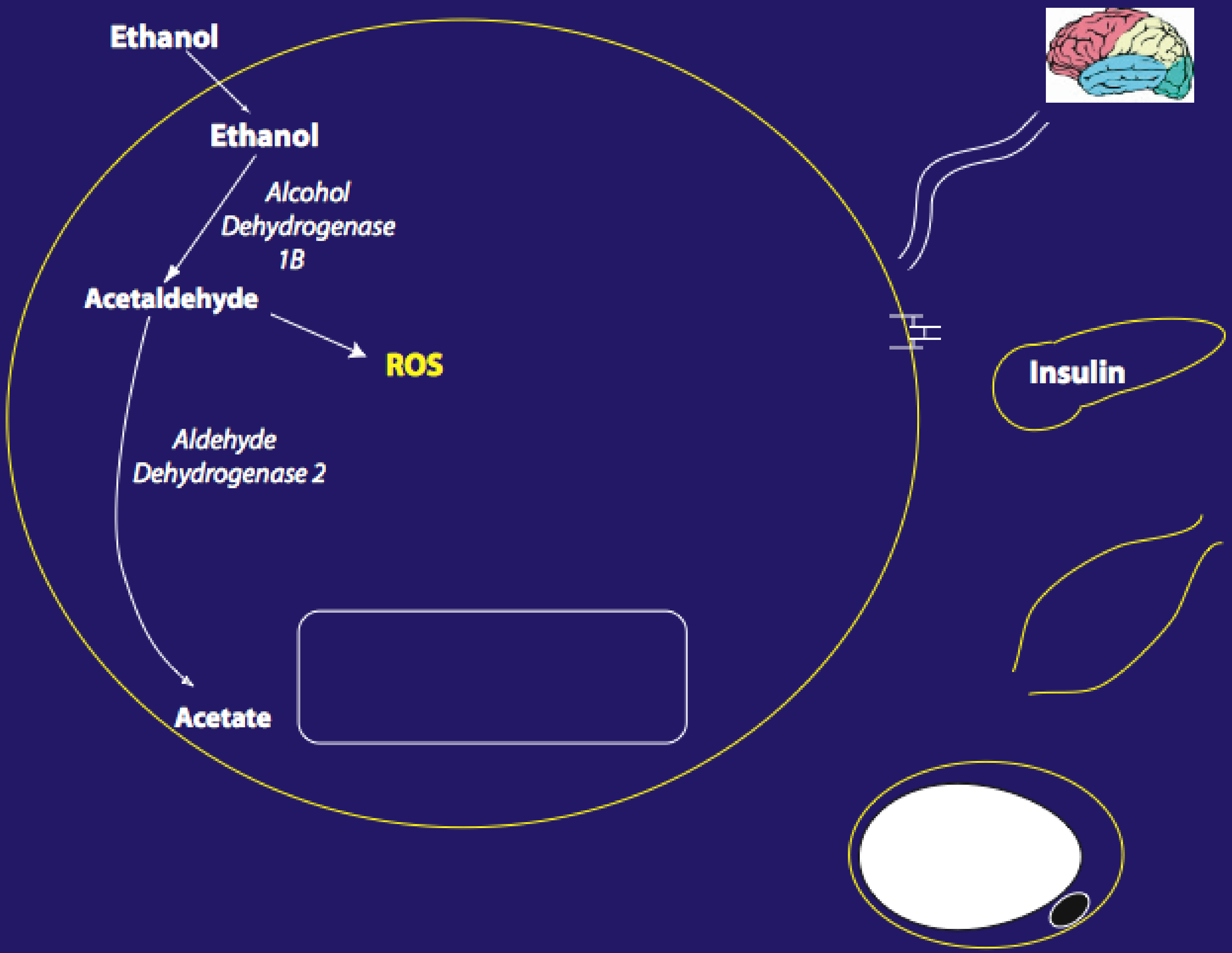
Metabolism of Ethanol



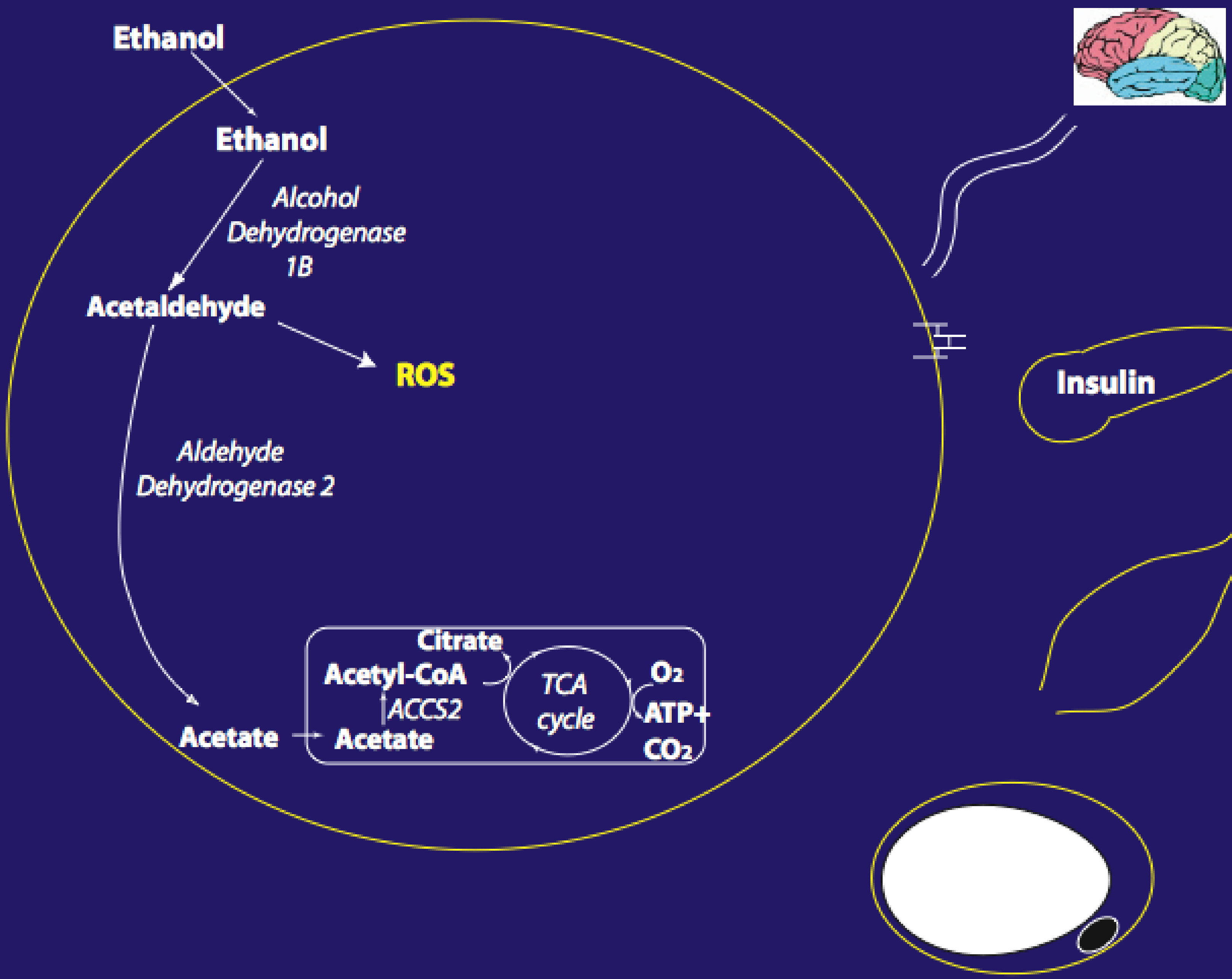
Metabolism of Ethanol



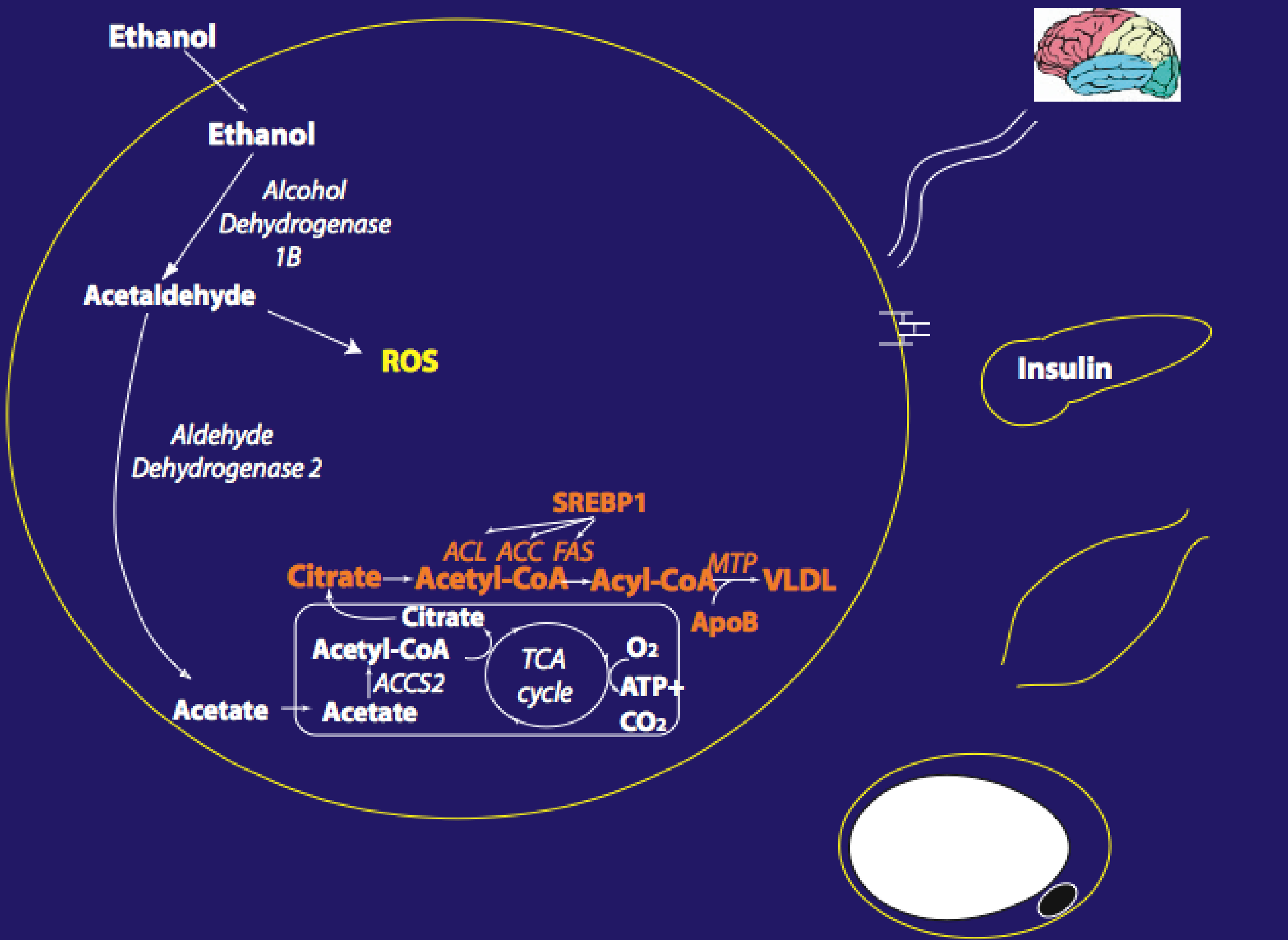
Metabolism of Ethanol



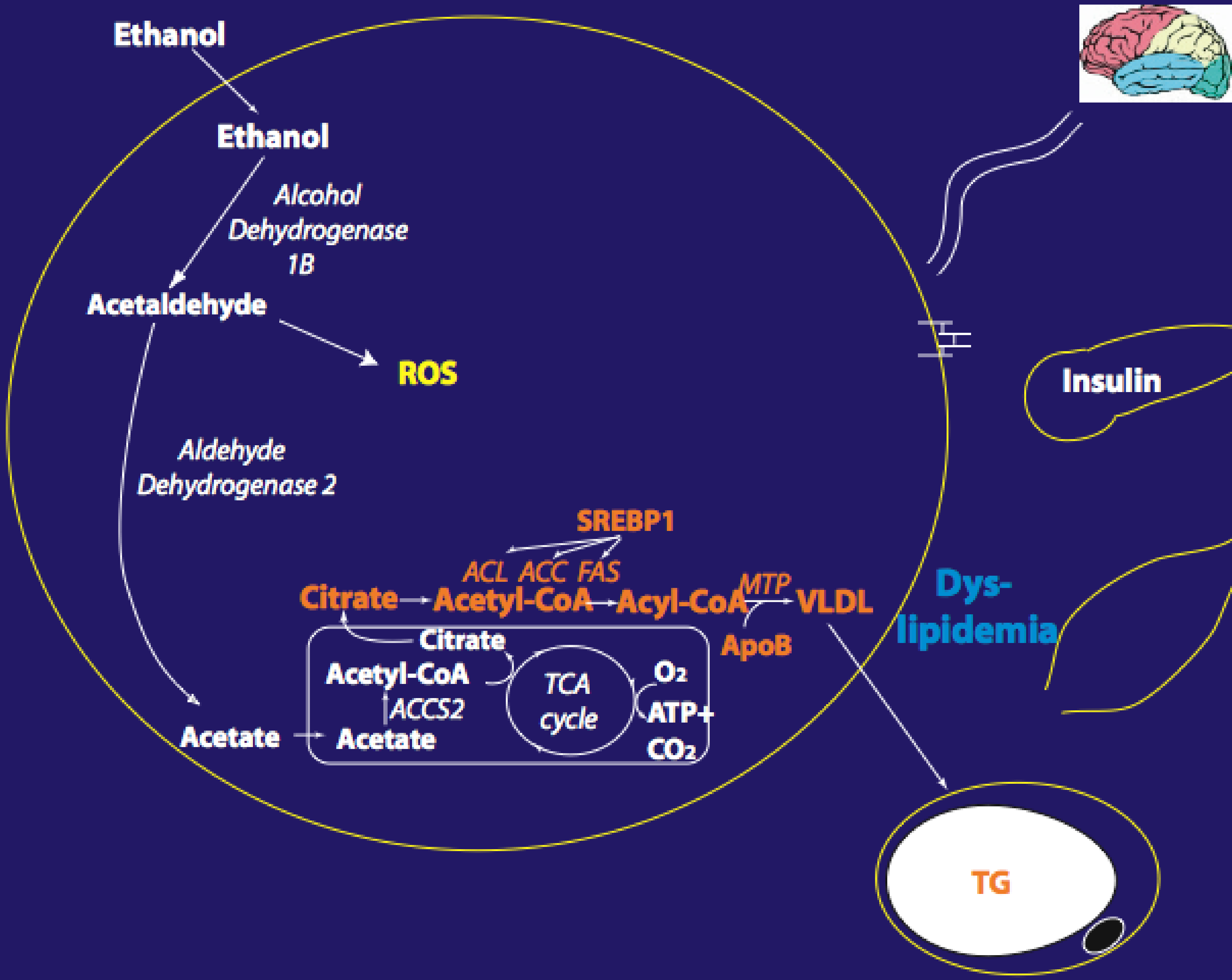
Metabolism of Ethanol



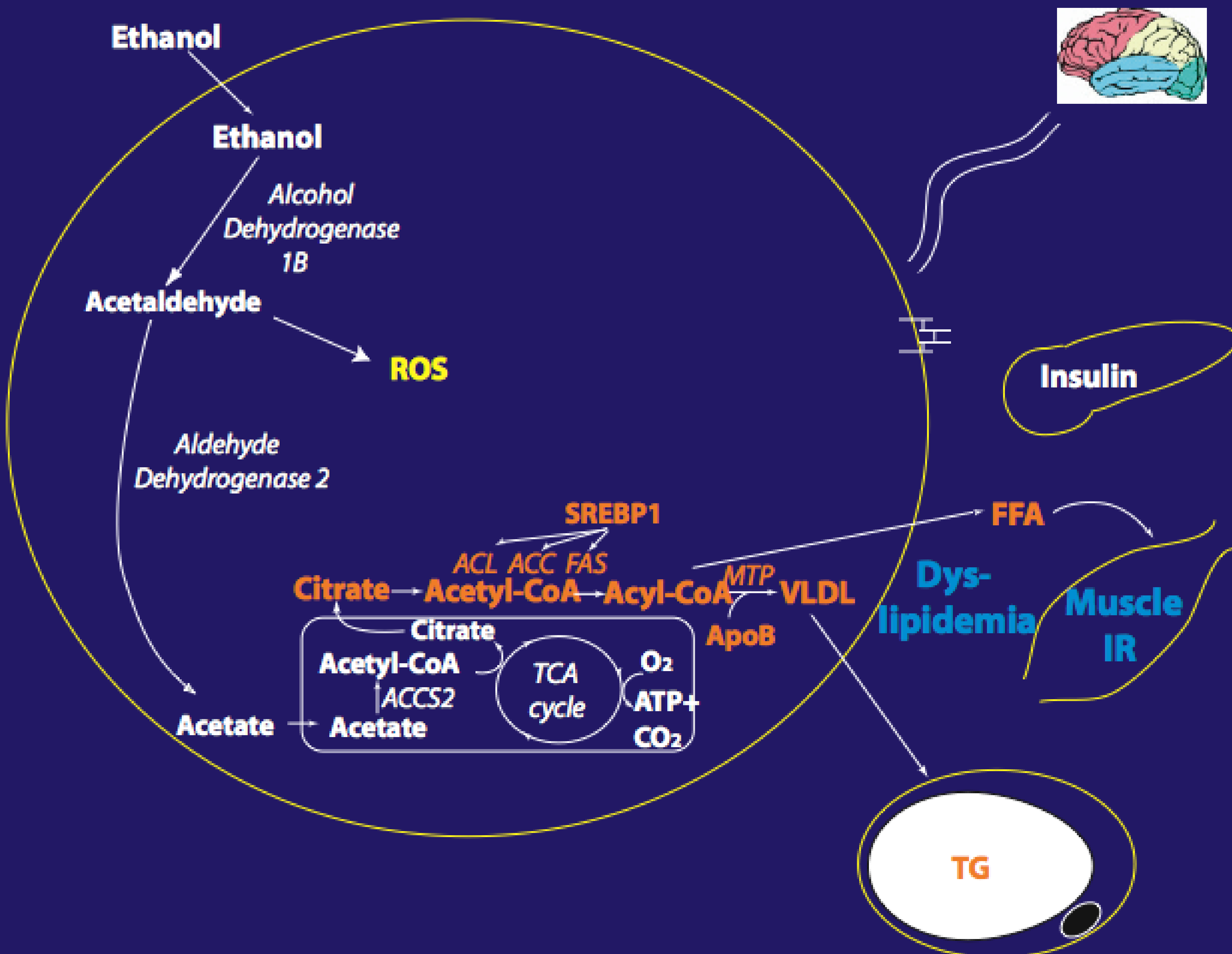
Metabolism of Ethanol



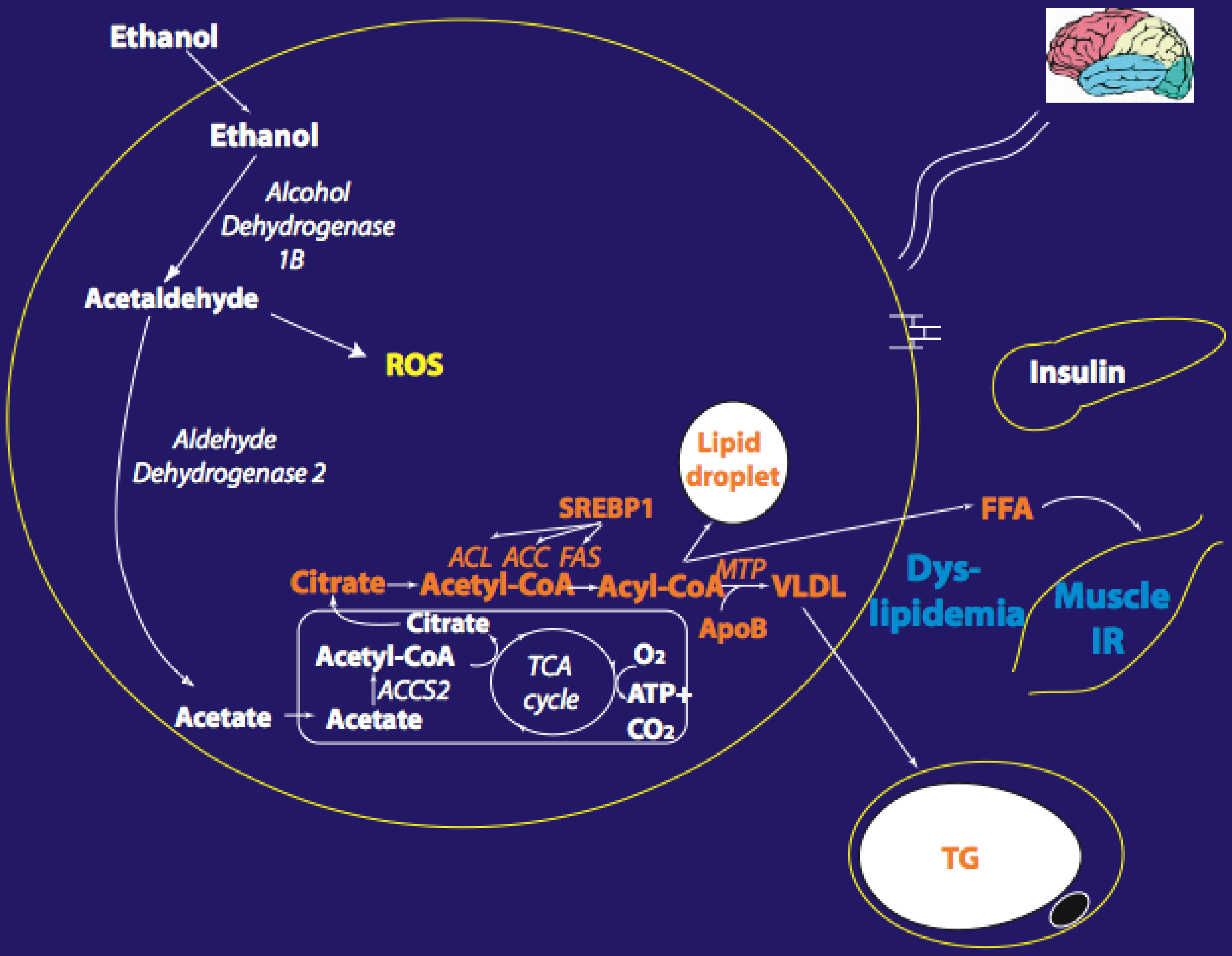
Metabolism of Ethanol



Metabolism of Ethanol



Metabolism of Ethanol



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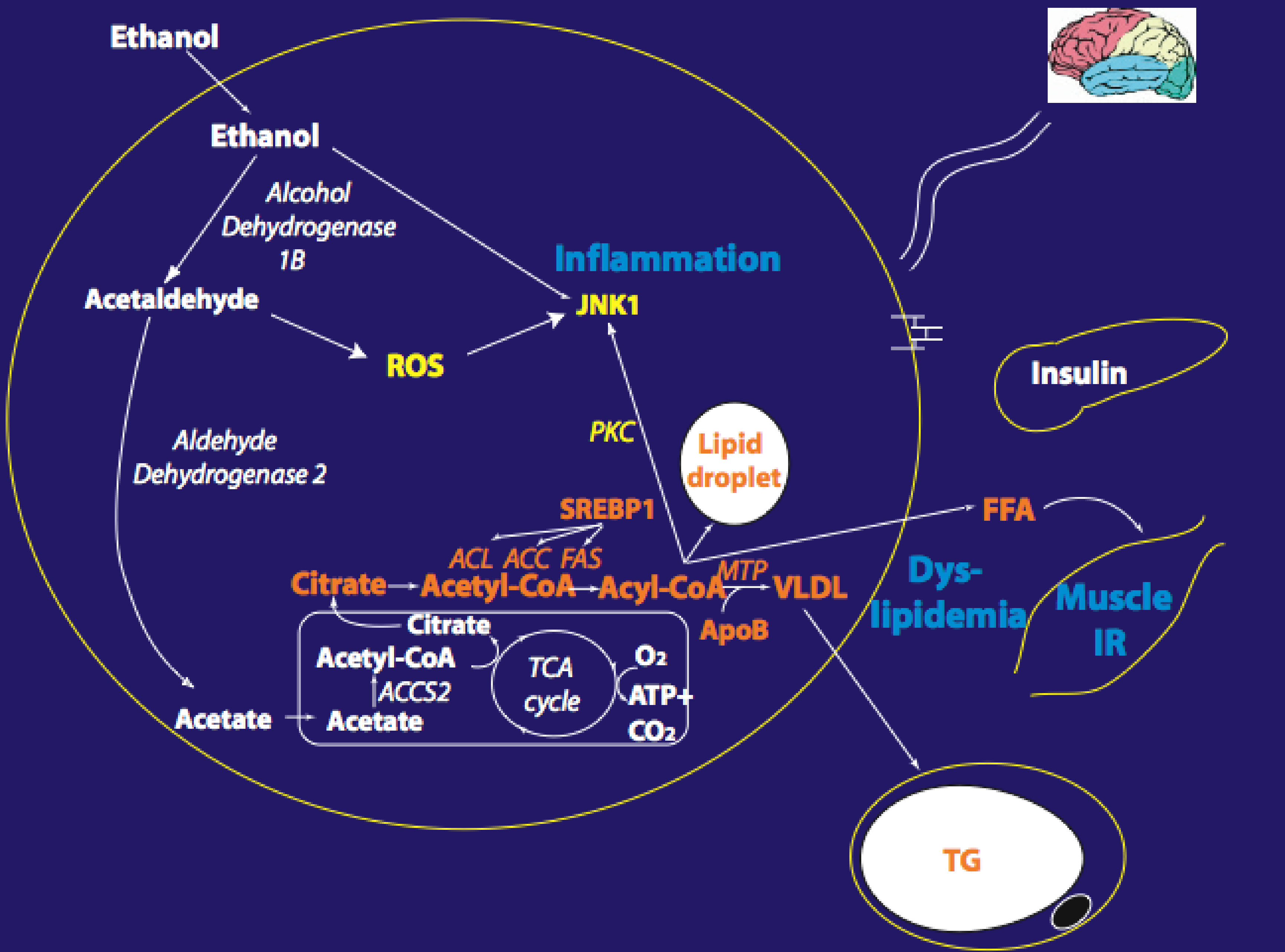
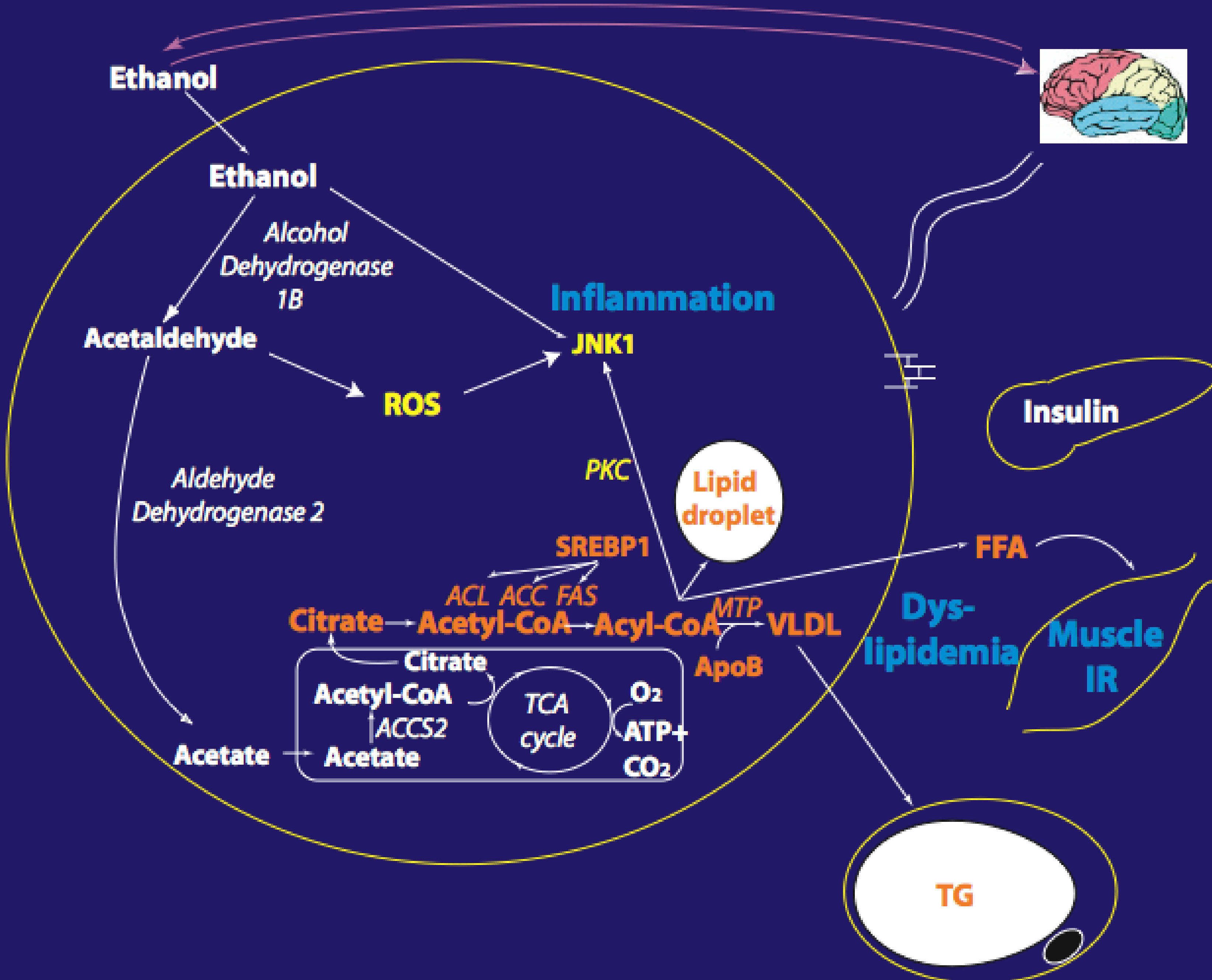
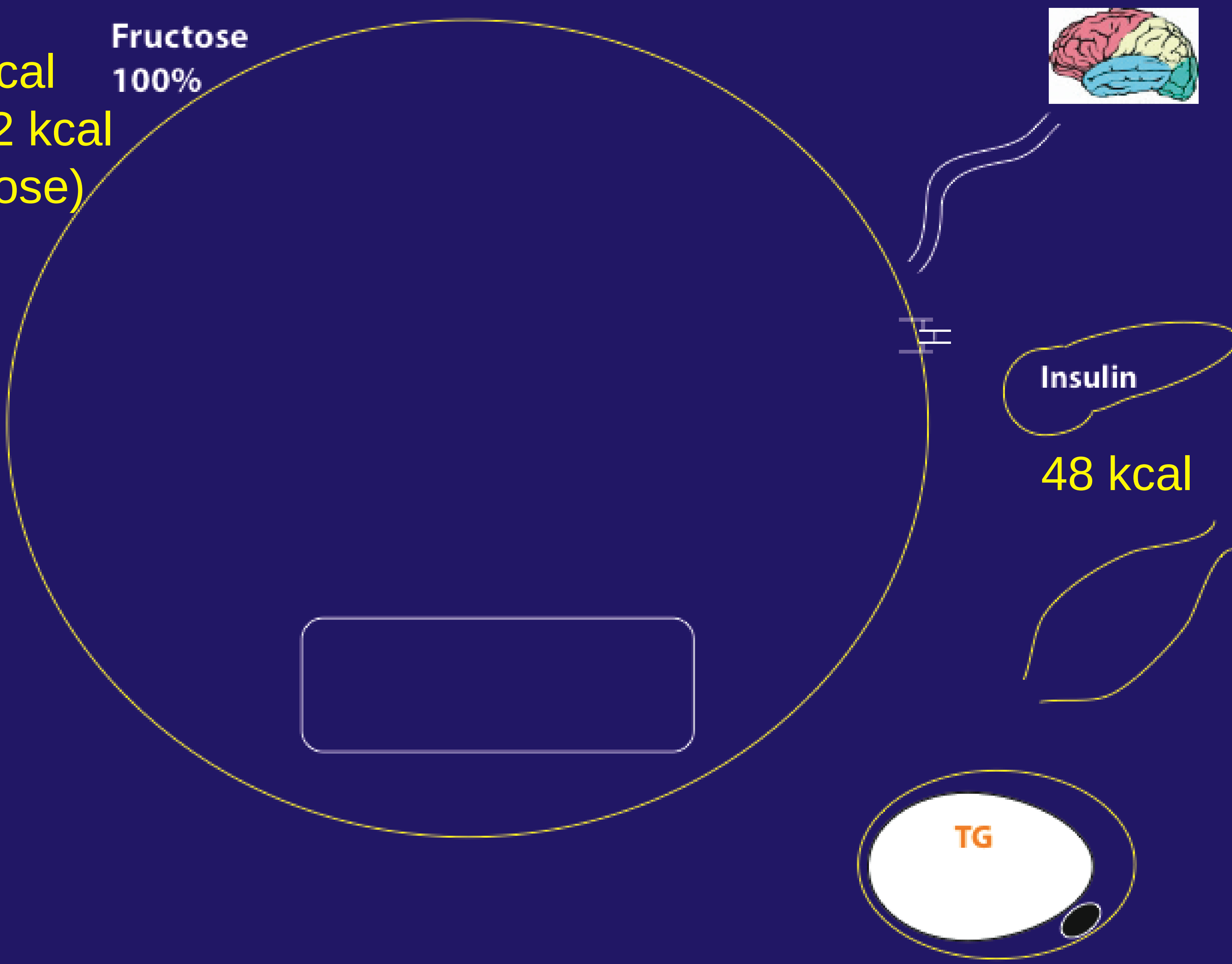


Metabolism of Ethanol



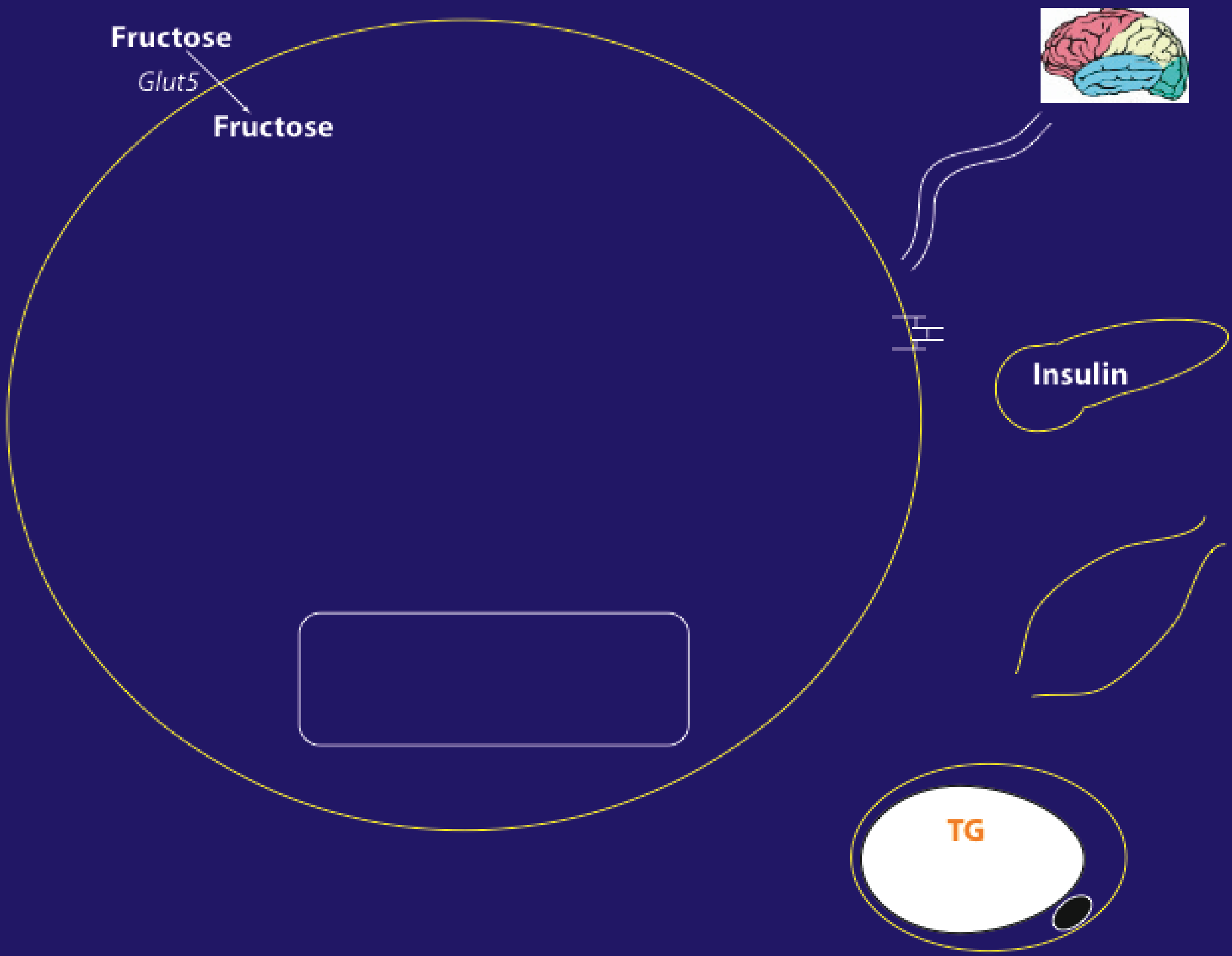
Detrimental Effects of Fructose

60 kcal
(+ 12 kcal glucose)

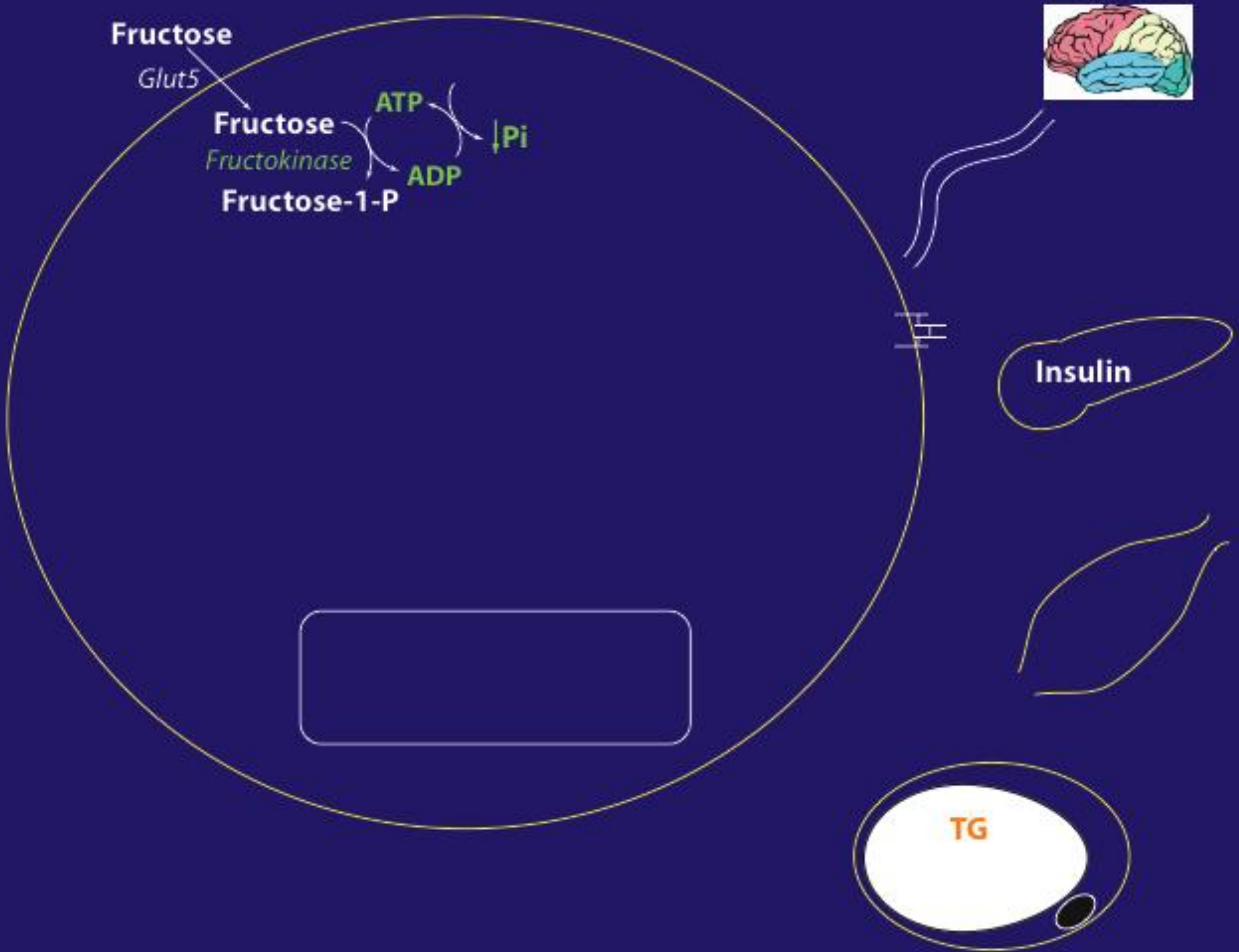


48 kcal

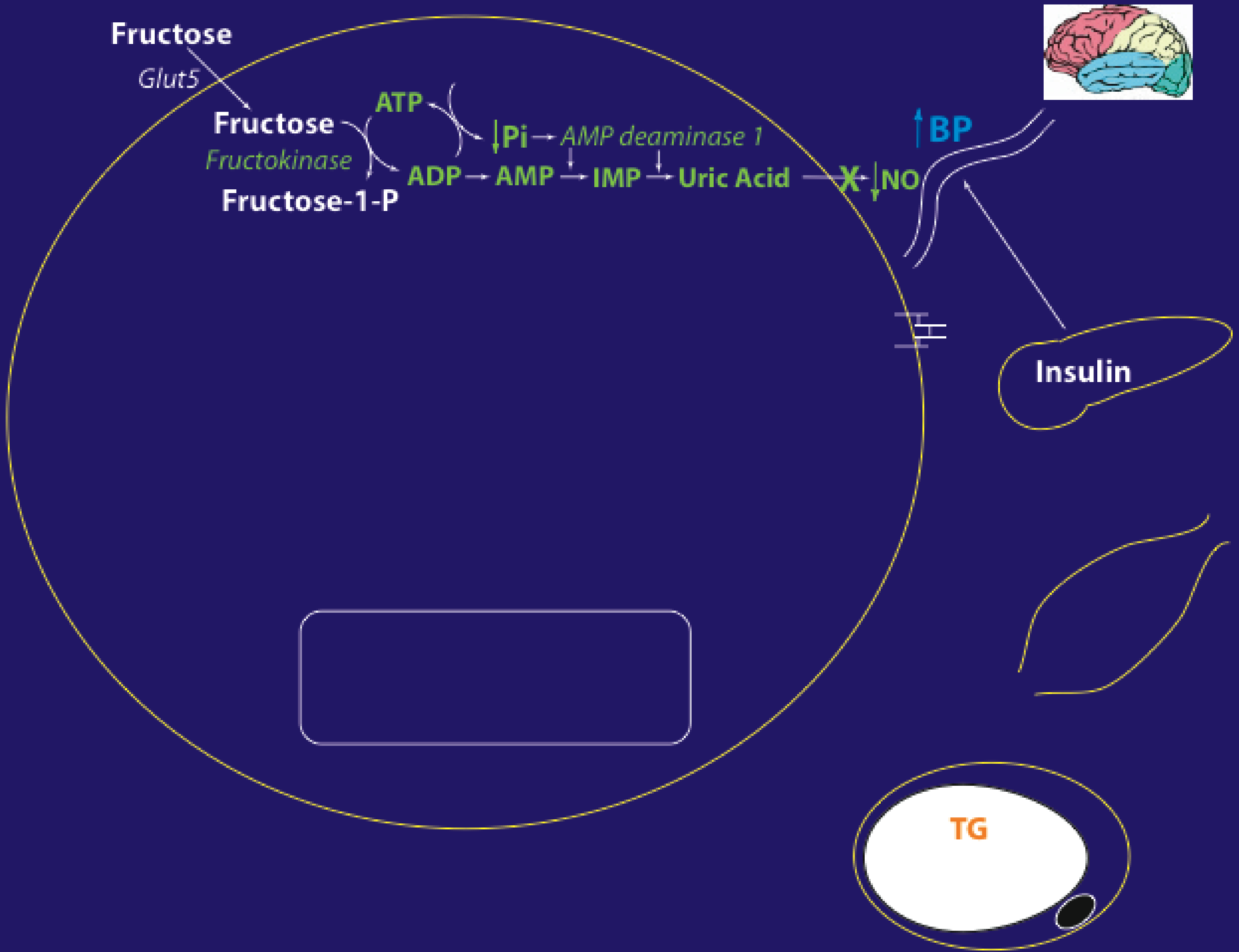
Detrimental Effects of Fructose



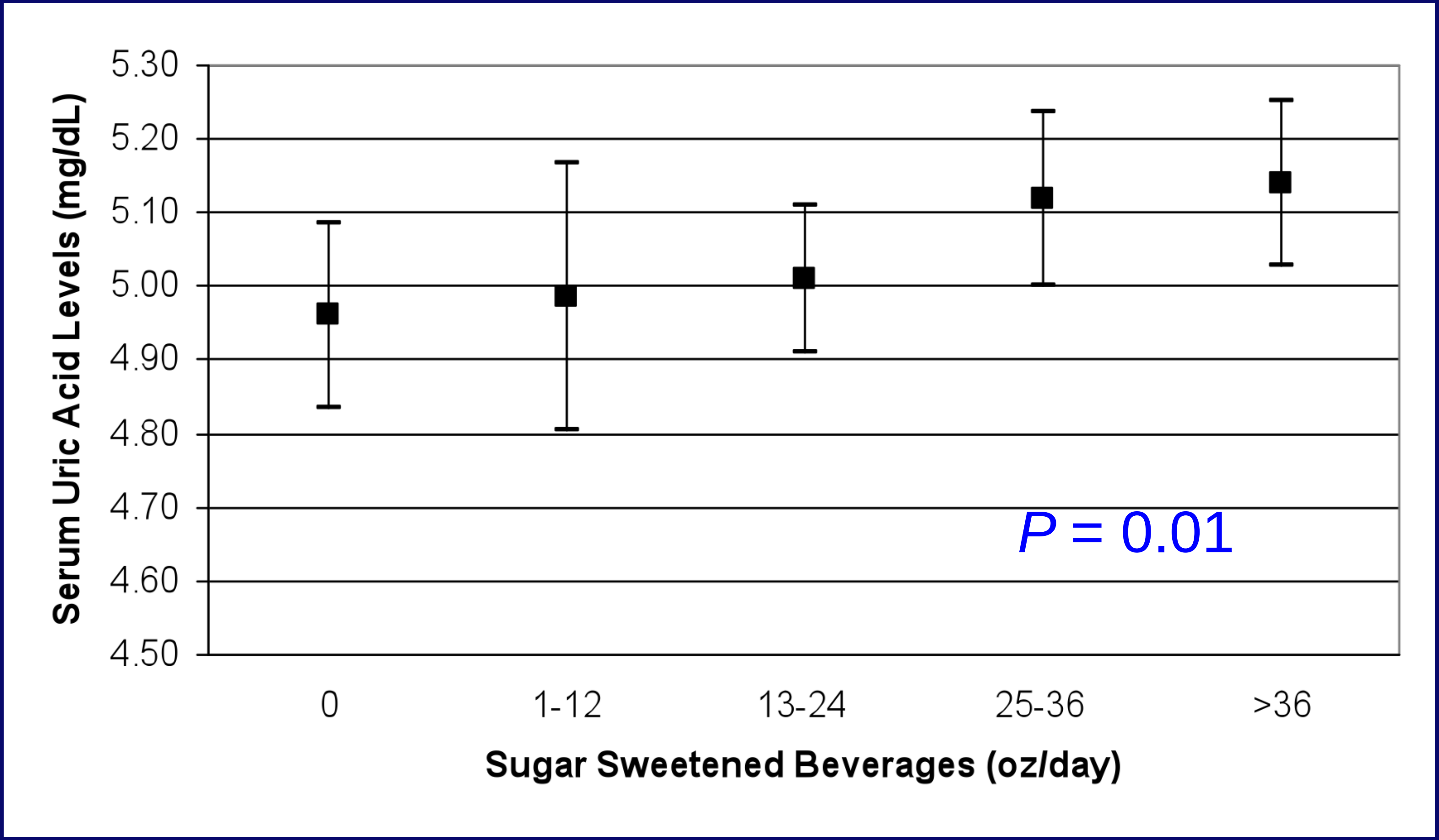
Detrimental Effects of Fructose



Detrimental Effects of Fructose

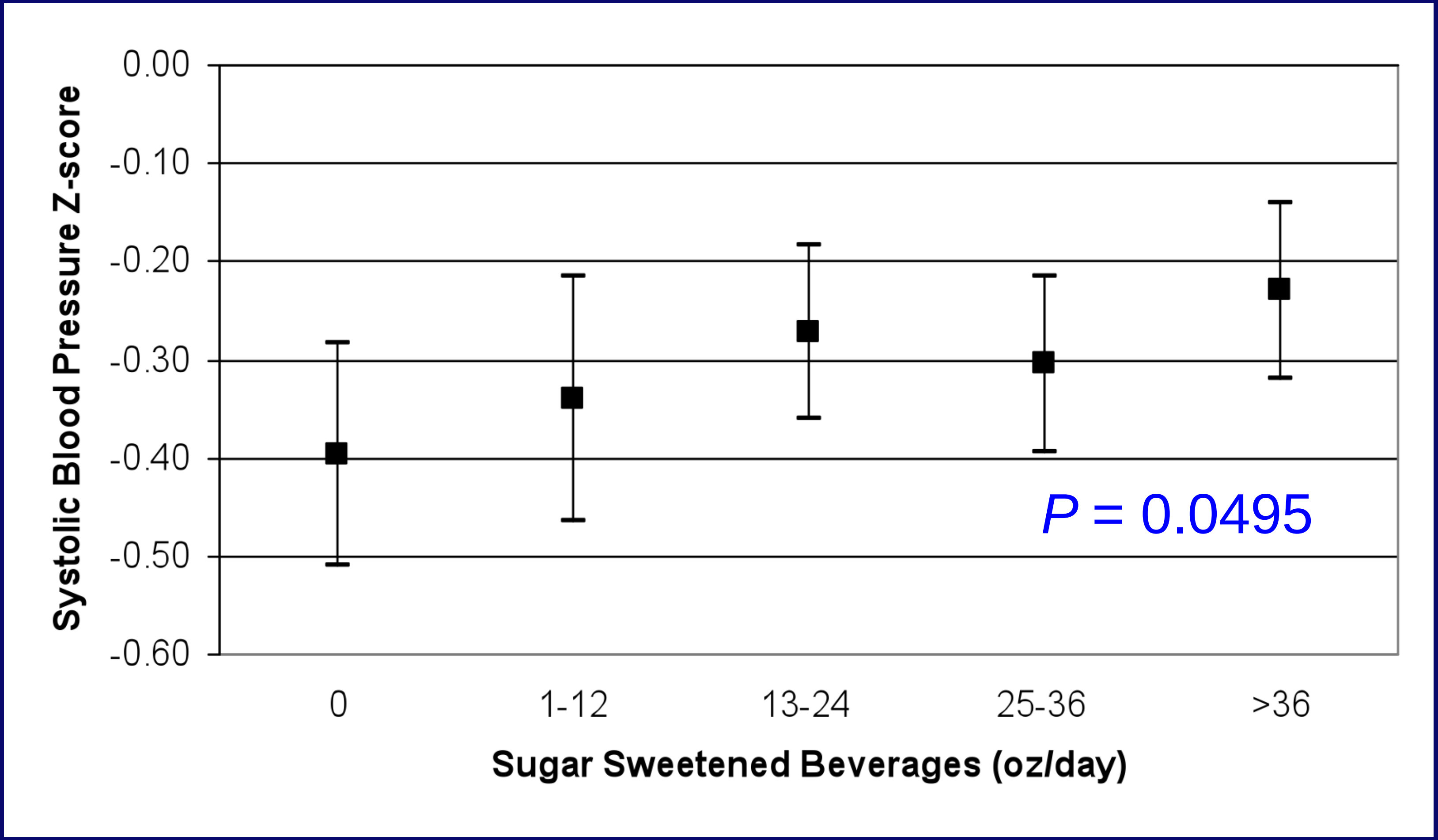


Relations between fructose, uric acid and hypertension in NHANES IV adolescents



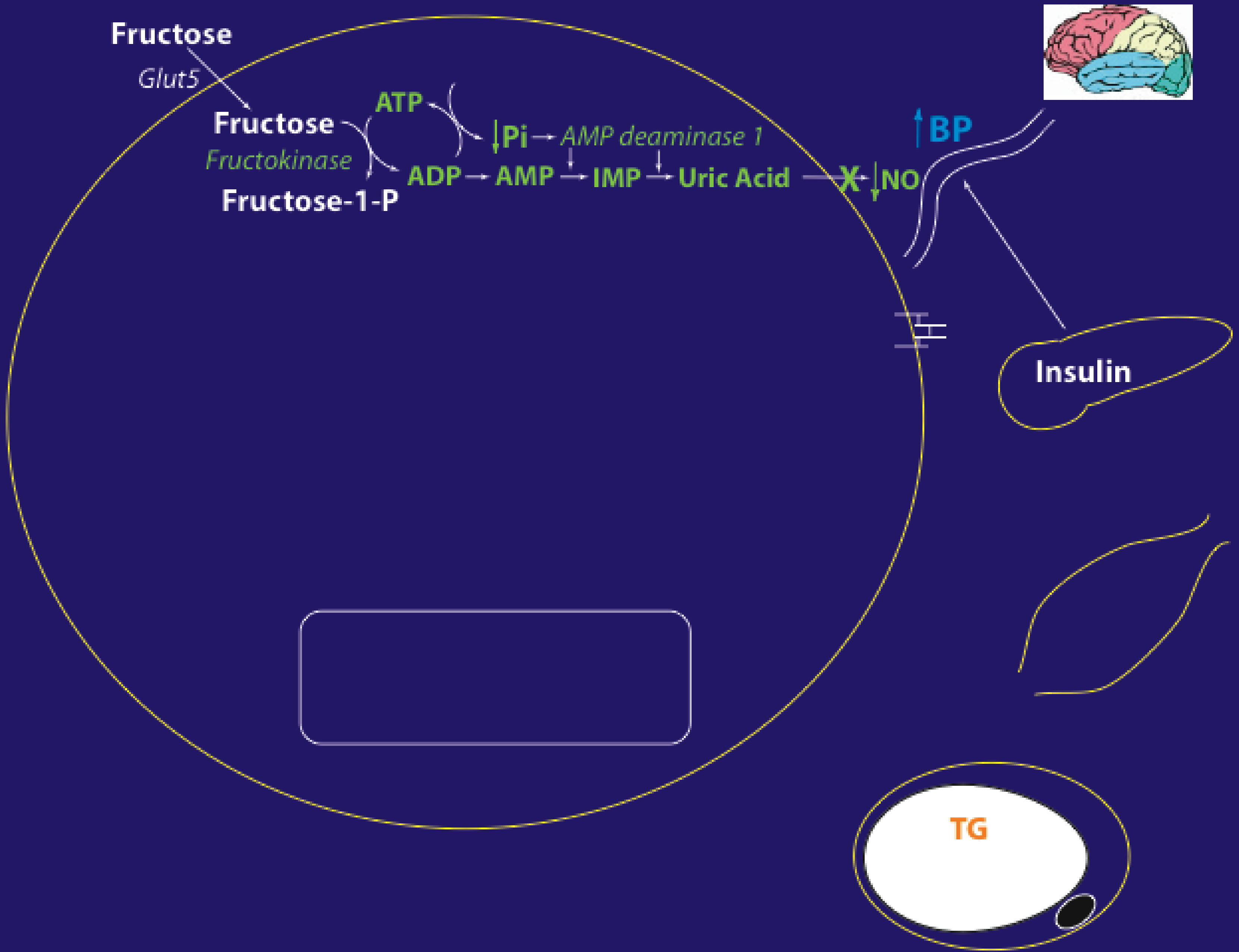
S Nguyen et al. J Pediatr 154:806, 2009

Relations between fructose, uric acid and hypertension in NHANES IV adolescents

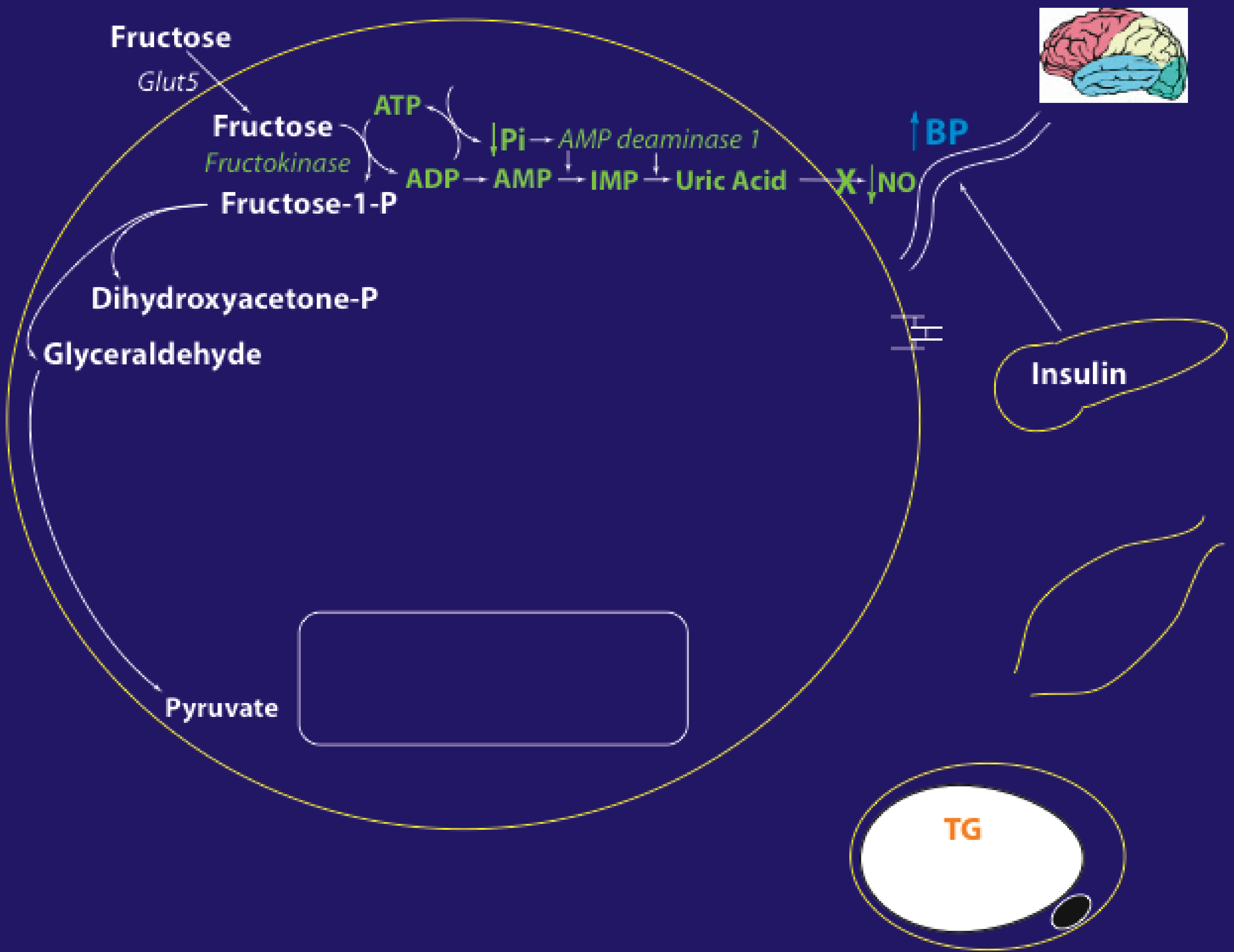


S Nguyen et al. J Pediatr 154:806, 2009

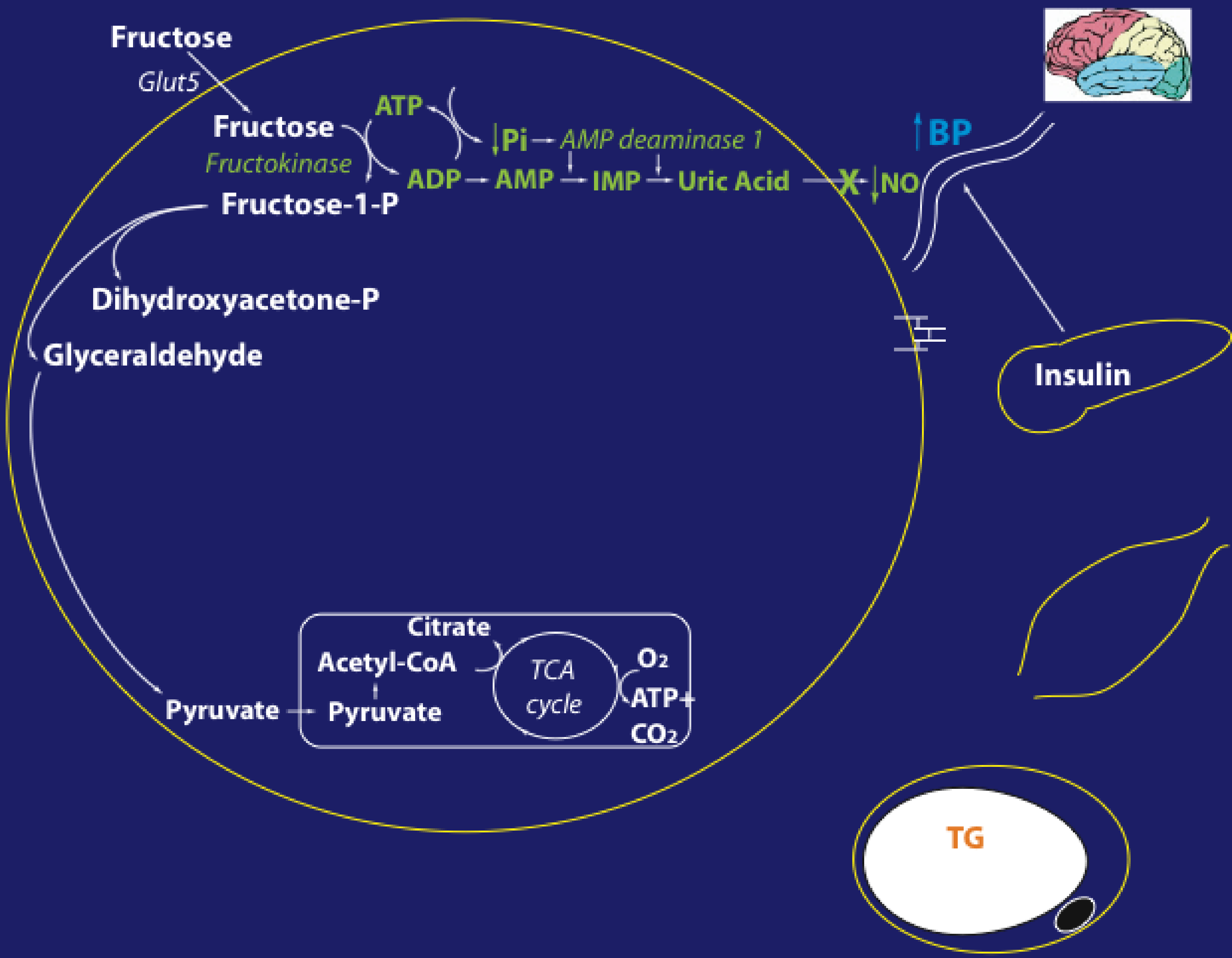
Detrimental Effects of Fructose



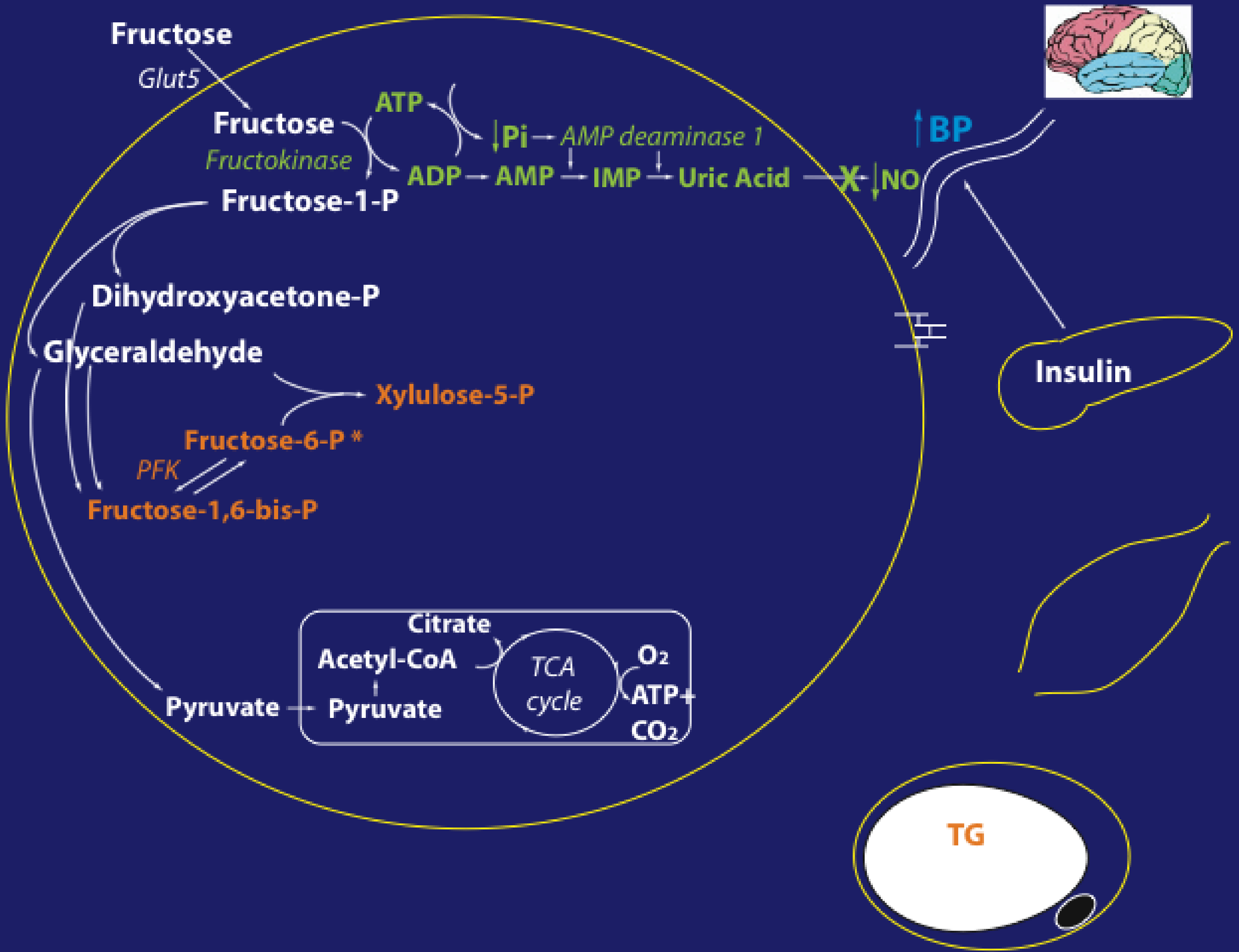
Detrimental Effects of Fructose



Detrimental Effects of Fructose



Detrimental Effects of Fructose



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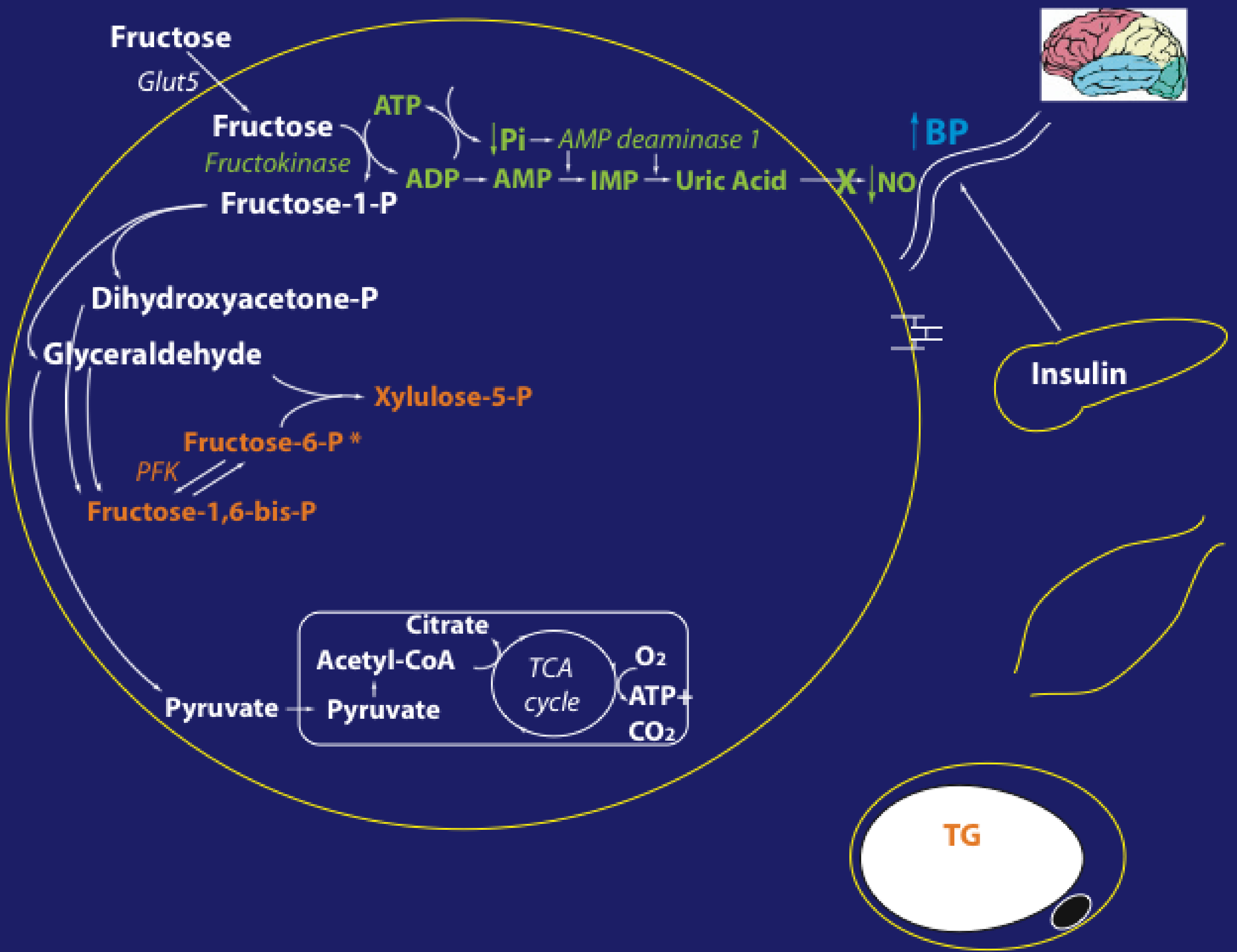
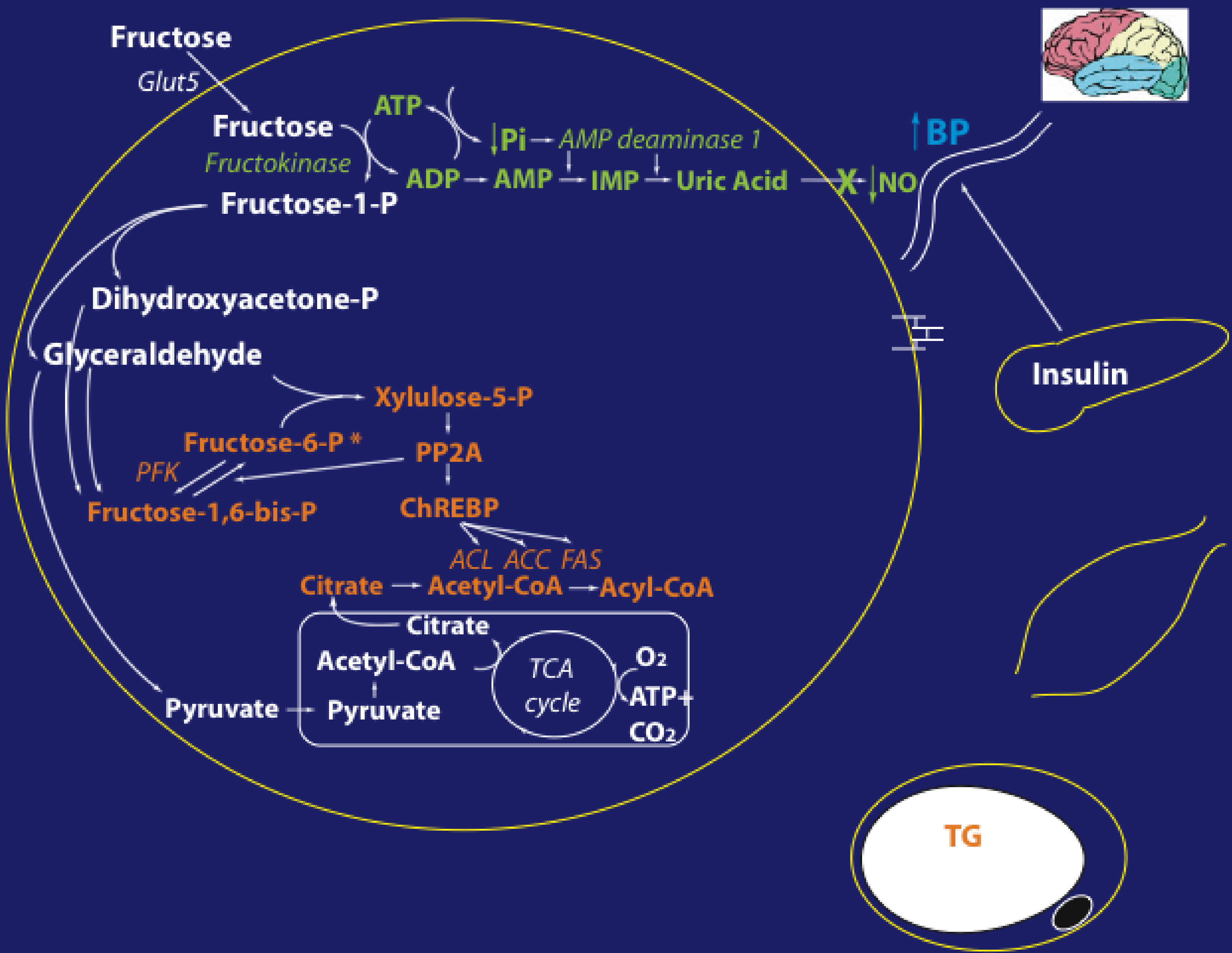
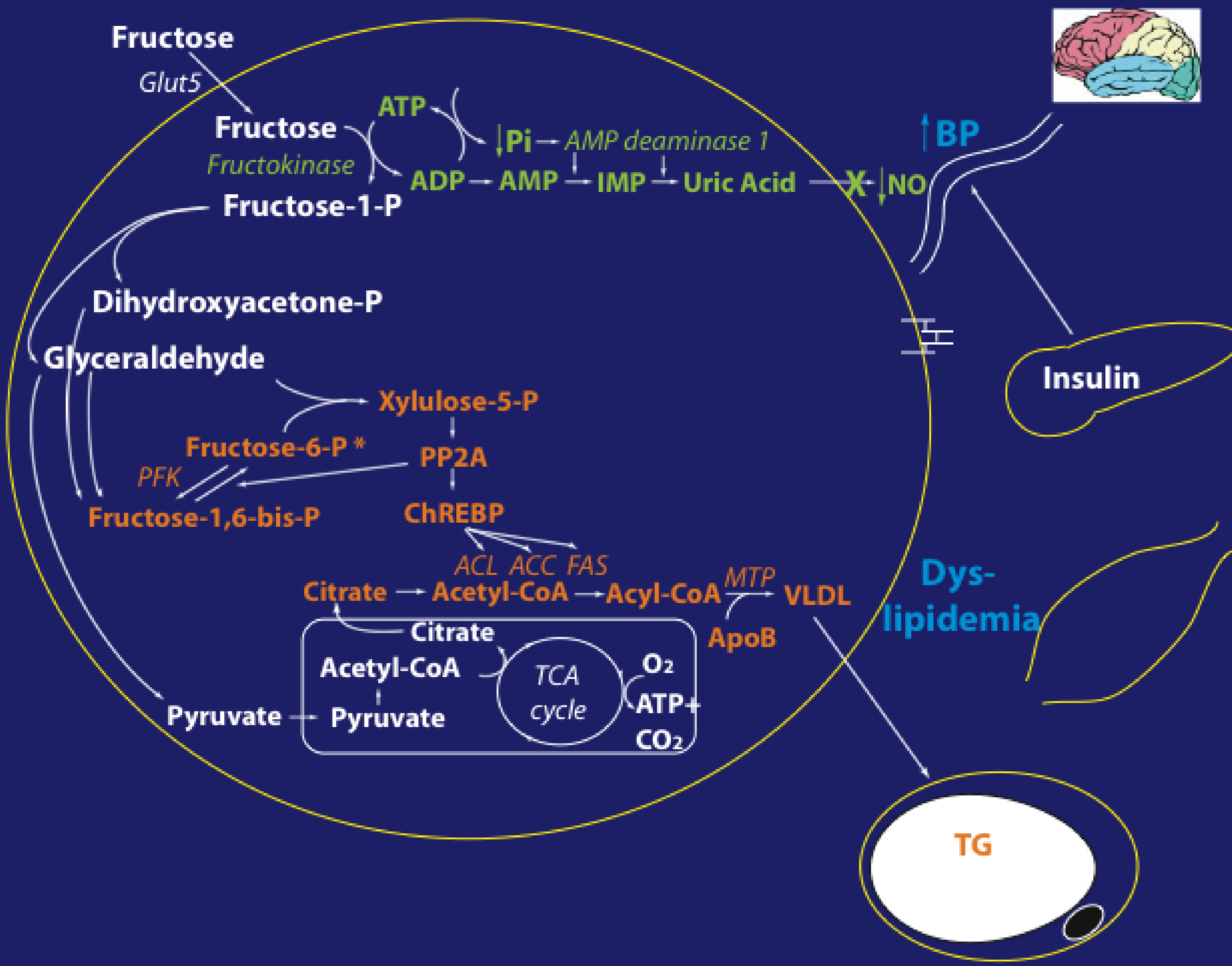


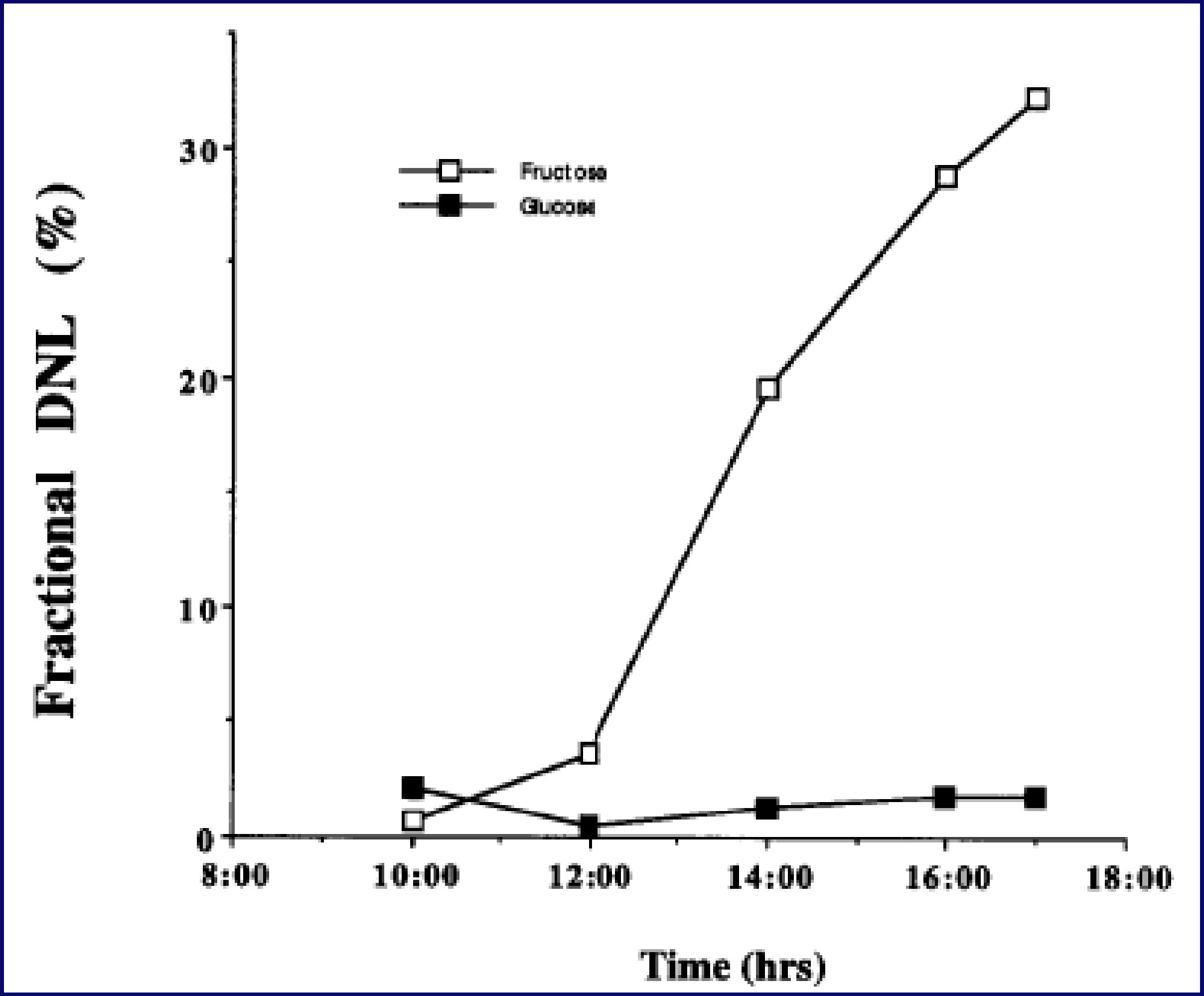
Detrimental Effects of Fructose



Detrimental Effects of Fructose



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

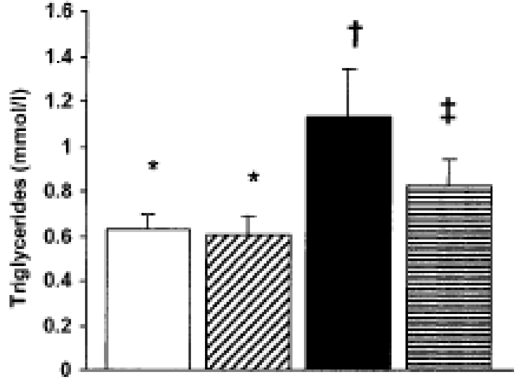


FIG. 3. Mean fasting triglyceride concentration after control condition (□), after 28 days of fish oil supplementation (▨), after 6 days of high-fructose diet (■), and after 28 days of fish oil supplementation plus high-fructose diet (▤) in seven men. Values are means ± SE represented by vertical bars.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

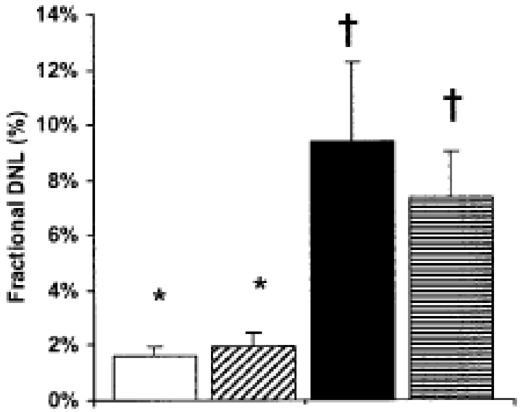


FIG. 4. Mean baseline fractional hepatic DNL after control condition (□), after 28 days of fish oil supplementation (▨), after 6 days of high-fructose diet (■), and after 28 days of fish oil supplementation plus high-fructose diet (▤) in seven men. Values are means ± SE represented by vertical bars.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

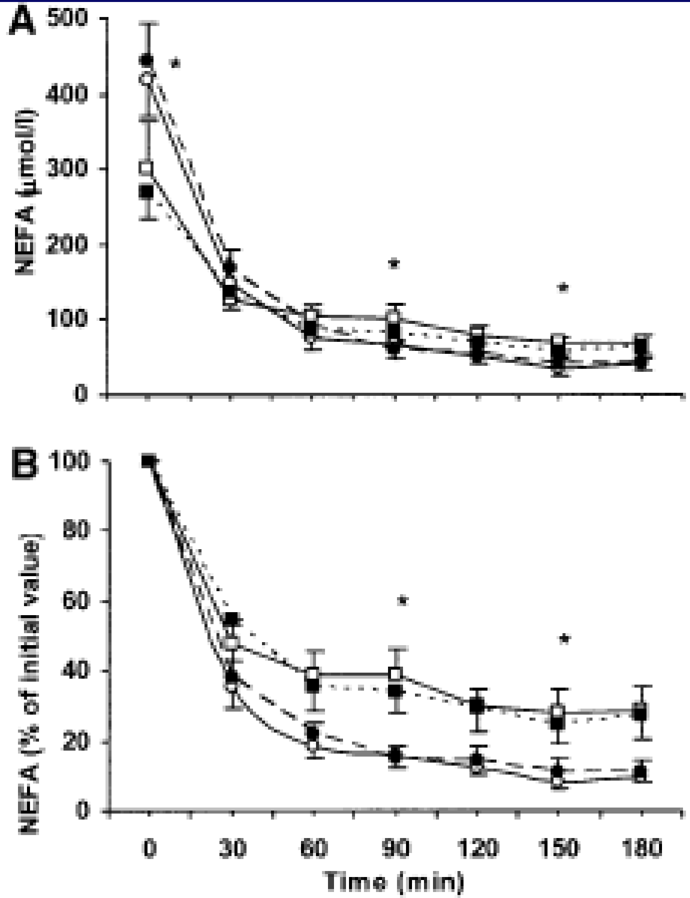
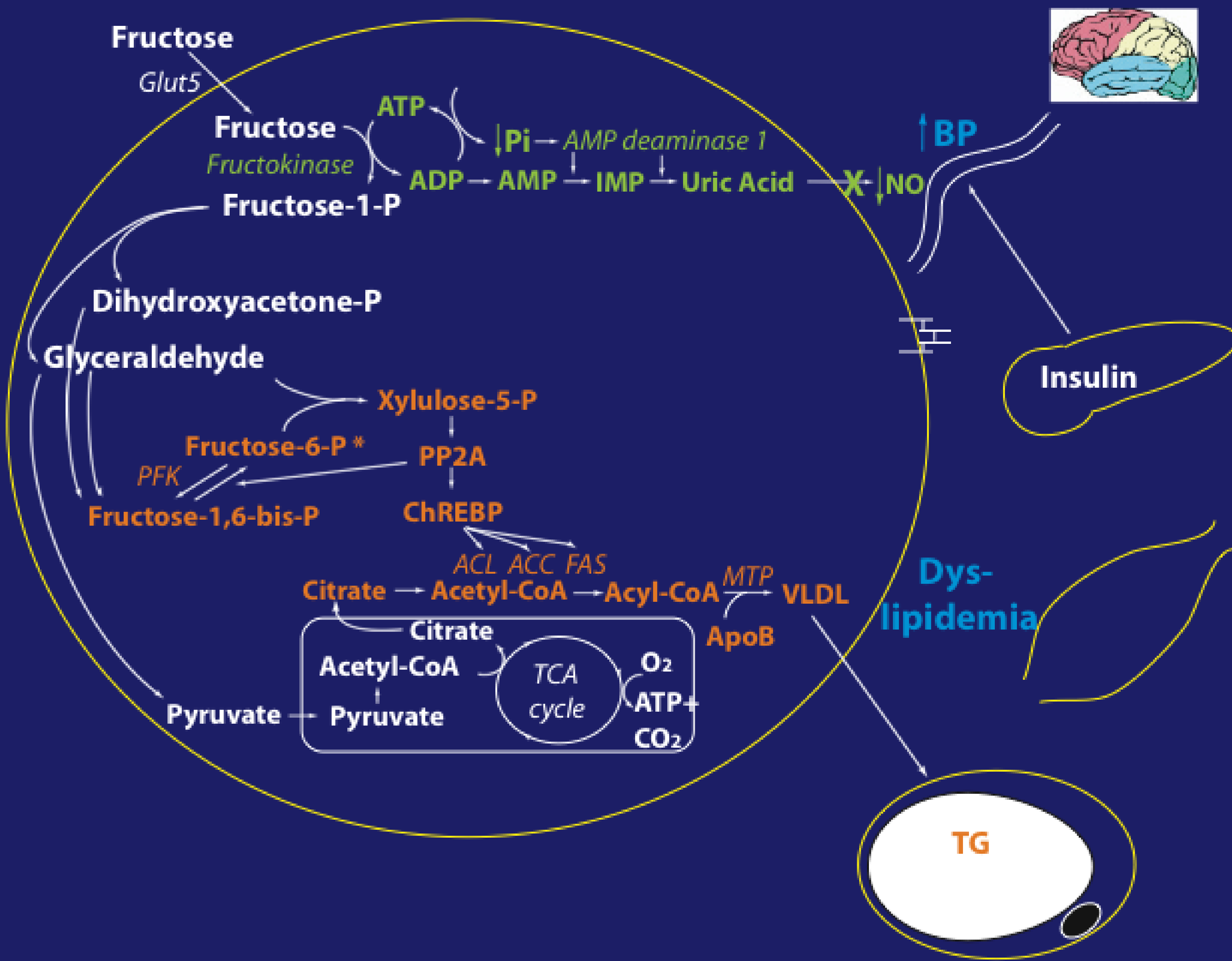


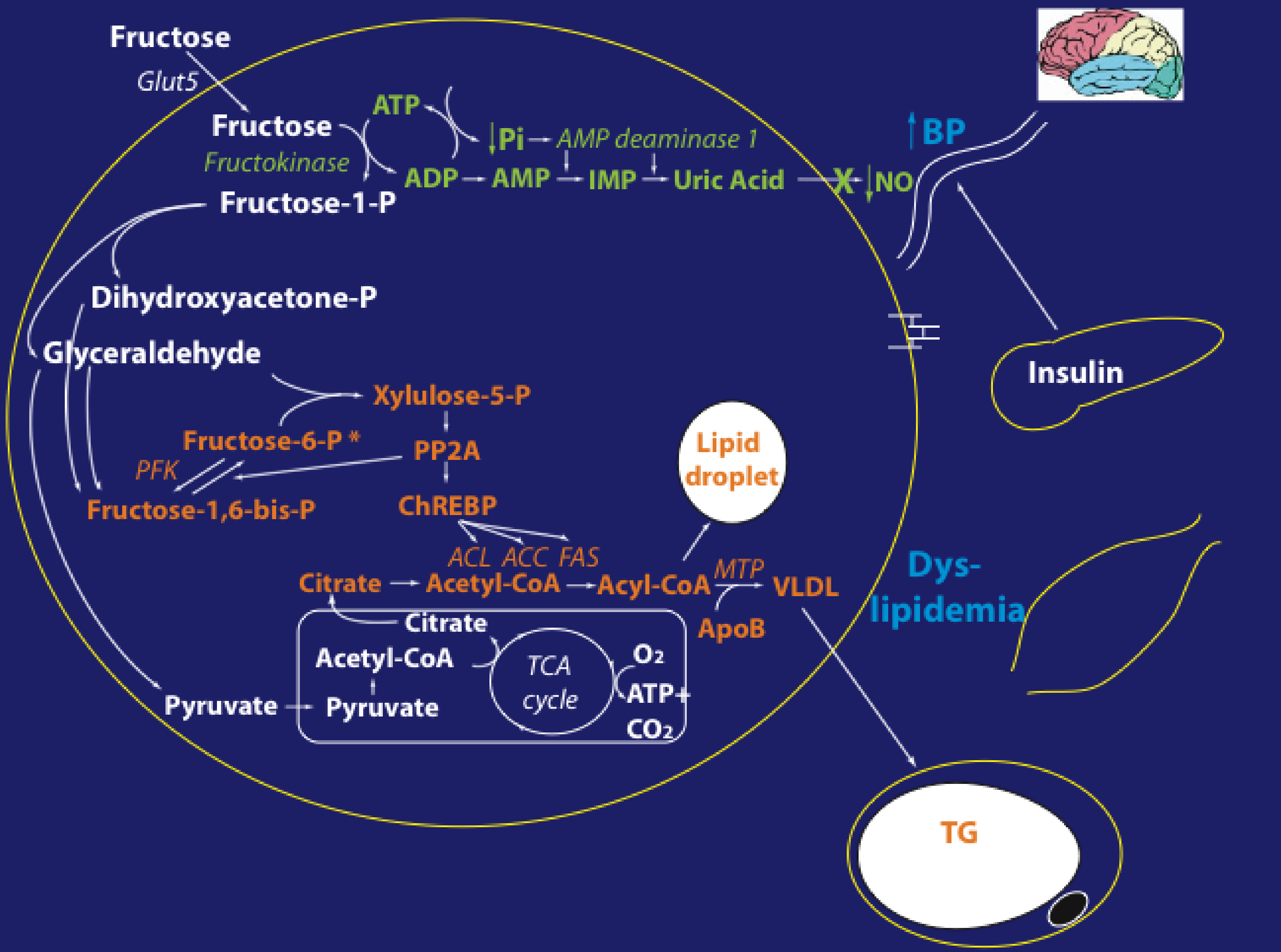
FIG. 7. NEFAs expressed as absolute values (*A*) and in percentage of the baseline value (*B*) during euglycemic-hyperinsulinemic clamping after control condition (○), after 28 days of fish oil supplementation (●), after 6 days of high-fructose diet (□), and after fish oil supplementation plus high-fructose 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

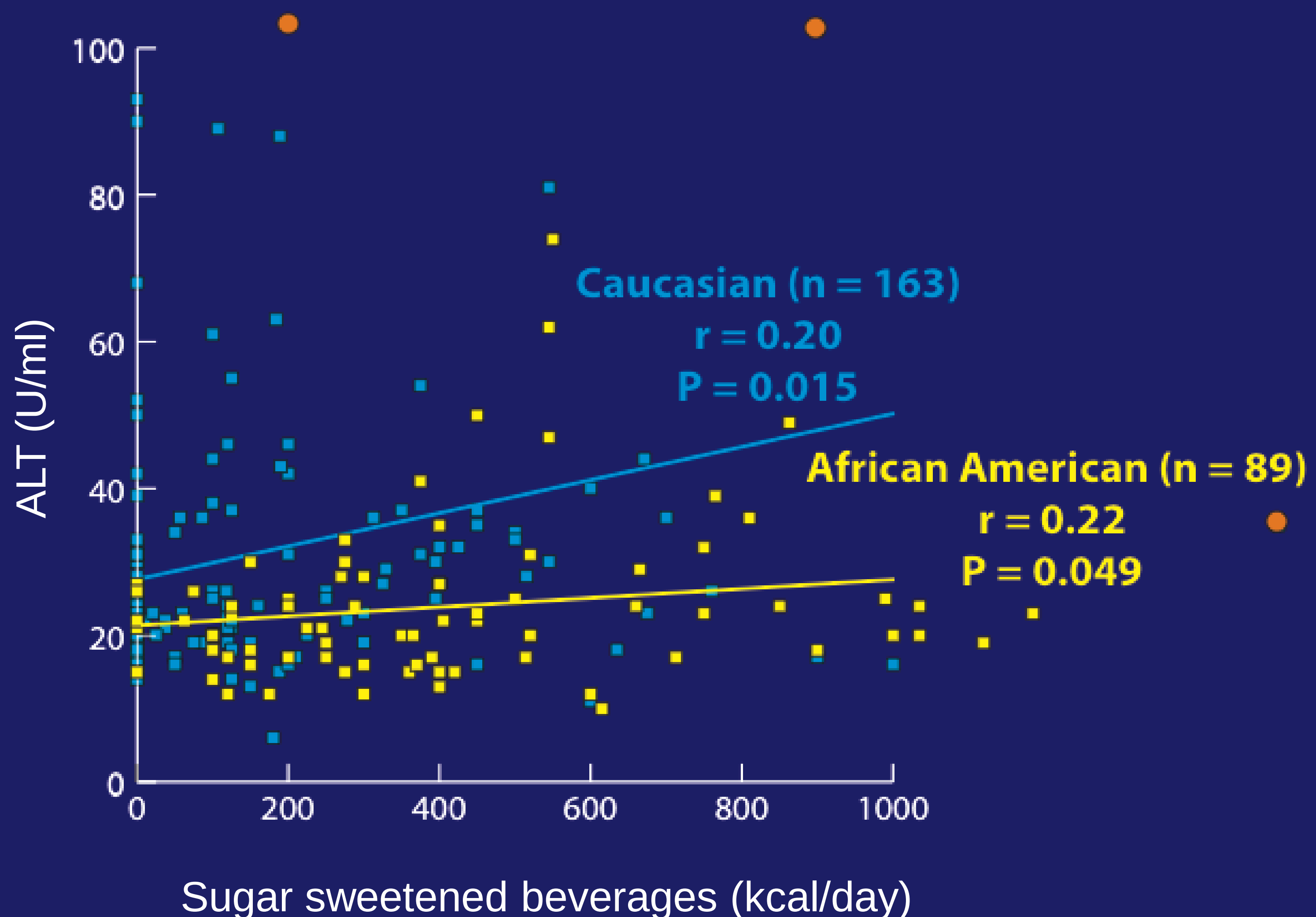
Detrimental Effects of Fructose



Detrimental Effects of Fructose

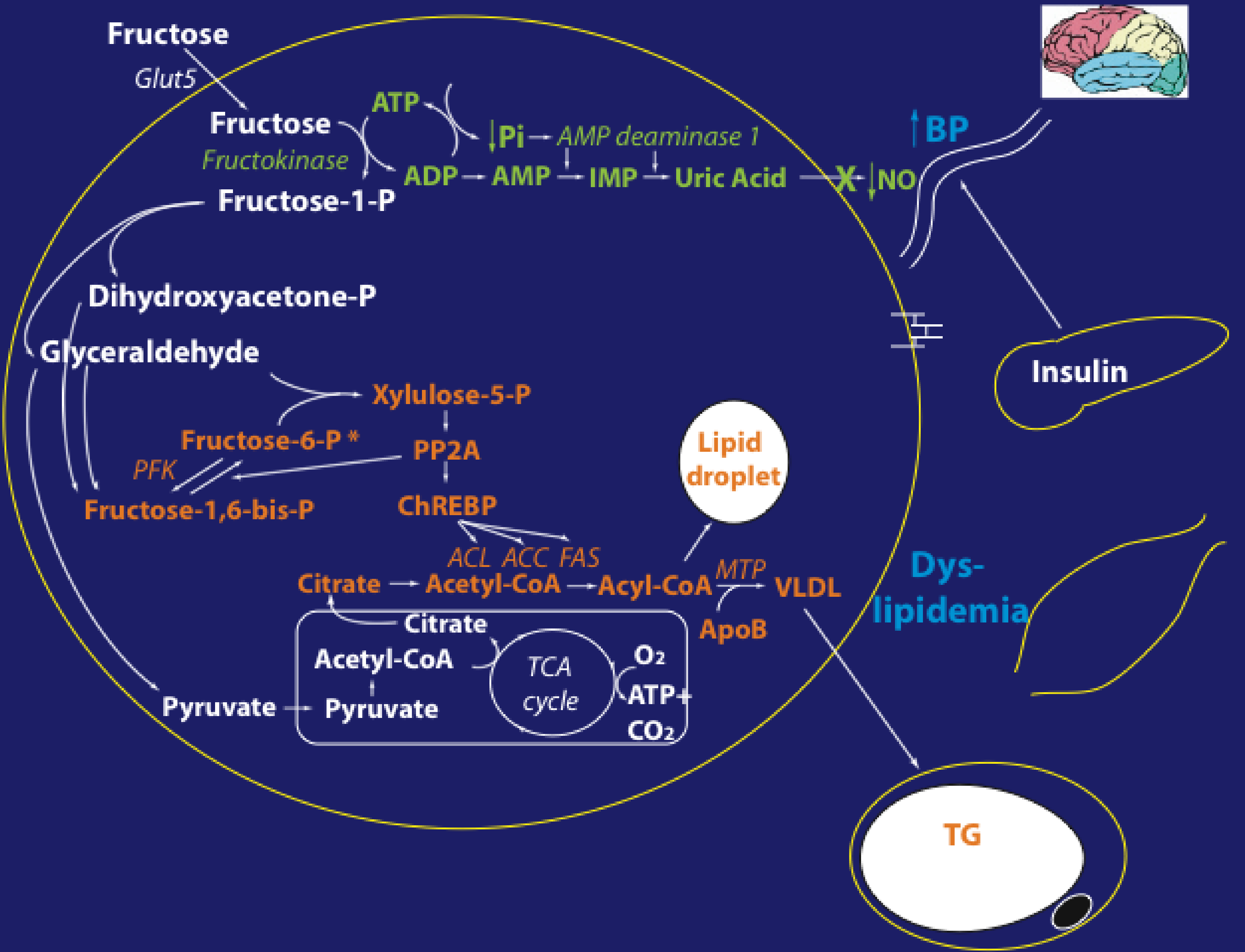


Associations between sugar sweetened beverage consumption and ALT in obese children

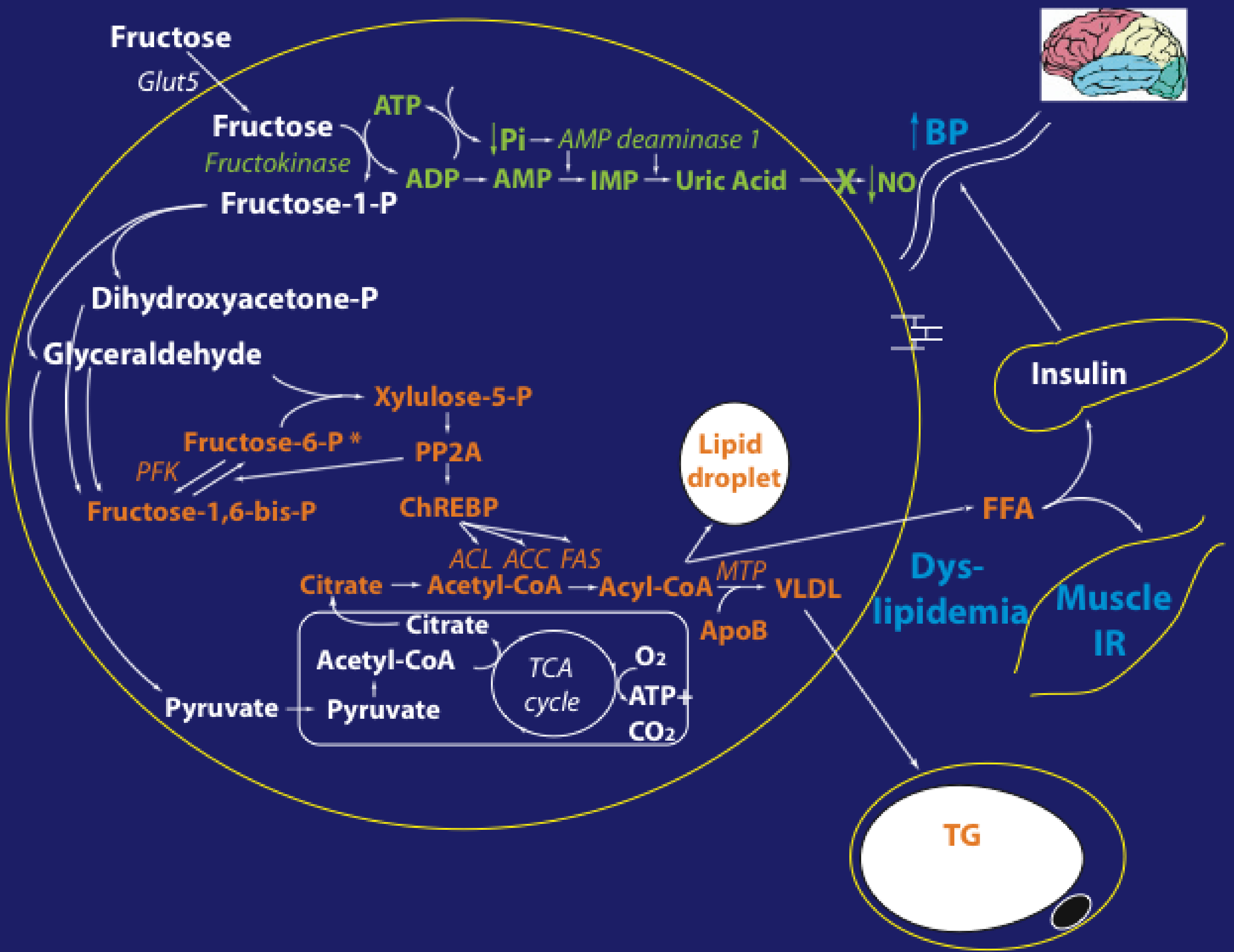


Valente et al. (unpuvlished)

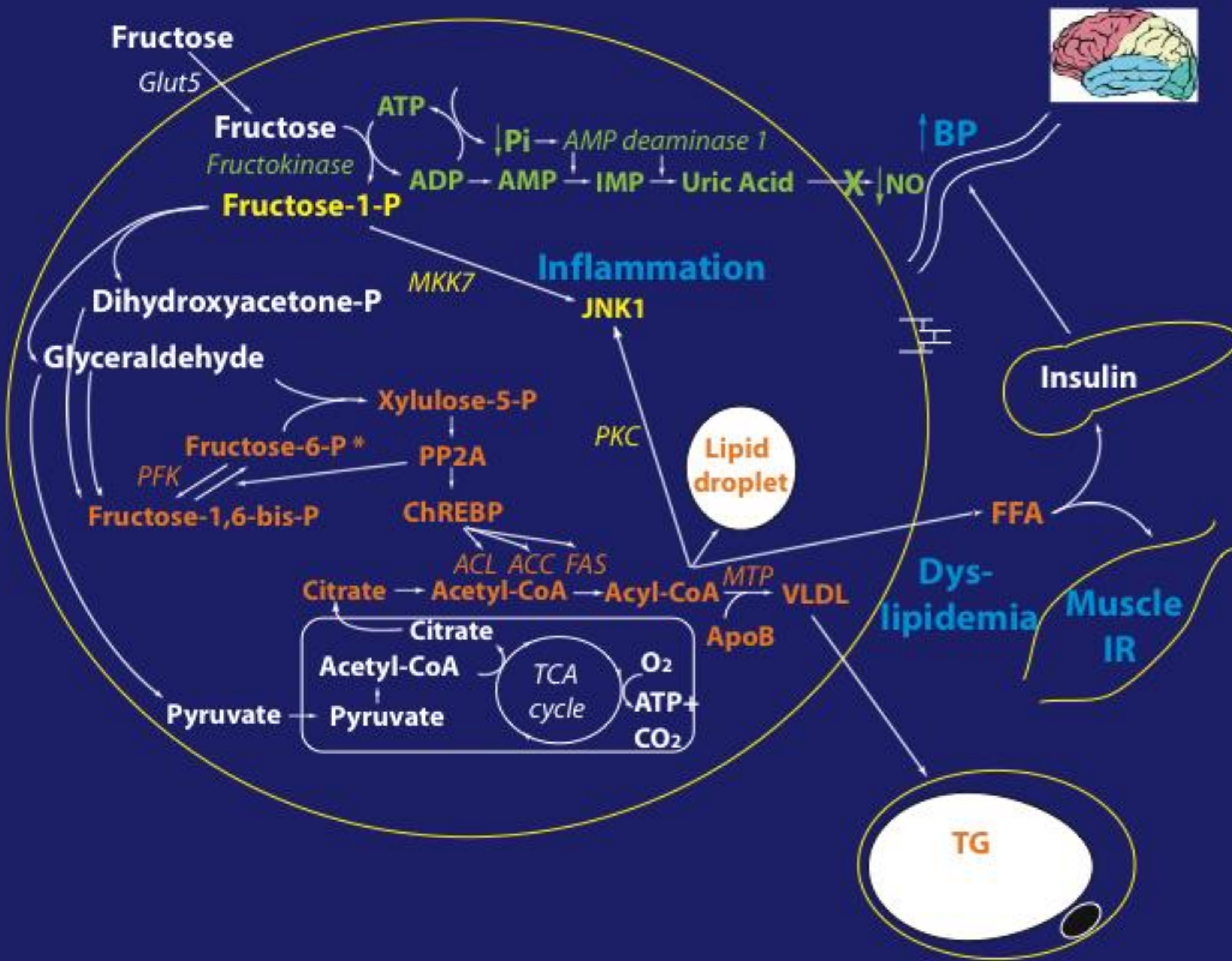
Detrimental Effects of Fructose



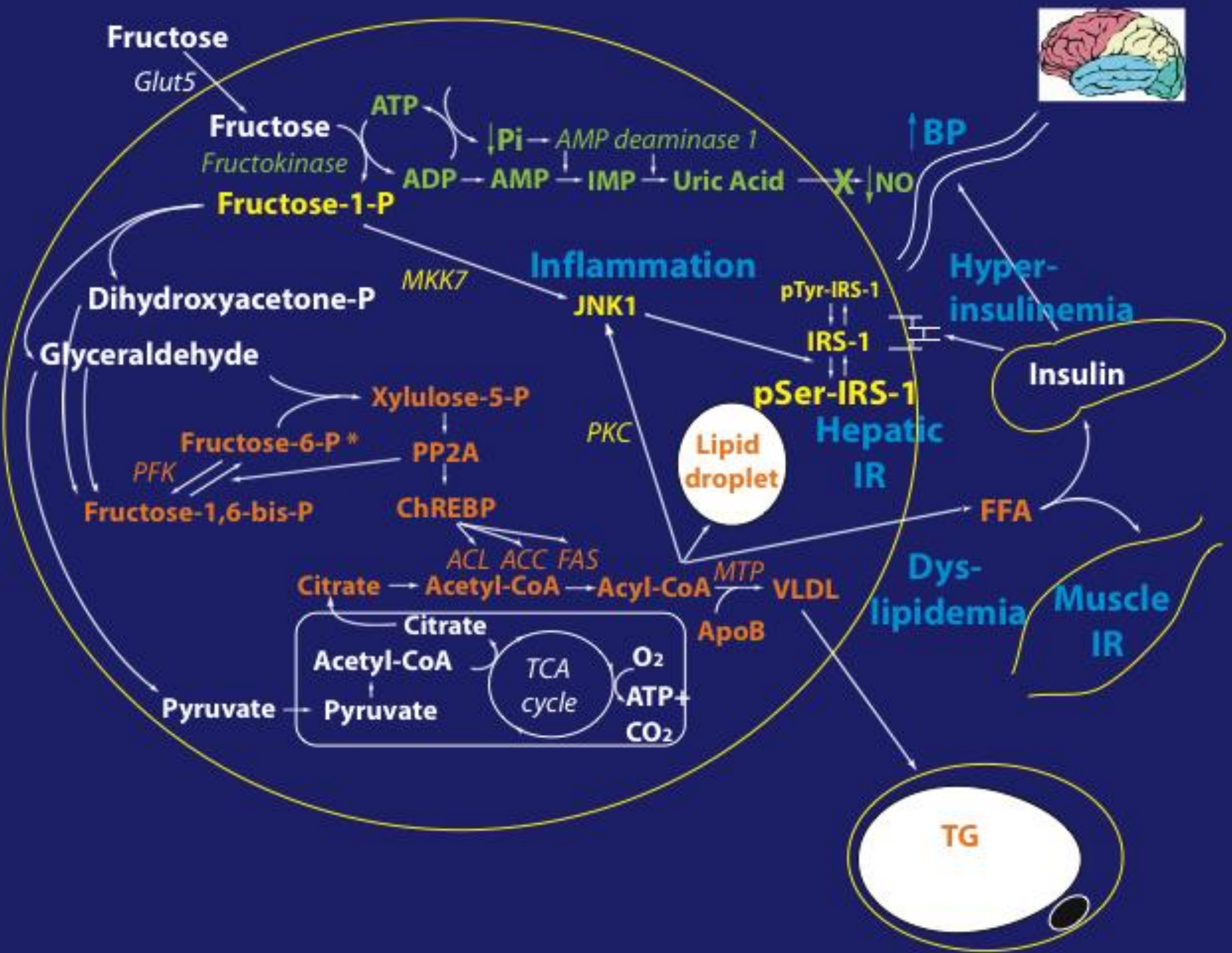
Detrimental Effects of Fructose



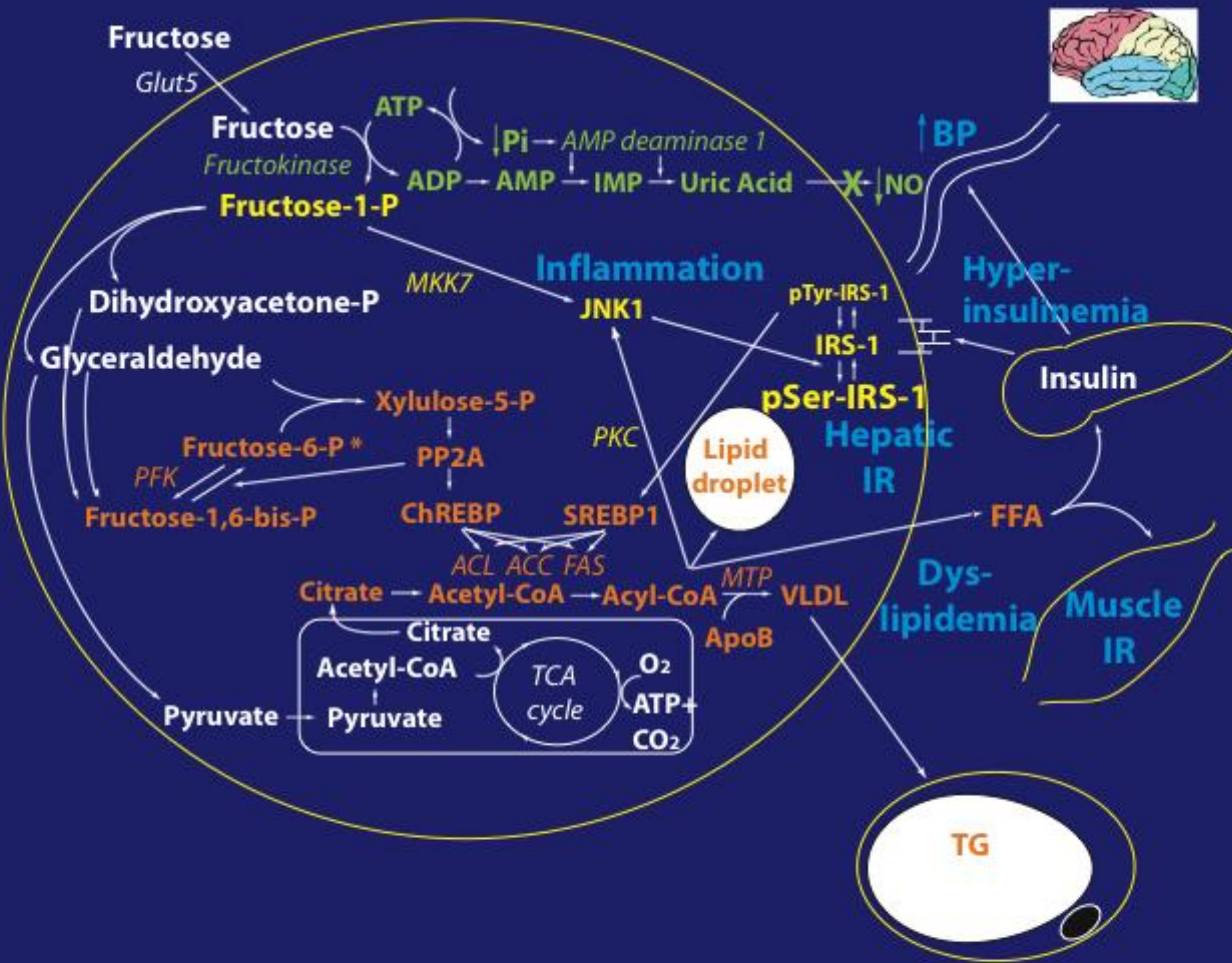
Detrimental Effects of Fructose



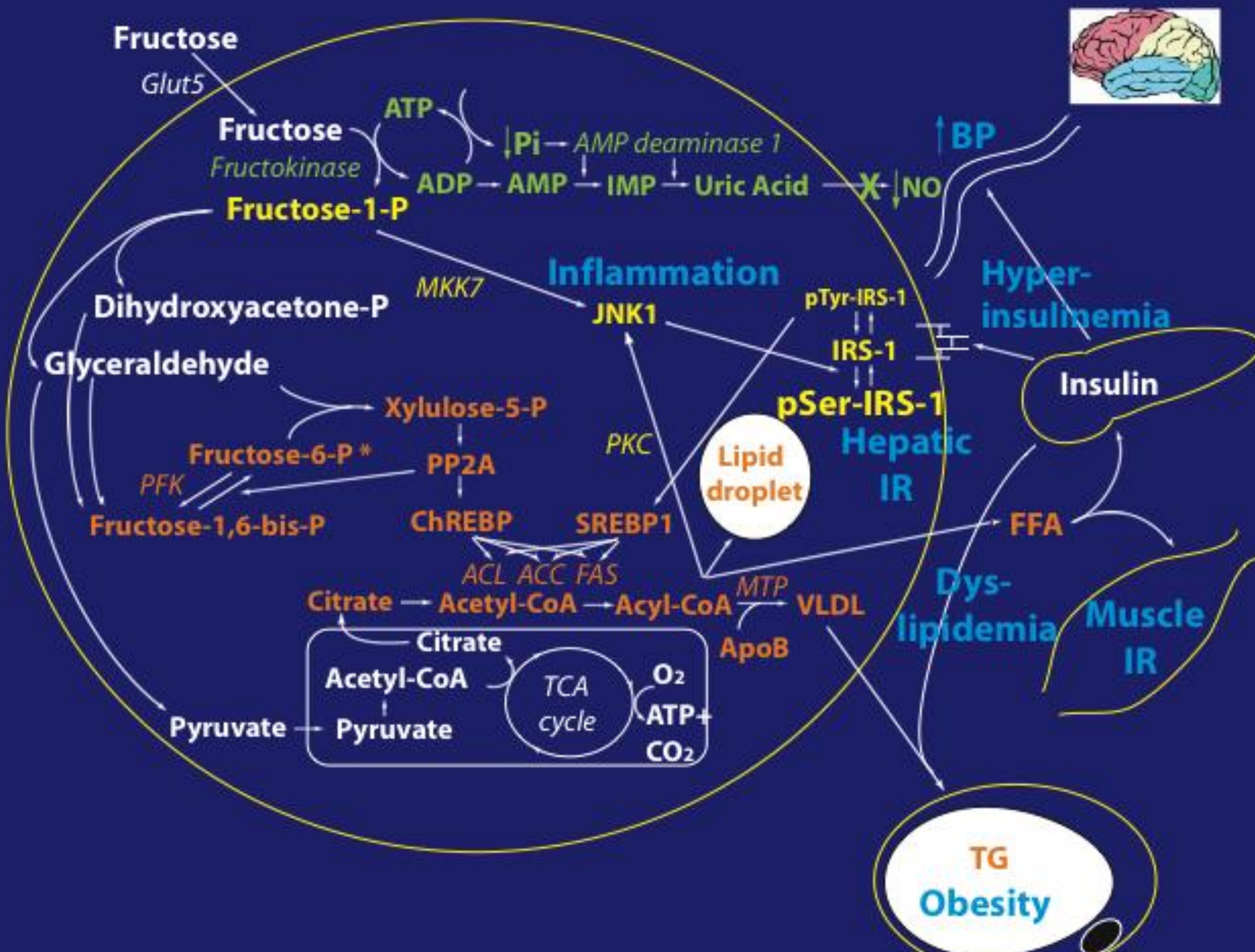
Detrimental Effects of Fructose



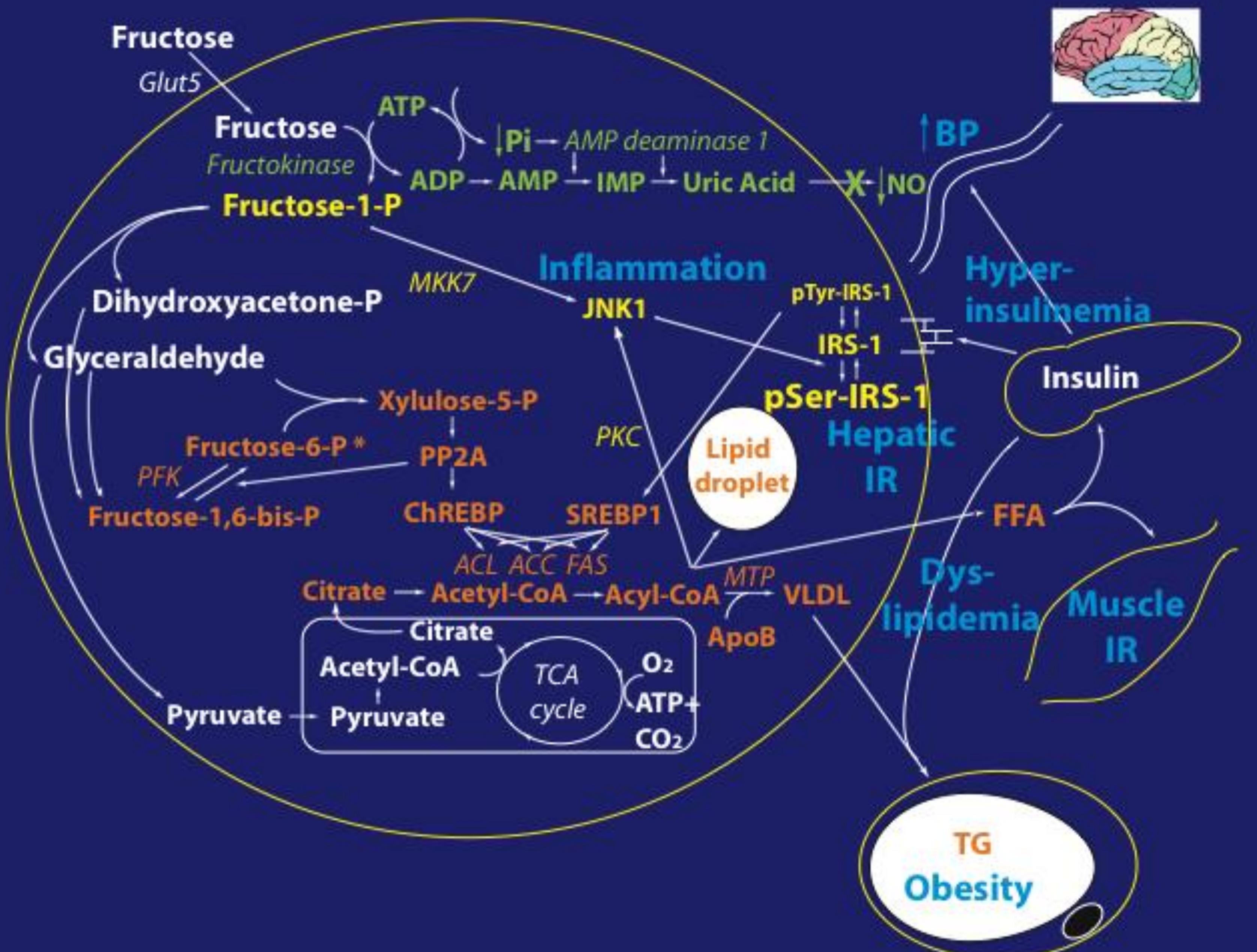
Detrimental Effects of Fructose



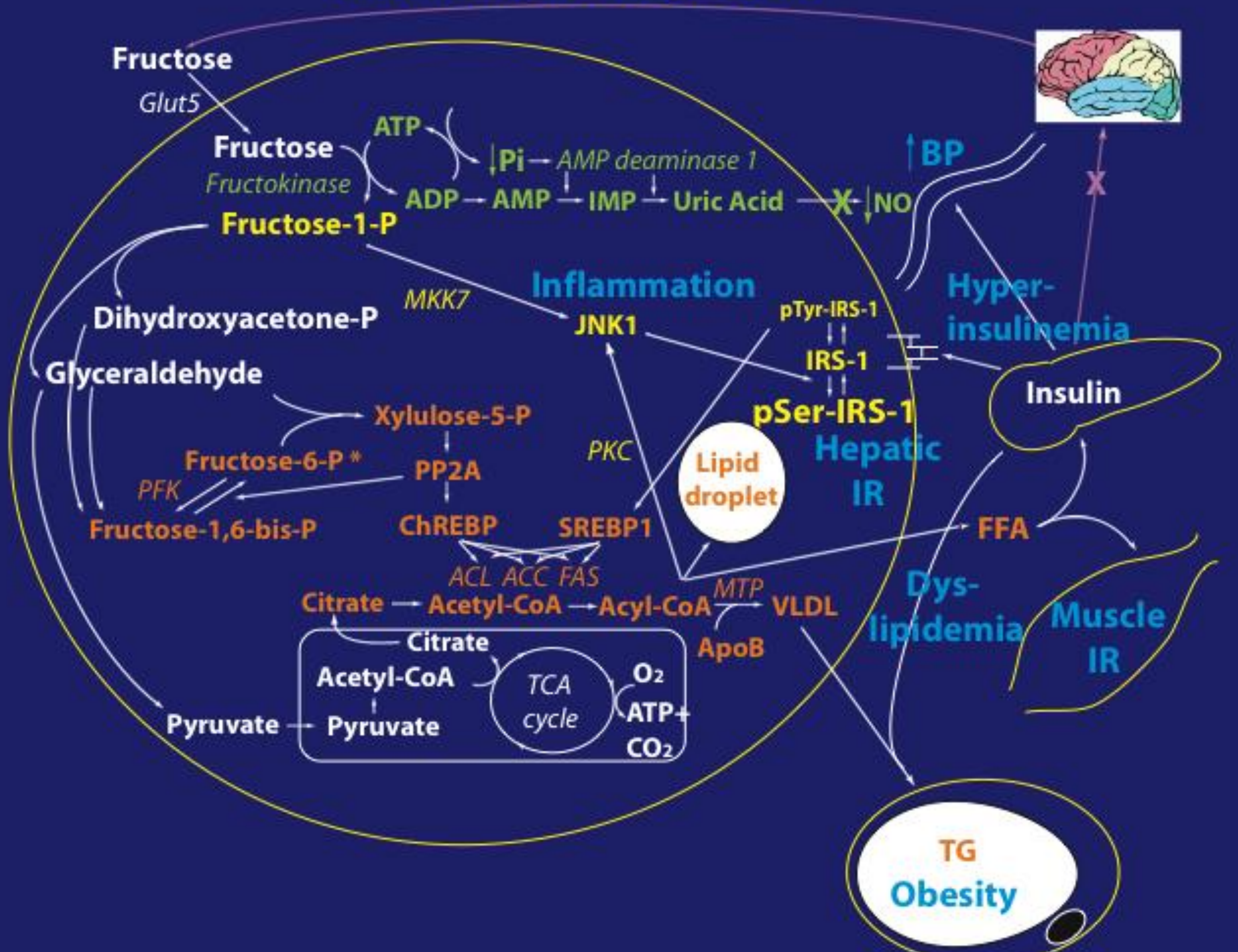
Detrimental Effects of Fructose



Detrimental Effects of Fructose



Detrimental Effects of Fructose



Protein Glycation and the Metabolic Syndrome

The furan ring of fructose is more unstable, so at equilibrium, fructose exists in the linear form

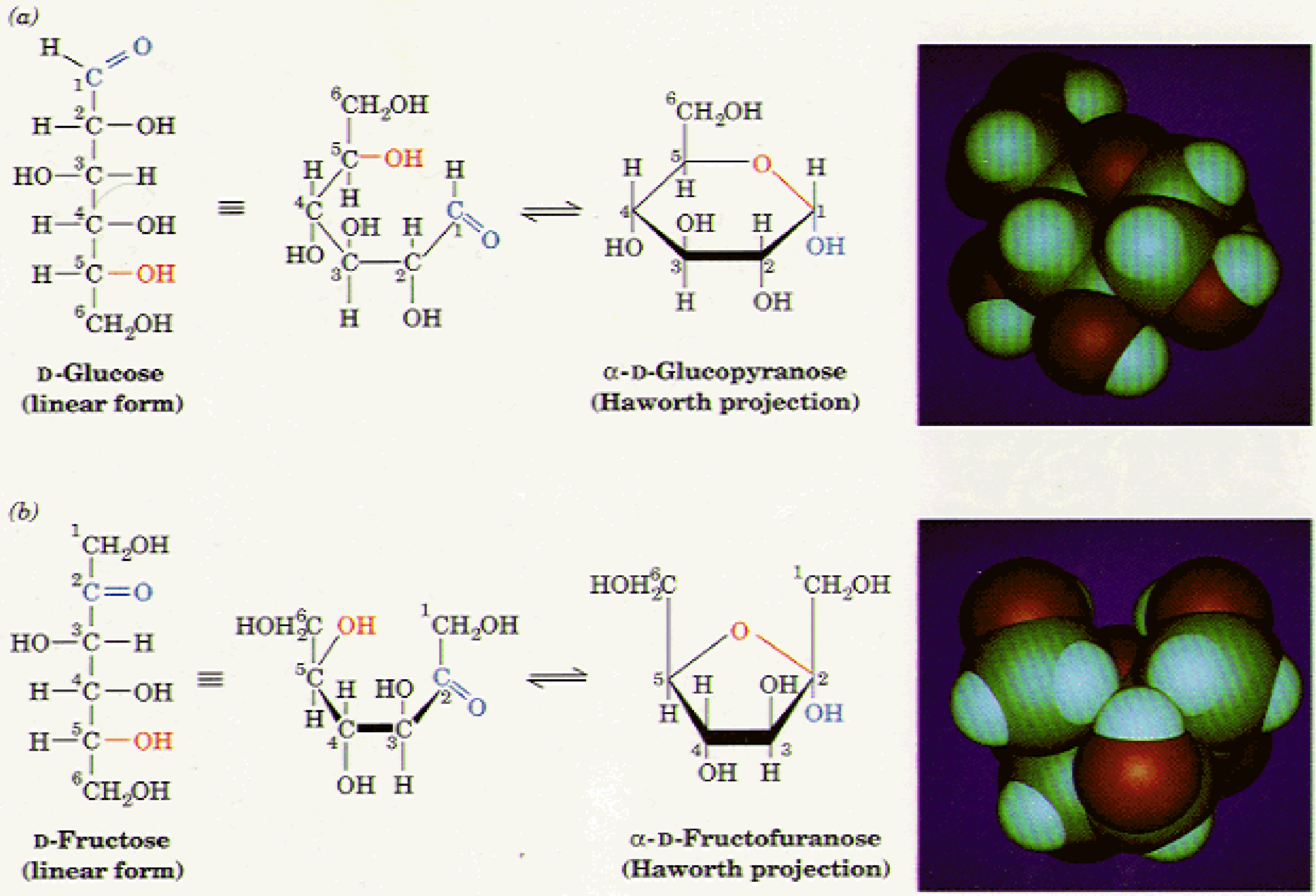


Figure 10-4. The cyclization of (*a*) D-glucose and (*b*) D-fructose.

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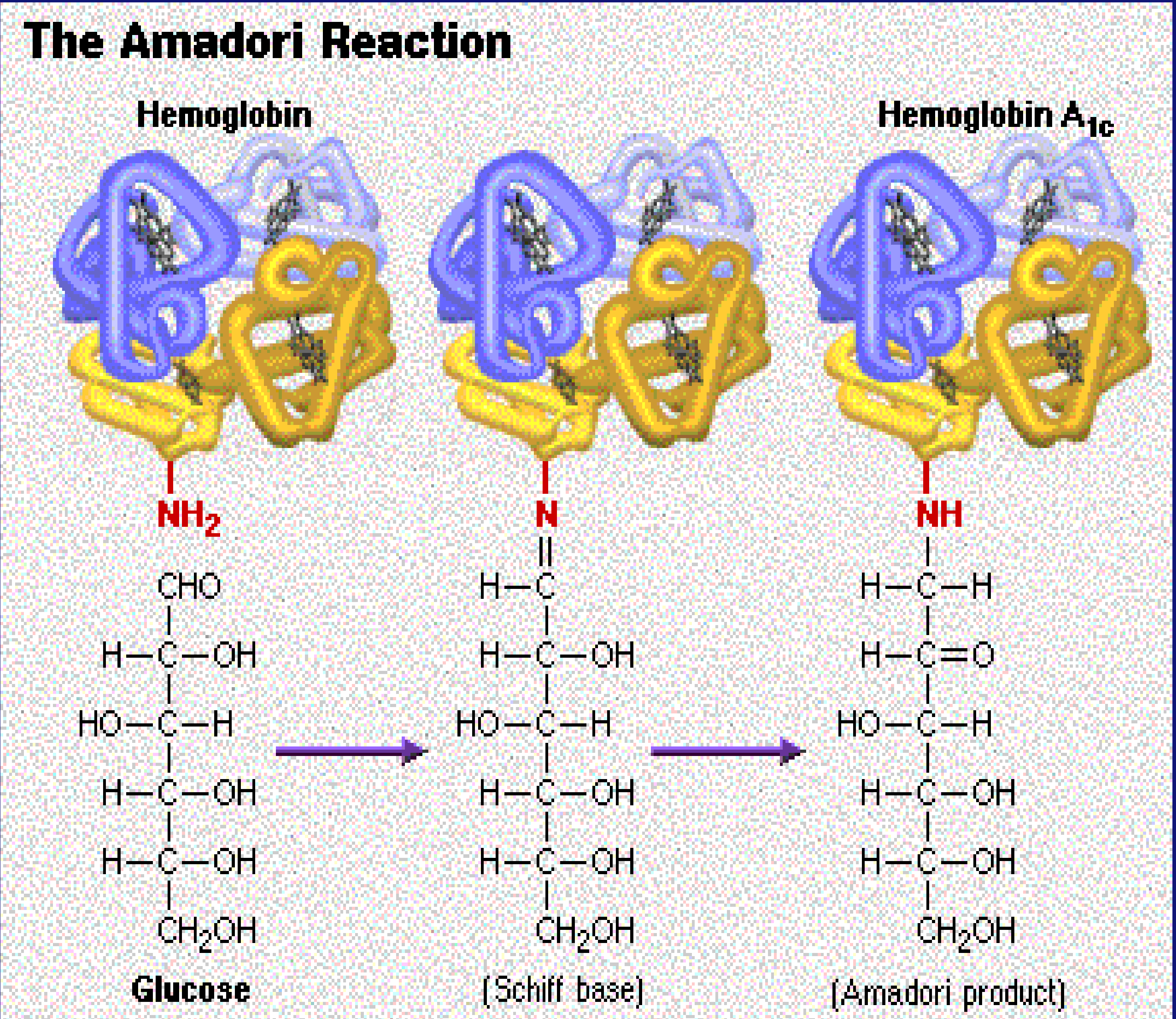
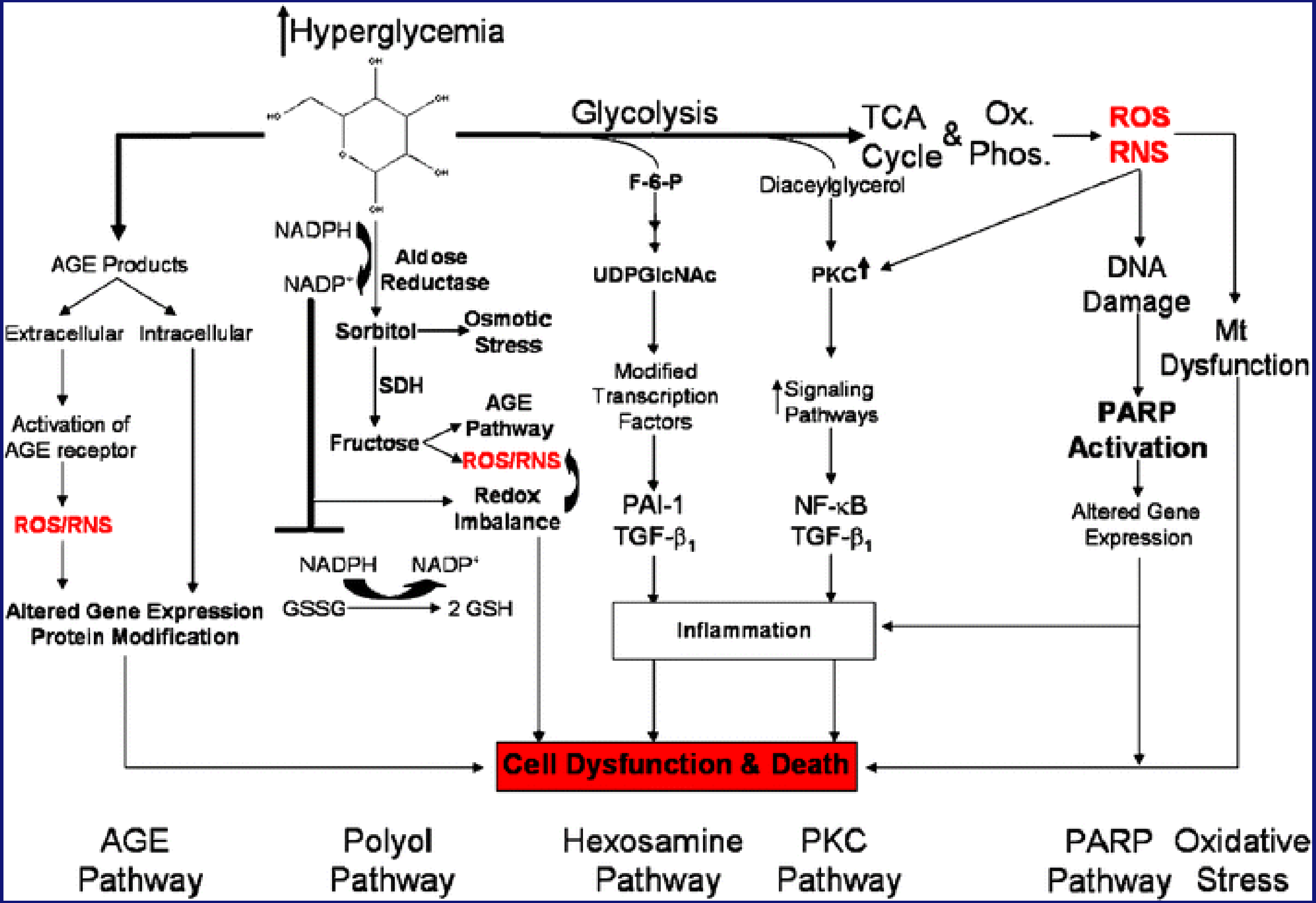


The Amadori Reaction
Hemoglobin
Hemoglobin A_{1c}
NH_2
N
NH
CHO
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH_2OH
Glucose
H—C
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH_2OH
(Schiff base)
H—C—H
H—C=O
HO—C—H
H—C—OH
H—C—OH
CH_2OH
(Amadori product)

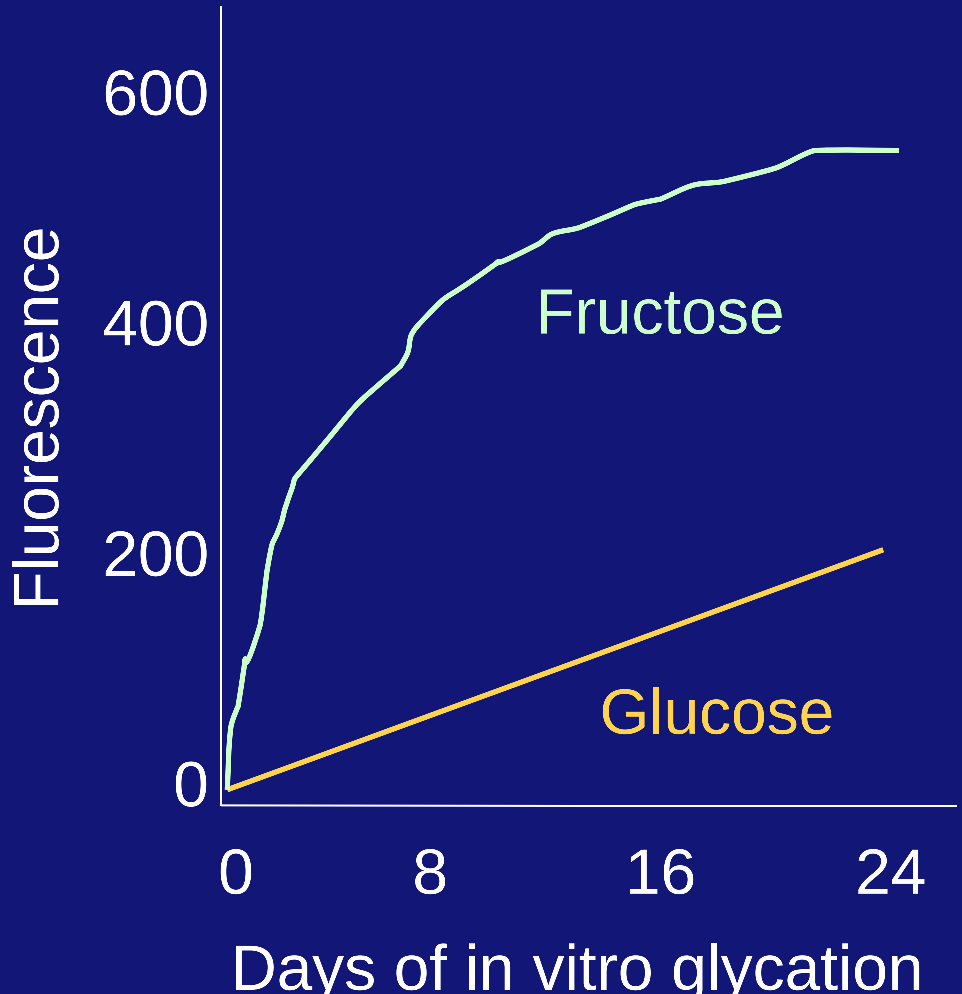
Generation of reactive oxygen species by carbohydrate



Figueroa-Romero et al. Rev Endo Metab Dis 9:301, 2008

Non-enzymatic glycation: fructose >> glucose

Fructose and glycation *in vitro*



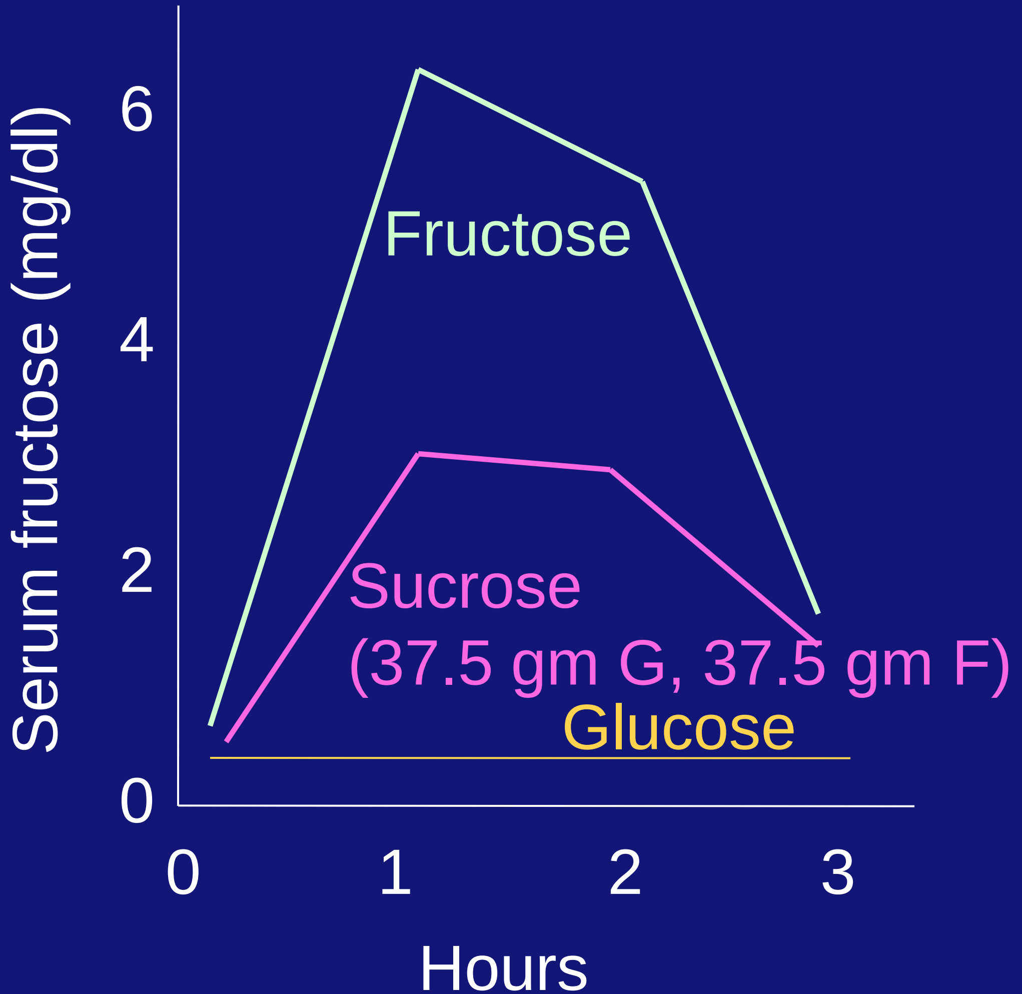
Ahmed and Furth, Clin Chem 38:1301, 1992

Rates of reactivity

	Rate (/mM/hr)	Carbonyl %
Glucose	0.6	0.002
Galactose	2.8	0.02
Fructose	4.5	0.7

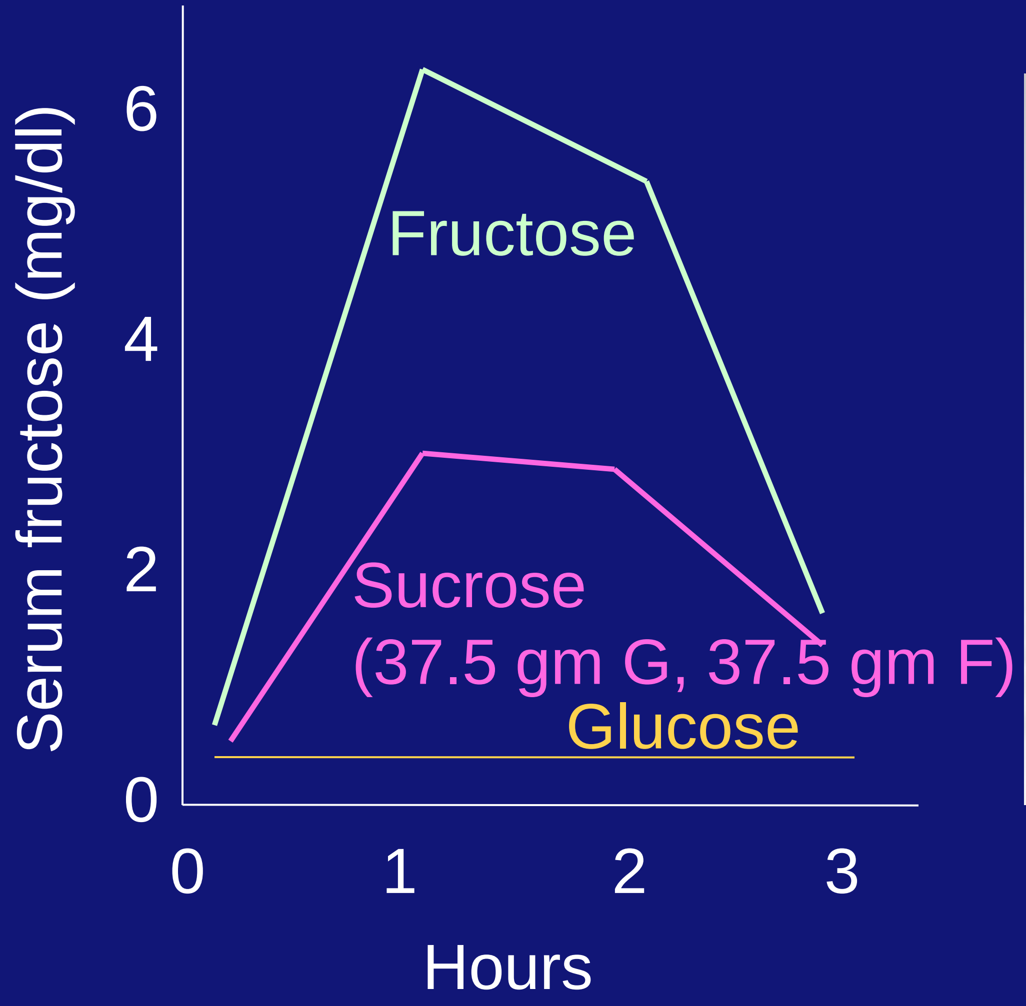
Bunn and Higgins, Science 213:222, 1981

Serum fructose levels after 75 gm (300 kcal) oral bolus



Kim et al. Diab Res Clin Pract 4:281, 1988

Serum fructose levels after 75 gm (300 kcal) oral bolus



250 kcal
34.5 gm F

Kim et al. Diab Res Clin Pract 4:281, 1988

Hepatocyte death *in vitro* upon fructose exposure (after generation of H_2O_2)

Treatment	ED_{50}	ED_{50} (with H_2O_2)
Fructose	1.5 ± 0.13 M	12 ± 2 mM
Glucose	>1.5 M	1.5 M
Glycoaldehyde	20 ± 2 mM	0.5 ± 0.1 mM
Glyoxal	5 ± 0.5 mM	0.02 ± 0.002 mM

Prevented by addition of:

- **antioxidant vitamins (VitB_1, VitB_6, VitC)**
- **P450 inhibitors**
- **hydroxyl radical and carbonyl scavengers**
- **heavy metal chelators**

Lee et al. Chemico-biological Interactions 178:332, 2009

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 (2^{o} dyslipidemia)
• Malnutrition	
• Obesity	• Obesity
• Hepatic dysfunction (ASH)	• Hepatic dysfunction (NASH)
• Fetal alcohol syndrome	• Fetal insulin resistance
• Addiction	• Habituation, if not addiction

What's the difference?

Calories	150	150
Percent CHO	10.5% (sucrose)	3.6% (alcohol)
Calories from		
fructose	75 (4.1 kcal/gm)	
other carbs	75 (glucose)	60 (maltose)
alcohol		90 (7 kcal/gm)
1st pass GI metabolism	0%	10%
Calories reaching liver	**90**	**92**

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Recognition at the American Heart Association

AHA Scientific Statement

Dietary Sugars Intake and Cardiovascular Health

A Scientific Statement From the American Heart Association

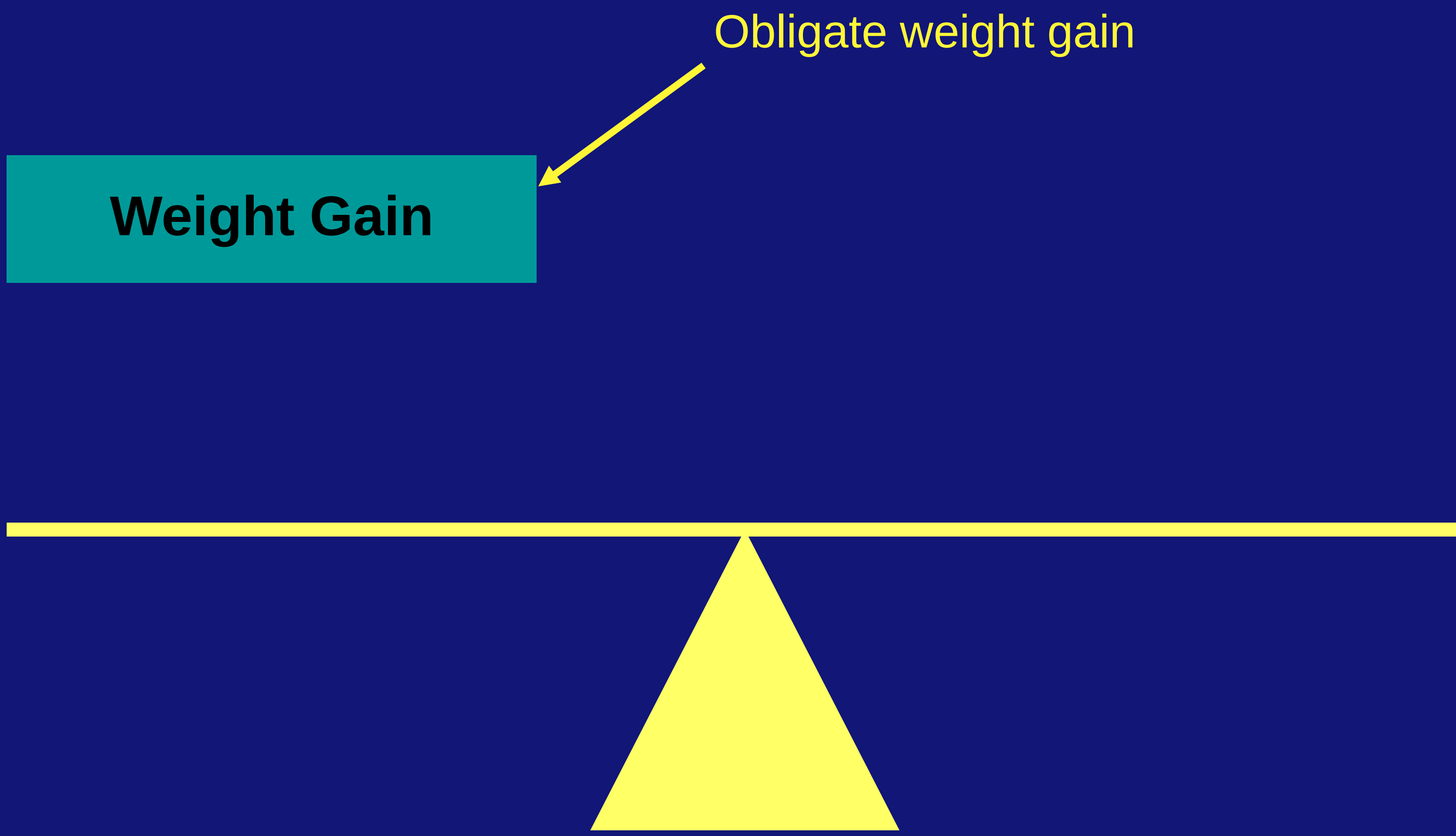
Rachel K. Johnson, PhD, MPH, RD, Chair; Lawrence J. Appel, MD, MPH, FAHA;
Michael Brands, PhD, FAHA; Barbara V. Howard, PhD, FAHA;
Michael Lefevre, PhD, FAHA; Robert H. Lustig, MD; Frank Sacks, MD, FAHA;
Lyn M. Steffen, PhD, MPH, RD, FAHA; Judith Wylie-Rosett, EdD, RD;
on behalf of the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention

Recommends reduction in sugar intake from 22 tsp/day to 9 tsp/day (males) and 6 tsp/day (females)

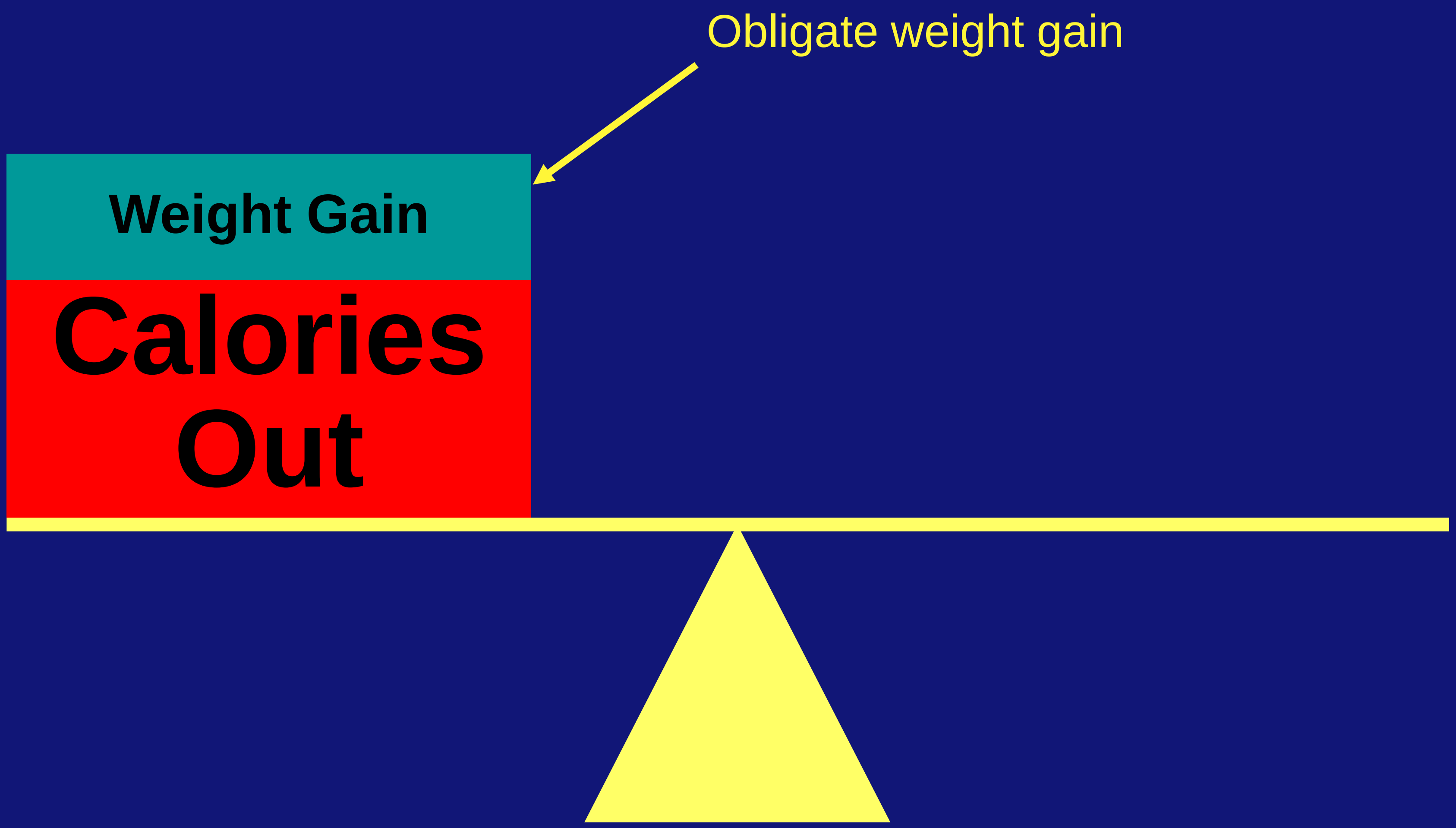
Circulation 120:1011, 2009

The First Law of Thermodynamics

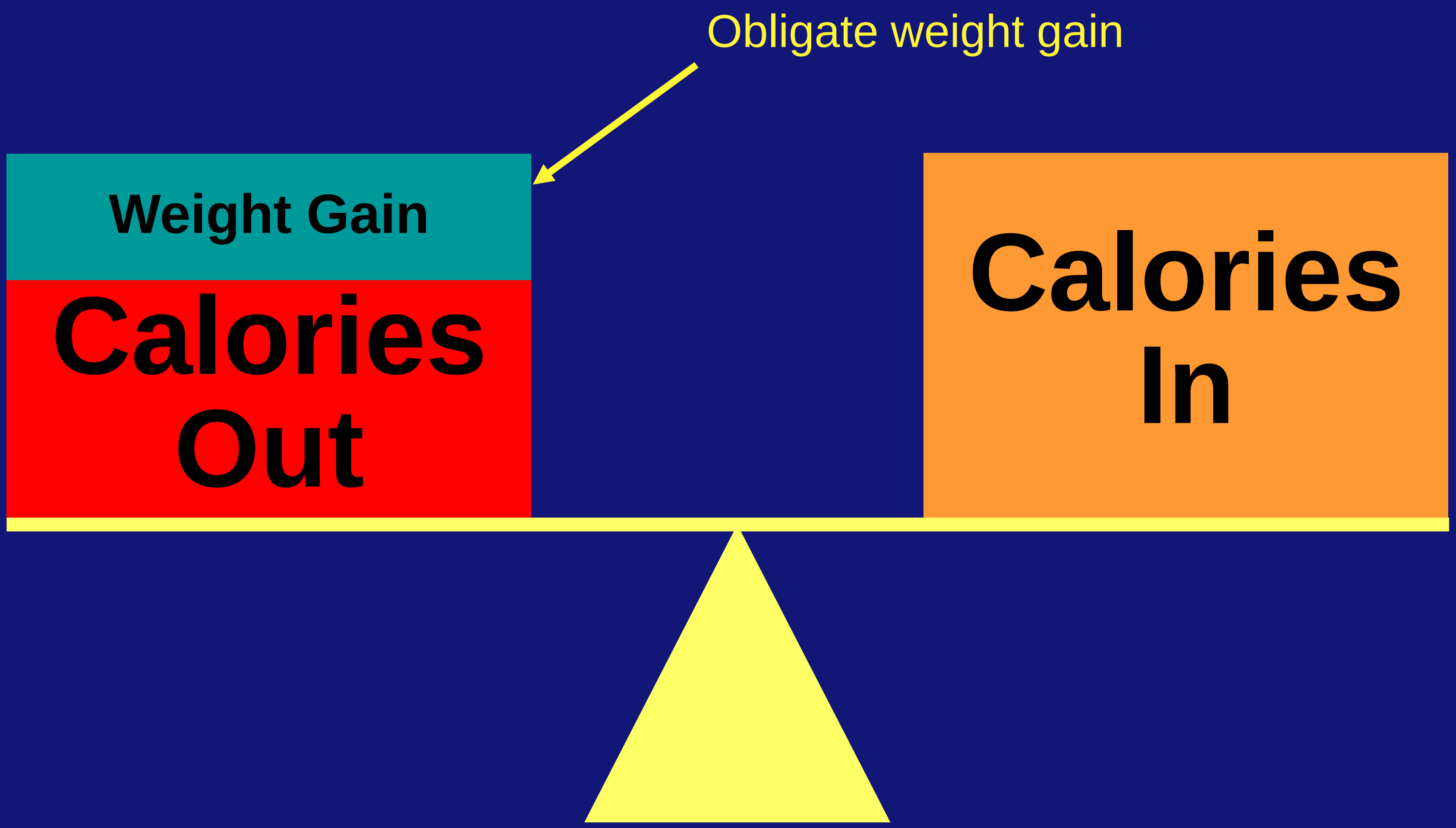
The First Law of Thermodynamics



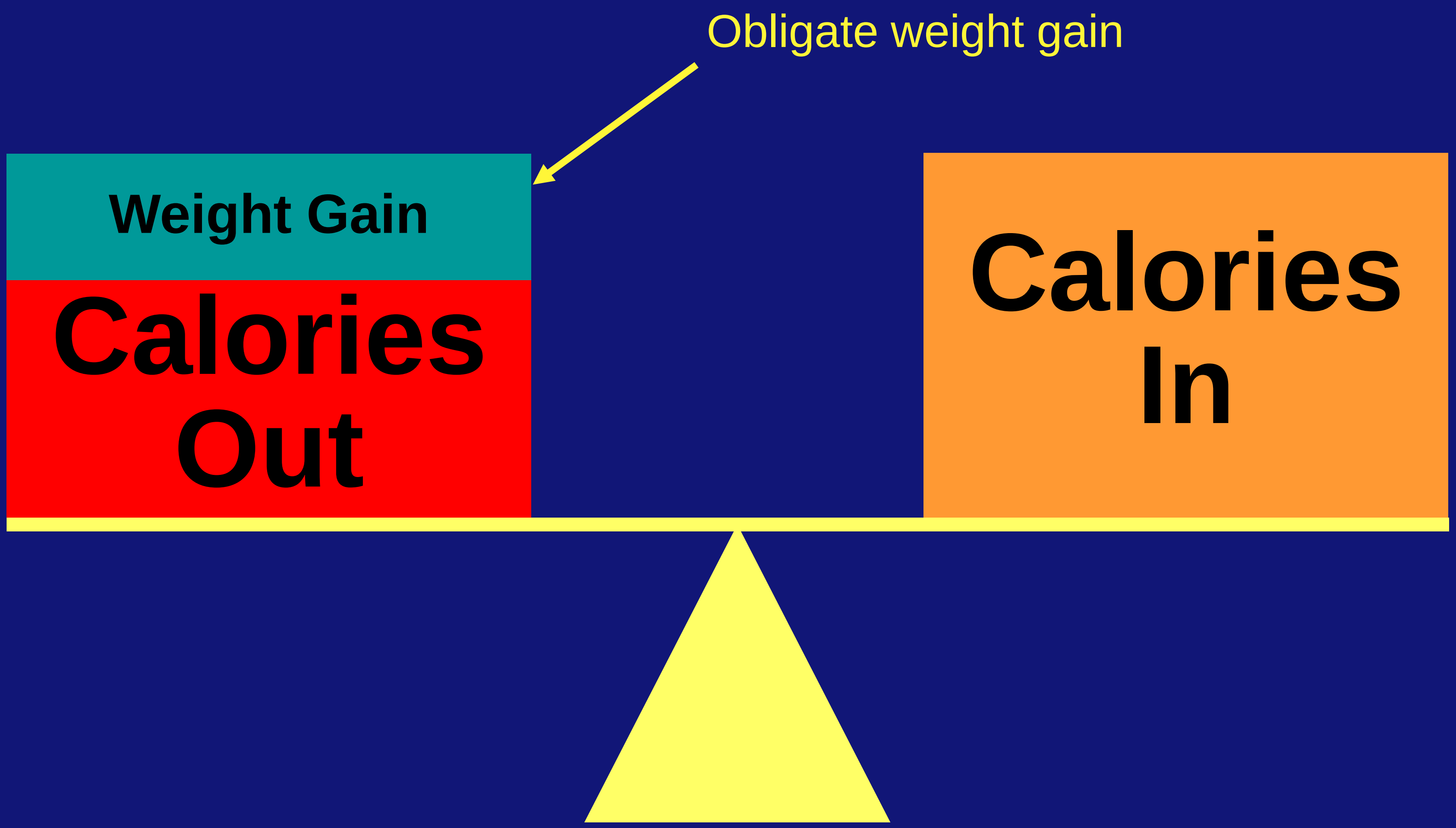
The First Law of Thermodynamics



The First Law of Thermodynamics



The First Law of Thermodynamics



The two aberrant behaviors are a result of our biochemistry
Our biochemistry is a result of our environment

Collaborators

UCSF Weight Assessment for Teen and Child Health

Elvira Isganaitis, M.D.
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Patrika Tsai, M.D., M.P.H.
Kristine Madsen, M.D., M.P.H.
Stephanie Nguyen, M.D.
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Sharon Fleming, Ph.D.
Lorene Ritchie, Ph.D.

UCSF Institute for Health Policy Studies

Laura Schmidt, Ph.D., M.P.H., L.C.S.W.
Claire Brindis, Dr.P.H.